

# World Journal of *Gastroenterology*

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## First United Arab Emirates consensus on diagnosis and management of inflammatory bowel diseases: A 2020 Delphi consensus

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## Abstract

Ulcerative colitis and Crohn's disease are the main entities of inflammatory bowel disease characterized by chronic remittent inflammation of the gastrointestinal tract. The incidence and prevalence are on the rise worldwide, and the heterogeneity between patients and within individuals over time is striking. The progressive advance in our understanding of the etiopathogenesis coupled with an unprecedented increase in therapeutic options have changed the management towards evidence-based interventions by clinicians with patients. This guideline was stimulated and supported by the Emirates Gastroenterology and Hepatology Society following a systematic review and a Delphi consensus process that provided evidence- and expert opinion-based recommendations. Comprehensive up-to-date guidance is provided regarding diagnosis, evaluation of disease severity, appropriate and timely use of different investigations, choice of appropriate therapy for induction and remission phase according to disease severity, and management of main complications.

**Key Words:** Ulcerative colitis; Crohn's disease; Infliximab; Adalimumab; Vedolizumab; Ustekinumab; Tofacitinib

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**Core Tip:** The prevalence of ulcerative colitis and Crohn's disease is on the rise. The advance in our understanding of the etiopathogenesis with an unprecedented increase in therapeutic options have changed the management towards tailoring evidence-based interventions. In this consensus, the diagnosis of inflammatory bowel diseases are based on the clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical findings. The therapeutic options have been revised in view of the treatment goals, which now aim to treat beyond "symptoms" to achieve mucosal healing when possible and to minimize intestinal injury and bowel damage with resultant disability.

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## INTRODUCTION

Inflammatory bowel diseases (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, progressive, and potentially disabling conditions affecting the gastrointestinal (GI) tract<sup>[1-6]</sup>. The incidence and prevalence of IBD is increasing worldwide at an alarming rate including in African countries, the Middle East, and the Asia Pacific<sup>[4,7-12]</sup>. Meanwhile, the aetiology remains unknown, although IBD is believed to be triggered by aberrant immune responses often in a genetically predisposed individual to certain environmental triggers<sup>[13-15]</sup>. Rapid strides in our understanding of the etiopathogenesis of IBD coupled with an unprecedented increase in therapeutic options including biological and "small molecule" therapies have redefined our treatment goals, which now aim to treat beyond "symptoms" to achieve mucosal healing when possible and limit intestinal injury and bowel damage with resultant disability<sup>[16-21]</sup>.

Due to the progressive change of IBD management, a two-round Delphi technique method was used to reach a consensus among nine expert gastroenterologists working in the United Arab Emirates.

## METHODOLOGY OF THE CONSENSUS

The consensus was promoted and supported by the Emirates Society of Gastroenterology and Hepatology; the president (MAK) selected the members of the committee among the public and private sectors across different Emirates of United Arab Emirates based on their competence on IBD. An extensive research of the relevant scientific literature was made by a medical writer company on Medline and EMBASE databases from the first published until December 2018 and then updated to December 2019 and made available to the committee members. Clinical priorities covered by the consensus were: adult cases, definition, clinical characteristics and diagnosis, investigations including imaging, monitoring, treatment of active phases and maintaining the remission, managing of perianal disease, and prevention of postsurgical recurrence in CD. Published guidelines and consensus from the European Crohn's Colitis Organization, British Society of Gastroenterology, American College of Gastroenterology, and American Gastroenterological Association were also taken into consideration.

Draft of statements/recommendations was compiled by a medical writer and distributed to the entire panel for the first assessment of the agreement. The statements were finalized by the panel in two face-to-face meetings. A Likert-type scale (1, strongly disagree; 2, disagree; 3, neutral; 4, agree; and 5, strongly agree) was used to measure the agreement. In cases of disagreement, uncertainty, or agreement less than 75% of participants, the panelists were required to submit comments and propose changes. In case of debate or conflict, revoting was recommended. The updated statements were then re-evaluated by the entire panel in the second round.

An agreement of 75% or more represented a strong recommendation; 50%-74.9% represented a recommendation, and less than 50% was represented as a suggestion. Percentage of the final agreement is given between brackets ([Table 1](#)) ([Supplementary Table 1](#)).

## CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

### UC

**Statement 1:** UC is suspected when a patient, especially in late adolescence or early adulthood, reports having bloody diarrhoea for more than two weeks, rectal bleeding, rectal urgency, tenesmus, mucopurulent exudate, faecal incontinence, nocturnal defecation, and crampy abdominal pain. [100]

**Statement 2:** Examination of suspected patients with mild or moderate UC is usually unremarkable; digital rectal examination can be done to confirm fresh blood in the rectum. [100]

**Statement 3:** IBD is suspected when the patient has a family history of UC or CD. [88.8]

**Statement 4:** Severe colitis is suspected when a patient presents with increased bowel frequency (six or more per day), abdominal pain/tenderness, anorexia, weight loss, tachycardia, reduced bowel sounds, and fever. [100]

UC is characterized by mucosal inflammation affecting the large intestine, typically starting in the rectum but often extending proximally to involve the colon to a variable distance<sup>[4,22,23]</sup>. Rectal sparing may occur in up to 3% of patients, and patchy inflammation may be present in those treated with topical therapy<sup>[24-27]</sup>. Likewise, localized inflammation at the cecum or around the appendix as well as so-called backwash ileitis may also be found<sup>[24-26]</sup>. UC may present at any age but typically presents between ages 15-30 and follows a relapsing-remitting course<sup>[4]</sup>. Up to 90% of patients may experience one or more episodes of relapse after the first attack, and active disease with frequent relapses in the first two years after diagnosis is linked with a worse prognosis<sup>[22,28]</sup>. UC typically presents with rectal bleeding, diarrhoea, tenesmus (a sense of pressure), and urgency often associated with crampy abdominal pain, faecal incontinence, and nocturnal diarrhoea<sup>[4,29]</sup>.

CD is characterized by transmural inflammation affecting any part of the digestive tract but typically involves the ileum and colon in a typically discontinuous manner<sup>[1,30,31]</sup>. Hallmark clinical symptoms are abdominal pain, diarrhoea (with or without bleeding), weight loss, fatigue, anaemia, recurrent fistulae, and growth failure (in children)<sup>[30]</sup>. A family history may raise the index of suspicion, but disease activity or severity are unaffected by family history<sup>[32,33]</sup>. Although more susceptibility loci are

Table 1 Breakdown of the agreement on different statements (*n* = 117)

Agreement (%)	Number of statements	Strength of recommendation
100	35	STRONG recommendation
88.8	48	STRONG recommendation
77.7	26	STRONG recommendation
66.6	3	Recommendation
50.0	4	Recommendation
37.5	1	Suggestion

known for both CD and UC, only a few have been associated with disease outcomes, such as the nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*) polymorphism, which is associated with a more progressive disease course in CD with a higher risk of intestinal obstruction and need for surgery<sup>[34,35]</sup>. Genetic testing cannot be used to diagnose IBD<sup>[36,37]</sup>.

**Statement 5:** The diagnosis of IBD is established by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. [100]

The diagnosis of IBD is therefore not based on a single diagnostic criterion but in fact a combination of clinical features, biochemical (including stool) examination, endoscopic assessment, histopathology, and in the case of CD radiological investigations to visualize the small intestine<sup>[38]</sup>.

At diagnosis, blood counts, electrolytes, liver enzymes, and inflammatory markers [C-reactive protein (CRP) and stool calprotectin] should be checked<sup>[39–41]</sup>. Physical examination may be unremarkable in mild to moderate disease, although digital rectal examination may show evidence of fresh blood in the rectum. Anaemia (iron and/or vitamin B<sub>12</sub> deficiency) and an elevated platelet count are common at diagnosis<sup>[39–41]</sup>. Serum CRP is an acute-phase reactant produced by the liver that rises in any case of inflammation including active IBD<sup>[42]</sup>. Its half-life is of 19 h, which makes it a useful marker to detect and monitor inflammation. Erythrocyte sedimentation rate (ESR) is a nonspecific marker of inflammation that may be increased in patients with IBD. Although sometimes helpful individually, it is not specific for active IBD<sup>[41]</sup>. Because up to half of patients with IBD can have normal CRP and ESR values when the activity is mild, their use in monitoring is limited<sup>[41]</sup>. An elevated CRP may correlate with the clinical activity in CD but less well with UC except in acute severe UC<sup>[29,30,43,44]</sup>. Faecal calprotectin (FC) is a calcium binding protein, derived from neutrophils with a specific release in the presence of intestinal inflammation, correlating well with endoscopic findings, and is a good marker of relapse and response to treatment and in differentiating patients with IBD from those with irritable bowel syndrome<sup>[45,46]</sup>. It lacks specificity to distinguish IBD from other causes of bowel inflammation<sup>[47]</sup>.

Stool cultures and *Clostridium difficile* toxin assay are recommended to rule out infective aetiology<sup>[48,49]</sup>. Loose stools for over 6 wk help to distinguish infective causes from inflammatory bowel disease<sup>[50,51]</sup>.

The diagnosis of IBD needs an endoscopic assessment, typically an ileo-colonoscopy for CD and sigmoidoscopy in the case of UC followed by an ileo-colonoscopy within 12 mo of diagnosis to establish disease phenotype, determine full disease extent, and risk stratify for dysplasia<sup>[52–54]</sup>. Accordingly, UC is characterized according to the Montreal classification as proctitis (E1), left-sided colitis (E2) (up to splenic flexure), and extensive colitis proximal to the splenic flexure or pancolitis up to the cecum (E3)<sup>[55,56]</sup>. As per the Truelove and Witts criteria, mild colitis is defined as fewer than four bowel movements daily with no fever, normal heart rate, haemoglobin > 11g/dL, and ESR < 20 mm/hr. The disease is defined as severe by bowel frequency greater than six times a day along with fever, tachycardia, anaemia, or an elevation in ESR<sup>[57]</sup>.

At histology, a combination of features including basal plasmacytosis, diffuse crypt atrophy and distortion, villous surface irregularity, and mucous depletion support a diagnosis of UC when in agreement with clinical symptoms<sup>[31]</sup>. Although no single feature is diagnostic<sup>[31,58]</sup>.

## CD

**Statement 6:** CD is suspected when a patient, especially young, presents with abdominal pain, weight loss, constipation, or chronic diarrhoea. [88.8]



**Statement 7:** A patient with CD commonly presents with systemic symptoms of malaise, anorexia, or fever. [77.7]

**Statement 8:** Symptoms of CD are nonspecific and mimics that of irritable bowel syndrome. Unexplained anaemia and growth failure should be considered to avoid delayed diagnosis. [100]

**Statement 9:** The symptoms of acute terminal ileal CD may be mistaken for acute appendicitis. [88.8]

**Statement 10:** Physical examination of patients with CD may reveal tenderness or a palpable mass. Some may present with perianal disease (abscess, fistula, fissure) [88.8]

**Statement 11:** Infections or drug-induced colitis must always be excluded [88.8]

CD is a chronic, progressive inflammatory disorder of the GI tract<sup>[1]</sup>. Classical symptoms include abdominal pain, chronic diarrhoea and fatigue, although patients may also present with weight loss, fever, anaemia, growth failure, recurrent fistulae, and extraintestinal manifestations<sup>[59]</sup>. Physical examination may reveal these findings. Additionally, abdominal examination may reveal tenderness particularly in the right iliac fossa or a palpable mass in the affected area. Some patients may also present with perianal disease in the form of an abscess, fistula, or fissure.

The most common symptom of CD is chronic diarrhoea, although some patients may have a normal bowel habit<sup>[60]</sup>. Terminal ileal disease may be mistaken for acute appendicitis. Fatigue is a very common and less well understood symptom of CD, which may be multifactorial and stem from inflammation, anaemia, and micronutrient, vitamin, and mineral deficiency. Fever, weight loss, or even growth failure (in younger individuals) may be presenting features<sup>[1,59]</sup>. This myriad of symptoms can often be mistaken for irritable bowel syndrome, which may delay the diagnosis of CD<sup>[1,2,16]</sup>.

In a population-based study from Manitoba, Canada, 41 % of patients had a three year or greater delay in diagnosis from the onset of symptoms<sup>[61]</sup>. In another study, the time to diagnose was on average seven years in patients with CD, even when those individuals meeting Rome criteria for irritable bowel syndrome were excluded from the analysis as compared with less than one year to diagnosis for patients with UC<sup>[62]</sup>. Stool cultures and *Clostridium difficile* toxin assay are recommended to rule out infective aetiologies<sup>[48,49]</sup>. Loose stools for over 6 wk help to distinguish infective causes from IBD<sup>[50,51]</sup>. Drug-induced colitis must also be excluded<sup>[59,63]</sup>.

**Statement 12:** Genetic or serological testing is currently not recommended yet for routine diagnosis of IBD. [100]

**Statement 13:** If diagnosis of IBD is in doubt despite an interval of appropriate treatment, a repeated endoscopy is required. [88.8]

The diagnosis of CD is based on a combination of investigative modalities. A clinical history and examination as appropriate, ileo-colonoscopy, small intestinal radiological assessment, laboratory tests, and histological examination of mucosal biopsies from endoscopy<sup>[64]</sup>. Mucosal biopsies from endoscopy or surgical resection specimens may show inflammation and/or crypt distortion. Endoscopic features more suggestive of CD are discontinuous segments of disease ("skip lesions"), ileal involvement, and granulomatous inflammation. Approximately 3% of UC patients may be reclassified as Crohn's colitis<sup>[65]</sup>. Conversely, 0.6%-3% will be reclassified to alternative colitis after initial diagnosis of CD<sup>[66]</sup>.

CD may be diagnosed on surgical samples when at least three histological features suggestive of CD [segmental crypt architectural abnormalities and mucin depletion, mucin preservation at the active sites, and focal chronic inflammation (without crypt atrophy)] are found in the absence of granulomas, or when an epithelioid granuloma is detected in combination with an additional feature<sup>[31,58]</sup>. Some patients cannot be assigned to either CD or answer to colitis and are labelled as IBD unclassified<sup>[65,66]</sup>. Thus, if the diagnosis of IBD is in doubt despite an interval of appropriate treatment, repeat endoscopy is required to help establish the diagnosis. Despite a growing number of identified susceptibility loci in both CD and UC, few have been associated with disease outcomes, such as the nucleotide-binding oligomerization domain-containing protein 2 polymorphism, which is associated with a more aggressive disease course in CD with a higher risk of intestinal stenosis and need for surgery<sup>[34,35]</sup>. Genetic testing cannot be used to diagnose IBD<sup>[36,37]</sup>.

## CLASSIFICATION AND SEVERITY

### UC

**Statement 14:** UC disease extent is defined by the maximal macroscopic extent at colonoscopy and classified as proctitis, left-sided colitis, and extensive colitis (according to the Montreal classification). [100]

The Montreal classification in adults<sup>[55]</sup> and Paris classification in children<sup>[67]</sup> are useful for the phenotypic classification of patients.

Knowledge of disease extent is a key determinant of prognosis as the risk of colectomy hinges on disease extension<sup>[68]</sup>. A systematic review reported a ten-year colectomy rate of 19% for extensive colitis, 8% for left-sided colitis, and 5% for proctitis<sup>[4]</sup>. Further risk factors for colectomy are male gender, young age, and elevated inflammatory biomarkers at diagnosis<sup>[4]</sup>. Backwash ileitis was associated with more aggressive disease and with primary sclerosing cholangitis<sup>[4]</sup>. Those with extensive colitis also have the highest risk of developing colorectal cancer<sup>[69,70]</sup>. Notably, disease extent can change after diagnosis<sup>[56,71]</sup>. Up to half with proctitis or proctosigmoiditis will develop more extensive disease. Of patients with proctitis initially, 10% will ultimately have extensive colitis<sup>[4,22,71]</sup>. Disease extent should be reported as the maximum extent of inflammation, remembering that information may regress over time. Furthermore, and especially in quiescent UC, endoscopic appearances may be underestimated. Biopsies should be taken to determine the full extent of involvement.

**Statement 15:** According to severity, UC is either in remission characterized by the absence of symptoms and the absence of an endoscopic acute inflammatory changes, or an active disease characterized by the presence of symptoms and endoscopically active mucosal findings. [77.7]

**Statement 16:** The severity of UC can be classified into mild, moderate, and severe based on clinical symptoms and signs, blood tests, and endoscopy. [100]

Although the Truelove and Witts criteria (discussed under statement 5) are relatively easy to use and useful in determining the opportunity for hospital admission, the index is not designed to provide a measure of severity and does not include nocturnal symptoms. Furthermore, it does not consider endoscopic severity.

Several scoring systems are available to classify disease severity in UC<sup>[72]</sup>. They aid objective assessment of disease and guide therapeutic and monitoring strategies. Their use allows clinicians to monitor patient progress during follow-up<sup>[17,54]</sup>.

The simple colitis clinical activity index is a reliable and responsive score with clear definitions for clinical response and remission<sup>[73]</sup>. Simple colitis clinical activity index scores range between 0 and 19 points and include nocturnal bowel movements and faecal urgency, which affect patient quality of life<sup>[73]</sup>. A SCCAI score < 2 indicates clinical remission, and a decrease of > 1.5 points from baseline correlates with patient-defined significant improvement<sup>[74]</sup>.

The Mayo Clinic Score (MCS) or index (partial Mayo Clinic index and endoscopic subscore) and ulcerative colitis disease activity index (UCDAI) represent a composite assessment of clinical symptoms (stool frequency and rectal bleeding) and endoscopic severity<sup>[75,76]</sup>.

Although not validated, the MCS is easy to calculate and has been applied for evaluating therapeutic outcomes in clinical trials<sup>[77]</sup>. The score evaluates stool frequency, rectal bleeding, a physician's global assessment, and mucosal inflammation at endoscopy with a value ranging from 0 to 3 and a maximum score of 12 points. Clinical improvement is generally defined as the drop of baseline scores by  $\geq 3$  points whereas clinical remission as an overall score  $\leq 2$  (and no individual sub-score > 1) or UCDAI  $\leq 1$ <sup>[75,76]</sup>. A partial Mayo score (PMS) < 1 indicates remission<sup>[17]</sup>. The PMS uses the clinical elements of the MCS and is well correlated with perceptions of treatment efficacy by the patients<sup>[78,79]</sup>.

Recently, the patient reported outcome (PRO), derived from components of the Mayo score has been put forward as an interim outcome measure when in combination with endoscopic findings. PROs appear to be well correlated with disease activity and may predict patient-defined remission<sup>[80]</sup>.

Several endoscopic scoring systems for UC are available. They include numerous descriptors namely, vascular pattern, mucosal erythema, mucosal granularity, mucosal oedema, mucopurulent exudate, bleeding, friability, erosions, and ulcers<sup>[54,81,82]</sup>. An extensive review of scoring systems is beyond the scope of this manuscript, but the reader is referred to an exhaustive review with images and videos for reference<sup>[54]</sup>.

The endoscopic component [Mayo endoscopic sub-score (MES)] of the MCS is the most widely used, and it assesses inflammation based on a 4-point scale (0-3): (0)

normal; (1) erythema, decreased vascular pattern, mild friability; (2) marked erythema, absent vascular pattern, friability, erosions; and (3) ulceration, spontaneous bleeding<sup>[75]</sup>. Mucosal healing is defined as a sub-score of 0-1, although this has not been formally validated<sup>[75,83]</sup>.

A post-hoc analysis of the active ulcerative colitis trial (ACT)-1 trial demonstrated that patients achieving a post-treatment MES of 0 or 1 had similar colectomy rates and were significantly less likely to undergo colectomy in the subsequent year than those with higher MES<sup>[84]</sup>. Higher steroid-free remission rates were noted in patients with MES of 0 at 1 year than those with an MES of 1<sup>[84]</sup>. Furthermore, MES of 0 was associated with a lower risk of clinical relapse than MES of 1 (5.0% *vs* 9.4%, respectively)<sup>[26,85,86]</sup>. The MES is relatively easier to use and has been used extensively in clinical trials. The lack of validation, inability to distinguish superficial from deep ulcers, that it reflects appearances of the most severely affected visualized segment and has no minimal insertion length are significant limitations<sup>[87]</sup>.

Variability in interobserver agreement can result from variability in the assessment of friability. This has led to the development of the Modified Mayo Score (MMES)<sup>[88]</sup>. The MMES classifies any degree of friability with a sub-score of 2. It divides the colon into five segments, and the score for each segment is added to give a Modified Score, which is multiplied by the maximal extent of inflammation and divided by the number of segments with active inflammation to give the final MMES<sup>[88]</sup>. Although MMES correlates with clinical, biological, and histological activity, this has not been validated. The Mayo score is most widely used in clinical practice.

Two scoring systems were developed in an attempt to develop a prospective validated tool: The ulcerative colitis endoscopic index of severity (UCEIS) and the ulcerative colitis colonoscopic index of severity (UCCIS)<sup>[89-91]</sup>. The UCEIS considers three endoscopic findings; vascular pattern, bleeding, and erosions/ulcers scored in the most severely affected part of the colon. It was initially developed as an 11-point score and then simplified to an 8-point tool scoring erosions/ulcers (0-2), vascular pattern (0-2), and bleeding (1-4) with a satisfactory interobserver agreement (kappa 0.5)<sup>[90]</sup>. Friability was excluded from this index. Although easy to use in clinical practice, thresholds for mild, moderate, and severe disease have not been defined. UCEIS does not define the extent of disease as it scores the most affected segment. It does demonstrate more responsiveness to ulcer size, depth, and change following treatment than the MCS<sup>[92-94]</sup>. Furthermore, a UCEIS of zero was associated with a lower risk of relapse than UCEIS of 1 (5% *vs* 22.4%)<sup>[94]</sup>. Both scores demonstrated a high degree of correlation for disease assessment by sigmoidoscopy and colonoscopy<sup>[95]</sup>.

The UCCIS has been prospectively validated<sup>[91]</sup>. It includes six variables: (1) Vascular pattern; (2) Granularity; (3) Ulceration; (4) Bleeding/friability; (5) Grading of segmental and global assessment of endoscopic severity with a predefined 4-point scale; and (6) Global assessment of endoscopic severity on a 10-cm visual analogue scale with good to excellent interobserver agreement<sup>[91]</sup>. Although correlation with clinical activity and CRP was demonstrated, a cut off level for endoscopic response and remission is not currently known<sup>[91]</sup>.

## CD

**Statement 17:** CD is classified according to disease location: terminal ileum, colon, ileocolonic, and upper GI (Montreal classification). [77.7]

**Statement 18:** CD is divided according to disease behaviour (stricturing, penetrating, nonstricturing/nonpenetrating, with or without perianal involvement) (according to Montreal classification). [100]

CD is widely classified using the Montreal classification in adults and the Paris classification in the paediatric IBD population<sup>[55,67]</sup>. Thus, L1 relates to terminal ileal CD, L2 to ileo-colonic CD, and L3 to colonic CD. Isolated upper GI disease (L4) is further subdivided into L4a (upper disease proximal to the ligament of Treitz) and L4b (upper disease distal to the ligament of Treitz and proximal to distal 1/3 of the ileum)<sup>[55]</sup>. Perianal disease is denoted by "P"<sup>[72]</sup>. Disease behaviour is designated as B1 (nonstricturing-nonpenetrating), B2 (stricturing), and B3 (penetrating) disease. Furthermore, age at diagnosis is denoted as A1 (< 17 years), A2 (17-40 years), and A3 (> 40 years).

The majority of patients (56%-81%) have an inflammatory phenotype at diagnosis and between 5% and 25 have stricturing or penetrating disease<sup>[1]</sup>. Indeed, a large population-based study reported a cumulative risk of 51% to develop an intestinal complication after 20 years of follow-up in patients presenting with inflammatory behaviour at diagnosis<sup>[96]</sup>. In addition, at multivariate analysis, ileal, ileocolonic, or upper GI involvement compared to colonic involvement alone were significantly

associated with onset of intestinal complications<sup>[96]</sup>. Risk factors for severe disease include young age at diagnosis<sup>[97]</sup>, initial extensive GI involvement, ileal/ileocolonic involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenotic disease phenotype<sup>[98]</sup>. Visceral adiposity is also associated with an increased risk of penetrating disease<sup>[99]</sup>.

## INVESTIGATIONS FOR IBD

**Statement 19:** Ileocolonoscopy with multiple biopsy specimens is the first-line procedure for diagnosing and determining the severity of IBD. [100]

**Statement 20:** For a reliable diagnosis of CD or UC, a minimum of two biopsies from five sites around the colon (including the rectum) as well as from the ileum should be obtained. [100]

The diagnosis of IBD needs an endoscopic assessment, typically an ileo-colonoscopy for CD and sigmoidoscopy in the case of UC followed by an ileo-colonoscopy within 12 mo of diagnosis to establish disease phenotype, determine full disease extent, and risk stratify for dysplasia<sup>[52-54]</sup>. A minimum of two biopsy samples must be obtained from five sites including the ileum and rectum at the first endoscopic assessment.

Endoscopic appearances of UC have been described above. The rectum is always involved but rectal sparing may be seen in up to 3% of patients<sup>[24]</sup>. Patchy inflammation of the rectum is seen in patients who have received topical therapy<sup>[26,27,100]</sup>. An isolated involvement of cecum or around the appendix as well as backwash ileitis may be seen in UC, but in the absence of supportive clinical presentation and histology, small bowel assessment should be arranged to consider CD<sup>[25]</sup>. Backwash ileitis may occur in up to 20% of patients with extensive UC<sup>[100]</sup>.

At histology, a combination of features including basal plasmacytosis, diffuse crypt atrophy and distortion, villous surface irregularity, and mucous depletion suggest a diagnosis of UC<sup>[31]</sup>. Although granulomas and focal crypt architectural abnormalities with focal or patchy chronic inflammation or mucin preservation may suggest CD, no single feature is diagnostic<sup>[31,58]</sup>. Endoscopic features suggestive of CD are discontinuous segments of disease (“skip lesions”), ileal involvement, and granulomatous inflammation. Approximately 3% of UC patients may be reclassified as Crohn’s colitis<sup>[65]</sup>. Conversely, 0.6%-3% will be reclassified to alternative colitis after initial diagnosis of CD<sup>[66]</sup>. Although a diagnosis of CD may be made on surgical samples<sup>[31,58]</sup>, some patients cannot be assigned to either CD or UC and are labelled as IBD unclassified<sup>[65,66]</sup>. Thus, if the diagnosis of IBD is in doubt despite an interval of appropriate treatment, repeat endoscopy is required to help establish the diagnosis<sup>[63]</sup>.

**Statement 21:** Stool specimens should be obtained to exclude common pathogens and specifically assayed for *Clostridium difficile* toxin. [88.8]

**Statement 22:** Laboratory markers of chronic inflammation may correlate with the severity of IBD. [50]

**Statement 23:** CRP broadly correlates with clinical severity. [77.7]

**Statement 24:** Elevated ESR, CRP, anaemia, number of bowel movements, and hypoalbuminemia are signs of severe clinical activity that predict the need for colectomy in severe acute colitis. [88.8]

**Statement 25:** Microbial testing should be done in patients with colitis with every disease flare. [100]

Stool cultures and *Clostridium difficile* toxin assay are recommended to exclude infective aetiologies<sup>[48,49]</sup>. Loose stools for over 6 wk help to distinguish infective causes from IBD<sup>[50,51]</sup>. In a recent UK study, 10% of IBD relapses were associated with enteric infections, 50% of which were *Clostridium difficile* related<sup>[101]</sup>. An American study reported that 18.1% and 16.1% of samples from CD and UC patients, respectively, were positive for GI pathogens using a multiplex PCR<sup>[102]</sup>. Norovirus and *Campylobacter* were more likely in CD patients, while UC patients were more likely to have *Campylobacter*, *Plesiomonas*, and *Escherichia coli* (compared with non-IBD samples)<sup>[102]</sup>. Thus, a comprehensive infection screen considering relevant clues from the clinical history should be considered for every flare of IBD. *Clostridium difficile* infection has been associated with worse outcomes in hospitalized IBD patients<sup>[103,104]</sup>.

An elevated ESR, CRP, anaemia, number of bowel movements, and hypoalbuminemia are signs of severe clinical activity that can predict the need for



colectomy in acute severe UC. A stool frequency  $> 8/d$  or stool frequency  $> 3/d$  with CRP  $> 45$  mg/L on day 3 of intravenous corticosteroid predicts the need for rescue therapy to prevent colectomy<sup>[44]</sup>. Several other mathematical models comprising stool frequency, CRP, and albumin on day 3 may also guide clinicians to use “rescue therapy” with infliximab (IFX) or cyclosporine to prevent the need for colectomy<sup>[105-107]</sup>.

FC is a calcium binding protein derived from neutrophils with a role in intestinal inflammation regulation. It is a useful inflammatory marker, correlating well with endoscopic findings. It is also a good marker of relapse and response to treatment and in differentiating patients with IBD from those with irritable bowel syndrome<sup>[45,46]</sup>. It lacks specificity to distinguish IBD from other causes of bowel inflammation<sup>[47]</sup>. Calprotectin values correlate well with endoscopic indices of disease activity and is therefore very helpful in different clinical settings, including diagnosis, relapse, and response to therapy<sup>[46,108-110]</sup>. A clear-cut threshold value to distinguish between IBD and functional bowel diseases has not been set yet<sup>[41,111]</sup>. However, an acceptable diagnostic accuracy can potentially be obtained at a cut-off value of  $150 \mu\text{g/g}$ <sup>[41]</sup>. It also appears to be strongly correlated with endoscopic inflammation in UC<sup>[112]</sup>. An elevated faecal calprotectin  $> 1000 \mu\text{g/g}$  stool on day 3 of intravenous corticosteroid along with a UCEIS  $> 6$  on admission is also a predictor of the need for colectomy<sup>[113]</sup>.

**Statement 26:** Serological testing currently available is not recommended for differentiating colonic CD from UC. [77.7]

Serological markers may have a role in supporting a diagnosis, though the accuracy of the best available tests (perinuclear anti-neutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies) is rather weak and therefore not effective at discriminating colonic CD from UC<sup>[114]</sup>. The incremental diagnostic value of antiglycan and antimicrobial antibodies, such as anti-OmpC (*Escherichia coli* outer membrane porin C) and CBIR1 (CBIR1 flagellin), is minimal and not clinically relevant<sup>[115]</sup>. Despite a growing number of identified susceptibility loci in both CD and UC, only a few have been associated with disease outcomes, such as the *NOD2* polymorphism that is associated with a more aggressive disease course in CD with a higher risk of intestinal stenosis and need for first surgery<sup>[34,35]</sup>. Genetic testing cannot be used to diagnose IBD<sup>[36,37]</sup>.

