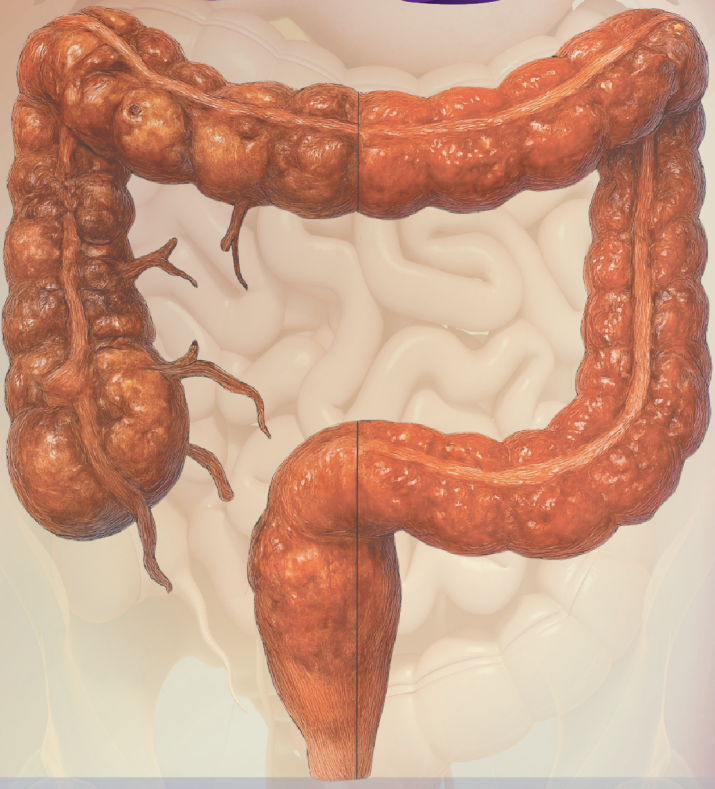
CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/612.25(GU)-e

INFLAMMATORY BOWEL DISEASE

2025



Ministry of Health Malaysia

Malaysian Society of Gastroenterology & Hepatology (MSGH)

Malaysian Society of Paediatric Gastroenterology, Hepatology, and Nutrition (MySPGHAN)

Academy of Medicine Malaysia

Developed and published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre 62590
Putrajaya, Malaysia

eISBN: 978-629-7842-25-7

Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
https://www.msgh.org.my
https://www.myspghan.my
https://www.iapmd.net/
https://colorectalmy.org/

STATEMENT OF INTENT

The clinical practice guideline (CPG) is meant to be a guide for clinical practice based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decisions appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

TABLE OF CONTENTS

TABLE OF CONTENTS

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG DG as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

DIAGNOSIS AND INVESTIGATIONS

- The diagnosis of inflammatory bowel disease (IBD) should be established through a comprehensive, integrated assessment encompassing clinical features (including extraintestinal manifestations), laboratory tests, endoscopic evaluation, histopathological findings and imaging studies.
- Tuberculosis (TB) workup should be performed in patients who pose a diagnostic challenge between Crohn's disease (CD) and intestinal TB.
- In all patients with suspected IBD, colonoscopy should be performed with the acquisition of at least two biopsy specimens each from a minimum of six bowel segments, and bowel preparation should be carried out using polyethylene glycol.
- Testing for cytomegalovirus reactivation on colonic biopsy should be performed in all patients with severe colitis refractory to immunosuppressive therapy.
- In patients with ulcerative colitis (UC), Nancy Histological Index should be used in routine clinical practice as it is the simplest and fastest histological scoring system.
- Computed tomography scan should be performed in acute clinical scenarios such as suspected bowel obstruction, perforation and severe complications where rapid diagnosis is required in patients with IBD.
- Magnetic resonance enterography or intestinal ultrasound should be performed in CD patients to assess disease activity and extent.
- Pelvic magnetic resonance imaging should be performed in patients with perianal disease to assess fistulae and identify associated complications.

THERAPEUTIC INTERVENTIONS

a) Conventional Therapy

Corticosteroids

- Oral systemic corticosteroids (CS) should be used for induction therapy in moderate to severe ulcerative colitis (UC).
- Oral budesonide (controlled-release) may be used to induce remission in mild to moderate UC if 5-aminosalicylic acid (5-ASA) is ineffective.

- Conventional CS therapy or oral budesonide for induction therapy should be limited to short-term use (≤8 weeks) in both UC and Crohn's disease (CD).

Immunomodulators

- Thiopurine should be used as maintenance therapy or as an adjunct with infliximab in moderate to severe IBD.
- Methotrexate (MTX) should not be used as induction and maintenance of remission in UC.
- MTX may be considered in CD as an adjunctive therapy for reducing immunogenicity associated with anti-tumour necrosis factor (anti-TNF) therapy.

5-aminosalicylic acid (5-ASA)

- Topical mesalazine therapies should be used for induction and maintenance therapy in patients with ulcerative proctitis.
- A combination of topical with oral mesalazine should be used for induction of remission, in patients with mild to moderate left sided or extensive colitis.
- Oral mesalazine therapy should be used for maintenance of remission in patients with mild left-sided or extensive UC.
- 5-ASA should not be used in CD.

b) Advanced Therapy

- In moderate to severe inflammatory bowel disease (IBD), infliximab should be used, alternatively adalimumab may be used for induction and maintenance therapy.
- In moderate to severe ulcerative colitis (UC), golimumab may be used as alternative for induction and maintenance therapy.
- In moderate to severe UC, vedolizumab should be used in induction and maintenance therapy.
- In moderate to severe IBD, guselkumab, mirikizumab, risankizumab, ustekinumab or vedolizumab should be used for induction and maintenance therapy.
- Etrasimod, ozanimod, tofacitinib or upadacitinib should be considered for both induction and maintenance therapy of moderate to severe UC.
- Upadacitinib may be used for induction and maintenance therapy of moderate to severe Crohn's disease (CD).

c) Positioning of treatment

- In advanced therapy naive patients with moderate to severe ulcerative colitis (UC), infliximab and vedolizumab should be considered in induction and maintenance therapy. Alternatively, adalimumab, etrasimod, golimumab, guselkumab, mirikizumab, ozanimod, risankizumab, tofacitinib or upadacitinib may be considered.
- In anti-tumour necrosis factor therapy experienced patients with moderate to severe UC, etrasimod, guselkumab, mirikizumab, ozanimod, risankizumab, tofacitinib, upadacitinib or ustekinumab should be given as induction and maintenance therapy.
- In non-fistulising and non-stricturing moderate to severe Crohn's disease (CD), adalimumab, guselkumab, infliximab, mirikizumab, risankizumab, ustekinumab, upadacitinib or vedolizumab should be given as induction and maintenance therapy.

d) Special Clinical Subgroup

Acute Severe Ulcerative Colitis (ASUC)

- Plain abdominal radiograph should be performed to exclude toxic megacolon, bowel obstruction and perforation.
- Testing for *Clostridium difficile* and cytomegalovirus (CMV) infection should be performed.
- Referral to the surgical team should be made early.
- Intravenous (IV) corticosteroids (CS) should be initiated and evaluated for response at day three.
- Those responding to IV CS should be maintained with azathioprine or an appropriate advanced therapy to sustain remission.
- Those not responding to IV CS should be treated with rescue therapy (IV infliximab or ciclosporin).
- Those who achieve remission with IV infliximab should be maintained with the same agent while those on ciclosporin, should be maintained with azathioprine or a suitable advanced therapy.
- Those not responding to rescue therapy, intensified infliximab dosing, oral janus kinase (JAK) inhibitors or surgical interventions should be considered.
- Venous thromboembolism prophylaxis should be given.

Fistulising Crohn's disease (CD)

- Infliximab should be used as the first line therapy in induction and maintenance of remission in fistulising CD.
- Alternatively, upadacitinib or ustekinumab should be used in fistulising CD patients with inadequate response to infliximab.

Extraintestinal manifestations (EIM)
- Inflammatory bowel disease (IBD) patients with EIM should be referred and co-managed with respective specialty.
- Anti-tumour necrosis factor therapy should be considered in patients with IBD with spondyloarthritis and/or reactive cutaneous EIM.
- Vedolizumab and ustekinumab should not be used in axial spondyloarthritis associated with IBD.

e) Psychological Assessments and Interventions

- Quality of life (QoL) assessments should be conducted routinely in patients with inflammatory bowel disease (IBD) to monitor disease impact and guide toward patient-centred management.
- Cognitive Behavioural Therapy (CBT) and/or Acceptance Commitment Therapy (ACT) should be considered in patients with IBD to improve psychological outcomes and QoL.

f) Non- Pharmacological Treatment: Dietary Modifications

- Patients with inflammatory bowel disease (IBD) should be screened for malnutrition at the time of diagnosis and at regular intervals.
- Nutritional support should be provided in the form of enteral or parenteral nutrition in malnourished IBD patients.

SURGICAL TREATMENT

- A multidisciplinary approach should be employed to guide decision-making and optimise perioperative outcomes when elective surgical intervention is needed in inflammatory bowel disease (IBD) patients.
- Laparotomy should be the preferred approach in patients with IBD who are hemodynamically unstable.
- Laparoscopic surgery may be considered in hemodynamically stable patients with IBD, provided appropriate surgical expertise is available.
- In patients with perianal Crohn's disease (CD) requiring emergency treatment, controlling sepsis through drainage and appropriate antibiotic therapy should be prioritised.
- Early referral to a colorectal surgeon should be considered in patients requiring surgery.

OTHER CONSIDERATIONS

- Routine vaccinations should be given for all inflammatory bowel disease (IBD) patients.
- Live vaccine should not be given to patients who are on immunosuppressive therapy.
- Urgent immunosuppressive treatment for patients with IBD should not be delayed while awaiting vaccination completion.

FOLLOW-UP AND SURVEILLANCE

- Monitoring in inflammatory bowel disease (IBD) patients should include:
  - short term treatment goals for clinical response
  - intermediate treatment goals for clinical remission and assessing inflammatory biomarkers (C-reactive protein and faecal calprotectin)
  - long-term treatment goals for endoscopic healing, histological remission, and quality of life outcomes
  - radiological modalities such as intestinal ultrasound and magnetic resonance imaging
- All IBD patients should have their first screening colonoscopy eight years after symptom onset due to the higher risk of colorectal cancer.
- In IBD patients with primary sclerosing cholangitis, endoscopic surveillance for dysplasia should be started at diagnosis and repeated yearly.

SPECIAL POPULATIONS

a) Pregnancy and Lactation

- Pre-conception counselling should be routinely offered to all women of childbearing age with inflammatory bowel disease (IBD) to optimise disease control prior to conception and to discuss medication safety.
- Live-attenuated vaccines should be avoided during the first year of life in children with IBD mothers exposed to biologics during pregnancy.
- Methotrexate, janus kinase inhibitors and sphingosine-1-phosphate receptor modulators should not be used in pregnant patients with IBD.

b) Paediatric

- In paediatric ulcerative colitis (UC):
  - oral 5-aminosalicylic acid (5-ASA) should be given as first line induction for mild to moderate disease
  - corticosteroids (CS) should be given as second line treatment in patients not responding to first line therapy
  - immunomodulators should be given in patients who are:
    - CS dependent
    - with two or more relapses per year
    - not responding to optimal dose of 5-ASA or intolerant to 5-ASA
  - infliximab should be given for both induction and maintenance of remission in chronically active or steroid-dependent disease unresponsive to 5-ASA and thiopurines
  - adalimumab should be considered in patients who lose response or are intolerant to infliximab
  - tofacitinib, upadacitinib, ustekinumab or vedolizumab may be considered following failure of anti-tumour necrosis factor (anti-TNF) therapy
  - combination therapy (two biologic agents or a biologic agent with small molecules) as dual targeted therapy may be a therapeutic option in refractory UC
  - in acute severe UC (ASUC):
    - IV methylprednisolone should be given as an initial treatment
    - concomitant infection and toxic megacolon should be excluded
    - paediatric UC activity index (PUCAI) score reassessment should be done at day 3 and 5 of treatment to decide on second line therapies (escalation to biologics/tacrolimus/ciclosporin/ surgery)
- In paediatric Crohn's disease (CD):
  - exclusive enteral nutrition (EEN) should be the first-line therapy for induction of remission in mild to moderate disease
  - CS may be considered for inducing remission if EEN is ineffective or not well tolerated in mild to moderate disease
  - anti-TNF therapy should be initiated in patients with high risk of complicated disease course including perianal or fistulising disease
  - immunomodulators should be used to maintain clinical remission either as monotherapy or in combination with conventional treatment or biologics, but it should not be used to induce remission
- CS should not be used as maintenance therapy in paediatric UC and CD.

GUIDELINES DEVELOPMENT AND OBJECTIVES

OBJECTIVES

The objective of this CPG on the Management of Inflammatory Bowel Disease (IBD) is to provide evidence-based recommendations and guidance to healthcare professionals in the holistic management of IBD on the following aspects:

- assessment and diagnosis
- treatment
- referral and follow-up

POPULATION, USERS AND SETTINGS

TARGET POPULATION

Inclusion Criteria

- All patients suspected and diagnosed with IBD.

Exclusion Criteria

- Irritable Bowel Syndrome
- Infective Colitis
- Colorectal Cancer
- Microscopic Colitis
- Eosinophilic Colitis
- Ischaemic Colitis
- Drug-induced Colitis

TARGET USERS

This document is intended to guide healthcare professionals and relevant stakeholders in primary and secondary/tertiary care of both public and private sector in the management of IBD including:

i. medical doctors
ii. allied health professionals
iii. trainees and medical students
iv. patients, caregivers and their advocates
v. policy makers

HEALTHCARE SETTINGS: Primary, secondary and tertiary care

SPONSORSHIP & FUNDING: The development of the CPG on Management of IBD was supported financially in its entirety by the MoH.

GROUPS AND ROLES

Development Group (DG): A multidisciplinary team that used a standard methodology based on systematic evidence review to plan, critically appraise and formulate evidence-based recommendations.

Review Committee (RC): A senior multidisciplinary group actively involved throughout the development process providing technical oversight.
External Reviewers (ER): Local and international subject matter experts that provided an independent assessment of the draft.
Disclosure Statements/ Conflicts of interest (CoI): All panel members both DG and RC declared financial and non-financial interests. None held shares in pharmaceutical firms or acts as consultants to such firms. Details are available upon request from the CPG Secretariat.
Meetings: The DG members met 48 times throughout the development of these guidelines

CLINICAL QUESTIONS AND SCOPE (*Refer* ***Appendix 1*** *on Clinical Questions***)**

A total of 11 main clinical questions (CQs) were developed under specific sections with patient-important outcomes prioritised. DG members were assigned individual CQs within these sections.

EVIDENCE RETRIEVAL (*Refer* ***Appendix 2****: Example of Search Strategy*)

Databases & sources: Medline (Ovid) and Cochrane Database of Systematic Reviews; supplementary searches in PubMed and others.
Limits: literature published in the last 10 years from 2015 to 2025 for all CQs on Humans and in English; In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted for studies related to the issues addressed.
Search period: All searches were conducted from 27 March 2024 to 20 June 2024. The literature search was repeated for all CQs at the end of the CPG development process, allowing any relevant papers published before 8 July 2025 to be included. Future CPG updates will consider evidence published after this cut-off date. Full details of the search strategy can be obtained from the CPG Secretariat.

EVIDENCE APPRAISAL AND FORMULATION OF RECOMMENDATIONS

All retrieved literature was appraised by at least two DG members using the Critical Appraisal Skills Programme (CASP) and Risk of Bias (RoB) checklists presented in evidence tables and discussed at DG meetings. Statements and recommendations were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the two groups. The CPG is largely based on systematic reviews, meta-analyses and clinical trials, with local practice taken into consideration.

Levels/Grades: Individual studies were graded using the U.S. Preventive Services Task Force (2015) levels of evidence; recommendation strength followed GRADE principles. The writing of the CPG adheres to AGREE II requirements.

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations**, **Assessment**, **Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG development group (DG).
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "**should**" being considered. Otherwise, weak recommendations use the word "**may**" in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

USE OF EXISTING GUIDELINES AND QUALITY APPRAISAL

References were also made to other guidelines on IBD as listed below:

i. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease. Dis Colon Rectum. (2020)
ii. The Medical Management of Paediatric Crohn's Disease: A European Crohn's and Colitis Organisation (ECCO) - European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Guideline Update. J Crohn's Colitis. (2021)
iii. The World Society of Emergency Surgery (WSES) - American Association for the Surgery of Trauma (AAST) guidelines: management of inflammatory bowel disease in the emergency setting. World J Emerg Surg. (2021)
iv. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohn's Colitis. (2022)
v. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment. J Crohn's Colitis. (2022)
vi. The European Society of Parenteral and Enteral Nutrition (ESPEN) guideline on Clinical Nutrition in inflammatory bowel disease. Clin Nutr. (2023)
vii. ECCO - European Society of Gastrointestinal and Abdominal Radiology (ESGAR) - European Society of Pathology (ESP) – International Bowel Ultrasonography Group (IBUS) Guideline on Diagnostics and Monitoring of Patients with Inflammatory Bowel Disease: Part 2. J Crohn's Colitis. (2025)
viii. British Society of Gastroenterology guidelines on inflammatory bowel disease in adults. Gut. (2025)
ix. American College of Gastroenterology (ACG) Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. (2025)
x. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. Am J Gastroenterol. (2025)

The evidence-based CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

EXTERNAL REVIEW, PUBLIC CONSULTATION & APPROVAL

The draft on completion underwent external peer review and was posted on the MoH Malaysia website for public consultation (≥ 30 days). The draft was then presented to the Technical Advisory Committee for CPG and the HTA & CPG Council, MoH Malaysia for review and approval. Further details on the CPG development methodology by MaHTAS are available in the Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines.
(available at: https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf)

IMPLEMENTATION, AUDIT & MONITORING (*Detailed out in* **Chapter 10)**
Priority recommendations include audit indicators (numerator/ denominator, target, data source, suggested frequency) to enable quality improvement and monitoring.

UPDATING POLICY

These guidelines were issued in 2025 and will be reviewed in a minimum period of four years (2029) or sooner if new evidence warrants earlier revision. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version at all time. This version can be found on the websites mentioned above.

DEVELOPMENT GROUP

Chairperson

Dr. Muhammad Firdaus Md Salleh
Consultant Gastroenterologist & Hepatologist
Hospital Sultanah Aminah, Johor

Members (alphabetical order)

Dr. Ahmad Fardi Sulaiman
Lecturer & Consultant
Colorectal Surgeon
Faculty of Medicine,
Universiti Sultan Zainal Abidin,
Terengganu

Dr. Azahirafairud Abdul Rahim
Consultant Acute Internal Medicine
Hospital Kuala Lumpur,
Kuala Lumpur

Ms. Chan Sze Min
Clinical Pharmacist
Hospital Selayang, Selangor

Assoc. Prof. Dr. Fariz Yahya
Lecturer & Consultant Rheumatologist
Faculty of Medicine,
Universiti Malaya, Kuala Lumpur

Dr. Hasniza Hasim
Consultant Family Medicine Specialist
Klinik Kesihatan Bandar Sungai Petani,
Kedah

Dr. Kam Choy Chen
Consultant Paediatric
Gastroenterologist & Hepatologist
Hospital Tunku Azizah Kuala Lumpur,
Kuala Lumpur

Dr. Karen Sharmini Sandanasamy
Head of Clinical Practice Guidelines Unit
Public Health Physician
Malaysian Health Technology
Assessment Section,
Ministry of Health, Putrajaya

Dr. Nik Razima Wan Ibrahim
Consultant Gastroenterologist
& Hepatologist
Hospital Ampang, Selangor

Dr. Norashikin Mohd Ranai
Lecturer & Consultant Paediatric
Gastroenterologist & Hepatologist
Faculty of Medicine,
Universiti Teknologi MARA (UiTM),
Selangor

Dr. Norasiah Abu Bakar
Consultant Gastroenterologist &
Hepatologist
Hospital Raja Perempuan Zainab II,
Kelantan

Dr. Nur Hanani Mat Daud
Senior Principal Assistant Director
Malaysian Health Technology
Assessment Section,
Ministry of Health, Putrajaya

Dr. Nurlida Abd Rahim
Family Medicine Specialist
Klinik Kesihatan Pendang, Kedah

Dr. Pavitratha Puspanathan
Consultant Anatomic Pathologist
Gastrointestinal & Hepatobiliary Pathology
Hospital Pulau Pinang, Pulau Pinang

Ms. Ruthra Devi Tharumalay
Clinical Psychologist
Hospital Putrajaya, Putrajaya

Dr. Khairul Hazim Hamdan
Consultant Colorectal Surgeon
Hospital Selayang, Selangor

Dr. Maalini Krishnasamy
Consultant Anatomic Pathologist
Gastrointestinal &
Hepatobiliary Pathology
Thomson Hospital, Selangor

Dr. Mohd Fairul Limun
Gastroenterologist & Hepatologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Mohd. Aminuddin Mohd. Yusof
Public Health Physician

Ms. Siti Hawa Mohd Taib
Clinical Dietitian
Pusat Perubatan Universiti Malaya,
Kuala Lumpur

Ms. Siti Maryam A. Rahim
Clinical Pharmacist
Hospital Ampang,
Selangor

Dr. Victoria Kok Shinq Ling
Consultant Gastroenterologist &
Hepatologist
Hospital Umum Sarawak,
Sarawak

Dr. Yap Soo Shu
Radiologist (Body Oncology Imaging)
Pantai Hospital, Pulau Pinang

REVIEW COMMITTEE

The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Dr. Kiew Kuang Kiat
Senior Consultant Gastroenterologist & Hepatologist
Hospital Sultanah Bahiyah, Kedah

Members (alphabetical order)

Dr. Alex Leow Hwong Ruey
Consultant Gastroenterologist & Hepatologist
Pantai Hospital, Kuala Lumpur

Dr. Ng Ruey Terng
Consultant Paediatric Gastroenterologist & Hepatologist
Subang Jaya Medical Centre and University Malaya Medical Centre, Kuala Lumpur

Dato' Dr. Fitjerald Henry
Senior Consultant Colorectal Surgeon
Sunway Medical University, Selangor

Datin Dr. Nik Raihan Nik Mustapha
Consultant Anatomic Pathologist
Gastrointestinal & Hepatobiliary Pathology

Prof. Dr. Hamzaini Abdul Hamid
Lecturer & Consultant Radiologist
Faculty of Medicine,
Universiti Kebangsaan Malaysia, Kuala Lumpur

Ms. Poh Wei Yoon
Clinical Pharmacist
Hospital Selayang, Selangor

Prof. Dr. Ida Normiha Hilmi
Lecturer & Senior Consultant Gastroenterologist & Hepatologist
Faculty of Medicine, Universiti Malaya, Kuala Lumpur

Datuk Dr. Raman Muthukaruppan
Senior Consultant Gastroenterologist & Hepatologist
Hospital Queen Elizabeth, Sabah

Dr. Izzuna Mudla Mohamed Ghazali
Deputy Director & Public Health Physician
Malaysian Health Technology Assessment Section
Ministry of Health, Putrajaya

Dr. Rohaiza Abd Kadir
Consultant Family Medicine Specialist
Klinik Kesihatan Marang, Terengganu

Assoc. Prof. Dr. Nazri Mustaffa
Lecturer & Consultant Gastroenterologist & Hepatologist
School of Medical Sciences,
Universiti Sains Malaysia, Kelantan

Mr. Tan Boon Seng
Patient Advocate
Crohn's and Colitis Society of Malaysia

EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft:

Dato' Dr. Ahmad Shanwani Mohamed Sidek
Senior Consultant Colorectal & General Surgeon
Hospital Raja Perempuan Zainab II, Kelantan

Dr. Cheah Wee Kooi
Consultant Physician &Geriatrician
Hospital Taiping,
Perak

Dr. Cord Langner, MD
Diagnostic and Research Institute of Pathology,
Medical University of Graz,
Austria

Dr. Farizan Abdul Ghaffar
Clinical Pharmacist
Hospital Sultan Idris Shah, Serdang
Selangor

Assoc. Prof. Dr. Julajak Limsrivilai
Lecturer & Senior Consultant
Gastroenterologist & Hepatologist
Mahidol University
Bangkok, Thailand

Prof. Dr. Lee Way Seah
Lecturer & Senior Consultant Paediatric
Gastroenterologist & Hepatologist
University Tunku Abdul Rahman,
Selangor

Dr. Nik Norashikin Nik Abdul Rahman
Consultant Family Medicine Specialist
Klinik Kesihatan Pengkalan Chepa,
Kelantan

Dr. Nur Asyikin Mohd Yunus
Consultant Internal Medicine
Hospital Tengku Ampuan Rahimah,
Selangor

Dr. Nurhashim Haron
Consultant General and Colorectal Surgeon Tawakkal Specialist Hospital,
Kuala Lumpur

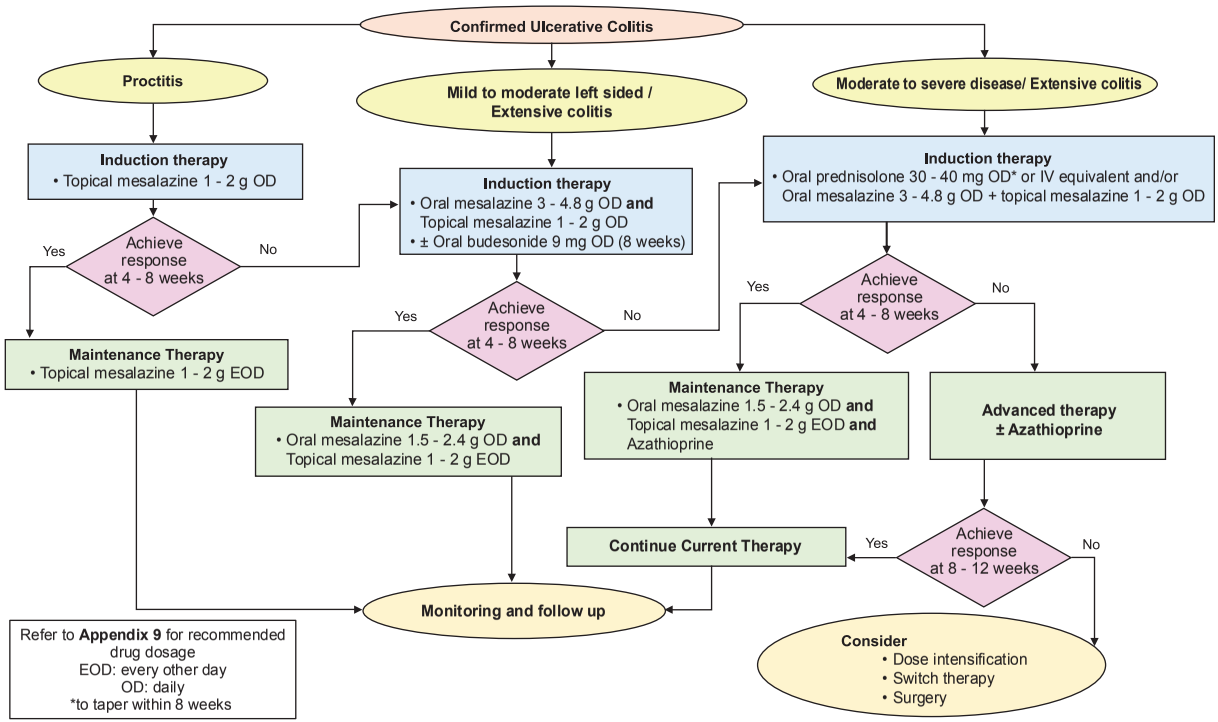
Dr. Ong Ping Seung
Consultant Rheumatologist
Hospital Raja Permaisuri Bainun,
Perak

Prof. Dr. Raja Affendi Raja Ali
Senior Consultant Gastroenterologist & Hepatologist
Sunway Medical University,
Selangor

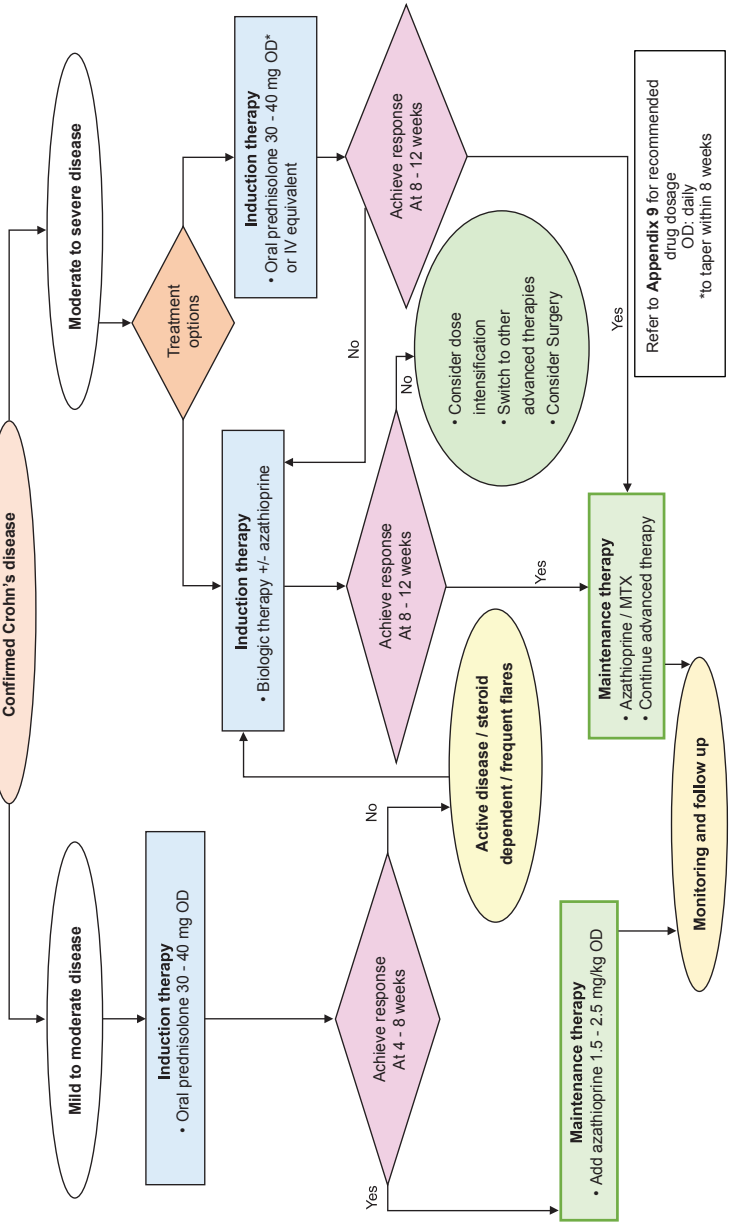
Prof. Dr. Simon Travis
Professor of Clinical Gastroenterology
University of Oxford,
England

Prof. Stuart Taylor
Professor of Medical Imaging
University College London,
England

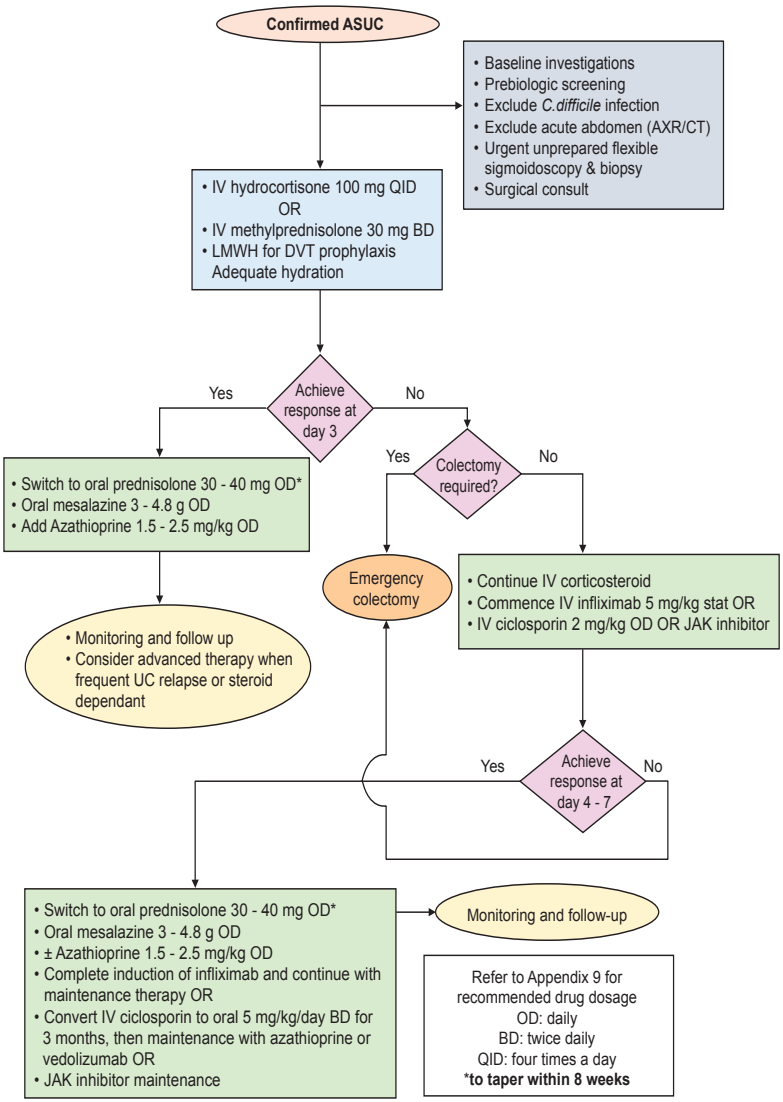
ALGORITHM 1: MANAGEMENT OF ULCERATIVE COLITIS



ALGORITHM 2: MANAGEMENT OF CROHN'S DISEASE



ALGORITHM 3: MANAGEMENT OF ACUTE SEVERE ULCERATIVE COLITIS (ASUC)



ALGORITHM 4: MANAGEMENT OF PERIANAL FISTULA

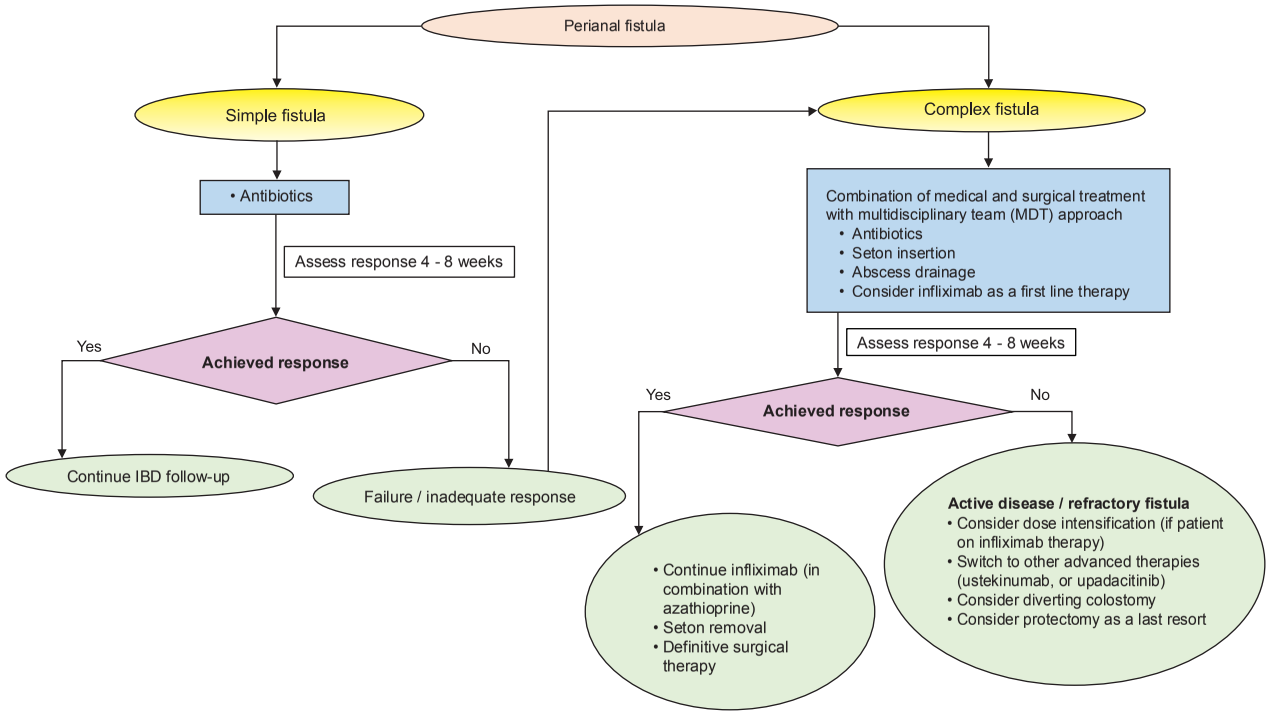


TABLE OF CONTENTS

TABLE OF CONTENTS

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG DG as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

DIAGNOSIS AND INVESTIGATIONS

- The diagnosis of inflammatory bowel disease (IBD) should be established through a comprehensive, integrated assessment encompassing clinical features (including extraintestinal manifestations), laboratory tests, endoscopic evaluation, histopathological findings and imaging studies.
- Tuberculosis (TB) workup should be performed in patients who pose a diagnostic challenge between Crohn's disease (CD) and intestinal TB.
- In all patients with suspected IBD, colonoscopy should be performed with the acquisition of at least two biopsy specimens each from a minimum of six bowel segments, and bowel preparation should be carried out using polyethylene glycol.
- Testing for cytomegalovirus reactivation on colonic biopsy should be performed in all patients with severe colitis refractory to immunosuppressive therapy.
- In patients with ulcerative colitis (UC), Nancy Histological Index should be used in routine clinical practice as it is the simplest and fastest histological scoring system.
- Computed tomography scan should be performed in acute clinical scenarios such as suspected bowel obstruction, perforation and severe complications where rapid diagnosis is required in patients with IBD.
- Magnetic resonance enterography or intestinal ultrasound should be performed in CD patients to assess disease activity and extent.
- Pelvic magnetic resonance imaging should be performed in patients with perianal disease to assess fistulae and identify associated complications.

THERAPEUTIC INTERVENTIONS

a) Conventional Therapy

Corticosteroids

- Oral systemic corticosteroids (CS) should be used for induction therapy in moderate to severe ulcerative colitis (UC).
- Oral budesonide (controlled-release) may be used to induce remission in mild to moderate UC if 5-aminosalicylic acid (5-ASA) is ineffective.

- Conventional CS therapy or oral budesonide for induction therapy should be limited to short-term use (≤8 weeks) in both UC and Crohn's disease (CD).

Immunomodulators

- Thiopurine should be used as maintenance therapy or as an adjunct with infliximab in moderate to severe IBD.
- Methotrexate (MTX) should not be used as induction and maintenance of remission in UC.
- MTX may be considered in CD as an adjunctive therapy for reducing immunogenicity associated with anti-tumour necrosis factor (anti-TNF) therapy.

5-aminosalicylic acid (5-ASA)

- Topical mesalazine therapies should be used for induction and maintenance therapy in patients with ulcerative proctitis.
- A combination of topical with oral mesalazine should be used for induction of remission, in patients with mild to moderate left sided or extensive colitis.
- Oral mesalazine therapy should be used for maintenance of remission in patients with mild left-sided or extensive UC.
- 5-ASA should not be used in CD.

b) Advanced Therapy

- In moderate to severe inflammatory bowel disease (IBD), infliximab should be used, alternatively adalimumab may be used for induction and maintenance therapy.
- In moderate to severe ulcerative colitis (UC), golimumab may be used as alternative for induction and maintenance therapy.
- In moderate to severe UC, vedolizumab should be used in induction and maintenance therapy.
- In moderate to severe IBD, guselkumab, mirikizumab, risankizumab, ustekinumab or vedolizumab should be used for induction and maintenance therapy.
- Etrasimod, ozanimod, tofacitinib or upadacitinib should be considered for both induction and maintenance therapy of moderate to severe UC.
- Upadacitinib may be used for induction and maintenance therapy of moderate to severe Crohn's disease (CD).

c) Positioning of treatment

- In advanced therapy naive patients with moderate to severe ulcerative colitis (UC), infliximab and vedolizumab should be considered in induction and maintenance therapy. Alternatively, adalimumab, etrasimod, golimumab, guselkumab, mirikizumab, ozanimod, risankizumab, tofacitinib or upadacitinib may be considered.
- In anti-tumour necrosis factor therapy experienced patients with moderate to severe UC, etrasimod, guselkumab, mirikizumab, ozanimod, risankizumab, tofacitinib, upadacitinib or ustekinumab should be given as induction and maintenance therapy.
- In non-fistulising and non-stricturing moderate to severe Crohn's disease (CD), adalimumab, guselkumab, infliximab, mirikizumab, risankizumab, ustekinumab, upadacitinib or vedolizumab should be given as induction and maintenance therapy.

d) Special Clinical Subgroup

Acute Severe Ulcerative Colitis (ASUC)

- Plain abdominal radiograph should be performed to exclude toxic megacolon, bowel obstruction and perforation.
- Testing for *Clostridium difficile* and cytomegalovirus (CMV) infection should be performed.
- Referral to the surgical team should be made early.
- Intravenous (IV) corticosteroids (CS) should be initiated and evaluated for response at day three.
- Those responding to IV CS should be maintained with azathioprine or an appropriate advanced therapy to sustain remission.
- Those not responding to IV CS should be treated with rescue therapy (IV infliximab or ciclosporin).
- Those who achieve remission with IV infliximab should be maintained with the same agent while those on ciclosporin, should be maintained with azathioprine or a suitable advanced therapy.
- Those not responding to rescue therapy, intensified infliximab dosing, oral janus kinase (JAK) inhibitors or surgical interventions should be considered.
- Venous thromboembolism prophylaxis should be given.

Fistulising Crohn's disease (CD)

- Infliximab should be used as the first line therapy in induction and maintenance of remission in fistulising CD.
- Alternatively, upadacitinib or ustekinumab should be used in fistulising CD patients with inadequate response to infliximab.

Extraintestinal manifestations (EIM)

- Inflammatory bowel disease (IBD) patients with EIM should be referred and co-managed with respective specialty.
- Anti-tumour necrosis factor therapy should be considered in patients with IBD with spondyloarthritis and/or reactive cutaneous EIM.
- Vedolizumab and ustekinumab should not be used in axial spondyloarthritis associated with IBD.

e) Psychological Assessments and Interventions

- Quality of life (QoL) assessments should be conducted routinely in patients with inflammatory bowel disease (IBD) to monitor disease impact and guide toward patient-centred management.
- Cognitive Behavioural Therapy (CBT) and/or Acceptance Commitment Therapy (ACT) should be considered in patients with IBD to improve psychological outcomes and QoL.

f) Non- Pharmacological Treatment: Dietary Modifications

- Patients with inflammatory bowel disease (IBD) should be screened for malnutrition at the time of diagnosis and at regular intervals.
- Nutritional support should be provided in the form of enteral or parenteral nutrition in malnourished IBD patients.

SURGICAL TREATMENT

- A multidisciplinary approach should be employed to guide decision-making and optimise perioperative outcomes when elective surgical intervention is needed in inflammatory bowel disease (IBD) patients.
- Laparotomy should be the preferred approach in patients with IBD who are hemodynamically unstable.
- Laparoscopic surgery may be considered in hemodynamically stable patients with IBD, provided appropriate surgical expertise is available.
- In patients with perianal Crohn's disease (CD) requiring emergency treatment, controlling sepsis through drainage and appropriate antibiotic therapy should be prioritised.
- Early referral to a colorectal surgeon should be considered in patients requiring surgery.

OTHER CONSIDERATIONS

- Routine vaccinations should be given for all inflammatory bowel disease (IBD) patients.
- Live vaccine should not be given to patients who are on immunosuppressive therapy.
- Urgent immunosuppressive treatment for patients with IBD should not be delayed while awaiting vaccination completion.

FOLLOW-UP AND SURVEILLANCE

- Monitoring in inflammatory bowel disease (IBD) patients should include:
  - short term treatment goals for clinical response
  - intermediate treatment goals for clinical remission and assessing inflammatory biomarkers (C-reactive protein and faecal calprotectin)
  - long-term treatment goals for endoscopic healing, histological remission, and quality of life outcomes
  - radiological modalities such as intestinal ultrasound and magnetic resonance imaging
- All IBD patients should have their first screening colonoscopy eight years after symptom onset due to the higher risk of colorectal cancer.
- In IBD patients with primary sclerosing cholangitis, endoscopic surveillance for dysplasia should be started at diagnosis and repeated yearly.

SPECIAL POPULATIONS

a) Pregnancy and Lactation

- Pre-conception counselling should be routinely offered to all women of childbearing age with inflammatory bowel disease (IBD) to optimise disease control prior to conception and to discuss medication safety.
- Live-attenuated vaccines should be avoided during the first year of life in children with IBD mothers exposed to biologics during pregnancy.
- Methotrexate, janus kinase inhibitors and sphingosine-1-phosphate receptor modulators should not be used in pregnant patients with IBD.

b) Paediatric

- In paediatric ulcerative colitis (UC):
  - oral 5-aminosalicylic acid (5-ASA) should be given as first line induction for mild to moderate disease
  - corticosteroids (CS) should be given as second line treatment in patients not responding to first line therapy
  - immunomodulators should be given in patients who are:
    - CS dependent
    - with two or more relapses per year
    - not responding to optimal dose of 5-ASA or intolerant to 5-ASA
  - infliximab should be given for both induction and maintenance of remission in chronically active or steroid-dependent disease unresponsive to 5-ASA and thiopurines
  - adalimumab should be considered in patients who lose response or are intolerant to infliximab
  - tofacitinib, upadacitinib, ustekinumab or vedolizumab may be considered following failure of anti-tumour necrosis factor (anti-TNF) therapy
  - combination therapy (two biologic agents or a biologic agent with small molecules) as dual targeted therapy may be a therapeutic option in refractory UC
  - in acute severe UC (ASUC):
    - IV methylprednisolone should be given as an initial treatment
    - concomitant infection and toxic megacolon should be excluded
    - paediatric UC activity index (PUCAI) score reassessment should be done at day 3 and 5 of treatment to decide on second line therapies (escalation to biologics/tacrolimus/ciclosporin/ surgery)
- In paediatric Crohn's disease (CD):
  - exclusive enteral nutrition (EEN) should be the first-line therapy for induction of remission in mild to moderate disease
  - CS may be considered for inducing remission if EEN is ineffective or not well tolerated in mild to moderate disease
  - anti-TNF therapy should be initiated in patients with high risk of complicated disease course including perianal or fistulising disease
  - immunomodulators should be used to maintain clinical remission either as monotherapy or in combination with conventional treatment or biologics, but it should not be used to induce remission
- CS should not be used as maintenance therapy in paediatric UC and CD.

GUIDELINES DEVELOPMENT AND OBJECTIVES

OBJECTIVES

The objective of this CPG on the Management of Inflammatory Bowel Disease (IBD) is to provide evidence-based recommendations and guidance to healthcare professionals in the holistic management of IBD on the following aspects:

- assessment and diagnosis
- treatment
- referral and follow-up

POPULATION, USERS AND SETTINGS

TARGET POPULATION

Inclusion Criteria

- All patients suspected and diagnosed with IBD.

Exclusion Criteria

- Irritable Bowel Syndrome
- Infective Colitis
- Colorectal Cancer
- Microscopic Colitis
- Eosinophilic Colitis
- Ischaemic Colitis
- Drug-induced Colitis

TARGET USERS

This document is intended to guide healthcare professionals and relevant stakeholders in primary and secondary/tertiary care of both public and private sector in the management of IBD including:

i. medical doctors
ii. allied health professionals
iii. trainees and medical students
iv. patients, caregivers and their advocates
v. policy makers

HEALTHCARE SETTINGS: Primary, secondary and tertiary care

SPONSORSHIP & FUNDING: The development of the CPG on Management of IBD was supported financially in its entirety by the MoH.

GROUPS AND ROLES

Development Group (DG): A multidisciplinary team that used a standard methodology based on systematic evidence review to plan, critically appraise and formulate evidence-based recommendations.

Review Committee (RC): A senior multidisciplinary group actively involved throughout the development process providing technical oversight.
External Reviewers (ER): Local and international subject matter experts that provided an independent assessment of the draft.
Disclosure Statements/ Conflicts of interest (CoI): All panel members both DG and RC declared financial and non-financial interests. None held shares in pharmaceutical firms or acts as consultants to such firms. Details are available upon request from the CPG Secretariat.
Meetings: The DG members met 48 times throughout the development of these guidelines

CLINICAL QUESTIONS AND SCOPE (*Refer* ***Appendix 1*** *on Clinical Questions***)**

A total of 11 main clinical questions (CQs) were developed under specific sections with patient-important outcomes prioritised. DG members were assigned individual CQs within these sections.

EVIDENCE RETRIEVAL (*Refer* ***Appendix 2****: Example of Search Strategy*)

Databases & sources: Medline (Ovid) and Cochrane Database of Systematic Reviews; supplementary searches in PubMed and others.
Limits: literature published in the last 10 years from 2015 to 2025 for all CQs on Humans and in English; In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted for studies related to the issues addressed.
Search period: All searches were conducted from 27 March 2024 to 20 June 2024. The literature search was repeated for all CQs at the end of the CPG development process, allowing any relevant papers published before 8 July 2025 to be included. Future CPG updates will consider evidence published after this cut-off date. Full details of the search strategy can be obtained from the CPG Secretariat.

EVIDENCE APPRAISAL AND FORMULATION OF RECOMMENDATIONS

All retrieved literature was appraised by at least two DG members using the Critical Appraisal Skills Programme (CASP) and Risk of Bias (RoB) checklists presented in evidence tables and discussed at DG meetings. Statements and recommendations were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the two groups. The CPG is largely based on systematic reviews, meta-analyses and clinical trials, with local practice taken into consideration.

Levels/Grades: Individual studies were graded using the U.S. Preventive Services Task Force (2015) levels of evidence; recommendation strength followed GRADE principles. The writing of the CPG adheres to AGREE II requirements.

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations**, **Assessment**, **Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG development group (DG).
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "**should**" being considered. Otherwise, weak recommendations use the word "**may**" in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

USE OF EXISTING GUIDELINES AND QUALITY APPRAISAL

References were also made to other guidelines on IBD as listed below:

i. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease. Dis Colon Rectum. (2020)
ii. The Medical Management of Paediatric Crohn's Disease: A European Crohn's and Colitis Organisation (ECCO) - European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Guideline Update. J Crohn's Colitis. (2021)
iii. The World Society of Emergency Surgery (WSES) - American Association for the Surgery of Trauma (AAST) guidelines: management of inflammatory bowel disease in the emergency setting. World J Emerg Surg. (2021)
iv. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohn's Colitis. (2022)
v. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment. J Crohn's Colitis. (2022)
vi. The European Society of Parenteral and Enteral Nutrition (ESPEN) guideline on Clinical Nutrition in inflammatory bowel disease. Clin Nutr. (2023)
vii. ECCO - European Society of Gastrointestinal and Abdominal Radiology (ESGAR) - European Society of Pathology (ESP) – International Bowel Ultrasonography Group (IBUS) Guideline on Diagnostics and Monitoring of Patients with Inflammatory Bowel Disease: Part 2. J Crohn's Colitis. (2025)
viii. British Society of Gastroenterology guidelines on inflammatory bowel disease in adults. Gut. (2025)
ix. American College of Gastroenterology (ACG) Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. (2025)
x. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. Am J Gastroenterol. (2025)

The evidence-based CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

EXTERNAL REVIEW, PUBLIC CONSULTATION & APPROVAL

The draft on completion underwent external peer review and was posted on the MoH Malaysia website for public consultation (≥ 30 days). The draft was then presented to the Technical Advisory Committee for CPG and the HTA & CPG Council, MoH Malaysia for review and approval. Further details on the CPG development methodology by MaHTAS are available in the Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines.
(available at: https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf)

IMPLEMENTATION, AUDIT & MONITORING (*Detailed out in* **Chapter 10)**
Priority recommendations include audit indicators (numerator/ denominator, target, data source, suggested frequency) to enable quality improvement and monitoring.

UPDATING POLICY

These guidelines were issued in 2025 and will be reviewed in a minimum period of four years (2029) or sooner if new evidence warrants earlier revision. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version at all time. This version can be found on the websites mentioned above.

DEVELOPMENT GROUP

Chairperson

Dr. Muhammad Firdaus Md Salleh
Consultant Gastroenterologist & Hepatologist
Hospital Sultanah Aminah, Johor

Members (alphabetical order)

Dr. Ahmad Fardi Sulaiman
Lecturer & Consultant
Colorectal Surgeon
Faculty of Medicine,
Universiti Sultan Zainal Abidin,
Terengganu

Dr. Azahirafairud Abdul Rahim
Consultant Acute Internal Medicine
Hospital Kuala Lumpur,
Kuala Lumpur

Ms. Chan Sze Min
Clinical Pharmacist
Hospital Selayang, Selangor

Assoc. Prof. Dr. Fariz Yahya
Lecturer & Consultant Rheumatologist
Faculty of Medicine,
Universiti Malaya, Kuala Lumpur

Dr. Hasniza Hasim
Consultant Family Medicine Specialist
Klinik Kesihatan Bandar Sungai Petani,
Kedah

Dr. Kam Choy Chen
Consultant Paediatric
Gastroenterologist & Hepatologist
Hospital Tunku Azizah Kuala Lumpur,
Kuala Lumpur

Dr. Karen Sharmini Sandanasamy
Head of Clinical Practice Guidelines Unit
Public Health Physician
Malaysian Health Technology
Assessment Section,
Ministry of Health, Putrajaya

Dr. Nik Razima Wan Ibrahim
Consultant Gastroenterologist
& Hepatologist
Hospital Ampang, Selangor

Dr. Norashikin Mohd Ranai
Lecturer & Consultant Paediatric
Gastroenterologist & Hepatologist
Faculty of Medicine,
Universiti Teknologi MARA (UiTM),
Selangor

Dr. Norasiah Abu Bakar
Consultant Gastroenterologist &
Hepatologist
Hospital Raja Perempuan Zainab II,
Kelantan

Dr. Nur Hanani Mat Daud
Senior Principal Assistant Director
Malaysian Health Technology
Assessment Section,
Ministry of Health, Putrajaya

Dr. Nurlida Abd Rahim
Family Medicine Specialist
Klinik Kesihatan Pendang, Kedah

Dr. Pavitratha Puspanathan
Consultant Anatomic Pathologist
Gastrointestinal & Hepatobiliary Pathology
Hospital Pulau Pinang, Pulau Pinang

Ms. Ruthra Devi Tharumalay
Clinical Psychologist
Hospital Putrajaya, Putrajaya

Dr. Khairul Hazim Hamdan
Consultant Colorectal Surgeon
Hospital Selayang, Selangor

Dr. Maalini Krishnasamy
Consultant Anatomic Pathologist
Gastrointestinal &
Hepatobiliary Pathology
Thomson Hospital, Selangor

Dr. Mohd Fairul Limun
Gastroenterologist & Hepatologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Mohd. Aminuddin Mohd. Yusof
Public Health Physician

Ms. Siti Hawa Mohd Taib
Clinical Dietitian
Pusat Perubatan Universiti Malaya,
Kuala Lumpur

Ms. Siti Maryam A. Rahim
Clinical Pharmacist
Hospital Ampang,
Selangor

Dr. Victoria Kok Shinq Ling
Consultant Gastroenterologist &
Hepatologist
Hospital Umum Sarawak,
Sarawak

Dr. Yap Soo Shu
Radiologist (Body Oncology Imaging)
Pantai Hospital, Pulau Pinang

REVIEW COMMITTEE

The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Dr. Kiew Kuang Kiat
Senior Consultant Gastroenterologist & Hepatologist
Hospital Sultanah Bahiyah, Kedah

Members (alphabetical order)

Dr. Alex Leow Hwong Ruey
Consultant Gastroenterologist & Hepatologist
Pantai Hospital, Kuala Lumpur

Dr. Ng Ruey Terng
Consultant Paediatric Gastroenterologist & Hepatologist
Subang Jaya Medical Centre and University Malaya Medical Centre, Kuala Lumpur

Dato' Dr. Fitjerald Henry
Senior Consultant Colorectal Surgeon
Sunway Medical University, Selangor

Datin Dr. Nik Raihan Nik Mustapha
Consultant Anatomic Pathologist
Gastrointestinal & Hepatobiliary Pathology

Prof. Dr. Hamzaini Abdul Hamid
Lecturer & Consultant Radiologist
Faculty of Medicine,
Universiti Kebangsaan Malaysia,
Kuala Lumpur

Ms. Poh Wei Yoon
Clinical Pharmacist
Hospital Selayang, Selangor

Prof. Dr. Ida Normiha Hilmi
Lecturer & Senior Consultant Gastroenterologist & Hepatologist
Faculty of Medicine, Universiti Malaya,
Kuala Lumpur

Datuk Dr. Raman Muthukaruppan
Senior Consultant Gastroenterologist & Hepatologist
Hospital Queen Elizabeth, Sabah

Dr. Izzuna Mudla Mohamed Ghazali
Deputy Director & Public Health Physician
Malaysian Health Technology Assessment Section
Ministry of Health, Putrajaya

Dr. Rohaiza Abd Kadir
Consultant Family Medicine Specialist
Klinik Kesihatan Marang, Terengganu

Assoc. Prof. Dr. Nazri Mustaffa
Lecturer & Consultant Gastroenterologist & Hepatologist
School of Medical Sciences,
Universiti Sains Malaysia, Kelantan

Mr. Tan Boon Seng
Patient Advocate
Crohn's and Colitis Society of Malaysia

EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft:

Dato' Dr. Ahmad Shanwani Mohamed Sidek
Senior Consultant Colorectal & General Surgeon
Hospital Raja Perempuan Zainab II, Kelantan

Dr. Cheah Wee Kooi
Consultant Physician &Geriatrician
Hospital Taiping,
Perak

Dr. Cord Langner, MD
Diagnostic and Research Institute of Pathology,
Medical University of Graz,
Austria

Dr. Farizan Abdul Ghaffar
Clinical Pharmacist
Hospital Sultan Idris Shah, Serdang
Selangor

Assoc. Prof. Dr. Julajak Limsrivilai
Lecturer & Senior Consultant
Gastroenterologist & Hepatologist
Mahidol University
Bangkok, Thailand

Prof. Dr. Lee Way Seah
Lecturer & Senior Consultant Paediatric
Gastroenterologist & Hepatologist
University Tunku Abdul Rahman,
Selangor

Dr. Nik Norashikin Nik Abdul Rahman
Consultant Family Medicine Specialist
Klinik Kesihatan Pengkalan Chepa,
Kelantan

Dr. Nur Asyikin Mohd Yunus
Consultant Internal Medicine
Hospital Tengku Ampuan Rahimah,
Selangor

Dr. Nurhashim Haron
Consultant General and Colorectal Surgeon Tawakkal Specialist Hospital,
Kuala Lumpur

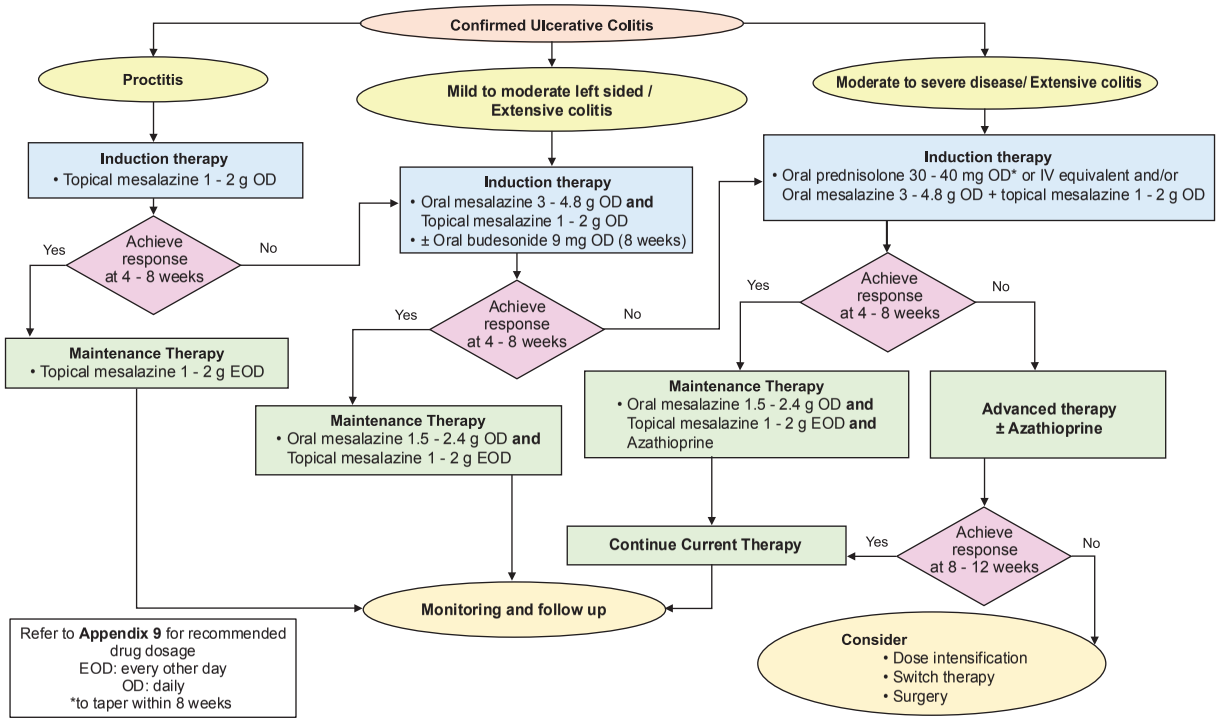
Dr. Ong Ping Seung
Consultant Rheumatologist
Hospital Raja Permaisuri Bainun,
Perak

Prof. Dr. Raja Affendi Raja Ali
Senior Consultant Gastroenterologist & Hepatologist
Sunway Medical University,
Selangor

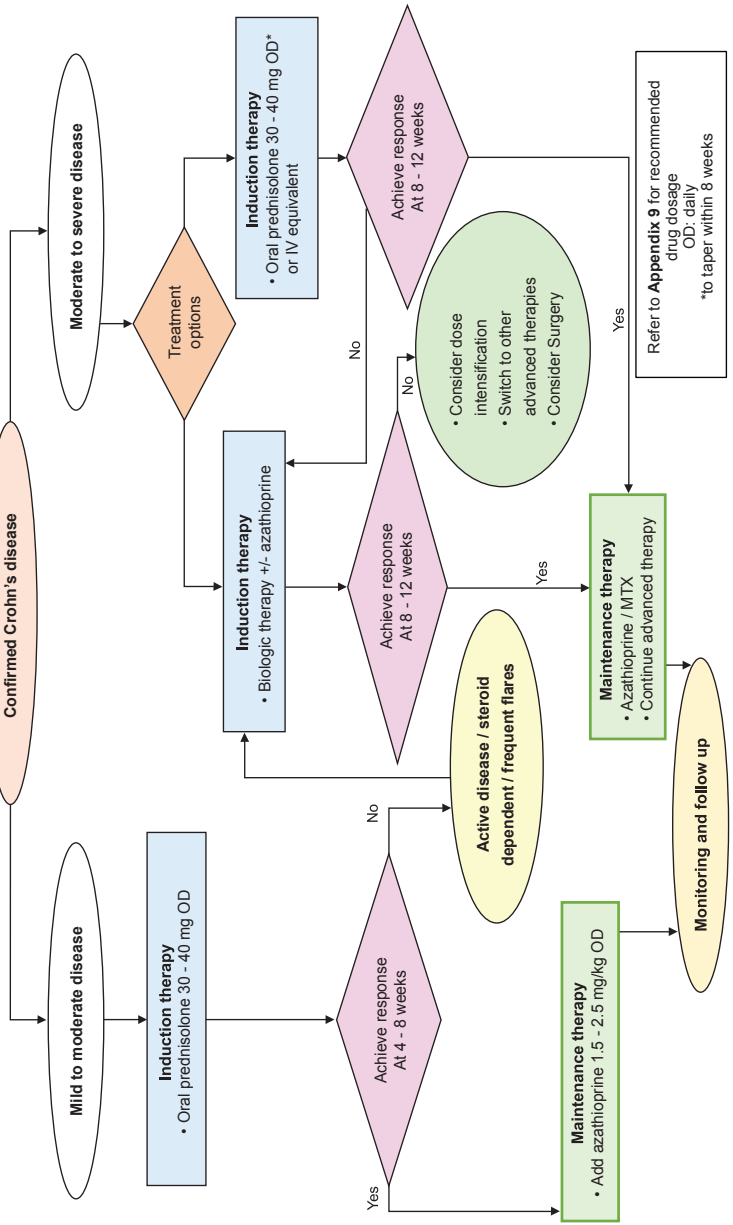
Prof. Dr. Simon Travis
Professor of Clinical Gastroenterology
University of Oxford,
England

Prof. Stuart Taylor
Professor of Medical Imaging
University College London,
England

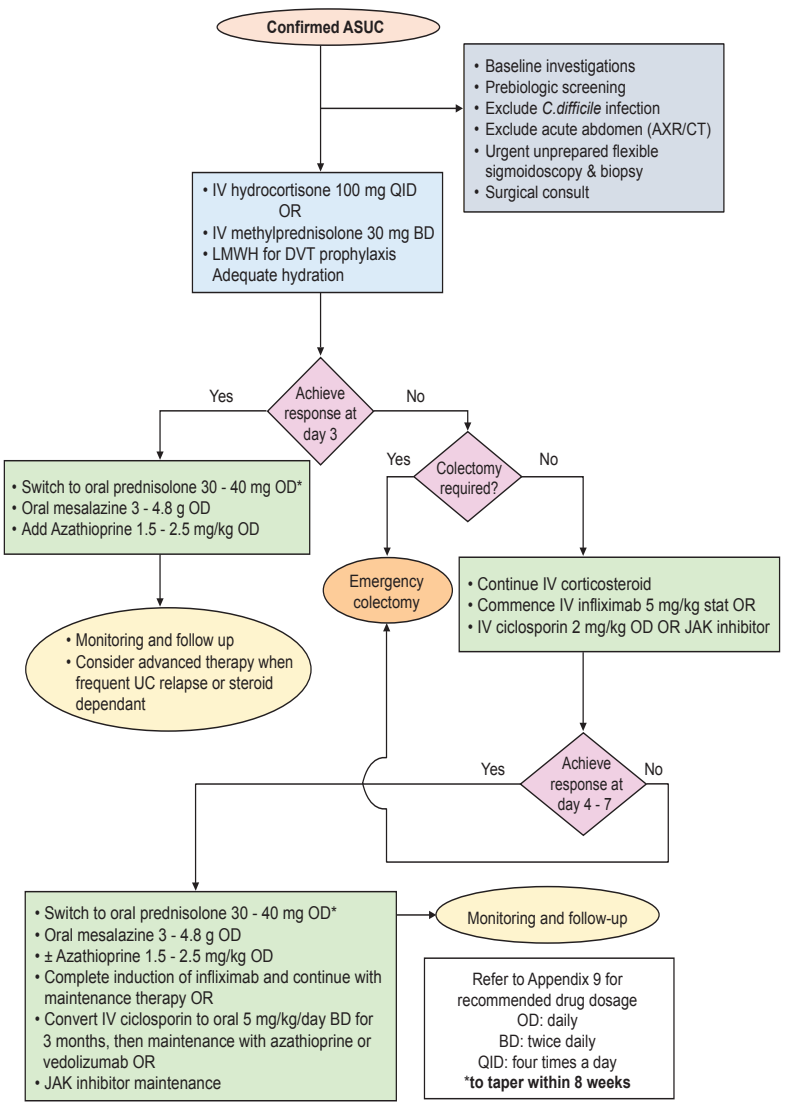
ALGORITHM 1: MANAGEMENT OF ULCERATIVE COLITIS



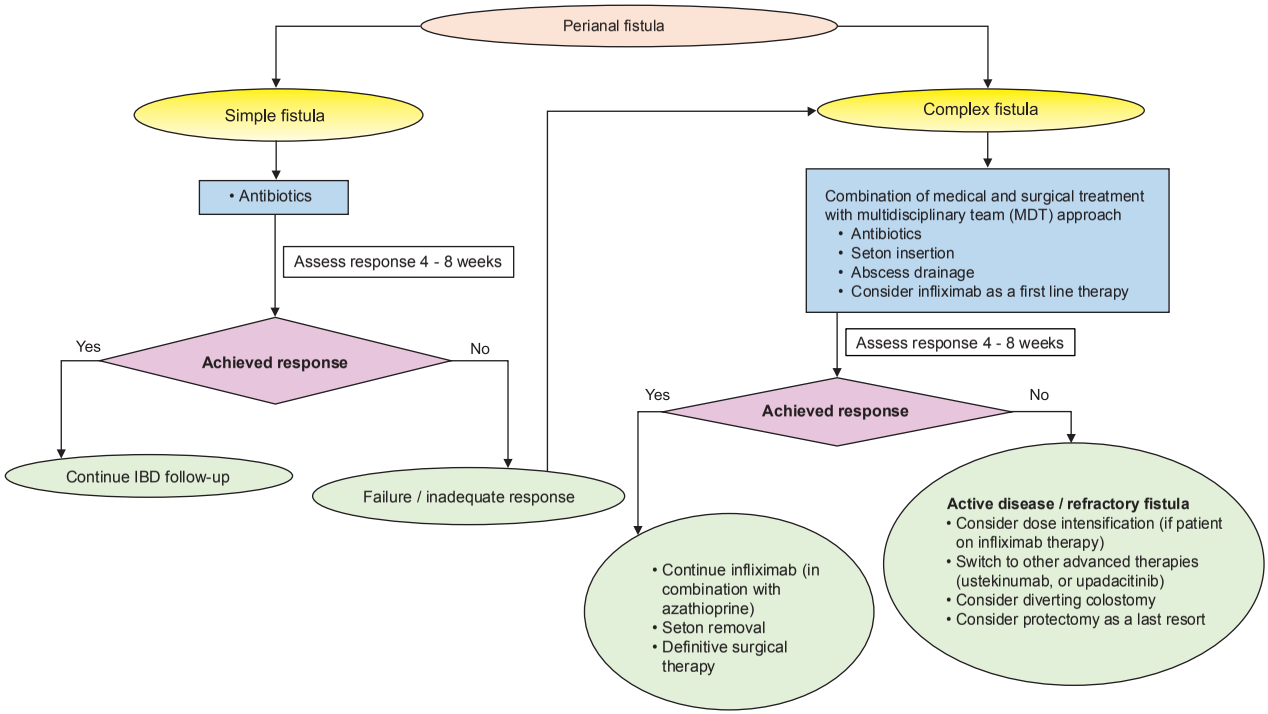
ALGORITHM 2: MANAGEMENT OF CROHN'S DISEASE



ALGORITHM 3: MANAGEMENT OF ACUTE SEVERE ULCERATIVE COLITIS (ASUC)



ALGORITHM 4: MANAGEMENT OF PERIANAL FISTULA



1. INTRODUCTION

Inflammatory bowel disease (IBD) refers to a group of idiopathic, chronic, and relapsing inflammatory disorders of the gastrointestinal (GI) tract, primarily encompassing ulcerative colitis (UC) and Crohn's disease (CD). UC is mainly confined to the colon, while CD can affect any segment of the alimentary tract, from the mouth to the anus.

Historically IBD is considered a disease predominantly affecting Western population. However, over the past few decades, the incidence of IBD had risen in Asian countries, including Malaysia, particularly over the past few decades. This increase may be linked to urbanisation and dietary changes.[1, level III; 2, level II-2]

In Malaysia, the mean crude incidence of IBD has shown a steady rise from 0.36 per 100,000 person-years (1980 - 1989) to 0.63 per 100,000 person-years (2000 – 2009). Notably, between 2010 and 2018, the mean crude incidence doubled to 1.46 per 100,000 person-years.[2, level II-2]

The onset of IBD can occur in early life contributing to considerable long-term morbidity. This disease is characterised by alternating period of remission and relapse throughout a patient's lifetime. Research from the United Kingdom indicates that the lifetime costs associated with IBD are comparable to those of major diseases, such as heart disease and cancer.[3, level III]

Effective management of IBD requires a proactive and preventive approach that includes regular patient monitoring, a clear understanding of disease progression and treatment outcomes, and robust clinical governance. A multidisciplinary team (MDT) comprising healthcare professionals from diverse specialties is essential to optimise patient care, reduce complications, and achieve sustained disease control.

In Malaysia, the overall management of IBD is challenging. Delays in diagnosis and treatment commonly occurs due to misdiagnosis as IBD-mimicking diseases, e.g *Mycobacterium Tuberculosis* (MTB), which is endemic within the region. These diagnostic delays may result in avoidable disease complications requiring emergency admission, surgical intervention and prolonged hospital stay. Additionally, a lack of knowledge and experience among healthcare providers regarding IBD poses significant barriers for optimal management

To address these challenges, a comprehensive yet concise clinical practice guideline (CPG) is essential. Such a resource would facilitate improved understanding and management of IBD across all levels of healthcare provisions in Malaysia, ultimately enhancing patient outcomes.

2. RISK FACTORS

In an umbrella review of meta-analyses investigating the associated risk factors of IBD, the findings are summarised in **Table 1** below:[4, level II-2]

Table 1: Risk Factors of IBD

Factor	IBD	CD	UC
Increase risk			
Smoking		√	
Urban living	√		
Appendicectomy		√	
Tonsillectomy		√	
Antibiotic exposure	√		
Oral contraceptive use	√		
Consumptions of soft drinks			√
Vitamin D deficiency	√		
Non-*Helicobacter pylori*-like enterohepatic *Helicobacter* species	√		
Reduce risk			
Physical activity		√	
Breast-fed	√		
Bed sharing		√	
Tea consumption			√
High level of folate	√		
High level of Vitamin D		√	
H Pylori infection	√	√	√

However, the quality assessment of each meta-analysis (MA) based on AMSTAR 2 were low.

3. DIAGNOSIS AND INVESTIGATIONS

The diagnosis of IBD requires an integrated approach that combines clinical assessment, laboratory tests, endoscopic evaluation, histological examination and imaging studies.

3.1 Clinical Features and Presentation

a) History Taking in Patients Suspected of IBD

Patients with IBD may present with various clinical presentations and manifestations. Symptoms may be mild to severe and may decrease or disappear during remissions. In the process of obtaining a patient's medical history in cases suspected of IBD, the World Gastroenterology Organisation (WGO) Global Guidelines have recommended to include the following:[5, level III]

- symptoms of diarrhoea (blood, mucus), abdominal pain, vomiting, weight loss, fistulas, perianal disease and fever
- the pattern, duration, frequency and chronology of symptoms
- presence of extraintestinal manifestations (EIM)
- past medical history of GI issues and previous surgeries
- history of TB, intestinal infection and travel history
- risk factors, including use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, smoking, and family history
- impact on function and quality of life

b) Clinical Presentation

The WGO Global Guidelines have outlined that constitutional and general symptoms may be present in both UC and CD as follows::[5, level III]

- Fever
- Loss of appetite
- Loss of weight
- Fatigue
- Night sweats
- Growth retardation
- Primary amenorrhea

Symptoms may be related to intestinal inflammation and damage:

- Diarrhoea:
  - Stool may contain mucus or blood
  - Nocturnal diarrhoea
  - Incontinence
- Constipation:
  - Symptom limited to the rectum (proctitis)
  - No passage of flatus in bowel obstruction
- Pain or rectal bleeding
- Bowel movement urgency
- Tenesmus

- Abdominal cramps and pain:
  - around the umbilicus, in the lower left quadrant in UC
  - in the right lower abdominal quadrant in CD
- Nausea and vomiting

Additionally, patients with IBD may develop:

- Intestinal complications
  - haemorrhage
  - bowel perforation
  - abscess
  - intestinal stricture leading to obstruction
  - toxic megacolon
  - malignancy
- Extraintestinal manifestations

c) Referral from primary care to tertiary centre

Patients with IBD often present initially to primary care with GI symptoms of varying severity. Primary care providers play a crucial role in early recognition of IBD symptoms and timely referral to a gastroenterology team.

- The CPG DG opines those patients presenting to primary care with either one or more of the following symptoms requires referral to tertiary care:
  - chronic diarrhoea (with or without blood / mucous) for ≥6 weeks
  - abdominal pain
  - constitutional symptoms
  - presence of extraintestinal manifestations (EIM)
  - presence of perianal disease

  The presence of these symptoms and risk factors, particularly when they are chronic and persistent, warrants a referral for a more definitive diagnosis and specialised management by a gastroenterologist.

d) Clinical Classification

The clinical classification of IBD has been established based on the Report of a Working Party from the 2005 Montreal World Congress of Gastroenterology (2005). Based on the Montreal classification for IBD, there are three predominant parameters. These include age at diagnosis, the location and behaviour of the condition as shown in **Table 2**.[6, level III]

The term 'indeterminate colitis' should be reserved only for cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either UC or CD after full examination.

Table 2: Montreal Classification for IBD

Clinical Classification	UC	CD
Disease onset	Peak incidence reported at the 3rd and 4th decade.	Categorised by age: A1 aged 16 years or younger A2 aged between 17-40 years A3 aged above 40 years
Location of disease	Categorised by extent: E1 ulcerative proctitis E2 left-sided UC (distal UC) E3 extensive UC (pancolitis)	Categorised by location: L1 Ileum (distal small intestine) L2 colon L3 ileocolonic L4 isolated upper disease
Behaviour and severity	Categorised by severity: S0 clinical remission S1 mild S2 moderate S3 severe	Categorised by behaviour: B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating *p* perianal disease modifier is added when concomitant perianal disease is present

Source:
Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of IBD: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A-36A.

The common scoring systems used in the management of IBD, including both UC and CD, as well as paediatric and general assessment tools are shown in **Appendix 3**.

e) Extraintestinal manifestations (EIM)
About 50% of patients with IBD may develop at least one EIM.[7, level II-2]

Based on European Crohn's and Colitis Organisation (ECCO) guidelines, EIM in IBD may occur in every system of the body and can broadly be classified as classical (inflammatory process occurring at distant sites), associations (the associations with other immune-mediated disorders), complications (complications of systemic inflammation) and treatment (side effects of IBD therapy), as shown in **Figure 1** below.[8]

The term 'indeterminate colitis' should be reserved only for cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either UC or CD after full examination.

Table 2: Montreal Classification for IBD

Clinical Classification	UC	CD
Disease onset	Peak incidence reported at the 3rd and 4th decade.	Categorised by age: A1 aged 16 years or younger A2 aged between 17-40 years A3 aged above 40 years
Location of disease	Categorised by extent: E1 ulcerative proctitis E2 left-sided UC (distal UC) E3 extensive UC (pancolitis)	Categorised by location: L1 Ileum (distal small intestine) L2 colon L3 ileocolonic L4 isolated upper disease
Behaviour and severity	Categorised by severity: S0 clinical remission S1 mild S2 moderate S3 severe	Categorised by behaviour: B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating *p* perianal disease modifier is added when concomitant perianal disease is present

Source:
Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of IBD: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A-36A.

The common scoring systems used in the management of IBD, including both UC and CD, as well as paediatric and general assessment tools are shown in **Appendix 3**.

e) Extraintestinal manifestations (EIM)
About 50% of patients with IBD may develop at least one EIM.[7, level II-2]

Based on European Crohn's and Colitis Organisation (ECCO) guidelines, EIM in IBD may occur in every system of the body and can broadly be classified as classical (inflammatory process occurring at distant sites), associations (the associations with other immune-mediated disorders), complications (complications of systemic inflammation) and treatment (side effects of IBD therapy), as shown in **Figure 1** below.[8]

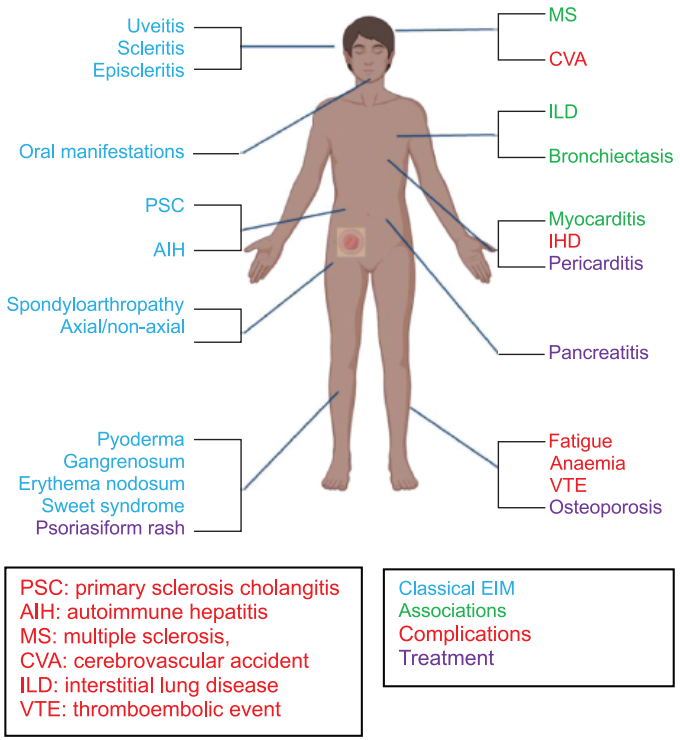


Figure 1: Extraintestinal manifestations (EIM) in IBD

Source: Gordon H, Burisch J, Ellul P et al., ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18(1):1-37

A systematic review (SR) and MA of 33 studies including 131,860 patients with IBD found 14,659 had ≥1 joint, ocular, or cutaneous EIM, with a pooled prevalence of 0.24 (95% confidence interval (CI), 0.19 to 0.31). The pooled prevalence was 0.27 (95% CI 0.19 to 0.37) in UC and 0.35 (95% CI 0.28 to 0.43) in CD.[9, level III]

- It is important to recognise EIM in patients with IBD to help individualise treatment.

Recommendation 1

- The diagnosis of inflammatory bowel disease should be established through a comprehensive, integrated assessment encompassing clinical features (including extraintestinal manifestations), laboratory tests, endoscopic evaluation, histopathological findings and imaging studies.

3.2 Investigations

3.2.1 Laboratory Investigations

a) Initial Investigations

According to the ECCO-ESGAR Guidelines for Diagnostic Assessment in IBD, the recommended initial diagnostic investigations for patients suspected of having IBD include:[10, level III]

- Full Blood Count (FBC)
- Liver Function Test (LFT)
- Electrolytes including blood urea serum electrolyte (BUSE) and creatinine, calcium, magnesium and phosphate
- Stool for microbiological analysis to exclude common GI infections such as *Clostridium difficile, Escherichia coli, Campylobacter, Yersinia, Salmonella* and *Shigella*

b) Inflammatory Biomarkers and Serologies

In a large MA on diagnostic utility of non-invasive tests for IBD, the sensitivities and specificities are as follow:[11, level III]

- For initial assessment -
  - Faecal calprotectin (FC) and faecal lactoferrin were the most sensitive markers in detecting IBD with sensitivities of 0.88 (95% CI 0.83 to 0.92) and 0.82 (95% CI 0.72 to 0.89) respectively while their specificities were 0.80 (95% CI 0.69 to 0.88) and 0.95 (95% CI 0.88 to 0.98) respectively.
  - Anti-Neutrophilic Cytoplasmic Antibody (ANCA) and Anti-Saccharomyces Cerevisiae Antibodies (ASCA) were the most specific markers in diagnosis of IBD with specificities of 0.97 (95% CI 0.96 to 0.98) and 0.96 (95% CI 0.94 to 0.97) respectively while their sensitivities were only 0.33 (95% CI 0.31 to 0.34) and 0.31 (95% CI 0.29 to 0.35) respectively.
  - to differentiate UC from CD, ASCA immunoglobulin A (IgA) showed the highest specificity of 0.96 (95% CI 0.94 to 0.97). To differentiate UC from CD, the only test included in analysis was ANCA with specificity of 0.89 (95% CI 0.87 to 0.90).
- Assessment of IBD disease activity -
  - FC (cut off of 50 µg/g) had highest sensitivity of 0.92 (95% CI 0.90 to 0.94) while specificity of 0.60 (95% CI 0.52 to 0.67) in a mixed population of IBD.
  - C-reactive protein (CRP) had a sensitivity 0.49 (95% CI 0.34 to 0.64) while specificity 0.92 (95% CI 0.72 to 0.98) in a mixed population of IBD.

- Assessment of clinical recurrence -
  - FC performed best with a sensitivity of 0.78 (95% CI 0.72 to 0.83) and specificity of 0.73 (95% CI 0.68 to 0.77) in IBD with almost similar findings for UC [sensitivity 0.75 (95% CI 0.7 to 0.79) and specificity 0.77 (95% CI 0.74 to 0.80)] and CD [sensitivity 0.75 (95% CI 0.64 to 0.84) and specificity 0.71 (95% CI 0.64 to 0.76)]. The quality assessment of the primary papers were low to moderate.