**Statement 27:** Diagnostic criteria for iron deficiency depend on the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin  $< 30 \mu\text{g/L}$  is an appropriate criterion. In the presence of inflammation, serum ferritin up to  $100 \mu\text{g/L}$  may still be consistent with iron deficiency. [88.8]

Up to 1/3 of patients with active IBD will have iron deficiency anaemia<sup>[116]</sup> leading to fatigue and negative impact on quality of life. It should be remembered that systemic inflammation may inhibit iron absorption<sup>[116]</sup>. In the presence of active disease, oral iron supplementation should be avoided, and in patients with inactive IBD, no more than  $100 \mu\text{g/L}$  of elemental iron should be administered daily<sup>[117,118]</sup>. Ferritin is an acute phase reactant, and it should be remembered that iron deficiency may be present with a level up to  $100 \mu\text{g/L}$  in case of active inflammation. The evaluation of transferrin saturation is therefore essential to distinguish true iron deficiency from a falsely elevated ferritin<sup>[63,117,118]</sup>. Intravenous iron may be administered to patients who are intolerant to oral iron or have active IBD with moderate to severe iron deficiency anaemia<sup>[116]</sup>.

**Statement 28:** Cross-sectional imaging magnetic resonance imaging (MRI) and computed tomography (CT) enterography and transabdominal ultrasonography (US) are used to complement endoscopy. [100]

**Statement 29:** Complementary radiological techniques using MRI, CT, and US should be used to rule-out stenotic lesions and are necessary when the lesion is impassable with the endoscope. [88.8]

MRI and CT enterography and US are used to complement endoscopy and have largely replaced fluoroscopic techniques over the years<sup>[63,72]</sup>. These techniques have the advantage of better classifying disease phenotype and behaviour by providing information on the bowel wall and extra enteric soft tissue pathology<sup>[119]</sup>. Small bowel US may be performed with or without bowel distension and the use of oral contrast<sup>[119]</sup>. Meta-analyses have shown no significant difference in accuracy for CD diagnosis with CT enterography, small bowel US, and MRI enterography<sup>[120-123]</sup>. Sensitivity and specificity ranges between 85% and 95%<sup>[120-123]</sup>. CT is extremely accurate for evaluation and monitoring of mural and extramural complications in CD patients, although it is not recommended to monitor disease activity due to significant radiation



exposure<sup>[124,125]</sup>. State-of-the-art low radiation dose CT scanners may significantly reduce the dose, but the use of nonionizing imaging is preferable, considering the young age of these patients and the need of repetition during the lifespan<sup>[121,124,125]</sup>. Thus, CT should be ideally used only in the emergency setting, and if small bowel US and MRI are not available<sup>[72,121]</sup>.

Magnetic resonance enterography and CT have shown high accuracy for detecting active CD<sup>[120,121]</sup>. Magnetic resonance enterography features of active disease include an increase in intestinal wall thickness and vascularity, contrast enhancement on T2 and diffusion weighted imaging signals, presence of ulcers, and extraluminal complications<sup>[120,121]</sup>. These findings are usually reported with specific activity scores<sup>[126,127]</sup>. Data supporting small bowel US are less consistent currently<sup>[128]</sup>.

They may also be useful when assessing areas impassable with an endoscope, particularly stenotic lesions<sup>[63]</sup>. Patients with CD have a 2-3 fold increased risk of colorectal cancer compared to an age-matched population and the risk of small bowel malignancy between 18 and 27 times. Stricturing in the context of CD may be complicated by dysplasia or cancer. Therefore, endoscopy and biopsies should be performed. Fibrotic structures may be assessed using modern imaging such as MRI and techniques in development such as magnetization transfer sequences, delayed contrast enhancement, contrast enhanced US, and elastography<sup>[127,129,130]</sup>. US detection of strictures may be improved by the use of oral contrast<sup>[131]</sup>.

**Statement 30:** CD patients with symptoms of the upper GI tract should receive esophagogastroduodenoscopy to rule out proximal involvement. [88.8]

CD affecting the upper GI tract may be present in 13%-16% of patients. It is usually accompanied by ileal and/or colonic disease<sup>[132,133]</sup>. Upper GI endoscopy should be performed in patients with dyspepsia, vomiting, or other upper GI symptoms but is not routinely indicated in adults with proven or suspected CD<sup>[51,72]</sup>. Focal gastritis may be a feature of CD<sup>[134]</sup>. In patients with IBD-unspecified, upper GI endoscopy may help to differentiate between UC and CD<sup>[63]</sup>. Upper GI endoscopy should be performed in patients with suspected CD<sup>[135]</sup>.

**Statement 31:** Small bowel capsule endoscopy (SBCE) should only be used when the clinical suspicion for CD remains high despite negative evaluations with ileocolonoscopy and radiological examinations (MRI/CT). This could be useful to assess the disease extent. [66.6]

**Statement 32:** SBCE is contraindicated in GI obstruction, strictures, and swallowing disorders. [100]

SBCE enables the entire small bowel to be assessed by a wireless capsule<sup>[136]</sup>. Specificity for the diagnosis of IBD was reported as 53% in one study using a consensus standard<sup>[137,138]</sup>. Minor mucosal abnormalities may obscure the diagnosis such as in those using nonsteroidal anti-inflammatory drugs<sup>[139,140]</sup>.

Several scoring systems are available to grade lesions<sup>[54,136,141]</sup>, but they are not used widely. At the present time, the use of capsule endoscopy is currently restricted to patients with a high index of suspicion of CD when cross-sectional imaging has been normal or nondiagnostic<sup>[63,140]</sup>.

SBCE is contraindicated in the presence of GI obstruction, strictures, and swallowing disorders. Given the size and rigidity of capsules, they may be retained within the small bowel in the context of stricturing disease. In a recent meta-analysis, the risk of capsule retention was 3.6% [95% confidence interval (CI): 1.7%-8.6%] despite considerable heterogeneity in studies<sup>[142]</sup>. Retention rates were much lower after use of a patency capsule or stricture exclusion with cross-sectional imaging at 2.7% (95%CI: 1.1%-6.4%)<sup>[142]</sup>. The use of a patency capsule is therefore recommended in patients with stricturing CD, suspected strictures, abdominal pain, distension, nausea, vomiting, history of small intestinal resection, abdominal or pelvic radiation, and chronic nonsteroidal anti-inflammatory drugs use<sup>[140,143]</sup>.

**Statement 33:** Device-assisted enteroscopy is an invasive procedure that may only be performed by an expert if the histological diagnosis of CD is needed or when endoscopic therapy is indicated, including dilatation of strictures, retrieval of impacted capsules, and treatment of bleeding. [88.8]

Balloon assisted enteroscopy may help visualize areas outside the scope of a standard endoscope and in that respect may have a similar diagnostic yield as capsule endoscopy. It offers the added advantage in expert hands of tissue biopsy or endoscopic therapy<sup>[144]</sup>. The examination is invasive, requires sedation or general anaesthesia, is expensive, and has risks<sup>[145]</sup>. A perforation rate of 0.15% (95%CI: 0.05%-0.45%) and complication rate (including perforation and bleeding) of 0.72% (95%CI:

0.56%-0.90%) have been reported<sup>[145,146]</sup>.

**Statement 34:** In acute severe UC, a plain abdominal radiograph should be performed to exclude colonic dilatation. [37.5]

Abdominal radiographs may provide vital information in patients with acute severe ulcerative colitis (ASUC). Mucosal islands (or 'thumb printing') are predictors of failure of medical therapy. The presence of faecal residue suggests uninflamed or normal colonic mucosa. Proximal constipation may be associated with left-sided or distal colonic inflammation. Proximal constipation may worsen distal disease and require laxatives in addition to treatment of UC<sup>[43,63]</sup>. Transverse colonic and caecal diameter (diameter greater than 5.5 cm is consistent with dilatation of the colon and impending toxic dilatation)<sup>[43,58]</sup>. Cross-sectional imaging may be required in patients suspected of having extraluminal complications and perforation<sup>[147]</sup>.

**Statement 35:** Flexible sigmoidoscopy should be used to confirm the diagnosis of severe colitis and help exclude infection, particularly cytomegalovirus (CMV). [88.8]

**Statement 36:** Enema preparation before flexible sigmoidoscopy is considered safe in patients with severe UC. [77.7]

Endoscopic assessment with a sigmoidoscopy helps to confirm the diagnosis of ASUC and also to obtain biopsies to diagnose or exclude CMV colitis<sup>[147]</sup>. Colonoscopy in ASUC is associated with a significant risk of colonic dilation and perforation. A sigmoidoscopy is preferred with minimal air insufflation and by an experienced endoscopist<sup>[43,147]</sup>. Although an enema if required may be administered, it is often unnecessary. Deep ulceration at sigmoidoscopy correlates with failure of corticosteroid therapy and need for rescue therapy or colectomy<sup>[148]</sup>. Corte *et al*<sup>[149]</sup> reported that a UCEIS score  $\geq 5$  was associated with a 50% likelihood of need for medical rescue treatment and 33% risk of colectomy compared with 27% and 9%, respectively, for those who scored  $\leq 4$ . In a retrospective review of 92 patients with ASUC, the UCEIS score correlated with MES (Spearman's rho, 0.762;  $P < 0.001$ ) and requirement for colectomy [adjusted odds ratio (OR) 3.25; 95%CI: 1.77- 5.97;  $P < 0.001$ ]<sup>[150]</sup>.

CMV colitis can affect 30% of patients with ASUC refractory to corticosteroid therapy<sup>[151,152]</sup>. Medically refractory disease treatment with corticosteroids and the presence of endoscopic ulceration are risk factors for CMV colitis. Biopsy should be taken from the base of the ulcer as CMV infection has a predilection for actively inflamed tissue. Histology for a viral cytopathic effect on haematoxylin eosin staining has poor sensitivity, but immunohistochemistry with culture methods and PCR based assays are favoured to confirm CMV colitis<sup>[151-153]</sup>. The presence of CMV infection increases the risk of medical refractoriness and colectomy. As such, if CMV infection is diagnosed in steroid refractory cases, then it should be treated with antiviral therapy<sup>[151,152]</sup>. The most commonly used agent is ganciclovir administered intravenously and then for 14 d with response rates approaching 70%. Oral therapy with valganciclovir may also be used in selected patients after discussion with infectious disease physicians<sup>[151,152]</sup>.

**Statement 37:** If colonic stenosis occurs in UC, then multiple endoscopic biopsies should be taken. CT should be performed to exclude carcinoma. [77.7]

Detection of a new colonic stricture should prompt multiple biopsies to rule out malignancy. Colonic strictures at diagnosis or during follow-up were associated in one study, with a 3.6% and 4.9% probability of colorectal cancer at five and ten years, respectively<sup>[154]</sup>. In the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du tube Digestif study (GETAID), dysplasia or cancer was detected in 3.5% of patients with IBD with colonic strictures<sup>[155]</sup>. Biopsies before endoscopic balloon dilatation are recommended<sup>[155,156]</sup>.

**Statement 38:** Endoscopic reassessment is appropriate whenever it seems necessary to change management. [88.8]

**Statement 39:** Colonoscopy is also recommended to determine response to treatment and for surveillance of cancer development. [100]

**Statement 40:** In IBD, therapy and follow-up can be guided by CRP levels and faecal markers, which are able to predict clinical relapse. [77.7]

Endoscopy is currently the standard for the diagnosis and assessment of mucosal activity, dysplasia surveillance, and the assessment of response to treatment<sup>[17,54]</sup>. The lack of correlation between symptoms and objective measures of disease activity and knowledge that chronic inflammation may lead to progressive gut damage with complications has brought the concept of "treating to target," which aims to treat gut

damage or disability<sup>[1,5,16]</sup>.

Endoscopic remission (mucosal healing) has emerged as a key goal of therapy. The “treat to target” concept was developed by the Selecting Therapeutic Targets in Inflammatory Bowel Disease committee (STRIDE), consisting of experts from the International Organization for the Study of IBD<sup>[17]</sup>. Its premise is the identification of a target for which treatment is commenced and optimized with periodic monitoring until the goal is achieved, taking patient considerations into account. Specifically, they refer to resolution of abdominal pain and normalization of bowel habits and endoscopic remission (or cross-sectional imaging when endoscopy is not feasible in CD)<sup>[17]</sup>. Mucosal healing is linked to a lasting clinical response and reduction in undesirable outcomes such as corticosteroid use, hospitalization, surgery, and colorectal cancer complicating IBD<sup>[157-162]</sup>. Meanwhile, endoscopy is the standard for mucosal assessment and allows adjustments in treatment to “target”<sup>[17,54,163]</sup>. Mucosal healing, or endoscopic remission, refers to the absence of ulceration in CD and resolution in mucosal friability or ulceration at colonoscopy or sigmoidoscopy in UC<sup>[17,52]</sup>. Several endoscopic scoring systems are available for UC and CD, which provide objectivity<sup>[17,52,54]</sup>.

Although biochemical targets (CRP or faecal calprotectin) were considered adjunctive targets in the STRIDE consensus in the absence of sufficient evidence at the time, recent evidence supports use of biochemical markers such as CRP and faecal calprotectin in monitoring response<sup>[100,164]</sup>. In a meta-analysis of 2822 IBD patients and 298 controls, a calprotectin level of 50 µg/g showed the best sensitivity (90.6%) to detect endoscopic disease activity with specificity (78.2%) at calprotectin > 100 µg/g<sup>[165]</sup>. In a separate meta-analysis calprotectin of 250 µg/g provided specificity of 82% compared to thresholds of 100 µg/g and 50 µg/g (specificity of 66% and 60%, respectively) to differentiate active IBD from remission<sup>[111]</sup>. FC of 250 µg/g had sensitivity of 80% compared to a sensitivity of 84% and 92% at cut-offs of 100 µg/g and 50 µg/g, respectively<sup>[111]</sup>. Calprotectin may also be used to guide therapy changes. FC is able to distinguish between active and inactive IBD with greater accuracy for UC than CD<sup>[111,166]</sup>. Calprotectin correlates with endoscopic and histologic inflammation in UC<sup>[167,168]</sup>.

The CALM (open-label randomized effect of tight control management on Crohn’s disease) study showed that a calprotectin level less than 250 µg/g stool, CD activity index (CDAI) < 150, CRP < 5 mg/L, and corticosteroid-free remission can be used as a target with dose increase of adalimumab and azathioprine (AZA) until these objectives were achieved<sup>[164]</sup>. At 12 mo, the ‘treat to target’ group achieved the primary end-point (CDEIS score < 4, without deep ulcers) in 45.9%, whilst 30.3% of the control group had a CDEIS score < 4, without deep ulcers ( $P = 0.010$ )<sup>[164]</sup>. Calprotectin may also predict future relapse to enable considerations with treatment de-escalation<sup>[63,164]</sup>. In the STORI (Stop Infliximab in Patients With Crohn’s Disease) trial, patients stopping anti-tumour necrosis factor (TNF) who achieved mucosal healing and a calprotectin  $\geq 300$  µg/g had a 30% relapse rate whereas those with both mucosal healing and a lower calprotectin had relapse rates of between 10% and 20%<sup>[169,170]</sup>. Serial measurements are more predictive of the likelihood of relapse<sup>[63]</sup>.

## MANAGEMENT–ACTIVE UC

**Statement 41:** The treatment strategy for UC is mainly based on the severity, distribution, and pattern of disease. Disease extent influences treatment modality and choice of (oral, topical) therapy. [77.7]

The therapeutic strategy for UC should be based on the specific diagnosis, an assessment of disease activity, distribution, and disease prognosis. Thus, patients with clinically mild active UC but with a history of steroid dependence or previous hospitalization should be considered for treatment appropriate for moderate to severe active UC given the significant impact these factors may have on disease prognosis<sup>[171]</sup>. Also, deep ulceration at sigmoidoscopy predicts the failure of corticosteroid therapy and need for rescue therapy or colectomy<sup>[148]</sup>.

### Proctitis

**Statement 42:** Suppository is the preferred initial treatment for mild or moderately active proctitis. Aminosalicylate (5-ASA) foam or enemas can be used as an alternative though less tolerated. [88.8]

**Statement 43:** Combined (oral and topical) therapy is more effective than topical alone

for the treatment of proctitis. [77.7]

5-ASA suppositories are the preferred initial treatment for mild or moderately active proctitis<sup>[172]</sup>. 5-ASA suppositories achieve higher mucosal concentrations through a topical effect than oral 5-ASA alone<sup>[173]</sup>. Suppositories are preferable over enema preparations as they may be better tolerated, and enemas may pool higher up in the sigmoid<sup>[172]</sup>. When oral 5-ASA is combined with topical therapies, response rates are higher<sup>[173,174]</sup>. Furthermore, topical 5-ASA is more effective than topical hydrocortisone enemas and corticosteroids<sup>[175,176]</sup>.

Although a dose response relationship has been observed for oral 5-ASA, this has not been the case with rectal 5-ASA. In a study comparing 1 g 5-ASA suppositories daily with 500 mg three times a day, the once daily dose was found to be more convenient and had similar efficacy<sup>[177]</sup>. No significant differences were observed with doses (1 g or 4 g daily) or formulation (liquid, gel, foam, or suppository) for topical therapy. 5-ASA was noted superior to rectal corticosteroids to induce symptomatic remission (OR 1.65; 95%CI: 1.1-2.5)<sup>[172]</sup>. 5-ASA suppositories are also effective for the maintenance of remission in ulcerative proctitis and it appears that alternate day or every third day therapy does not reduce the rate of remission<sup>[172,176]</sup>.

**Statement 44:** Refractory proctitis may require treatment with systemic steroids, immunosuppressants, and/or biologics. [100]

Before labelling proctitis as “refractory,” it is important to ensure that the patient has been adherent to the treatment and that a differential diagnosis is considered. Proximal constipation maybe an exacerbating factor, which should be addressed as also coexisting irritable bowel symptoms. Infections (lymphogranuloma venereum, herpes simplex virus, syphilis, *Neisseria gonorrhoeae*, Giardia, and amoebiasis) and other pathologies such as solitary rectal ulcer, psoriatic colitis, rectal prolapse, and chemical colitis should also be considered<sup>[178]</sup>.

If compliance is established for those not responding to optimized 5-ASA, then a 5 mg prednisolone suppository may be added while continuing 5-ASA suppositories<sup>[176,179]</sup>. If the patient does not respond to this strategy, then a course of corticosteroid may be needed. Escalation to a thiopurine or biologic may be necessary<sup>[180,181]</sup>.

### Left sided UC

**Statement 45:** 5-ASA enema combined with oral 5-ASA is more effective than oral or topical 5-ASA or topical steroids alone in the treatment of mild to moderate active left-sided UC. [88.8]

**Statement 46:** Topical steroids alone are not more effective than topical 5-ASA. [50]

**Statement 47:** Once-daily dosing with 5-ASA is as effective as divided doses in mild to moderate active left- sided UC. [77.7]

**Statement 48:** Systemic corticosteroids are appropriate in patients with moderate to severe activity and in those with mild activity who do not respond to 5-ASA. [88.8]

**Statement 49:** Budesonide multimatrix (MMX) can be considered in patients with mild to moderate disease who are intolerant or refractory to 5-ASA. [77.7]

In a meta-analysis of 4 randomized controlled trials (RCT), combination therapy with rectal 5-ASA enemas (1 g/d) and oral 5-ASA (at least 2 g/d) was more effective than using oral 5-ASA on its own to induce remission in left sided UC [relative risk (RR) induction failure 0.65; 95%CI: 0.47-0.91]<sup>[174]</sup>. These findings were supported by another study that showed when comparing the two regimens an RR of 0.86 for failure with combination treatment (95%CI: 0.81-0.91)<sup>[182]</sup>. An oral 5-ASA dose of at least 2 g/d is recommended to induce remission with mildly active UC.<sup>[182,183]</sup>

Topical steroid preparations are not more effective than 5-ASA, and they should be used when patients either do not tolerate or are unresponsive to 5-ASA<sup>[172,179]</sup>. A 5 mg prednisolone suppository may be added for patients not responding to 5-ASA topical therapy while continuing 5-ASA suppositories at bedtime<sup>[63]</sup>. A double-blind double-dummy four-group prospective randomized trial compared budesonide 2 mg, budesonide 4 mg, 5-ASA 1 g, or budesonide 2 mg and 5-ASA 1 g in an 8-wk study. The primary endpoint was resolution of clinical symptoms for three consecutive days. Budesonide 4 mg was more effective than 2 mg but no different to 1 g 5-ASA or the combination of budesonide 2 mg and 5-ASA at a dose of 1 g<sup>[184]</sup>.

Budesonide MMX is a topically acting corticosteroid with high first pass metabolism and few systemic side-effects. In a recent study in UC with failure of 5-ASA,



budesonide MMX 9 mg for 8 wk was superior at achieving clinical and endoscopic remission as compared to ongoing 5-ASA and placebo ( $P = 0.049$ )<sup>[185]</sup>. Oral budesonide is also safe and more effective than placebo for the induction of remission in patients with mild active UC. In a RCT, clinical remission was achieved by 17.9% of patients given 9 mg budesonide MMX, 13.2% given 6 mg budesonide MMX, and 12.1% of those receiving 5-ASA as compared to 7.4% in the placebo group ( $P = 0.0143$ ,  $P = 0.139$ ,  $P = 0.22$ )<sup>[183]</sup>. A Cochrane systematic review rated the quality of evidence as moderate. No clear benefit for extensive UC was demonstrated, but the efficacy was significant for left sided disease with endoscopic healing rates at 27.6% *vs* 17.1% for budesonide MMX and placebo, respectively<sup>[186,187]</sup>. Budesonide MMX is associated with fewer systemic side effects than classical corticosteroids (33% *vs* 55%) but not associated with either adrenal suppression or significant reduction in bone mineral density. Although there are no adequately powered comparative studies between budesonide MMX and conventional corticosteroids, budesonide MMX could be positioned as an alternative to conventional corticosteroids in mild to moderate UC unresponsive to 5-ASA<sup>[188-191]</sup>.

### **Moderate-severe and extensive UC**

**Statement 50:** Mild to moderate active extensive UC should initially be treated with a 5-ASA enema combined with oral 5-ASA. [88.8]

**Statement 51:** Corticosteroids have potent anti-inflammatory properties and are effective for induction of remission in UC but have no efficacy for maintenance of remission, and their long-term use can lead to adverse events. [88.8]

The dose response effect of 5-ASA for induction of response in UC was investigated in the ASCEND (Delayed-release oral mesalamine for the treatment of mildly to moderately active ulcerative colitis) trials<sup>[171,192,193]</sup>. In ASCEND I, patients with mild to moderate active UC were randomized to 2.4 g or 4.8 g of mesalazine<sup>[192]</sup>. At week 6, the proportion of patients experiencing improvement in either group was similar (51% *vs* 56%,  $P =$  not significant). Patients with moderate active UC responded better to 4.8 g daily, but those with mildly active disease did not<sup>[192]</sup>. The ASCEND II study showed that patients with moderately active UC had a better response to 4.8 g daily than 2.4 g daily (72% *vs* 59%,  $P = 0.036$ )<sup>[193]</sup>. Post hoc analysis of ASCEND I and II showed greater mucosal healing in the 4.8 g/d group as compared with 2.4 g/d<sup>[194]</sup>. The ASCEND III trial randomized patients with moderate active UC to receive 2.4 g daily or 4.8 g daily mesalazine<sup>[171]</sup>. The primary endpoint of treatment success was defined as complete clinical remission or partial response showed no differences between the groups. A small but significant difference in remission with 43% of patients on 4.8 g/d *vs* 35% on 2.4 g daily was observed at 6 wk<sup>[171]</sup>. In a subgroup analysis, patients receiving oral 5-ASA and rectal therapies had a greater likelihood of response to 4.8 g/d<sup>[171]</sup>.

In a recent meta-analysis, the low dose of 2-2.4 g of 5-ASA was equally effective as 4.8 g/d (RR 0.91; 95%CI: 0.85-0.98)<sup>[182]</sup>, but the subgroup patients with moderate active UC might benefit from a higher dose of 4.8 g per day<sup>[195]</sup>. Symptomatic remission following the initiation of 5-ASA was achieved at week 2 in 10%-30% of patients, by week 4 in 30%-45%, and by week 8 in 35%-50%<sup>[196-199]</sup>. Once daily dosing of 5-ASA has been shown to be as effective as divided doses and could improve compliance<sup>[195]</sup>.

For patients with mild active UC who do not respond to 5-ASA and those with moderate to severe UC activity, oral corticosteroids can induce remission. Corticosteroids were more effective than placebo for the induction of remission (RR 0.65; 95%CI: 0.45-0.93) in a meta-analysis<sup>[200]</sup>. Prednisolone is usually started at a dose of 40-60 mg daily with a clinical response typically within 5-7 d of treatment and no benefit with doses over 60 mg daily<sup>[201]</sup>. Tapering should be tailored by clinical symptoms and response. However, steroid sparing agents should also be considered appropriately as corticosteroids have no role in maintenance of remission<sup>[202,203]</sup>.

**Statement 52:** In moderate disease refractory to oral steroids, anti-TNF, vedolizumab (VDZ), ustekinumab, and tofacitinib may be valid options. [88.8]

Anti-TNF, anti-integrin, Tofacitinib (Janus kinase inhibitor), and ustekinumab (anti-p40 subunit inhibitor of IL-12/23) are currently licensed for patients with moderately active UC refractory to oral corticosteroids.

Anti-TNF agents (IFX, adalimumab, and golimumab) have all demonstrated superiority over placebo in the induction of clinical response and remission in UC<sup>[204-206]</sup>. In the ACT-1 and ACT-2 studies, patients with moderate to severe UC, failing corticosteroids and/or thiopurines (and/or 5-ASA for ACT-2) received 5 mg/kg or 10 mg/kg IFX or placebo at 0, 2, and 6 wk and were followed through week 54 (ACT-1) or week 30 (ACT-2)<sup>[83]</sup>. Patients in both 5 mg/kg and 10 mg/kg had a similar clinical response at week 8 with pooled data showing 67% for 5 mg/kg *vs* 33%



for placebo. Clinical remission rates at week 30 were 30% for 5 mg/kg (placebo 13%) with remission sustained through week 54. Corticosteroid free remission rates were 22% for 5 mg/kg by week 30 and sustained through week 54<sup>[83]</sup>. The SUCCESS (Efficacy and Safety of Infliximab Monotherapy *vs* Combination Therapy *vs* AZA Monotherapy in Ulcerative Colitis) study showed that in patients in whom corticosteroid therapy had failed, the combination of IFX and AZA was more effective with higher clinical remission rates at week 16 (40%) compared to IFX alone (22%)<sup>[207]</sup>.

In the ULTRA (Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab) 1 and 2 trials, adalimumab showed efficacy for induction and maintenance of remission in UC<sup>[208,209]</sup>. Adalimumab 160 mg at week 0, followed by 80 mg at week 2, and then 40 mg every other week achieved remission in 19% of patients in ULTRA 1 (9% placebo) and 21% of patients in ULTRA 2 (11% placebo). In the ULTRA 2 maintenance study, clinical remission at week 52 was 22% (12% for placebo) in the anti-TNF-naïve group<sup>[208,209]</sup>. Corticosteroid free remission was achieved by week 52 in 14% patients (placebo 6%). In the open label ULTRA 3 extension study, 25% of patients remained in clinical remission at four years<sup>[210]</sup>.

Golimumab is the third anti-TNF to have regulatory approval for the treatment of moderate to severe active UC<sup>[211,212]</sup>. In the PURSUIT (An Efficacy and Safety Study of Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis) trial, patients with UC with failure to respond to 5-ASA, oral corticosteroids, AZA, mercaptopurine, or those steroid-dependent were enrolled. These patients were all anti-TNF naïve. At week 6, 51% of patients achieved clinical response on 200 mg/100 mg and 54.9% on 400 mg/200 mg, both proving significantly superior to placebo (30.3%,  $P < 0.0001$ ). Clinical remission was achieved at week 6 in 17.8% in both 200 mg/100 mg and 17.9% (400 mg/200 mg) *vs* placebo (6.4%,  $P < 0.0001$ )<sup>[211,212]</sup>. Real world studies also demonstrated similar effectiveness data<sup>[213,214]</sup>.

VDZ was approved for the management of moderate to severe active UC in 2015. In the GEMINI (Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis) I study, the primary endpoint was clinical response at week 6 (defined by a reduction in the Mayo score of  $\geq 3$  points and a decrease of at least 30% from baseline, with a decrease of  $\geq 1$  point on the rectal bleeding subscore, absolute score 0–1)<sup>[215]</sup>. For maintenance, the primary endpoint was clinical remission at week 52. Of 374 patients randomized to VDZ or placebo, clinical response at week 6 was achieved in 47.1% in the VDZ group as compared with 25.5% in the placebo group (95%CI: 11.6–31.7;  $P < 0.001$ ). At 52 wk, 41.8% of patients on VDZ 8-weekly, 44.8% on VDZ 4-weekly, and 15.9% of patients receiving placebo achieved clinical remission. VDZ was noted to be superior to placebo for clinical response (RR = 0.82, 95%CI: 0.75–0.91), induction of remission (RR = 0.86, 95%CI: 0.80–0.91), endoscopic remission (RR = 0.82, 95%CI: 0.75–0.91), and remission at 52 wk in week 6 responders (RR = 2.73, 95%CI: 1.78–4.18) in a Cochrane review<sup>[216]</sup>.

In the GEMINI open label extension, patients with  $\geq 248$  wk of cumulative VDZ treatment were included ( $n = 154$ ). Among patients responding to induction therapy who completed the maintenance study, 40.9% of patients had 248 wk of treatment; 98% achieved clinical response, and 90% had clinical remission<sup>[217]</sup>. Post hoc analysis noted improvements in PROs of reduction in rectal bleeding and stool frequency by 2 wk<sup>[218]</sup>. Real-world data provided further evidence for effectiveness and safety of VDZ<sup>[217,219–221]</sup>.

Recent systematic reviews with network meta-analysis ranked VDZ and IFX highest for induction of clinical remission in biologic-naïve UC patients<sup>[222]</sup>, and VDZ was associated with the lowest risk of serious adverse events and infections<sup>[223]</sup>. The VARSITY (Vedolizumab *vs* Adalimumab for Moderate-to-Severe Ulcerative Colitis) trial was the first head-to-head comparison that compared intravenous infusions of VDZ with subcutaneous adalimumab in a double-blind, double-dummy RCT<sup>[224]</sup>. Clinical remission at week 52 was achieved in significantly more patients who received VDZ than in those receiving adalimumab (31.3% *vs* 22.5%) as did endoscopic improvement (39.7% *vs* 27.7%). The percentage of patients who had corticosteroid free remission at week 52 (a key secondary endpoint) was higher in the adalimumab group (21.8% *vs* 12.6%). Adverse events were higher in the adalimumab group. Previous anti-TNF exposure was allowed (but capped at 25%), and no dose escalation was allowed<sup>[225]</sup>.

Tofacitinib, a nonselective inhibitor of the Janus kinase enzyme was approved by the United States Food and Drug Administration for treatment of moderate to severe UC in 2018. In the OCTAVE (Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis) 1 and 2 studies, patients with moderate to severe active UC who had failed conventional treatment with 5-ASA, corticosteroids, and/or immunomodulators and approximately 50% of whom had also failed anti-TNF

therapies were treated with 10 mg bd tofacitinib in the induction trials<sup>[226]</sup>. Clinical remission at week 8 was achieved in more patients receiving tofacitinib 10 mg twice a day (bd) (18.5% and 16.6%, respectively) than those receiving placebo (8.2% and 3.6%, respectively)<sup>[226]</sup>. In the maintenance trial at 52 wk, 46% of patients receiving tofacitinib 10 mg bd and 34.3% of patients receiving 5 mg bd achieved remission compared with 11.1% who received placebo<sup>[226]</sup>.

Clinical responders to induction therapy entered the maintenance trial SUSTAIN (Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis) and demonstrated clinical remission in 34.3% of patients treated with tofacitinib 5 mg bd and 40.6% in the 10 mg bd group as opposed to 11.1% in the placebo group ( $P < 0.001$  in both treatment arms *vs* placebo)<sup>[226]</sup>.

Herpes zoster was seen in 5.1% of tofacitinib treated patients at 10 mg bd as compared to 0.5% patients on placebo<sup>[226]</sup>. Herpes zoster vaccination should be considered before starting treatment in people above 50 years, who are considered at high risk for recurrent shingles. No live vaccination should be administered for three months after stopping a biologic, and tofacitinib should not be commenced for 4 wk after live vaccine administration<sup>[227]</sup>. An open label study in patients with rheumatoid arthritis comparing tofacitinib 5 mg or 10 mg bd with anti-TNF noted a 5-fold increased risk of pulmonary embolism in individuals over 50 years and with at least one cardiovascular risk factor in patients on tofacitinib 10 mg bd compared to those on anti-TNF<sup>[227,228]</sup>. The European Medical Agency advises against using the higher (10 mg bd) dose of tofacitinib in patients with an increased risk of pulmonary embolus including recent surgery, coagulation disorders, previous thromboembolism, heart failure, malignancy, combined contraception, or hormone replace therapy<sup>[228]</sup>.

Ustekinumab is the most recently approved biologic for moderate to severe active UC patients who have failed to respond or have intolerance to corticosteroids, immunomodulators, anti-TNF therapy, or VDZ<sup>[229]</sup>. The UNIFI trial randomized patients 1:1:1 to receive a single intravenous dose of placebo, 130 mg ustekinumab, or approximately 6 mg/kg ustekinumab (patients weighing  $\leq 55$  kg received 260 mg; patients weighing  $> 55$  kg and  $\leq 85$  kg received 390 mg; and patients weighing  $> 85$  kg received 520 mg). Clinical remission at week 8 (Mayo score  $\leq 2$  points with no individual subscore  $> 1$ ) was the primary endpoint and achieved by 15.6% on 130 mg ustekinumab, 15.5% on the approximately 6 mg/kg dose, and 5.3% on placebo ( $P < 0.001$ )<sup>[229]</sup>. Endoscopic healing (Mayo endoscopy subscore of 0 or 1) was 26.3%, 27%, and 13.8% in the three groups, respectively ( $P < 0.001$ ). Clinical response (decrease from baseline Mayo score of  $\geq 30\%$  and  $\geq 3$  points with either a decrease from baseline in the rectal bleeding subscore of  $\geq 1$  or a rectal bleeding subscore of 0 or 1) was 51.3%, 61.8%, and 31.3% in the three respective groups ( $P < 0.001$ ). Improvement in the IBD questionnaire, mucosal healing, and histological healing (defined as  $0 \leq 5\%$  neutrophils in epithelium, no crypt destruction, and no erosions, ulcerations, or granulations) was noted in active treatment arms compared to placebo at 20.3%, 18.4%, and 8.9%, respectively, at week 8. There were no differences in adverse events compared to placebo. In particular, there were no malignancies, opportunistic infections, or tuberculosis. Five-hundred and twenty three patients in clinical response at week 8 were rerandomized in the maintenance study (lasting 44 wk) to placebo, 8-weekly, or 12-weekly dosing with remission rates of 24%, 38.4%, and 43.8%, respectively ( $P = 0.002$  for 8-weekly and  $P < 0.001$  for 12-weekly *vs* placebo<sup>[229]</sup>). There were no statistically significant benefits of 8-weekly dosing (compared to 12-weekly, although numerically higher) and were restricted to the anti-TNF refractory population. The safety profile was similar to that in CD UNITI studies<sup>[229]</sup>.

### Acute Severe UC

**Statement 53:** Acute severe UC is defined as having bloody diarrhoea  $\geq 6$ /d. Any signs of systemic toxicity are an indication for hospital admission. [88.8]

**Statement 54:** Patients with severe UC should be assessed on the third day of intravenous (IV) steroid therapy; nonresponders are shifted to IFX or cyclosporine. Colectomy is recommended if there is no improvement following 4–7 d of salvage therapy. [77.7]

**Statement 55:** In severe active UC, in case of serious contraindication to steroids, IFX or cyclosporine are an alternative to the recommended IV steroids. [88.8]

Although the majority of patients tend to have a mild to moderate disease course, between 20%-25% of patients may experience a severe flare needing hospitalization for medical treatment and consideration for colectomy if medical therapy fails<sup>[230]</sup>. ASUC is associated with a 30%-40% risk of colectomy after one or more severe exacerbations,

and 10%-20% may need colectomy at their first admission<sup>[231-233]</sup>. ASUC is defined by the Truelove and Witts criteria<sup>[57]</sup> with  $\geq 6$  bloody stools per day and pulse rate  $> 90$  per minute, temperature  $> 37.8$  °C, or haemoglobin  $< 10.5$  g/L or ESR  $> 30$  mm/h and European Crohn's and Colitis Organization criteria<sup>[49]</sup>, which includes CRP  $> 30$  mg/L<sup>[49]</sup>. Patients with ASUC should be hospitalized in a specialist gastroenterology facility for multidisciplinary care. The aim is clinical remission as defined by  $\leq 3$  stools per day without rectal bleeding<sup>[49]</sup>.

A full blood count, urea, electrolytes (including serum magnesium), creatinine, ESR, CRP, liver chemistry, lipid profile, abdominal radiograph, and stool tests for culture, microscopy, and sensitivity along with *Clostridium difficile* testing should be arranged<sup>[43,49,63]</sup>. Nearly 50% of patients may prove refractory to IV hydrocortisone therapy<sup>[234]</sup>. In anticipation for rescue therapy, additional tests including tuberculosis screening (interferon gamma release assay and chest radiograph), hepatitis B serology (hepatitis B surface antigen and hepatitis B core antibody; commonly known as HbsAg and HbcAb respectively), thiopurine methyltransferase activity (if not known previously), CMV IgG and IgM, human immunodeficiency virus, and varicella zoster serology should be arranged for patients who do not show a response by day 3 of IV steroid therapy<sup>[43,49,63]</sup>.

Intravenous corticosteroid therapy, namely hydrocortisone (100 mg three to four times a day) or methylprednisolone (60 mg/d), is the cornerstone of treatment. Higher doses offer no additional benefit. In the study by Truelove *et al.*<sup>[235]</sup>, 49 patients with ASUC were treated with intravenous prednisone, and a clinical remission rate of 73 percent was noted 5 d after treatment. In a subsequent systematic review of 32 trials of corticosteroid therapy for ASUC involving 1991 patients, 67% of patients responded to steroids with 29% having a colectomy<sup>[201]</sup>. Mortality was 1%, and outcomes had not changed between 1974 and 2006<sup>[201]</sup>. Rescue therapy (or surgery) should be considered for patients unresponsive to steroid therapy between days 3 and 5. The more recently reported CONSTRUCT (Infliximab *vs* ciclosporin for steroid-resistant acute severe ulcerative colitis) study also demonstrated a response rate of intravenous steroids in 49% of patients<sup>[234]</sup>. Prolonged corticosteroid therapy beyond 7-10 d provided no additional benefit and increased the risk of toxicity<sup>[43,201]</sup>.

There are many stratification tools using clinical criteria to predict the need for timely rescue therapy or colectomy<sup>[43,49,63]</sup>. Of these, the Travis criterion is widely used and suggests that at day 3 of corticosteroid therapy, patients with a stool frequency greater than 8 per day or a stool frequency of 3 per day and CRP  $> 45$  mg/dL have an 85% likelihood of requiring colectomy in the current hospitalization<sup>[44]</sup>. Rescue therapy in the form of either IFX or cyclosporine may be effective. Patients not responding to rescue therapy with either IFX or cyclosporine should be offered prompt colectomy.

The efficacy of cyclosporine in acute steroid-refractory UC was studied by Lichtiger *et al.*<sup>[236]</sup>. Of 11 patients with steroid-refractory UC, 9 who received cyclosporine (4 mg/kg) as a continuous intravenous infusion improved, whereas the 9 patients who received placebo had no improvement. Colectomy was needed in 3 of 11 and 4 of 9 patients in the cyclosporine and placebo groups, respectively<sup>[236]</sup>. In an RCT<sup>[237]</sup> comparing 4 mg/kg with 2 mg/kg intravenous cyclosporine, both groups showed equal efficacy for severe steroid-refractory UC<sup>[237]</sup>. At day 8, response was 82% and 83%, respectively, in both groups with no difference in short-term colectomy rates.

Long-term success of cyclosporine rescue requires concomitant immunosuppression with a thiopurine<sup>[238]</sup>. A study of ASUC patients treated with intravenous cyclosporine with a median follow-up of 1.5 yrs showed that concomitant thiopurine therapy was the only factor associated with reduction in the risk of colectomy (OR 0.01; 95% CI: 0.00-0.09;  $P < 0.0001$ )<sup>[238]</sup>.

If oral cyclosporine is used as bridging therapy, then a thiopurine should be added, aiming to taper the dose of cyclosporine in a few months<sup>[239-241]</sup>. Patients with previous inadequate response to thiopurine are unsuitable for cyclosporine therapy<sup>[49]</sup>. A number of serious infections have been associated with cyclosporine in 5% of patients and mortality in 1%-3%<sup>[239,242,243]</sup>. A number of adverse events are linked to cyclosporine therapy and include nephrotoxicity (6.3%), seizures (3.6%), anaphylaxis (0.9%), and death (1.8%). Additionally, paraesthesia, hypertension, hypertrichosis, headache, minor infections, hyperkalaemia, hypomagnesaemia, and gingival swelling are also known to occur<sup>[239,242,243]</sup>. Cyclosporine is administered intravenously at a dose of 2 mg/kg/d aiming for levels between 150 ng/mL and 250 ng/mL using a monoclonal assay. Responders may be switched to an oral dose, twice the intravenous dose, administered in two doses and aiming for a trough concentration of 100-200 ng/mL<sup>[239-241]</sup>. A thiopurine should be initiated during hospitalization. Prophylaxis for *Pneumocystis jirovecii* (sulfamethoxazole and trimethoprim) must also be initiated for the duration of triple therapy for 3 mo. At the end, cyclosporine can be stopped, and

AZA continued<sup>[244-246]</sup>.

IFX is widely used as rescue therapy in ASUC<sup>[247]</sup>. In an early study, Jarnerot *et al*<sup>[249]</sup> randomized 45 patients with acute severe steroid-refractory UC (4 d after initiating steroids) to either a single infusion of IFX (5 mg/kg) or placebo. In the IFX group, 7 of 24 patients (29%) had a colectomy within 3 mo as compared with 14 of 21 patients in the placebo group<sup>[248]</sup>. Long-term (3 yrs) follow-up data of this cohort revealed a lower colectomy rate in IFX compared to controls (50% *vs* 76%) ( $P = 0.01$ )<sup>[249]</sup>. IFX carries risks such as reactivation of latent tuberculosis, opportunistic infections, and sepsis that require screening for tuberculosis and hepatitis and should be avoided in the presence of infection or sepsis<sup>[244-246]</sup>. Contraindications for IFX include congestive cardiac failure (New York Heart Association Class III/IV), demyelinating disease, sepsis, active tuberculosis, and active infection<sup>[244-246]</sup>. Mortality risk between IFX and cyclosporine are comparable<sup>[247]</sup>.

**Statement 56:** The choice between options for salvage/rescue, either IFX or cyclosporine, should be individualized. [88.8]

**Statement 57:** Prolonged use of corticosteroids should be avoided as being ineffective as maintenance therapy and may lead to increased risk of postoperative complications. [88.8]

**Statement 58:** Only a single attempt at rescue therapy with IFX or cyclosporine should be considered before referral for colectomy. [100]

Cyclosporine and IFX have demonstrated equal efficacy in head-to-head comparison studies<sup>[234,250,251]</sup>. The open-label CySIF (Cyclosporine *vs* IFX in patients with severe ulcerative colitis) trial included 115 patients previously naïve to IFX and cyclosporine with a Lichtiger score > 10 points (range 0-21) with ASUC refractory to at 5 d of intravenous steroids<sup>[251]</sup>. The patients were 1:1 randomized to receive intravenous cyclosporine (2 mg/kg per day for 1 wk, followed by oral cyclosporine until day 98) or IFX (5 mg/kg on days 0, 14 and 42). AZA was commenced in both groups at day 7 in patients with a clinical response. Treatment failure defined by absence of a clinical response at day 7 was the primary endpoint as was relapse between day 7 and day 98, absence of steroid-free remission at day 98, any severe adverse event leading to treatment discontinuation, colectomy, or death<sup>[251]</sup>. There were no statistically significant differences in treatment failure in patients given cyclosporine (60%) and those on IFX (54%) ( $P = 0.52$ ). Nine (16%) patients in the cyclosporine group and 14 (25%) in the IFX group had severe adverse events but not statistically different<sup>[251]</sup>. Mucosal healing was similar in both groups (47% in the cyclosporine group and 45% in IFX-treated patients) and colectomy rates (17% in the cyclosporine group and 21% in IFX-treated patients) were also comparable<sup>[251]</sup>. Long-term follow-up of patients treated in the CySIF trial showed no difference in colectomy-free survival at 1 year and 5 years in patients treated with either cyclosporine or IFX<sup>[252]</sup>.

The CONSTRUCT (Infliximab *vs* ciclosporin for steroid-resistant acute severe ulcerative colitis) trial was a mixed-methods, open-label, pragmatic randomized trial including 270 patients<sup>[234]</sup>. Patients were randomly allocated (1:1) to receive either IFX (5 mg/kg intravenous at baseline and again at 2 wk and 6 wk after the first infusion) or cyclosporine (2 mg/kg per day by continuous infusion for up to 7 d, followed by twice-daily tablets delivering 5.5 mg/kg per day for 12 wk). The primary outcome was quality-adjusted survival. There was no statistically significant difference between groups for the primary endpoint or for the secondary endpoints of colectomy rates, time to colectomy, serious adverse events, or death. IFX, however, was associated with a greater treatment cost<sup>[234]</sup>. The availability of biologics similar to IFX will now positively impact the cost of IFX treatment. A meta-analysis did not show any difference in short-term response at 3 mo and 12 mo in RCTs<sup>[253]</sup>.

In a study of 740 patients with steroid-refractory ASUC with median follow-up of 71 mo, there was no difference in colectomy rates between patients treated with IFX or cyclosporine (26.2% *vs* 25.4%) at 5 yrs, but there was a significantly lower rate of serious adverse events in the cyclosporine group *vs* IFX (15.4% *vs* 26.5%) ( $P = 0.001$ )<sup>[254]</sup>.

The choice of either IFX or cyclosporine as rescue therapy must be individualized considering nuances of each therapy. The statistical power (80% power to detect a 30% difference between groups) in the CysIF study was low, making a type II error likely, which is not detecting a difference between drugs if there is a difference. IFX was administered as per the standard induction regimen whilst cyclosporine levels were monitored. Increasingly, our knowledge of IFX dosing is being informed by the understanding of the pharmacokinetics of IFX<sup>[43,247,255]</sup>. A high TNF burden, proteolytic degradation of drug<sup>[256]</sup>, and increased intestinal loss of IFX influences the success of



IFX therapy<sup>[257,258]</sup>. Elevated CRP (a surrogate for inflammatory activity), low albumin (active UC with increase in intestinal permeability and faecal drug loss), and severe endoscopic lesions can predict poor outcomes<sup>[257,258]</sup>. IFX therapy was associated with a reduction in hospital stay (median 4 d) (interquartile range 4.0-5.75) with IFX compared with 11 d (interquartile range 7.75-13.25) with cyclosporine<sup>[259]</sup>. In the CONSTRUCT trial, patients and physicians noted greater treatment satisfaction with IFX<sup>[234]</sup>. Improving knowledge of pharmacokinetics of IFX in ASUC will enable more efficient use of IFX as a rescue treatment.

Sequential rescue therapy is not currently recommended before referral for a colectomy. Studies of cyclosporine and IFX as sequential rescue therapy show limited efficacy, and the risk of adverse effects is concerning. A German study found a high risk of serious side effects (16% patients) including one death<sup>[260]</sup>. Another study of 86 patients receiving sequential therapy (cyclosporine followed by IFX) reported colectomy-free rates of 61% and 41% at 3 and 12 mo, respectively; the risk of infectious complications was 10%<sup>[261]</sup>. Chaparro *et al*<sup>[262]</sup> reported a 30% colectomy-free survival for sequential therapy (cyclosporine followed by IFX), 23% rate of adverse effects, and a death from nosocomial pneumonia<sup>[262]</sup>. A systematic review of ten studies with 314 participants receiving sequential therapy noted short term response rates of 62.4% and remission rate of 38.9% with colectomy rates of 28.3% at 3 mo and 42.3% at 12 mo<sup>[263]</sup>. There is insufficient evidence to support sequential therapy currently. With risks of severe immunosuppression, this approach is not supported by current guidelines<sup>[49,63,147,264]</sup>. Prolonged corticosteroid therapy beyond 7-10 d provides no additional benefit and increases the risk of toxicity and postoperative complications<sup>[43,201,265]</sup>.

Colectomy involves excision of the colon, proximal rectum, and distal rectal mucosa and may be considered “curative” for acute colitis. Colectomy needs to be urgently considered in emergencies including refractory haemorrhage, toxic dilatation, intestinal perforation, or inadequate response to medical therapy. Inappropriate delay in considering colectomy can lead to risk of adverse outcomes and/or death<sup>[266,267]</sup>. This emphasizes the need for an “exit strategy” in steroid-refractory ASUC patients by day 3-5 of hospitalization by the gastroenterologist involving the patient, surgeon, and a stoma therapist. Timely consideration (within 7 d) of colectomy in patients with ASUC or steroid-refractory disease is associated with improved perioperative outcomes and reduced in-hospital mortality and morbidity<sup>[268]</sup>.

### Steroid-dependent UC

**Statement 59:** Azathioprine can be used as a steroid-sparing agent in steroid-dependent UC. [100]

**Statement 60:** Anti-TNF agents, VDZ, tofacitinib, and ustekinumab are effective for induction of remission in steroid-refractory or steroid-dependent moderate to severe UC. They are also effective in moderate colitis refractory to thiopurines. [88.8]

Thiopurines (AZA and mercaptopurine) are effective steroid sparing agents for the maintenance of remission in moderate to severe active UC<sup>[269-271]</sup>. They are not effective for induction of remission. In a meta-analysis of three randomized studies, thiopurine maintenance favoured placebo (RR 0.6, 95%CI: 0.37-0.95)<sup>[270]</sup>. In a subsequent meta-analysis, treatment with thiopurine was associated with 23% absolute risk reduction (number needed to treat = 5) to prevent one recurrence (OR 2.59, 95%CI: 1.26-5.3). The most recently published Cochrane review of four studies of AZA *vs* placebo reported a benefit of AZA over placebo (44% *vs* 65% failure, respectively, RR 0.68; 95%CI: 0.54-0.86)<sup>[272]</sup>.

Anti-TNF and anti-integrin agents are effective for the induction of remission in steroid refractory and steroid dependent moderate to severe active UC. Janus kinase inhibitor (tofacitinib) and ustekinumab (anti-p40 subunit inhibitor of IL12/23) are also currently licensed for patients with moderate active UC refractory to oral corticosteroids. They are also effective in moderate to severe active UC refractory to thiopurines. A full discussion of this can be found under Statement 52 and 55 above.

## MANAGEMENT-MAINTENANCE OF REMISSION IN UC

**Statement 61:** The goal of maintenance therapy in UC is to maintain steroid-free remission defined clinically and endoscopically. [100]

**Statement 62:** Choice of maintenance treatment is determined by disease extent, disease course, response to previous maintenance treatment, severity, and treatment of



the most recent flare as well as the safety of maintenance treatment. [88.8]

**Statement 63:** For patients achieving remission with 5-ASA, the use of 5-ASA oral and/or topical should be used as maintenance therapy depending on disease extent. [88.8]

**Statement 64:** Once daily oral 5-ASA preparations are preferred over sulphasalazine for maintaining remission due to reducing toxicity. [88.8]

The aim of maintenance treatment in UC is steroid-free remission defined both clinically and endoscopically<sup>[273]</sup>. Several scoring systems are available to classify disease severity in UC<sup>[72]</sup>. They aid objective assessment of disease and guide therapeutic and monitoring strategies, and their strength lies in the potential to monitor patient progress during follow-up<sup>[17,54]</sup>. Several clinical scoring systems are available and are discussed in detail under statements 16 and 17.

Of these, the MCS is easier to use and has been used widely in adult clinical trials<sup>[77]</sup>. The MCS (0-12) includes stool frequency, rectal bleeding, a physician's global assessment, and endoscopic assessment. Clinical improvement is defined as the reduction of baseline scores by  $\geq 3$  points and clinical remission as an overall score  $\leq 2$  (and no individual sub-score  $> 1$ ) or UCDAI  $\leq 1$ <sup>[75,76]</sup>. A PMS  $< 1$  indicates remission<sup>[17]</sup>. The PMS uses the nonendoscopic components of the total score and correlates well with PROs with treatment<sup>[78,79]</sup>. Recently, the PRO2, derived from components of the Mayo score, has been proposed as an interim outcome measure when combined with endoscopic data. PROs appear to correlate well with established activity and may improve the ability to predict patient defined remission<sup>[80]</sup>.

Endoscopic remission (mucosal healing) has emerged as a key goal of therapy. "Treat to target" has emerged as our new standard in well-selected patients and is discussed under statement 40.

The therapeutic strategy for maintenance of remission in UC is ascertained by disease extent, disease course response to previous maintenance treatment severity, and treatment of the recent flare as well as safety of maintenance treatment. These are discussed in detail under statements 41 through 55.

Patients achieving remission on 5-ASA therapy should have maintenance treatment with 5-ASA long term to maintain remission. 5-ASA has shown efficacy at doses of 2 g daily or higher in a Cochrane meta-analysis as discussed under 5-ASA above<sup>[195]</sup>. Topical therapy is also effective and should be continued where possible to maintain remission<sup>[172,174]</sup>. 5-ASA adherence can be a challenge and particularly so with topical therapy and once daily dosing. Alternate day or every third day therapy for topical treatment does not reduce the rate of remission and may be associated with better adherence<sup>[172,176,274]</sup>.

Oral 5-ASA was associated with a higher rate of failure to maintain clinical or endoscopic remission (RR 1.14; 95%CI: 1.03-1.27) than sulfasalazine and a higher rate of failure to maintain remission in general (RR 1.08; 95%CI: 0.92-1.26) in a Cochrane review<sup>[275]</sup>. Sulfasalazine may often cause side effects such as headache and nausea. Additionally, allergy to the sulpha moiety and need for multiple dosing can limit its use<sup>[147]</sup>. Furthermore, it has a nonuniversal, reversible, nondose dependent effect on male infertility<sup>[276,277]</sup>. Resolution of sperm abnormalities occurs approximately three months after sulfasalazine discontinuation. Prospective fathers should discontinue sulfasalazine 3-4 mo prior to attempting conception given the negative impact on semen quality. They can be switched to a 5-ASA compound that is compatible with use throughout conception<sup>[278]</sup>.

**Statement 65:** 5-ASA maintenance treatment should be continued long-term; this may reduce the risk of colon cancer. [77.7]

5-ASA has been shown to have a protective effect against colorectal neoplasia risk in IBD<sup>[279]</sup>. A systematic review concluded that 5-ASA therapy was associated with an OR of 0.6 (95%CI: 0.42-0.9;  $P = 0.04$ ) for the development of colorectal cancer<sup>[280]</sup>. Two recent meta-analyses confirmed these findings<sup>[281,282]</sup>. It is unclear if this is a true biological effect or hinges on control of inflammation, which is known to be a driver of colorectal neoplasia risk in IBD<sup>[283-285]</sup>. Indeed, in patients on immunosuppressive therapy, data have shown no additional benefits of 5-ASA and stopping 5-ASA in patients on anti-TNF therapy did not worsen disease course<sup>[286]</sup>. Given the weight of the evidence currently, 5-ASA maintenance treatment should be continued long term for the chemoprophylactic benefit in addition to maintenance of remission achieved.

**Statement 66:** Thiopurines are effective in maintaining remission in patients with early or frequent relapse while taking 5-ASA, patients who are intolerant to it, patients who

are steroid-dependent, and patients responding to cyclosporine. [88.8]

Thiopurines (AZA and mercaptopurine) are effective steroid sparing agents for the maintenance of remission in moderate to severe active UC<sup>[269-271]</sup>. They are not effective for induction of remission. In a meta-analysis of three randomized studies, thiopurine maintenance favoured placebo (RR 0.6; 95%CI: 0.37-0.95)<sup>[270]</sup>. In a subsequent meta-analysis, treatment with thiopurine was associated with an absolute risk reduction of 23% (number needed to treat = 5) to prevent one recurrence (OR 2.59; 95%CI: 1.26-5.3). A Cochrane review of four thiopurine maintenance studies *vs* placebo showed a benefit of AZA (44% *vs* 65% failure, respectively, RR 0.68; 95%CI: 0.54-0.86)<sup>[272]</sup>.

**Statement 67:** In patients responding to anti-TNF, maintaining remission by continuing anti-TNF therapy with or without thiopurines is appropriate. [100]

Patients who have responded to anti-TNF therapy should be maintained on anti-TNF therapy with or without thiopurines. A systematic review and meta-analysis of six placebo-controlled, double-blind studies showed that IFX, adalimumab, and golimumab demonstrated more efficacy than placebo for clinical remission maintenance in UC<sup>[205]</sup>. The UC-SUCCESS study showed that in patients in whom corticosteroid therapy had failed, the combination of IFX and AZA was more effective with higher clinical remission rates at week 16 (40%) compared to IFX alone (22%)<sup>[207]</sup>.

**Statement 68:** VDZ is efficient in inducing and maintaining remission in patients who failed anti-TNF. [88.8]

In the GEMINI trials, the primary endpoint was clinical remission at week 52. Of 374 patients randomized to VDZ or placebo, 47.1% achieved clinical response at week 6 in the VDZ group when compared with 25.5% in the placebo group (95%CI: 11.6–31.7;  $P < 0.001$ ). At week 52, 41.8% of patients treated with VDZ 8 weekly, 44.8% treated with VDZ 4 weekly, and 15.9% of patients receiving placebo were in clinical remission. VDZ was superior to placebo for clinical response (RR = 0.82; 95%CI: 0.75-0.91), induction of remission (RR = 0.86; 95%CI: 0.80-0.91), endoscopic remission (RR = 0.82; 95%CI: 0.75-0.91), and remission at 52 wk in week 6 responders (RR = 2.73; 95%CI: 1.78-4.18) in a Cochrane systematic review<sup>[216]</sup>. More patients naïve to TNF antagonists achieved endoscopic remission than patients with TNF antagonist failure at weeks 26 and 52. The GEMINI open label extension included patients with a minimum 248 wk of cumulative VDZ treatment ( $n = 154$ ). Among induction responders and those who completed the maintenance study, 40.9% of patients had 248 wk of treatment; 98% achieved clinical response, and 90% had clinical remission<sup>[217]</sup>. Significant improvements in PROs of reduction in rectal bleeding and stool frequency as early as 2 wk were reported in post hoc analysis of GEMINI trials<sup>[218]</sup>.

The US-VICTORY (Vedolizumab for Health OuTcomes in InflammatORY Bowel Diseases) study reported on 321 VDZ-treated UC patients, 71% of whom had failed anti-TNF treatment<sup>[217]</sup>. Clinical and endoscopic remission was achieved at 12 mo by 51% and 41% of patients, respectively. Lower rates of clinical [hazard ratio (HR): 0.53; 95%CI: 0.38–0.75] and endoscopic remission (HR: 0.51; 95%CI: 0.29–0.88) were noted in those with previous anti-TNF exposure<sup>[217]</sup>. The EVOLVE (Retrospective Real-World Comparative Analysis Highlights Safety of Vedolizumab and Anti-TNF $\alpha$  Therapies in Biologic-Naïve Patients study for UC) was a retrospective study of the safety and effectiveness of VDZ compared with anti-TNF agents in a real-world cohort of biologic naïve patients<sup>[221]</sup>. At 24 mo, clinical response (91% *vs* 86%), clinical remission (79% *vs* 66%), and mucosal healing (92% *vs* 84%) were high in VDZ and anti-TNF patients, respectively, with no real differences between groups. Treatment persistence (75% *vs* 54%;  $P < 0.01$ ) was greater with VDZ than anti-TNF, whilst more anti-TNF treated patients required dose escalation than the VDZ group (25% *vs* 31%;  $P < 0.05$ )<sup>[221]</sup>.

**Statement 69:** Thiopurines are appropriate to maintain remission in thiopurine-naïve patients. [100]

The role of thiopurines in the maintenance of remission in steroid dependent UC has been discussed above under statement 66.