In a SR on the use of CRP, erythrocyte sedimentation rate (ESR), FC and faecal lactoferrin to differentiate adults with IBD, irritable bowel syndrome (IBS) and healthy controls:[12, level III]

- CRP and FC were clinically useful in ruling out IBD at a CRP level of ≤0.5 milligrams per deciliter (mg/dl or a calprotectin level of ≤40 µg/g, there was a ≤1% probability of having IBD.
- elevated CRP levels were predictive of IBD; levels of ≥1.7 mg/dl and >2.7 mg/dl had a predictive probability of >52% and >90% of IBD, respectively.
- likelihood of a diagnosis of IBD increased as level of FC increased with maximal predictive value of 78.7% at 100 mg/g.
- faecal lactoferrin was better at predicting IBS than IBD; even at a level of 460 µg/g, there was a 50.3% likelihood of IBS compared with a 16.7% probability of IBD.
- ESR was not a reliable predictor of IBD. Even at an extreme ESR level of 200 mm/h, the probability of IBD was only 1.6%.

The quality of included primary studies was rated as fair using the quality assessment of diagnostic accuracy studies (QUADAS).

In the local settings, ASCA and ANCA is not routinely performed for diagnosis of IBD due to its limited availability and high cost.

c) Additional investigations

i. Investigations for TB

In cases where differentiation between CD and intestinal TB is challenging, additional investigations are warranted. These may include:[13]

- Chest X-ray (CXR)
- Interferon Gamma Release Assay (IGRA)
- Histopathological examination and microbiological testing of tissue samples

In the local practice, colonic biopsies are routinely sent for TB polymerase chain reaction (PCR), MTB culture & sensitivity (C&S) and staining for Ziehl- Neelsen special stain.

ii. Genetic testing

Genetic testing and evaluation for primary immunodeficiency should be considered for paediatric patients with disease onset of younger than 6

years old (Very Early-Onset IBD) after assessment and evaluation by a paediatric gastroenterologist.[14]

Genetic testing is not an absolute indication for establishing a diagnosis of paediatric CD.[14]

Recommendation 2
- The following baseline investigations should be done in patients with suspected inflammatory bowel disease (IBD):
  - full blood count (FBC)
  - liver function test (LFT)
  - electrolytes
  - C-reactive protein (CRP)
  - stool culture & sensitivity and stool for *Clostridium difficile* infection
  - faecal calprotectin (FC)
- Tuberculosis (TB) workup should be performed in patients who pose a diagnostic challenge between Crohn's disease (CD) and intestinal TB.

3.2.2 Endoscopic Examination and Biopsy

Endoscopic assessment is an important component of the diagnostic workup, assessing disease activity, monitoring treatment response, and determining remission in IBD. The use of endoscopic scoring systems provides a standardised and uniform basis for assessment, offering greater objectivity and facilitating comparability between evaluations. Several validated endoscopic scores are available for use in both UC and CD.

In UC, the Mayo Endoscopic Score (MES) and the UC Endoscopic Index of Severity (UCEIS) are commonly used. Endoscopic response is defined as a reduction of the MES by 1 or the UCEIS score by 2. The value of the UCEIS is the precise definitions of each level agreed by a Delphi process between specialists.[15, level I; 16, level III]

In CD, the commonly used endoscopic scoring systems are the Simple Endoscopic Score for CD (SES-CD) and the CD Endoscopic Index of Severity (CDEIS).[17, level II-2; 18, level III] Endoscopic response is defined as an SES-CD reduction of 50% or a CDEIS reduction of 50%. Endoscopic healing is defined as an SES-CD of <3, absence of ulceration, or a CDEIS of <4. In post-surgery CD patients, the Rutgeerts' score is also used to risk-stratify patients for medical therapy.[19, level II-2]

There is currently no recommendations on the preferred endoscopic scoring system used; however, these scoring systems may be integrated into clinical practice to optimise patient outcomes. **Table 3** shows a summary of the common scoring systems used in UC and CD.

Table 3: Common Endoscopic Scoring Systems in IBD

Scoring system	IBD type	Assessment Purpose	Scoring description	Level of validations
MES[15, level I]	UC	Assessing endoscopic activity and severity	0 - Normal or inactive disease 1 - Mild disease: erythema, decreased vascular pattern, mild friability 2 - Moderate disease: marked erythema, absent vascular pattern, moderate friability, erosions 3 - Severe disease: Spontaneous bleeding, ulcerations	Not validated
UCEIS[20, level III]	UC	Assessing endoscopic activity and severity	Based on 3 variable subscores: A. Vascular patterns: 0 - Normal 1 - Patchy obliteration 2 - Obliterated B. Bleeding: 0 - None 1 - Mucosal 2 - Luminal mild 3 - Luminal moderate to severe C. Erosions and ulcerations: 0 - None 1 - Erosions 2 - Superficial ulcerations 3 - Deep ulcerations	
SES-CD[17, level II-2]	CD	Assess endoscopic activity	A. Ulcers: Absent (0), between 0.1-0.5 cm (1), >2 cm (2) B. Ulcerated Surface: None (0), <10% of the segment (1), 10-20% of the segment (2), >30% of the segment (3) C. Affected Surface: None (0), <50% of the segment (1), 50-75% of the segment (2), >75% of the segment (3) D. Narrowing: None (0), single stenosis passable by colonoscope (1), multiple and passable by colonoscope (2), not passable (3) Grading (0-56 points)	partially validated

CDEIS[18, level III]	CD	Assess endoscopic activity	A. Deep ulcerations: 0 - absent or 12 - present B. Superficial ulcerations: 0 - absent or 6 - present C. Length of ulcerated mucosa (0 – 10 cm) Score 0 to 10 D. Length of diseased mucosa (0 – 10 cm) Score 0 to 10 E. Ulcerated stenosis: 0 - absent or 3 - present F. Nonulcerated stenosis: 0 - absent or 3 - present Grading (0-44) using the above descriptive features	partially validated
Rutgeerts' Score[19, level II-2]	CD	Assess post-surgical recurrence in CD	i0. Post-surgery remission - No lesions in the distal ileum i1. Post-surgery remission - Not more than 5 anastomotic aphthous lesions in the distal ileum i2. Substantial post-surgery remission - More than 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or ulcers up to 1 cm confined to ileocolonic anastomosis i3. Advanced post-surgery recurrence - Diffuse aphthous ileitis with diffusely inflamed mucosa between multiple aphthae i4. Advanced post-surgery recurrence - Diffuse inflammation, with larger lesions: large ulcers and/or nodules/ cobble and/or narrowing/ stenosis	partially validated

Adapted from: Buchner AM, Farraye FA, Iacucci M. AGA Clinical Practice Update on Endoscopic Scoring Systems in IBD: Commentary. Clin Gastroenterol Hepatol. 2024;22(11):2188-2196

Colonoscopy is essential in the diagnosis of IBD. Upper GI and small bowel endoscopy may be necessary in selected cases. High-definition (HD) endoscopy using conventional white light endoscopy (WLE) and/or image-enhanced endoscopy (IEE) is widely utilised to improve mucosal visualisation. Endoscopic biopsies of the gut mucosa play a crucial role in establishing the diagnosis of IBD.

Bowel Preparation for Endoscopic Procedures

Patients undergoing small bowel endoscopy and/or colonoscopy require adequate bowel preparation. The preferred purgative agent is polyethylene glycol (PEG) because it is less likely to induce inflammation or damage to colonic mucosa, thereby facilitating more accurate histological visualisation.[10, level III] A low-volume (≤ 2 L) PEG solution administered using a split dose preparation is recommended as it offers comparable efficacy to high-volume PEG solutions with improved patient tolerability and compliance.[21]

According to the ECCO guidelines on the use of endoscopy in IBD, the key statements include:[10, level III]

- **Endoscopic features**
  - no endoscopic feature is specific for UC or CD
  - the most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation and rectal involvement
  - the most useful endoscopic features in CD are discontinuous lesions, presence of strictures and fistulae, and perianal involvement
  - other colitides resembling IBD include infectious colitis [e.g., Tuberculous, cytomegalovirus (CMV) infection], drug-induced colitis, ischemic colitis, and radiation colitis need to be excluded

- **Biopsy Recommendations**
  - biopsies should be obtained preferably before commencing treatment, as it can potentially alter the mucosal morphology
  - a minimum of two biopsy specimens each from at least six segments of the colon (including the terminal ileum, ascending, transverse, descending, sigmoid and rectum) should be taken and placed in separate vials
  - samples should be collected from both mildly and severely inflamed areas to accurately represent the extent and variability of inflammation
  - biopsies should also be obtained from areas with 'normal-appearing' mucosa, ulcers, depressed lesions, stenotic regions, or any unusual polypoid lesions or masses

In the local settings, a proforma on Endoscopic Specimen Submission for Histologic Assessment for Chronic Idiopathic IBD & Other Colitides

is recommended to be filled by clinicians and submitted together with the histopathology specimens (refer to **Appendix 5**).

In return, the pathologist should report the findings in the Histologic Assessment & Reporting of Endoscopic Specimens for Chronic Idiopathic IBD & Other Colitides section (refer to **Appendix 6**).

Recommendation 3
- Colonoscopy should be performed in all patients with suspected inflammatory bowel disease (IBD) as part of the initial diagnostic workup.
- For bowel preparation, polyethylene glycol should be used in patients with suspected or confirmed IBD.
- A minimum of two biopsy specimens each (endoscopically normal and abnormal mucosa) should be obtained across at least six segments of the bowel and placed in separate clearly labelled vials in patients with IBD.

3.2.3 Histology and scoring system

Histologic examination plays a key role in the diagnosis of patients with IBD. There are specific histological abnormalities in a biopsy that can support the diagnosis of IBD and are defined as the following:[22, level III]

- **Chronicity features**
  - crypt distortion (loss of parallel crypt architecture, an increase in crypt branching, and /or variation in crypt size and shape) and crypt atrophy (reduction in the proportion of the total colorectal mucosal area that the crypts occupy)
  - metaplasia (presence of Paneth cell distal to the splenic flexure), presence of pyloric glands (replacement of original epithelium with glands resembling those in the gastric antrum)
  - chronic inflammation (increase in lamina propria lymphoplasmacytic infiltrates, basal plasmacytosis, lymphoid hyperplasia)

- **Activity features**
  - acute inflammation composed of neutrophils (lamina propria infiltration, cryptitis, crypt abscess, presence of erosion and ulceration signifies a higher degree of activity)
  - mucin depletion (unequivocal reduction of goblet cell mucin in crypts and surface epithelium)

- **Granulomas**
  - distinct collection of at least five histiocytes/macrophages that can also contain multinucleated giant cells, may be well or poorly defined, lacks necrosis and may have lymphoid cuff; may be found in CD

(Note - The presence of eosinophils however does not define disease activity or chronicity)

Refer to **Figures 2, 3** and **4** for the histopathological features of IBD.

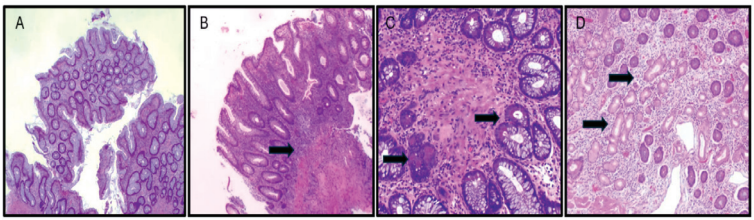


Figure 2: Histology of chronicity features:
A) Architectural distortion in colonic mucosa
B) Increase in lamina propria chronic inflammatory cells with basal plasmacytosis (arrow)
C) Paneth cell metaplasia in the rectum (arrow)
D) Pseudopyloric metaplasia in terminal ileum (arrow)

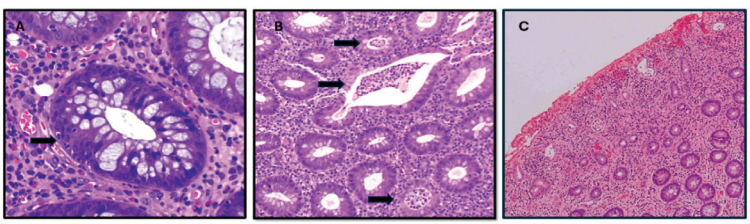


Figure 3: Histology of active inflammation:
A) Cryptitis (arrow)
B) Crypt Abscess (arrow)
C) Surface ulceration with fibro-granulation tissue formation

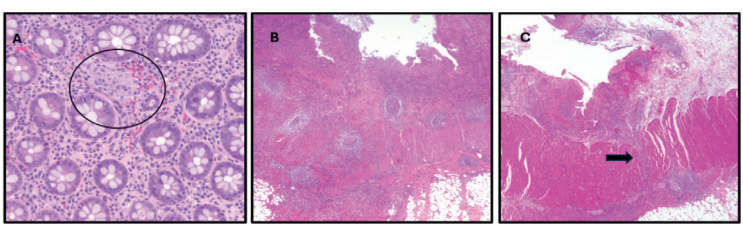


Figure 4: Histological features of CD:
A) Microgranuloma
B) Transmural chronic inflammation with numerous lymphoid follicles/ aggregates
C) Fissuring ulcer extending from luminal surface transmurally (arrow)

The ECCO and European Society of Pathology (ESP) consensus guidelines highlights several standards for histopathology diagnosis in IBD, they include:[23 - 24]

Ulcerative colitis

- Typical (microscopic features): widespread crypt architectural distortion, a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis and active component, causing cryptitis and crypt abscesses.
- The preserved crypt architecture and the absence of a transmucosal inflammatory cell infiltrate do not rule out UC at an early stage. Therefore, repeat biopsies are recommended not sooner than six weeks after the initial assessment for the diagnosis of UC.
- Untreated children with UC may present with normal mucosa/mild patchy inflammation at disease onset or unusual inflammation pattern such as patchiness and rectal sparing.
- Upper GI inflammation may be present in children and rarely in adults with UC.
- Granulomas are not a specific feature of UC and if present are related to crypt injury.

Crohn's disease

- Typical (microscopic features): focal (discontinuous) chronic inflammation, focal (discontinuous) crypt irregularity/distortion and granulomas. Granulomas in CD are predominantly micro- to small-sized, poorly formed and non-caseating, unrelated to crypt injury.
- CD in children is associated with more colitis and less ileitis with higher frequency of granuloma compared to adult. Focal inflammation in the upper GI tract is common in CD.

General guidelines

- Testing for CMV reactivation on colonic biopsy should be performed in all patients with severe colitis refractory to immunosuppressive therapy.
- CMV testing should be performed on ulcer base tissue via CMV immunohistochemistry staining or PCR testing.
- Confirmation of dysplasia by an independent expert GI pathologist is recommended.
- For proper histologic evaluation of pouchitis, biopsies from the anterior and posterior wall avoiding suture line are useful. Samples from the posterior wall are more likely to show pouchitis related inflammatory changes.
- Histology is not a good tool to identify bacterial infection of the small or large intestine, especially for *Clostridium difficile* infection.

The histopathological features for the diagnosis of IBD is outlined in **Table 4** and **Table 5**.

Table 4: Macroscopic features used for the diagnosis of IBD

Features	Ulcerative Colitis	Crohn's Disease
Localisation GI tract	Colon and rectum	Whole GI tract
Ileum	Not involved except in backwash-ileitis	Often involved
Colon	Left > right	Right > left
Rectum	Commonly involved	Typically spared
Distribution GI tract	Diffuse (continuous)	Segmental (discontinuous)
Ulcers	Superficial ulcers	Aphtoid ulcers, confluent deep linear ulcers
Pseudopolyps	Common	Uncommon
Skip-lesions	Absent	Present
Cobblestone-pattern	Absent	Present
Deep fissures	Absent except in fulminant colitis	Present
Fistulae	Absent except in fulminant colitis	Present
Mucosal atrophy	Marked	Minimal
Thickness of the wall	Normal	Increased
Fat wrapping	Absent	Present
Strictures	Uncommon	Present

Table 5: Microscopic features used for the diagnosis of IBD in treatment-naïve patients

Features	Ulcerative Colitis	Crohn's Disease
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse(continuous) Decrease proximally	Focal (discontinuous) Variable
Patchiness	Uncommon	Common
Localisation	Superficial Transmucosal Sometimes in submucosa	Transmural
Serositis	Absent except in fulminant colitis	Present
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except with ruptured crypts	Present
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Not uncommon
Pyloric gland metaplasia	Rare	Present

Source: Magro F, Gionchetti P, Eliakim R et al., Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis. 2017;11(6):649-670.

Recommendation 4

- Testing for Cytomegalovirus reactivation should be performed using immunohistochemistry staining or PCR testing preferably on ulcer-base colonic biopsy tissue in patients with severe colitis refractory to immunosuppressive treatment.

Several histological scoring systems have been developed to provide a standardised evaluation of microscopic inflammation, particularly for UC. These tools are used to assess disease severity, monitor activity, prognosis and evaluate response to treatment usually in the research setting. However, more recently these have been shown to be useful in routine clinical use. The Geboes Score (GS), Robarts Histological Index (RHI), and Nancy Histological Index (NHI) are the most widely utilised scoring systems for disease activity in UC. Among them, the NHI is the simplest and most suitable for routine clinical practice. Currently, GS and RHI are only used in clinical trials. Currently, there are no validated scoring systems to be applied for CD because of the patchy distribution of the disease and the transmural extension of the inflammation in CD.

In a randomised controlled trial (RCT) comparing measurement properties of three commonly used histological indices GS, RHI and NHI in assessing mucosal healing in moderate to severe active UC, findings showed:[25, level I]

- inter-rater reliability based on intraclass correlation coefficient (ICC) was:
  - Excellent for RHI (ICC = 0.905)
  - Good for NHI (ICC = 0.640)
  - Fair for GS (ICC = 0.530)
- construct-related validity showed performance of GS and RHI was good vs NHI fair (using Spearman correlations, r)
- known group analysis for validity assessment: performance of GS and RHI were excellent and NHI was good based on Mayo endoscopy, full Mayo score and IBD Questionnaire (IBDQ) quartiles
- sensitivity to change (Cohen's d):
  - GS: –0.96 (good)
  - RHI: –0.67 (moderate)
  - NHI: –0.39 (low)
- all three provided reliable and construct-valid scores that were sensitive to changes in disease activity over time

In a diagnostic study comparing the use of NHI, RHI and GS in routine practice for UC, NHI and GS appeared most suitable for assessment of inflammation. Additional significant findings were:[26, level III]

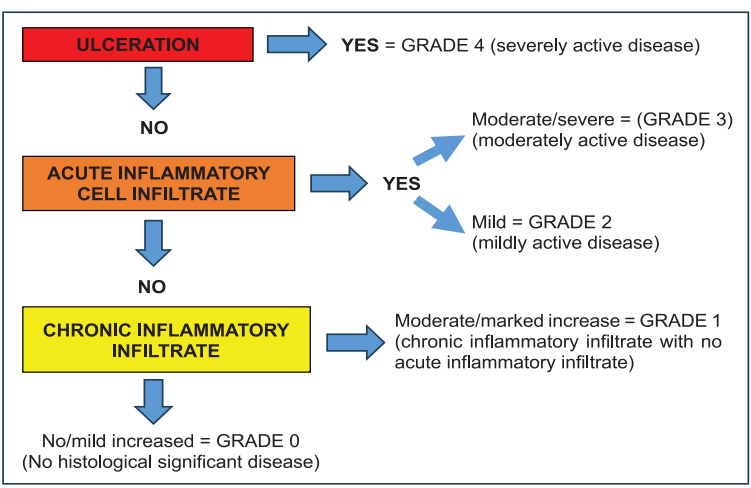
- inter-rater agreement for NHI (k=0.861), GS (k=0.820) and RHI (k=0.592)

- inter-rater agreement for NHI (k=0.861), GS (k=0.820) and RHI (k=0.592)
- intra-rater agreement for NHI (k=0.973), GS (k=0.942) and RHI (k=0.892)
- average time to rate per slide was shortest for NHI (72.06 s), followed by GS (77.55 s) and RHI (92.67 s)
- all scoring systems correlated well with Mayo endoscopic partial score by Spearman's correlation coefficient; NHI (r_s=0.412,), GS subcategories (r_s=0.469) and RHI (r_s=0.357)

In another diagnostic study on reliability and responsiveness of histologic indices [Global Histologic Disease Activity Score (GHAS), GS, NHI and RHI] for the assessment of activity of CD:[27, level III]

- ICC revealed substantial to almost perfect ranging from 0.63 - 0.87 across all indices.
- The intra-rater reliability was also substantial to almost perfect (ICC 0.74 - 0.95).
- In responsiveness of disease activity, there was small to large responsiveness [area under curve (AUC) 0.57 - 0.94] for established indices when either treatment assignment or the Visual Analogue Scale (VAS) based definition of improvement was used.

The Nancy Histological Index (NHI) Assessment & Scoring is shown in **Figure 5.**



Note: For practical reasons erosions should be scored as grade 4 ("severely active disease")

Figure 5: Nancy Histological Index (NHI) Assessment & Scoring

Source: Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. Gut. 2017;66(1):43-49

Recommendation 5
- In patients with ulcerative colitis (UC), Nancy Histological Index should be used in routine clinical practice as it is the simplest and fastest histological scoring system.
- Geboes Score and the Robarts Histological Index may also be used as reliable histological scoring systems to asses disease activity and mucosal healing in patients with UC.

3.2.4 Radiological investigations

Imaging modalities used in the management of IBD range from abdominal radiographs to advanced techniques such as intestinal ultrasound (IUS), computed tomography enterography (CTE) and magnetic resonance enterography (MRE).

a) Plain abdominal radiograph

Plain abdominal radiographs are commonly used as the first-line imaging modality in emergency cases where bowel obstruction or perforation is clinically suspected. However, they have no value at diagnosis and routine surveillance.[10, level III]

b) Barium studies

Barium studies are infrequently used due to the potential risk of increased cumulative radiation exposure, the limitation of providing only two-dimensional images and the restricted and indirect insight into the condition of the bowel wall and extraluminal extension of CD.[10, level III]

c) Intestinal Ultrasound

IUS is a well-tolerated and radiation-free imaging modality to evaluate the intestines in IBD. Nonetheless, its diagnostic accuracy may be hindered by the presence of intraluminal gas and large patient body habitus. In some cases, contrast-enhanced IUS has been utilised to improve diagnostic accuracy especially in evaluating vascularity associated with inflammatory processes. The sonographic indices to monitor the disease activity include the bowel wall thickness (BWT), color doppler signal (CDS), bowel-wall stratification (BWS), and i-fat (refer **Appendix 7** for intestinal ultrasound scoring indices).[28, level III]

d) Advanced Cross-Sectional Imaging

Computed tomography (CT) scan and magnetic resonance imaging (MRI) are the most commonly used modalities, providing detailed visualisation of the small bowel and enabling the detection of related complications and EIM.

i. Computed Tomography (CT) Scan

The primary advantages of CT scan are its rapid accessibility and fast image acquisition, making it especially valuable in the diagnosis of

acute abdomen, such as suspected bowel obstruction and perforation. In emergency settings where time is critical, CT scan enables prompt diagnosis and timely intervention. Additionally, its diagnostic accuracy is comparable to that of MRE, providing a reliable alternative when MRI is not readily available or feasible.[10, level III]

ii. Magnetic Resonance Imaging (MRI)

MRI is highly effective in the evaluation of small bowel (i.e. MRE) and perianal disease. It offers superior soft tissue contrast and does not involve ionising radiation. These qualities make MRI suitable for long-term surveillance.

In UC, MRI-based scoring systems have not yet been standardised or broadly adopted, and ongoing research is focused on validating their clinical applicability.

In CD, several MRI-based scoring systems have been developed to quantify inflammatory activity. These include the Magnetic Resonance Index of Activity (MaRIA) Score, Lemann Score, Clermont Score, Magnetic Resonance Enterography Global Score (MEGS), CD MRI Index (CDMI) and the simplified MaRIA (sMARIA) Score. While valuable in standardising disease activity assessment in trials, these scoring systems are not routinely used in everyday clinical practice. Instead, qualitative assessment by experienced radiologists typically guides management decisions, with scoring tools remaining optional in standard radiology reports (refer to **Appendix 8** for MRI scoring system in CD).

In an MA comparing the accuracy of capsule endoscopy (CE), MRE and small intestinal contrast ultrasound (SICUS) for detecting active small bowel inflammation in the patients with suspected and/or established CD, the findings were:[29, level III]

- the overall diagnostic yield of CE vs MRE were comparable [odd ratio (OR=1.17, 95% CI 0.83 to 1.67)], regardless of disease status.
- subgroup analysis by age group (adult vs paediatric) also revealed non-significant (NS) difference in diagnostic yield between CE and MRE (OR=1.17 95% CI 0.83 to 1.67).
- CE was superior to MRE for detecting proximal small bowel disease (OR=2.79, 95% CI 1.2 to 6.48); however, risk of capsule retention should be considered.

The studies included were generally of good quality with low risk of bias (RoB) based on QUADAS-2.

An MA of five diagnostic studies compared the accuracy and safety of CTE vs MRE in diagnosing CD. It showed:[30, level III]

- MRE was more sensitive (sensitivity of 0.88 vs 0.85) but less specific (specificity of 0.87 vs 0.89) than CTE.

- MRE and CTE had comparable high diagnostic performance (AUC of 0.925 vs 0.934).
- MRE was safer than CTE for evaluating CD recurrence by minimising cumulative radiation dose.

The primary papers were of high quality based on QUADAS assessment.

An MA in evaluating diagnostic performance of MRE compared to colonoscopy in detecting colonic abnormalities in CD revealed:[31, level III]

- MRE had high diagnostic performance with AUC of 0.95 (95% CI 0.92 to 0.96).
- MRE also had a high specificity of 95% (95% CI 0.92 to 0.97) while sensitivity was only 69% (95% CI 0.52 to 0.82).
- Age-based subgroup analysis, MRE had higher sensitivity in paediatric population at 80% (95% CI 0.47 to 0.94) whilst only 62% (95% CI 0.42 to 0.79) in adults. Nonetheless, comparing specificities was equivalent with 95% (95% CI 0.91 to 0.97) in the paediatric population and 94% (95% CI 0.88 to 0.97) in adults.
- Regarding segmental data, the left colon had the highest sensitivity, 60% (95% CI 35 to 80) and the lowest specificity, 92% (95% CI 88 to 94). The transverse colon showed the lowest sensitivity, 49% (95% CI 32 to 66), and highest specificity, 95% (95% CI 81 to 99).

The included studies were generally assessed as moderate to high quality based on the QUADAS-2 tool.

A cohort study assessed the correlation between colonoscopy, MRE, and FC. It showed that all three biometric tests were statistically correlated and produced reliably congruent results:[32, level II-2]

- High correlation between FC levels and CDEIS scores ($r=0.913$, $p<0.0001$).
- Median FC levels was also higly corelated with MaRIA scores on MRE ($p<0.01$).
- Cut-off FC value of 250 µg/mL was predictive of active disease -
  - on colonoscopy with CDEIS, AUC=0.932 (95% CI 0.861 to 0.956)
  - on MRE with MaRIA, AUC=0.922 (95% CI 0.874 to 0.957)

In a 5-year diagnostic study assessing accuracy of the new sMaRIA score in comparison with the endoscopic score and FC in CD, the findings were:[33, level III]

- sMaRIA was accurate in predicting CD activity.
  - sMaRIA ≥1 indicated active disease (AUC of 0.94, 95% CI 0.91 to 0.97)
  - sMaRIA ≥3 indicated severe disease (AUC of 0.93, 95% CI 0.89 to 0.97)
- There was strong correlation between sMARIA and SES-CD ($r=0.95$, $p<0.01$); and FC ($r=0.91$, $p<0.01$).

A landmark diagnostic study (METRIC pragmatic trial) on the diagnostic accuracy of MRE and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed CD in adult patients, significant findings revealed:[34, level II-1]

- For small bowel disease:
  - MRE was more sensitive than ultrasound in disease presence (97% vs 92%) and extent (80% vs 70%)
  - MRE was more specific than ultrasound for disease presence (96% vs 84%) and extent (95% vs 81%)
  - MRE was more sensitive than ultrasound to identify active small bowel disease (96% vs 90%)
- NS difference in sensitivity and specificity between MRE and small bowel ultrasonography in identifying the existence or extent of colonic disease

The CPG DG opines the following on the diagnostic comparison of IUS, CTE and MRE in CD, as summarised in **Table 6**.

Table 6: Diagnostic Comparison of IUS, CTE and MRE in Crohn's Disease

Manifestations / Modality	IUS	CTE	MRE
Active inflammatory changes • Bowel wall thickness (>3 mm) • Ulcerations • Oedema • Mural hyperenhancement • Comb sign • Perienteric oedema and/or inflammation • Lymph nodes	✓✓	✓✓	✓✓
Chronicity: • Fibrofatty Proliferation • Pseudosacculations	✓	✓✓	✓✓
Stricture	✓✓	✓	✓✓*
Penetrating (Including fistula, sinus, abscess)	✓✓**	✓✓	✓✓
Perforation	×	✓✓	✓
Disease extent and complexity	✓	✓✓	✓✓
Complications • Mesenteric Venous Thrombosis and/or Occlusion • Neoplasm	✓	✓✓	✓✓
EIM (abdomen)* **	×	✓	✓
Image reproducibility	✓	✓✓	✓✓
Operator dependency	Variable	Low	Low
Radiation	None	Present	None
Feasibility	Easily feasible	Easily feasible	Long waiting list

*differentiating fibro-stenotic from inflammatory stricture
**less sensitive for deep seated abscess
***sclerosing cholangitis and sacroiliitis

Symbol	Meaning
✓✓	Best or preferred
✓	Can detect, less optimal
✗	Not suitable or rarely used

3.2.5 Perianal CD

In perianal CD, the evaluation of fistula activity, extent and associated abscess formation is effectively conducted using imaging modalities such as pelvic MRI, endoanal ultrasonography (EAUS) and transperineal ultrasonography (PUS).[35]

EAUS and PUS have intrinsic limitations in visualising complex or high-lying fistulas, especially when it comes to identifying deeply located abscesses.[35]

Pelvic MRI serves as the leading imaging technique for diagnosing and tracking perianal CD, due to its superior accuracy and consistent performance in evaluating fistula activity over time. Its capacity to identify involvement of adjacent organ systems such as the genitourinary and musculoskeletal structures as well as associated complications, including hidradenitis suppurativa, proctitis, pouchitis, and malignancy, should also be emphasised.[35]

3.2.6 Paediatric CD

For paediatric patients with luminal CD, non-invasive imaging modalities such as bowel ultrasound or MRI imaging are useful to assess transmural disease activity and monitor therapeutic response.[36]

- CTE can be considered as an alternative in patients with CD when MRE/IUS is not available.

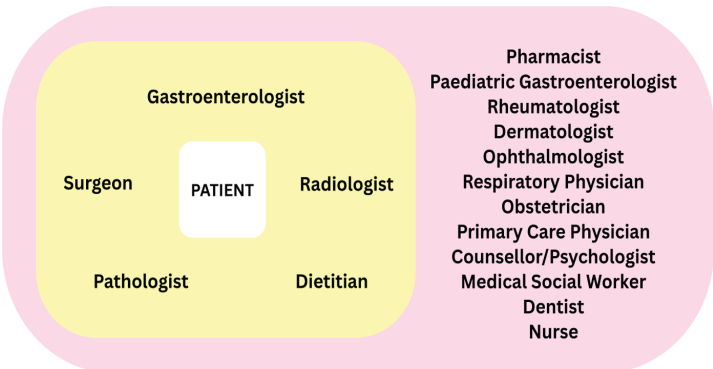
Recommendation 6

- Computed tomography scan should be performed in acute clinical scenarios such as suspected bowel obstruction, perforation and severe complications where rapid diagnosis is required in patients with inflammatory bowel disease.
- Magnetic resonance enterography or intestinal ultrasound should be performed in Crohn's disease patients to assess disease activity and extent.
- Pelvic magnetic resonance imaging should be performed in patients with perianal disease to assess fistulae and identify associated complications.

4. THERAPEUTIC INTERVENTIONS

4.1. General Considerations in Treatment

The British Society of Gastroenterology (BSG) recommends an MDT approach as shown in **Figure 6** in the management of patients with IBD.[21; 37, level III]



The core members (in yellow) of the recommended MDT should consist gastroenterologist, surgeon, pathologist, radiologist and dietitian. In the local setting, the primary treating team will coordinate the MDT. Other disciplines (in pink) may support the management of patients with IBD when needed.

Figure 6: Multidisciplinary Team in Management of Patients with IBD

Adapted from:

1. Lamb CA, Kennedy NA, Raine T et al., British Society of Gastroenterology consensus guidelines on the management of IBD in adults. Gut. 2019;68 (Suppl 3):s1-s106.
2. East JE, Gordon M, Nigam GB, et al. British Society of Gastroenterology guidelines on colorectal surveillance in IBD. Gut. 2026.

Before commencing treatment, patients have to be counselled regarding the risks of treatment, including how these risks can be minimised. In patients planning for advanced therapy, a pre-advanced therapy checklist should be completed to ensure treatment suitability, safety screening, and optimisation of baseline investigations (refer to **Appendix 4** for the checklist).

4.2 Pharmacological Treatment

4.2.1 Conventional therapy

a) Steroids

Corticosteroids (CS) are a mainstay of treatment for acute flares of UC and CD. However, systemic CS are associated with adverse effects (AEs) such as moon facies, acne, infection (including an increased risk of abdominal and pelvic abscess in CD patients), ecchymoses,

hypertension, diabetes mellitus, osteoporosis, cataracts, glaucoma and growth failure in children.[38, level III]

Budesonide is an oral CS designed for the treatment of IBD that may reduce systemic AEs due to its extensive (90%) first-pass hepatic metabolism by the cytochrome p-450 enzyme system.[38, level III]

A network meta-analysis (NMA) reporting the safety of oral systemic CS (prednisolone) vs low systemic–bioavailability formulations [budesonide, budesonide multi-matrix system (MMX), and beclomethasone dipropionate] in adults with IBD (31 RCTs, n=5,689) revealed the following:[39, level I]

- Budesonide MMX was associated with significantly fewer CS related AEs compared to:
  - prednisolone: OR=0.25 (95% CI 0.13 to 0.49)
  - beclomethasone dipropionate: OR=0.35 (95% CI 0.13 to 1.00). Furthermore, budesonide MMX did not have significantly fewer AEs than standard budesonide (OR=0.64, 95% CI 0.37 to 1.11) and demonstrated safety on par with placebo.
- Other treatments were less safe than placebo, while budesonide (standard) was safer than prednisolone (OR=0.39, 95% CI 0.27 to 0.57).
- Safety ranking (long-term exposure averaging ~7 months per patient) placed budesonide MMX highest in safety, surpassing all comparators including placebo, according to surface under the cumulative ranking curve (SUCRA) values and network hierarchy.

The overall risk of bias across the included trials was appraised as “high to unclear”.

Based on the 2025 BSG guidelines on IBD in adults, the following are recommended in the use of CS in UC and CD:[40]

- Prednisolone is recommended for induction of remission in moderate to severe UC.
- Budesonide MMX is suggested for the induction of remission in mild to moderate UC for patients in whom 5- ASA induction therapy fails or is not tolerated, and who wish to avoid systemic CS.
- Budesonide is suggested for induction of remission of patients mild to moderate CD for not ≥ 8 weeks.
- Conventional CS is suggested for induction of remission of patients moderate to severe CD for not ≥ 8 weeks.

CS are not recommended for maintenance of remission in patients with CD.

In another NMA compared the efficacy and safety of budesonide-MMX, mesalamine at different doses, and placebo in the treatment of mild to moderate UC, the results showed:[41, level I]

- Induction and endoscopic remission of budesonide-MMX and mesalamine at various doses vs placebo were-
  - budesonide-MMX 9 mg/day OR=2.68 (95% CI 1.75 to 4.10)
  - mesalamine >2.4 g/day OR=2.75 (95% CI 1.94 to 3.90)
  - mesalamine 1.6 to 2.4 g/day OR=2.17 (95% CI 1.55 to 3.05)
  - NS difference between budesonide-MMX and mesalamine (any dose)
- Safety Profile
  - NS difference in serious adverse effects (SAEs) between budesonide-MMX, mesalamine (any dose), and placebo.
- SUCRA ranking: Mesalamine >2.4 g/day ranked highest for overall effectiveness and safety.

The RoB of the included studies were low.

A Cochrane SR comparing different doses of budesonide with placebo or conventional CS for the induction and maintenance of clinical remission in adults with active CD reported the following findings:[42, level I]

- Induction of clinical remission (Week 8)
  - Budesonide 9 mg/day vs placebo: relative risk (RR)=1.93 (95% CI 1.37 to 2.73)
  - Budesonide 15 mg/day vs placebo: RR=2.25 (95% CI 1.35 to 3.76)
  - NS difference for budesonide 3 mg/day vs placebo
  - Budesonide 9 mg/day was less effective than conventional CS RR=0.85 (95% CI 0.74 to 0.97)
- Maintenance of clinical remission (12 months)
  - NS between budesonide (3 mg/day or 6 mg/day) and placebo
- Safety
  - Budesonide 9 mg/day had a better safety profile than conventional CS RR=0.65 (95% CI 0.52 to 0.80)
  - NS difference between budesonide (3, 9, and 15 mg/day) and placebo

b) Immunomodulators

Immunomodulators, such as azathioprine and methotrexate (MTX), modulate the immune response with the aim of maintaining remission and reducing CS dependence in IBD. Due to their delayed onset of action, they are not typically used for rapid symptom control. Additionally, they are used in combination with biologics to reduce immunogenicity and enhance treatment durability.[43,level III]

i) Azathioprine

Azathioprine, a prodrug of 6-mercaptopurine (6-MP), is a thiopurine that exert immunosuppressive effects by inhibiting purine synthesis and reducing lymphocyte proliferation through their active metabolites.[44, level III]

In a Cochrane SR, azathioprine and 6-MP may be more effective than placebo for maintenance of remission in UC (RR=0.66, 95% CI 0.54 to 0.82). There were no AEs reporting done. Overall RoB of the included trials were moderate.[45, level I]

Based on the 2025 BSG guidelines on IBD in adults and the ECCO Guideline on Therapeutics in UC, thiopurines are not suggested for induction of remission but are suggested for maintenance of remission for moderate to severe UC patients who have achieved remission.[40; 46]

Another Cochrane SR comparing azathioprine (at daily doses of 1.0 to 2.5 mg/kg/day) vs placebo in active CD found NS difference in the induction of clinical remission at weeks 12 to 17 (RR=1.23, 95% CI 0.97 to 1.55). Patient on concomitant steroid therapy was associated with a greater likelihood of tapering prednisolone to below 10 mg/day compared to placebo (RR=1.34, 95% CI 1.02 to 1.77), suggesting a potential steroid-sparing effect of azathioprine. Based on Cochrane RoB, the quality of primary papers were moderate.[47, level I]

In one other Cochrane SR, azathioprine was more effective than placebo in maintaining clinical remission over 6 to 18 months (RR=1.19, 95% CI 1.05 to 1.34) in active CD. However, azathioprine was associated with a poorer safety profile than placebo, with significantly higher proportion of patients experiencing AEs (RR=1.29, 95% CI 1.02 to 1.64) and SAEs (RR=2.45, 95% CI 1.22 to 4.90) respectively. Frequently reported AEs include leukopenia, pancreatitis, nausea and allergic reaction.[48, level I]

Based on the 2025 BSG guidelines on IBD in adults, purine analogues are not suggested for use as monotherapy in induction and maintenance of remission for patients with moderate to severe CD.[40] Conversely, American College of Gastroenterology (ACG) Clinical Guideline: Management of CD in Adults suggest azathioprine (at doses of 1.5–2.5 mg/kg/d) and 6-MP (at doses of 0.75–1.5 mg/kg/d) for maintenance of remission in patients with moderately to severely active CD who had induction of remission with CS.[49]

A randomised, double-blind trial (SONIC study) evaluated the efficacy and safety of infliximab monotherapy, azathioprine monotherapy, and their combination in 508 adults with moderate to severe CD who were naïve to immunosuppressive and biologic therapy.[50, level I]

- Primary outcome (week 26, corticosteroid-free clinical remission): Achieved in 56.8% of patients receiving combination therapy, compared with 44.4% receiving infliximab alone (p=0.02) and 30.0% receiving azathioprine alone (p<0.001 vs combination; p=0.006 vs infliximab).
- Mucosal healing at week 26: Observed in 43.9% of patients on combination therapy, versus 30.1% with infliximab alone (p=0.06)

and 16.5% with azathioprine alone (p<0.001 vs combination; p=0.02 vs infliximab).