## MANAGEMENT–ACTIVE CD

**Statement 70:** The management plan for a patient with CD should take into account the activity, site, and behaviour of disease, and should always be discussed with the patient. [100]

**Statement 71:** Determining the activity of disease may be more difficult in CD than UC and should rely on objective evidence, *e.g.*, inflammatory markers or colonoscopy. [77.7]

**Statement 72:** It is important to confirm disease activity as a cause of recurrent symptoms, although unnecessary to re-evaluate the distribution of disease unless this will alter management [77.7]

Management decisions for CD must take into account disease location, behaviour, and activity. Accordingly the Montreal classification is used to classify CD according to age (A1 < 17 years at diagnosis, A2 17-40, A3 > 40), location (L1-ileal, L2-colonic, L3- ileocolonic, L4 isolated upper GI), and disease behaviour (B1-nonstricturing nonpenetrating, B2-structuring, B3-fistulizing, and “p” for perianal disease modifier)<sup>[55,56]</sup>. These classification systems aid clinical decision making regarding medical or surgical treatment. A third of patients will have ileal, ileocolonic, or colonic disease, and in 6%–14% the disease location may change over time<sup>[287,288]</sup>. Inflammatory disease is noted in 56% to 81% at diagnosis, whilst 5% to 25% will have stricturing or penetrating disease behaviour at diagnosis<sup>[287]</sup>.

The likelihood of developing an intestinal complication in patients with inflammatory behaviour was 51% at 20 years after diagnosis. Ileal, ileocolonic, or upper GI involvement compared to colonic involvement were significantly associated with shorter time to the development of intestinal complications<sup>[96]</sup>.

In a population-based study, perianal fistulae occurred in 10%-26%, and the cumulative risk was 26% at 20 years after diagnosis<sup>[96]</sup>.

Determining clinical disease activity should be based on objective and validated scoring systems<sup>[72]</sup>. The CDAI is time-consuming, requires data input from patients, and focuses on diarrhoea (which may have other pathophysiological reasons and not only inflammation), cannot be used in patients with stomas, and is not validated for use after surgery. The Harvey Bradshaw score is more practical for clinical application<sup>[72]</sup>.

Biochemical markers can be a useful surrogate of inflammation, but 40% of patients with IBD and mild inflammation can have normal CRP and ESR values limiting their use in monitoring<sup>[289]</sup>.

Ileocolonoscopy with biopsy is the gold standard first line investigation for suspected CD. Ileoscopy with biopsy histology is superior in establishing the diagnosis of mild ileal CD, although terminal ileal intubation may not always be possible<sup>[72]</sup>.

Patients may have isolated proximal small bowel disease beyond the reach of even complete ileocolonoscopy. Ileoscopy and radiological imaging are complementary in diagnosis of ileal CD<sup>[290,291]</sup>. Dedicated small bowel should be conducted in addition to ileocolonoscopy in patients with suspected CD and those with unspecified colitis at ileocolonoscopy<sup>[72]</sup>. Mucosal biopsy is necessary for a comprehensive assessment of the colon and distal ileum<sup>[52,290]</sup>.

Endoscopic assessment is not always necessary for the monitoring of disease activity or detection of recrudescence of inflammation. Faecal markers may have a role in the noninvasive monitoring of CD activity. FC is a sensitive marker of disease activity and correlates with several endoscopic activity indices<sup>[292]</sup>. A calprotectin > 160 µg/g has a sensitivity of 91.7% and a specificity of 82.9% to predict relapse in patients with IFX-induced remission<sup>[293-295]</sup>.

### **Mild to moderate active luminal CD**

**Statement 73:** Oral budesonide is the preferred treatment for the mildly active localized ileocecal CD. [88.8]

Controlled ileal release (CIR) budesonide is effective for control of symptoms of mild to moderate active localized ileocecal CD. CIR budesonide is a pH-dependent ileal release oral corticosteroid with high topical activity and low systemic bioavailability (about 10%-20%)<sup>[296,297]</sup>. A randomized double blind trial reported that CIR budesonide 9 mg daily for 8 wk was as effective as prednisolone 40 mg daily (tapering to 5 mg at 8 wk) for the induction of remission in patients with mild to moderate active ileo-caecal CD with efficacy (CDAI < 150) at 51% for budesonide at 8 wk compared with 52.5% for prednisolone and significantly fewer side effects<sup>[298]</sup>. Once daily 9 mg is as effective as 3 mg three times daily<sup>[299]</sup> and was demonstrated effective over placebo at achieving remission<sup>[300-302]</sup>. Somewhat lower efficacy of CIR budesonide should be considered in context of its pharmacokinetic profile, releasing drug in the ileum and right colon, topical effect with extensive first-pass metabolism, and consequent lower systemic corticosteroid exposure<sup>[300-302]</sup>. Budesonide is inferior to prednisolone (RR 0.52, 95% CI 0.28-0.95) in the context of more severe disease (CDAI >

300). When remission is achieved budesonide may be tapered over 1-2 wk<sup>[296,297]</sup>.

**Statement 74:** 5-ASA should not be used for induction of remission and achieving mucosal healing in patients with active CD. [88.8]

Oral and topical mesalamine is no more effective than placebo for the induction of remission and achieving mucosal healing in patients with active CD<sup>[303-305]</sup>. Although sulfasalazine (3-6 g daily) may be an effective treatment of mild to moderate active colonic CD and/or ileocolonic CD (but not small bowel disease), it is not more effective than placebo for achieving mucosal healing in CD<sup>[303,306,307]</sup>.

**Statement 75:** Metronidazole should not be used as primary therapy for luminal inflammatory CD. [100]

A wide range of antibiotics have been studied in the induction of remission for CD<sup>[308]</sup>. The precise mechanisms whereby broad-spectrum antibiotics work is uncertain but might include immunosuppressive activity (*e.g.*, metronidazole), treatment of bacterial overgrowth, and suppression of a bacteria-induced antigenic stimulus. However, metronidazole has been demonstrated as not more effective than placebo at inducing remission in patients with CD<sup>[309]</sup>.

In a paediatric randomized trial of 73 patients with CD, azithromycin 75 mg/kg for 5 d a week for 4 wk followed by metronidazole 20 mg/kg for 4 wk was compared with metronidazole only for 8 wk. A remission rate of 66% for azithromycin/metronidazole was noted as compared to 29% for metronidazole ( $P = 0.025$ )<sup>[310]</sup>.

**Statement 76:** Antimycobacterial therapy has not been shown to be effective and should not be used as primary therapy. [100]

In a randomized placebo-controlled trial of 2 yrs of treatment with clarithromycin, rifabutin, and clofazimine in 213 patients with active CD, early benefit of antibiotics was noted. However, there were no significant differences in relapse rates during follow-up<sup>[311]</sup>. In another phase 3 trial using higher doses, 331 patients with moderate to severe active CD were randomized to RHB-104 (clarithromycin 95 mg, rifabutin 45 mg, and clofazimine 10 mg) five capsules twice daily or placebo for 52 wk in addition to the pre-study therapy. Remission was achieved at 26 wk in 37% *vs* 23% on placebo ( $P = 0.007$ ), and durable remission (from week 16 to 52) was achieved in 18% *vs* 9% on placebo ( $P = 0.019$ )<sup>[312]</sup>. Data on mucosal healing or duration of benefit at the end of therapy are not available. In the absence of credible supportive evidence, antimycobacterial therapy should not be used as primary therapy for CD.

**Statement 77:** Biologic therapy should be considered in CD patients with high disease activity and features indicating a poor prognosis. [88.8]

Anti-TNF therapies (IFX, adalimumab, and certolizumab pegol) have been shown to be effective for treatment of patients with CD with an inadequate response to treatment with corticosteroids, thiopurines, and methotrexate<sup>[83,84,313-316]</sup>. Notably, combo therapy using IFX with immunomodulators is more effective than monotherapy with either agent and are discussed under statement 89<sup>[317-320]</sup>. Anti-integrin (VDZ) and anti-interleukin ustekinumab (blocking p40 subunit of IL12/23) have been licensed for the management of steroid and/or immunomodulator refractory CD<sup>[215,220,321-328]</sup>. Details on trials and supportive evidence are discussed under individual statements below.

**Statement 78:** Mild oesophageal or gastroduodenal CD may be treated with a proton pump inhibitor with close monitoring, while more severe or refractory disease requires additional systemic corticosteroids or a biologic-based strategy. [88.8]

The prevalence of upper GI tract CD in adults is 0.3%-5%<sup>[134]</sup>. Routine endoscopic evaluation in asymptomatic patients (predominantly children) may disclose mild endoscopic changes in nearly 64% of patients and histological abnormalities in up to 70% of patients<sup>[329]</sup>. Endoscopic lesions may be mucosal nodularity, ulcers (aphthous and linear), antral thickening, and duodenal strictures<sup>[330]</sup>. Histologic features may include granuloma, focal cryptitis of the duodenum, and focally enhanced gastritis<sup>[331]</sup>.

The European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT II) was a multidisciplinary international panel that published guidance on the management of special situations including upper GI CD<sup>[332]</sup>. The EPACT II panel recommends proton pump inhibitors as first line therapy in the absence of stenosis and steroids as second line and IFX being recommended as third line treatment, respectively<sup>[332]</sup>. The Panel deemed adalimumab of uncertain benefit, and 5-ASA certolizumab and natalizumab were deemed inappropriate. Balloon dilatation was recommended as first line therapy in the presence of stenosis followed by proton pump inhibitors and then steroids, thiopurines, or surgery as subsequent options. The benefit of IFX was uncertain. Enteral nutrition may be required and is best delivered



by a gastrostomy tube in the context of severe or stricturing disease<sup>[332]</sup>. In isolated lesions of the oesophagus, other diagnoses such as reflux disease, tuberculosis, fungal disease, sarcoidosis, Behcet's disease, and malignancy should be considered<sup>[333]</sup>.

**Statement 79:** Any patient who has an early relapse after a course of steroids should started immunomodulator or biologic therapy to reduce the risk of a further relapse and/or prolonged steroid therapy. [88.8]

In patients with moderate to severe CD who have a relapse after corticosteroid therapy, thiopurine analogues (6-mercaptopurine and AZA) may be used. Mercaptopurine and its prodrug, AZA, have steroid-sparing effects for the maintenance of remission in CD<sup>[334,335]</sup>. Their slow onset (8-12 wk) makes them ineffective for short-term induction in active, symptomatic disease<sup>[334,335]</sup>. Thiopurines were more effective than placebo for maintenance of remission in CD, although quality of evidence for this has been reported as low [number needed to treat (NNT) = 9]<sup>[335]</sup>. A systematic review with network meta-analysis showed a benefit of thiopurines compared with placebo for the maintenance of remission of CD, although anti-TNF therapy was more effective than thiopurines<sup>[334]</sup>. Intramuscular methotrexate 25 mg weekly given to patients with chronic active CD despite 3 mo of prednisolone therapy showed improved clinical remission rates compared with placebo at 16 wk with reduction in corticosteroid requirements<sup>[336]</sup>. Methotrexate was found efficacious as maintenance therapy<sup>[337]</sup>. These findings were confirmed by a Cochrane review<sup>[338]</sup> and another network meta-analysis showing benefit of methotrexate (OR 0.24; 95%CI: 1.1-4.8)<sup>[334]</sup>. Dosing and monitoring of thiopurines is discussed under statement 97 below. The side effect profile of AZA and 6-mercaptopurine includes allergic reactions, pancreatitis, myelosuppression, nausea, infections, hepatotoxicity, and malignancy, especially nonmelanoma skin cancer and lymphoma<sup>[339,340]</sup>.

If methotrexate is considered in women with child-bearing capability, highly effective contraception must be in place<sup>[341]</sup>. There is some inconsistency in the evidence regarding whether men should be advised not to conceive whilst using methotrexate or within three months of stopping it in view of concerns regarding its effects on spermatogenesis and teratogenicity<sup>[278,342]</sup>. Adverse effects of methotrexate include nausea and vomiting, liver and pulmonary toxicity, bone marrow suppression, and skin cancer; risk of lymphoma has not been convincingly demonstrated in patients with CD<sup>[63,336,343,344]</sup>. The white cell count and liver biochemistry should be routinely monitored during methotrexate therapy<sup>[63,336,343,344]</sup>.

Anti-TNF antibodies (IFX, adalimumab, and certolizumab pegol) are effective for treatment of patients with CD who respond inadequately to standard<sup>[83,84,313-316]</sup>. Combination therapy of IFX with immunomodulators is more effective than either agent given alone is discussed under statement 89<sup>[317-320]</sup>. Anti-integrin (VDZ) and anti-interleukin ustekinumab (blocking p40 subunit of IL12/23) have been licensed for the management of steroid and/or immunomodulator refractory CD<sup>[215,220,321-328]</sup>. Details on trials and supportive evidence are discussed under individual statements below.

**Statement 80:** Particular care should be taken to consider serious infections as a complication of immunosuppressive therapy, including biologics and steroids. [88.8]

Infection is the most frequently encountered consequence of biological therapy in patients with IBD<sup>[245,246]</sup>. A systematic review and meta-analysis of 49 randomized placebo controlled studies reported that biological agents were associated with a moderate increase in the risk of any infection (OR 1.19; 95%CI: 1.10-1.29) and significantly increased risk for opportunistic infections (OR 1.90; 95%CI: 1.21-3.01) but do not influence the risk of serious infections in patients with IBD<sup>[345]</sup>. Serious infection risk was significantly lower with biologic studies with a low risk of bias, perhaps reflecting control of active inflammation (OR 0.56; 95%CI: 0.35-0.90)<sup>[345]</sup>.

A pooled analysis of primary safety data across ten IBD clinical trials in adults receiving IFX and immunomodulatory therapy did not find an increase in the risk of infections or serious infections with long term IFX treatment compared to placebo<sup>[346]</sup>. Patients with UC but not CD who received immunomodulator treatment (versus treatment without immunomodulator) demonstrated an increased risk of infection<sup>[346]</sup>. Patients should be screened and vaccinated for vaccine preventable illnesses in line with international guidelines<sup>[63,244-246]</sup>.

A recent systematic review and meta-analysis evaluated the comparative risk of serious infections from immunosuppressive therapy<sup>[344]</sup>. As compared to anti-TNF monotherapy, the risk of serious infection was higher with combination of anti-TNF and an immunosuppressive agent (RR 1.19; 95%CI: 1.03-1.37), with anti-TNF and a corticosteroid (RR 1.64; 95%CI: 1.33-2.03), or with all three drugs (RR 1.35; 95%CI: 1.04-1.77). Monotherapy with an immunosuppressive agent was associated with a lower



risk of serious infections than monotherapy with an anti-TNF agent (RR 0.61; 95%CI: 0.44-0.84) or a TNF antagonist with an immunosuppressive agent (RR 0.56; 95%CI: 0.39-0.81). IFX was associated with a lower risk of serious infections compared with adalimumab therapy in patients with UC (RR 0.57; 95%CI: 0.33-0.97) but not CD (RR 0.91; 95%CI: 0.49-1.70). Combination therapies for IBD including TNF antagonists, especially with corticosteroids, are associated with a higher risk of serious infection, whereas monotherapy with an immunosuppressive agent is associated with a lower risk compared with monotherapy with a TNF antagonist<sup>[344]</sup>.

**Statement 81:** The choice of biologic therapy depends on availability, route of delivery, patient preference and cost because they all have similar efficacy in luminal CD and similar adverse-event profiles. [88.8]

Biological therapies appear to have similar efficacy in luminal CD. In the absence of head to head studies, network meta-analyses suggested that in biologic naïve patients IFX and adalimumab ranked highest for the induction of clinical remission, whilst in anti-TNF experienced patients, ustekinumab and VDZ were ranked highest for the induction of clinical remission<sup>[222]</sup>. For maintenance therapy, adalimumab and IFX were most likely to maintain remission in responders, whilst ustekinumab had the lowest risk of serious infections<sup>[222]</sup>.

There is no head-to-head comparison of ustekinumab *vs* VDZ in patients with IBD who have failed anti-TNF therapy, but indirect comparisons do not show differences in efficacy<sup>[321]</sup>. Response is generally worse in patients with a longer disease duration or those refractory to other therapies<sup>[323,347,348]</sup>. The VICTORY study compared outcomes among VDZ-treated and anti-TNF-treated patients with CD. After propensity score matching, with more than 500 patients included in the analysis, there was no significant difference in clinical and steroid free remission at 1-yr<sup>[349]</sup>. Shorter disease duration was associated with higher response rates to VDZ in CD but not in UC<sup>[349]</sup>.

Advancing age and increasing comorbidity or possibly with a history of malignancy may favour nonsystemic therapy. Route of administration and cost of therapy may also drive treatment choice, with significant reductions in cost through biosimilar anti-TNF drugs<sup>[350]</sup>. Drug factors, route of administration, disease severity and activity, and informed patient choice will govern the decision on which biologic is chosen<sup>[350]</sup>.

### **Moderate-to-severe CD**

**Statement 82:** The severely active localized ileocecal CD should initially be treated with systemic corticosteroids. [100]

**Statement 83:** Conventional corticosteroids do not consistently achieve mucosal healing and should be used sparingly as a bridge to more tailored therapy. [88.8]

**Statement 84:** Intravenous corticosteroids and or biologic therapy can be used to treat severe CD in the absence of any contraindications. [100]

Patients with moderate to severe active localized ileocecal CD should be offered conventional corticosteroids orally, or intravenous for more severe disease, to alleviate symptoms of a flare<sup>[306,307]</sup>. Every effort should be made to limit exposure<sup>[202,203]</sup> as even short-term use of corticosteroids are associated with adverse events, such as bone loss, mood disorder, insomnia, hypertension, elevated blood glucose, glaucoma, acne, weight gain, and hypoadrenalism. Prednisolone is typically commenced at doses ranging from 40 to 60 mg/d<sup>[351]</sup>, continued for 1-2 wk and tapered by 5 mg weekly until 20 mg and then by 2.5-5.0 mg weekly<sup>[351]</sup>. Corticosteroid tapers should generally not be carried out for more than 3 mo<sup>[306,307]</sup>. Oral prednisone doses or equivalent corticosteroids exceeding 60 mg a day offer no additional advantage. Notably 1 in 5 patients will be refractory to steroids, and an additional third may become steroid dependent with symptoms of relapse at the attempt to taper<sup>[351,352]</sup>. Corticosteroids are unable to maintain remission or achieve mucosal healing<sup>[84,200,317]</sup>. In addition, corticosteroids may favour perforating complications (abscess and fistula) and are therefore relatively contraindicated in such cases. As such, steroid-sparing agents should be used in patients with severe disease phenotypes and to achieve and maintain meaningful remission<sup>[1,16,17,20,158]</sup>.

**Statement 85:** For patients with moderate to severe active CD, biologic therapy without an immunomodulator should be used for induction of symptomatic remission. [77.7]

Anti-TNF therapies are effective for patients with CD with an inadequate response to treatment with corticosteroids, thiopurines, and methotrexate<sup>[83,84,313-316]</sup>. Combination therapy using IFX and immunomodulators is more effective than either drug as monotherapy<sup>[317-320]</sup>. The effect of combining an immunomodulator with adalimumab

or certolizumab pegol is less well studied<sup>[353,354]</sup>. Evidence to support continuation of an immunomodulator when an anti-TNF antibody is commenced after failure of the immunomodulator is lacking. The rationale in that situation would be to prevent antidrug antibody formation in the light of significant disease<sup>[353,354]</sup>. Anti-TNF treatments are more effective than placebo for induction of response, remission, and complete and partial mucosal healing in patients with CD<sup>[204,355]</sup>. Anti-TNF treatments have a rapid onset of action, as early as 2 wk of initiating therapy. Anti-TNF treatments are more effective when given earlier in the course of disease, especially when given within 2 yrs of disease-onset<sup>[161,164,210,317]</sup>.

**Statement 86:** Combination therapy of IFX with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or IFX alone in patients who are naïve to those agents. [100]

The SONIC (Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease) study demonstrated that combination therapy with AZA and IFX was more effective than immunomodulators or IFX monotherapy in patients who were naïve to these drugs<sup>[317]</sup>. This is likely to be a synergistic effect with the additional benefit of preventing immunogenicity from IFX. Adding an immunosuppressant may reduce requirement for dose escalation with IFX and also need for drug switching through reduction of immunogenicity and boosting trough levels<sup>[318]</sup>. A network meta-analysis also demonstrated superiority of combination therapy using IFX with AZA over monotherapy<sup>[334]</sup>. The recently reported PANTS (Personalized anti-TNF therapy in Crohn's disease) study (a 3 year observational cohort) also demonstrated immunogenicity rates of 26% and 28% with originator and biosimilar IFX, respectively, and that immunomodulator use reduced the risk of immunogenicity (HR = 0.37;  $P < 0.0001$ )<sup>[356]</sup>.

Combination therapy using IFX and methotrexate was not noted to be more effective than IFX monotherapy in maintaining remission up to 50 wk, although it was deemed as safe<sup>[338,343]</sup>. A recent Cochrane review also reached a similar conclusion. Methotrexate does reduce immunogenicity to IFX<sup>[338,343]</sup>. Taken together, the evidence suggests that when using IFX combined with AZA where possible (or methotrexate if AZA cannot be used) should always be preferred. If there are contraindications to both AZA and methotrexate, an alternative to IFX should be considered unless there is a strong clinical reason to use IFX, such as perianal CD<sup>[357]</sup>.

**Statement 87:** Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for CD. [50]

Cyclosporine, tacrolimus, and mycophenolate mofetil therapy are not recommended for use in CD<sup>[358-361]</sup>.

**Statement 88:** Immunosuppressive naïve patients who are dependent on corticosteroids should be treated with immunosuppressants and/or biologic therapy. [77.7]

A full discussion can be found under statements 79, 80, and 86.

### **Steroid-dependent CD**

**Statement 89:** Methotrexate (up to 25 mg once weekly intramuscularly or subcutaneously) may be effective and should be considered in patients with steroid-dependent CD. [66.6]

Intramuscular methotrexate 25 mg weekly given to patients with chronic active CD despite 3 mo of prednisolone therapy showed improved clinical remission rates compared with placebo at 16 wk with reduction in corticosteroid requirements<sup>[336]</sup>. Methotrexate was found efficacious as maintenance therapy<sup>[337]</sup>. These findings were confirmed by a Cochrane review<sup>[338]</sup> and another network meta-analysis showing benefit of methotrexate (OR 0.24; 95%CI: 1.1-4.8)<sup>[334]</sup>. Oral methotrexate has reduced bioavailability compared with parenteral administration, and 15 milligrams of subcutaneous methotrexate may be preferred to intramuscular under the circumstances as it may be easier to administer and less painful<sup>[362,363]</sup>. It is recommended that induction therapy is administered *via* the subcutaneous route, and patients may be switched to oral methotrexate during the maintenance phase. Folic acid should be administered at a dose of 5 mg weekly (typically one to two days after administration of methotrexate) or at a dose of 1 milligram daily to reduce GI and liver toxicity<sup>[63]</sup>.

**Statement 90:** Biologics should be used to treat CD that is resistant/dependent to treatment with corticosteroids. [100]

Anti-TNF therapies (IFX, adalimumab, and certolizumab pegol) are effective for

patients with CD with an inadequate response to treatment with corticosteroids, thiopurines, and methotrexate<sup>[83,84,313-316]</sup>. Combination therapy using IFX and immunomodulators is more effective than either drug<sup>[317-320]</sup>. The effect of combining an immunomodulator with adalimumab or certolizumab pegol is less well studied but is likely to be superior to therapy with anti-TNF agent monotherapy because all anti-TNF treatments are eventually immunogenic, and immunomodulators may reduce the rate of antidrug antibody formation<sup>[204,335]</sup>. Anti-TNF treatments have rapid onset of effect with benefit often noted within 2 wk of initiating therapy. Anti-TNF treatments are more effective when given earlier in the course of disease, especially within 2 yrs of disease onset<sup>[161,164,210,317]</sup>. Anti-integrin (VDZ) and anti-interleukin ustekinumab (blocking p40 subunit of IL12/23) have been licensed for the management of steroid and/or immunomodulator refractory CD<sup>[215,220,321-328]</sup>. Details on trials and supportive evidence are discussed under individual statements below.

**Statement 91:** In view of the adverse effects of cigarette smoking on the course of CD, smoking should be discouraged in all patients. [100]

Cigarette smoking has an adverse effect on disease activity in CD<sup>[364]</sup>. All IBD patients should be asked about cigarette smoking. Smokers with CD have an increased rate of surgery, IBD-related hospital admissions, and peripheral arthritis compared to nonsmokers<sup>[365,366]</sup>. Active smoking is associated with penetrating disease and increases relapse risk even after discontinuation of biologic therapy<sup>[367,368]</sup>. Conversely, in those who stop smoking, there are fewer flares and a reduced need for steroids and immunomodulatory therapy<sup>[369]</sup>. Smokers with CD should be offered smoking cessation advice<sup>[370,371]</sup> by suggesting behavioural therapy in combination with pharmacotherapy (nicotine replacement, bupropion, or varenicline)<sup>[372]</sup>. Pregnant women should be counselled regarding risks and benefits of nicotine replacement therapy<sup>[372]</sup>.

**Statement 92:** In localized disease, thiopurines or methotrexate should be considered for maintaining remission achieved by systemic steroids. [77.7]

Thiopurines and methotrexate are not effective for induction of remission. Thiopurines have been demonstrated to be more effective than placebo for maintenance of remission in CD, although quality of evidence for this has been reported as low (NNT = 9)<sup>[335]</sup>. A systematic review with network meta-analysis showed a benefit of thiopurines compared with placebo for the maintenance of remission of CD, although anti-TNF therapy was more effective than thiopurines<sup>[334]</sup>. The role of methotrexate in maintenance of remission is discussed under statement 79.

**Statement 93:** Thiopurine S-methyltransferase (TPMT) testing should be performed before initial use of thiopurines. [77.7]

**Statement 94:** Upon relapse, escalation of the maintenance treatment can be considered to prevent disease progression. Steroids should not be used to maintain remission. [100]

TPMT is involved in the metabolism of AZA. A subset of patients with low TPMT activity may be at increased risk of adverse events from AZA and consequent discontinuation of therapy<sup>[373,374]</sup>. In a prospective study patients dosed according to TPMT status performed better than those in the standard therapy group (2.6% risk of haematological side effects with TPMT directed dosing *vs* 22.9% in standard therapy group, RR 0.11, 95% CI: 0.01-0.85)<sup>[375]</sup>. TPMT-directed dosing appears to be cost-effective<sup>[373,374]</sup>.

The starting dose of AZA is 2-2.5 mg/kg body weight and for mercaptopurine 1-1.5mg/kg in those with normal TPMT activity<sup>[63]</sup>. Patients homozygous or compound heterozygous for TPMT (absent TPMT activity) have a very high risk of thiopurine-induced myelosuppression, and azathioprine should be avoided. In individuals who have heterozygous TPMT type, 50% of the standard dose may improve tolerance<sup>[375]</sup>. Genetic variation in the *NUDT15* (*Nudix hydrolase 15*) enzyme has also been associated with myelosuppression<sup>[376,377]</sup>. Although initially described in East Asians, this is also seen in those of European ancestry<sup>[378]</sup>. The Clinical Pharmacogenetics Implementation Consortium recommends *NUDT15* testing in Asians with dose reduction or thiopurine avoidance in deficiency states<sup>[376]</sup>.

Thiopurines may be started at the full dose after determining TPMT status. There is no clear evidence in favour of gradually increasing the dose from low to the maximum weight-based dose. Such a strategy may in fact cause a significant delay in achieving a target dose and consequent clinical response<sup>[379]</sup>. Measurement of thiopurine metabolites, thioguanine, and methyl-mercaptopurine may enable monitoring by detection of nonadherence to treatment, suboptimal dosing, or administration of a

high dose<sup>[380]</sup>.

Thioguanine levels of 230-400 pmol/8Å~108 erythrocytes are associated with better clinical response, and methyl-mercaptopurine levels over 5000 pmol/8Å~108 erythrocytes are associated with more liver toxicity<sup>[381]</sup>. Small prospective studies have not shown clinical benefit of a metabolite driven strategy<sup>[382,383]</sup>. In patients on combination therapy with IFX and thiopurines, a lower thioguanine of 125 pmol/8Å~108 erythrocytes appears adequate to achieve therapeutic levels of IFX<sup>[384]</sup>. Another recent study suggested a target level of > 105 pmol/8Å~108 erythrocytes<sup>[385]</sup>. Optimizing thiopurine doses in nonresponders can be considered before further escalation or change in treatment where possible.

## MANAGEMENT-MAINTENANCE OF REMISSION IN CD

**Statement 95:** For CD patients with extensive disease, thiopurines and/or biologics are recommended for maintenance of remission. [77.7]

The role of thiopurines in the maintenance of remission in CD is discussed above under statement 94 The role of biologics for the maintenance of remission is discussed below.

**Statement 96:** In CD patients with aggressive/severe disease course or poor prognostic factors, biologics approved for the disease should be considered. [88.8]

**Statement 97:** Biologics should be given for CD refractory to thiopurine or methotrexate [88.8]

Biologics should be considered for the treatment of aggressive CD or associated with poor prognostic factors and for CD refractory to thiopurines or methotrexate.

Features linked with a severe disease course include young age at diagnosis<sup>[97]</sup>, extensive GI involvement, ileal/ileocolonic involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stricturing disease phenotype<sup>[98]</sup>. Visceral adiposity is also a marker for greater risk of penetrating disease<sup>[99]</sup>. A detailed discussed can be found under statements 88, 89, 93, and specific biological agents discussed below.

**Statement 98:** If remission has been achieved with the combination of anti-TNF therapy and thiopurines in treatment naïve CD patients, maintenance with the same regimen is recommended. [88.8]

The data and merits of combination therapy are discussed under statement 86.

**Statement 99:** If remission has been achieved in CD patients with biologic monotherapy, maintenance with biologic monotherapy is appropriate. [88.8]

IFX was the first anti-TNF (and biologic) used in IBD demonstrating benefit in luminal CD. In the ACCENT 1 (Maintenance infliximab for Crohn's disease) study, 573 patients with active luminal disease were administered a single 5 mg/kg intravenous dose. Response was assessed at week 2, and patients were then randomized to placebo injections at weeks 2, 6, and then 8 weekly (group 1), or IFX 5 mg/kg at the same schedule, or IFX 5 mg/kg at weeks 2 and 6, then 10 mg/kg 8 weekly<sup>[314]</sup>. By week 2, clinical response was noted in 58%. Among responders at week 30, 39% treated with 5 mg/kg maintenance and 45% on 10 mg/kg were in clinical remission with similar remission rates observed at week 54<sup>[314]</sup>.