Among the AEs were serious infections which occurred in 3.9% of patients in the combination therapy group, 4.9% in the infliximab group, and 5.6% in the azathioprine group.

ii) Methotrexate (MTX)

MTX is a folate antimetabolite that inhibits DNA synthesis, repair and cellular replication. It may exert immunomodulatory and anti-inflammatory effects in IBD.[51, level III]

The BSG Guidelines and the ACG Clinical Guidelines Update on IBD in adults suggested against using MTX for induction and maintenance of remission in moderate to severe UC.[40; 52, level III]

A Cochrane SR examining MTX for induction of remission in refractory CD at 16 weeks found evidence from a single large RCT that intramuscular (IM) MTX at a dose of 25 mg/week had significantly increased remission compared to placebo (RR=0.75, 95% CI 0.61 to 0.93). However, NS difference was observed in other included trials. Across placebo-controlled studies, MTX and placebo showed comparable rates of AEs. Nonetheless, the afore mentioned RCT reported a significantly higher rate of treatment discontinuation in the MTX arm (RR=8.00, 95% CI 1.09 to 58.51), primarily due to nausea, vomiting, and elevated liver enzymes. The quality assessment of primary papers were of low risk.[53, level I]

Another Cochrane SR evaluated MTX for maintenance of remission in CD. One RCT demonstrated that IM MTX at a dose of 15 mg/week was significantly more effective than placebo, with (RR=1.67, 95% CI 1.05 to 2.67). NS difference was observed with oral low-dose MTX (12.5 mg/week). Among the AEs reported were nausea and dyspepsia, mild alopecia, mild increase in aspartate transaminase levels, peritoneal abscess, hypoalbuminemia, severe rash and atypical pneumonia. Overall RoB of the included trials were moderate.[54, level I]

The 2025 BSG guidelines on IBD in adults suggested against using MTX for induction and maintenance of remission in moderate to severe CD.40 However, ACG Clinical Guideline: Management of CD in Adults suggested MTX (up to 25 mg once weekly IM or SC) for maintenance of remission in patients with moderate to severe CD who achieved remission with CS induction therapy. If steroid-free remission is sustained for 4 months with parenteral MTX 25 mg once weekly, MTX dose may be reduced to 15 mg once weekly.[52, level III]

In a 50-week, double-blind, placebo-controlled trial, compared MTX and infliximab with infliximab alone in patients with CD who had initiated prednisone induction therapy (15 - 40 mg/day) within the preceding

6 weeks. Findings showed the combination of infliximab and MTX, although safe, was no more effective than infliximab alone in patients with CD receiving treatment with prednisone (30.6% vs 29.8%), (HR=1.16, 95% CI 0.62 to 2.17).[55, level I]

c) 5-aminosalicylic acid (5-ASA)

5-ASA such as mesalazine, exerts its anti-inflammatory effects primarily through a topical action on the colonic mucosa. The mechanism of action is thought to involve inhibition of prostaglandin and leukotriene synthesis, possibly via blockade of cyclo-oxygenase and lipoxygenase pathways. The site of drug release along the GI tract depends on the specific formulation. 5-ASA is available for oral administration (capsules, tablets, or recently in the form of granules) as well as for rectal administration (enema, foam, or suppository).[56]

An NMA evaluated the effectiveness of oral, topical, and combination 5-aminosalicylic acid (5-ASA) therapies compared with each other or placebo in patients with active ulcerative colitis (UC). The analysis demonstrated that several 5-ASA regimens significantly reduced the likelihood of failure to achieve remission compared with placebo.[57, level I]

- For induction of clinical remission vs placebo (≥14 days):
  - combination of oral and topical mesalazine (OR=0.43, 95% CI 0.22 to 0.80)
  - topical mesalazine (OR=0.53, 95% CI 0.45 to 0.61)
  - high-dose oral mesalazine (≥3.3 g/day) (OR=0.80, 95% CI 0.72 to 0.89)
  - standard-dose oral mesalazine (2 g to 3 g/day) (OR=0.84, 95% CI 0.76 to 0.93)
  - standard-dose balsalazide (≥4.6 g/day) (OR=0.80, 95% CI 0.65 to 0.99)
  - subgroup analysis for patients with left-sided colitis or extensive colitis, combined oral and topical mesalazine ranked first with RR of 0.31 (95% CI 0.12 to 0.82) above high dose and standard dose oral mesalazine
  - NS between topical and low dose oral mesalazine
  - subgroup analysis for patients with proctitis and proctosigmoiditis, topical mesalazine ranked first with RR of 0.50 (95% CI 0.39 to 0.63) and was the only efficacious therapy compared to placebo
- For induction of endoscopic remission vs placebo:
  - combined oral and topical mesalazine (RR=0.57, 95% 0.45 to 0.73)
  - topical mesalazine alone (RR=0.58, 95% 0.51 to 0.66)
  - high-dose oral mesalazine (RR=0.67, 95% 0.58 to 0.77)
  - standard-dose oral balsalazide (RR=0.76, 95% 0.65 to 0.88)
  - subgroup analysis for patients with left-sided colitis or extensive colitis, combined oral and topical mesalazine ranked first

(RR=0.61, 95% CI 0.47 to 0.79) with topical mesalazine second (RR=0.64, 95% CI 0.44 to 0.95) and high dose mesalazine third (RR=0.68, 95% CI 0.60 to 0.79)
    - subgroup analysis for patients with proctitis and proctosigmoiditis, the ranking of therapies was combined oral and topical mesalazine, (RR=0.50, 95% CI 0.27 to 0.94), topical mesalazine (RR=0.57, 95% CI 0.49 to 0.67), and high-dose oral mesalazine (RR=0.67, 95% CI 0.49 to 0.90)
- For prevention of relapse for quiescent UC:
    - in subgroup analysis in patients with left-sided or extensive colitis, combined oral and topical mesalazine and topical mesalazine alone were ranked first and second (RR=0.46, 95% CI 0.28 to 0.75 and RR=0.48, 95% CI 0.31 to 0.73, respectively). In patients with proctitis or proctosigmoiditis, topical mesalazine was the only therapy shown to significantly reduce relapse compared with placebo (RR = 0.56, 95% CI 0.42 to 0.76).

The authors concluded that 5-ASAs were "safe and well tolerated, regardless of regimen," whether oral, topical, or combined therapies. The methodological quality of included RCTs was assessed using the Cochrane RoB, with most trials judged to have low to moderate risk of bias."

Based on the ACG Clinical Guideline Update: UC in Adults, the following use of 5-ASAs are recommended for the management of UC.[52, level III]

- Rectal 5-ASA therapies at a dose of 1 g/day for induction and maintenance of remission, in patients with mild to moderate active ulcerative proctitis.
- Rectal 5-ASA enemas at a dose of at least 1 g/day combined with oral 5-ASA at a dose of at least 2.0 g/daily is recommended compared to oral 5-aminosalicylate therapy alone for induction of remission in patients with mild to moderate active left-sided UC.
- Oral 5-ASA at a dose of at least 2.0 g daily to induce remission in patients with mild to moderate active extensive colitis.
- Oral 5-ASA therapy (at least 1.5 g/d) for maintenance of remission in patients with mildly active left-sided or extensive UC.

Based on the ECCO Guideline on Therapeutics in UC: Medical Treatment, the following 5-ASAs usage are recommended in management of UC:[46]

- For induction of remission:
    - oral 5-ASAs at a dose of ≥2 g/day for patients with mild-to-moderate active UC
    - topical (rectal) 5-ASA at a dose of ≥1 g/d for patients with active distal colitis
    - oral 5-ASA (≥2 g/d) combined with topical (rectal) 5-ASA over oral 5-ASA monotherapy for patients with active UC of at least

rectosigmoid extent
- For maintenance of remission:
  - oral 5-ASA at a dose ≥2 g/day for UC patients
  - topical (rectal) 5-ASA for patients with distal UC and doses ranged between 1 g three times weekly and 1 g daily, administered as suppositories or enemas over a period of 12 months to 24 months

A rapid health technology review evaluated the efficacy and safety of mesalamine (5 ASA) compared to no treatment or placebo, and versus alternative therapies including CS and immunosuppressants in active CD:[58, level I]

Induction of Remission (NMA Findings)
- High dose mesalamine vs placebo
  - Overall: OR=2.11 (95% CI 1.39 to 3.31)
  - Subgroup [Crohn's disease activity index (CDAI) 150 to 450]: (OR=2.23, 95% CI 1.15 to 4.16)
- High dose budesonide vs low dose mesalamine
  - OR=3.02 (95% CI 1.25 to 6.78)
- Systemic CS vs mesalamine
  - vs high dose mesalamine: OR=1.83 (95% CI 1.16 to 2.88)
  - vs low dose mesalamine: OR=3.64 (95% CI 1.50 to 8.34)
- NS differences with low dose mesalamine vs placebo: OR=1.05 (95% CI 0.49 to 2.45)
- NS difference with high dose mesalamine vs budesonide (high or low dose)
  - vs high dose budesonide: OR=1.52 (95% CI 0.97 to 2.28)
  - vs low dose budesonide: OR=0.73 (95% CI 0.34 to 1.50)

RCT reported;
- NS differences in remission rates or reduction in mean CDAI scores between mesalamine and budesonide at weeks 2, 4, or 8 (p=0.526)

As for AEs:

In an SR, NS differences in pancreatitis events between mesalamine and azathioprine and no deaths due to drug-induced pancreatitis.

The ECCO Guideline on Therapeutics in CD: Medical Treatment, recommends against the use of 5-ASA for induction of remission and maintenance of CD.[59]

Recommendation 7
Corticosteroids
- Oral systemic corticosteroids (CS) should be used for induction therapy in moderate to severe ulcerative colitis (UC).
- Oral budesonide (controlled-release) may be used to induce remission in mild to moderate UC if 5-aminosalicylic acid (5-ASA) is ineffective.
- Conventional CS therapy or oral budesonide for induction therapy should be limited to short-term use (≤8 weeks) in both UC and Crohn's disease (CD).

Immunomodulators
- Thiopurine should be used as maintenance therapy or as an adjunct with infliximab in moderate to severe IBD.
- Methotrexate (MTX) should not be used as induction and maintenance of remission in UC.
- MTX may be considered in CD as an adjunctive therapy for reducing immunogenicity associated with anti-tumour necrosis factor (anti-TNF) therapy.

5-aminosalicylic acid (5-ASA)
- Topical mesalazine therapies should be used for induction and maintenance therapy in patients with ulcerative proctitis.
- A combination of topical with oral mesalazine should be used for induction of remission, in patients with mild to moderate left sided or extensive colitis.
- Oral mesalazine therapy should be used for maintenance of remission in patients with mild left-sided or extensive UC.
- 5-ASA should not be used in CD.

4.2.2 Advanced therapy

a) Biologics

i. Anti-tumour Necrosis Factor (Anti-TNF)

Among the anti-TNF registered in Malaysia are infliximab and adalimumab. Infliximab is a chimeric monoclonal antibody directed against tumour necrosis factor alpha (TNF-α), in the treatment of moderate to severe IBD.

Adalimumab

Adalimumab is a recombinant human monoclonal antibody directed against tumour necrosis TNF-α used in the treatment of moderate to severe IBD.

A landmark, placebo-controlled trial (ULTRA I) investigated the efficacy and safety of SC adalimumab in patients with moderate to severe UC who were biologic-naïve and refractory to CS and/or immunomodulators.[60, level I]

At week 8, clinical remission rates were:

- 18.5% in the high-dose induction group (adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6),
- 10.0% in the low-dose induction group (adalimumab 80 mg at week 0, 40 mg at weeks 2, 4 and 6), and
- 9.2% in the placebo group

Adalimumab was significantly more effective than placebo at inducing clinical remission at week 8, particularly with the higher induction regimen. There was no difference in AEs or SAEs between adalimumab and placebo.

An open-label extension of the ULTRA I trial evaluated the long-term efficacy and safety of subcutaneous (SC) adalimumab 40 mg every other week in patients with moderate to severe UC. At week 52, the following outcomes were reported:[61, level I]

- Clinical remission - 29.5%
- Clinical response - 53.6%
- Mucosal healing - 46.7%

Among patients who were on CS at baseline, 56.0% achieved CS-free status at week 52, and 26.1% were in clinical remission without CS. No new AEs reported.

CLASSIC-I trial (Clinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease) demonstrated that adalimumab at varying induction doses (at week 0 and 2) was significantly more superior than placebo in inducing remission in anti-TNF naïve patients with moderate to severe CD. Remission rates at week 4 were 36%, 24% and 12% for adalimumab 160 mg/80 mg, adalimumab 80 mg/40 mg and placebo, respectively. Injection site reactions were the most frequently reported AEs in the adalimumab groups. There was NS difference in AEs and SAEs between adalimumab and placebo.[62, level I]

In CLASSIC II, patients in remission at week 4 of CLASSIC I were re-randomised to adalimumab 40 mg every other week, 40 mg weekly, or placebo. Adalimumab was more effective than placebo in maintaining remission through week 56, with remission rates of 79%, 83% and 44%, respectively. Nasopharyngitis, aggravated CD and sinusitis are the most commonly reported treatment-emergent AEs.[63, level I]

The CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial also demonstrated similar findings as CLASSIC II trial in anti-TNF naïve and experienced CD patients. A significantly greater proportion of week-4 responders receiving adalimumab remained in clinical remission compared to those on placebo, based on:[64, level I]

- Maintenance therapy at week 26
  - Clinical remission rates were 40%, 47% and 17% for adalimumab 40 mg every other week, 40 mg weekly and placebo respectively
- Maintenance therapy at week 56
  - clinical remission rates were 36%, 41% and 12% for adalimumab 40 mg every other week, 40 mg weekly and placebo respectively

NS differences in efficacy between different dosing intervals of adalimumab were observed. Treatment discontinuation due to AEs was less frequent with adalimumab than with placebo.

Infliximab

In a landmark study of two trials, Active UC Trials 1 and 2 (ACT 1 and ACT 2), demonstrated that IV infliximab (5 mg/kg or 10 mg/kg) was significantly more effective than placebo in moderate to severe UC patients. The findings for IV infliximab 5 mg/kg, 10 mg/kg and placebo, respectively, were:[65, level I]

-Induction Therapy Outcomes at week 8

- clinical remission rates
  - ACT 1: 38.8%, 32.0% and 14.9%
  - ACT 2: 33.9%, 27.5% and 5.7%
- mucosal healing rates
  - ACT 1: 62.0%, 59.0% and 33.9%
  - ACT 2: 60.3%, 61.7% and 30.9%

-Maintenance Therapy Outcomes at week 30

- clinical remission
  - ACT 1: 33.9%, 36.9% and 15.7%
  - ACT 2: 25.6%, 35.8% and 10.6%
- clinical remission with discontinuation of CS
  - ACT 1: 24.3%, 19.2% and 10.1%
  - ACT 2: 25.7%, 16.4% and 8.9%
- mucosal healing rates
  - ACT 1: 50.4%, 49.2% and 24.8%
  - ACT 2: 46.3%, 56.7% and 30.1%

-Long-Term Outcomes (Week 54, ACT 1):

- clinical remission rates
  - 34.7%, 34.4% and 16.5%
  - 25.7%, 16.4% and 8.9% (with discontinuation of CS)
- mucosal healing rates
  - 45.5%, 46.7% and 18.28%

Safety Profile:

- common AEs: infections
- reported SAEs included:
  - prostatic and rectal adenocarcinoma
  - colonic dysplasia
  - basal-cell carcinoma

In another landmark study in CD patients (ACCENT I), IV infliximab at doses of 5 mg/kg or 10 mg/kg every eight weeks was significantly more effective in achieving clinical response and remission rates compared with placebo for long-term maintenance therapy at week 54 ($p<0.01$). No difference in AEs were reported.[66, level I]

A Cochrane SR of RCTs demonstrated that infliximab, either as monotherapy or in combination with purine analogues (azathioprine or 6-MP), was significantly more effective than placebo or purine analogues alone in inducing clinical remission, clinical response, and in some cases, endoscopic remission in adults with CD.[67, level I]
Key findings were:

- Infliximab doses of 5 mg/kg/day and 10 mg/kg/day vs placebo (week 4)
  - clinical remission RR=4.55 (95% CI 1.53 to 13.50)
  - clinical response RR=4.09 (95% CI 1.63 to 10.25)
- Infliximab 5 mg/kg/day with purine analogues vs purine analogues alone (weeks 24 to 26)
  - clinical remission RR=1.92 (95% CI 1.59 to 2.32)
  - clinical response RR=1.64 (95% CI 1.31 to 2.05) at weeks 26
  - endoscopic remission RR=2.27 (95% CI 1.31 to 3.94)
- Infliximab 5 mg/kg/day vs purine analogues alone (weeks 26)
  - clinical remission RR=1.50 (95% CI 1.15 to 1.95)
  - clinical response RR=1.44 (95% CI 1.13 to 1.82)
  - endoscopic remission NS difference
- Infliximab vs biosimilar
  - clinical remission and response NS difference

NS differences were found in AEs between treatment groups. The overall RoB of included studies was rated as moderate to low.

An observational study (REMSWITCH) evaluated the effectiveness of switching patients with IBD from IV infliximab to SC infliximab. Switching to SC infliximab120 mg every 2 weeks was found to be feasible, safe, and well accepted, and was associated with a low risk of relapse. Relapse was defined as either:

- clinical recurrence [partial Mayo score >2 or Harvey Bradshaw Index (HBI) >4] requiring therapeutic escalation, or
- an increase in fecal calprotectin >150 mg/g compared with baseline

Patients previously treated with standard or moderately intensified IV infliximab regimens (e.g. 5 mg/kg every 8 weeks, 10 mg/kg every 8 weeks, or 10 mg/kg every 6 weeks) maintained good disease control after switching to SC 120 mg every 2 weeks. However, those on very high-intensity IV dosing (10 mg/kg every 4 weeks) had a significantly higher relapse rate when switched to SC 120 mg every 2 weeks. For this subgroup, the authors recommended switching instead to SC infliximab 240 mg every 2 weeks to reduce relapse risk.[68, level II-2]

Golimumab

The Program of UC Research Studies Utilising an Investigational Treatment: Subcutaneous (PURSUIT-SC) study, an integrated phase 2/3 study, analysed the effectiveness and safety of SC golimumab vs placebo administered at week 0 and 2 as induction therapy in anti-TNF naive-patients with moderate to severe UC. The findings showed at week 6:[69, level I]

- proportion of clinical remission rates were 17.8% (p<0.001), 17.9% (p<0.001) and 6.4% for golimumab 200 mg/100 mg, 400/200 mg and placebo respectively
- proportion of mucosal healing rates were 42.3% (p=0.0014), 45.1% (p<0.001) and 28.7% for golimumab 200 mg/100 mg, 400/200 mg and placebo respectively

AE and SAE rates through week 6 were comparable across groups with headache and nasopharyngitis being the most frequently reported events in both golimumab and placebo. UC exacerbation was the most common SAE.

A follow-up RCT (PURSUIT-M) evaluated the efficacy and safety of SC golimumab 50 mg and 100 mg every 4 weeks as maintenance therapy in moderate to severe UC who responded to induction treatment. The results found that at week 54:[70, level I]

- Clinical remission: 27.8% (golimumab 100 mg) vs 15.6% (placebo), p=0.004
- Mucosal healing: 42.4% (golimumab 100 mg) vs 26.6% (placebo), p=0.002
- NS difference between golimumab 50 mg and placebo for either outcome.

SAE occurred in 8.4%, 14.3% and 7.7% of patients on golimumab 50 mg, 100 mg and placebo respectively, while serious infections were reported in 3.2%, 3.2%, and 1.9%, respectively.

ii. Anti-integrin

Vedolizumab

Vedolizumab is a humanised monoclonal antibody that selectively targets gut-specific α4β7 integrin in moderate to severe IBD.

In a landmark study (GEMINI 1), vedolizumab at different intervals was significantly more effective than placebo in bio-naïve and bio-experienced patients with UC based on:[71, level I]

- induction therapy at week 6
  - clinical response rates were 47.1% vs 25.5%
  - clinical remission rates were 16.9% vs 5.4%
  - mucosal healing rates were 40.9% vs 24.8%

- maintenance therapy at week 52
  - clinical remission rates were 41.8%, 44.8% and 15.9% for vedolizumab every 8 weeks, every 4 weeks and placebo respectively
  - mucosal healing rates were 51.6%, 56% and 19.8% for vedolizumab every 8 weeks, every 4 weeks and placebo respectively

No difference in AEs and SAEs between vedolizumab and placebo.

An RCT comparing vedolizumab and adalimumab in bio-naïve and bio-experienced patients with moderate to severe UC demonstrated that the former was superior at week 52 in terms of:[72, level I]

- clinical remission with percentage point difference of 8.8% (95% CI 2.5 to 15.0)
- endoscopic improvement with percentage point difference of 11.9% (95% CI 5.3 to 18.5)

There was NS difference in CS-free clinical remission in the subgroup of patients who were receiving CS at baseline. Exposure-adjusted incidence rates of infections and serious infections were less with vedolizumab than adalimumab (infections, 23.4 vs 34.6 events per 100 patient-years; serious infections, 1.6 vs 2.2 events per 100 patient-years).

iii. Anti-interleukin

Guselkumab

Guselkumab is a dual-acting, human immunoglobulin G (IgG)1, IL-23p19 subunit inhibitor that is effective in the treatment of IBD.

In a landmark study (QUASAR) in moderate to severe UC patients (bio-naive and biologic/JAK inhibitor experienced) guselkumab was significantly more effective than placebo based on:[73, level I]

- induction at week 12 with IV 200 mg every 4 weeks
  - clinical remission with adjusted treatment difference 15% (95% CI 10 to 20)
  - endoscopic remission with adjusted treatment difference 10% (95% CI 10 to 20)
  - histological remission with adjusted treatment difference 22% (95% CI 10 to 20)
- maintenance at week 44
  - clinical remission with SC 200 mg every 4 weeks with adjusted treatment difference 30%, (95% CI 21 to 38) and SC 100 mg every 8 weeks, with adjusted treatment difference 25% (95% CI 16 to 34)
  - endoscopic remission with SC 200 mg every 4 weeks with adjusted treatment difference 17%, (95% CI 9 to 25), SC 100 mg every 8 weeks with adjusted treatment difference 18% (95% CI 10 to 27)
  - histological remission with SC 200 mg every 4 weeks with adjusted treatment difference 33%, (95% CI 24 to 42), SC

100 mg every 8 weeks with adjusted treatment difference 31% (95% CI 22 to 41)

The proportion of patients with AEs was similar across treatment groups. The most frequently reported AEs were worsening UC, COVID-19, arthralgia, headache and upper respiratory tract infection.

In a large multicentre phase 3, randomised, double-blind, placebo-controlled trial (GRAVITI), 347 adults with moderately to severely active CD were assigned to:[74, level I]

- Induction: guselkumab 400 mg SC at weeks 0, 4, 8 → Maintenance: 100 mg SC every 8 weeks, or
- Induction: guselkumab 400 mg SC at weeks 0, 4, 8 → Maintenance: 200 mg SC every 4 weeks, or placebo (with rescue at week 16).
- Findings showed:
  - Week 12
    - Clinical remission: 56.1% vs 21.4% placebo; difference 34.9% (95% CI 25.1 to 44.6).
    - Endoscopic response: 41.3% vs 21.4% placebo; difference 19.9% (95% CI 10.2 to 29.6).
  - Week 48 (maintenance):
    - Clinical remission: 60.0% (100 mg every 8 weeks), 66.1% (200 mg every 4 weeks) vs 17.1% placebo; differences 42.8% (95% CI 31.6 to 54.0) and 48.9% (95% CI 37.9 to 59.9).
    - Endoscopic response: 44.3% (100 mg every 8 weeks), 51.3% (200 mg every 4 weeks) vs 6.8% placebo; differences 37.5% (95% CI 27.3 to 47.7) and 44.6% (95% CI 34.1 to 55.0).
    - Endoscopic remission: 30.4% (100 mg every 8 weeks), and 38.3% (200 mg every 4 weeks) vs 6.0% placebo; differences 24.5% (95% CI 15.2 to 33.9) and 32.4% (95% CI 22.6 to 42.30).
    - Deep remission: 26.1% (100 mg every 8 weeks) and 33.9% (200 mg every 4 weeks) vs 4.3% placebo; differences 21.8% (95% CI 13.1 to 30.6) and 29.8% (95% CI 20.5 to 39.2).
- CS-free outcomes
  - At week 48, 62.5% (100 mg every 8 weeks) and 81.6% (200 mg every 4 weeks) of baseline steroid users were steroid-free vs 18.2% placebo.
  - Of those in clinical remission at week 48, 97.9% had ≥90 days CS-free remission.
- Safety
  - SAEs: 15.5 events/100 patient-years (pt-yrs) (100 mg every 8 weeks), 13.2/100 pt-yrs (200 mg every 4 weeks), vs 37.1/100 pt-yrs (placebo).
  - No active TB, anaphylaxis, or MACE reported.

Two identically designed phase 3, randomised, double-blind, placebo- and active comparator-controlled trials (GALAXI-2 and GALAXI-3) found that guselkumab (200 mg and 100 mg) was effective and safe in the treatment for adults with moderately to severely active CD. Significant findings showed:[75, level I]

- **GALAXI-2**:
  - Clinical response (week 12) + remission (week 48): 55% (guselkumab 200 mg), 49% (guselkumab 100 mg) vs 12% placebo.
  - Clinical response (week 12) + endoscopic response (week 48): 38% and 39% vs 5% placebo.
- **GALAXI-3**:
  - Clinical response + remission: 48% and 47% vs 13% placebo.
  - Clinical response + endoscopic response: 36% and 34% vs 6% placebo.
- In the head-to-head with ustekinumab (pooled data): Guselkumab showed superiority in achieving endoscopic response at week 48.
  - Guselkumab 200 mg group: Adjusted treatment difference vs ustekinumab was 15%.
  - Guselkumab 100 mg group: Adjusted treatment difference vs ustekinumab was 11%.
- Superiority was also demonstrated for endoscopic remission, composite outcomes, and deep remission however not statistically significant.
- CS-free outcomes
  - 90% of patients who achieved remission on guselkumab maintained CS-free remission at week 48.
- SAEs occurred in:
  - 7% of guselkumab 200 mg group (9.7 events/100 pt-yrs)
  - 11% of guselkumab 100 mg group (14.9 events/100 pt-yrs)
  - 12% of ustekinumab group (18.4 events/100 pt-yrs)
  - 15% of placebo group (23.8 events/100 pt-yrs)
- No deaths reported.

Mirikizumab

Mirikizumab is a monoclonal antibody that selectively binds to the IL-23 p19 subunit, inhibiting by interaction with the IL-23R complex.

In a landmark trial (LUCENT-1), mirikizumab (IV 300 mg induction at weeks 0,4 and 8 followed by maintenance SC 200 mg every 4 weeks) vs placebo was used in biologic naïve and/or biologic experienced patients with moderate to severe UC, the significant findings were:[76, level I]

- clinical remission rates were 49.9% vs 25.1%
- endoscopic remission rates were 58.6% vs 29.1%

AEs were similar in both groups during the induction and maintenance therapies.

Another landmark trial of mirikizumab (VIVID-1) in biologic naïve and/or biologic experienced in comparison with placebo during induction and maintenance therapy for moderate to severe CD patients, findings showed:[77, level I]

- Clinical remission rates at week 12 were 37.7% with mirikizumab versus 25.1% with placebo (p<0.001; absolute difference= 12.6 percentage points; 99.5% CI 15.9 to 35.6).
- Endoscopic remission rates at week 52 were 48.4% with mirikizumab versus 9.0% with placebo (p<0.001; absolute difference = 39.4 percentage points; 99.5% CI 1.6 to 12.1).

The incidence of overall AEs and treatment discontinuations was lower with mirikizumab compared to placebo. SAEs events occurred in 10.3% of patients receiving mirikizumab and 17.1% of those on placebo.

Risankizumab

Risankizumab is a monoclonal antibody that selectively binds to the IL-23 p19 subunit, inhibiting by interaction with the IL-23R complex. Risankizumab is not a registered biologic for local use in UC.

In a landmark study (INSPIRE), phase 3, double-blind, placebo-controlled trial, evaluated the effectiveness and safety of risankizumab as induction therapy in patients with moderately to severely active UC. The findings showed:[78, level I]

- Clinical remission at week 12, was higher with risankizumab vs placebo (20.3% vs 6.2%).
- Endoscopic and histologic improvements at week 12 with risankizumab vs placebo. These included:
  - endoscopic remission (10.6% vs 3.4%)
  - histologic-endoscopic mucosal remission (HEMR; 6.3% vs 0.6%)

A landmark rrandomised controlled trial (COMMAND study) evaluated SC risankizumab at doses of 180 mg and 360 mg every 8 weeks versus placebo as maintenance therapy in patients with moderate to severe UC.[79, level I]

- Clinical remission at maintenance:
  - Risankizumab 180 mg: 40.2%
  - Risankizumab 360 mg: 37.6%
  - Placebo: 25.1%
  - Adjusted treatment difference vs placebo: 16.3% and 14.2%, respectively; p ≤ 0.01
- Maintenance of clinical remission (among initial responders):
  - Risankizumab 180 mg: 70.2%
  - Risankizumab 360 mg: 50.0%
  - Placebo: 39.6% (p<0.01 for risankizumab vs placebo)
- Endoscopic remission:
  - Risankizumab 360 mg: 24.3%

- Risankizumab 180 mg: 23.2%
- Placebo: 14.8% (p<0.05)

Rates of serious AEs (events per 100 patient-years [E/100PY]) were lower in the risankizumab groups compared with placebo. Similarly, SAEs were also reduced (RZB180: 1.6; RZB360: 4.0; placebo: 8.0).

Two landmark trials (ADVANCE and MOTIVATE) on varying doses of IV risankizumab vs placebo during induction therapy at week 12 in moderate to severe CD, reported:[80, level I]

- In ADVANCE trial
  - clinical remission rates for risankizumab 600 mg, 1200 mg and placebo were 45%, 42% and 25% respectively.
  - endoscopic response rates in risankizumab 600 mg, 1200 mg and placebo were 40%, 32% and 12% respectively.
- In MOTIVATE trial
  - clinical remission rates in risankizumab 600 mg, 1200 mg and placebo were 42%, 40% and 20%.
  - endoscopic response rates in risankizumab 600 mg, 1200 mg and placebo were 29%, 34% and 11% respectively.

The most frequently reported AEs in both studies (≥5% of patients in any group) groups were headache and nasopharyngitis.

In another landmark trial of SC risankizumab during maintenance therapy at week 52 (FORTIFY) in moderate to severe CD, the significant findings were:[81, level I]

- clinical remission rates for risankizumab 180 mg, 360 mg and placebo were 67% (95% CI 60 to 74), 62% (95% CI 54 to 70) and 48% (95% CI 41 to 56) respectively.
- endoscopic remission rates for risankizumab 180 mg, 360 mg and placebo were 30% (95% CI 23 to 37), 39% (95% CI 31 to 47) and 13% (95% CI 8 to 18) respectively.

AEs and SAEs were similar across three groups.

In a head-to-head trial comparing the efficacy and safety of risankizumab vs ustekinumab in anti-TNF exposure in moderate to severe CD, the findings were:[82, level I]

- NS difference in clinical remission rate at week 24
- endoscopic remission rate at week 48 was 31.8% (95% CI 26.1 to 37.5) vs 16.2% (95% CI 11.8 to 20.7)

The incidence of AEs and SAEs were similar across both groups.

Ustekinumab

Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23).

In a landmark trial (UNIFI) on moderate to severe UC patients (bio-naïve and bio-experienced), ustekinumab of different dosing and intervals were significantly more effective than placebo based on:[83, level I]

- Induction therapy at week 8 -
  - clinical remission rates were 15.6%, 15.5% and 5.3% for intravenous (IV) ustekinumab 130 mg, IV ustekinumab 6 mg/kg and placebo respectively
  - endoscopic remission rates were 26.3%, 27.0% and 13.8% for IV ustekinumab 130 mg, IV ustekinumab 6 mg/kg and placebo respectively
- Maintenance therapy at week 44 -
  - clinical remission rates were 43.8%, 38.4% and 24.0% for SC ustekinumab 90 mg every 8 weeks, every 12 weeks and placebo respectively
  - endoscopic remission rates were 51.1%, 43.6% and 28.6% for SC ustekinumab 90 mg every 8 weeks, every 12 weeks and placebo respectively

The incidence of SAEs (death and cancer) with ustekinumab was similar with placebo.

In another three landmark trials (UNITI-1, UNITI-2 and IM-UNITI), ustekinumab was significantly more effective than placebo for induction and maintenance therapy in moderate to severe CD patients (bio-naïve and/or bio-experienced) based on the following findings:[84, level I]

- Induction therapy at week 6
  - clinical response rates were 34.4%, 33.7% and 21.5% for IV ustekinumab 130 mg, 6 mg/kg and placebo respectively in UNITI-1
  - clinical response rates were 51.7%, 55.5% and 28.7% for IV ustekinumab 130 mg, 6 mg/kg and placebo respectively in UNITI-2
- Induction therapy at week 8
  - clinical remission rates were 15.9%, 20.9% and 7.3% for IV ustekinumab 130 mg, 6 mg/kg and placebo respectively in UNITI-1
  - clinical remission rates were 30.6%, 40.2% and 19.6% for IV ustekinumab 130 mg, 6 mg/kg and placebo respectively in UNITI-2
- Maintenance therapy at week 44
  - clinical remission rates were 53.1%, 48.8% and 35.9% for SC ustekinumab 90 mg every 8 weeks, every 12 weeks and placebo respectively in IM-UNITI

Overall, AEs were similar among treatment groups within each trial.

Recommendation 8
Biologics
i) Anti-TNF
- In moderate to severe inflammatory bowel disease (IBD), infliximab should be used, alternatively adalimumab may be used for induction and maintenance therapy.
- In moderate to severe ulcerative colitis (UC), golimumab may be used as alternative for induction and maintenance therapy.

ii) Anti-Integrin
- In moderate to severe UC, vedolizumab should be used in induction and maintenance therapy.

iii) Anti-interleukin
- In moderate to severe IBD, guselkumab, mirikizumab, risankizumab or ustekinumab should be used for induction and maintenance therapy.

b) Small Molecules
Small molecules therapy such as janus kinase (JAK) inhibitors (tofacitinib and upadacitinib) and selective sphingosine-1-phosphate (S1P) receptor modulator (etrasimod) are used in moderate to severe IBD.

i. Etrasimod
In two independent randomised, multicentre, double-blind, placebo-controlled, phase 3 trials, ELEVATE UC 52 and ELEVATE UC 12, adults with active moderate to severe UC and an inadequate or loss of response or intolerance to at least one approved ulcerative colitis therapy were randomly assigned (2:1) to once-daily oral etrasimod 2 mg or placebo. Findings showed:[85, level I]
- ELEVATE UC 52 (treat-through 52 wks):
  - Week 12 remission: 27.0% etrasimod vs 7.4% placebo; absolute difference 19.8% (95% CI 12.9 to 26.6)
  - Week 52 remission: 32% etrasimod vs 7% placebo; absolute difference 25.4% (95% CI 18.4 to 32.4)
- ELEVATE UC 12 (induction): Week 12 remission: 24.8% etrasimod vs 15.2% placebo; absolute difference 9.7% (95% CI 1.1 to 18.2)

No deaths or malignancies were reported in either trial; overall well-tolerated.

There is currently insufficient published evidence to support the use of etrasimod in CD.

ii. Ozanimod
In a single multicentre, randomised, double-blind, placebo-controlled phase 3 trial (TRUE NORTH), ozanimod 0.92 mg was evaluated vs

placebo as induction and maintenance therapy in adults with moderate to severe UC.[86, level I]

- Induction phase (Week 10):
  - Clinical remission rate: 18.4% with ozanimod vs 6.0% with placebo (95% CI 7.5 to 17.2).
- Maintenance phase (Week 52):
  - Clinical remission rate: 37.0% with ozanimod vs 18.5% with placebo (95% CI 10.8 to 26.4).
  - Endoscopic improvement rate: 45.7% with ozanimod vs 26.4% with placebo (95% CI 11.0 to 27.7).

No deaths or malignancies were reported. The drug was generally well tolerated, with serious infections occurring in <2% of patients in both arms.

Evidence for ozanimod in CD remains limited to support on routine use.

iii. Tofacitinib

Three landmark studies (OCTAVE Induction 1 and 2, and OCTAVE Sustain) evaluated the effectiveness and safety of tofacitinib vs placebo as induction and maintenance therapy in moderate to severe UC. The results were:[87, level I]

- induction therapy at week 8
  - clinical remission rates were 18.5% vs 8.2% in OCTAVE 1 and 16.8% vs 3.6% in OCTAVE 2
  - mucosal healing 31.3% vs 15.6 % in OCTAVE 1 and 28.4% vs 11.6% in OCTAVE 2
- maintenance therapy at week 52 (OCTAVE SUSTAIN)
  - remission rates were 40.6%, 34.3% and 11.1% in tofacitinib 10 mg, 5 mg and placebo respectively
  - mucosal healing rates were 45.7%, 37.4% and 13.1% in tofacitinib 10 mg, 5 mg and placebo respectively

In terms of safety, both AEs and SAEs were comparable between tofacitinib and placebo in all three trials. However, subgroup analysis showed that the rates of overall infection and herpes zoster infection were higher with tofacitinib than with placebo. Apart from that, nonmelanoma skin cancer, cardiovascular events and increased lipid levels were also higher with tofacitinib.

iv. Upadacitinib

Upadacitinib is a JAK inhibitor that is effective in treatment of moderate to severe IBD.

In three other landmark studies comparing upadacitinib vs placebo in bio-naive and bio-experienced patients with moderate to severe UC, the former was significantly more effective on the following outcomes:[88, level I]

- induction at week 8
  - clinical remission rates were 26% vs 5% in U-ACHIEVE substudy 2 and 33% vs 4% in U-ACCOMPLISH
  - endoscopic remission rates were 14% vs 1% in U-ACHIEVE substudy 2 and 18% vs 2% in U-ACCOMPLISH
- maintenance at week 52 (U-ACHIEVE substudy 3)
  - clinical remission rates were 52%, 42% and 12% with upadacitinib 30 mg, 15 mg and placebo respectively
  - endoscopic remission rates were 26%, 24% and 6% with upadacitinib 30 mg, 15 mg and placebo respectively

SAEs were herpes zoster infections and opportunistic infections (OIs). Other AEs reported were nasopharyngitis, worsening of UC, creatine phosphokinase elevation, arthralgia and upper respiratory tract infections (URTI).

Three landmark studies in moderate to severe CD patients (bio-naive and bio-experienced) showed upadacitinib was significantly more effective than placebo based on:[89, level I]

- induction at week 12
  - clinical remission rates of 49.5% vs 29.1% in U-EXCEL and 38.9% vs 21.1% in U-EXCEED
  - endoscopic remission rates of 28.9% vs 7.4% in U-EXCEL and 19.1% vs 2.3% in U-EXCEED
- maintenance at week 52 (U-ENDURE)
  - clinical remission rates were 47.6%, 37.3% and 15.1% with upadacitinib 30 mg, 15 mg and placebo respectively
  - endoscopic remission rates were 28.6%, 19.1% and 5.5% with upadacitinib 30 mg, 15 mg and placebo respectively
  - AEs reported were herpes zoster infection, exacerbation of CD, nasopharyngitis, headache and URTI.

Infection may develop as a complication either related to the disease or its treatment. In an MA, which assessed the incidence rate of OIs in patients with IBD on advanced therapies, the study reported:[90, level I]

- the incidence rate of reported OIs in patients with IBD exposed to advanced therapies was higher (0.42/100 person-years) than those on placebo (0.21/100 person-years)
- the incidence rates were higher in both UC and CD patients exposed to advanced therapies than in patients on placebo (0.41/100 person-years vs 0.16/100 person-years) and (0.42/100 person-years vs 0.23/100 person-years), respectively

However, clinicians should be vigilant in detecting and recognising OIs in IBD and consider balancing the benefits and risks of individual therapies in the medical management of IBD.

Recommendation 9
- Etrasimod, ozanimod, tofacitinib or upadacitinib should be considered for both induction and maintenance therapy for moderate to severe ulcerative colitis.
- Upadacitinib may be used for induction and maintenance therapy for moderate to severe Crohn's disease.

4.2.3 Positioning of Treatment

Selection of biologic therapy in IBD should be guided by a comprehensive understanding of the disease, the range of available therapies, and the patient's treatment history and circumstances particularly whether they are biologic-naïve or biologic-experienced in order to deliver a personalised and effective treatment plan. This decision-making strategy is aligned with current clinical trial evidence and represents a shift from previous practices and other international guideline approaches.

In another NMA on biologic therapies and small molecules for moderate to severe UC, the significant findings:[91, level I]

- Induction of clinical remission vs placebo:
  - upadacitinib OR=9.43 (95% CI 5.12 to 17.37)
  - risankizumab OR=7.28 (95% CI 4.03 to 13.13)
  - guselkumab OR=3.92 (95% CI 1.94 to 7.94)
  - ustekinumab OR=3.51 (95% CI 1.83 to 6.74)
  - infliximab OR=3.28 (95% CI 2.14 to 5.04)
  - tofacitinib OR=3.26 (95% CI 1.74 to 6.09)
  - vedolizumab OR=2.38 (95% 1.30 to 4.35)
  - adalimumab OR=2.28 (95% 1.41 to 3.68)
- Based on SUCRA ranked, upadacitinib was the highest followed by risankizumab, guselkumab, ustekinumab, ozanimod and infliximab.
- Maintenance of clinical remission vs placebo:
  - upadacitinib 30 mg OR=7.87 (95% CI 4.24 to 14.60)
  - upadacitinib 15 mg OR=5.39 (95% CI 2.89 to 10.06)
  - filgotinib 200 mg OR=4.68 (95% CI 2.28 to 9.60)
  - guselkumab 200 mg OR=4.37 (95% CI 2.64 to 7.23)
  - vedolizumab OR=4.18 (95% CI 2.79 to 6.26)
  - tofacitinib OR=4.18 (95% CI 2.37 to 7.38)
  - guselkumab 100 mg OR=3.53 (95% CI 2.13 to 5.84)
  - SC infliximab OR=2.89 (95% CI 1.74 to 4.79)
  - adalimumab OR=2.83 (95% CI 1.74 to 4.59)
  - ustekinumab OR=2.31 (95% CI 1.65 to 3.22)
  - IV infliximab OR=2.07 (95% CI 1.43 to 2.98)
  - risankizumab 180 mg OR=2.00 (95% 1.23 to 3.27)
  - risankizumab 360 mg OR=1.80 (95% 1.10 to 2.93)

- Based on SUCRA ranked, upadacitinib 30 mg was the highest followed by upadacitinib 15 mg, filgotinib 200 mg, guselkumab and vedolizumab.
- Among biologic experienced UC patients, for induction of endoscopic improvement vs placebo:
  - upadacitinib OR=14.87 (95% CI 5.87 to 37.66)
  - ozanimod OR=3.74 (95% CI 1.75 to 8.02)
  - risankizumab OR=3.13 (95% CI 1.79 to 5.47)
  - ustekinumab OR=2.62 (95% CI 1.88 to 3.67)
  - golimumab 400 mg/200 mg OR=2.05 (95% CI 1.42 to 2.95)
  - golimumab 200 mg/100 mg OR=1.82 (95% CI 1.26 to 2.64)
- Among biologic experienced UC patients, for maintenance of endoscopic improvement vs placebo:
  - upadacitinib 30 mg OR=16.02 (95% CI 6.19 to 20.47)
  - upadacitinib 15 mg OR=9.69 (95% CI 3.73 to 25.17)
  - etrasimod OR=8.57 (95% CI 1.92 to 38.36)
  - tofacinitib OR=3.95 (95% CI 2.39 to 6.53)
  - mirikizumab OR=3.92 (95% CI 1.95 to 7.90)
  - vedolizumab OR=3.36 (95% CI 1.63 to 6.93)
  - ozanimod OR= 2.56 (95% CI 1.60 to 4.09)
  - etrolizumab OR=2.35 (95% CI 1.14 to 4.85)
  - ustekinumab OR=2.32 (95% CI 1.69 to 3.20)
  - risankizumab 180 mg OR=2.22 (95% CI 1.35 to 3.64)
- Among biologic naive UC patients, for induction of endoscopic improvement vs placebo:
  - upadacitinib OR=6.80 (95% CI 3.83 to 12.09)
  - risankizumab OR=4.97 (95% CI 2.72 to 9.07)
  - guselkumab 400 mg OR=3.75 (95% CI 1.26 to 11.16)
  - filgotinib 200 mg OR=3.68 (95% CI 1.31 to 10.36)
  - infliximab OR=2.99 (95% CI 2.11 to 4.25)
  - etrasimod OR=2.57 (95% CI 1.54 to 4.30)
  - ustekinumab OR=2.25 (95% CI 1.13 to 4.47)
  - tofacitinib OR=2.07 (95% CI 1.18 to 3.62)
  - etrolizumab OR=3.05 (95% CI 1.48 to 6.29)
  - adalimumab OR=2.11 (95% CI 1.26 to 3.51)
  - golimumab 200 mg/400 mg OR=1.82 (95% CI 1.09 to 3.04)
- Among biologic naive UC patients, for maintenance of endoscopic improvement vs placebo:
  - upadacitinib 30 mg OR=7.07 (95% CI 2.47 to 20.24)
  - risankizumab 360 mg OR=5.93 (95% CI 1.82 to 19.31)
  - etrasimod OR=4.54 (95% CI 1.66 to 12.43)
  - upadacitinib 15 mg OR=4.02 (95% CI 1.41 to 11.45)
  - mirikizumab OR=3.20 (95% CI 1.32 to 7.76)
  - golimumab OR=3.13 (95% CI 1.48 to 6.65)
  - infliximab OR=2.85 (95% CI 1.58 to 5.13)
- Upadacitinib ranked first in induction and maintenance of endoscopic improvement in both biologic naïve and experienced patients.

Based on Cochrane RoB, the primary papers used in this study were of low risk.

In another NMA evaluating biologic therapies for moderate to severe UC, the significant findings:[92, level I]

a) In terms of clinical remission in biologic naïve patients:
   - Clinical remission vs placebo:
     - upadacitinib 45 mg OR=9.59 (95% CI 4.01 to 25.83)
     - ozanimod 0.92 mg OR=4.10 (95% CI 1.60 to 11.35)
     - infliximab 5 mg/kg OR=3.91 (95% CI 2.41 to 6.30)
     - vedolizumab 300 mg OR=3.28 (95% CI 1.44 to 7.92)
     - golimumab 200/100 mg OR=3.23 (95% CI 1.31 to 8.06)
     - infliximab 10 mg/kg OR=3.19 (95% CI 1.74 to 6.05)
     - tofacitinib 10 mg OR=2.29 (95% CI 1.07 to 5.27)
   - Based on SUCRA ranking:
     - upadacitinib 45 mg (97%)
     - infliximab 5 mg/kg (74%)
     - ozanimod 0.92 mg (73%)
     - vedolizumab 300 mg (62%)
   - The median intention to treat (ITT) rates at the end of maintenance treatment:
     - induction therapy of upadacitinib 45 mg with upadacitinib 30 mg as maintenance therapy: 40.6% (95% CI 15.8 to 65.9)
     - induction and maintenance therapy of tofacitinib 10 mg: 39.0% (95% CI 17.6 to 58.6)
     - induction therapy of tofacitinib 10 mg with tofacitinib 5 mg as maintenance therapy: 37.5% (95% CI 16.5 to 57.6)

b) In terms of endoscopic improvement in biologic naïve patients:
   - Endoscopic improvement vs placebo:
     - upadacitinib 45 mg OR=6.93 (95% CI 3.92 to 12.81)
     - ozanimod 0.92 mg OR=3.59 (95% CI 1.93 to 7.00)
     - infliximab 5 mg/kg OR=3.07 (95% CI 2.03 to 4.62)
     - infliximab 10 mg/kg OR=3.05 (95% CI 2.20 to 4.21)
     - vedolizumab 300 mg OR=2.54 (95% CI 1.47 to 4.42)
     - tofacitinib 10 mg OR=2.07 (95% CI 1.23 to 3.69)
     - filgotinib 200 mg OR=2.01 (95% CI 1.13 to 3.70)
     - ustekinumab 6 mg/kg OR=1.88 (95% CI 1.02 to 3.54)
     - golimumab 200/100 mg OR=1.83 (95% CI 1.11 to 3.01)
     - adalimumab 160/80 mg OR=1.59 (95% CI 1.12 to 2.27)
   - Based on SUCRA ranking:
     - upadacitinib 45 mg (99%)
     - ozanimod 0.92 mg (81%)
     - infliximab 5 mg/kg and 10 mg/kg (74%)
   - The median ITT rates at the end of maintenance treatment:
     - induction therapy of upadacitinib 45 mg with upadacitinib 30 mg as maintenance therapy 55.0% (95% CI 28.8 to 73.5)

- induction therapy of upadacitinib 45 mg with upadacitinib 15 mg as maintenance therapy 43.1% (95% CI 18.3 to 66.6)
- induction and maintenance therapy of tofacitinib 10 mg: 42.7% (95% CI 22.1 to 60.6)

c) In term of clinical remission in biologic exposed patients were:
- clinical remission vs placebo:
  - upadacitinib 45 mg OR=9.80 (95% CI 5.23 to 24.98)
  - ustekinumab 6 mg/kg OR=5.90 (95% CI 2.57 to 17.08)
  - tofacitinib 10 mg OR=5.20 (95% CI 2.73 to 12.20)
  - ozanimod 0.92 mg OR=3.49 (95% CI 1.26 to 8.95)
  - filgotinib 200 mg 3.27 (95% CI 1.40 to 7.46)
  - vedolizumab 300 mg 3.19 (95% CI 1.34 to 7.08)
- based on SUCRA ranking:
  - upadacitinib 45 mg (97%)
  - ustekinumab 6 mg/kg (77%)
  - tofacitinib 10 mg (72%)
- the median ITT rates at the end of maintenance treatment:
  - Induction therapy of upadacitinib 45 mg with upadacitinib 30 mg as maintenance therapy: 51.0% (95% CI 26.0 to 73.5)
  - Induction therapy of upadacitinib 45 mg with upadacitinib 15 mg as maintenance therapy: 46.9% (95% CI 22.3 to 71.2)
  - Induction and maintenance therapy of filgotinib 100 mg: 17.7% (95% CI 5.8 to 40.5)

d) In term of endoscopic improvement in biologic exposed patients were:
- Endoscopic improvement vs placebo:
  - upadacitinib 45 mg OR=15.08 (95% CI 6.30 to 43.88)
  - filgotinib 200 mg OR=4.79 (95% CI 2.13 to 12.12)
  - tofacitinib 10 mg OR=3.69 (95% CI 1.53 to 9.58)
  - ustekinumab 6 mg/kg OR= 2.56 (95% CI 1.06 to 6.62)
- Based on SUCRA ranking:
  - upadacitinib 45 mg (99%)
  - tofacitinib 10 mg (80%)
  - ustekinumab 6 mg/kg (72%)
- The median ITT rate at the end of maintenance treatment:
  - induction therapy of upadacitinib 45 mg with upadacitinib 30 mg as maintenance therapy (54.1%, 95% CI 30.8 to 73.9)
  - induction therapy of upadacitinib 45 mg with upadacitinib 15 mg as maintenance therapy (46.6%, 95% CI 23.5 to 69.1)
  - induction and maintenance therapy of tofacitinib 10 mg (21.7%, 95% CI 8.9 to 40.9)

e) In term of safety during induction therapy, based on SUCRA ranking, NS AE reported.

f) In term of safety during maintenance therapy, for all AEs, in comparison with placebo, there were NS for all active comparators except for golimumab 100 mg (OR=1.901, 95% CI 1.04 to 4.45)

Based on PROFILE (Predicting Outcomes for CD using a molecular biomarker) study, in newly diagnosed CD, a top-down strategy (combination of infliximab 5 mg/kg and immunomodulators) vs accelerated step-up approach using conventional therapy (azathioprine, low dose mercaptopurine with allopurinol or MTX). the significant findings at week 48 showed:[93, level I]

- steroid- & surgery free remission rates: percentage difference 64 % (95% CI 57 to 72)
- endoscopic remission rates: percentage difference 23% (95% CI 11 to 36)

The most frequent AEs was a disease flare.

In another NMA on the effectiveness of advanced therapies in the treatment of moderate to severe CD, it showed:[94, level I]

- For clinical remission compared with placebo:
  - guselkumab 200 mg/4 weekly RR=10.86 (95% CI 6.40 to 18.60)
  - mirikizumab 300 mg/4 weekly RR=9.09 (95% CI 4.28 to 18.47)
  - guselkumab 100 mg/4 weekly RR=8.70 (95% CI 5.35 to 14.08)
  - risankizumab 360 mg/8 weekly RR=8.70 (95% CI 4.51 to 6.75)
  - risankizumab 180 mg/8 weekly RR=8.08 (95% CI 4.17 to 15.18)
  - ustekinumab 90 mg/8 weekly RR=7.51 (95% CI 4.63 to 12.02)
  - ustekinumab 90 mg/12 weekly RR=6.62 (95% CI 2.89 to 15.00)
  - adalimumab 40 mg/2 weekly RR=6.27 (95% CI 2.84 to 13.61)
  - upadacitinib 30 mg OD RR=4.07 (95% CI 2.16 to 7.74)
  - upadacitinib 15 mg OD RR=3.14 (95% CI 1.66 to 6.09)
  - infliximab 10 mg/8 weekly RR=3.10 (95% CI 1.40 to 6.65)
- Based on SUCRA ranked, guselkumab 200 mg/4 weekly was the highest followed by mirikizumab 300 mg/4 weekly, guselkumab 100 mg/4 weekly and risankizumab 360 mg/8 weekly.
- For endoscopic remission compared with placebo:
  - guselkumab 200 mg RR=12.71(95% CI 6.84 to 24.31)
  - guselkumab 100 mg/4 weekly RR=10.68 (95% CI 5.83 to 20.01)
  - risankizumab 360 mg/8 weekly RR=9.40(95% CI 4.65 to 19.10)
  - risankizumab 180 mg/8 weekly RR=8.68 (95% CI 4.27 to 17.28)
  - ustekinumab 90 mg/8 weekly RR=6.59 (95% CI 3.56 to 12.19)
  - adalimumab 40 mg/2 weekly RR=5.31 (95% CI 2.15 to 12.75)
  - upadacitinib 30 mg OD RR=4.76 (95% CI 2.37 to 9.76)
  - upadacitinib 15 mg OD RR=3.30 (95% CI 1.62 to 6.73)
- Based on SUCRA ranked, guselkumab 200 mg/4 weekly was the highest followed by guselkumab 100 mg/4 weekly and risankizumab 360 mg/8 weekly.
- In biologic naïve patients for clinical remission, guselkumab 200 mg/4 weekly was superior to:

- vedolizumab 300 mg/ 8 weekly (OR=8.24, 95% CI 2.34 to 28.57)
- infliximab 5 mg/kg 8 weekly (OR=7.97, 95% CI 2.61 to 24.67)
- upadacitinib 15 mg OD (OR=5.77, 95% CI 1.75 to 18.74)
- infliximab 10 mg/kg 8 weekly (OR=5.06, 95% CI 1.72 to 15.45)
- upadacitinib 30 mg OD (OR=4.65, 95% CI 1.36 to14.96)

- In biologic experienced patients for clinical remission, guselkumab 200 mg 4 weekly superior to vedolizumab 300 mg 8 weekly with OR=9.24 (95% CI 2.12 to 42.83).
- In achieving endoscopic response, guselkumab 200 mg 4 weekly was superior to upadacitinib 30 mg OD with OR=4.34 (95% CI 1.15 to 7.22) and upadacitinib 15 mg OD with OR=4.97 (95% CI 1.35 to 19.69).

There were no AEs reported. Quality assessment was done but not reported.

In an another NMA looked at the effectiveness of biologic therapies for achieving endoscopic outcomes in moderate to severe CD, the significant findings were:[95, level I]

- In induction of endoscopic remission:
  - JAK inhibitors with RR=4.63 (95% CI 2.28 to 9.43) and IL23 antagonists with RR=3.40 (95% CI 2.34 to 4.93) and anti-TNF with RR=1.86, (95% CI 1.18 to 2.95) were more effective than placebo
  - among biologic naïve patients, IL23 antagonist with RR=2.53 (95% CI 1.44 to 4.43) was more effective than placebo
  - among biologic experienced patients, anti-IL12/23, anti-IL23 and JAK1 inhibitors were more effective than placebo with RR=8.18 (95% CI 2.85 to 23.50), RR=5.76 (95% CI 3.23 to 10.29) and RR=5.58 (95% CI 2.43 to 12.77) respectively.
  - JAK1 inhibitors was ranked highest followed by anti-IL23 agents
- In maintenance of endoscopic remission:
  - JAK inhibitors with RR=4.96 (95% CI 2.46 to 10.00), IL23 with RR=2.67 (95% CI 1.74 to 4.11) antagonists and anti-TNF with RR=9.14 (95% CI 2.21 to 37.80) were more effective than placebo
  - TNF antagonists ranked highest followed by anti-IL12/23 agents and JAK1 inhibitors

Quality assessment of primary papers was low to unclear risk.

Recommendation 10

- In advanced therapy naive patients with moderate to severe ulcerative colitis, infliximab and vedolizumab should be considered in induction and maintenance therapy. Alternatively, adalimumab, etrasimod, golimumab, guselkumab, mirikizumab, ozanimod, risankizumab, tofacitinib or upadacitinib may be considered.
- In anti-tumour necrosis factor therapy experienced patients with moderate to severe UC, etrasimod, guselkumab, mirikizumab, ozanimod, risankizumab, tofacitinib, upadacitinib or ustekinumab should be given as induction and maintenance therapy.
- In non-fistulising and non-stricturing moderate to severe Crohn's Disease, adalimumab, guselkumab, infliximab, mirikizumab, risankizumab, ustekinumab, upadacitinib or vedolizumab should be given as induction and maintenance therapy.

4.2.4 Special Clinical Subgroups

a) Acute Severe UC

Acute severe UC (ASUC) is a life-threatening medical emergency with considerable morbidity. A multidisciplinary approach, including early surgical input, is crucial for optimal management.

ASUC is diagnosed based on the Truelove and Witts criteria which consist of the presence of bloody stools ≥6 times a day and at least one signs of systemic toxicity (refer **Table 7**).[40]

Table 7: Truelove & Witts Criteria

	Mild	Moderate	Severe
Bloody stools/day with	<4	4-6	>6
Pulse	<90 bpm	<90	>90
Temperature	<37.5 °C	<37.8C	>37.8C
Haemoglobin	>11.5 mg/dL	>10.5 gm/dL	<10.5 gm/dL
ESR	<20 mm/h	<30 mm/h	>30 mm/h
CRP	Normal	<30 mg/dL	>30 mg/dL

Source: Moran GW, Gordon M, Sinopolou V, et al. IBD guideline development group. British Society of Gastroenterology guidelines on IBD in adults: 2025. Gut. 2025;74(Suppl 2):s1-s101

In patients with ASUC, an abdominal radiograph should be performed, and exclusion of CMV and *Clostridium difficile* infections is warranted.[52, level III]

In an MA of 12 observational studies and three RCTs comparing infliximab and ciclosporin as rescue agents in steroid-refractory ASUC, the findings were:[96, level I]

- infliximab had lower colectomy rates than ciclosporin in observational studies at one year (OR=1.84, 95% CI 1.13 to 3.01) and at two years (OR=1.91, 95% CI 1.11 to 3.28) but not at three years; however, there was NS difference in RCTs at the different study end points
- infliximab had lower SAEs than ciclosporin in observational studies (OR=1.80, 95% CI 1.17 to 2.79) but NS in RCTs; however, there was also NS difference in AE and mortality

The risk of bias varied across studies, with RCTs generally having lower risk of bias compared with observational studies.

In an RCT on patients hospitalised with ASUC, tofacitinib (10 mg TDS for seven days), used as an add-on therapy to haematocrit (HCT) 100 mg every six hours, was more effective than HCT alone in terms of:[97, level I]

- improved treatment responsiveness at day seven (OR=3.42, 95% CI 1.37 to 8.48)
- less requirement for both medical (infliximab) and surgical (colectomy) rescue therapies at day 7 (p=0.01) and at day 90 (p=0.003)

Most of the treatment-related AEs were mild.

Based on the BSG guidelines on IBD in adults 2025, the following are recommended in the management of ASUC.[40]

- Hospitalised patients should be treated with high dose IV CS, such as methylprednisolone 30 mg every 12 hours or hydrocortisone 100 mg 6-hourly.
- Patients responding to IV CS should be treated with a purine analogue (azathioprine/mercaptopurine) or suitable maintenance advanced medical therapy.
- Patients not responding to at least 3 days of IV CS, as judged by a suitable scoring system, should be treated with rescue therapy in the form of IV infliximab or ciclosporin. Ciclosporin can be bridged to purine analogues (if naive) or a suitable advanced therapy according to local practice.
- Early referral and communication with specialist colorectal surgical and stoma care teams is advised.
- Patients who have not responded within seven days of rescue therapy with infliximab or ciclosporin, or those with complications (including toxic megacolon, severe haemorrhage or perforation), require subtotal colectomy and ileostomy.
- For patients who do not respond to initial IV CS, an intensified dosing regimen of infliximab should be considered in a select group of patients, especially if serum albumin levels are low.
- Oral JAK inhibitors may be considered in selected patients with ASUC who are CS-refractory and, after careful consideration and counselling of benefits and risks, via an MDT approach.

Based on the ACG Clinical Guideline Update: UC in Adults, the following are recommended in the management of ASUC.[52, level III]

- Testing for *Clostridium difficile* and CMV infection.
- Pharmacologic deep vein thrombosis (DVT) prophylaxis as compared with no prophylaxis to prevent VTE.
- Against routine use of broad-spectrum antibiotics in the management of ASUC.
- Against total parenteral nutrition (PN) for the purpose of bowel rest in ASUC.
- A total of 60 mg/d of methylprednisolone or hydrocortisone 100 mg 3 or 4 times per day to induce remission.
- Patients failing to adequately respond to IV CS by three days, medical rescue therapy with infliximab or ciclosporin.
- Patients who achieve remission with infliximab treatment, maintenance of remission with the same agent.
- Patients who achieve remission with ciclosporin treatment, maintenance of remission with thiopurines or vedolizumab.

The Treatment Algorithms for IBD have recommended to have a combined surgical and medical management in ASUC. When medical treatment is indicated, patient is required to be started on IV hydrocortisone 100 mg QDS or methylprednisolone 40 mg BD, DVT prophylaxis, IV antibiotics if coexisting sepsis and to ensure adequate hydration.[98, level III]

In a case series, 6 anti-TNF exposed patients presented with ASUC was initiated with upadacitinib 45 mg OD following non-response to IV corticosteroid at day 3 using the Oxford Criteria. The following outcomes were reported:[99, level III]

- All patients achieved clinical response using modified Oxford criteria for ASUC (bowel opening <4/day, CRP<15) by day 7 of admission.
- One patient proceeded to colectomy at week 15 due to ongoing disease.
- Four patients (67%) achieved clinical remission and IUS response at week 8.

Among AEs included were colectomy for refractory disease and acne not requiring treatment. NS AEs were identified over the 16-week follow-up.

A pre and post study evaluated the efficacy and safety of upadacitinib 45 mg OD from baseline in 14 ASUC patients who were both biologic naïve and experienced. The findings following 8 weeks of induction therapy showed that:[100, level III]

- Clinical remission rate was 28.6%.
- Endoscopic remission rate was 14.3%.

- Surgical resection rates were 7.1% and 14.3% at week 8 and week 16 respectively.

AEs included herpes simplex virus infection and elevated thrombin time.

Recommendation 11

In patients with acute severe ulcerative colitis (ASUC),

- plain abdominal radiograph should be performed to exclude toxic megacolon, bowel obstruction and perforation
- testing for *Clostridium difficile* and cytomegalovirus infection should be performed
- referral to the surgical team should be made early
- intravenous (IV) corticosteroids (CS) should be initiated and evaluated for response at day three
- those responding to IV CS should be maintained with azathioprine or an appropriate advanced therapy to sustain remission
- those not responding to IV CS should be treated with rescue therapy (IV infliximab or ciclosporin)
- those who achieve remission with IV infliximab should be maintained with the same agent while those on ciclosporin, should be maintained with azathioprine or a suitable advanced therapy
- those not responding to rescue therapy, intensified infliximab dosing, oral janus kinase inhibitors or surgical interventions should be considered
- venous thromboembolism prophylaxis should be given

b) Penetrating Disease (Fistulising Disease)

Fistulas are debilitating complications of CD that affect up to 50% of patients. It can manifest at the perianal region or anywhere in the GI tract. Treating fistulising CD is challenging. The common complications that can arise are mainly abscesses.

In an MA, the effectiveness of medical therapies vs placebo in fistulising CD patients, significant findings were:[101, level I]

- induction of fistula response rates (≥50% closure) were with tacrolimus, anti-TNF and mesenchymal stem cell with (RR=3.82, 95% CI 1.17 to 12.40), (RR=1.45, 95% CI 1.08 to 1.95) and RR=1.27, 95% CI 1.02 to 1.59) respectively
- induction of fistula remission rates was only with anti-TNF (RR=2.01, 95% CI 1.36 to 2.97)
- maintenance of fistula response rates were with anti-TNF and ustekinumab, (RR=1.97, 95% CI 1.34 to 2.89) and (RR=1.82, 95% CI 1.04 to 3.17) respectively
- a combination of anti-TNF with antibiotic (ciprofloxacin) achieved fistula response (RR=1.58, 95% CI 1.09 to 2.28) as compared to anti-TNF alone

In an MA on biologic therapy for induction of fistula response (≥50% closure) and fistula remission (complete closure) in CD, the significant findings were:[102, level I]

- in inducing fistula response,
  - anti-TNF and ustekinumab were more effective compared to placebo with (RR=1.44, 95% CI 1.09 to 1.90) and (RR=1.66, 95% CI 1.10 to 2.51) respectively
  - infliximab was superior to adalimumab with (OR=0.24, 95% CI 0.06 to 0.99) but not significant with other active comparators
- infliximab alone was superior to placebo in inducing fistula remission (OR=0.17, 95% CI to 0.03 0.87)

Based on Cochrane RoB, the primary papers used in this study were of low risk.

In a post hoc analysis of three landmark trials (U-EXCEL, U-EXCEED and U-ENDURE) upadacitinib demonstrated significant efficacy compared to placebo in the management of fistulising CD.[103, level I]

- induction therapy at week 12
  - resolution of drainage in perianal fistulas rates was 44.7% vs 5.6%
  - closure of external perianal fistula opening rates was 22.1% vs 4.8%
  - resolution of drainage of any fistulas rates was 47.7% vs 9.1%
  - closure of any external fistula openings rates was 20.8% vs 6.4%
- maintenance therapy at week 52
  - closure of external perianal fistula opening rates were 18.8%, 16.0% and 0% in upadacitinib 15 mg, 30 mg and placebo respectively
  - closure of any external fistula openings rates were 17.9%, 15.8% and 0% in upadacitinib 30 mg, 15 mg and placebo, respectively

According to BSG, infliximab is recommended as first-line advanced therapy for perianal CD. Patients with inadequate response to infliximab may be offered other advanced therapies.[40]

Recommendation 12

- Infliximab should be used as a first line therapy in induction and maintenance of remission in fistulising Crohn's disease (CD).
- Alternatively, upadacitinib or ustekinumab should be used in fistulising CD patients with inadequate response to infliximab.

c) Extraintestinal Manifestations (EIM)

Up to 50% of patients with IBD will develop at least one EIM (refer Figure 1). The presence of EIM may affect the choice of treatment for IBD.

Based on the ECCO guidelines, there is a need for a multidisciplinary approach when managing EIMs in IBD. The following were highlighted (refer to **Table 8**, **Table 9** and **Table 10**):[8]

- Anti-TNF and JAK inhibitor therapies are recommended for the treatment of axial spondyloarthritis associated with IBD.
- Worsening of existing arthropathy in 35.9% of patients receiving vedolizumab and 22.5% of patients receiving ustekinumab for luminal IBD, with a small proportion also developing new-onset joint disease.
- Treatment with anti-TNF, particularly infliximab, is recommended for the treatment of pyoderma gangrenosum. Other treatments that may be considered include systemic steroids, ciclosporin, ustekinumab, dapsone, metronidazole, and tetracyclines.

Table 8: Management of axial and non-axial spondyloarthritis in IBD

Drug class	Agents	Axial spondyloarthritis	Non-axial spondyloarthritis
5-ASA	Sulfasalazine	✗	✓
Immunomodulator	Azathioprine	✗	✗
	Methotrexate	✗	✓✓
Anti-TNF*	Adalimumab	✓✓	✓✓
	Infliximab	✓✓	✓✓
JAK inhibitor	Tofacitinib	✓	✓✓
	Upadacitinib	✓✓	✓✓
Anti-integrin	Vedolizumab	✗	✗
Anti-IL-12/23	Ustekinumab	✗	✓
S1P-receptor modulator	Ozanimod	✗	✗

*Does not apply for etanercept

✓✓	can be used
✓	may be used
✗	should not be used

Source: Gordon H, Burisch J, Ellul P et al., ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18(1):1-37

Table 9: Diagnosis and management of common cutaneous EIMs in IBD

Classification of EIM	Cutaneous EIM	Diagnostic features	Management
Reactive	Erythema nodosum	Symmetrical, raised, tender, erythematous, or violaceous SC nodules (1–5 cm). Extensor surface of lower limbs (pretibial), head and neck, trunk, arms	• Treat underlying IBD • Supportive: bed rest, elevation, analgesia, compression hosiery • Skin directed: topical CS • Systemic CS (if severe), potassium iodide, dapsone, anti-TNF, hydroxychloroquine
	Pyoderma gangrenosum	Single or multiple erythematous papules/pustules, rapid necrosis to excavating ulcers with irregular violaceous margins and purulent (sterile) material, 2–20 cm, often following trauma (pathergy), secondary infection may occur. Shins and perianal areas most common	• Supportive: wound care, analgesia, avoidance of trauma • Skin directed: topical CS, topical tacrolimus • Systemic: CS, anti-TNF, dapsone, tetracyclines, metronidazole • Severe: IV cyclosporin, anti-TNF, ustekinumab, JAK inhibitors
	Sweet syndrome (acute febrile neutrophilic dermatosis)	Acute onset of tender erythematous papules and nodules on limbs, trunk, head, and neck; varying sizes, associated with fever and neutrophilia	• Treatment of underlying IBD • Skin directed: topical CS • Systemic: CS, immunomodulators, anti-TNF, granulocyte-monocyte apheresis
	Oral lesions	Aphthous ulcers: painful ovoid or round ulcers, labial or buccal mucosa, pseudomembranous base and erythematous margin Periodontitis: swelling, redness, bleeding of gingiva, loose teeth, associated with perianal disease and smoking Periostomatitis vegetans: pustules, haemorrhagic erosions, ulcers Orofacial granulomatosis: recurrent and persistent buccal	• Treat underlying IBD • Antiseptic and anaesthetic mouthwashes • Topical CS • Systemic: CS, anti-TNF

		swelling and oral ulcers, facial palsy, cervical lymphadenopathy	
Specific	Metastatic CD	Extrainstestinal sites: legs, intertriginous areas – facial, genital. Abscess, fistulas, ulcers, nodules	• Topical, intralesional, or systemic CS • Systemic: antibiotics (metronidazole), immunomodulators (azathioprine), anti-TNF
Associated	Hidradenitis suppurativa	Recurrent, painful inflamed skin lesions, developing abscesses and interconnected sinus tracts in flexural sites (axillae, inguinal, perianal)	• Supportive: pain management, wound care • Lifestyle modification: smoking cessation, optimize BMI • Skin directed: topical clindamycin, antiseptic wash • Systemic antibiotics (tetracycline, clindamycin plus rifampicin), retinoids, dapsone, anti-TNF • Surgery in selected cases • Consensus management guidelines are available
Complications	Anti-TNF adverse effects	Paradoxical psoriasis: erythematosus, scaly plaques, pustules, itching and burning; body, scalp, face; flexures > extensors (in contrast to typical psoriasis), palmoplantar pustulosis, nail involvement Eczema-like/psoriasiform eczema: xerosis and itchy, erythematous, ill-defined plaques and vesicles, Staphylococcus superinfection may occur Paradoxical hidradenitis suppurativa: typical HS with recurrent inflamed nodules, abscesses, sinus tracts, fistulae and scarring	Paradoxical psoriasis: • Skin directed: emollients, soap substitutes, topical corticosteroids, vitamin D analogues • Discontinuation of anti-TNF (required in 3–35% of cases) • Systemic: consider ustekinumab if severe or recurrent; acitretin, MTX, or ciclosporin as alternatives Eczema-like and psoriasiform eczema: • Skin directed: emollients, soap substitutes, medical cream, topical CS, topical CS/antibiotic combinations, topical tacrolimus • Systemic treatment: oral antibiotics for *Staphylococcus aureus* superinfections, antihistamines • Discontinuation of anti-TNF if severe and refractory; consider ustekinumab

			Palmoplantar pustulosis: • Skin directed: ultrapotent topical CS (with addition of salicylic acid or coal tar) • Systemic treatment: tetracyclines, acitretin, MTX, or ciclosporin may be considered in severe or refractory cases

Source: Gordon H, Burisch J, Ellul P et al., ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18(1):1-37

Table 10: Diagnosis and management of ocular manifestations of IBD

Ocular EIM	Diagnostic features	Risk of vision loss	Management
Uveitis	Clinical: discomfort or pain, may be bilateral, hyperaemia (especially around the corneal limbus), blurred vision, headache, photophobia. May be associated with intestinal disease activity. Assessment: Slit-lamp examination + ophthalmic imaging, exclusion of infection, and differentiation between anterior, intermediate, posterior, or panuveitis.	Yes	Urgent ophthalmology referral if suspected. First line: local CS in intermediate, posterior, or panuveitis; intravitreal or systemic steroids may also be needed. Second line: systemic CS, steroid-sparing agents, or biologic therapy (anti-TNF).
Scleritis	Clinical: pain (severe, more often at night/waking from sleep), unilateral or bilateral, diffuse or focal/nodular hyperaemia in anterior scleritis; grey may appear white in posterior scleritis. Associated with active intestinal disease. Classification: Anterior (diffuse/nodular), posterior. Does not blanch with topical application of 10% phenylephrine. DDX: episcleritis.	Yes	Urgent ophthalmology referral if suspected. First line: oral NSAIDs or systemic CS (especially for posterior and necrotising). Adjuvant therapy to consider: topical NSAIDs, topical CS, systemic immunomodulators, or second-line immunosuppressants (azathioprine, MTX). Second line: steroid-sparing immunomodulators, biologics (anti-TNF).

Ocular EIM	Diagnostic features	Risk of vision loss	Management
Episcleritis	Clinical: painless or mild discomfort, unilateral or bilateral, hyperaemia. Associated with active intestinal disease. Diagnosis: hyperaemia blanches with topical phenylephrine. DDX: conjunctivitis, dry eye.	No	Treatment of underlying disease, topical lubricants, and cool compresses. Topical NSAIDs may be considered.

DDX - differential diagnosis; NSAID - non-steroidal anti-inflammatory drug

Adapted from: Gordon H, Burisch J, Ellul P et al., ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18 (1):1-37

Recommendation 13
- Inflammatory bowel disease (IBD) patients with extraintestinal manifestations (EIM) should be referred and co-managed with respective specialty.
- Anti-tumour necrosis factor therapy should be considered in patients with IBD with spondyloarthritis and/or reactive cutaneous EIM.
- Vedolizumab and ustekinumab should not be used in axial spondyloarthritis associated with IBD.

4.3 Psychological Assessments and Interventions

Patients with IBD may experience poor quality of life (QoL) and may have anxiety and depressive symptoms.[104, level I] Hence, it is important that the QoL of these patients be regularly assessed for:
- Food-related QoL and diet
- Disability (limitations in activities of daily living)
- Fatigue
- Depression
- Anxiety
- Sexual dysfunction
- Body images

These parameters can be assessed using the IBDQ or short IBDQ (SIBDQ) tools.[105, level III]

Psychological interventions that are shown to be effective in the management of psychological symptoms in patients with IBD include Cognitive Behavioural Therapy (CBT) and Acceptance Commitment Therapy (ACT). In the local healthcare settings, structured CBT and ACT are provided by trained clinical psychologists and referrals may be required by the treating psychiatrists.

4.3.1 Cognitive Behavioural Therapy (CBT)

An RCT compared structured CBT with a wait-list control group in patients with IBD showed that CBT was more effective in improving:[104, level I]

- Disease-specific-QoL (IBDQ with Cohen's d of 0.64 ($p<0.01$)
- Generic QoL (Short-Form (SF-36) Health Survey) on the Mental Component Summary with Cohen's d of 1.089.38 ($p<0.01$)
- Depression by Hospital Anxiety and Depression Scale - Depression (HADS-D) with Cohen's d of 0.48 ($p<0.01$) and Centre of Epidemiological Studies – Depression (CES-D) with Cohen's d of 0.78 ($p<0.01$)
- Anxiety (Hospital Anxiety and Depression Scale - Anxiety (HADS-A) with Cohen's d of 0.58 ($p<0.01$)

4.3.2 Acceptance Commitment Therapy (ACT)

Two high-quality RCTs support the effectiveness of ACT in improving psychological outcomes in patients with IBD.[106 - 107, level I]

In a RCT comparing ACT vs treatment as usual (TAU) group in patients with IBD, showed ACT was more effective in reducing:[106, level I]

- stress (measured by Depression Anxiety Stress Scale (DASS-21)) at weeks 8 and 20, respectively ($p=0.001$)
- depression (DASS_21) ($p=0.010$)

In another RCT compared ACT vs CBT for individuals with IBD and coexistent psychological distress, ACT was more effective in the following outcomes:[107, level I]

- Health-related QoL with mean difference [(MD)=0.07,95% CI 0.01 to 0.12]
- CD activity (MD=-9.43, 95% CI -13.72 to -5.13)

Recommendation 14

- Quality of life assessments should be conducted routinely in patients with inflammatory bowel disease (IBD) to monitor disease impact and guide toward patient-centred management.
- Cognitive Behavioural Therapy and/or Acceptance Commitment Therapy should be considered in patients with IBD to improve psychological outcomes and QoL.

4.4 Non-pharmacological Interventions

Non-pharmacological interventions can play a supportive role in managing IBD. They include dietary modification, faecal microbiota transplantation (FMT), probiotics and exercise, which aim to alleviate symptoms, enhance QoL, and potentially reduce inflammation. These non-pharmacological interventions are further discussed below.

a) Dietary Modification

There is no retrievable evidence on specific adult IBD diet that can be recommended to promote remission in patients with active IBD.

In an open label RCT among adults aged 18–55 years with mild-to-moderate CD assessed the feasibility and effect of CD exclusion diet (CDED) [a whole food diet specifically designed for patients with CD, coupled with partial enteral nutrition (PEN)] on induction and maintenance of remission, compliance, and endoscopic remission. Findings showed:[108, level I]

- clinical remission was achieved in 68% of patients receiving CDED with PEN and 57% with CDED alone at 6 weeks
- 80% maintained remission at 24 weeks
- 35% achieved endoscopic remission

No SAEs or treatment-related AEs were reported in either the CDED with PEN group or the CDED alone group.

The European Society of Parenteral and Enteral Nutrition (ESPEN) guideline, states that there is no “IBD diet” that can be recommended to promote remission in IBD patients with active disease. However, there are a few recommendations that could be used in the management of patients with IBD as outlined below:[109]

Type of IBD	ESPEN Recommendations
Prevention of IBD	
All IBD	• A diet rich in fruit and vegetables, rich in n-3 fatty acids, and low in n-6 fatty acids is associated with a decreased risk of developing IBD. • Ultra-processed food and dietary emulsifiers such as carboxymethylcellulose could be associated with an increased risk of IBD and, therefore, generally, such exclusions can be recommended.
Nutrition Screening	
All IBD	• Patients with IBD are at risk and therefore should be screened for malnutrition at the time of diagnosis and thereafter on a regular basis. • Documented malnutrition in patients with IBD should be treated appropriately because malnutrition worsens the prognosis, complication rates, mortality, and quality of life.
Nutrition Assessment	
All IBD	• In general, energy delivery should be 30 - 35 kcal/kg/day, since the energy requirements of patients with IBD are similar to those of the healthy population. • Protein requirements are increased in active IBD, and intake should be increased (to 1.2 - 1.5 g/kg/day in adults) relative to that recommended in the general population. • The protein requirements in remission are generally not elevated and provision should be similar (about 1 g/kg/d in adults) to that recommended for the general population. • Patients with IBD should be checked for micronutrient deficiencies regularly, including in the remission phase, and specific deficits should be appropriately corrected. • Iron supplementation should be recommended in all patients with IBD when iron deficiency anaemia is present. The goal of iron supplementation is to correct anaemia and normalize iron stores. • Oral iron should be considered as first-line treatment in patients with iron deficiency or mild anaemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron. • IV iron should be considered as first-line treatment in patients with clinically active IBD, those with previous intolerance to oral iron, those with haemoglobin below 100 g/L, and patients who need erythropoiesis-stimulating agent. • All patients with IBD should undergo individual counselling by a dietitian as part of the multidisciplinary approach to improve nutritional therapy and avoid malnutrition and nutrition-related disorders.
Dietetic Recommendation in Active Disease	
All IBD	• There is no “IBD diet” that can be generally recommended to promote remission in patients with IBD with active disease.
	• Patients with IBD (adults and children) with active disease, under treatment with CS, or with suspected hypovitaminosis D, should be monitored for serum 25 (OH) vitamin D status, and if required calcium/vitamin D supplementation should be prescribed for prevention of low bone mineral density. Osteopenia and osteoporosis should be managed according to current osteoporosis guidelines.
	• Patients with IBD with hyperoxaluria often also have fat malabsorption and these patients should be counselled regarding fat malabsorption.
CD	• In adult patients, CD Exclusion Diet can be considered with or without enteral nutrition (EN) in mild to moderate active CD.
	• CD can be accompanied by malabsorption or maldigestion, and dietary counselling may consider this.

	• In patients with CD with intestinal strictures or stenosis in combination with obstructive symptoms, a diet with adapted texture, or exclusive EN via a tube ending distal to the obstruction (post-stenosis) can be recommended.
Medical Nutrition Therapy in Active IBD	
All IBD	• Oral nutritional supplement (ONS) is the first step when medical nutrition is indicated in IBD, as supportive therapy in addition to normal food.
	• If oral feeding is not sufficient then EN can be considered as supportive therapy. EN using formulas or liquids usually take preference over PN unless it is completely contraindicated.
	• In patients with IBD in whom nutritional deprivation has extended over many days, standard precautions and interventions to prevent refeeding syndrome should be considered, particularly with respect to phosphate and thiamine.
	• For EN in IBD, nasal tubes or percutaneous access can be used.
	• Tube feeding in IBD should be preferentially administered via an enteral feeding pump, in particular, if EN is administered via a jejunal and not a gastric tube.
	• Tube feeding in IBD should be preferentially administered via • an enteral feeding pump, in particular, if EN is administered via a jejunal and not a gastric tube.
	• Standard EN (polymeric diet with moderate fat content) should be employed for primary and supportive nutritional therapy in active IBD.
	• Specific formulations or substrates (e.g. glutamine, n-3-fatty acids) should not be recommended in the use of EN or PN in patients with IBD
UC	• Primary nutritional therapy (EN or PN) should not be recommended in adults or children with UC.
	• EN appears safe and can be recommended as supportive therapy according to standard nutritional practice in patients with severe UC.
	• PN may usually not be used in UC unless the patient cannot be fed effectively otherwise.
CD	• PN shall be performed in IBD (i) when oral nutrition or EN is not sufficiently possible (e.g. when the GI tract is dysfunctional or in patients with CD with short bowel), (ii) when there is an obstructed bowel where there is no possibility of placement of a feeding tube beyond the obstruction or where this has failed, or (iii) when other complications occur such as an anastomotic leak or a high output intestinal fistula.
	• IBD patients with severe diarrhoea or a high output jejunostomy or ileostomy should have fluid output and urine sodium monitored, and fluid input can be adapted accordingly (decrease hypotonic fluids and increase saline solutions, but also limit hypertonic fluids), with consideration of food intolerances that may enhance fluid output.
	• Parenteral infusions (fluid and electrolytes) can be needed in the case of ongoing high output stomas.
	Patients with CD and with a distal (low ileal or colonic) fistula and low output can usually receive all nutritional support via the enteral route (generally as food).
	• Patients with CD and with a proximal fistula and/or a very high output should receive nutritional support by partial or exclusive PN.
CD	• Exclusive EN is effective and can be recommended as the first line of treatment to induce remission in children and adolescents with mild active CD.

Dietetic and other recommendations specific for the remission phase	
All IBD	• Patients should follow the principles of healthy dietary patterns and avoid individual nutritional triggers. If particular clinical problems are still present during the remission phase, the diet should be adjusted accordingly.
	• Selected IBD patients, e. g. those treated with sulphasalazine and MTX should be supplemented prophylactically with vitamin B9/folic acid.
	• Neither EN nor PN can be recommended as primary therapy for maintaining remission in IBD.
	• Patients with IBD and obesity should be advised to reduce weight only in phases of stable remission and then according to current obesity guidelines
CD	• When more than 20 cm of the distal ileum, whether or not in combination with the ileocecal valve, is resected, or when vitamin B12 deficiency is documented, vitamin B12 should be administered to patients with CD.
	• ONS or EN can be recommended in patients with CD in remission if malnutrition cannot be treated sufficiently by dietary counselling.

- All patients with IBD who are at high risk of malnutrition should be referred to a dietitian for individualised nutritional assessment and medical nutrition therapy, as part of a multidisciplinary approach to improve nutritional status.
- In adult patients, Crohn's disease (CD) exclusion diet may be considered with or without enteral nutrition (EN) in mild to moderate active CD.

Recommendation 15
- Patients with inflammatory bowel disease (IBD) should be screened for malnutrition at the time of diagnosis and at regular intervals.
- Nutritional support should be provided in the form of enteral or parenteral nutrition in malnourished IBD patients.

b) Faecal Microbiota Transplantation

Faecal Microbiota Transplantation (FMT) is a procedure that involves transferring healthy donor stool containing beneficial bacteria into the patient's gut. The goal is to restore balance of gut microbiota, potentially control intestinal inflammation and treat various GI conditions.

A Cochrane SR compared the effectiveness and safety of FMT and control in IBD:[110, level I]
- In UC, FMT induced clinical remission at 6 - 12 weeks follow-up with RR of 1.79 (95% CI 1.13 to 2.84) and endoscopy remission at 8 - 12 weeks follow-up with RR of 1.45 (95% CI 0.64 to 3.29); the outcomes were based on low certainty of evidence in GRADE.
- In CD, none of the included studies reported data on the use of FMT for induction of remission.