In the CLASSIC (Adalimumab induced clinical remission in Crohn's disease) I study of adalimumab in moderate to severe CD naïve to anti-TNF therapy, adalimumab was administered 160 mg subcutaneously followed by 80 mg at week 2. Clinical remission (CDAI < 150) was achieved in 36% ( $P = 0.001$  vs placebo) compared to 24% (80 mg/40 mg), 18% (40 mg/20 mg), and 12% on placebo<sup>[386]</sup>. In CHARM (The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) study of maintenance therapy, induction responders (to 80 mg subcutaneous and 40 mg at two weeks) were given placebo, 40 mg every two weeks, or 40 mg weekly, with 12%, 36% and 41%, respectively, in clinical remission at week 56<sup>[315]</sup>. The GAIN (Gauging Adalimumab Efficacy in Infliximab Nonresponders) trial showed efficacy of adalimumab in patients with active CD and loss of response or intolerance to IFX<sup>[316]</sup>. In the EXTEND (extend the safety and efficacy of adalimumab through endoscopic healing) trial, adalimumab demonstrated efficacy in inducing and maintaining endoscopic mucosal healing<sup>[313]</sup> with improved outcomes in those who achieved deep remission<sup>[387]</sup>. These data demonstrate that anti-TNF treatments may maintain remission when it has been induced as monotherapy. The benefits of combination



therapy (at least with IFX) are discussed under statement 103.

**Statement 100:** IFX monotherapy is effective at maintaining biologics-induced remission, but because of the potential for immunogenicity and loss of response, the combination with thiopurines or methotrexate should be considered. [88.8]

A discussion of the data and merits of combination therapy with IFX can be found under statement 86.

The data for combination therapy with adalimumab and an immunomodulator is not as strong as for IFX. A meta-analysis demonstrated that combination therapy of adalimumab with an immunomodulator was slightly better than adalimumab monotherapy for induction of remission, but 1 year remission rates were not different, and dose escalation was not reduced compared to monotherapy<sup>[353]</sup>. The DIAMOND (Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease) trial compared adalimumab monotherapy to combination therapy with AZA in 176 Japanese CD patients and showed similar rates of remission at week 26 and 52<sup>[354]</sup>.

The weight of the evidence suggests that although both IFX and adalimumab are immunogenic, at least for IFX, the combination with thiopurines or methotrexate should be considered.

**Statement 101:** Combination therapies are associated with increased risk of malignancies, and their use should always be balanced carefully against the substantial benefits associated with these treatments and discussed with the patient. [88.8]

The benefits and risks of combination therapy must be individualized in addition to infection risk. The potential risks of malignancies need to be carefully considered and discussed with the patient. Patients treated with thiopurines may have a higher risk, especially among males and those patients diagnosed at younger ages and in those over 65 years of age<sup>[335,340,388]</sup>. The rare but increased risk of hepatosplenic T-cell lymphoma in young patients when a thiopurine is combined with an anti-TNF should be considered and discussed<sup>[389]</sup>.

Adverse effects of thiopurines include nausea, infections, allergic reactions, pancreatitis, myelosuppression, hepatotoxicity, and malignancy, particularly lymphoma and nonmelanoma skin cancer<sup>[339,340]</sup>.

A recent nationwide study from France reported that the risk of lymphoma was higher among those exposed to thiopurine monotherapy [adjusted hazard ratio (aHR), 2.60; 95% CI: 1.96-3.44;  $P < 0.001$ ], anti-TNF monotherapy (aHR 2.41; 95% CI: 1.60-3.64;  $P < 0.001$ ), or combination therapy (aHR 6.11; 95% CI: 3.46-10.8;  $P < 0.001$ )<sup>[390]</sup>. The risk was higher in patients exposed to combination therapy *vs* those exposed to thiopurine monotherapy (aHR 2.35; 95% CI: 1.31-4.22;  $P < 0.001$ ) or anti-TNF monotherapy (aHR 2.53; 95% CI: 1.35-4.77;  $P < .001$ ). The use of thiopurine monotherapy or anti-TNF monotherapy was associated with a small but statistically significant increased risk of lymphoma compared with exposure to neither medication, and this risk was higher with combination therapy than with each of these treatments used alone<sup>[390]</sup>. In the context of prior malignancy, biological treatment must be carefully considered. A delay of at least two years after successful cancer eradication seems appropriate and increased up to five years for malignancies with a high risk of late metastatic spread (including breast, melanoma, and renal cell carcinoma)<sup>[391]</sup>. The New York Crohn's and Colitis Organization followed 333 patients with IBD and a history of cancer for up to five years and found no differences in the rate of cancer free survival between patients treated with anti-TNF alone or in combination or no immunosuppression<sup>[392]</sup>. Recent European Crohn's Colitis Organization guidelines provide a comprehensive discussion on malignancy in relation to IBD and its treatment<sup>[393]</sup>.

**Statement 102:** VDZ should be used for maintenance of remission of VDZ-induced remission of CD. [100]

VDZ was shown to be effective at inducing and maintaining remission in moderately active CD in the GEMINI 2 trial<sup>[394]</sup>. It included patients with moderate to severe active CD and evidence of inflammation (CRP  $> 2.87$  mg/L, faecal calprotectin  $> 250$   $\mu$ g/g stool and evidence of ulceration at colonoscopy and imaging). Two coprimary endpoints were considered at week 6: clinical remission (CDAI  $\leq 150$  points) and a CDAI-100 response ( $\geq 100$ -point decrease in CDAI). The primary endpoint for maintenance treatment was clinical remission at week 52. Of 368 randomized patients, 14.5% achieved remission on VDZ as opposed to 6.8% on placebo ( $P = 0.02$ ); a CDAI-100 response was achieved by 31.3% of VDZ-treated patients as opposed to 25.7% on placebo ( $P = 0.23$ ). Clinical remission was achieved at week 52 in 39% of those treated with VDZ 8 weekly, 36.4% receiving VDZ 4 weekly,

and 21.6% receiving placebo<sup>[394]</sup>.

In the GEMINI 3 trial during a 10 wk induction period, 416 patients with moderate to severe active CD were included, 76% of whom anti-TNF therapy had previously failed<sup>[395]</sup>. The primary endpoint was clinical remission at week 6. Secondary endpoints included clinical remission at week 10 and a CDAI-100 response at week 6 and week 10. Of 315 CD patients with anti-TNF intolerance or failure, 15.2% treated with VDZ and 12.1% on placebo achieved clinical remission at week 6 ( $P = 0.433$ ). Clinical remission was achieved at week 10 by 26.6% patients treated with VDZ as opposed to 12.1% on placebo (95%CI: 1.3–3.6,  $P < 0.001$ ). In a subgroup analysis, VDZ proved more effective than placebo for induction of remission in anti-TNF naïve patients (35.3 vs 16.0%,  $P = 0.025$ )<sup>[395]</sup>.

A subsequent analysis of patients in GEMINI 2 and GEMINI 3 with 516 anti-TNF naïve and 960 anti-TNF exposed patients reported clinical remission in anti-TNF naïve patients at week 6 (22.7% vs 10.6%, 95%CI: 3.7–21.4) and week 10 (26.6 vs 15.4%, 95%CI: 1.5–21.1)<sup>[396]</sup>. Anti-TNF naïve patients achieved higher rates of clinical remission at week 52 compared with placebo (48.9% vs 26.8%, 95%CI: 8.9–35.4). Although clinical remission with VDZ and placebo at week 6 were comparable (13.3% vs 9.7%, 95%CI: 1.6–9.8) in patients previously unresponsive to anti-TNF agents, clinical remission at week 10 was higher in VDZ-treated patients (21.8% vs 11.0%, 95%CI: 4.5–18.6)<sup>[396]</sup>.

In the maintenance study, higher clinical remission rates were noted for VDZ-treated patients with prior anti-TNF failure against placebo at week 52 (27.7% vs 12.8%, 95%CI: 4.7–25.0)<sup>[396]</sup>. Prior anti-TNF antagonist failure is associated with more refractoriness to induction therapy, but responders to VDZ have a durable treatment benefit irrespective of prior TNF antagonist exposure.

In the GEMINI open label extension study, clinical responders from the randomized trials who completed at least 52 wk of treatment were followed<sup>[397,398]</sup>. There were 61 of 146 patients who had 248 wk of therapy. Clinical response and remission were maintained in 95% and 89%, respectively, of these patients with treatment benefits through weeks 52 and 248<sup>[397,398]</sup>. A systematic review including 994 participants reported clinical response and remission rates at week 6 of 54% (95%CI: 41%–66%) and 22% (95%CI: 13%–35%), respectively, with similar rates at week 14. Clinical remission was noted in 32% (95%CI: 12%–62%) of patients at week 52<sup>[219]</sup>. A recent systematic review with meta-analysis of real-world studies reported that 30% of CD patients were in clinical remission by week 14 (95%CI: 25%–34%) and at 12 mo (95%CI: 20%–42%) with higher rates in bio-naïve patients [48% of patients at week 14 (95%CI: 28%–68%) and 44% of patients at 12 mo (95%CI: 18%–75%)]<sup>[399]</sup>.

The VICTORY (Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases) study of 212 patients with moderate to severe CD reported 12 mo clinical remission, mucosal healing, and deep remission (clinical remission and mucosal healing) rates of 35%, 63%, and 26%, respectively<sup>[400]</sup>. Clinical remission was less likely in individuals with prior TNF-antagonist exposure (HR 0.40; 95%CI: 0.20–0.81), smoking history (HR 0.47; 95%CI: 0.25–0.89), active perianal disease (HR 0.49; 95%CI: 0.27–0.88), and severe active disease activity (HR 0.54; 95%CI: 0.31–0.95)<sup>[400]</sup>. After adjusting for disease-related factors including previous exposure to TNF antagonists, patients with early CD (< 2 yrs) were significantly more likely to achieve clinical remission than patients with later-stage CD (aHR 1.59; 95%CI: 1.02–2.49), corticosteroid-free clinical remission (aHR, 3.39; 95%CI: 1.66–6.92), and endoscopic remission (aHR 1.90; 95%CI: 1.06–3.39)<sup>[349]</sup>. The VERSIFY (efficacy of vedolizumab on endoscopic healing in moderately to severely active Crohn's disease) study reported endoscopic, radiologic, and histologic healing in 101 patients who received VDZ therapy with moderate to severe CD (CDAI 220–450) and a simple endoscopic score for CD (SES-CD) of 7 or more, and failure of conventional therapy<sup>[401]</sup>. The primary endpoint was endoscopic remission (SES-CD score  $\leq 4$ ) at week 26 and was achieved by 11.9% of patients (95%CI: 6.3–9.8). At week 52, 17.9% of patients were in endoscopic remission (95%CI: 8.9–30.4). Anti-TNF naïve patients achieved higher rates of endoscopic remission than patients with TNF-antagonist failure at weeks 26 and 52. A higher proportion of patients with moderate CD (SES-CD 7–15) achieved endoscopic remission at weeks 26 and 52 than patients with severe CD (SES-CD scores above 15). Magnetic resonance enterography evidence of remission was noted in 21.9% of patients at week 26 (95%CI: 9.3–40.0) and in 38.1% at week 52 (95%CI: 18.1–61.6). By week 52, 20.5% of patients had a histologic response in the colon (95%CI: 9.8–35.3) and 34.3% of patients had a histologic response in the ileum (95%CI: 19.1–52.2)<sup>[401]</sup>.

**Statement 103:** Ustekinumab should be used for the maintenance of remission of the ustekinumab-induced response of CD. [100]

Ustekinumab inhibits the p-40 subunit of IL-12 and IL-23 and is efficacious in CD

patients exposed to corticosteroids and/or immunomodulators or anti-TNF agents. Ustekinumab was evaluated in the Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease (UNITI and IM-UNITI) trials in patients with CD. UNITI-1 enrolled patients who had prior anti-TNF failure or intolerance. Clinical response was achieved at week 8 in 37.8% of ustekinumab 6 mg/kg treated patients ( $P < 0.001$  vs placebo), 33.5% with 130 mg, ( $P = 0.001$  vs placebo), and 20.2% with placebo<sup>[323]</sup>.

In the UNITI-2 study, patients without previous failure of treatment (mostly anti-TNF naïve, and some with previous successful use of anti-TNF therapy) were enrolled. By 8 wk, 57.9% in the 6 mg/kg, 47.4% receiving 130 mg, and 32.1% on placebo ( $P < 0.001$  vs both doses) had a clinical response<sup>[402]</sup>. Patients who responded at week 8 in both studies were randomized to the IM-UNITI maintenance study. Among these, 53.1% on 90 mg subcutaneously every 8 wk, ( $P = 0.005$  vs placebo), 48.8% on 90 mg subcutaneously every 12 wk ( $P = 0.04$  vs placebo), and 35.9% on placebo were in remission at 44 wk. IM-UNITI had 45% anti-TNF refractory patients. By week 44, 41.1% were in remission on ustekinumab 90 mg subcutaneously every 8 wk compared to 26.2% on placebo ( $P = 0.10$ ). An increasing body of real-world experience supports the benefit of ustekinumab<sup>[324-326,328]</sup>.

Although there are no published head-to-head studies comparing ustekinumab and other biologics, indirect comparisons suggest no difference in efficacy<sup>[321]</sup>. Experience from multiple clinical trials in CD has shown that patients with longer disease duration have lower response rates as do those who have proven refractory to other therapies<sup>[347]</sup>. Data for ustekinumab use in pregnancy are limited to case studies and registry data. In the rheumatological literature, ustekinumab was not associated with increased risk of miscarriage or congenital malformation, although controlled data are not available<sup>[403,404]</sup>. Ustekinumab is contraindicated in patients with active tuberculosis, sepsis, or opportunistic infections, including gut infections such as *Clostridium difficile*. The safety profile appears reassuring. Data from psoriasis studies have shown that anti-TNF therapies are associated with a greater risk of serious infection (1.9-2.9/100 patient years) compared to ustekinumab (0.93/100 patient years), although the dose of ustekinumab used in CD was lower<sup>[405]</sup>.

In a study of 167 Crohn's patients failing anti-TNF therapy and treated with ustekinumab, no malignancy, tuberculosis, or deaths were attributed to ustekinumab. Although 11.4% developed arthralgia<sup>[328]</sup>, this was not noted on active treatment compared to the placebo in the IM-UNITI maintenance trial<sup>[323]</sup>.

**Statement 104:** Loss of response to a biologic agent should be first managed by dose optimization guided by measurement of serum levels, if available, and antidrug antibodies followed by switching to a different drug within class or a different mechanism of action. [77.7]

Loss of response to an anti-TNF may be a primary (no response to induction therapy) or a secondary loss of response. In patients who have primary nonresponse to an anti-TNF, the probability of response to a second agent is low. Switching mechanism may be more successful. Therapeutic drug monitoring has a role, with emerging evidence suggesting that drug levels in primary nonresponders may be lower than in responders, and antidrug antibodies may occur within a few weeks of treatment initiation<sup>[406,407]</sup>.

Secondary loss of response to anti-TNF therapy may be due to immune-mediated neutralizing antibodies to the drug, non-neutralizing, drug-clearing antibodies, or nonimmune-mediated mechanisms. Therapeutic drug monitoring may help in decision-making and prove cost-effective<sup>[408,409]</sup>.

In a prospective study of IBD patients with secondary loss of response to IFX, mucosal healing occurred in half of patients who had their dose increased and was associated with a rise in trough levels<sup>[410]</sup>. Increasing trough levels of IFX by shortening the infusion interval to six weeks may be as effective as shortening to 4 wk or administering 10 mg/kg dose<sup>[411]</sup>. A proportion of patients may have detectable drug levels and a low titre of antidrug antibodies<sup>[412]</sup>. Starting immunomodulator therapy (unless already started) may negate the antibodies and recapture response, particularly with an increase in anti-TNF dose<sup>[413]</sup>. If the antibody titre is high with a low drug level, a switch possibly in the same class may be appropriate if the patient had responded to this class of therapy. There is a risk of forming antibodies to the next drug in class and switching to another mechanism of action may also be appropriate<sup>[414]</sup>. Another important scenario to consider with loss of response and active disease is the presence of "adequate" drug levels. This implies mechanistic failure relating to the drug and switch to an alternative mechanism of action ("out of class").

**Statement 105:** 5-ASA is not recommended for maintenance of medically induced

remission in CD. [77.7]

A Cochrane review found that oral 5-ASA has no efficacy in maintaining clinical remission in CD<sup>[415]</sup>. Several meta-analyses have reported similar negative findings for both induction and maintenance of remission with 5-ASA<sup>[301,302,416,417]</sup>. Although some studies have shown possible benefit for sulphasalazine in the induction of clinical remission<sup>[306,307]</sup>, there was no benefit in maintenance and no benefit for 5-ASA for the induction of remission in colonic CD<sup>[418]</sup>. As such, 5-ASA cannot be recommended for the maintenance of medically induced remission in CD.

**Statement 106:** Antibiotics are not effective for induction of remission in CD. [88.8]

A wide range of antibiotics have been studied in the induction of remission for CD<sup>[308]</sup>. The precise mechanisms whereby broad-spectrum antibiotics work is uncertain but might include direct immunosuppression (*e.g.*, metronidazole), reduction of bacterial overgrowth, and suppression of a bacteria-induced antigenic stimulus. Metronidazole has not been shown to be effective as primary therapy for luminal inflammatory CD. Ciprofloxacin appears to have similar efficacy to mesalamine in active CD but is not more effective than placebo to induce remission<sup>[308,419,420]</sup>. Neither of these agents influences mucosal healing in CD<sup>[308,419,420]</sup>.

**Statement 107:** Budesonide should not be used to maintain remission of CD beyond 6 mo. [77.7]

Six randomized placebo-controlled studies have evaluated the effect of budesonide on maintenance of remission in CD<sup>[421-426]</sup>. Relapse rates at 12 mo for 3 to 6 mg budesonide ranged from 40% to 74% and were not significantly different from placebo. Subsequent meta-analyses have shown lack of efficacy in maintenance of remission with only slight improvements in mean time to symptom relapse<sup>[427-430]</sup>. These meta-analyses included budesonide doses of 3 mg and 6 mg wherein more adverse events, such as abnormal adrenocorticoid stimulation tests and alteration in bone mineral density, were reported compared with placebo; however changes were lower than those with conventional corticosteroids<sup>[427-430]</sup>. It is not recommended that budesonide be used for the maintenance of remission of CD beyond 6 mo.

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## FISTULIZING CD

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**Statement 108:** Drainage of abscesses should be undertaken before treatment of fistulizing CD with biologics. [100]

**Statement 109:** Placement of setons increases the efficacy of anti-TNF and should be considered in treating complex perianal fistula. [88.8]

**Statement 110:** Anti-TNF with and without thiopurines is effective and should be considered in treating complex perianal fistulae in CD. [100]

**Statement 111:** The addition of antibiotics to anti-TNF is more effective than anti-TNF alone and should be considered in treating complex perianal fistulae. [50]

**Statement 112:** Antibiotics may be effective and should be considered in treating simple perianal fistulae. [88.8]

Upon suspicion of an intra-abdominal abscess, abdominopelvic cross-sectional imaging of the abdomen is recommended. Both CT enterography and MR enterography have a diagnostic accuracy greater than 90% for the preoperative diagnosis of abscesses<sup>[431]</sup>. Preoperative CT guided abscess drainage may lead to a lower rate of postsurgical complications<sup>[432]</sup>. For smaller abscesses (< 5 mm), surgical drainage is not required.

Asymptomatic simple perianal fistulae do not need specific treatment. Symptomatic simple fistulae are addressed with noncutting setons or fistulotomy. Complex fistulae with or without abscess require seton placement together with medical treatment<sup>[433]</sup>. The decision on when to remove setons depends on treatment and drainage of any abscess. Surgical advancement flaps may be employed to close simple or complex fistulae in the absence of active infection or inflammation<sup>[434,435]</sup>.

Major fistulae (such as gastric-small bowel, proximal small bowel) may be associated with diarrhoea or small intestinal bacterial overgrowth for which surgery or medical therapy may be required. Prior to the initiation of immunosuppressive therapy with either biologics or antimetabolite therapy, complications such as abscesses should be considered using cross-sectional imaging and treated with



drainage before initiation of biologic therapy or immunosuppression<sup>[436]</sup>. High-output fistulae need surgical intervention (proximal bowel diversion, bowel segment resection, or fistula closure). Low-output fistulae may respond to immunomodulator or biologic therapy as monotherapy or as combination treatment; evidence supporting the use of immunomodulation is weak<sup>[357]</sup>.

Proximal diversion (“defunctioning”) to enable rectal and/or perianal healing is required in conjunction with initiation of anti-TNF therapy to promote healing of the perianal disease. A systematic review reported that the long-term success of diverting ostomy is rather low<sup>[437]</sup>.

Patients with simple fistulae with no active mucosal involvement in the rectum have good response to fistulotomy or mucosal advancement flap surgery, whilst patients with mucosal involvement are more likely to benefit from seton placement than fistulotomy<sup>[433-435]</sup>. Setons enable drainage of sepsis and inflammatory fistula tracts; this should be conducted before initiation of biologic therapy and has been associated with a better overall fistula healing and recurrence rate, longer duration of fistula closure, and prevention of repeated abscesses<sup>[438-441]</sup>. Although other agents such as immunomodulators, VDZ, or anti-TNF- $\alpha$  agents may also be considered in individual circumstances, the weight of the evidence supports IFX<sup>[357]</sup>. Thiopurines may alleviate symptoms of perianal fistulae but have a slow onset of action and have been shown to be effective for treating fistulizing CD<sup>[357]</sup>.

In the ACCENT II (A Crohn’s Disease Clinical Trial Evaluating Infliximab In a New Long-term Treatment Regimen in Patients with Fistulizing Crohn’s Disease) trial, induction response with fistula closure occurred in 69% of patients at 14 wk. Patient randomization to IFX subsequently had a significantly longer median time to loss of response compared to those receiving placebo ( $> 40$  wk *vs* 14 wk), with 36% of patients with absence of fistula drainage after 54 wk of IFX treatment compared to 19% of placebo patients ( $P = 0.009$ )<sup>[357]</sup>. Higher IFX trough levels may be needed for perianal fistulizing disease, with target levels  $> 10$   $\mu\text{g/mL}$  associated with improved outcomes<sup>[442]</sup>.

The efficacy of adalimumab has not been tested in a trial with the primary endpoint of fistula healing. In the CHARM (Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial, adalimumab had increased efficacy compared to placebo for closure of abdominal or perianal fistulae as a secondary endpoint<sup>[315]</sup>.

Of 117 patients with draining fistulae at baseline, complete fistula closure at week 56 was seen in 33% of patients on adalimumab as opposed to 13% on placebo ( $P = 0.016$ )<sup>[315]</sup>.

Furthermore, 90% (28/31) of patients with healed fistulae by week 56 (including those on placebo) maintained healing after a year on open label treatment<sup>[443]</sup>.

In another RCT of 76 patients with active perianal fistulizing disease receiving open label therapy with 24 wk adalimumab combined with either ciprofloxacin 500 mg BD for 12 wk or placebo, after 12 wk the primary endpoint of 50% reduction in draining fistulae was seen in 71% in the combination adalimumab/ciprofloxacin group compared to 47% in the adalimumab/placebo group ( $P = 0.047$ )<sup>[444]</sup>. Notably, at week 24 (12 wk after stopping antibiotic therapy) there was no significant difference between the two groups, suggesting that antibiotics may assist healing but not affect long-term outcome<sup>[444]</sup>.

Antibiotics may heal simple, superficial perianal fistulae and have an adjunctive role in treating perianal sepsis associated with more complex fistulae as discussed above<sup>[445-447]</sup>. Treatment usually involves metronidazole (10-20 mg/kg/d orally for 4-8 wk) and/or ciprofloxacin (500 mg orally twice daily for 4-8 wk), or levofloxacin (500-750 mg once daily for 4-8 wk) for both fistula and treatment of concurrent mucosal disease. Metronidazole and ciprofloxacin conversely have not demonstrated effective healing for complex perianal fistulae but may improve fistula-related symptoms<sup>[448]</sup>.

**Statement 113:** Anti-TNF with or without thiopurines may be effective and should be considered in treating enterocutaneous and rectovaginal fistulae in CD. [88.8]

Internal fistulae more challenging to treat and data on the management of enterocutaneous, enterovesical, and rectovaginal fistulae are limited.

Response to medical therapy (fistulae closure) as reported in a systematic review was complete in 38.3% of rectovaginal fistulae and 65.9% of enterovesical fistulae<sup>[449]</sup>. In the case of enterovesical fistulae, risk factors for the need for surgery include sigmoid origin, small bowel obstruction, abscess formation, ureteric obstruction, or urinary tract infection<sup>[450]</sup>.

In a study of 47 patients with genital fistulae, antibiotics did not demonstrate

efficacy, thiopurines showed 13% complete and 24% partial response, and anti TNF- $\alpha$  therapy showed 17% complete and 30% partial response. A third of patients had surgery with 22% showing complete response after first surgery and 39% after reintervention. Overall, fistula closure was achieved in 30% of patients<sup>[451]</sup>.

Current optimal management of rectovaginal fistulae involves use of medical therapy (thiopurine monotherapy or anti-TNF or combination therapy) as first-line treatment. The aim of medical therapy is to heal mucosal inflammation and facilitate surgical intervention. Surgical options for the treatment of rectovaginal fistulae includes fistula excision with interposition of healthy tissue between the rectum and vagina. Active infection must be treated and resolved before attempting repair. Subsequently, a mucosal advancement flap can then be performed.

Likewise, enterocutaneous or enterovesical fistulae may be treated with immunomodulator therapy or anti-TNF antibodies or both. Prospective trial data are lacking. The fistulae and any associated complications need to be addressed collectively<sup>[452,453]</sup>.

Medical therapy has a role in the treatment of a fistula associated with active inflammation but not to treat a postoperative fistula<sup>[454]</sup>. In the GETAID study of 48 patients with enterocutaneous fistula and 21 postoperative fistulae (within 30 days of surgery, mainly intestinal resections), approximately 33% had multiple tracts, and 25% had high output<sup>[455]</sup>.

Of patients receiving anti-TNF therapy, fistula healing occurred in a third, 50% of whom relapsed over a median 3 year follow-up. A third developed an intra-abdominal abscess whilst receiving anti-TNF therapy. Fifty-four percent of patients required surgery. Predictors of poor healing and surgery included complexity (multiple tracts) and associated stenosis<sup>[455]</sup>. Complex fistulae are associated with adverse outcomes including mortality<sup>[455]</sup>. Patients with enterocutaneous fistulae need multidisciplinary management decisions.

Among anti-TNF agents, higher quality evidence is available for IFX relative to adalimumab in the setting of nonperianal fistulizing CD. In the ACCENT II trial that had 25 women with 27 draining rectovaginal fistulae at baseline, fistula closure at week 14 was achieved for 45% of fistulae with IFX induction therapy<sup>[357]</sup>. IFX maintenance was associated with a longer duration of fistula closure compared to placebo therapy (median 46 wk *vs* 33 wk). Enterocutaneous fistulae were present in less than 10% of the total number of patients. There has been no RCT of efficacy in fistulizing CD with adalimumab<sup>[303]</sup>.

## PREVENTION OF POST-SURGICAL RECURRENCE

**Statement 114:** Thiopurines may be used to prevent clinical and endoscopic recurrence and are more effective than 5-ASA or placebo. However, they are not effective at preventing severe endoscopic recurrence. [88.8]

**Statement 115:** In high-risk patients, biologics should be started within 4 wk of surgery in order to prevent postoperative CD. [88.8]

**Statement 116:** In postoperative CD, IFX can be combined with an immunomodulator to decrease immunogenicity and decrease the loss of response. [66.6]

Up to 50% of patients with CD may require intestinal resection within ten years of diagnosis. The cumulative risk of surgery in patients with CD at one, five and ten years is estimated at 16.3%, 30.3%, and 46.6%, respectively<sup>[456]</sup>. Surgery is not curative, and a quarter of these patients will need further resection within five years of index surgery<sup>[456]</sup>. Furthermore, endoscopic recurrence defined by using the Rutgeert's score occurs in 30%-90% of patients at the neoterminal ileum within 12 mo of surgery and in most patients by five years<sup>[457-462]</sup>. Several risk factors, such as penetrating disease phenotype,  $\geq 2$  previous CD-related surgeries and cigarette smoking, may adversely affect postoperative disease course<sup>[463-469]</sup>. Additional risk factors include perianal disease, extensive small bowel resection a short interval between diagnosis and first surgery ( $< 10$  yrs), and young age of onset ( $< 30$  yrs)<sup>[462,470]</sup>.

Thiopurines have been shown to be effective at maintenance of remission after surgery in the TOPPIC (Trial of Mercaptopurine *vs* Placebo to Prevent Recurrence of Crohn's Disease) trial. Clinical or endoscopic recurrence at three years were similar, although a post hoc analysis did find that the mercaptopurine treated group was more likely to achieve endoscopic healing (Rutgeert's score i0)<sup>[471]</sup>. In the POCER trial (Postoperative Crohn's Endoscopic Recurrence Study), thiopurine use was associated with lower endoscopic and clinical recurrence<sup>[472]</sup>. Thiopurines are slower to act and as

such may be more suited to less severe endoscopic recurrence (Rutgeert's i2)<sup>[470,472]</sup>.

In another meta-analysis, thiopurines showed more efficacy than placebo for the prevention of clinical recurrence at one year (mean difference, 8%; 95% CI: 1%–15%;  $P = 0.021$ ; NNT = 13) and two years (mean difference, 13%; 95% CI: 2%–24%;  $P = 0.018$ ; NNT = 8) after surgery, and endoscopic recurrence (i2-4) (mean difference, 23%; 95% CI: 9–37%;  $P = 0.0016$ ; NNT = 4) at one year after surgery<sup>[473]</sup>. A meta-analysis of five controlled trials showed that they were not more effective than placebo or mesalamine (controls) for preventing clinical recurrence (year 1 RR 0.88; 95% CI: 0.60–1.30;  $P = 0.53$  and year 2 RR 0.76; 95% CI: 0.55–1.05;  $P = 0.10$ ) but did show more efficacy for the prevention of endoscopic recurrence (year 1 RR 0.71; 95% CI: 0.53–0.94;  $P = 0.02$ )<sup>[474]</sup>. Notably, patients receiving thiopurines had more adverse events leading to drug withdrawal as compared with controls (RR 2.57; 95% CI: 1.47–4.51;  $P = 0.001$ )<sup>[474]</sup>.

There is little evidence to support the use of mesalazine in the prevention of postoperative recurrence of CD<sup>[470]</sup>. A systematic review with meta-analysis showed modest benefit with reduction in clinical recurrence compared to placebo (RR 0.59; 95% CI: 0.43–0.82), but the evidence supporting its use to prevent endoscopic recurrence was subject to imprecision, inconsistency, and publication bias<sup>[475]</sup>.

Antibiotics have the potential to avoid relapse for at least three months after surgery<sup>[476]</sup>. Metronidazole (20 mg/kg daily) was not well tolerated (23% drop out) during the three month trial and was associated with neuropathic complications, which are dose-related and raise concerns with longer term use<sup>[477]</sup>. Ornidazole may also be effective but is also limited by significant side-effects (32% drop out during the one year trial treatment)<sup>[478]</sup>. In a small pilot study, ciprofloxacin did not show much benefit over placebo<sup>[479]</sup>. Trials with rifaximin are awaited in the postoperative setting, and its gut specificity may carry appeal<sup>[480]</sup>.

Anti-TNF therapy has been shown in several studies to reduce clinical and endoscopic recurrence<sup>[470,475,481–483]</sup>. A randomized three arm study compared postoperative adalimumab against AZA and 5-ASA with a two year follow-up. Endoscopic recurrence was significantly lower in the adalimumab group (adalimumab 6.3%, AZA 64.7%, 5-ASA 83.3%) and significantly reduced clinical recurrence (12.5%, 64.7%, and 50%, respectively)<sup>[484]</sup>. The POCER (Postoperative Crohn's Endoscopic Recurrence Study) trial was a randomized trial that compared an active care model using endoscopic assessment at six months postoperatively with standard care (no colonoscopy at six months)<sup>[472]</sup>. Patients received metronidazole for three months postoperatively, and those at high risk of recurrence received thiopurines (or adalimumab if intolerant). Treatment was escalated in the active care group if endoscopic recurrence was found at the 6 mo colonoscopy to thiopurine, fortnightly adalimumab with thiopurine, or weekly adalimumab. Endoscopic recurrence at 18 mo was 49% in the active group *vs* 67% in the standard care group ( $P = 0.03$ ), and clinical recurrence was 27% and 40%, respectively ( $P = 0.08$ )<sup>[472]</sup>.

Two meta-analyses have studied the efficacy of anti-TNF treatments for preventing postoperative CD<sup>[476,485]</sup>. Van Loo *et al*<sup>[485]</sup> demonstrated IFX superiority to placebo in preventing clinical and endoscopic recurrence. A network meta-analysis of 21 controlled trials across 5-ASA, antibiotic, and immunomodulator treatments showed that anti-TNF monotherapy was associated with a reduced risk of clinical relapse (RR 0.04; 95% CI: 0.00–0.14) and endoscopic relapse (RR 0.01; 95% CI: 0.00–0.05) compared with placebo<sup>[476]</sup>. Anti-TNF monotherapy was the most effective intervention for prevention of postoperative recurrence (clinical relapse RR 0.02–0.20; endoscopic relapse RR 0.005–0.04). On this basis, anti-TNF therapy can be considered first line for patients at high risk for postoperative recurrence and for patients who have tried and failed or are intolerant to thiopurines. It is not known if combination thiopurine with an anti-TNF therapy is more effective than monotherapy, although the combination of IFX and AZA achieves higher response and remission rates and may also prevent immunogenicity to IFX<sup>[317]</sup>.

## MANAGEMENT–INTRA-ABDOMINAL ABSCESS

**Statement 117:** An intra-abdominal abscess should be treated with antibiotics and a drainage procedure, either radiographically or surgical. [77.7]

When an intra-abdominal abscess is suspected, abdominopelvic cross-sectional imaging should be arranged. Both CT enterography and MR enterography have a diagnostic accuracy of greater than 90% for the preoperative detection of abscesses<sup>[431]</sup>. Preoperative CT guided abscess drainage may lead to a lower rate of postsurgical

complications<sup>[432]</sup>. For smaller abscesses (< 5 mm), surgical drainage is not required.

## CONCLUSION

The incidence and prevalence of UC and CD are on the rise worldwide, and their heterogeneity between patients and within individuals over time is striking. The progressive advance in our understanding of the etiopathogenesis coupled with an unprecedented increase in therapeutic options have progressively changed the management towards tailoring evidence-based interventions by clinicians in partnership with patients.

This guideline was stimulated and supported by the Emirates Gastroenterology and Hepatology Society following an extensive systematic review and a Delphi consensus process provides evidence- and expert opinion-based recommendations.

Comprehensive up-to-date guidance is provided regarding evaluation of disease severity, appropriate and timely use of different investigations, and choice of appropriate therapy for induction and remission phase in view of the treatment goals, which now aim to treat beyond symptoms to achieve mucosal healing when possible and to minimize intestinal injury and bowel damage with resultant disability.

## REFERENCES

- 1 **Peyrin-Biroulet L**, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010; **105**: 289-297 [PMID: [19861953](#) DOI: [10.1038/ajg.2009.579](#)]
- 2 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: [21530745](#) DOI: [10.1053/j.gastro.2011.01.055](#)]
- 3 **Burisch J**, Kiudelis G, Kupcinskas L, Kievit HAL, Andersen KW, Andersen V, Salupere R, Pedersen N, Kjeldsen J, D'Incà R, Valpiani D, Schwartz D, Odes S, Olsen J, Nielsen KR, Vegh Z, Lakatos PL, Toca A, Turcan S, Katsanos KH, Christodoulou DK, Fumery M, Gower-Rousseau C, Zammit SC, Ellul P, Eriksson C, Halfvarson J, Magro FJ, Duricova D, Bortlik M, Fernandez A, Hernández V, Myers S, Sebastian S, Oksanen P, Collin P, Goldis A, Misra R, Arebi N, Kaimakliotis IP, Nikuina I, Belousova E, Brinar M, Cukovic-Cavka S, Langholz E, Munkholm P; Epi-IBD group. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut* 2019; **68**: 423-433 [PMID: [29363534](#) DOI: [10.1136/gutjnl-2017-315568](#)]
- 4 **Fumery M**, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol* 2018; **16**: 343-356. e3 [PMID: [28625817](#) DOI: [10.1016/j.cgh.2017.06.016](#)]
- 5 **Torres J**, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis* 2012; **18**: 1356-1363 [PMID: [22162423](#) DOI: [10.1002/ibd.22839](#)]
- 6 **Feagan BG**. Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy (REACT2). [accessed 2019 Apr 12]. In: ClinicalTrials.gov [Internet]. Robarts Clinical Trials - Western University. Accessed 11 August 2019. Available from: <https://clinicaltrials.gov/ct2/show/NCT01698307?>
- 7 **Sharara AI**, Al Awadhi S, Alharbi O, Al Dhabab H, Mounir M, Salese L, Singh E, Sunna N, Tarcha N, Mosli M. Epidemiology, disease burden, and treatment challenges of ulcerative colitis in Africa and the Middle East. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 883-897 [PMID: [30096985](#) DOI: [10.1080/17474124.2018.1503052](#)]
- 8 **Zayyani NR**, Malaty HM, Graham DY. Increasing Incidence of Crohn's Disease with Familial Clustering in the Kingdom of Bahrain: A 25-Year Population-based Study. *Inflamm Bowel Dis* 2017; **23**: 304-309 [PMID: [28092308](#) DOI: [10.1097/MIB.0000000000001016](#)]
- 9 **Zobeiri M**, Bashiri H, Askari L, Keshavars AA, Tavafzadeh R, Fatahi K, Najafi F. Epidemiologic Characteristics of Patients with Inflammatory Bowel Disease in Kermanshah, Iran. *Middle East J Dig Dis* 2017; **9**: 164-169 [PMID: [28894519](#) DOI: [10.15171/mejdd.2017.68](#)]
- 10 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54. quiz e30 [PMID: [22001864](#) DOI: [10.1053/j.gastro.2011.10.001](#)]
- 11 **Ng SC**, Kaplan GG, Tang W, Banerjee R, Adigopula B, Underwood FE, Tanyingoh D, Wei SC, Lin WC, Lin HH, Li J, Bell S, Niewiadomski O, Kamm MA, Zeng Z, Chen M, Hu P, Ong D, Ooi CJ, Ling KL, Miao Y, Miao J, Janaka de Silva H, Niriella M, Aniwan S, Limsrivilai J, Pisesspongsa P, Wu K, Yang H, Ng KK, Yu HH, Wang Y, Ouyang Q, Abdullah M, Simadibrata M, Gunawan J, Hilmi I, Lee Goh K, Cao Q, Sheng H, Ong-Go A, Chong VH, Ching JYL, Wu JCY, Chan FKL, Sung JY. Population Density and Risk of Inflammatory Bowel Disease: A Prospective Population-Based Study in 13 Countries or Regions in Asia-Pacific. *Am J Gastroenterol* 2019; **114**: 107-115 [PMID: [30177785](#) DOI: [10.1038/s41395-018-0233-2](#)]
- 12 **Ng SC**, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufceena MNF, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisesspongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang



- YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJY, Chan FKL; Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013; **145**: 158-165. e2 [PMID: [23583432](#) DOI: [10.1053/j.gastro.2013.04.007](#)]
- 13 **Ananthakrishnan AN.** Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 205-217 [PMID: [25732745](#) DOI: [10.1038/nrgastro.2015.34](#)]
- 14 **Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium; Barrett JC; Alizadeh BZ; Parkes M; Bk T; Daly MJ; Kubo M; Anderson CA; Weersma RK.** Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47**: 979-986 [PMID: [26192919](#) DOI: [10.1038/ng.3359](#)]
- 15 **Torres J, Colombel JF.** Genetics and phenotypes in inflammatory bowel disease. *Lancet* 2016; **387**: 98-100 [PMID: [26490194](#) DOI: [10.1016/S0140-6736\(15\)00464-X](#)]
- 16 **Peyrin-Biroulet L, Panés J, Sandborn WJ, Vermeire S, Danese S, Feagan BG, Colombel JF, Hanauer SB, Rycroft B.** Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. *Clin Gastroenterol Hepatol* 2016; **14**: 348-354. e17 [PMID: [26071941](#) DOI: [10.1016/j.cgh.2015.06.001](#)]
- 17 **Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Geary R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF.** Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: [26303131](#) DOI: [10.1038/ajg.2015.233](#)]
- 18 **Gower-Rousseau C, Sarter H, Savoye G, Tavernier N, Fumery M, Sandborn WJ, Feagan BG, Duhamel A, Guillon-Dellac N, Colombel JF, Peyrin-Biroulet L; International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group; International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group.** Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. *Gut* 2017; **66**: 588-596 [PMID: [26646934](#) DOI: [10.1136/gutjnl-2015-310151](#)]
- 19 **Allen PB, Gower-Rousseau C, Danese S, Peyrin-Biroulet L.** Preventing disability in inflammatory bowel disease. *Therap Adv Gastroenterol* 2017; **10**: 865-876 [PMID: [29147137](#) DOI: [10.1177/1756283X17732720](#)]
- 20 **Siegel CA, Whitman CB, Spiegel BMR, Feagan B, Sands B, Loftus EV Jr, Panaccione R, D'Haens G, Bernstein CN, Geary R, Ng SC, Mantzaris GJ, Sartor B, Silverberg MS, Riddell R, Koutroubakis IE, O'Morain C, Lakatos PL, McGovern DPB, Halfvarson J, Reinisch W, Rogler G, Kruis W, Tysk C, Schreiber S, Danese S, Sandborn W, Griffiths A, Moum B, Gasche C, Pallone F, Travis S, Panes J, Colombel JF, Hanauer S, Peyrin-Biroulet L.** Development of an index to define overall disease severity in IBD. *Gut* 2018; **67**: 244-254 [PMID: [27780886](#) DOI: [10.1136/gutjnl-2016-312648](#)]
- 21 **Koliani-Pace JL, Siegel CA.** Beyond disease activity to overall disease severity in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2017; **2**: 624-626 [PMID: [28786381](#) DOI: [10.1016/S2468-1253\(17\)30212-1](#)]
- 22 **Langholz E, Munkholm P, Davidsen M, Binder V.** Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology* 1994; **107**: 3-11 [PMID: [8020674](#) DOI: [10.1016/0016-5085\(94\)90054-x](#)]
- 23 **Kim B, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH.** Proximal disease extension and related predicting factors in ulcerative proctitis. *Scand J Gastroenterol* 2014; **49**: 177-183 [PMID: [24325564](#) DOI: [10.3109/00365521.2013.867360](#)]
- 24 **Park SH, Yang SK, Park SK, Kim JW, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH.** Atypical distribution of inflammation in newly diagnosed ulcerative colitis is not rare. *Can J Gastroenterol Hepatol* 2014; **28**: 125-130 [PMID: [24619632](#) DOI: [10.1155/2014/834512](#)]
- 25 **Park SH, Loftus EV Jr, Yang SK.** Appendiceal skip inflammation and ulcerative colitis. *Dig Dis Sci* 2014; **59**: 2050-2057 [PMID: [24705639](#) DOI: [10.1007/s10620-014-3129-z](#)]
- 26 **Kim B, Barnett JL, Kleer CG, Appelman HD.** Endoscopic and histological patchiness in treated ulcerative colitis. *Am J Gastroenterol* 1999; **94**: 3258-3262 [PMID: [10566726](#) DOI: [10.1111/j.1572-0241.1999.01533.x](#)]
- 27 **Odze R, Antonioli D, Peppercorn M, Goldman H.** Effect of topical 5-aminosalicylic acid (5-ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. *Am J Surg Pathol* 1993; **17**: 869-875 [PMID: [8352372](#) DOI: [10.1097/00000478-199309000-00002](#)]
- 28 **Höie O, Wolters F, Riis L, Aamodt G, Solberg C, Bernklev T, Odes S, Mouzas IA, Beltrami M, Langholz E, Stockbrügger R, Vatn M, Moum B; European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD).** Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort. *Am J Gastroenterol* 2007; **102**: 1692-1701 [PMID: [17555460](#) DOI: [10.1111/j.1572-0241.2007.01265.x](#)]
- 29 **Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF.** Ulcerative colitis. *Lancet* 2017; **389**: 1756-1770 [PMID: [27914657](#) DOI: [10.1016/S0140-6736\(16\)32126-2](#)]
- 30 **Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L.** Crohn's disease. *Lancet* 2017; **389**: 1741-1755 [PMID: [27914655](#) DOI: [10.1016/S0140-6736\(16\)31711-1](#)]
- 31 **Feakins RM; British Society of Gastroenterology.** Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. *J Clin Pathol* 2013; **66**: 1005-1026 [PMID: [23999270](#) DOI: [10.1136/jclinpath-2013-201885](#)]
- 32 **Carbonnel F, Macaigne G, Beaugerie L, Gendre JP, Cosnes J.** Crohn's disease severity in familial and

- sporadic cases. *Gut* 1999; **44**: 91-95 [PMID: 9862832 DOI: 10.1136/gut.44.1.91]
- 33 **Henriksen M**, Jahnsen J, Lygren I, Vatn MH, Moum B; IBSEN Study Group. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? *Am J Gastroenterol* 2007; **102**: 1955-1963 [PMID: 17573793 DOI: 10.1111/j.1572-0241.2007.01368.x]
  - 34 **Abreu MT**, Taylor KD, Lin YC, Hang T, Gaiennie J, Landers CJ, Vasiliauskas EA, Kam LY, Rojany M, Papadakis KA, Rotter JI, Targan SR, Yang H. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology* 2002; **123**: 679-688 [PMID: 12198692 DOI: 10.1053/gast.2002.35393]
  - 35 **Alvarez-Lobos M**, Arostegui JI, Sans M, Tassies D, Plaza S, Delgado S, Lacy AM, Pique JM, Yagüe J, Panés J. Crohn's disease patients carrying Nod2/CARD15 gene variants have an increased and early need for first surgery due to stricturing disease and higher rate of surgical recurrence. *Ann Surg* 2005; **242**: 693-700 [PMID: 16244543 DOI: 10.1097/01.sla.0000186173.14696.ea]
  - 36 **Limdi JK**, Siminovitch KA, Newman W. Genetic dissection of inflammatory bowel disease: unravelling etiology and improving diagnostics. *Expert Rev Clin Immunol* 2005; **1**: 609-617 [PMID: 20477602 DOI: 10.1586/1744666X.1.4.609]
  - 37 **Mirkov MU**, Verstockt B, Cleynen I. Genetics of inflammatory bowel disease: beyond NOD2. *Lancet Gastroenterol Hepatol* 2017; **2**: 224-234 [PMID: 28404137 DOI: 10.1016/S2468-1253(16)30111-X]
  - 38 **Maaser C**, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annesse V, Calabrese E, Baumgart DC, Bettenworth D, Borralho Nunes P, Burisch J, Castiglione F, Eliakim R, Ellul P, González-Lama Y, Gordon H, Halligan S, Katsanos K, Kopylov U, Kotze PG, Krustinš E, Laghi A, Limdi JK, Rieder F, Rimola J, Taylor SA, Tolan D, van Rheenen P, Verstockt B, Stoker J; European Crohn's and Colitis Organization [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part I: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019; **13**: 144-164 [PMID: 30137275 DOI: 10.1093/ecco-jcc/jjy113]
  - 39 **Gasche C**, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004; **53**: 1190-1197 [PMID: 15247190 DOI: 10.1136/gut.2003.035758]
  - 40 **Voudoukis E**, Karmiris K, Oustamanolakis P, Theodoropoulou A, Sfiridaki A, Paspatis GA, Koutroubakis IE. Association between thrombocytosis and iron deficiency anemia in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2013; **25**: 1212-1216 [PMID: 23839158 DOI: 10.1097/MEG.0b013e328363e354]
  - 41 **Menees SB**, Powell C, Kurlander J, Goel A, Chey WD. 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**: 444-454 [PMID: 25732419 DOI: 10.1038/ajg.2015.6]
  - 42 **Vermeire S**, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 661-665 [PMID: 15472532 DOI: 10.1097/00054725-200409000-00026]
  - 43 **Jain S**, Ahuja V, Limdi JK. Optimal management of acute severe ulcerative colitis. *Postgrad Med J* 2019; **95**: 32-40 [PMID: 30636193 DOI: 10.1136/postgradmedj-2018-136072]
  - 44 **Travis SP**, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905-910 [PMID: 8984031 DOI: 10.1136/gut.38.6.905]
  - 45 **Chang MH**, Chou JW, Chen SM, Tsai MC, Sun YS, Lin CC, Lin CP. Faecal calprotectin as a novel biomarker for differentiating between inflammatory bowel disease and irritable bowel syndrome. *Mol Med Rep* 2014; **10**: 522-526 [PMID: 24788223 DOI: 10.3892/mmr.2014.2180]
  - 46 **Schoepfer AM**, Beglinger C, Straumann A, Trummel M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009; **15**: 1851-1858 [PMID: 19462421 DOI: 10.1002/ibd.20986]
  - 47 **Langhorst J**, Elsenbruch S, Mueller T, Rueffer A, Spahn G, Michalsen A, Dobos GJ. Comparison of 4 neutrophil-derived proteins in feces as indicators of disease activity in ulcerative colitis. *Inflamm Bowel Dis* 2005; **11**: 1085-1091 [PMID: 16306771 DOI: 10.1097/01.mib.0000187980.08686.18]
  - 48 **Gomollón F**, Dignass A, Annesse V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25 [PMID: 27660341 DOI: 10.1093/ecco-jcc/jjw168]
  - 49 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organization [ECCO]. 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**: 649-670 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]
  - 50 **Arasaratnam RP**, Brown S, Forbes A, Fox MR, Hungin P, Kelman L, Major G, O'Connor M, Sanders DS, Sinha R, Smith SC, Thomas P, Walters JRF. Guidelines for the investigation of chronic diarrhea in adults: British Society of Gastroenterology, 3rd edition. *Gut* 2018; **67**: 1380-1399 [PMID: 29653941 DOI: 10.1136/gutjnl-2017-315909]
  - 51 **Crooks B**, Limdi JK, McLaughlin J. How to manage chronic diarrhea in the elderly? *Frontline Gastroenterol* 2019; **10**: 427-433 [PMID: 31656570 DOI: 10.1136/flgastro-2018-101097]
  - 52 **American Society for Gastrointestinal Endoscopy Standards of Practice Committee**, Shergill AK, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Foley K, Hwang JH, Jue TL, Khashab MA, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD, DeWitt JM. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc* 2015; **81**: 1101-21. e1-13 [PMID: 25800660 DOI: 10.1016/j.gie.2014.10.030]
  - 53 **Limdi JK**, Farraye FA. An Update on Surveillance in Ulcerative Colitis. *Curr Gastroenterol Rep* 2018; **20**: 7 [PMID: 29516293 DOI: 10.1007/s11894-018-0612-2]

- 54 **Limdi JK**, Picco M, Farfay FA. A review of endoscopic scoring systems and their importance in a treat-to-target approach in inflammatory bowel disease (with videos). *Gastrointest Endosc* 2020; **91**: 733-745 [PMID: [31786161](#) DOI: [10.1016/j.gie.2019.11.032](#)]
- 55 **Satsangi J**, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55**: 749-753 [PMID: [16698746](#) DOI: [10.1136/gut.2005.082909](#)]
- 56 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV Jr, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. 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 [PMID: [16151544](#) DOI: [10.1155/2005/269076](#)]
- 57 **TRUELOVE SC**, WITTS LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: [13260656](#) DOI: [10.1136/bmj.2.4947.1041](#)]
- 58 **Tanaka M**, Saito H, Fukuda S, Sasaki Y, Munakata A, Kudo H. Simple mucosal biopsy criteria differentiating among Crohn disease, ulcerative colitis, and other forms of colitis: measurement of validity. *Scand J Gastroenterol* 2000; **35**: 281-286 [PMID: [10766322](#) DOI: [10.1080/003655200750024155](#)]
- 59 **Harbord M**, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, Burisch J, De Vos M, De Vries AM, Dick AD, Juillerat P, Karlsen TH, Koutroubakis I, Lakatos PL, Orchard T, Papay P, Raine T, Reinshagen M, Thaci D, Tilg H, Carbonnel F; European Crohn's and Colitis Organization. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis* 2016; **10**: 239-254 [PMID: [26614685](#) DOI: [10.1093/ecco-jcc/jjv213](#)]
- 60 **Sands BE**. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004; **126**: 1518-1532 [PMID: [15168364](#) DOI: [10.1053/j.gastro.2004.02.072](#)]
- 61 **Burgmann T**, Clara I, Graff L, Walker J, Lix L, Rawsthorne P, McPhail C, Rogala L, Miller N, Bernstein CN. The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis--how much is irritable bowel syndrome? *Clin Gastroenterol Hepatol* 2006; **4**: 614-620 [PMID: [16630762](#) DOI: [10.1016/j.cgh.2006.03.003](#)]
- 62 **Pimentel M**, Chang M, Chow EJ, Tabibzadeh S, Kirit-Kiriak V, Targan SR, Lin HC. Identification of a prodromal period in Crohn's disease but not ulcerative colitis. *Am J Gastroenterol* 2000; **95**: 3458-3462 [PMID: [11151877](#) DOI: [10.1111/j.1572-0241.2000.03361.x](#)]
- 63 **Lamb CA**, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group; Gaya DR; Iqbal TH; Taylor SA; Smith M; Brookes M; Hansen R; Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; **68**: s1-s106 [PMID: [31562236](#) DOI: [10.1136/gutjnl-2019-318484](#)]
- 64 **Lennard-Jones JE**. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989; **170**: 2-6; discussion 16 [PMID: [2617184](#) DOI: [10.3109/00365528909091339](#)]
- 65 **Romberg-Camps MJ**, Dagnelie PC, Kester AD, Hesselink-van de Kruijs MA, Cilissen M, Engels LG, Van Deursen C, Hameeteman WH, Wolters FL, Russel MG, Stockbrügger RW. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 371-383 [PMID: [19174787](#) DOI: [10.1038/ajg.2008.38](#)]
- 66 **Moum B**, Ekbo M, Vatn MH, Aadland E, Sauar J, Lygren I, Schulz T, Stray N, Fausa O. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population based study in south eastern Norway. *Gut* 1997; **40**: 328-332 [PMID: [9135520](#) DOI: [10.1136/gut.40.3.328](#)]
- 67 **Levine A**, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, Fell J, Ruemmele FM, Walters T, Sherlock M, Dubinsky M, Hyams JS. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011; **17**: 1314-1321 [PMID: [21560194](#) DOI: [10.1002/ibd.21493](#)]
- 68 **Spekhorst LM**, Visschedijk MC, Alberts R, Festen EA, van der Wouden EJ, Dijkstra G, Weersma RK; Dutch Initiative on Crohn and Colitis. Performance of the Montreal classification for inflammatory bowel diseases. *World J Gastroenterol* 2014; **20**: 15374-15381 [PMID: [25386087](#) DOI: [10.3748/wjg.v20.i41.15374](#)]
- 69 **Katsanos KH**, Vermeire S, Christodoulou DK, Riis L, Wolters F, Odes S, Freitas J, Hoie O, Beltrami M, Fornaciari G, Clofent J, Bodini P, Vatn M, Nunes PB, Moum B, Munkholm P, Limonard C, Stockbrugger R, Rutgeerts P, Tsianos EV; EC-IBD Study Group. Dysplasia and cancer in inflammatory bowel disease 10 years after diagnosis: results of a population-based European collaborative follow-up study. *Digestion* 2007; **75**: 113-121 [PMID: [17598963](#) DOI: [10.1159/000104731](#)]
- 70 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut* 2004; **53**: 1813-1816 [PMID: [15542520](#) DOI: [10.1136/gut.2003.038505](#)]
- 71 **Langholz E**, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol* 1996; **31**: 260-266 [PMID: [8833356](#) DOI: [10.3109/00365529609004876](#)]
- 72 **Sturm A**, Maaser C, Calabrese E, Annese V, Fiorino G, Kucharzik T, Vavricka SR, Verstockt B, van Rheenen P, Tolan D, Taylor SA, Rimola J, Rieder F, Limdi JK, Laghi A, Krustinš E, Kotze PG, Kopylov U, Katsanos K, Halligan S, Gordon H, González Lama Y, Ellul P, Eliakim R, Castiglione F, Burisch J, Borralho Nunes P, Bettenworth D, Baumgart DC, Stoker J; European Crohn's and Colitis Organization [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. *J Crohns Colitis* 2019; **13**: 273-284 [PMID: [30137278](#) DOI: [10.1093/ecco-jcc/jjy114](#)]
- 73 **Walmsley RS**, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998; **43**: 29-

- 32 [PMID: [9771402](#) DOI: [10.1136/gut.43.1.29](#)]
- 74 **Higgins PD**, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005; **54**: 782-788 [PMID: [15888785](#) DOI: [10.1136/gut.2004.056358](#)]
  - 75 **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**: 1625-1629 [PMID: [3317057](#) DOI: [10.1056/NEJM198712243172603](#)]
  - 76 **Sutherland LR**, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, Martin T, Sparr J, Prokipchuk E, Borgen L. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987; **92**: 1894-1898 [PMID: [3569765](#) DOI: [10.1016/0016-5085\(87\)90621-4](#)]
  - 77 **D'Haens G**, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; **132**: 763-786 [PMID: [17258735](#) DOI: [10.1053/j.gastro.2006.12.038](#)]
  - 78 **Lewis JD**, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008; **14**: 1660-1666 [PMID: [18623174](#) DOI: [10.1002/ibd.20520](#)]
  - 79 **Turner D**, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 1081-1088 [PMID: [19577010](#) DOI: [10.1016/j.cgh.2009.06.024](#)]
  - 80 **Jairath V**, Khanna R, Zou GY, Stitt L, Mosli M, Vandervoort MK, D'Haens G, Sandborn WJ, Feagan BG, Levesque BG. Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. *Aliment Pharmacol Ther* 2015; **42**: 1200-1210 [PMID: [26388424](#) DOI: [10.1111/apt.13408](#)]
  - 81 **Baron JH**, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964; **1**: 89-92 [PMID: [14075156](#) DOI: [10.1136/bmj.1.5375.89](#)]
  - 82 **Feagan BG**, Sandborn WJ, D'Haens G, Pola S, McDonald JWD, Rutgeerts P, Munkholm P, Mittmann U, King D, Wong CJ, Zou G, Donner A, Shackelton LM, Gilgen D, Nelson S, Vandervoort MK, Fahmy M, Loftus EV Jr, Panaccione R, Travis SP, Van Assche GA, Vermeire S, Levesque BG. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. *Gastroenterology* 2013; **145**: 149-157. e2 [PMID: [23528626](#) DOI: [10.1053/j.gastro.2013.03.025](#)]
  - 83 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: [16339095](#) DOI: [10.1056/NEJMoa050516](#)]
  - 84 **Rutgeerts P**, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63**: 433-442; quiz 464 [PMID: [16500392](#) DOI: [10.1016/j.gie.2005.08.011](#)]
  - 85 **Barreiro-de Acosta M**, Vallejo N, de la Iglesia D, Uribarri L, Bastón I, Ferreira-Iglesias R, Lorenzo A, Domínguez-Muñoz JE. Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study. *J Crohns Colitis* 2016; **10**: 13-19 [PMID: [26351390](#) DOI: [10.1093/ecco-jcc/jjv158](#)]
  - 86 **Boal Carvalho P**, Dias de Castro F, Rosa B, Moreira MJ, Cotter J. Mucosal Healing in Ulcerative Colitis--When Zero is Better. *J Crohns Colitis* 2016; **10**: 20-25 [PMID: [26438714](#) DOI: [10.1093/ecco-jcc/jjv180](#)]
  - 87 **Samaan MA**, Mosli MH, Sandborn WJ, Feagan BG, D'Haens GR, Dubcenco E, Baker KA, Levesque BG. A systematic review of the measurement of endoscopic healing in ulcerative colitis clinical trials: recommendations and implications for future research. *Inflamm Bowel Dis* 2014; **20**: 1465-1471 [PMID: [24831558](#) DOI: [10.1097/MIB.0000000000000046](#)]
  - 88 **Lobatón T**, Bessissow T, De Hertogh G, Lemmens B, Maedler C, Van Assche G, Vermeire S, Bisschops R, Rutgeerts P, Bitton A, Afif W, Marcus V, Ferrante M. The Modified Mayo Endoscopic Score (MMES): A New Index for the Assessment of Extension and Severity of Endoscopic Activity in Ulcerative Colitis Patients. *J Crohns Colitis* 2015; **9**: 846-852 [PMID: [26116558](#) DOI: [10.1093/ecco-jcc/jjv111](#)]
  - 89 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lémann M, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Bernhardt CA, Mary JY, Sandborn WJ. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012; **61**: 535-542 [PMID: [21997563](#) DOI: [10.1136/gutjnl-2011-300486](#)]
  - 90 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Schnell P, Bernhardt CA, Mary JY, Sandborn WJ. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013; **145**: 987-995 [PMID: [23891974](#) DOI: [10.1053/j.gastro.2013.07.024](#)]
  - 91 **Samuel S**, Bruining DH, Loftus EV Jr, Thia KT, Schroeder KW, Tremaine WJ, Faubion WA, Kane SV, Pardi DS, de Groen PC, Harmsen WS, Zinsmeister AR, Sandborn WJ. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013; **11**: 49-54. e1 [PMID: [22902762](#) DOI: [10.1016/j.cgh.2012.08.003](#)]
  - 92 **Ikeya K**, Hanai H, Sugimoto K, Osawa S, Kawasaki S, Iida T, Maruyama Y, Watanabe F. The Ulcerative Colitis Endoscopic Index of Severity More Accurately Reflects Clinical Outcomes and Long-term Prognosis than the Mayo Endoscopic Score. *J Crohns Colitis* 2016; **10**: 286-295 [PMID: [26581895](#) DOI: [10.1093/ecco-jcc/jjv210](#)]
  - 93 **Saigusa K**, Matsuoka K, Sugimoto S, Arai M, Kiyohara H, Takeshita K, Mizuno S, Mori K, Nanki K, Takeshita T, Nakazato Y, Yajima T, Naganuma M, Hisamatsu T, Ogata H, Iwao Y, Kanai T. Ulcerative colitis endoscopic index of severity is associated with long-term prognosis in ulcerative colitis patients