- There was NS clinical and endoscopic remission in maintenance for both UC and CD with very low certainty evidence.
- There was NS difference in SAEs* and any AE** between FMT and control based on very uncertain evidence.

*AEs of a serious nature included infections, pneumonia, small bowel perforation and worsening of UC that required IV steroids or surgery.
**AEs commonly reported include abdominal pain, nausea, flatulence, bloating, headaches and dizziness.

In an MA on adults with UC, FMT was demonstrated to have better outcomes compared with control in terms of:[111, level I]

- clinical remission with RR of 1.73 (95% CI 1.41 to 2.12)
- endoscopy remission with RR of 1.74 (95% CI 1.24 to 2.44)

There was NS difference in safety profile between FMT and control. RoB in the primary papers based on Cochrane RoB was low to moderate.

c) Probiotics

Patients with IBD may have altered and/or reduced gut microbiota. Probiotics are live microorganisms that may have beneficial effects on the gut. There are many strains (Saccharomyces, Bifidobacterium, Lactobacillus, VSL#3 etc) of various dosage which have been studied in RCTs in IBD.

A SR assessed the efficacy of adjunctive probiotic therapy alongside standard treatment in patients with inactive to mild IBD, findings showed:[112, level I]

- one small study showed reduced clinical relapse (CDAI score <150) with the use of *Saccharomyces boulardii* (1g daily) (p=0.04)
- there were higher remission rates in mild UC, shown by improvement in clinical activity (p<0.001) and histological findings (p<0.05). VSL#3** was the most effective probiotics strain for mild UC

Probiotic treatment was well-tolerated in all patients, with no AEs reported. The primary studies included in this review were generally assessed as having a low RoB based on the Cochrane RoB.

d) Exercise

Exercise interventions among patients with IBD as an adjunct may improve symptoms and QoL. Among the physical activities studied below in patients with IBD include:

i. low to high intensity interval trainings
ii. endurance and muscle trainings
iii. aerobics
iv. resistance exercises
v. walking

In a SR on usual care plus either exercise vs no exercise in inactive/ quiescent to mild IBD patients, it reported:[113, level I]

- three walking sessions/week over three months improved IBDQ score ($p<0.05$) and HBI score ($p<0.01$)
- supervised moderate intensity outdoor running over ten weeks improved IBDQ score ($p<0.004$)
- a 12-week personalised exercised program showed improve fatigue and Health -Related QoL, ($p<0.001$) respectively

Quality assessment using the Cochrane RoB tool 2 (RoB 2) and the Newcastle-Ottawa Scale (NOS) showed most primary papers had low RoB.

- FMT appears to be a promising treatment option for induction of remission in UC. However high quality of evidence is required before it can be recommended in IBD.
- Probiotics and exercise may be considered as adjunct therapies in IBD.

5. TRADITIONAL AND COMPLEMENTARY MEDICINE

Alternative and supplementary therapies have been used as adjunct treatment in patients with IBD. These include the use of herbal supplements e.g. curcumin, saffron and cannabis. Other non-conventional therapies include probiotics, exercise and acupuncture.

5.1 Curcumin

Curcumin is an extract from turmeric with known anti-inflammatory properties.

In a SR on curcumin (0.45 g to 3 g per day) vs placebo among patients with IBD receiving standard treatment, the findings were as follows:[114, level I]

- rate of remission using Simple Clinical Colitis Activity Index Questionnaire (SCCAIQ) was higher in the curcumin group (54% to 83.9% vs 0 to 43.8%)
- the number of relapses was lower in the curcumin group (4.65% vs 20.51%)
- curcumin was well-tolerated with only 7.8% of patients experiencing mild AEs (e.g. bloating and nausea)

The primary papers were at high RoB based on the Cochrane Handbook for bias analysis.

5.2 Saffron

Saffron is a spice from the flower of dried stigmas of Crocus Sativus and has anti-oxidant and anti-inflammatory properties.

An RCT on saffron 25 mg – 200 mg vs placebo among mild to moderate UC patients receiving TAU showed symptom improvement with the mean SCCAIQ score after 8 weeks (-0.82 ± 1.05 vs -0.02 ± 1.31, p= 0.004).[115, level I]

5.3 Medical Cannabis

Medical cannabis is a plant-based supplement derived from marijuana and is available in various forms. It contains tetrahydrocannabinol or delta-9-tetrahydrocannabinol, which may help in relieving GI symptoms e.g. nausea and reduction in intestinal motility and improvement in QoL among patients with IBD.

A MaHTAS executive summary on use of medical cannabis in IBD reported:[116, level I]

- cannabis improved QoL and symptoms, reduced length of stay and risk of parenteral nutrition
- it did not induce clinical remission, inflammatory markers, flares and complications

- there was insufficient evidence to support the use of medicinal cannabis products as a disease modifying medication

5.4 Alternative Therapies

5.4.1 Acupuncture ± Moxibustion

Acupuncture ± moxibustion is a widely used Chinese traditional medicine that may help in the improvement of the QoL in patients with CD.

In a MA on the use of acupuncture with moxibustion vs placebo among mild CD patients on TAU, findings showed improvement in CDAI score (OR=3.23, 95% CI 1.43 to 7.30) with mild AEs reported e.g. scald, ecchymoma, mild burn and SC haematoma. Most of the primary papers based on Cochrane RoB had some concerns with regards to its risk assessment.[117, level I]

- It should be emphasised that the use of alternative and supplementary therapies to complement standard treatment of IBD needs to be further studied.
- Patients should continue with standard treatment even if they wish to use alternative or supplementary therapies in IBD.

6. SURGICAL TREATMENT

Surgical intervention plays an essential role in the comprehensive management of IBD, particularly in patients with UC or CD who develop complications or fail medical therapy.

The goals of surgical treatment in IBD include symptom control, management of complications (e.g., strictures, fistulas, perforation), and reduction of malignancy risk, while preserving QoL and minimising postoperative morbidity. Safe and effective surgical techniques are tailored to disease severity, location, patient comorbidities and treatment history.

6.1 Emergency Surgery

Emergency surgery remains a critical component in the management of IBD, particularly in life-threatening or medically refractory scenarios. Despite advances in biologic and immunomodulatory therapies, a subset of patients with UC or CD may develop complications requiring urgent surgical intervention. Recognition of appropriate surgical indications and timely multidisciplinary collaboration are essential to improve outcomes and reduce morbidity and mortality.

6.1.1 Indications for Emergency Surgery

The ECCO Guidelines and expert consensus provide clear criteria for when surgery is necessary in emergencies.[118]

a) Acute Severe Ulcerative colitis (ASUC)

- Surgery should be considered in those who fail to show clinical improvement or deteriorate within 48 – 72 hours after initiating first-line medical therapy.
- Failure of rescue therapy (e.g., ciclosporin or infliximab) warrants early surgical consultation and planning.
- Immediate surgery is mandatory in cases of:
  - Free perforation
  - Life-threatening haemorrhage
  - Hemodynamic instability
  - Generalised peritonitis
- Recommended procedure: Subtotal colectomy with end ileostomy is the procedure of choice in ASUC when life-threatening complications or treatment failure occur.

b) Toxic Megacolon

- Surgery is indicated if complicated by:
  - Colonic perforation
  - Massive bleeding with hemodynamic instability
  - Clinical deterioration despite 24 – 48 hours of medical therapy

c) Uncontrolled GI Haemorrhage

- In stable patients:
  - Initial localisation via upper and lower GI endoscopy
  - If bleeding persists: CT angiography to guide further treatment
- In unstable patients:
  - Immediate surgery is required when haemorrhage causes hemodynamic compromise

d) Free Perforation

- Surgical exploration is indicated with radiological evidence of pneumoperitoneum and free intra-abdominal fluid is seen.

e) Intestinal Obstruction

- Surgery is necessary for symptomatic strictures unresponsive to medical therapy and not amenable to endoscopic dilatation.

6.1.2 Surgical Approach to Emergency IBD Surgery

- Laparotomy is preferred in hemodynamically unstable patients.[118]
- Laparoscopic surgery may be considered in hemodynamically stable patients, provided appropriate surgical expertise is available.[118]

6.2 Elective Surgery

Patients with IBD who do not fulfil the criteria for emergency surgery may also require surgical intervention. A multidisciplinary approach should be employed to guide decision-making and optimise perioperative outcomes when elective surgical intervention is needed.

6.2.1 Elective Surgery in UC

a) Indications

In an evidence-based guideline, elective surgical intervention is indicated in the following clinical scenarios:[119]

- **Medically Refractory Disease**
  - Patients who fail to respond to optimised medical therapy
  - For patients treated with high-dose CS or advanced therapy, a staged surgical approach is recommended, typically involving subtotal colectomy with end ileostomy followed by completion proctectomy and ileal pouch anal anastomosis (IPAA)
- **UC-Associated Colorectal Neoplasia**
  Patients with confirmed or suspected dysplasia or colorectal cancer should undergo timely endoscopic evaluation for early detection and surveillance (Refer **Chapter 8.4**).

6.2.2 Elective Surgery in CD

a) Indications

The following are indications for elective surgery in CD.[122 - 123]

- **Medically Refractory CD**
- **Inflammatory Indications**
  - In severe acute colitis unresponsive to medical therapy or with signs of perforation.
- **Strictures**
  - Localised ileocecal CD with obstructive symptoms and minimal active inflammation.
  - Colonic strictures that are not adequately surveyable via endoscopy.
  - However, endoscopic dilation is appropriate for short-segment, non-inflammatory, symptomatic small bowel or anastomotic strictures.
- **Penetrating Disease**
  - Free perforation warrants immediate surgical resection.
  - Abscesses may initially be managed with antibiotics and/or drainage, followed by interval elective resection.
  - Persistent enteric fistulas despite medical therapy should be considered for surgical management.
- **Haemorrhage**
  - Stable patients may undergo endoscopic or radiologic intervention, but for unstable patients' urgent surgical management is required.
- **CD-Related Colorectal Neoplasia**
  - Patients with long-standing Crohn's colitis involving ≥1/3 of the colon or multiple segments require regular endoscopic surveillance.
  - Visible dysplasia that is completely excised should be monitored with surveillance.
  - Visible dysplasia not amenable to excision, invisible dysplasia surrounding a lesion, or colorectal adenocarcinoma should prompt pan-proctocolectomy with or without IPAA.
  - Invisible dysplasia should be re-evaluated by an experienced endoscopist within 3 – 6 months.
- **Growth Retardation in Childhood**
  - In prepubertal or pubertal patients with reduced height velocity over 6 – 12 months despite optimal medical and nutritional therapy, elective surgery may be considered.

b) Surgical Considerations and Approach in CD

- Laparoscopic techniques should be considered where expertise is available.
- The extent of mesenteric excision remains controversial; individualisation based on disease characteristics is advised.
- Colonic disease with rectal sparing

- segmental colectomy may be considered for localised disease.
- total colectomy is advised for more extensive disease.

- Surgical approach for rectal disease
  - Pan-proctocolectomy with end ileostomy or proctectomy with colostomy should be performed in most cases.
- Pan-proctocolectomy with IPAA may be considered in select patients with colonic CD and no perianal or small bowel disease, acknowledging a higher long-term pouch failure risk.
- Anastomotic Techniques Post-Ileocecal Resection;
  Side-to-side, side-to-end, or end-to-end anastomosis, either handsewn or stapled, may be chosen based on the surgeon's preference and experience.

6.3 Perianal CD

This condition is a common complication in CD, presenting either as an emergency (e.g., perianal abscess) or a chronic condition (e.g., complex perianal fistula). Management strategies must consider disease severity, patient stability and long-term outcomes. Emergency treatment aims to control sepsis and avoid fistula formation, while elective strategies aim for durable healing of complex fistulae using both surgical and emerging biologic methods.

6.3.1 Emergency Management of Perianal Sepsis

In the emergency treatment of perianal fistulising CD, the following are recommended:[118]

- The aim of surgery is to treat the sepsis by draining the abscess.
- No active probing should be performed to identify a fistula during initial drainage of a perianal abscess.
- If a fistula is visually apparent during abscess drainage, a fistulotomy should not be performed. A loose draining seton should be inserted instead.
- There is no role for additional surgical fistula treatment (e.g. advancement flaps, seton drainage) during emergency surgery.
- Assessment of the rectum for signs of proctitis should be performed during abscess drainage, when feasible.

6.3.2 Elective Management of Complex Perianal Fistula

For elective surgical management in treating perianal fistula, the ECCO guideline on surgical treatments recommended the following:[124]

- therapeutic options such as advancement flaps, ligation of the intersphincteric fistula tract, and fibrin glue can be considered for complex fistula treatment.
- allogeneic adipose-derived stem cell therapy may be effective and safe in the treatment of complex perianal fistulae.
- autologous adipose-derived stem cells may show potential benefits with acceptable safety and tolerability.

- in cases of pelvic sepsis unresponsive to other therapies, a diverting stoma may control symptoms and local infection. However, healing rates and the likelihood of stoma reversal remain low.

6.4 Peri-operative Care in IBD

Preoperative optimisation in patients with IBD is essential to minimise perioperative complications and improve surgical outcomes. Many patients undergoing surgery for IBD are malnourished, immunosuppressed, or experiencing active disease, all of which can increase surgical morbidity. Targeted interventions can significantly enhance recovery and reduce postoperative complications.[120 - 124]

Based on evidence-based guidelines, the use of preoperative interventions targeting nutrition, medications, and thromboembolic risk can significantly enhance recovery and reduce complications, particularly in those undergoing restorative procedures such as IPAA. Components of preoperative optimisation include:[120 - 124]

a) Nutritional and Hematologic Optimisation

- Correction of altered body composition and nutritional imbalances is recommended prior to surgery.
- Patients should undergo a nutritional evaluation and be provided enteral or parenteral nutritional support if malnourished (refer to **Chapter 4.4a**).
- Iron supplementation is advised in patients with iron-deficiency anaemia to improve hematologic status and reduce transfusion requirements.
- Smoking cessation should be encouraged.

b) Corticosteroid Management

- Patients receiving >20 mg of prednisolone daily for >6 weeks are at increased risk of early postoperative and pouch-related complications.
- Weaning off CS is strongly recommended prior to elective surgery.
- If CS weaning is not feasible, postponement of elective surgery should be considered until dose reduction is achieved.

c) Immunomodulators and Biologic Therapy

- Preoperative use of immunomodulators such as thiopurines or ciclosporin is not associated with increased risk of postoperative complications and can be continued if clinically indicated.
- Patients on biologics might be at increased risk of developing early and late pouch-specific complications; therefore, a three-stage or two-stage modified approach with deferred pouch construction could be considered under these circumstances.

d) Venous Thromboembolism (VTE) Prophylaxis

All surgical IBD patients should receive VTE prophylaxis, including both mechanical and pharmacologic measures, as appropriate for their risk profile.

Recommendation 16

- A multidisciplinary approach should be employed to guide decision-making and optimise perioperative outcomes when elective surgical intervention is needed in inflammatory bowel disease (IBD) patients.
- Laparotomy should be the preferred approach in patients with IBD who are hemodynamically unstable.
- Laparoscopic surgery may be considered in hemodynamically stable patients with IBD, provided appropriate surgical expertise is available.
- In patients with perianal Crohn's disease (CD) requiring emergency treatment, controlling sepsis through drainage and appropriate antibiotic therapy should be prioritised.
- Early referral to a colorectal surgeon should be considered in patients requiring surgery.

7. OTHER CONSIDERATIONS

7.1 Vaccination

A vaccination history is recommended before starting any immunosuppressive treatment. The general recommendations for vaccination follow the Malaysian Immunisation Programme (Kementerian Kesihatan Malaysia, updated version 2023). All suitable vaccinations should be given as soon as possible, ideally before starting immunosuppressive treatment. However, urgent immunosuppressive treatment should not be delayed while awaiting vaccination completion.

Consensus and evidence-based guidelines have recommended the following vaccines in patients with IBD as in **Table 11**.[24; 125 - 126, level III]

Table 11: Recommended Vaccinations (Inactivated and Live Vaccines) for Patients with IBD

Vaccines	Remarks
Inactivated Vaccine	
*Haemophilus influenza type b	Recommended in unimmunised patients
*Hepatitis B	Achieve antibody response >10 IU/L
*Pneumococcal	Recommend booster five years after first dose
*Tetanus, reduced Diphtheria, acellular pertussis/tetanus and diphtheria T(dap/DT)	
*Human Papillomavirus (HPV)	Pap smear for HPV screening is recommended for female patients.
Influenza	Recommended yearly.
Recombinant Herpes Zoster (RZV)	Regardless of age, the recombinant zoster vaccine is recommended. Highly recommended if patients are on small molecule.
Meningococcal	Recommended for adults with high-risk medical conditions (refer to Guidelines for Adult Immunisation, 3rd Edition; Malaysian Society of Infectious Diseases and Chemotherapy)
Live Vaccine	
*Measles, Mumps, Rubella (MMR)	Recommended to be given prior to immunosuppressive treatment. **Contraindicated in patients on immunosuppressive treatment

*Please check vaccination records as these vaccinations are given as per the National Immunisation Programme

**Live Vaccines (BCG, MMR, rotavirus) are contraindicated in patients who are already on immunosuppressive treatment (steroids ≥ 20 mg/day or equivalent for ≥ 2 weeks, high dose thiopurines or MTX, biological therapy and tofacitinib).

The BSG consensus guidelines on the management of IBD in adults recommended that live vaccines should be given at least four weeks before commencing immunosuppressives or biologic treatment.

However, if immunosuppressive treatment has been given, live vaccines should not be given until at least 3 months after discontinuing the immunosuppressive treatment.[37, level III]

In an evidence-based guideline, immunisation of close-contacts, including household contacts known as the *cocoon strategy*, is recommended to protect immunosuppressed patients.[24]

Most vaccinations are safe and effective in patients with IBD. In an MA, the safety of immunisation in patients with IBD showed:[127, level II-2]

- mild AEs (pain, swelling and erythema) (OR=0.24, 95% CI 0.09 to 0.42)
- mild adverse systemic reactions (myalgia, arthralgia, fatigue, headache, nausea, chills and fever) with OR= 0.16 (95% CI 0.06 to 0.29)
- risk of developing AEs following immunisation was highest after RZV vaccination (local OR=0.75, 95% CI 0.63 to 0.84 and systemic OR=0.57, 95% CI 0.45 to 0.68)
- minimal risk of flare following vaccination OR=0.02 (95% CI 0.01 to 0.04)

7.1.1 COVID-19 Vaccination

COVID-19 vaccination, including booster doses, is beneficial for all individuals, including patients with IBD. It was found to be effective and safe with minimal risk of flares.

A population-based cohort study on the effectiveness of COVID-19 vaccination in patients with IBD showed NS difference in the following comparisons:[128, level II-2]

- risk of COVID-19 infection between vaccinated patients with IBD and controls
- time to disease flare between vaccinated and non-vaccinated patients with IBD
- time to first COVID-19 infection between patients with IBD on anti-TNF and/or CS vs all other patients with IBD

A cohort study in patients with IBD reported the following AEs of COVID-19 vaccination:[129, level II-2]

- local AEs (e.g. redness, pain, itching, swelling, tenderness, warmth at injection site) within 7 days after vaccination were mild after each dose
- systemic AEs (e.g. fever, chills, fatigue, headache, joint pain, muscle aches, nausea, allergic reaction, rash) were mild to moderate after each dose
- only 2% of patients had a disease flare post-COVID-19 vaccination

Although patients with IBD and healthy controls achieved serological response (antispike antibody ≥70 AU/mL), the mean antispike antibody value was significantly higher in healthy controls than patients with IBD. Hence, decision-making regarding re-vaccination can be considered.[130, level II-2]

A cohort study involving predominantly IBD patients with immune-mediated inflammatory diseases demonstrated that antibody levels significantly declined after the second dose of the COVID-19 vaccine compared to healthy controls, particularly among patients receiving anti-TNF therapy. However, subsequent booster doses (third and fourth doses) significantly improved antibody levels in this population.[131, level II-2]

7.1.2 Pre-travel Vaccination

Pre-travel vaccinations, including travel-related preventable illnesses, should be individualised and follow the World Health Organisation[132] and Centers for Disease Control and Prevention.[133]

- Live vaccines if required, should be given at least four weeks, before commencing immunosuppressives or biologic treatment.
- However, if immunosuppressive treatment has been given, live vaccines should not be given until at least 3 months after discontinuing the immunosuppressive treatment.

Recommendation 17

- Routine vaccinations should be given for all inflammatory bowel disease (IBD) patients.
- Live vaccine should not be given to patients who are on immunosuppressive therapy.
- Urgent immunosuppressive treatment for patients with IBD should not be delayed while awaiting vaccination completion.

7.2 Secondary Osteoporosis

Secondary osteoporosis is a recognised complication in patients with IBD, primarily due to impaired nutrient absorption and exposure to drugs such as glucocorticoids. A detailed guideline on assessment, screening and treatment of osteoporosis can be found in the CPG Management of Osteoporosis 2022 (3rd Edition).[134]

7.3 Smoking and IBD

All patients should be advised against smoking. Smoking cessation should follow the CPG Treatment of Tobacco Use Disorder 2016 (1st Edition).[135]

7.4 Therapeutic Drug Monitoring (TDM)

In local clinical setting, reactive TDM is advocated for patients undergoing biologic therapy for IBD. This approach involves measuring drug trough levels and anti-drug antibody concentrations in patients who exhibit loss of response or adverse reactions to biologic treatments. Reactive TDM aids in distinguishing between pharmacokinetic issues (e.g., low drug levels) and immunogenicity (e.g., presence of anti-drug antibodies), thereby guiding clinicians in optimising therapeutic strategies.

8. FOLLOW-UP AND SURVEILLANCE

IBD is a chronic condition requiring lifelong follow-up to monitor disease activity, manage AEs, and conduct surveillance for potential malignancies. A multidisciplinary approach, ideally within a tertiary care center, is advocated to provide comprehensive care. Based on the ECCO-ESGAR and BSG guidelines and Selecting Therapeutic Targets in IBD-II (STRIDE-II) consensus, patients with IBD should be regularly assessed for:[10, level III; 21; 105, level III]

- Clinical response and remission
- Biochemical response
- Endoscopy response
- Histological remission
- Radiological response

Common practices among clinicians are based on the following targets outlined in STRIDE-II. Refer to **Figure 7**.

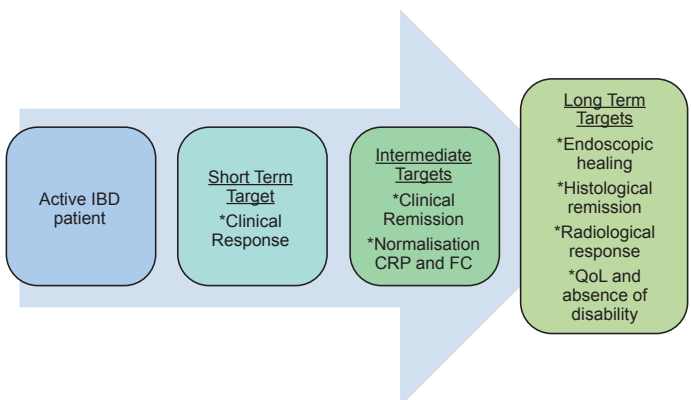


Figure 7: Treatment Targets for Patients with IBD

Adapted from: Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in IBD (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570- 1583

Patients with worsening of symptoms and/or red-flag signs should be assessed urgently for disease flares, loss of response to treatment or disease progression.

8.1 Clinical Response and Remission

Achieving and maintaining clinical response and remission are primary goals in the management of IBD.[10, level III; 105, level III]

a) Clinical response

- is assessed using Patient Reported Outcome version 2 (PRO2):
- a decrease of at least 50% PRO2 scores (rectal bleeding and stool frequency) within 3 to 6 months for UC patients
- a decrease of at least 50% PRO2 score (abdominal pain and stool frequency) at 3 months for CD patients

b) Clinical remission

- is measured using PRO2, Partial Mayo score and HBI
- a PRO2 score (rectal bleeding=0 and stool frequency=0), Partial Mayo (<3 and no score >1) within 3 to 6 months for UC patients
- PRO2 score (abdominal pain ≤1 and stool frequency ≤13), HBI <5 at 3 months for CD patients

8.2 Laboratory Assessment

The two widely used inflammatory biomarkers for monitoring of disease in patients with IBD are CRP and FC.[10, level III; 105, level III]

- The aim is for the normalisation of CRP (below upper limit of normal) and FC (100 to 250 mcg/g) at least three months after the initiation of treatment.

Abnormal levels of FC (within one month apart) may predict disease flare in asymptomatic patients.

Assessment for malabsorption should also be done at regular intervals.Other laboratory tests recommended in patients with IBD include: [10, level III; 105, level III]

- Baseline laboratory tests [refer to **Recommendation 2**] (at least three monthly)
- Anaemia workup

In cases of suspected disease flare or refractory to treatment, the following additional tests are recommended:[10, level III;105, level III]

- Stool tests including *Clostridium difficile* toxins A, B and GDH
- Serology tests e.g., CMV PCR

8.3 Endoscopic Assessment

Endoscopic assessment is useful for follow up, reassessment of flares and early detection of dysplasia in IBD. As recommended in current clinical guidelines:[10, level III; 21; 105, level III]

a) On follow-up

- Follow-up ileo-colonoscopy with segmental biopsies should be performed in patients with IBD three to six monthly after diagnosis (Refer to **Recommendation 3**).
- Validated scoring systems (SES-CD, CDEIS, Mayo score, UCEIS) are used in assessing mucosal healing after initiation of treatment.

b) Endoscopic reassessment of disease is recommended to be performed in the following circumstances:
- Suspected relapse
- Persistent disease activity
- New unexplained symptoms
- Before the switching of therapy

c) On surveillance
- HD endoscopy with/without IEE is recommended for surveillance, reassessment of disease extent and to exclude dysplasia.
- All patients should have a first screening colonoscopy at eight years after symptom onset due to the higher risk of colorectal cancer.
- Following the first screening colonoscopy, IBD patients with 1st degree relative of colorectal cancer (any age) should have subsequent surveillance every three years.
- Following the first screening colonoscopy, subsequent management of IBD patients with dysplasia should be individualised.
- IBD patients without 1st degree family history of colorectal cancer and dysplasia, should follow the timeline of endoscopic surveillance as per **Table 12**.

Table 12: Timeline of endoscopic surveillance according to risk factors after first screening colonoscopy

Risk level	Risk factors	Surveillance
Very low risk	No additional risk factors	Every 10 years or if disease flare
Small risk	Mild active endoscopic or histological inflammation OR extensive disease OR post inflammatory polyps	Every 3 years
Moderate risk	Moderate active endoscopic or histological inflammation OR Primary Sclerosing Cholangitis (with or without transplant) OR Stricture in last 5 years OR Dysplasia in last 5 years	Yearly
Large risk	Severe active endoscopic or histological inflammation after optimised medical therapy	Discuss colectomy

Adapted from: East JE, Gordon M, Nigam GB, et al. British Society of Gastroenterology guidelines on colorectal surveillance in inflammatory bowel disease. Gut 2026; 75: 442-475.

Stopping surveillance is a decision to be taken holistically with the patient/caregivers and health care provider taking into account the patients' age, comorbidity and frailty risks, willingness to undergo further colonoscopies, colorectal cancer and surgical risks.[21]

In high-risk cases, (previous dysplasia or PSC), in addition to targeted biopsies, 4-corner non-targeted specimens from all colonic segments or at every 10 cm throughout the colon needs to be performed.[21]

8.4 Histologic Assessment

Even though endoscopic mucosal healing is achieved, underlying histologic inflammation may persist in intestinal and colonic biopsies making histologic assessment for patients on follow-up important.

Definitions of histological remission of the mucosa in UC following treatment include: histological normalisation; absence of inflammation; absence of neutrophils/erosion/ulceration in the mucosa; Robarts histopathology index ≤ 3; Nancy index = 0; Geboes ≤ 2.0.[23]

In an MA looking at the role of histological healing in IBD showed:[136, level II-2]

- In UC, persistent histologic activity was associated with higher risk of relapse (OR=2.41, 95% CI 1.91 to 3.04).
- More stringent Geboes score cut-offs showed a progressively stronger association with relapse risk:
  - Geboes < 3.1 (OR=2.40, 95% CI 1.57 to 3.65)
  - Geboes < 2.1 (OR=3.91, 95% CI 2.21 to 6.91)
  - Geboes=0 (OR=7.40, 95% CI 2.00 to 18.27)
- Among individual histologic features, basal plasmacytosis (OR=1.95, 95% CI 1.10 to 3.46), neutrophilic infiltrations (OR=2.30, 95% CI 1.14 to 4.63), mucin depletion (OR=2.05, 95% CI 1.12 to 3.73) and crypt architectural irregularities (OR=2.22, 95% CI 1.30 to 3.80) predicted relapse.
- There was no association between histologic activity and relapse in CD.

The quality assessment of the primary studies based on New Castle Ottawa Scale (NOS) were moderate to high risk of bias.

The following are recommended practices during histological examination in patients with IBD:[10, level III; 21; 105, level III]

- Exclusion of CMV infection in suspected flares, persistent disease activity, emergent of new/unexplained symptoms and before the switching of therapy.
- An independent GI pathologist should be consulted to confirm the presence of dysplasia.

If dysplasia is detected during follow-up, MDT discussions to determine management is highly recommended. Most dysplasia identified can be endoscopically resected. However, histological assessment of grade of dysplasia and margin involvement is essential. Those with high-risk features or endoscopically unresectable lesions are considered for surgery.[21]

8.5 Radiological Assessment

Assessment of disease activity with ultrasound and cross-sectional imaging (CT and MRE) can complement endoscopic findings. MRE, IUS and/or CE is recommended for the assessment of small bowel disease.[10, level III; 21; 105, level III]

Reassessment should be considered in cases of post-operative disease recurrence, relapse, penetrating complications, persistent disease activity, new unexplained symptoms and before switching therapy.[10, level III; 21; 105, level III]

- Patients with IBD should have lifelong multidisciplinary team follow-up, preferably at a tertiary care centre.

Recommendation 18

- Monitoring in inflammatory bowel disease (IBD) patients should include:
  - short term treatment goals for clinical response
  - intermediate treatment goals for clinical remission and assessing inflammatory biomarkers (C-reactive protein and faecal calprotectin)
  - long-term treatment goals for endoscopic healing, histological remission, radiological response and quality of life outcomes
  - radiological modalities such as intestinal ultrasound (IUS) and magnetic resonance imaging (MRI)
- All IBD patients should have their first screening colonoscopy eight years after symptom onset due to the higher risk of colorectal cancer.
- In IBD patients with primary sclerosing cholangitis (PSC), endoscopic surveillance for dysplasia should be started at diagnosis and repeated yearly.

9. SPECIAL POPULATIONS

9.1 Pregnancy and Lactation

The increasing prevalence of IBD among individuals of reproductive age presents unique challenges during pregnancy and lactation. Patients who are planning to conceive or are already pregnant require specialised counselling and close monitoring. A multidisciplinary approach involving gastroenterologists, obstetricians, and other relevant specialists is essential to ensure an optimal balance between maternal disease control, fetal and infant safety.[137; 138, level III]

This chapter provides an overview of safe and evidence-based pharmacological treatments during pregnancy and breastfeeding, including the use of aminosalicylates, CS, antibiotics, immunomodulators and biologics.

In the ECCO guideline on risk of IBD drugs in pregnancy and lactation, the following were emphasized as in **Table 13**.[137]

- 5-ASA and sulphasalazine is regarded as low-risk. Supplementation with folate 2 mg/day is recommended to prevent toxicity of sulphasalazine treatment preventing folate absorption.
- CS (short-term), including budesonide, is regarded as low-risk for managing flares.
- Metronidazole and ciprofloxacin can be administered in case of perianal or abdominal sepsis or pouchitis. However, ciprofloxacin should be avoided during the first trimester of pregnancy given the risk of arthropathies in children.
- Thiopurine are not associated with significant neonatal adverse outcomes.
- Calcineurin inhibitors; Data for ciclosporin and tacrolimus are limited.
- Anti-TNF antibodies are regarded as low-risk. No increased risk of adverse pregnancy outcomes has been identified with vedolizumab and ustekinumab.
- Both MTX and thalidomide are teratogenic and contraindicated in pregnancy.
- JAK inhibitors and sphingosine-1-phosphate (S1P) receptor modulators are contraindicated during pregnancy.
- Lactation: Drugs that are considered low-risk during pregnancy are also considered low-risk during breastfeeding and thus can be continued.

Table 13: Overview of Risk of Drugs During Pregnancy and Lactation in IBD

Medication group	Drugs	Pregnancy risk	Lactation risk	Comments
CS	Prednisolone Budesonide	Low risk	Low risk	Short-term use generally safe; no strong link to birth defects
Antibiotics	Metronidazole	Low risk	Avoid	Mainly used in CD patients with pouchitis, perianal disease, or abdominal sepsis
	Ciprofloxacin	Low risk, Avoid in first trimester	Low risk	
Amino salicylates	Mesalazine Sulphasalazine	Low risk	Low risk	No increased risk of birth defects or major complications. Folate supplementation (2 mg/day) is recommended with sulphasalazine to prevent toxicity.
Immunomodulators	Thiopurines	Low risk	Low risk	Generally safe; not linked to birth defects or major AEs
	Ciclosporin, Tacrolimus	Low risk, limited data	Limited data	Limited IBD-specific data; with no clear link to birth defects. May be considered in severe cases, but use requires careful risk-benefit assessment.
	MTX Thalidomide	Contraindicated	Contraindicated	Both are teratogenic and strictly contraindicated in pregnancy. Can cause severe birth defects, fetal loss, and high neonatal mortality. Discontinue 3 months before conception.
Anti-TNFα	Infliximab Adalimumab	Low risk	Low risk	Not linked to birth defects or poor outcomes; safe as mono or combo therapy.
Anti-α4β7 integrin	Vedolizumab	Low risk, limited data	Low risk	**Appear safe**, but data are limited; close monitoring recommended.
Anti-IL-12 and anti IL-23	Ustekinumab Risankizumab	Low risk, limited data	Low risk	
JAK inhibitors	Tofacitinib Upadacitinib Filgotinib	Contraindicated	No data; avoid	**Contraindicated** due to limited human data and animal studies showing fetal harm. Safety in pregnancy is unproven; avoid use until more evidence is available.
Sphingosine-1-phosphate receptor modulators	Ozanimod	Contraindicated	No data; avoid	

Adapted from:

1. Torres J, Chaparro M, Julsgaard M et al., European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. J Crohns Colitis. 2023;17(1):1-27
2. Mahadevan U, Seow CH, Barnes EL, et al. Global Consensus Group for Pregnancy and IBD. Global Consensus Statement on the Management of Pregnancy in Inflammatory Bowel Disease. Am J Gastroenterol. 2026;121(1):31-79.

9.1.1 Special considerations

Exposure to IBD medications in utero, particularly immunosuppressants and biologics, may affect how infants respond to vaccinations during their first year of life. While inactivated vaccines are considered safe and should be administered in accordance with the national immunisation schedules, the use of live attenuated vaccines requires caution due to the potential presence of residual drug levels in the infant's circulation. These factors must be considered when planning vaccination schedules to ensure both safety and effectiveness.

According to the ECCO guidelines on vaccination safety in infants exposed to IBD medications in utero.[137]

- Inactivated vaccines are safe to administer during the first year of life in infants exposed to thiopurines or biologics.
- Live attenuated vaccines should be delayed until infant's drug levels are undetectable or until the infant is at least one year old.

9.1.2 Management of IBD During Pregnancy and Lactation

Given the limited evidence on the treatment of IBD during pregnancy and lactation, the DG provides the following consensus-based recommendations:

- Pre-conception counselling should be routinely offered to all women of childbearing age with IBD to optimise disease control prior to conception and to discuss medication safety.
- Conventional therapies are generally considered safe during pregnancy and lactation, with the exception of thalidomide and MTX, which are strictly contraindicated due to their known teratogenic effects.
- Biologic therapies (e.g. anti-TNF agents, anti-integrin and anti-interleukin) are considered safe for use during both pregnancy and breastfeeding.
- JAK inhibitors and S1P receptor modulators are contraindicated due to insufficient safety data and potential fetal risk.
- In infants born to mothers who were exposed to anti-TNF during pregnancy, live-attenuated vaccines (e.g. BCG, MMR, varicella, and OPV) should be withheld during the first year of life, or until the biologic is no longer detectable in the infant's bloodstream. However, special considerations should be applied for rotavirus vaccination (may be given in infants).[139, level II-2]

Given the limited evidence on the treatment of IBD during pregnancy and lactation, the DG provides the following consensus:

- Conventional therapies are generally considered safe during pregnancy and lactation, with the exception of thalidomide and MTX, which are strictly contraindicated due to their known teratogenic effects.
- Biologic therapies (e.g. anti-TNF agents) are considered safe for use during both pregnancy and breastfeeding.
- JAK inhibitors and S1P receptor modulators are contraindicated due to insufficient safety data and potential fetal risk.

Recommendation 19

- Pre-conception counselling should be routinely offered to all women of childbearing age with inflammatory bowel disease (IBD) to optimise disease control prior to conception and to discuss medication safety.
- Live-attenuated vaccines should be avoided during the first year of life in children with IBD mothers exposed to anti-tumour necrosis factor during pregnancy.
- Methotrexate, janus kinase inhibitors and sphingosine-1-phosphate (S1P) receptor modulators should not be used in pregnant patients with IBD.

9.2 Paediatrics

The increasing burden of paediatric IBD (PIBD) carries unique challenges. Paediatric onset IBD often presents with a more extensive and aggressive disease phenotype, with a prolonged course of disease as the child grows.[140, level III]

Safe and effective management of PIBD must prioritise growth, development, and psychosocial well-being, necessitating a multidisciplinary approach to care. This CPG focuses more on the non-pharmacological, pharmacological, and positioning treatment with regard to the management of PIBD.

9.2.1. Pharmacological

a) Conventional therapy

i. Corticosteroids

Corticosteroids (CS) have been used to induce remission in both UC and CD, as they are effective in rapidly reducing inflammation and controlling acute disease flares. However, their long-term use in children is not recommended due to significant AEs, including growth suppression, excessive weight gain, bone demineralization, and an increased risk of infections. CS should be reserved for short-term induction therapy and avoided as a maintenance strategy in PIBD.[141, level II-2]

The ECCO-ESPGHAN guideline regarding the use of CS in medical management of paediatric UC recommended the following:[142]

- CS should be used as second-line treatment for mild-to-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
- severe UC should normally be treated with IV CS. A short trial of oral steroids could be considered in selected children who appear well with normal or near-normal lab values
- steroids are not recommended for maintaining remission; steroid sparing strategies should be applied
- complications include osteopenia, acne, glaucoma, cataracts and growth suppression

The ECCO-ESPGHAN guideline regarding the use of CS in medical management of paediatric CD recommended the following:[36]

- in children with active luminal CD, CS may be considered for induction of remission when EEN is not an option
- starting dose for CS is weight dependent, and must be tapered once clinical remission is achieved (no later than 4 weeks after initiation)
- reported AEs are increased risk of infection, elevated risk of intra-abdominal or pelvic abscesses, weight gain, insomnia and cushingoid facies

ii. Immunomodulator (azathioprine, MTX**)**

Immunomodulators are used in IBD to maintain remission and for its steroid-sparing effects. It is also used as an adjunct with biologics to reduce immunogenicity.

The ECCO-ESPGHAN guideline recommended the use of immunomodulators in paediatric UC as follows:[142]

- thiopurines were recommended for maintaining remission in children who are CS-dependent or relapsing frequently (2 relapses per year) despite optimal 5-ASA treatment and in 5-ASA intolerant
- thiopurines should not be used for induction of remission
- thiopurines should be reserved as second-line therapy after 5-ASA has failed for maintaining remission in UC considering their safety profile
- blood monitoring in blood counts and liver enzymes is recommended in patient on thiopurine
- thiopurines should be discontinued in clinically significant myelosuppression or pancreatitis. Reintroduction of thiopurines after leucopenia can be considered at a lower dose
- MTX may rarely be considered in UC patients who fail to respond or are intolerant to thiopurines, when other alternatives are not possible or available

- oral tacrolimus (FK-506) may be considered in selected outpatient UC children as another option to steroids for bridging to thiopurines or vedolizumab
- dose-independent AEs include fever, pancreatitis, rash, arthralgias, nausea, vomiting, and diarrhea with the use of thiopurines
- dose-dependent toxicities with thiopurines include leucopenia, thrombocytopenia, infections and hepatitis
- other rarer risks on the use of thiopurines include Hodgkin lymphoma and Hepatosplenic T-cell lymphoma

The Medical Management of Paediatric CD: an ECCO-ESPGHAN Guideline Update recommended the following on immunomodulators:[36]

- in children with active CD, thiopurine monotherapy should not be used to induce remission
- in patients who have achieved remission, thiopurines (azathioprine or 6-MP) can be used to maintain remission
- MTX can be used to maintain clinical remission as first choice immunomodulator or after thiopurine failure or intolerance
- reported AEs with the use of thiopurine were haematological toxicity, pancreatitis and increase transaminases
- rare AEs of thiopurine were hepatosplenic T-cell lymphoma and non-melanoma skin cancer

iii. 5-Aminosalicylic acid (5-ASA)

The ECCO-ESPGHAN guideline on the use of 5-ASA in paediatric UC recommended the following:[142]

- oral 5-ASA compounds are recommended as first-line induction and maintenance therapy for mild-to-moderate UC
- combined oral and rectal 5-ASA therapies are more effective than oral monotherapy
- rectal monotherapy should be reserved for mild-to-moderate ulcerative proctitis. When rectal therapy is used, 5-ASA is preferred over CS
- the effective induction dose should be continued as maintenance dose. Dose reduction, within the suggested dose range, may be considered after several months of sustained remission
- allergic reaction (<0.1%) is rare. Vast majority of AEs are mild (e.g. headache, and GI symptoms)
- SAEs are rare and include renal, pancreatic, pulmonary and cardiac complications

a) Advanced Therapy - Biologics

i. Anti-TNF (infliximab, adalimumab)

The ECCO-ESPGHAN guideline had the following consideration on the use of anti-TNF in paediatric UC:[142]

Infliximab is recommended for both induction and maintenance of remission in children with chronically active or steroid-dependent UC that is refractory to 5-ASA and thiopurines.