- treated with infliximab. *Dig Endosc* 2016; **28**: 665-670 [PMID: [26997640](#) DOI: [10.1111/den.12655](#)]
- 94 **Arai M**, Naganuma M, Sugimoto S, Kiyohara H, Ono K, Mori K, Saigusa K, Nanki K, Mutaguchi M, Mizuno S, Bessho R, Nakazato Y, Hosoe N, Matsuoka K, Inoue N, Ogata H, Iwao Y, Kanai T. The Ulcerative Colitis Endoscopic Index of Severity is Useful to Predict Medium- to Long-Term Prognosis in Ulcerative Colitis Patients with Clinical Remission. *J Crohns Colitis* 2016; **10**: 1303-1309 [PMID: [27194529](#) DOI: [10.1093/ecco-jcc/jjw104](#)]
  - 95 **Colombel JF**, Ordás I, Ullman T, Rutgeerts P, Chai A, O'Byrne S, Lu TT, Panés J. Agreement Between Rectosigmoidoscopy and Colonoscopy Analyses of Disease Activity and Healing in Patients With Ulcerative Colitis. *Gastroenterology* 2016; **150**: 389-95. e3 [PMID: [26526713](#) DOI: [10.1053/j.gastro.2015.10.016](#)]
  - 96 **Thia KT**, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010; **139**: 1147-1155 [PMID: [20637205](#) DOI: [10.1053/j.gastro.2010.06.070](#)]
  - 97 **Duricova D**, Fumery M, Annese V, Lakatos PL, Peyrin-Biroulet L, Gower-Rousseau C. The natural history of Crohn's disease in children: a review of population-based studies. *Eur J Gastroenterol Hepatol* 2017; **29**: 125-134 [PMID: [27748673](#) DOI: [10.1097/MEG.0000000000000761](#)]
  - 98 **Torres J**, Caprioli F, Katsanos KH, Lobatón T, Micie D, Zerôncio M, Van Assche G, Lee JC, Lindsay JO, Rubin DT, Panaccione R, Colombel JF. Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases. *J Crohns Colitis* 2016; **10**: 1385-1394 [PMID: [27282402](#) DOI: [10.1093/ecco-jcc/jjw116](#)]
  - 99 **Van Der Sloot KW**, Joshi AD, Bellavance DR, Gilpin KK, Stewart KO, Lochhead P, Garber JJ, Giallourakis C, Yajnik V, Ananthakrishnan AN, Alizadeh BZ, Xavier RJ, Khalili H. Visceral Adiposity, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: 82-88 [PMID: [27893544](#) DOI: [10.1097/MIB.0000000000000978](#)]
  - 100 **Abdelrazeq AS**, Wilson TR, Leitch DL, Lund JN, Leveson SH. Ileitis in ulcerative colitis: is it a backwash? *Dis Colon Rectum* 2005; **48**: 2038-2046 [PMID: [16175321](#) DOI: [10.1007/s10350-005-0160-3](#)]
  - 101 **Mylonaki M**, Langmead L, Pantes A, Johnson F, Rampton DS. Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. *Eur J Gastroenterol Hepatol* 2004; **16**: 775-778 [PMID: [15256979](#) DOI: [10.1097/01.meg.0000131040.38607.09](#)]
  - 102 **Axelrad JE**, Joelson A, Green PHR, Lawlor G, Lichtiger S, Cadwell K, Lebowitz B. Enteric Infections Are Common in Patients with Flares of Inflammatory Bowel Disease. *Am J Gastroenterol* 2018; **113**: 1530-1539 [PMID: [30072777](#) DOI: [10.1038/s41395-018-0211-8](#)]
  - 103 **Negrón ME**, Barkema HW, Rioux K, De Buck J, Checkley S, Proulx MC, Frolkis A, Beck PL, Dieleman LA, Panaccione R, Ghosh S, Kaplan GG. Clostridium difficile infection worsens the prognosis of ulcerative colitis. *Can J Gastroenterol Hepatol* 2014; **28**: 373-380 [PMID: [25157528](#) DOI: [10.1155/2014/914303](#)]
  - 104 **Negrón ME**, Rezaie A, Barkema HW, Rioux K, De Buck J, Checkley S, Beck PL, Carroll M, Fedorak RN, Dieleman L, Panaccione R, Ghosh S, Kaplan GG. Ulcerative Colitis Patients With Clostridium difficile are at Increased Risk of Death, Colectomy, and Postoperative Complications: A Population-Based Inception Cohort Study. *Am J Gastroenterol* 2016; **111**: 691-704 [PMID: [27091322](#) DOI: [10.1038/ajg.2016.106](#)]
  - 105 **Lindgren SC**, Flood LM, Kilander AF, Löfberg R, Persson TB, Sjö Dahl RI. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998; **10**: 831-835 [PMID: [9831403](#) DOI: [10.1097/00042737-199810000-00003](#)]
  - 106 **Ho GT**, Mowat C, Goddard CJ, Fennell JM, Shah NB, Prescott RJ, Satsangi J. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* 2004; **19**: 1079-1087 [PMID: [15142197](#) DOI: [10.1111/j.1365-2036.2004.01945.x](#)]
  - 107 **Seo M**, Okada M, Yao T, Mataka H, Maeda K. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *J Gastroenterol* 2002; **37**: 29-34 [PMID: [11824797](#) DOI: [10.1007/s535-002-8129-2](#)]
  - 108 **Schoepfer AM**, Trummel M, Secholzer P, Seibold-Schmid B, Seibold F. Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. *Inflamm Bowel Dis* 2008; **14**: 32-39 [PMID: [17924558](#) DOI: [10.1002/ibd.20275](#)]
  - 109 **Gisbert JP**, Bermejo F, Pérez-Calle JL, Taxonera C, Vera I, McNicholl AG, Algaba A, López P, López-Palacios N, Calvo M, González-Lama Y, Careros JA, Velasco M, Maté J. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm Bowel Dis* 2009; **15**: 1190-1198 [PMID: [19291780](#) DOI: [10.1002/ibd.20933](#)]
  - 110 **von Roon AC**, Karamountzos L, Purkayastha S, Reese GE, Darzi AW, Teare JP, Paraskeva P, Tekkis PP. Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. *Am J Gastroenterol* 2007; **102**: 803-813 [PMID: [17324124](#) DOI: [10.1111/j.1572-0241.2007.01126.x](#)]
  - 111 **Lin JF**, Chen JM, Zuo JH, Yu A, Xiao ZJ, Deng FH, Nie B, Jiang B. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. *Inflamm Bowel Dis* 2014; **20**: 1407-1415 [PMID: [24983982](#) DOI: [10.1097/MIB.0000000000000057](#)]
  - 112 **Zittan E**, Kelly OB, Kirsch R, Milgrom R, Burns J, Nguyen GC, Croitoru K, Van Assche G, Silverberg MS, Steinhart AH. Low Fecal Calprotectin Correlates with Histological Remission and Mucosal Healing in Ulcerative Colitis and Colonic Crohn's Disease. *Inflamm Bowel Dis* 2016; **22**: 623-630 [PMID: [26829408](#) DOI: [10.1097/MIB.0000000000000652](#)]
  - 113 **Jain S**, Kedia S, Bopanna S, Sachdev V, Sahni P, Dash NR, Pal S, Vishnubhatla S, Makharia G, Travis SPL, Ahuja V. Faecal Calprotectin and UCEIS Predict Short-term Outcomes in Acute Severe Colitis: Prospective Cohort Study. *J Crohns Colitis* 2017; **11**: 1309-1316 [PMID: [29088461](#) DOI: [10.1093/ecco-jcc/jjx084](#)]
  - 114 **Reese GE**, Constantinides VA, Simillis C, Darzi AW, Orchard TR, Fazio VW, Tekkis PP. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006; **101**: 2410-2422 [PMID: [16952282](#) DOI: [10.1111/j.1572-0241.2006.00840.x](#)]

- 115 **Dubinsky MC**, Kugathasan S, Mei L, Picornell Y, Nebel J, Wrobel I, Quiros A, Silber G, Wahbeh G, Katzir L, Vasiliauskas E, Bahar R, Otley A, Mack D, Evans J, Rosh J, Hemker MO, Leleiko N, Crandall W, Langton C, Landers C, Taylor KD, Targan SR, Rotter JJ, Markowitz J, Hyams J; Western Regional Pediatric IBD Research Alliance; Pediatric IBD Collaborative Research Group; Wisconsin Pediatric IBD Alliance. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008; **6**: 1105-1111 [PMID: [18619921](#) DOI: [10.1016/j.cgh.2008.04.032](#)]
- 116 **Dignass AU**, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, Gomollon F, Iqbal T, Katsanos K, Koutroubakis I, Magro F, Savoye G, Stein J, Vavricka S; European Crohn's and Colitis Organization [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis* 2015; **9**: 211-222 [PMID: [25518052](#) DOI: [10.1093/ecco-jcc/jju009](#)]
- 117 **Stoffel NU**, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, Moretti D, Zimmermann MB. Iron absorption from oral iron supplements given on consecutive vs alternate days and as single morning doses vs twice-daily split dosing in iron-depleted women: two open-label, randomized controlled trials. *Lancet Haematol* 2017; **4**: e524-e533 [PMID: [29032957](#) DOI: [10.1016/S2352-3026\(17\)30182-5](#)]
- 118 **Stoffel NU**, Zeder C, Fort E, Swinkels DW, Zimmermann MB, Moretti D. Prediction of human iron bioavailability using rapid c-ELISAs for human plasma hepcidin. *Clin Chem Lab Med* 2017; **55**: 1186-1192 [PMID: [28628474](#) DOI: [10.1515/cclm-2017-0097](#)]
- 119 **Taylor SA**, Avni F, Cronin CG, Hoeffel C, Kim SH, Laghi A, Napolitano M, Petit P, Rimola J, Tolan DJ, Torkzad MR, Zappa M, Bhatnagar G, Puylaert CAJ, Stoker J. The first joint ESGAR/ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging. *Eur Radiol* 2017; **27**: 2570-2582 [PMID: [27757521](#) DOI: [10.1007/s00330-016-4615-9](#)]
- 120 **Horsthuis K**, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008; **247**: 64-79 [PMID: [18372465](#) DOI: [10.1148/radiol.2471070611](#)]
- 121 **Panés J**, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, Mendoza JL, Paredes JM, Quiroga S, Ripollés T, Rimola J. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 125-145 [PMID: [21615440](#) DOI: [10.1111/j.1365-2036.2011.04710.x](#)]
- 122 **Dong J**, Wang H, Zhao J, Zhu W, Zhang L, Gong J, Li Y, Gu L, Li J. Ultrasound as a diagnostic tool in detecting active Crohn's disease: a meta-analysis of prospective studies. *Eur Radiol* 2014; **24**: 26-33 [PMID: [23921767](#) DOI: [10.1007/s00330-013-2973-0](#)]
- 123 **Liu W**, Liu J, Xiao W, Luo G. A Diagnostic Accuracy Meta-analysis of CT and MRI for the Evaluation of Small Bowel Crohn Disease. *Acad Radiol* 2017; **24**: 1216-1225 [PMID: [28595876](#) DOI: [10.1016/j.acra.2017.04.013](#)]
- 124 **Butcher RO**, Nixon E, Sapundzieski M, Filobos R, Limdi JK. Radiation exposure in patients with inflammatory bowel disease--primum non nocere? *Scand J Gastroenterol* 2012; **47**: 1192-1199 [PMID: [22827741](#) DOI: [10.3109/00365521.2012.706829](#)]
- 125 **Desmond AN**, O'Regan K, Curran C, McWilliams S, Fitzgerald T, Maher MM, Shanahan F. Crohn's disease: factors associated with exposure to high levels of diagnostic radiation. *Gut* 2008; **57**: 1524-1529 [PMID: [18443021](#) DOI: [10.1136/gut.2008.151415](#)]
- 126 **Steward MJ**, Punwani S, Proctor I, Adjei-Gyamfi Y, Chatterjee F, Bloom S, Novelli M, Halligan S, Rodriguez-Justo M, Taylor SA. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *Eur J Radiol* 2012; **81**: 2080-2088 [PMID: [21924572](#) DOI: [10.1016/j.ejrad.2011.07.013](#)]
- 127 **Rimola J**, Ordás I, Rodriguez S, García-Bosch O, Aceituno M, Llach J, Ayuso C, Ricart E, Panés J. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. *Inflamm Bowel Dis* 2011; **17**: 1759-1768 [PMID: [21744431](#) DOI: [10.1002/ibd.21551](#)]
- 128 **Puylaert CA**, Tielbeek JA, Bipat S, Stoker J. Grading of Crohn's disease activity using CT, MRI, US and scintigraphy: a meta-analysis. *Eur Radiol* 2015; **25**: 3295-3313 [PMID: [26080794](#) DOI: [10.1007/s00330-015-3737-9](#)]
- 129 **Rieder F**, Latella G, Magro F, Yuksei ES, Higgins PD, Di Sabatino A, de Bruyn JR, Rimola J, Brito J, Bettenworth D, van Assche G, Bemelman W, d'Hoore A, Pellino G, Dignass AU. European Crohn's and Colitis Organization Topical Review on Prediction, Diagnosis and Management of Fibrostenosing Crohn's Disease. *J Crohns Colitis* 2016; **10**: 873-885 [PMID: [26928961](#) DOI: [10.1093/ecco-jcc/jjw055](#)]
- 130 **Ma X**, Li Y, Jia H, Zhang J, Wang G, Liu X, Song Y. Contrast-enhanced ultrasound in the diagnosis of patients suspected of having active Crohn's disease: meta-analysis. *Ultrasound Med Biol* 2015; **41**: 659-668 [PMID: [25619783](#) DOI: [10.1016/j.ultrasmedbio.2014.09.013](#)]
- 131 **Greenup AJ**, Bressler B, Rosenfeld G. Medical Imaging in Small Bowel Crohn's Disease-Computer Tomography Enterography, Magnetic Resonance Enterography, and Ultrasound: "Which One Is the Best for What?" *Inflamm Bowel Dis* 2016; **22**: 1246-1261 [PMID: [27070909](#) DOI: [10.1097/MIB.0000000000000727](#)]
- 132 **Witte AM**, Veenendaal RA, Van Hogezaand RA, Verspaget HW, Lamers CB. Crohn's disease of the upper gastrointestinal tract: the value of endoscopic examination. *Scand J Gastroenterol Suppl* 1998; **225**: 100-105 [PMID: [9515760](#) DOI: [10.1080/003655298750027308](#)]
- 133 **Annunziata ML**, Caviglia R, Papparella LG, Cicala M. Upper gastrointestinal involvement of Crohn's disease: a prospective study on the role of upper endoscopy in the diagnostic work-up. *Dig Dis Sci* 2012; **57**: 1618-1623 [PMID: [22350786](#) DOI: [10.1007/s10620-012-2072-0](#)]
- 134 **Rutgeerts P**, Onette E, Vantrappen G, Geboes K, Broeckaert L, Talloen L. Crohn's disease of the stomach and duodenum: A clinical study with emphasis on the value of endoscopy and endoscopic biopsies. *Endoscopy* 1980; **12**: 288-294 [PMID: [7428736](#) DOI: [10.1055/s-2007-1021762](#)]

- 135 **Casella G**, D'Inca R, Oliva L, Daperno M, Saladino V, Zoli G, Annese V, Fries W, Cortellezzi C; Italian Group - IBD. Prevalence of celiac disease in inflammatory bowel diseases: An IG-IBD multicentre study. *Dig Liver Dis* 2010; **42**: 175-178 [PMID: [19786375](#) DOI: [10.1016/j.dld.2009.08.005](#)]
- 136 **Niv Y**, Ilani S, Levi Z, Hershkowitz M, Niv E, Fireman Z, O'Donnel S, O'Morain C, Eliakim R, Scapa E, Kalantzis N, Kalantzis C, Apostolopoulos P, Gal E. Validation of the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score): a multicenter prospective study. *Endoscopy* 2012; **44**: 21-26 [PMID: [22125196](#) DOI: [10.1055/s-0031-1291385](#)]
- 137 **Doherty GA**, Moss AC, Cheifetz AS. Capsule endoscopy in suspected Crohn's disease: "yield" does not equal "diagnosis". *Am J Gastroenterol* 2010; **105**: 2111; author reply 2111-2 [PMID: [20818355](#) DOI: [10.1038/ajg.2010.203](#)]
- 138 **Solem CA**, Loftus EV Jr, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, Tremaine WJ, Egan LJ, Faubion WA, Schroeder KW, Pardi DS, Hanson KA, Jewell DA, Barlow JM, Fidler JL, Huprich JE, Johnson CD, Harmsen WS, Zinsmeister AR, Sandborn WJ. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. *Gastrointest Endosc* 2008; **68**: 255-266 [PMID: [18513722](#) DOI: [10.1016/j.gie.2008.02.017](#)]
- 139 **Bourreille A**, Ignjatovic A, Aabakken L, Loftus EV Jr, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, Despott EJ, Fortun PF, Heuschkel R, Kammermeier J, Leighton JA, Mantzaris GJ, Moussata D, Lo S, Paulsen V, Panés J, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger JM, Yamamoto H, Travis S, Colombel JF, Van Gossum A; World Organization of Digestive Endoscopy (OMED) and the European Crohn's and Colitis Organization (ECCO). Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009; **41**: 618-637 [PMID: [19588292](#) DOI: [10.1055/s-0029-1214790](#)]
- 140 **Pennazio M**, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: [25826168](#) DOI: [10.1055/s-0034-1391855](#)]
- 141 **Gralnek IM**, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008; **27**: 146-154 [PMID: [17956598](#) DOI: [10.1111/j.1365-2036.2007.03556.x](#)]
- 142 **Rezapour M**, Amadi C, Gerson LB. Retention associated with video capsule endoscopy: systematic review and meta-analysis. *Gastrointest Endosc* 2017; **85**: 1157-1168. e2 [PMID: [28069475](#) DOI: [10.1016/j.gie.2016.12.024](#)]
- 143 **Rondonotti E**, Spada C, Adler S, May A, Despott EJ, Koulaouzidis A, Panter S, Domagk D, Fernandez-Urien I, Rahmi G, Riccioni ME, van Hooft JE, Hassan C, Pennazio M. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. *Endoscopy* 2018; **50**: 423-446 [PMID: [29539652](#) DOI: [10.1055/a-0576-0566](#)]
- 144 **Despott EJ**, Gupta A, Burling D, Tripoli E, Konieczko K, Hart A, Fraser C. Effective dilation of small-bowel strictures by double-balloon enteroscopy in patients with symptomatic Crohn's disease (with video). *Gastrointest Endosc* 2009; **70**: 1030-1036 [PMID: [19640518](#) DOI: [10.1016/j.gie.2009.05.005](#)]
- 145 **Arulanandan A**, Dulai PS, Singh S, Sandborn WJ, Kalmaz D. Systematic review: Safety of balloon assisted enteroscopy in Crohn's disease. *World J Gastroenterol* 2016; **22**: 8999-9011 [PMID: [27833391](#) DOI: [10.3748/wjg.v22.i40.8999](#)]
- 146 **Xin L**, Liao Z, Jiang YP, Li ZS. Indications, detectability, positive findings, total enteroscopy, and complications of diagnostic double-balloon endoscopy: a systematic review of data over the first decade of use. *Gastrointest Endosc* 2011; **74**: 563-570 [PMID: [21620401](#) DOI: [10.1016/j.gie.2011.03.1239](#)]
- 147 **Rubin DT**, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol* 2019; **114**: 384-413 [PMID: [30840605](#) DOI: [10.14309/ajg.000000000000152](#)]
- 148 **Carbonnel F**, Lavergne A, Lémann M, Bitoun A, Valleur P, Hautefeuille P, Galian A, Modigliani R, Rambaud JC. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; **39**: 1550-1557 [PMID: [8026269](#) DOI: [10.1007/bf02088063](#)]
- 149 **Corte C**, Fernandopulle N, Catuneanu AM, Burger D, Cesarini M, White L, Keshav S, Travis S. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. *J Crohns Colitis* 2015; **9**: 376-381 [PMID: [25770163](#) DOI: [10.1093/ecco-jcc/jjv047](#)]
- 150 **Xie T**, Zhang T, Ding C, Dai X, Li Y, Guo Z, Wei Y, Gong J, Zhu W, Li J. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) vs Mayo Endoscopic Score (MES) in guiding the need for colectomy in patients with acute severe colitis. *Gastroenterol Rep (Oxf)* 2018; **6**: 38-44 [PMID: [29479441](#) DOI: [10.1093/gastro/gox016](#)]
- 151 **Lawlor G**, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis* 2010; **16**: 1620-1627 [PMID: [20232408](#) DOI: [10.1002/ibd.21275](#)]
- 152 **Mourad FH**, Hashash JG, Kariyawasam VC, Leong RW. Ulcerative Colitis and Cytomegalovirus Infection: From A to Z. *J Crohns Colitis* 2020; **14**: 1162-1171 [PMID: [32103246](#) DOI: [10.1093/ecco-jcc/jjaa036](#)]
- 153 **McCurdy JD**, Jones A, Enders FT, Killian JM, Loftus EV Jr, Smyrk TC, Bruining DH. A model for identifying cytomegalovirus in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2015; **13**: 131-7; quiz e7 [PMID: [24993369](#) DOI: [10.1016/j.cgh.2014.05.026](#)]
- 154 **Lovasz BD**, Lakatos L, Golovics PA, David G, Pandur T, Erdelyi Z, Balogh M, Szita I, Molnar C, Komaromi E, Vegh Z, Mandel MD, Kiss LS, Lakatos PL. Risk of colorectal cancer in Crohn's disease patients with colonic involvement and stenosing disease in a population-based cohort from Hungary. *J*

- Gastrointestin Liver Dis* 2013; **22**: 265-268 [PMID: [24078982](#)]
- 155 **Fumery M**, Pineton de Chambrun G, Stefanescu C, Buisson A, Bressenot A, Beaugerie L, Amiot A, Altwegg R, Savoye G, Abitbol V, Bouguen G, Simon M, Duffas JP, Hébuterne X, Nancey S, Roblin X, Leteurtre E, Bommelaer G, Lefevre JH, Brunetti F, Guillon F, Bouhnik Y, Peyrin-Biroulet L. Detection of Dysplasia or Cancer in 3.5% of Patients With Inflammatory Bowel Disease and Colonic Strictures. *Clin Gastroenterol Hepatol* 2015; **13**: 1770-1775 [PMID: [26001338](#) DOI: [10.1016/j.cgh.2015.04.185](#)]
  - 156 **Laine L**, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015; **148**: 639-651. e28 [PMID: [25702852](#) DOI: [10.1053/j.gastro.2015.01.031](#)]
  - 157 **Shah SC**, Colombel JF, Sands BE, Narula N. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 1245-1255. e8 [PMID: [26829025](#) DOI: [10.1016/j.cgh.2016.01.015](#)]
  - 158 **Shah SC**, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 317-333 [PMID: [26607562](#) DOI: [10.1111/apt.13475](#)]
  - 159 **Froslie KF**, Jahnsen J, Moum BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: [17681162](#) DOI: [10.1053/j.gastro.2007.05.051](#)]
  - 160 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53 [PMID: [15972298](#) DOI: [10.1136/gut.2005.068809](#)]
  - 161 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: [21723220](#) DOI: [10.1053/j.gastro.2011.06.054](#)]
  - 162 **Rutter M**, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004; **126**: 451-459 [PMID: [14762782](#) DOI: [10.1053/j.gastro.2003.11.010](#)]
  - 163 **Dulai PS**, Jairath V. How Do We Treat Inflammatory Bowel Diseases to Aim For Endoscopic Remission? *Clin Gastroenterol Hepatol* 2020; **18**: 1300-1308 [PMID: [31887449](#) DOI: [10.1016/j.cgh.2019.12.020](#)]
  - 164 **Colombel JF**, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, Danalioglu A, Novacek G, Armuzzi A, Hébuterne X, Travis S, Danese S, Reinisch W, Sandborn WJ, Rutgeerts P, Hommes D, Schreiber S, Neimark E, Huang B, Zhou Q, Mendez P, Petersson J, Wallace K, Robinson AM, Thakkar RB, D'Haens G. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomized, controlled phase 3 trial. *Lancet* 2018; **390**: 2779-2789 [PMID: [29096949](#) DOI: [10.1016/S0140-6736\(17\)32641-7](#)]
  - 165 **Rokkas T**, Portincasa P, Koutroubakis IE. Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis. *J Gastrointestin Liver Dis* 2018; **27**: 299-306 [PMID: [30240474](#) DOI: [10.15403/jgld.2014.1121.273.pti](#)]
  - 166 **Mosli MH**, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015; **110**: 802-19; quiz 820 [PMID: [25964225](#) DOI: [10.1038/ajg.2015.120](#)]
  - 167 **Yamaguchi S**, Takeuchi Y, Arai K, Fukuda K, Kuroki Y, Asonuma K, Takahashi H, Saruta M, Yoshida H. Fecal calprotectin is a clinically relevant biomarker of mucosal healing in patients with quiescent ulcerative colitis. *J Gastroenterol Hepatol* 2016; **31**: 93-98 [PMID: [26212346](#) DOI: [10.1111/jgh.13061](#)]
  - 168 **Guardiola J**, Lobatón T, Rodríguez-Alonso L, Ruiz-Cerulla A, Arjol C, Loayza C, Sanjuan X, Sánchez E, Rodríguez-Moranta F. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. *Clin Gastroenterol Hepatol* 2014; **12**: 1865-1870 [PMID: [24993368](#) DOI: [10.1016/j.cgh.2014.06.020](#)]
  - 169 **Louis E**, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Paintaud G, Piver E, Colombel JF, Lemann M; Groupe D'etudes Thérapeutiques Des Affections Inflammatoires Digestives. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; **142**: 63-70. quiz e31 [PMID: [21945953](#) DOI: [10.1053/j.gastro.2011.09.034](#)]
  - 170 **Louis E**. Fecal calprotectin: towards a standardized use for inflammatory bowel disease management in routine practice. *J Crohns Colitis* 2015; **9**: 1-3 [PMID: [25536671](#) DOI: [10.1093/ecco-jcc/jju012](#)]
  - 171 **Sandborn WJ**, Regula J, Feagan BG, Belousova E, Jojic N, Lukas M, Yacyszyn B, Krzeski P, Yeh CH, Messer CA, Hanauer SB. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009; **137**: 1934-43. e1-3 [PMID: [19766640](#) DOI: [10.1053/j.gastro.2009.08.069](#)]
  - 172 **Marshall JK**, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010; **20**: CD004115 [PMID: [20091560](#) DOI: [10.1002/14651858.CD004115.pub2](#)]
  - 173 **Safdi M**, DeMicco M, Sninsky C, Banks P, Wruble L, Deren J, Koval G, Nichols T, Targan S, Fleishman C, Wiita B. A double-blind comparison of oral vs rectal mesalamine vs combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997; **92**: 1867-1871 [PMID: [9382054](#)]
  - 174 **Ford AC**, Khan KJ, Achkar JP, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2012; **107**: 167-176; author reply 177 [PMID: [22108446](#) DOI: [10.1038/ajg.2011.410](#)]
  - 175 **Farup PG**, Hovde O, Halvorsen FA, Raknerud N, Brodin U. Mesalazine suppositories vs hydrocortisone foam in patients with distal ulcerative colitis. A comparison of the efficacy and practicality of two topical