- adalimumab may be considered in those who initially respond to infliximab but then lose response or are intolerant to infliximab

Safety considerations for anti-TNF therapy include:

- acute infusion reactions and delayed hypersensitivity reactions
- serious and OIs
- potential risk of psoriasis and skin cancers

An evidence-based guideline has recommended the use of anti-TNF therapy in paediatric CD in the following scenarios:[36]

- for inducing remission in new onset patients with high risk for a complicated disease course (extensive disease, deep colonic ulcers, stricturing disease without pre-stenotic dilatation and fistulising disease)
- as primary induction and maintenance therapy for children with high risk of poor outcomes (extensive disease, deep colonic ulcers, stricturing disease without pre-stenotic dilatation, fistulising disease)
- should be considered early in patients with severe growth delay or in those who do not reach clinical [paediatric CD activity index (PCDAI)<10] and biochemical (FC<250 µg/g) remission after induction with EEN and CS
- for induction and maintenance of remission in patients who fail to achieve or maintain remission with an immunomodulator

In a multicentre RCT on first-line infliximab (FL- infliximab of 5 mg/kg at weeks 0, 2, 6, 14 and 22) vs conventional treatment followed by azathioprine in newly-diagnosed moderate to severe paediatric CD, the findings were:[143, level I]

- FL-infliximab was more effective in induction of remission at week 52 (41% vs 15%, p=0.004)
- 43% (95% CI 30 to 57) in the FL- infliximab group required treatment escalation by week 52 compared to 75% of patients (95% CI 60 to 86) in conventional group
- NS difference between QoL score between two groups
- in terms of growth, patients on FL- infliximab showed significant improvement in growth at week 52 with a change in median height standard deviation score (SDS) from –0.07 [interquartile range (IQR) –0.84 to 0.76] at baseline to 0.02 (IQR –0.81 to 0.70)
- however, patients on conventional treatment showed significant reduction score of median height SDS from −0.53 (IQR −1.06 to 0.26) at baseline to −0.66 (IQR −1.13 to 0.11) at week 52

NS difference of occurrence of AEs in the FL- infliximab group vs the conventional treatment group.

In the landmark *IMAgINE 1* multicentre, double-blind, RCT the efficacy and safety of high-dose (20 - 40 mg every other week) vs low-dose (10 - 20 mg every other week) adalimumab were evaluated as maintenance

therapy in children and adolescents aged 6-17 years with moderate to severe CD following findings showed:[144, level I]

- high dose adalimumab was more effective in maintaining clinical response and clinical remission at week 52 and week 26 respectively in infliximab -naïve compared to infliximab-experienced patients (p=0.026)
- high-dose adalimumab resulted in higher rate of remission for patients with disease duration of ≤3 years (p=0.036) or <13 years of age (p=0.05) compared with low-dose adalimumab
- both treatment groups showed significant improvement in z-scores for height velocity at week 26 (p<0.001, p=0.008) and week 52 (p<0.001, p=0.001) compared to baseline.
- in terms of safety, 52.6% reported treatment emergent AEs including infections (*Yersinia* and viral infection) during induction
- no deaths, malignancies, demyelinating disease or active TB were reported

The follow-up prospective cohort study (*IMAgINE 2*) assessing the long-term effectiveness and safety of adalimumab in paediatric CD demonstrated that adalimumab was effective in maintaining clinical benefits over a 5-year period.[145, level II-2]

- at week 240, 45% of patients remained in clinical remission and 50% maintained a clinical response, compared to baseline remission and response rates of 67% and 95%, respectively, at the start of the *IMAgINE 1* study
- sustained improvement in disease activity was observed, with the mean PCDAI score decreased from 40.1 at baseline to 10.2 at week 52, and further to 6.5 by week 240
- improved growth velocity, with the median height velocity z-score increasing from -2.81 at baseline to 0.85 at week 48 and normalising to 0.0 at week 92
- health-related QoL also showed significant improvement at both week 52 and week 240 (both p=0.001)

In terms of safety:

- serious AEs were reported in 48% of patients but most were primarily due to worsening or flare of CD
- most infectious AEs were mild to moderate and not related to treatment
- in patients who received dose escalation, similar or lower AE rates were reported in comparison with previous study (*IMAgINE 1*)
- patients receiving concomitant CS at onset of study experienced more serious AEs than those not receiving CS
- importantly, no deaths, malignancies, demyelinating disorders, or cases of active TB were reported throughout the 5-year follow-up

b) Emerging Treatments

i. Biologics

- **Anti-integrin (vedolizumab)**

In a pre and post observational study on the effectiveness of vedolizumab (177 mg/m² body surface area up to 300 mg maximum) in children with IBD compared to baseline, the findings were:[146, level III]

- vedolizumab was effective in inducing steroid-free and exclusive enteral nutrition-free remission (SENFCR) in children with UC and CD (34% and 18%) at week 6 and (42% and 32%) at week 14
- in children who weighed <30 kg, the optimal drug concentration associated with SENFCR was >25 µg/mL at week 6 (AUC=0.89, 95% CI 0.71 to 1.00) and 7 µg/mL at week 14 (AUC=0.69, 95% CI 0.41 to 0.98) with a dose of 200 mg/m² body surface area or 10 mg/kg
- in terms of safety, 23% reported at least one AE

- **Anti-interleukin (ustekinumab)**

In a cohort study on effectiveness and safety of ustekinumab in paediatric CD findings reported were:[147, level II-2]

- steroid-free clinical remission rates were 59% and 50% at week 26 and 52 respectively
- in terms of safety, 65% reported mild to moderate AEs (upper respiratory tract infection, acute gastroenteritis, cystitis and pneumonia). No SAE reported.

In another cohort study on efficacy and safety of ustekinumab in paediatric CD findings reported were:[148, level II-2]

- CS and EEN-free response rate was 72.9% with remission rate of 40.5% at week 12
- 40.5% achieved CS- and EEN-free clinical remission at week 52
- there were seven reported mild to moderate AEs. No malignancies or SAE were reported

In a narrative review on the effectiveness and tolerance of ustekinumab in PIBD who had treatment failure with anti-TNF agent, at 3 months compared to baseline, showed:[149, level III]

- PCDAI and paediatric UC activity index (PUCAI) score significantly decreased ($p<0.05$).
- 75% of patients had normalisation of CRP
- significant increment of mean weight and body mass index ($p<0.001$)
- in terms of safety, no SAEs were reported

ii. Small Molecules

Small molecules (tofacitinib and upadacitinib) are used in refractory IBD. There are scarce data available regarding the use of small molecules in paediatric IBD.[150, level II-2]

- **Tofacitinib**

A cohort study evaluated the effectiveness and safety of tofacitinib for medically refractory paediatric-onset IBD, findings showed:[151, level II-2]

- 42.9% of tofacitinib treated patients showed clinical response at the end of 12-week induction period and 33.3% attained steroid-free remission
- 41.2% of tofacitinib treated patients showed clinical response and steroid-free remission at 52 weeks maintenance phase
- tofacitinib was discontinued in 8 subjects because of refractory disease, including 8 who ultimately underwent colectomy, and in 1 subject who developed a sterile intra-abdominal abscess

There were no AEs of thrombi, zoster reactivation, or clinically significant hyperlipidemia reported.

In a narrative review on efficacy and safety of tofacitinib in paediatric UC who had treatment failure with at least 1 biologic agent, the findings reported were:[152, level III]

- 16% achieved CS-free clinical remission and 30% demonstrated clinical response both at week 8
- 23% achieved CS-free clinical remission at week 24
- no SAEs were reported

- **Upadacitinib**

In a RCT on the efficacy and safety of upadacitinib vs placebo for patients with perianal fistulising CD, the significant findings reported were:[103, level I]

- upadacitinib 45 mg was more effective in inducing resolution of perianal fistulas drainage (44.7% vs 5.6%) and closure of perianal fistula external opening (22.1% vs 4.8%) at the end of induction at 12 weeks
- upadacitinib 15 mg and 30 mg were more effective in closure of perianal fistula external opening (18.8% vs 0%, 16% vs 0%) respectively

The rates of AEs, SAEs and fistula related AEs were low across all treatment groups.

In a pre and post observational study on the efficacy and safety of upadacitinib in induction of remission at week 8 in Paediatric CD, the significant findings were:[150, level III]

- the median weighted PCDAI score decreased from 30 to 8
- 68% had achieved normalisation of CRP and 58% had FC <150 mcg/g

The most common AEs reported were severe acne and hypertriglyceridemia.

9.2.2 Non-Pharmacological

Exclusive Enteral Nutrition (EEN)

Exclusive Enteral Nutrition (EEN) is a well-established and highly effective first-line therapy for the induction of remission in paediatric CD. It involves the exclusive use of a nutritionally complete liquid formula either polymeric or elemental, administered orally or via a feeding tube over a defined period. EEN not only induces clinical and mucosal remission but also offers additional benefits, including improved nutritional status, enhanced growth outcomes, and maintenance of QoL. Importantly, it achieves these therapeutic goals while minimising the risk of AEs.[153, level II-2]

In a retrospective cohort study on EEN vs CS for induction therapy in children with newly-diagnosed CD, the following findings were reported:[154, level II-2]

- EEN was more effective in induction of clinical remission (PCDAI ≤7.5) at 12 weeks (86.6% vs 58.1%; p<0.01).
- EEN was effective in reducing the risk of exposure to CS at 2- and 4-year post-diagnosis in both steroid-naïve (47.3% and 39.6%, repectively) and anti-TNF naïve (74.3% and 94.7%, respectively) over a 6 years period.
- Fewer EEN-treated patients required anti-TNF therapy at maximum follow-up compared to those initially treated with CS (44.7% vs 60%).
- EEN-treated patients had significantly greater linear growth recovery than CS at 1-year post-diagnosis (p<0.01) with higher percentage showed positive change in height z-score (60.8% vs 40%; p=0.06). However, NS difference in linear growth was observed at 2-,4- and 6-year follow-up.

The above findings was supported in another prospective cohort study on EEN vs CS in children with mild to moderate CD where the findings were:[153, level II-2]

- EEN was more effective in induction of remission at week 12 (63% vs 41%; p=0.05).
- EEN was more effective in improving height z-score at week 78 (-0.226 ± 1 standard deviation vs -0.763 ±- 1.3 standard deviation; p=0.055).
- NS differences were observed between the two groups in terms of relapse episodes at week 78, complications, or the need for surgical intervention at week 104.

9.2.3 Positioning Treatment

The following recommendations are made on the management and treatment positioning in PIBD based on the ECCO-ESPGHAN evidence-based guideline:[36; 142; 155]

a) Ulcerative Colitis

i. Induction therapy

- Oral 5-ASA is recommended as first line induction for mild to moderate UC.
- Rectal 5-ASA monotherapy is recommended as the first line for mild to moderate ulcerative proctitis.
- Combination oral and rectal 5-ASA therapy is more effective than oral monotherapy mild to moderate UC.
- CS is used as a second line treatment in mild to moderate UC not responding to 5-ASA and as first line in severe UC.

ii. Maintenance

- 5-ASA can be used for maintenance as monotherapy.
- Immunomodulators are recommended in children who are:
  - CS dependent
  - two or more relapses per year
  - not responding to optimal dose of 5-ASA / intolerant to 5-ASA

iii. Acute severe colitis (ASC) defined as PUCAI score of >65

- IV Methylprednisolone 1 mg/kg/day up to 40 mg/day once daily is recommended as initial treatment for ASC.
- Higher dose of IV Methylprednisolone (1.5 mg/kg/day up to 60 mg/day once daily is recommended in more severe end of the spectrum and in children who failed oral CS therapy).
- Investigations to look for concomitant infection and toxic megacolon should be carried out.
- If there is evidence of toxic megacolon the following is recommended:
  - nil by mouth
  - IV antibiotics
  - surgical consultation

PUCAI score reassessment should be done at day 3 and 5 of treatment to decide on second line therapies (escalation to biologics/tacrolimus/ciclosporin/surgery).

b) Crohn's Disease

i. Induction therapy

- EEN is recommended as the first-line therapy for inducing remission in children with active luminal CD.
- CS may be considered for inducing remission if EEN is not an option.

- Anti-TNF is recommended in newly diagnosed CD with high risk of complicated disease course (deep ulceration, extensive disease, perianal / fistulising disease or poor growth) as it is associated with improved long-term outcome and reduced disease complications.
- Immunomodulators should not be used to induce remission because of their slow onset of action and it is less effective as a single agent.

ii. Maintenance

- Immunomodulators (thiopurines or MTX) may be used to maintain clinical remission as monotherapy.
- In patients on anti-TNF as induction, combination with immunomodulator is recommended with proactive TDM and dose optimisation.
- In patients with other biologics (vedolizumab or ustekinumab) or small molecules as induction, treatment should be continued with the respective induction agent with recommended monitoring of response and dose optimisation as per protocol.

iii. Perianal/fistulising disease

- In patients with perianal or fistulising disease, anti-TNF is recommended as primary induction and maintenance therapy in combination with antibiotics and/or surgery.

Recommendation 20

- In paediatric ulcerative colitis (UC):
  - oral 5-aminosalicylic acid (5-ASA) should be given as first line induction for mild to moderate disease
  - corticosteroids (CS) should be given as second line treatment in patients not responding to first line therapy
  - immunomodulators should be given in patients who are:
    - CS dependent
    - with two or more relapses per year
    - not responding to optimal dose of 5-ASA or intolerant to 5-ASA
  - infliximab should be given for both induction and maintenance of remission in chronically active or steroid-dependent disease unresponsive to 5-ASA and thiopurines
  - adalimumab should be considered in patients who lose response or are intolerant to infliximab
  - tofacitinib, upadacitinib, ustekinumab or vedolizumab may be considered following failure of anti-tumour necrosis factor (anti-TNF) therapy
  - combination therapy (two biologic agents or a biologic agent with small molecules) as dual targeted therapy may be a therapeutic option in refractory UC
  - in acute severe UC (ASUC):
    - IV methylprednisolone should be given as initial treatment
    - concomitant infection and toxic megacolon should be excluded
    - paediatric UC activity index (PUCAI) score reassessment should be done at day 3 and 5 of treatment to decide on second line therapies (escalation to biologics/tacrolimus/ciclosporin/ surgery)
- In paediatric Crohn's disease (CD):
  - exclusive enteral nutrition (EEN) should be the first-line therapy for the induction of remission in mild to moderate disease
  - CS may be considered for inducing remission if EEN is ineffective or not well tolerated in mild to moderate disease
  - anti-TNF therapy should be initiated in patients with high risk of complicated disease course including perianal or fistulising disease
  - immunomodulators should not be used to induce remission
  - immunomodulators should be used to maintain clinical remission either as monotherapy or in combination with conventional treatment or biologics
  - in patients who achieved remission with anti-TNF, combination with immunomodulator should be given as maintenance
- CS should not be used as maintenance therapy in paediatric UC and CD.

10. IMPLEMENTING THE GUIDELINES

The management of IBD should be guided by an evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

10.1. Facilitating and Limiting Factors

Existing facilitating factors for application of the recommendations in the CPG include:

- online dissemination of the CPG to healthcare providers nationwide
- regular gastroenterology scientific meetings/congress
- IBD preceptorship training and training of trainers
- Patient's Support Groups e.g. MyIBDKids, Crohn's and Colitis Society of Malaysia
- MDT discussions, continuous medical education (CME) activities
- IBD special interest group
- Malaysian IBD registry

Existing barriers for application of the recommendations of the CPG are:

- insufficient knowledge on IBD assessment and its treatment among healthcare providers
- inadequate accessibility to IBD training at all levels of healthcare
- limitation to treatment accessibility in IBD management
- lack of post-basic training in IBD for allied healthcare
- lack of awareness, knowledge and understanding on IBD among patients and caregivers

10.2. Potential Resource Implications

The recommendations in this CPG require additional resources in terms of funds, healthcare infrastructures and human resources/expertise for their successful implementation as discussed below.

There are mainly two factors that are contributing in the successful implementation of this guideline. Firstly, the patient related factors which are lack of awareness hence delaying their health seeking treatment. Health care provider factors include delay in recognising and diagnosing the disease. In addition, there are lack of expertise in a multidisciplinary treatment approach (IBD specialists, colorectal surgeons, radiologists, GI pathologists, dietitians, clinical psychologists and IBD nurses).

Limited availability of therapeutic agents for IBD can hinder effective disease management. Restricted formularies and limited budgets may reduce access to appropriate treatment options. For patients with moderate to severe UC or CD, initiating biologic therapy in secondary or tertiary centres is particularly challenging due to high costs. This

may result in delayed treatment and prolonged use of conventional systemic agents. Therefore, a specific allocation for advanced therapy is essential to ensure timely initiation of therapy and better outcomes for patients.

In addition, access to advanced imaging modalities such as MRE, IUS and CTE is often limited in resource-constrained settings. These tools are critical for accurate disease assessment and monitoring, and their wider availability would support earlier diagnosis, more precise treatment decisions, and improved quality of care.

Training programmes for healthcare providers are needed to ensure they are equipped with the latest knowledge and skills in IBD management. These include ongoing education and certification programmes to keep healthcare providers updated on best practices and emerging treatments. These will improve IBD management which include treatment adherence and will prevent disease deterioration and frequent relapses.

Several key performance indexes on IBD management being monitored by MoH is in line with the CPG recommendations. Thus, the following are proposed as clinical audit indicators for the CPG:

$$\text{Percentage of moderate to severe CD patients treated with advanced therapy} = \frac{\text{Number of moderate to severe CD patients treated with advanced therapy}}{\text{Number of moderate to severe CD patients requiring advanced therapy in the same period}} \times 100\%$$

Target 75%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

Reference

1. Aniwan S, Santiago P, Loftus EV Jr, et al. The epidemiology of inflammatory bowel disease in Asia and Asian immigrants to Western countries. United European Gastroenterol J. 2022;10(10):1063-1076.
2. Mokhtar NM, Nawawi KNM, Verasingam J, et al. A four-decade analysis of the incidence trends, sociodemographic and clinical characteristics of inflammatory bowel disease patients at single tertiary centre, Kuala Lumpur, Malaysia. BMC Public Health. 2019;19(Suppl 4):550.
3. Luces C, Bodger K. Economic burden of inflammatory bowel disease: a UK perspective. Expert Rev Pharmacoecon Outcomes Res. 2006;6(4):471-82.
4. Piovani D, Danese S, Peyrin-Biroulet L, et al. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. Gastroenterology. 2019;157(3):647-659.e4.
5. Bernstein CN, Eliakim A, Fedail S, et al. World Gastroenterology Organisation Global Guidelines Inflammatory Bowel Disease: Update August 2015. J Clin Gastroenterol. 2016;50(10):803-818.
6. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A-36A.
7. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and Risk Factors for Extraintestinal Manifestations in the Swiss Inflammatory Bowel Disease Cohort. American Journal of Gastroenterology. 2011;106(1):110-119.
8. Gordon H, Burisch J, Ellul P, et al. ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18(1):1-37.
9. Kilic Y, Kamal S, Jaffar F, et al. Prevalence of Extraintestinal Manifestations in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2024;30(2):230-239.
10. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13(2):144-164.
11. Shi JT, Zhang Y, She Y, et al. Diagnostic Utility of Non-invasive Tests for Inflammatory Bowel Disease: An Umbrella Review. Front Med (Lausanne). 2022;9:920732.
12. Menees SB, Powell C, Kurlander J, et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015;110(3):444-54.
13. Malaysia Ministry of Health (MoH). Clinical Practice Guidelines on Management of Tuberculosis (Fourth Edition). Putrajaya: MoH; 2021.
14. Uhlig HH, Charbit-Henrion F, Kotlarz D, et al. Clinical Genomics for the Diagnosis of Monogenic Forms of Inflammatory Bowel Disease: A Position Paper From the Paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2021;72(3):456-473.
15. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-9.
16. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145(5):987-95.
17. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505-12.

18. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30(7):983-9.
19. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956-63.
20. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012;61(4):535-42.
21. East JE, Gordon M, Nigam GB, et al. British Society of Gastroenterology guidelines on colorectal surveillance in inflammatory bowel disease. Gut. 2026:75:442-475
22. Feakins R, Borralho Nunes P, Driessen A, et al. Definitions of Histological Abnormalities in Inflammatory Bowel Disease: an ECCO Position Paper. J Crohns Colitis. 2024;18(2):175-191.
23. Magro F, Langner C, Driessen A, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis. 2013;7(10):827-51.
24. Kucharzik T, Ellul P, Greuter T, et al. ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. J Crohns Colitis. 2021;15(6):879-913.
25. Peyrin-Biroulet L, Arenson E, Rubin DT, et al. A Comparative Evaluation of the Measurement Properties of Three Histological Indices of Mucosal Healing in Ulcerative Colitis: Geboes Score, Robarts Histopathology Index and Nancy Index. J Crohns Colitis. 2023;17(11):1733-1743.
26. Curte A, Becheanu G, Andrei G, et al. Histological scoring systems in ulcerative colitis patients: a routine practice perspective. Archives of the Balkan Medical Union. 2020;55(1):64-71.
27. Solitano V, Schaeffer DF, Hogan M, et al. Reliability and Responsiveness of Histologic Indices for the Assessment of Crohn's Disease Activity. Clin Gastroenterol Hepatol. 2024;22(9):1898-1907 e25.
28. Yanai H, Feakins R, Allocca M, et al. ECCO-ESGAR-ESP-IBUS Guideline on Diagnostics and Monitoring of Patients with Inflammatory Bowel Disease: Part 2. J Crohns Colitis. 2025;19(7).
29. Kopylov U, Yung DE, Engel T, et al. Diagnostic yield of capsule endoscopy versus magnetic resonance enterography and small bowel contrast ultrasound in the evaluation of small bowel Crohn's disease: Systematic review and meta-analysis. Dig Liver Dis. 2017;49(8):854-863.
30. Davari M, Keshtkar A, Sajadian ES, et al. Safety and effectiveness of MRE in comparison with CTE in diagnosis of adult Crohn's disease. Med J Islam Repub Iran. 2019;33:132.
31. Chavoshi M, Mirshahvalad SA, Kasaeian A, et al. Diagnostic Accuracy of Magnetic Resonance Enterography in the Evaluation of Colonic Abnormalities in Crohn's Disease: A Systematic Review and Meta-Analysis. Acad Radiol. 2021;28 Suppl 1:S192-S202.
32. Somwaru AS, Khanijow V, Katabathina VS. Magnetic resonance enterography, colonoscopy, and fecal calprotectin correlate in colonic Crohn's disease. BMC Gastroenterol. 2019;19(1):210.
33. Roseira J, Ventosa AR, de Sousa HT, et al. The new simplified MARIA score applies beyond clinical trials: A suitable clinical practice tool for Crohn's disease that parallels a simple endoscopic index and fecal calprotectin. United European Gastroenterol J. 2020;8(10):1208-1216.
34. Taylor SA, Mallett S, Bhatnagar G, et al. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. Lancet Gastroenterol Hepatol. 2018;3(8):548-558.

35. Kucharzik T, Tielbeek J, Carter D, et al. ECCO-ESGAR Topical Review on Optimizing Reporting for Cross-Sectional Imaging in Inflammatory Bowel Disease. J Crohns Colitis. 2022;16(4):523-543.
36. van Rheenen PF, Aloi M, Assa A, et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. J Crohns Colitis. 2021;15(2).
37. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68
38. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369(9573):1641-57.
39. Bonovas S, Nikolopoulos GK, Lytras T, et al. Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: Systematic review and network meta-analysis. Br J Clin Pharmacol. 2018;84(2):239-251.
40. Moran GW, Gordon M, Sinopolou V, et al. British Society of Gastroenterology guidelines on inflammatory bowel disease in adults: 2025. Gut. 2025;74(Suppl 2):s1-s101.
41. Bonovas S, Nikolopoulos GK, Piovani D, et al. Comparative assessment of budesonide-MMX and mesalamine in active, mild-to-moderate ulcerative colitis: A systematic review and network meta-analysis. Br J Clin Pharmacol. 2019;85(10):2244-2254.
42. Kuenzig ME, Rezaie A, Kaplan GG, et al. Budesonide for the Induction and Maintenance of Remission in Crohn's Disease: Systematic Review and Meta-Analysis for the Cochrane Collaboration. J Can Assoc Gastroenterol. 2018;1(4):159-173.
43. Hashash JG, Fadel CGA, Rimmani HH, et al. Biologic monotherapy versus combination therapy with immunomodulators in the induction and maintenance of remission of Crohn's disease and ulcerative colitis. Ann Gastroenterol. 2021;34(5):612-624.
44. Rios-Usuga C, Martinez-Gutierrez M, Ruiz-Saenz J. Antiviral Potential of Azathioprine and Its Derivative 6- Mercaptopurine: A Narrative Literature Review. Pharmaceuticals (Basel). 2024;17(2):174
45. Hasskamp J, Meinhardt C, Patton PH, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2025;2(2):CD000478.
46. Raine T, Bonovas S, Burisch J, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohns Colitis. 2022;16(1):2-17.
47. Chande N, Townsend CM, Parker CE, et al. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;10(10):CD000545.
48. Chande N, Patton PH, Tsoulis DJ, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;2015(10):CD000067.
49. Lichtenstein GR, Loftus EV, Afzali A, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2025;120(6):1225-1264.
50. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-95.
51. Al Ameel T, Al Sulais E, Raine T. Methotrexate in inflammatory bowel disease: A primer for gastroenterologists. Saudi J Gastroenterol. 2022;28(4):250-260.
52. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. Am J Gastroenterol. 2025;120(6):1187-1224.
53. McDonald JW, Wang Y, Tsoulis DJ, et al. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev. 2014;2014(8):CD003459.
54. Patel V, Wang Y, MacDonald JK, et al. Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014;2014(8):CD006884.

55. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology. 2014;146(3):681-688.e1.
56. Słoka J, Madej M, Strzalka-Mrozik B. Molecular Mechanisms of the Antitumor Effects of Mesalazine and Its Preventive Potential in Colorectal Cancer. Molecules. 2023;28(13):5081
57. Barberio B, Segal JP, Quraishi MN, et al. Efficacy of Oral, Topical, or Combined Oral and Topical 5-Aminosalicylates, in Ulcerative Colitis: Systematic Review and Network Meta-analysis. J Crohns Colitis. 2021;15(7):1184-1196.
58. Farrell K, Horton J. CADTH Health Technology Review Mesalamine for the Treatment of Crohn Disease. 2022
59. Gordon H, Minozzi S, Kopylov U, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2024;18(10):1531-1555.
60 Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60(6):780-7.
61. Reinisch W, Sandborn WJ, Panaccione R, et al. 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Inflamm Bowel Dis. 2013;19(8):1700-9.
62. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130(2):323-33
63. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232-9.
64. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52-65.
65. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-76.
66. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541-9.
67. Gordon M, Sinopoulou V, Akobeng AK, et al. Infliximab for medical induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2023;11(11):CD012623.
68. Buisson A, Nachury M, Reymond M, et al. Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study. Clin Gastroenterol Hepatol. 2023;21(9):2338-2346.e3.
69. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85-95
70. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96-109.e1.
71. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine. 2013;369(8):699-710.
72. Sands BE, Peyrin-Biroulet L, Loftus EV, Jr., et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019;381(13):1215-1226.
73. Rubin DT, Allegretti JR, Panés J, et al. Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies. Lancet. 2025;405(10472):33-49.
74. Hart A, Panaccione R, Steinwurz F, et al. Efficacy and Safety of Guselkumab Subcutaneous Induction and Maintenance in Participants With Moderately to

74 Severely Active Crohn's Disease: Results From the Phase 3 GRAVITI Study. Gastroenterology. 2025;169(2):308-325.
75. Panaccione R, Feagan BG, Afzali A, et al. Efficacy and safety of intravenous induction and subcutaneous maintenance therapy with guselkumab for patients with Crohn's disease (GALAXI-2 and GALAXI-3): 48-week results from two phase 3, randomised, placebo and active comparator-controlled, double-blind, triple-dummy trials. Lancet. 2025;406(10501):358-375.
76. D'Haens G, Dubinsky M, Kobayashi T, et al. Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2023;388(26):2444-2455.
77. Ferrante M, D'Haens G, Jairath V, et al. Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study. Lancet. 2024;404(10470):2423-2436.
78. Loftus EV, Panaccione R, Parkes G, et al. Risankizumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Efficacy and Safety in the Randomized Phase 3 INSPIRE Study. In: Highlights in UC from the ACG 2023 Meeting. Gastroenterology & Hepatology. 2023;19.
79. Panaccione R BP, Blumenstein I, et al. Efficacy of risankizumab maintenance therapy by clinical remission and endoscopic improvement status in patients with moderately to severely active ulcerative colitis: post hoc analysis of the COMMAND phase 3 study. Gastroenterology & Hepatology. 2024;20.
80. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet. 2022;399(10340):2015-2030.
81. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet. 2022;399(10340):2031-2046.
82. Peyrin-Biroulet L, Chapman JC, Colombel JF, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease. N Engl J Med. 2024;391(3):213-223.
83. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-1214.
84. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946-1960.
85. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet. 2023;401(10383):1159-1171.
86. Sandborn WJ, Feagan BG, D'Haens G, et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2021;385(14):1280-1291.
87. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017;376(18):1723-1736.
88. Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. Lancet. 2022;399(10341):2113-2128.
89. Loftus EV, Jr., Panes J, Lacerda AP, et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023;388(21):1966-1980
90. Olivera PA, Lasa JS, Zubiaurre I, et al. Opportunistic Infections in Patients with Inflammatory Bowel Disease Treated with Advanced Therapies: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Crohns Colitis. 2023;17(2):199-210.

91. Shehab M, Alrashed F, Alsayegh A, et al. Comparative Efficacy of Biologics and Small Molecule in Ulcerative Colitis: A Systematic Review and Network Meta-analysis. Clin Gastroenterol Hepatol. 2025;23(2):250-262.
92. Panaccione R, Collins EB, Melmed GY, et al. Efficacy and Safety of Advanced Therapies for Moderately to Severely Active Ulcerative Colitis at Induction and Maintenance: An Indirect Treatment Comparison Using Bayesian Network Meta-analysis. Crohns Colitis 360.2023;5(2)
93. Noor NM, Lee JC, Bond S, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol. 2024;9(5):415-427.
94. Disher T, Naessens D, Sanon M, et al. One-Year Efficacy of Guselkumab Versus Advanced Therapies for the Treatment of Moderately to Severely Active Crohn's Disease: A Network Meta-Analysis. Adv Ther. 2025;42(6):2708-2727.
95. Vuyyuru SK, Nguyen TM, Murad MH, et al. Comparative Efficacy of Advanced Therapies for Achieving Endoscopic Outcomes in Crohn's Disease: A Systematic Review and Network Meta-Analysis. Clin Gastroenterol Hepatol. 2024;22(6):1190-1199.e15.
96. Szemes K, Soos A, Hegyi P, et al. Comparable Long-Term Outcomes of Cyclosporine and Infliximab in Patients With Steroid-Refractory Acute Severe Ulcerative Colitis: A Meta-Analysis. Front Med (Lausanne). 2019;6:338.
97. Singh A, Goyal MK, Midha V, et al. Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): A Randomized Controlled Trial. Am J Gastroenterol. 2024;119(7):1365-1372.
98. Ng SC HI, Goh KL, et al. Malaysian Inflammatory Bowel Disease (IBD) Treatment Algorithms. Putrajaya, Malaysia 2022.
99. Gilmore R, Tan WL, Fernandes R, et al. Upadacitinib Salvage Therapy for Infliximab-Experienced Patients with Acute Severe Ulcerative Colitis. J Crohns Colitis. 2023;17(12):2033-2036.
100. Zhang J, Li R, Chen L, et al. Effectiveness and safety of upadacitinib in acute severe ulcerative colitis patients from single Chinese IBD Center: a monocentric study. Clin Exp Med. 2024;24(1):233.
101. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(12):1879-1892.
102. Shehab M, Alrashed F, Heron V, et al. Comparative Efficacy of Biologic Therapies for Inducing Response and Remission in Fistulizing Crohn's Disease: Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Inflamm Bowel Dis. 2023;29(3):367-375.
103. Colombel JF, Lacerda AP, Irving PM, et al. Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials. Clin Gastroenterol Hepatol. 2025;23(6):1019-1029.
104. Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. J Consult Clin Psychol. 2017;85(9):918-925.
105. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583.
106. Wynne B, McHugh L, Gao W, et al. Acceptance and Commitment Therapy Reduces Psychological Stress in Patients With Inflammatory Bowel Diseases. Gastroenterology. 2019;156(4):935-945 e1.

107. Naude C, Skvarc D, Maunick B, et al. Acceptance and Commitment Therapy for Adults Living With Inflammatory Bowel Disease and Distress: A Randomized Controlled Trial. Am J Gastroenterol. 2024;120(8):1839-1851.
108. Yanai H, Levine A, Hirsch A, et al. The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomised trial. Lancet Gastroenterol Hepatol. 2022;7(1):49-59.
109. Bischoff SC, Bager P, Escher J, et al. ESPEN guideline on Clinical Nutrition in inflammatory bowel disease. Clin Nutr. 2023;42(3):352-379.
110. Imdad A, Pandit NG, Zaman M, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev. 2023;4(4):CD012774.
111. Feng J, Chen Y, Liu Y, et al. Efficacy and safety of fecal microbiota transplantation in the treatment of ulcerative colitis: a systematic review and meta-analysis. Sci Rep. 2023;13(1):14494.
112. Lorentz A, Muller L. Probiotics in the Treatment of Inflammatory Bowel Disease in Adulthood: A Systematic Review. J Gastrointestin Liver Dis. 2022;31(1):74-84.
113. Sabir G, Abdelhady HA, Oumar Abakar A, et al. The Potential Benefits of Exercise in Managing Inflammatory Bowel Disease: A Systematic Review. Cureus. 2024;16(9):e68948.
114. Coelho MR, Romi MD, Ferreira D, et al. The Use of Curcumin as a Complementary Therapy in Ulcerative Colitis: A Systematic Review of Randomized Controlled Clinical Trials. Nutrients. 2020;12(8).
115. Tahvilian N, Masoodi M, Faghihi Kashani A, et al. Effects of saffron supplementation on oxidative/antioxidant status and severity of disease in ulcerative colitis patients: A randomized, double-blind, placebo-controlled study. Phytother Res. 2021;35(2):946-953.
116. Malaysian Health Technology Assessment Section (MaHTAS). Cannabis for medical use: executive summary. Putrajaya: Ministry of Health Malaysia (MoH); 2022.
117. Bae JH, Kang SY, You SE, et al. The Effects of Acupuncture on Crohn's Disease: a systematic review and meta-analysis. J Pharmacopuncture. 2023;26(3):211-226.
118. De Simone B, Davies J, Chouillard E, et al. WSES-AAST guidelines: management of inflammatory bowel disease in the emergency setting. World J Emerg Surg. 2021;16(1):23.
119. Holubar SD, Lightner AL, Poylin V, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Ulcerative Colitis. Dis Colon Rectum. 2021;64(7):783-804.
120. Spinelli A, Bonovas S, Burisch J, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment. J Crohns Colitis. 2022;16(2):179-189.
121. Magro F, Gionchetti P, Eliakim R et al., Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis. 2017;11(6):649-670
122. Lightner AL, Vogel JD, Carmichael JC, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease. Dis Colon Rectum. 2020;63(8):1028-1052.
123. Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP Consensus on Surgery for Crohn's Disease. J Crohns Colitis. 2018;12(1):1-16.
124. Adamina M, Bonovas S, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment. J Crohns Colitis. 2020;14(2):155-168.
125. Benchimol EI, Tse F, Carroll MW, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 1: Live Vaccines. Gastroenterology. 2021;161(2):669-680

126. Jones JL, Tse F, Carroll MW, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 2: Inactivated Vaccines. J Can Assoc Gastroenterol. 2021;4(4):e72-e91.
127. Desalermos A, Pimienta M, Kalligeros M, et al. Safety of Immunizations for the Adult Patient With Inflammatory Bowel Disease-A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2022;28(9):1430-1442.
128. Lev-Tzion R, Focht G, Lujan R, et al. COVID-19 Vaccine Is Effective in Inflammatory Bowel Disease Patients and Is Not Associated With Disease Exacerbation. Clin Gastroenterol Hepatol. 2022;20(6):e1263-e1282.
129. Weaver KN, Zhang X, Dai X, et al. Impact of SARS-CoV-2 Vaccination on Inflammatory Bowel Disease Activity and Development of Vaccine-Related Adverse Events: Results From PREVENT-COVID. Inflamm Bowel Dis. 2022;28(10):1497-1505.
130. Jorgensen KK, Hoivik ML, Chopra A, et al. Humoral immune response to SARS-CoV-2 vaccination in patients with inflammatory bowel disease on immunosuppressive medication: association to serum drug levels and disease type. Scand J Gastroenterol. 2023;58(8):874-882.
131. Cheung MW, Dayam RM, Shapiro JR, et al. Third and Fourth Vaccine Doses Broaden and Prolong Immunity to SARS-CoV-2 in Adult Patients with Immune-Mediated Inflammatory Diseases. J Immunol. 2023;211(3):351-364.
132. World Health Organisation (WHO) (Available at https://www.who.int/travel-advice)
133. Centers for Disease Control and Prevention (CDC) (Available at https://www.cdc.gov/travel)
134. Malaysia Ministry of Health (MoH). Clinical Practice Guidelines on Management of Osteoporosis (3rd Edition). Putrajaya: MoH; 2022.
135. Malaysia Ministry of Health (MoH). Clinical Practice Guidelines on Treatment of Tobacco Use Disorder (1st edition). Putrajaya: MoH; 2016.
136. Gupta A, Yu A, Peyrin-Biroulet L, et al. Treat to Target: The Role of Histologic Healing in Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2021;19(9):1800-1813 e4.
137. Torres J, Chaparro M, Julsgaard M, et al. European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. J Crohns Colitis. 2023;17(1):1-27.
138. Hossein-Javaheri N, Youssef M, Jeyakumar Y, et al. The Management of Inflammatory Bowel Disease during Reproductive Years: An Updated Narrative Review. Reproductive Medicine. 2023;4(3):180-197.
139. Ernest-Suarez K, Murguía-Favela LE, Constantinescu C, et al. Live Rotavirus Vaccination Appears Low-risk in Infants Born to Mothers With Inflammatory Bowel Disease on Biologics. Clin Gastroenterol Hepatol. 2025;23(5):835-845.
140. Grover Z. A narrative review of pitfall and progress in management of inflammatory bowel disease in children. Pediatric Medicine. 2023;6
141. Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. JAMA Pediatr. 2015;169(11):1053-60.
142. Wine E, Aloi M, Van Biervliet S, et al. Management of paediatric ulcerative colitis, part 1: Ambulatory care-An updated evidence-based consensus guideline from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organisation. J Pediatr Gastroenterol Nutr. 2025;81(3):765-815.
143. Jongsma MME, Aardoom MA, Cozijnsen MA, et al. First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's disease: an open-label multicentre randomised controlled trial. Gut. 2022;71(1):34-42.

144. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology. 2012;143(2):365-74.e2.
145. Faubion WA, Dubinsky M, Ruemmele FM, et al. Long-term Efficacy and Safety of Adalimumab in Pediatric Patients with Crohn's Disease. Inflamm Bowel Dis. 2017;23(3):453-460.
146. Atia O, Shavit-Brunschwig Z, Mould DR, et al. Outcomes, dosing, and predictors of vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. Lancet Gastroenterol Hepatol. 2023;8(1):31-42.
147. Takeuchi I, Arai K, Kyodo R, et al. Ustekinumab for children and adolescents with inflammatory bowel disease at a tertiary children's hospital in Japan. J Gastroenterol Hepatol. 2021;36(1):125-130.
148. Pujol-Muncunill G, Navas-López VM, Ledder O, et al. STEP-CD study: ustekinumab use in paediatric Crohn's disease-a multicentre retrospective study from paediatric IBD Porto group of ESPGHAN. Eur J Pediatr. 2024;183(8):3253-3262.
149. Koudsi M, Martinez-Vinson C, Pigneur B, et al. Ustekinumab Use in Pediatric Inflammatory Bowel Disease: A French Multicenter Study From the Pediatric GETAID. J Pediatr Gastroenterol Nutr. 2023;76(6):763-770.
150. Cohen S, Spencer EA, Dolinger MT, et al. Upadacitinib for Induction of Remission in Paediatric Crohn's Disease: An International Multicentre Retrospective Study. Aliment Pharmacol Ther. 2025;61(8):1372-1380.
151. Moore H, Dubes L, Fusillo S, et al. Tofacitinib Therapy in Children and Young Adults With Pediatric-onset Medically Refractory Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2021;73(3):e57-e62.
152. Ledder O, Dolinger M, Dubinsky MC, et al. Tofacitinib in Pediatric Ulcerative Colitis: A Retrospective Multicenter Experience. Inflamm Bowel Dis. 2025;31(2):425-431.
153. Cohen-Dolev N, Sladek M, Hussey S, et al. Differences in Outcomes Over Time With Exclusive Enteral Nutrition Compared With Steroids in Children With Mild to Moderate Crohn's Disease: Results From the GROWTH CD Study. J Crohns Colitis. 2018;12(3):306-312.
154. Connors J, Basseri S, Grant A, et al. Exclusive Enteral Nutrition Therapy in Paediatric Crohn's Disease Results in Long-term Avoidance of Corticosteroids: Results of a Propensity-score Matched Cohort Analysis. J Crohns Colitis. 2017;11(9):1063-1070.
155. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric 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 Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;67(2):292-310.

Appendix 1

CLINICAL QUESTIONS

1. DIAGNOSIS

1.1 What is the effective assessment of disease severity in IBD? Aetiology, risk factors, clinical presentation, complications

1.2 What are the appropriate tests in people with suspected IBD?
- Blood tests
- Stool tests
- Further investigations
- Histopathology

2. MEDICAL TREATMENT

2.1 What are the effective and safe pharmacological treatments in IBD?
- Conventional
- Advanced Therapy
- Positioning of Treatment
- Special Clinical Subgroups

2.2 What are the effective and safe psychological treatments in IBD?

2.3 What are the effective and safe non-pharmacological treatments in IBD?

3. TRADITIONAL AND COMPLEMENTARY MEDICINE

What are the effective and safe traditional and complementary medicine in IBD?

4. SURGICAL TREATMENT

What are the effective and safe surgical treatments in IBD?

5. OTHER CONSIDERATIONS

What are the other considerations in the treatments of IBD?
- Vaccination
- Secondary Osteoporosis
- Smoking and IBD
- Therapeutic Drug Monitoring (TDM)

6. FOLLOW-UP AND SURVEILLANCE

What and how is the follow-up and surveillance performed in IBD?
- Clinical Response and Remission
- Laboratory assessment
- Endoscopic Assessment
- Histology Assessment
- Radiological Assessment

7. SPECIAL POPULATION

7.1 Pregnancy

What are the effective and safe treatments in IBD with pregnancy and lactation?

7.2 Paediatric age group

What are the effective and safe treatments of IBD in children?

Appendix 2

EXAMPLE OF SEARCH STRATEGY

Clinical Questions: **What are the effective and safe pharmacological treatment in IBD?**

1. INFLAMMATORY BOWEL DISEASES/
2. (inflammatory bowel adj2 disease*).tw.
3. COLITIS, ULCERATIVE/
4. (ulcerative adj1 colitis).tw.
5. idiopathic proctocolitis.tw.
6. (inflammatory bowel disease adj5 ulcerative colitis type).tw.
7. CROHN DISEASE/
8. (granulomatous adj1 colitis).tw.
9. (crohn* adj1 (disease* or enteritis)).tw.
10. (granulomatous adj1 enteritis).tw.
11. (terminal adj1 ileitis).tw.
12. ileocolitis.tw.
13. Corticosteroid*.tw.
14. GLUCOCORTICOIDS/
15. (glucocorticoid* adj1 effect*).tw.
16. glucocorticoid*.tw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
18. 13 or 14 or 15 or 16
19. 17 and 18
20. limit 19 to (english language and humans and yr=”2015 -Current” and “all adult (19 plus years)”)

Appendix 3

COMMON SCORING SYSTEMS USED IN MANAGEMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

Disease	Scoring System	Purpose	Score Range	Notes
Ulcerative Colitis	Mayo Score	Clinical + Endoscopic	0-12	0-2 = Remission 3-5 = Mild 6-10 = Moderate 11-12 = Severe
	Truelove & Witts	Disease severity classification	Mild Moderate Severe (ASUC)	Refer to Table 7 in the text
	UCEIS	Endoscopic severity	0-8	Vascular pattern, bleeding, ulcers
	Rachmilewitz	Endoscopic assessment	0-12	Mucosal granularity, bleeding, vascular pattern
	PUCAI	Pediatric disease activity	0-85	<10 = remission >65 = severe
Crohn's Disease	CDAI	Clinical disease activity	0->600	<150 = remission >450 = severe
	HBI	Simplified clinical index	0->16	4 = remission
	SES-CD	Endoscopic severity	0-56	Higher = more inflammation
	Rutgeerts	Post-op recurrence	i0-i4	After ileocolonic resection
	PCDAI	Pediatric disease activity	0-100	<10 = remission
General	IBD-Control	Patient-reported control	0-16	Short form for QoL & symptom tracking

Adapted from:

1. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: A randomized study. N Engl J Med. 1987;317(26):1625–1629.
2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. BMJ. 1955;2(4947):1041–1048.
3. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative colitis Endoscopic Index of Severity (UCEIS). Gut. 2012;61(4):535–542.
4. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298(6666):82–86.
5. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133(2):423–432.
6. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's diseaseactivity index: National Cooperative Crohn's diseaseStudy. Gastroenterology. 1976;70(3):439–444.
7. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980;1(8167):514.
8. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505–512.
9. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956–963.
10. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12(4):439–447.

Appendix 4

PRE-ADVANCED THERAPY CHECKLIST

	Yes	No	Remarks
Sign and symptoms of active TB or past history of TB or close family member contact of active TB			
IGRA (TB Quantiferon Gold or T-spot)			Positive/Negative
Baseline CXR			Normal/Abnormal
History of allergies			
History of demyelinating disease			
History of heart failure			
Baseline echocardiogram (in > 60 years old)			
Hepatitis B surface antigen (HBsAg)			Reactive/ Non-reactive
Antibody to hepatitis B core antigen (anti-HBc)			Reactive/ Non-reactive/ Not-applicable
Antibody to hepatitis B surface protein (anti-HBs)			
Antibody to hepatitis C virus (Anti-HCV)			Reactive/ Non-reactive
Human immunodeficiency virus (HIV)			Reactive/ Non-reactive
Epstein- Barr virus immunoglobulin G (EBV IgG)			Positive/ Negative
Varicella zoster virus immunoglobulin G (VZV IgG)			Positive/ Negative
Contraception (if relevant)			
Bacillus Calmette-Guerin (BCG) vaccination			
Influenza vaccination			
Pneumococcal vaccination			
Varicella zoster vaccination			
Covid vaccination			

Adapted from:

1. Maaser C, Sturm A, Vavricka SR et al., ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13(2):144-164
2. Benchimol EI, Tse F, Carroll MW, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients with Inflammatory Bowel Disease (IBD)-Part 1: Live Vaccines. J Can Assoc Gastroenterol. 2021;4(4):e59-e71
3. Jones JL, Tse F, Carroll MW, et al. Canadian association of gastroenterology clinical practice guideline for immunizations in patients with inflammatory bowel disease (IBD)—part 2: inactivated vaccines. Journal of the Canadian Association of Gastroenterology. 2021;4(4):e72-91
4. Lamb CA, Kennedy NA, Raine T et al., British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-s106

Appendix 5

PROFORMA ON ENDOSCOPIC SPECIMEN SUBMISSION FOR HISTOLOGIC ASSESSMENT FOR CHRONIC IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD) & OTHER COLITIDES

HOSPITAL _____

CLINICAL INFORMATION (to be filled up by clinician/endoscopist)

NAME:	
MRN/ID:	DATE:
Please ☐ tick/fill up all relevant clinical/endoscopic information concerning this patient.	
1	Known case of IBD? ☐ No ☐ Yes; specify duration:
2	Current clinical episode ☐ Asymptomatic/surveillance ☐ Symptomatic
	2.1 Main symptoms ☐ Diarrhoea (please detail out): ☐ Per-rectal bleed ☐ Abdominal pain ☐ Perianal discharge ☐ Mucus and/or blood in stool ☐ Anaemia ☐ Weight loss ☐ Others (specify)
	2.2 Duration ☐ …… Days ☐ ……Weeks ☐ …… Months ☐ ……Years
3	Endoscopic Findings
	3.1 Procedure-type: ☐ Colonoscopy (state extent of intubation): ☐ Sigmoidoscopy
	3.2 Luminal/mucosal features: ☐ Normal ☐ Abnormal (give details below) Appearance of abnormal mucosa: ☐ Ulceration ☐ Erosion ☐ Inflammation ☐ Loss of vascular pattern ☐ Pseudopolyps ☐ Diverticuli ☐ Others (please describe) Distribution: ☐ Continuous ☐ Distal colitis ☐ Pancolitis ☐ Discontinuous/Skip ☐ Focal/Patchy ☐ Segmental
	3.3 Sites involved: ☐ Terminal ileum ☐ Ileocaecal valve/junction ☐ Caecum ☐ Ascending colon ☐ Hepatic flexure ☐ Transverse colon ☐ Splenic flexure ☐ Descending colon ☐ Sigmoid ☐ Rectosigmoid ☐ Rectum
	3.4 Suspicious for dysplasia &/or neoplasia:
	☐ No ☐ Yes (describe appearance and specify site):
	3.5 Other comments
	3.6 Biopsied site(s) Gentle reminder: A minimum of two biopsies from terminal ileum and at least five sites along the colon, including the rectum, should be sampled for optimal assessment. ☐ Terminal ileum ☐ ICV/junction ☐ Caecum ☐ Ascending colon

	☐ Hepatic flexure	☐ Transverse colon	☐ Splenic flexure	☐ Descending colon
	☐ Sigmoid	☐ Rectosigmoid	☐ Rectum	☐ ……
	3.7 Other procedures performed: ☐ No ☐ Yes (please describe findings) ☐ OGDS ☐ Small bowel enteroscopy			
4	Other relevant clinical history (drugs/treatment [e.g. MMF, immune checkpoint inhibitors, bowel surgery]; family hx of TB, immune deficiency and malabsorption in paediatric patients, etc.)			
5	Relevant laboratory tests results (e.g. Stool culture; C.diff toxin, CRP, FC)			
6	Radiological findings if available			
7	Clinical impression/differential diagnoses ☐ Suspected IBD → ☐ Possible UC ☐ Possible CD ☐ Uncertain ☐ Known IBD (☐ UC or ☐ CD or ☐ IBDU) → ☐ Surveillance ☐ Disease flare ☐ Other (specify): ☐ Acute/infective-type colitis ☐ Other(s); please specify			
8	Endoscopist (signature, stamp and date required)			

Source:
Anatomic Pathology Malaysia. Reporting Proforma. Malaysia: Ministry of Health Malaysia; (Available at: https://sites.google.com/moh.gov.my/anatomic-pathologymalaysia/ publication/reporting-proforma?authuser=0)

Appendix 6

HISTOLOGIC ASSESSMENT & REPORTING OF ENDOSCOPIC SPECIMENS FOR CHRONIC IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD) & OTHER COLITIDES
Version 2/2024

PATHOLOGIST'S REPORT (MICROSCOPY SUMMARY WORKSHEET)

This is a histologic summary/checklist and may not necessarily replace routine narrative reporting

NAME:				HPE No:
MRN/ID:				DATE:
If applicable, more than one item may be ☑				
1. Overall histology: ☐ Normal ☐ Abnormal ☐ Minimal/minor change(s)				
2. Distribution of changes				
	2.1 Pattern: ☐ Diffuse/continuous ☐ Focal/patchy/discontinuous ☐ Not applicable; no abnormality detected/normal histology			
	2.2 Involved sites (specify): ☐ Not applicable; no abnormality detected/normal histology ☐ Terminal ileum ☐ ICV/junction ☐ Caecum ☐ Ascending colon ☐ Hepatic flexure ☐ Transverse colon ☐ Splenic flexure ☐ Descending colon ☐ Sigmoid colon ☐ Rectosigmoid ☐ Rectum ☐ Unable to comment due to (specify): ☐ Specimens from different segments all placed in one container ☐ Localised sampling ☐ Other(s):			
3. Features of chronicity				
	3.1 Increase chronic inflammatory cells: ☐ No ☐ Mild ☐ Moderate ☐ Marked - basal plasmacytosis: ☐ No ☐ Mild/focal ☐ Moderate/Marked ☐ Unable to assess (superficial/minimal biopsy material or head-on embedding)			
	3.2 Mucosal architectural distortion: ☐ None ☐ Mild ☐ Moderate ☐ Marked Description:			
	3.3 Metaplasia	Paneth cell:	☐ No	☐ Yes
		Pseudopyloric:	☐ No	☐ Yes
4. Mucosal activity: ☐ Yes ☐ None				

	4.1 Features: ☐ Ulceration ☐ Crypt abscesses ☐ Surface epithelial neutrophils ☐ Erosion ☐ Cryptitis ☐ Lamina propria neutrophils
	4.2 Severity: ☐ Mild ☐ Moderate ☐ Severe
5. Granulomas: ☐ No ☐ Yes	
	Granuloma characteristics (tick all features that are present): ☐ Small/Micro-granulomas ☐ Medium-sized ☐ Large-sized ☐ In superficial mucosa ☐ non-caseating ☐ Caseating ☐ Isolated/non-coalesced ☐ In deeper mucosa/submucosa ☐ Coalesced ☐ Occasional per biopsy area ☐ Multiple per biopsy area ☐ In endoscopically normal looking/non-inflamed areas
6. Dysplasia: ☐ Negative ☐ Indefinite ☐ Low grade ☐ High grade	
7. Other histologic changes/ Additional comments: Examples	
	☐ Increased intraepithelial lymphocytes ☐ with ☐ without subepithelial collagen plate thickening ☐ Significant mucosal eosinophilia ☐ Others (describe):
8. Diagnostic category (in correlation with clinical, endoscopic and other relevant investigation findings)	
	☐ **IBD**
	☐ Ulcerative colitis; definite/likely/ on follow up ☐ Ulcerative colitis favoured over CD — Degree of mucosal activity: ☐ None ☐ Mild ☐ Mod ☐ Severe
	☐ Crohn's disease; definite/likely/on follow up ☐ Crohn's diseasefavoured over UC — Degree of mucosal activity: ☐ None ☐ Mild ☐ Mod ☐ Severe
	☐ IBD Unspecified (IBDU) - Reasons for inability to specify: — Degree of mucosal activity: ☐ None ☐ Mild ☐ Mod ☐ Severe
	☐ **non-IBD**
	☐ Acute/Infective-type colitis ☐ Intestinal TB ☐ Ischemic colitis ☐ Microscopic colitis: ☐ Lymphocytic ☐ Collagenous ☐ SRUS/Mucosal prolapse syndrome ☐ Other (specify):
	☐ **Unascertained (see examples below)**
	i. Granulomatous colitis with overlapping features between CD and TB. ii. Active colitis with subtle/modest chronicity changes; prolonged infection is possible but cannot exclude early phase IBD. iii. Active/acute colitis; histology suggests infective-type colitis but does not correlate with clinical symptoms/findings. Thus, IBD cannot be excluded. iv. Predominantly mucosal eosinophilia; differentials to consider include helminthiasis, food allergy, drug-induced colitis and eosinophilic colitis (the latter is a diagnosis by clinical exclusion).
	☐ **Normal histology** ☐ **Minor histologic changes**
9. Final Interpretation & Comments	

Source:
Anatomic Pathology Malaysia. Reporting Proforma. Malaysia: Ministry of Health Malaysia; (Available at: https://sites.google.com/moh.gov.my/anatomic-pathologymalaysia/ publication/reporting-proforma?authuser=0)

COMMONLY USED INTESTINAL ULTRASOUND SCORING INDICES FOR ULCERATIVE COLITIS (UC)

Scoring Index	Formula	BWT	CDS	BWS	i-FAT	Strengths	Limitations	Evidence	Validation
IBUS-SAS	Scored 0–100 =4 × BWT + 15 × i-fat + 7 × CDS + 4 × BWS	Normal ≤3 mm Active >3 mm	0 = absent 1 = short signals 2 = long signals inside bowel 3 = long signals inside and outside bowel	0 = normal 1 = uncertain 2 = focal ≤3 cm 3 = extensive >3 cm	0 = absent 1 = uncertain 2 = present	Multiple studies highlighting reproducible sensitivity, specificity, and accuracy	More granular; onerous to calculate	Strong correlation with endoscopic activity, both MES and UCEIS Optimal cut-off for predicting moderate endoscopic activity was higher using UCEIS	Not validated
MUC	=1.4 × BWT + 2 × BWF	BWT = mm	1=present 0 =absent	—	—	Multiple studies with reproducible results Highly correlated with endoscopic activity	Only includes two parameters	MUC < 6.2 predicted endoscopic improvement MUC at week 12 was an independent predictor for MES < 1 and MES = 0 MUC < 6.2 at week 12 predicted long-term endoscopic response MUC > 6.2 predicted endoscopic activity	Validated using endoscopy as a reference standard

Abbreviations: BWF = Bowel Wall Flow; BWT = Bowel Wall Thickness; BWS = Bowel Wall Stratification; CDS = Colour Doppler Signal; IBUS-SAS = International Bowel Ultrasound Segmental Activity Score; i-fat = inflammatory fat; MES = Mayo Endoscopic Score; MUC = Milan Ultrasound Criteria; UCEIS = Ulcerative Colitis Endoscopic Index of Severity

COMMONLY USED INTESTINAL ULTRASOUND SCORING INDICES FOR CROHN'S DISEASE (CD)

Scoring Index	Formula	BWT	CDS	BWS	i-fat	Strengths	Limitations	Evidence	Validation
IBUS-SAS	Scored 0–100 =4×BWT + 15×i-fat + 7×CDS + 4×BWS	Normal - ≤3 mm; Active - >3 mm	0 = absent; 1 = short signals; 2 = long signals inside bowel; 3 = long signals inside and outside bowel	0 = normal; 1 = uncertain; 2 = focal ≤3 cm; 3 = extensive >3 cm	0 = absent; 1 = uncertain 2 = present	Incorporates BWT, BWS, CDS, i-FAT Most investigated Strong predictor of endoscopic remission Most responsive score	More granular [onerous to calculate]	Multiple studies show reproducible sensitivity, specificity and accuracy; Strong intra- and inter-rater reliability	Validated in multiple studies; good correlation with endoscopic scores; high sensitivity and specificity for detecting endoscopic activity in CD
BUSS	= 0.75× BWT + 1.65× CDS	Normal ≤3 mm; Active >3 mm	0 = absent; 1 = present	—	—	Simple calculation Strong predictor of endoscopic remission Correlates with histologic remission	Less specific than IBUS-SAS Less responsive	Strong correlation with SES-CD; Strong intra- and inter-rater reliability	Validated and shows good correlation with endoscopic activity and has demonstrated accuracy in assessing response to therapy in CD

Abbreviations: BUSS = Bowel Ultrasound Score, BWT = Bowel Wall Thickness, BWS = Bowel Wall Stratification, CDS = Colour Doppler Signal, IBUS-SAS = International Bowel Ultrasound Segmental Activity Score, i-fat = inflammatory fat, MRI = Magnetic Resonance Imaging, SES-CD = Simple Endoscopic Score for Crohn's Disease.

Adapted from:
Yanai H, Feakins R, Allocca M, et al. ECCO-ESGAR-ESP-IBUS Guideline on Diagnostics and Monitoring of Patients with Inflammatory Bowel Disease: Part 2. J Crohns Colitis. 2025;19(7):jjaf107.

MRI SCORING SYSTEMS FOR CROHN'S DISEASE

Scoring System	Key Imaging Features	Formula / Highlights	Reference Standard	Cut-off for Activity / Severity
Magnetic Resonance Index of Activity (MaRIA)	WT, RCE, oedema, ulcer	**MaRIAseg** = 1.5·WT + 0.02·RCE + 5·oedema + 10·ulcer **MaRIAglobal** = ∑MaRIAseg	CDEIS, colonoscopy	Active = ≥7 Severe = ≥11
Simplified MaRIA (sMaRIA)	WT > 3 mm, oedema, fat stranding, ulcer (binary)	MaRIAs = 1·WT+ 1·oedema + 1·fat stranding + 2·ulcers.	CDEIS, colonoscopy	Active = ≥1 Severe = ≥2 (standard threshold) or ≥3 (high-specificity threshold)
Clermont Score	WT, ADC (in place of RCE), oedema, ulcer	Clermont = 1.646·WT – 1.321·ADC + 5.613·oedema + 8.306·ulcer + 5.039	MaRIA, ileocolonoscopy	Active = >8.4 Severe = >12.5
Crohn's disease RI Index (CDMI)	WT, T2 signal (visually scored)	CDMI = 1.79 + 1.34·mural thickness + 0.94·mural T2 score.	Histopathologic scoring, biopsy	Active inflammation = ≥4.1
Magnetic Resonance Enterography Global Score (MEGS)	WT (graded), mural T2 & T1 signal, enhancement pattern, haustral loss, disease length, lymph nodes, comb sign, abscess, fistulae	Composite per-segment weighted score across 9 GI segments; plus, extra points for lymph nodes, comb sign, abscess, fistula.	clinical markers (FCP, CRP, HBI)	MEGS correlates positively with FCP (r = 0.46), CRP (r = 0.388)
Lemann Index	Multimodal: clinical exam, history, MRE, and endoscopy evaluations	Structural damage score—quantifies cumulative bowel damage via an index combining clinical, imaging, and endoscopic data.	Clinical/imaging/endoscopy multimodal	No specific imaging cut-offs;assesses cumulative damage

Abbreviations: ADC = Apparent Diffusion Coefficient, CDEIS = Crohn's Disease Endoscopic Index of Severity, CRP = C-reactive Protein, FCP = Faecal Calprotectin, HBI = Harvey–Bradshaw Index, MARIA = Magnetic Resonance Index of Activity, MEGS = Magnetic Resonance Enterography Global Score, MRE = Magnetic Resonance Enterography, RCE = Relative Contrast Enhancement, T1 = T1-weighted imaging, T2 = T2-weighted imaging, and WT = Wall Thickness.

RECOMMENDED DOSING, ADVERSE EFFECTS AND CONTRAINDICATION FOR MEDICATIONS USED IN ADULTS AND CHILDREN WITH IBD

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
ORAL CORTICOSTEROIDS (SYSTEMIC)				
Prednisolone **High bioavailability with extensive systemic absorption* **Strong anti-inflammatory effect with higher risk of AEs*	PO 30 - 40 mg once daily; taper down 5 mg weekly (Duration: ≤ 8 weeks) Paediatric dose (weight-dependant) 1 mg/kg/day (max 40 mg/day) once daily for 1 - 2 weeks (not more than 4 weeks) Then taper down by 5 mg weekly (Duration: ≤ 8 weeks)	• Adrenal suppression • Hypertension • Dyslipidemia • Fluid retention • Hypokalemia • Hypernatremia • Arrhythmias • Cardiac failure • Psychiatric disturbances • Cushingoid appearance • Weight gain • Peptic ulcer • Hyperglycemia • Infection • Osteoporosis • Increase ocular pressure • Glaucoma	• Hypersensitivity to prednisone/ prednisolone or any component of the formulation • Co-administration of live or live attenuated vaccines • Systemic infections • Herpes simplex infections	• Adrenal suppression • Kaposi sarcoma • Bariatric surgery • GI disease • Head injury • Myasthenia Gravis • Ocular disease • Renal impairment • Seizure disorder • Systemic sclerosis • Thyroid disease
ORAL CORTICOSTEROIDS (LOCALLY ACTING AND CONTROLLED RELEASE)				
Budesonide **Low bioavailability with effective local action in the gut and reduced systemic exposure*	PO 9 mg once daily (Duration: ≤ 8 weeks)	• Hypertension • Peripheral oedema • Cushingoid features • Bruising • Headache • Muscle spasm	• Hypersensitivity to budesonide or any component of the formulation • Lecithin (derived from soya oil, peanut oil) or any excipients	• Adrenal suppression • Anaphylactoid reactions • Immunosuppression • Myopathy • Psychiatric disturbances

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
**Lower risk of AEs compared to prednisolone*		• Respiratory tract infection		
5-AMINOSALICYLIC ACID (5-ASA)				
5-ASA (Mesalazine)	Oral formulation: 1. Mesalazine 500 mg MR tablet Induction: 3.0 - 4.0 g/day in divided doses Maintenance: 1.5 - 2.0 g/day in divided dose 2. Mesalazine 1.2 g gastro-resistant prolonged release tablet Induction: 3.6 - 4.8 g/day once daily Maintenance: 2.4 g/day once daily 3. Mesalazine 1.5 g gastro-resistant prolonged release granules Induction: 3.0 - 4.5 g once daily Maintenance: 1.5 - 3.0 g once daily 4. Mesalazine 2 g prolonged release granules Induction: 4.0 g/day in divided doses	Delayed hypersensitivity reactions: • Myocarditis • Pericarditis • Interstitial nephritis • Increase ALT • Hepatotoxicity • Pancreatitis • Neutropenia • Thrombocytopenia • Aplastic anemia • Interstitial pulmonary disease • Steven-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Intolerance syndrome • Nephrotoxicity	• Hypersensitivity to mesalazine, aminosalicylate, salicylates, or any component of the formulation • Severe hepatic impairment • Severe renal impairment (egfr <30 ml/min) - gastro-resistant prolonged release tablet	• Photosensitivity • Hepatic impairment • Renal impairment • Cardiac hypersensitivity • Chronic lung function • Asthma • Pregnancy • Lactation

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
	Maintenance: 2.0 g/day in divided dose Paediatric dosage: Induction: Oral Mesalazine 50 - 70 mg/kg/day up to 100 mg/kg/day or 4.8 g daily Rectal Mesalazine 25 mg/kg up to 1g daily Maintenance: The induction dose that achieves clinical effectiveness may be used for maintenance, with dose reduction as appropriate within the recommended range of 50 - 70 mg/kg/day.			
	Topical formulation: 1. Mesalazine 1 g suppository 1 g rectally once daily (retained in the rectum 1 to 3 hours) 2. Mesalazine 1 g/100 ml enema 1 g rectally once daily 3. Mesalazine 2 g/30 ml enema 2 g rectally once daily Paediatric dosage: Rectal Mesalazine 25 mg/kg up to 1g daily			

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
IMMUNOMODULATORS				
Azathioprine	PO Initially 50 mg once daily; titrate up to 2.5 mg/kg once daily over ≥12 weeks as indicated and tolerated Paediatric dosage: PO initially 1 mg/kg/day then titrate up to 2 – 2.5 mg/kg/day	• Nausea • Vomiting • Diarrhoea • Thrombocytopenia • Macrocytic anemia • Pancytopenia • Infections • Hepatotoxicity • Malignancy • Pancreatitis	• Hypersensitivity to azathioprine or any component of the formulation	• Hepatic impairment • Renal impairment • Myastenia gravis • Maintenance azathioprine monotherapy may be continued during pregnancy. • Initiation during pregnancy not recommended
Methotrexate (MTX)	Moderate to severe CD Induction: • IM or SC 15 - 25 mg once weekly (in combination with folic acid) • PO, IM or SC 12.5 - 15 mg once weekly (in combination with biologic therapy) • Max 25 mg once weekly Maintenance: IM or SC up to 25 mg once weekly. If remission maintained for 4 months, may reduce to 15 mg once weekly. Paediatric dosage: PO 15 mg/m^2 (max 25 mg) once a week PO Folate 5 mg 24 – 72 hours after MTX once a week	• SJS • TEN • Erythema muliforme • Stomatitis • Nausea • Vomiting • Bone marrow suppression • Anemia • Agranulocytosis • Increased liver enzymes • Hepatoxicity • Infection • Nephrotoxicity • Encephalopathy • Headache • Leukoencephalopathy	• Hypersensitivity to MTX or any component of the formulation • Pregnancy • Lactation • Severe myelosuppression • Serious renal and liver impairment • Increase risk of toxicity in the presence of third space fluid (pleural effusion, ascites)	• Active infections • Administration schedule as a weekly dose

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
Mercaptopurine (6-MP)	Moderate UC Maintenance: PO 1 - 1.5 mg/kg/day Moderate CD Maintenance: PO 0.75 - 1.5 mg/kg/day	• Skin rash • Anorexia • Diarrhoea • Nausea • Vomiting • Bone marrow depression • Malaise	• Hypersensitivity to mercaptopurine or any component of the formulation	• Bone marrow suppression • Hepatotoxicity • Immunosuppression • Macrophage activation syndrome • Photosensitivity • Secondary malignancy
ANTI-TUMOUR NECROSIS FACTOR (ANTI-TNF)				
Infliximab	Induction: IV 5 mg/kg at week 0, 2, and 6 Maintenance: IV 5-10 mg/kg every 8 weeks Paediatric dosage: Induction: IV 5 – 10 mg/kg at week 0, 2 and 6 Maintenance: IV 5 – 10 mg/kg every 4 – 8 weeks	• Influenza • Herpes infections • Headache • Infusion related reactions • GI disturbances • Rashes • Pruritus	• Hypersensitivity to infliximab or any component of the formulation • Severe infections (e.g. TB) • Sepsis • Abscesses • Oppotunistic infections • Moderate or severe heart failure	• Antibody formation • Cardiovascular/ Cerebrovascular reactions following infusion • Hematologic disorders

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
Adalimumab	Induction: SC 160 mg at week 0 (either 4 injections in a day, or 2 injections for two days), then 80 mg at week 2, then Maintenance: SC 40 mg every other week Paediatric dosage: Induction at week 0: > 40 kg: 160 mg < 40 kg: 80 mg Maintenance: > 40kg: 80 mg week 2 then continue with 40 mg every other week < 40 kg: 40 mg week 2 onwards every other week	• Antibody formation • Demyelinating disease (multiple sclerosis, optic neuritis, Guillain-Barre syndrome) • Dermatologic reactions • Heart failure • Hepatitis B re-activation • Hepatotoxicity • Infection • Injection-site reactions • Malignancy • TB	• Hypersensitivity to adalimumab or any component of the formulation	• Antibody formation • Hematologic disorders • Active infection • Immunocompromised (HIV positive)
ANTI-INTEGRIN				
Vedolizumab	Induction: IV 300 mg at week 0, 2, and 6 Maintenance: IV 300 mg every 8 weeks Paediatric dosage: Induction: 200 mg/m^2 or 10 mg/kg (max 300 mg) at week 0, 2 and 6 Maintenance: 200 mg/m^2 or 10 mg/kg (max 300 mg) every 8 weeks from week 14	• Infusion related reactions • Increase ALT and AST (>3 times upper limit of normal) • Progressive multifocal leukoencephalopathy • Nasopharyngitis • Headache • Athralgia	• Serious and hypersensitivity to vedolizumab or any component of the formulation	• Infection (discontinue if severe) • Co-administration of live or live attenuated vaccines

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
Adalimumab	Induction: SC 160 mg at week 0 (either 4 injections in a day, or 2 injections for two days), then 80 mg at week 2, then Maintenance: SC 40 mg every other week Paediatric dosage: Induction at week 0: > 40 kg: 160 mg < 40 kg: 80 mg Maintenance: > 40kg: 80 mg week 2 then continue with 40 mg every other week < 40 kg: 40 mg week 2 onwards every other week	• Antibody formation • Demyelinating disease (multiple sclerosis, optic neuritis, Guillain-Barre syndrome) • Dermatologic reactions • Heart failure • Hepatitis B re-activation • Hepatotoxicity • Infection • Injection-site reactions • Malignancy • TB	• Hypersensitivity to adalimumab or any component of the formulation	• Antibody formation • Hematologic disorders • Active infection • Immunocompromised (HIV positive)
ANTI-INTEGRIN				
Vedolizumab	Induction: IV 300 mg at week 0, 2, and 6 Maintenance: IV 300 mg every 8 weeks Paediatric dosage: Induction: 200 mg/m^2 or 10 mg/kg (max 300 mg) at week 0, 2 and 6 Maintenance: 200 mg/m^2 or 10 mg/kg (max 300 mg) every 8 weeks from week 14	• Infusion related reactions • Increase ALT and AST (>3 times upper limit of normal) • Progressive multifocal leukoencephalopathy • Nasopharyngitis • Headache • Athralgia	• Serious and hypersensitivity to vedolizumab or any component of the formulation	• Infection (discontinue if severe) • Co-administration of live or live attenuated vaccines

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
ANTI-INTERLEUKIN				
Ustekinumab	Induction: • 55 kg and less: IV 260 mg single dose • >55 kg to 85 kg: IV 390 mg single dose • >85 kg: IV 520 mg Maintenance: • SC 90 mg every 8 weeks (starting 8 weeks after IV induction dose) Paediatric dosage: Induction: IV 6 mg/kg rounded 130 mg (max 520 mg) Maintenance: BSA adjusted dose SC 90 mg or 45 mg every 8 weeks from week 8	• Anaphylaxis • Infusion related reaction (immediate) • Hypersensitivity reactions (immediate and delayed) • Infection • Malignancy • Non-infectious pneumonia • Posterior reversible encephalopathy syndrome • TB	• Hypersensitivity to ustekinumab or any component of the formulation	• Antibody formation • Hypersensitivity reactions • Infections • Malignancy • Non-infectious pneumonia • Posterior reversible encephalopathy syndrome • TB
Risankizumab	Moderate to severe UC Induction: IV 1200 mg at weeks 0, 4 and 8 Maintenance: SC 180 to 360 mg at week 12, then every 8 weeks thereafter Moderate to severe CD Induction: IV 600 mg at weeks 0, 4 and 8 Maintenance: SC 180 to 360 mg at week 12, then every 8 weeks thereafter	• Antibody formation • Infection • Upper respiratory tract infection • Skin rash • Abdominal pain • Anemia • Fatigue • Athralgia • Arthrophy • Fever • Injection site reaction	• Serious hypersensitivity to risankizumab or any component of the formulation	• Antibody formation • Hepatotoxicity • Hypersensitivity reactions (discontinue if serious) • Infection • TB

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
Guselkumab	Moderate to severe UC Induction: IV 200 mg at weeks 0, 4, and 8 Maintenance: SC 100 mg every 8 weeks or 200 mg every 4 weeks	• Abdominal pain • Antibody formation • Infection • Respiratory tract infection	• Serious hypersensitivity to guselkumab or any component of the formulation	• Antibody formation • Hepatotoxicity • Hypersensitivity reactions (discontinue if serious) • Infection • TB
*Mirikizumab	UC Induction: IV 300 mg at weeks 0, 4 and 8 Maintenance: SC 200 mg at weeks 12, then every 4 weeks thereafter **If dose is missed, administer as soon as possible and then resume every 4 week dosing*. CD Induction: IV 900 mg at weeks 0, 4 and 8 Maintenance: SC 300 mg at week 12, then every 4 weeks dosing	• Antibody development • Infections • Upper respiratory tract infection • Skin rash • Increased liver enzymes • Herpes virus infection • Injection-site infection • Headache • Arthralgia • Infusion-related reaction • Hypersensitivity reactions	• Serious hypersensitivity reactions to mirikizumab or any component of the formulation	• Hepatotoxicity • Hypersensitivity reactions • Infections • TB • Pre-existing liver cirrhosis

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
ORAL JANUS KINASE INHIBITOR				
Tofacitinib	UC Induction: PO 10 mg twice daily for at least 8 weeks, maximum 16 weeks or transition of maintenance dose **Discontinue if inadequate response after 16 weeks with PO 10 mg twice daily* Maintenance: PO 5 mg twice daily	• Bone marrow suppression • Myocardial infarction • Cerebrovascular accident • GI perforation • Hepatotoxicity • Infection • TB • Herpes zoster infections • Hepatitis B re-activation • Malignancy • Thrombosis • Infection • Hyperlipidemia	• Serious hypersensitivity to tofacitinib or any component of the formulation	• Hypersensitivity reactions (discontinue if serious) • Interstitial lung disease (ILD)
Upadacitinitib	UC Induction: PO 45 mg once daily for at least 8 weeks Maintenance: PO 15 - 30 mg once daily **Discontinue if inadequate response with PO 30 mg once daily* CD Induction: PO 45 mg once daily for at least 12 weeks Maintenance: PO 15 - 30 mg once daily **Discontinue if inadequate response with PO 30 mg once daily*	• GI perforation • Anemia • Lymphocytopenia • Neutropenia • Increase ALT and AST • Infection • Major cardiovascular events • Malignancy • Thrombosis • TB • Dermatological disorders • Headache • URTI	• Hypersensitivity to upadacitinib or any component of the formulation	• GI perforation • Anemia • Lymphocytopenia • Neutropenia • TB

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
CALCINEURIN INHIBITOR				
Ciclosporin	ASUC IV 2 mg/kg/day, infused continuously over 24 hours Maintenance PO 5 mg/kg BD (for 3 months) Paediatric dosage: ASUC IV 2 mg/kg/day, infused continuously over 24 hours up to 7 days or until response	• Gingival hyperplasia • Thrombotic microangiopathy • Hepatotoxicity • Hyperkalaemia • Infections • Malignancy • Nephrotoxicity • Neurotoxicity	• Hypersensitivity to ciclosporin or any component of the formulation • IV ciclosporin is contraindicated in hypersensitivity to polyoxyethylated castor oil (Cremophor EL)	• Hepatic impairment • Psoriasis
SPHINGOSINE-1-PHOPSHATE (S1P)				
*Etrasimod	UC PO 2 mg once daily	• Infections • Bradycardia • Hypertension • Hypercholesterolemia • Nausea • Urinary tract infection • Lymphocytopenia • Increased liver enzymes (cholestasis, hyperbilirubinemia, increased gamma-glutamyl transferase ALP, ALT and AST) • Herpes virus infection • Dizziness • Headache • Arthralgia • Decreased visual acuity	History of • myocardial infarction, • unstable angina, • stroke transient ischemic attack • decompensated heart failure requiring hospitalisation or class III or IV heart failure in the past 6 months, • second-degree or third-degree atrioventricular block, sick sinus syndrome, or sino-atrial block, unless patient has a functioning pacemaker	• Immune reconstitution inflammatory syndrome (IRIS) • Increased blood pressure • Infections • Opportunistic fungal or viral infection • Liver injury • Macular edema • Malignancy • Posterior reversible encephalopathy

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
*Ozanimod	UC Induction: PO 0.23mg once daily (Day 1 - Day 4), then 0.46mg once daily (Day 5 - Day 7) Maintenance: PO 0.92mg once daily (starting Day 8 onwards) *If missed during the first 2 weeks of treatment, re-initiate the titration regimen with 0.23mg once daily. *If a dose missed after the first 2 weeks of treatment, continue with treatment as planned.	• Transient dose-dependent decreases in heart rate • Bradycardia • Orthostatic hypotension • Hypertension (delayed – usually after 3 months of initiation) • Cutaneous malignancy • Increased liver enzymes (increased gamma-glutamyl transferase ALP, ALT and AST) • Lymphocytopenia/ infection • Macular edema • Respiratory effects • Progressive multifocal leukoencephalopathy and sequele • Posterior reversible encephalopathy syndrome	• Myocadiac infarction • Unstable angina • Transient ischemic attack • Decompensated heart failure requiring hospitalisation or class III or IV heart failure in the last 6 months • Second or third-degree atrioventricular block, unless the patient has a functioning pacemaker • Severe untreated apnoea • Concomitant use of a monoamine oxidase inhibitor	• Infections • Varicella zoster infections • Hepatic impairment

*Unavailable in Malaysia

Adapted from:

1. Ministry of Health Malaysia. *Ministry of Health Medicines Formulary (MOH Formulary Book*). Putrajaya: Pharmaceutical Services Division, Ministry of Health Malaysia; 2025.
2. Wolters Kluwer. *UpToDate* [Internet]. Waltham (MA): Wolters Kluwer; [cited 2025 August 26]. Available from: https://www.uptodate.com
3. Wolters Kluwer. *Lexicomp* [Internet]. Hudson (OH): Wolters Kluwer; [cited 2025 August 26]. Available from: https://www.lexicomp.com
4. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. Am J Gastroenterol. 2025;120(6):1187-1224.

LIST OF ABBREVIATIONS

µg/g	micrograms per gram
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ACG	American College of Gastroenterology
ACT	acceptance commitment therapy
AE	adverse effects
ALP	alanine phosphatase
ALT	alanine aminotransferase
ANCA	anti-neutrophilic cytoplasmic antibody
Anti-TNF	anti-tumour necrosis factor
ASC	acute severe colitis
ASCA	anti-saccharomyces cerevisiae antibodies
ASUC	acute severe ulcerative colitis
AST	aspartate aminotransferase
AUC	area under curve
BD	bis die (twice daily)
BSG	British Society of Gastroenterology
CBT	cognitive behavioural therapy
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDED	Crohn's disease exclusion diet
CDEIS	Crohn's disease endoscopic index of severity
CE	capsule endoscopy
CI	confidence interval
CMV	cytomegalovirus
CPG	clinical practice guidelines
CRP	c-reactive protein
CS	corticosteroid
CT	computed tomography
CTE	computed tomography enterography
CXR	chest x-ray
DASS	depression anxiety stress scale
DG	development group
dl	deciliter
DVT	deep vein thrombosis
EAUS	endoanal ultrasonography
ECCO	European Crohn's and Colitis Organisation
EEN	exclusive enteral nutrition
EIM	extraintestinal manifestation
EN	enteral nutrition
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESPEN	European Society of Parenteral and Enteral Nutrition
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and Nutrition
ESR	erythrocyte sedimentation rate
FBC	full blood count
FC	faecal calprotectin
FL-infliximab	first-line infliximab
FMT	faecal microbiota transplantation
GI	gastrointestinal

GRADE	grading recommendations, assessment, development and evaluation
GS	Geboes score
HBI	Harvey Bradshaw Index
HCT	haematocrit
HD	high-definition
HIV	human immunodeficiency virus
HPV	human papillomavirus
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IBS	irritable bowel syndrome
ICC	intraclass correlation coefficient
IEE	image-enhanced endoscopy
IgG	immunoglobulin G
IGRA	interferon gamma release assay
IL	interleukin
IM	intramuscular
IPAA	ileal pouch anal anastomosis
IQR	interquartile range
IRA	ileorectal anastomosis
ITT	intention to treat
IUS	intestinal ultrasound
IV	intravenous
JAK	janus kinase
kg	kilogram
LFT	liver function test
MA	meta-analysis
MaHTAS	Malaysian Health Technology Assessment Section
MaRIA	magnetic resonance index of activity
MD	mean difference
MDT	multidisciplinary team
MES	Mayo endoscopic score
mg	milligramme
MMR	measles, mumps, rubella
MMX	multi-matrix system (budesonide formulation)
MRE	magnetic resonance enterography
MRI	magnetic resonance imaging
MoH	ministry of health
MTB	mycobacterium tuberculosis
MTX	methotrexate
NHI	Nancy histological index
NMA	network meta-analysis
NOS	Newcastle-Ottawa Scale
NS	non-significant
OD	once daily
OIs	opportunistic infections
ONS	oral nutritional supplement
OR	odd ratio
p	p value
PCDAI	pediatric Crohn's disease activity index
PCR	polymerase chain reaction
PEG	polyethylene glycol

PEN	partial enteral nutrition
PIBD	paediatric inflammatory bowel disease
PN	parenteral nutrition
PO	per oral
PRO2	patient reported outcome version 2
PUCAI	pediatric ulcerative colitis activity index
PUS	transperineal ultrasonography
PSC	primary sclerosing cholangitis
pt-yrs	patient-years
QoL	quality of life
QUADAS	quality assessment of diagnostic accuracy studies
RC	review committee
RCT	randomised controlled trial(s)
RHI	Robarts histological index
RR	relative risk
RoB	risk of bias
RZV	recombinant herpes zoster
S1P	sphingosine-1-phosphate
SAEs	serious adverse effects
SC	subcutaneous
SCCAIQ	simple clinical colitis activity index questionnaire
SDS	standard deviation score
SENFCR	steroid-free and exclusive enteral nutrition-free remission
SES-CD	simple endoscopic score for CD
SIBDQ	short IBDQ
sMaRIA	simplified magnetic resonance index of activity
SR	systematic review
TAU	treatment as usual
TB	tuberculosis
TDM	therapeutic drug monitoring
TDS	ter die sumendum (three times a day)
TNF	tumour necrosis factor
UC	ulcerative colitis
UCEIS	ulcerative colitis endoscopic index of severity
URTI	upper respiratory tract infections
VS	versus
VTE	venous thromboembolism
WGO	world gastroenterology organisation

ACKNOWLEDGEMENT

The DG members of these guidelines would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Technical Advisory Committee of CPG for their valuable input and feedback
- Health Technology Assessment and CPG Council for approval of the CPG
- Mr Latif Abqari bin Nazeri, Assistant medical officer and Information Specialist, MaHTAS on the retrieval of evidence

MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
62590 Putrajaya, Malaysia