- treatment regimens. *Scand J Gastroenterol* 1995; **30**: 164-170 [PMID: [7732340](#) DOI: [10.3109/00365529509093256](#)]
- 176 **Cohen RD**, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000; **95**: 1263-1276 [PMID: [10811338](#) DOI: [10.1111/j.1572-0241.2000.01940.x](#)]
  - 177 **Römkens TE**, Kampschreur MT, Drenth JP, van Oijen MG, de Jong DJ. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. *Inflamm Bowel Dis* 2012; **18**: 2190-2198 [PMID: [22419617](#) DOI: [10.1002/ibd.22939](#)]
  - 178 **Lamb CA**, Lamb EI, Mansfield JC, Sankar KN. Sexually transmitted infections manifesting as proctitis. *Frontline Gastroenterol* 2013; **4**: 32-40 [PMID: [23914292](#) DOI: [10.1136/flgastro-2012-100274](#)]
  - 179 **Cohen RD**, Dalal SR. Systematic Review: Rectal Therapies for the Treatment of Distal Forms of Ulcerative Colitis. *Inflamm Bowel Dis* 2015; **21**: 1719-1736 [PMID: [26020604](#) DOI: [10.1097/MIB.0000000000000379](#)]
  - 180 **Mallet AL**, Bouguen G, Conroy G, Roblin X, Delobel JB, Bretagne JF, Siproudhis L, Peyrin-Biroulet L. Azathioprine for refractory ulcerative proctitis: A retrospective multicenter study. *Dig Liver Dis* 2017; **49**: 280-285 [PMID: [28089625](#) DOI: [10.1016/j.dld.2016.12.001](#)]
  - 181 **Bouguen G**, Roblin X, Bourreille A, Feier L, Filippi J, Nancey S, Bretagne JF, Flourié B, Hébuterne X, Bigard MA, Siproudhis L, Peyrin-Biroulet L. Infliximab for refractory ulcerative proctitis. *Aliment Pharmacol Ther* 2010; **31**: 1178-1185 [PMID: [20222911](#) DOI: [10.1111/j.1365-2036.2010.04293.x](#)]
  - 182 **Feagan BG**, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012; **10**: CD000543 [PMID: [23076889](#) DOI: [10.1002/14651858.CD000543.pub3](#)]
  - 183 **Sandborn WJ**, Travis S, Moro L, Jones R, Gaultier T, Bagin R, Huang M, Yeung P, Ballard ED 2nd. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. *Gastroenterology* 2012; **143**: 1218-1226. e2 [PMID: [22892337](#) DOI: [10.1053/j.gastro.2012.08.003](#)]
  - 184 **Kruis W**, Neshta V, Pesegova M, Alekseeva O, Andreev P, Datsenko O, Levchenko O, Abdulkhakov S, Lozynskyy Y, Mostovoy Y, Soloviev K, Dorofeyev AE, Vieth M, Stiess M, Greinwald R, Mohrbacher R, Siegmund B. Budesonide Suppositories Are Effective and Safe for Treating Acute Ulcerative Proctitis. *Clin Gastroenterol Hepatol* 2019; **17**: 98-106. e4 [PMID: [29702300](#) DOI: [10.1016/j.cgh.2018.04.027](#)]
  - 185 **Rubin DT**, Cohen RD, Sandborn WJ, Lichtenstein GR, Axler J, Riddell RH, Zhu C, Barrett AC, Bortey E, Forbes WP. Budesonide Multimatrix Is Efficacious for Mesalamine-refractory, Mild to Moderate Ulcerative Colitis: A Randomised, Placebo-controlled Trial. *J Crohns Colitis* 2017; **11**: 785-791 [PMID: [28333362](#) DOI: [10.1093/ecco-jcc/jjx032](#)]
  - 186 **Sherlock ME**, MacDonald JK, Griffiths AM, Steinhart AH, Seow CH. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2015; **26**: CD007698 [PMID: [26497719](#) DOI: [10.1002/14651858.CD007698.pub3](#)]
  - 187 **Sandborn WJ**, Danese S, D'Haens G, Moro L, Jones R, Bagin R, Huang M, David Ballard E, Masure J, Travis S. Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies. *Aliment Pharmacol Ther* 2015; **41**: 409-418 [PMID: [25588902](#) DOI: [10.1111/apt.13076](#)]
  - 188 **Löfberg R**, Danielsson A, Suhr O, Nilsson A, Schiöler R, Nyberg A, Hultcrantz R, Kollberg B, Gillberg R, Willén R, Persson T, Salde L. Oral budesonide vs prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 1996; **110**: 1713-1718 [PMID: [8964395](#) DOI: [10.1053/gast.1996.v110.pm8964395](#)]
  - 189 **Schoon EJ**, Bollani S, Mills PR, Israeli E, Felsenberg D, Ljunghall S, Persson T, Haptén-White L, Graffner H, Bianchi Porro G, Vatn M, Stockbrügger RW; Matrix Study Group. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. *Clin Gastroenterol Hepatol* 2005; **3**: 113-121 [PMID: [15704045](#) DOI: [10.1016/s1542-3565\(04\)00662-7](#)]
  - 190 **Danese S**, Siegel CA, Peyrin-Biroulet L. Review article: integrating budesonide-MMX into treatment algorithms for mild-to-moderate ulcerative colitis. *Aliment Pharmacol Ther* 2014; **39**: 1095-1103 [PMID: [24641622](#) DOI: [10.1111/apt.12712](#)]
  - 191 **Travis SP**, Danese S, Kupcinskas L, Alexeeva O, D'Haens G, Gibson PR, Moro L, Jones R, Ballard ED, Masure J, Rossini M, Sandborn WJ. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomized CORE II study. *Gut* 2014; **63**: 433-441 [PMID: [23436336](#) DOI: [10.1136/gutjnl-2012-304258](#)]
  - 192 **Hanauer SB**, Sandborn WJ, Dallaire C, Archambault A, Yacyshyn B, Yeh C, Smith-Hall N. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol* 2007; **21**: 827-834 [PMID: [18080055](#) DOI: [10.1155/2007/862917](#)]
  - 193 **Hanauer SB**, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S, Regalli G, Yeh C, Smith-Hall N, Ajayi F. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005; **100**: 2478-2485 [PMID: [16279903](#) DOI: [10.1111/j.1572-0241.2005.00248.x](#)]
  - 194 **Lichtenstein GR**, Ramsey D, Rubin DT. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing--ASCEND I and II combined analysis. *Aliment Pharmacol Ther* 2011; **33**: 672-678 [PMID: [21255059](#) DOI: [10.1111/j.1365-2036.2010.04575.x](#)]
  - 195 **Wang Y**, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016; **4**: CD000543 [PMID: [27101467](#) DOI: [10.1002/14651858.CD000543.pub4](#)]
  - 196 **Lichtenstein GR**, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, Lees K, Joseph RE, Sandborn WJ. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007; **5**: 95-102 [PMID: [17234558](#) DOI: [10.1016/j.cgh.2006.10.025](#)]

- 197 **Mansfield JC**, Gaffer MH, Cann PA, McKenna D, Thornton PC, Holdsworth CD. A double-blind comparison of balsalazide, 6.75 g, and sulfasalazine, 3 g, as sole therapy in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2002; **16**: 69-77 [PMID: [11856080](#) DOI: [10.1046/j.1365-2036.2002.01151.x](#)]
- 198 **Pruitt R**, Hanson J, Safdi M, Wruble L, Hardi R, Johanson J, Koval G, Riff D, Winston B, Cross A, Doty P, Johnson LK. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002; **97**: 3078-3086 [PMID: [12492193](#) DOI: [10.1111/j.1572-0241.2002.07103.x](#)]
- 199 **Levine DS**, Riff DS, Pruitt R, Wruble L, Koval G, Sales D, Bell JK, Johnson LK. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002; **97**: 1398-1407 [PMID: [12094857](#) DOI: [10.1111/j.1572-0241.2002.05781.x](#)]
- 200 **Ford AC**, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, Moayyedi P. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 590-9; quiz 600 [PMID: [21407179](#) DOI: [10.1038/ajg.2011.70](#)]
- 201 **Turner D**, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007; **5**: 103-110 [PMID: [17142106](#) DOI: [10.1016/j.cgh.2006.09.033](#)]
- 202 **Selinger CP**, Parkes GC, Bassi A, Limdi JK, Ludlow H, Patel P, Smith M, Saluke S, Ndlovu Z, George B, Saunders J, Adamson M, Fraser A, Robinson J, Donovan F, Parisi I, Tidbury J, Gray L, Pollok R, Scott G, Raine T. Assessment of steroid use as a key performance indicator in inflammatory bowel disease-analysis of data from 2385 UK patients. *Aliment Pharmacol Ther* 2019; **50**: 1009-1018 [PMID: [31595533](#) DOI: [10.1111/apt.15497](#)]
- 203 **Selinger CP**, Parkes GC, Bassi A, Fogden E, Hayee B, Limdi JK, Ludlow H, McLaughlin S, Patel P, Smith M, Raine T. A multi-centre audit of excess steroid use in 1176 patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017; **46**: 964-973 [PMID: [28949018](#) DOI: [10.1111/apt.14334](#)]
- 204 **Ford AC**, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 644-659, quiz 660 [PMID: [21407183](#) DOI: [10.1038/ajg.2011.73](#)]
- 205 **Danese S**, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, Bonovas S. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. *Ann Intern Med* 2014; **160**: 704-711 [PMID: [24842416](#) DOI: [10.7326/M13-2403](#)]
- 206 **Stidham RW**, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, Elmunzer BJ, Saini SD, Vijan S, Waljee AK. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor- $\alpha$  agents for the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2014; **39**: 660-671 [PMID: [24506179](#) DOI: [10.1111/apt.12644](#)]
- 207 **Panaccione R**, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; **146**: 392-400. e3 [PMID: [24512909](#) DOI: [10.1053/j.gastro.2013.10.052](#)]
- 208 **Reinisch W**, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomized controlled trial. *Gut* 2011; **60**: 780-787 [PMID: [21209123](#) DOI: [10.1136/gut.2010.221127](#)]
- 209 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-65. e1-3 [PMID: [22062358](#) DOI: [10.1053/j.gastro.2011.10.032](#)]
- 210 **Colombel JF**, Sandborn WJ, Ghosh S, Wolf DC, Panaccione R, Feagan B, Reinisch W, Robinson AM, Lazar A, Kron M, Huang B, Skup M, Thakkar RB. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3. *Am J Gastroenterol* 2014; **109**: 1771-1780 [PMID: [25155227](#) DOI: [10.1038/ajg.2014.242](#)]
- 211 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johans J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Hibi T, Rutgeerts P; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 85-95; quiz e14 [PMID: [23735746](#) DOI: [10.1053/j.gastro.2013.05.048](#)]
- 212 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johans J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 96-109. e1 [PMID: [23770005](#) DOI: [10.1053/j.gastro.2013.06.010](#)]
- 213 **Samaan MA**, Pavlidis P, Digby-Bell J, Johnston EL, Dhillon A, Paramsothy R, Akintimehin AO, Medcalf L, Chung-Faye G, DuBois P, Koumoutsos I, Powell N, Anderson SHC, Sanderson J, Hayee BH, Irving PM. Golimumab: early experience and medium-term outcomes from two UK tertiary IBD centres. *Frontline Gastroenterol* 2018; **9**: 221-231 [PMID: [30047549](#) DOI: [10.1136/flgastro-2017-100895](#)]
- 214 **Limdi JK**. Golimumab for ulcerative colitis: adding perspective to the pursuit. *Frontline Gastroenterol* 2018; **9**: 232-233 [PMID: [30047548](#) DOI: [10.1136/flgastro-2017-100929](#)]
- 215 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: [23964932](#) DOI: [10.1056/NEJMoa1215734](#)]
- 216 **Mosli MH**, MacDonald JK, Bickston SJ, Behm BW, Tsoulis DJ, Cheng J, Khanna R, Feagan BG. Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systematic review and meta-analysis. *Inflamm Bowel Dis* 2015; **21**: 1151-1159 [PMID: [25844963](#) DOI: [10.1093/ibd/ibv001](#)]

- 10.1097/MIB.0000000000000396]
- 217 **Narula N**, Peerani F, Meserve J, Kochhar G, Chaudrey K, Hartke J, Chilukuri P, Koliani-Pace J, Winters A, Katta L, Schmidt E, Hirten R, Faleck D, Parikh MP, Whitehead D, Boland BS, Singh S, Sagi SV, Fischer M, Chang S, Barocas M, Luo M, Lasch K, Bohm M, Lukin D, Sultan K, Swaminath A, Hudesman D, Gupta N, Shen B, Kane S, Loftus EV, Siegel CA, Sands BE, Colombel JF, Sandborn WJ, Dulai PS. Vedolizumab for Ulcerative Colitis: Treatment Outcomes from the VICTORY Consortium. *Am J Gastroenterol* 2018; **113**: 1345 [PMID: 29946178 DOI: 10.1038/s41395-018-0162-0]
  - 218 **Feagan BG**, Lasch K, Lissos T, Cao C, Wojtowicz AM, Khalid JM, Colombel JF. Rapid Response to Vedolizumab Therapy in Biologic-Naïve Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2019; **17**: 130-138. e7 [PMID: 29857145 DOI: 10.1016/j.cgh.2018.05.026]
  - 219 **Engel T**, Ungar B, Yung DE, Ben-Horin S, Eliakim R, Kopylov U. Vedolizumab in IBD-Lessons From Real-world Experience; A Systematic Review and Pooled Analysis. *J Crohns Colitis* 2018; **12**: 245-257 [PMID: 29077833 DOI: 10.1093/ecco-jcc/jjx143]
  - 220 **Kopylov U**, Verstockt B, Biedermann L, Sebastian S, Pugliese D, Sonnenberg E, Steinhagen P, Arebi N, Ron Y, Kucharzik T, Roblin X, Ungar B, Shitrit AB, Ardizzone S, Molander P, Coletta M, Peyrin-Biroulet L, Bossuyt P, Avni-Biron I, Tsoukali E, Allocca M, Katsanos K, Raine T, Sipponen T, Fiorino G, Ben-Horin S, Eliakim R, Armuzzi A, Siegmund B, Baumgart DC, Kamperidis N, Maharshak N, Maaser C, Mantzaris G, Yanai H, Christodoulou DK, Dotan I, Ferrante M. Effectiveness and Safety of Vedolizumab in Anti-TNF-Naïve Patients With Inflammatory Bowel Disease-A Multicenter Retrospective European Study. *Inflamm Bowel Dis* 2018; **24**: 2442-2451 [PMID: 29788318 DOI: 10.1093/ibd/izy155]
  - 221 **Bressler B**, Mantzaris G, Silverberg M, Zezo P, Stein D, Colby C, Lissos T, Natsios A, Radulescu G, Patel H, Demuth D, Yarur A. Real-world effectiveness and safety of vedolizumab and anti-TNF in biologic-naïve ulcerative colitis patients: Results from the EVOLVE study. *J Crohns Colitis* 2019; **13**: S400-S401 [DOI: 10.1093/ecco-jcc/jjy222.745]
  - 222 **Singh S**, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018; **47**: 162-175 [PMID: 29205406 DOI: 10.1111/apt.14422]
  - 223 **Bonovas S**, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018; **47**: 454-465 [PMID: 29205421 DOI: 10.1111/apt.14449]
  - 224 **Sands BE**, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törüner M, Jonaitis L, Abhyankar B, Chen J, Rogers R, Lirio RA, Bornstein JD, Schreiber S; VARSITY Study Group. Vedolizumab vs Adalimumab for Moderate-to-Severe Ulcerative Colitis. *N Engl J Med* 2019; **381**: 1215-1226 [PMID: 31553834 DOI: 10.1056/NEJMoa1905725]
  - 225 **Farrell RJ**. Biologics beyond Anti-TNF Agents for Ulcerative Colitis - Efficacy, Safety, and Cost? *N Engl J Med* 2019; **381**: 1279-1281 [PMID: 31553842 DOI: 10.1056/NEJMe1910742]
  - 226 **Sandborn WJ**, Su C, Panes J. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017; **377**: 496-497 [PMID: 28767341 DOI: 10.1056/NEJMe1707500]
  - 227 **Koncz T**. XELJANZ (tofacitinib): Restriction of 10 mg twice daily dose in patients who are at high risk of pulmonary embolism. Available from: <http://assets.publishing.service.gov.uk/media/5d07b073e5274a0b832e49b3/tofac-DHPC.pdf>
  - 228 **EMA Press office**. EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots. Nov 15 2019. In: European Medicines Agency, Science Medicines Health [Internet]. Available from: <https://www.ema.europa.eu/en/news/ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots>
  - 229 **Sands BE**, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S, Targan S, Abreu MT, Hisamatsu T, Szapary P, Marano C; UNIFI Study Group. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2019; **381**: 1201-1214 [PMID: 31553833 DOI: 10.1056/NEJMoa1900750]
  - 230 **Dinesen LC**, Walsh AJ, Protic MN, Heap G, Cummings F, Warren BF, George B, Mortensen NJ, Travis SP. The pattern and outcome of acute severe colitis. *J Crohns Colitis* 2010; **4**: 431-437 [PMID: 21122540 DOI: 10.1016/j.crohns.2010.02.001]
  - 231 **Aratari A**, Papi C, Clemente V, Moretti A, Luchetti R, Koch M, Capurso L, Caprilli R. Colectomy rate in acute severe ulcerative colitis in the infliximab era. *Dig Liver Dis* 2008; **40**: 821-826 [PMID: 18472316 DOI: 10.1016/j.dld.2008.03.014]
  - 232 **Jain S**, Kedia S, Sethi T, Bopanna S, Yadav DP, Goyal S, Padhan R, Venigalla PM, Sahni P, Dash NR, Pal S, Makharia G, Travis SPL, Ahuja V. Predictors of long-term outcomes in patients with acute severe colitis: A northern Indian cohort study. *J Gastroenterol Hepatol* 2018; **33**: 615-622 [PMID: 28801987 DOI: 10.1111/jgh.13921]
  - 233 **Lynch RW**, Lowe D, Protheroe A, Driscoll R, Rhodes JM, Arnott ID. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther* 2013; **38**: 935-945 [PMID: 24004000 DOI: 10.1111/apt.12473]
  - 234 **Williams JG**, Alam MF, Alrubaiy L, Arnott I, Clement C, Cohen D, Gordon JN, Hawthorne AB, Hilton M, Hutchings HA, Jawhari AU, Longo M, Mansfield J, Morgan JM, Rapport F, Seagroave AC, Sebastian S, Shaw I, Travis SP, Watkins A. Infliximab vs cyclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomized trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 15-24 [PMID: 27595142 DOI: 10.1016/S2468-1253(16)30003-6]
  - 235 **Truelove SC**, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974; **1**: 1067-1070 [PMID: 4135487 DOI: 10.1016/S0140-6736(74)90552-2]
  - 236 **Lichtiger S**, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845 [PMID: 8196726 DOI: 10.1056/NEJM199406303302601]
  - 237 **Van Assche G**, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg vs 2 mg/kg intravenous cyclosporine in

- severe ulcerative colitis. *Gastroenterology* 2003; **125**: 1025-1031 [PMID: [14517785](#) DOI: [10.1016/s0016-5085\(03\)01214-9](#)]
- 238 **Cheifetz AS**, Stern J, Garud S, Goldstein E, Malter L, Moss AC, Present DH. Cyclosporine is safe and effective in patients with severe ulcerative colitis. *J Clin Gastroenterol* 2011; **45**: 107-112 [PMID: [20679905](#) DOI: [10.1097/MCG.0b013e3181e883dd](#)]
- 239 **Moskovitz DN**, Van Assche G, Maenhout B, Arts J, Ferrante M, Vermeire S, Rutgeerts P. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006; **4**: 760-765 [PMID: [16716758](#) DOI: [10.1016/j.cgh.2006.04.001](#)]
- 240 **Bamba S**, Tsujikawa T, Saotome T, Okuno T, Saito Y, Sasaki M, Andoh A, Fujiyama Y. Pneumatosis coli with ulcerative colitis as a rare complication of colonoscopy. *Clin J Gastroenterol* 2010; **3**: 233-236 [PMID: [26190327](#) DOI: [10.1007/s12328-010-0169-6](#)]
- 241 **Walch A**, Meshkat M, Vogelsang H, Novacek G, Dejaco C, Angelberger S, Mikulits A, Miehsler W, Gangl A, Reinisch W. Long-term outcome in patients with ulcerative colitis treated with intravenous cyclosporine A is determined by previous exposure to thiopurines. *J Crohns Colitis* 2010; **4**: 398-404 [PMID: [21122535](#) DOI: [10.1016/j.crohns.2010.01.001](#)]
- 242 **Campbell S**, Travis S, Jewell D. Cyclosporin use in acute ulcerative colitis: a long-term experience. *Eur J Gastroenterol Hepatol* 2005; **17**: 79-84 [PMID: [15647646](#) DOI: [10.1097/00042737-200501000-00016](#)]
- 243 **Sternthal MB**, Murphy SJ, George J, Kornbluth A, Lichtiger S, Present DH. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 937-943 [PMID: [18177449](#) DOI: [10.1111/j.1572-0241.2007.01718.x](#)]
- 244 **Farraye FA**, Melmed GY, Lichtenstein GR, Kane SV. Corrigendum: ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. *Am J Gastroenterol* 2017; **112**: 1208 [PMID: [28534523](#) DOI: [10.1038/ajg.2017.145](#)]
- 245 **Farraye FA**, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. *Am J Gastroenterol* 2017; **112**: 241-258 [PMID: [28071656](#) DOI: [10.1038/ajg.2016.537](#)]
- 246 **Rahier JF**, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Vige N, Yazdanpanah Y, Eliakim R, Colombel JF; European Crohn's and Colitis Organization (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: [24613021](#) DOI: [10.1016/j.crohns.2013.12.013](#)]
- 247 **Sebastian S**, Myers S, Nadir S, Subramanian S. Systematic Review: Efficacy and Safety of Accelerated Induction Regimes in Infliximab Rescue Therapy for Hospitalized Patients with Acute Severe Colitis. *Dig Dis Sci* 2019; **64**: 1119-1128 [PMID: [30535888](#) DOI: [10.1007/s10620-018-5407-7](#)]
- 248 **Järnerot G**, Hertvig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Danielsson A, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; **128**: 1805-1811 [PMID: [15940615](#) DOI: [10.1053/j.gastro.2005.03.003](#)]
- 249 **Gustavsson A**, Järnerot G, Hertvig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Verbaan H, Hellström PM, Magnuson A, Halfvarson J, Tysk C. Clinical trial: colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study. *Aliment Pharmacol Ther* 2010; **32**: 984-989 [PMID: [20937043](#) DOI: [10.1111/j.1365-2036.2010.04435.x](#)]
- 250 **Croft A**, Walsh A, Doecke J, Cooley R, Howlett M, Radford-Smith G. Outcomes of salvage therapy for steroid-refractory acute severe ulcerative colitis: ciclosporin vs. infliximab. *Aliment Pharmacol Ther* 2013; **38**: 294-302 [PMID: [23786158](#) DOI: [10.1111/apt.12375](#)]
- 251 **Laharie D**, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, Zerbib F, Savoye G, Nachury M, Moreau J, Delchier JC, Cosnes J, Ricart E, Dewit O, Lopez-Sanroman A, Dupas JL, Carbonnel F, Bommelaer G, Coffin B, Roblin X, Van Assche G, Esteve M, Färkkilä M, Gisbert JP, Marteau P, Nahon S, de Vos M, Franchimont D, Mary JY, Colombel JF, Lémann M; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Cyclosporin vs infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomized controlled trial. *Lancet* 2012; **380**: 1909-1915 [PMID: [23063316](#) DOI: [10.1016/S0140-6736\(12\)61084-8](#)]
- 252 **Laharie D**, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, Zerbib F, Savoye G, Vuitton L, Moreau J, Amiot A, Cosnes J, Ricart E, Dewit O, Lopez-Sanroman A, Fumery M, Carbonnel F, Bommelaer G, Coffin B, Roblin X, van Assche G, Esteve M, Färkkilä M, Gisbert JP, Marteau P, Nahon S, de Vos M, Lambert J, Mary JY, Louis E; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. *Gut* 2018; **67**: 237-243 [PMID: [28053054](#) DOI: [10.1136/gutjnl-2016-313060](#)]
- 253 **Narula N**, Marshall JK, Colombel JF, Leontiadis GI, Williams JG, Muqtadir Z, Reinisch W. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids. *Am J Gastroenterol* 2016; **111**: 477-491 [PMID: [26856754](#) DOI: [10.1038/ajg.2016.7](#)]
- 254 **Ordás I**, Domènech E, Mañosa M, García-Sánchez V, Iglesias-Flores E, Peñalva M, Cañas-Ventura A, Merino O, Fernández-Bañares F, Gomollón F, Vera M, Gutiérrez A, García-Planella E, Chaparro M, Aguas M, Gento E, Muñoz F, Aguirresarobe M, Muñoz C, Fernández L, Calvet X, Jiménez CE, Montoro MA, Mir A, De Castro ML, García-Sepulcre MF, Bermejo F, Panés J, Esteve M. Long-Term Efficacy and Safety of Cyclosporine in a Cohort of Steroid-Refractory Acute Severe Ulcerative Colitis Patients from the ENEIDA Registry (1989-2013): A Nationwide Multicenter Study. *Am J Gastroenterol* 2017; **112**: 1709-1718 [PMID: [28675163](#) DOI: [10.1038/ajg.2017.180](#)]
- 255 **Sebastian S**, Myers S, Argyriou K, Martin G, Los L, Fiske J, Ranjan R, Cooper B, Goodoory V, Ching HL, Jayasooriya N, Brooks J, Dhar A, Shenoy AH, Limdi JK, Butterworth J, Allen PB, Samuel S, Moran GW, Shenderey R, Parkes G, Lobo A, Kennedy NA, Subramanian S, Raine T. Infliximab induction regimens in



- steroid-refractory acute severe colitis: a multicentre retrospective cohort study with propensity score analysis. *Aliment Pharmacol Ther* 2019; **50**: 675-683 [PMID: [31456297](#) DOI: [10.1111/apt.15456](#)]
- 256 **Dotan I**, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, Ben Yehoyada M, Mould DR. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014; **20**: 2247-2259 [PMID: [25358062](#) DOI: [10.1097/MIB.0000000000000212](#)]
- 257 **Brandse JF**, Mathôt RA, van der Kleij D, Rispens T, Ashruf Y, Jansen JM, Rietdijk S, Löwenberg M, Ponsioen CY, Singh S, van den Brink GR, D'Haens GR. Pharmacokinetic Features and Presence of Antidrug Antibodies Associate With Response to Infliximab Induction Therapy in Patients With Moderate to Severe Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2016; **14**: 251-8. e1-2 [PMID: [26545802](#) DOI: [10.1016/j.cgh.2015.10.029](#)]
- 258 **Brandse JF**, van den Brink GR, Wildenberg ME, van der Kleij D, Rispens T, Jansen JM, Mathôt RA, Ponsioen CY, Löwenberg M, D'Haens GR. Loss of Infliximab Into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis. *Gastroenterology* 2015; **149**: 350-5. e2 [PMID: [25917786](#) DOI: [10.1053/j.gastro.2015.04.016](#)]
- 259 **Löwenberg M**, Duijvis NW, Ponsioen C, van den Brink GR, Fockens P, D'Haens GR. Length of hospital stay and associated hospital costs with infliximab vs cyclosporine in severe ulcerative colitis. *Eur J Gastroenterol Hepatol* 2014; **26**: 1240-1246 [PMID: [25171024](#) DOI: [10.1097/MEG.0000000000000187](#)]
- 260 **Maser EA**, Deconda D, Lichtiger S, Ullman T, Present DH, Kornbluth A. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. *Clin Gastroenterol Hepatol* 2008; **6**: 1112-1116 [PMID: [18928936](#) DOI: [10.1016/j.cgh.2008.04.035](#)]
- 261 **Leblanc S**, Allez M, Seksik P, Flourie B, Peeters H, Dupas JL, Bouguen G, Peyrin-Biroulet L, Duclos B, Bourreille A, Dewit O, Bouhnik Y, Michetti P, Chaussade S, Saussure P, Mary JY, Colombel JF, Lémann M; GETAID. Successive treatment with cyclosporine and infliximab in steroid-refractory ulcerative colitis. *Am J Gastroenterol* 2011; **106**: 771-777 [PMID: [21386832](#) DOI: [10.1038/ajg.2011.62](#)]
- 262 **Chaparro M**, Burgueño P, Iglesias E, Panés J, Muñoz F, Bastida G, Castro L, Jiménez C, Mendoza JL, Barreiro-de Acosta M, Senent SG, Gomollón F, Calvet X, García-Planella E, Gómez M, Hernández V, Hinojosa J, Mañosa M, Nyssen OP, Gisbert JP. Infliximab salvage therapy after failure of ciclosporin in corticosteroid-refractory ulcerative colitis: a multicentre study. *Aliment Pharmacol Ther* 2012; **35**: 275-283 [PMID: [22142227](#) DOI: [10.1111/j.1365-2036.2011.04934.x](#)]
- 263 **Narula N**, Fine M, Colombel JF, Marshall JK, Reinisch W. Systematic Review: Sequential Rescue Therapy in Severe Ulcerative Colitis: Do the Benefits Outweigh the Risks? *Inflamm Bowel Dis* 2015; **21**: 1683-1694 [PMID: [25839775](#) DOI: [10.1097/MIB.0000000000000350](#)]
- 264 **Harbord M**, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, Kucharzik T, Molnár T, Raine T, Sebastian S, de Sousa HT, Dignass A, Carbonnel F; European Crohn's and Colitis Organization [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis* 2017; **11**: 769-784 [PMID: [28513805](#) DOI: [10.1093/ecco-jcc/jjx009](#)]
- 265 **Randall J**, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg* 2010; **97**: 404-409 [PMID: [20101648](#) DOI: [10.1002/bjs.6874](#)]
- 266 **Roberts SE**, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007; **335**: 1033 [PMID: [17977817](#) DOI: [10.1136/bmj.39345.714039.55](#)]
- 267 **Tøttrup A**, Erichsen R, Sværke C, Laurberg S, Sørensen HT. Thirty-day mortality after elective and emergency total colectomy in Danish patients with inflammatory bowel disease: a population-based nationwide cohort study. *BMJ Open* 2012; **2**: e000823 [PMID: [22492386](#) DOI: [10.1136/bmjopen-2012-000823](#)]
- 268 **Pal S**, Sahni P, Pande GK, Acharya SK, Chattopadhyay TK. Outcome following emergency surgery for refractory severe ulcerative colitis in a tertiary care centre in India. *BMC Gastroenterol* 2005; **5**: 39 [PMID: [16316474](#) DOI: [10.1186/1471-230X-5-39](#)]
- 269 **Jewell DP**, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974; **4**: 627-630 [PMID: [4441827](#) DOI: [10.1136/bmj.4.5945.627](#)]
- 270 **Khan KJ**, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 630-642 [PMID: [21407186](#) DOI: [10.1038/ajg.2011.64](#)]
- 271 **Sood A**, Midha V, Sood N, Kaushal V. Role of azathioprine in severe ulcerative colitis: one-year, placebo-controlled, randomized trial. *Indian J Gastroenterol* 2000; **19**: 14-16 [PMID: [10659481](#)]
- 272 **Timmer A**, Patton PH, Chande N, McDonald JW, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016; **(5)**: CD000478 [PMID: [27192092](#) DOI: [10.1002/14651858.CD000478.pub4](#)]
- 273 **Ungaro R**, Colombel JF, Lissos T, Peyrin-Biroulet L. A Treat-to-Target Update in Ulcerative Colitis: A Systematic Review. *Am J Gastroenterol* 2019; **114**: 874-883 [PMID: [30908297](#) DOI: [10.14309/ajg.0000000000000183](#)]
- 274 **Kane SV**, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol* 2001; **96**: 2929-2933 [PMID: [11693328](#) DOI: [10.1111/j.1572-0241.2001.04683.x](#)]
- 275 **Feagan BG**, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012; **10**: CD000544 [PMID: [23076890](#) DOI: [10.1002/14651858.CD000544.pub3](#)]
- 276 **Riley SA**, Lecarpentier J, Mani V, Goodman MJ, Mandal BK, Turnberg LA. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut* 1987; **28**: 1008-1012 [PMID: [2889648](#) DOI: [10.1136/gut.28.8.1008](#)]
- 277 **Banerjee A**, Scarpa M, Pathak S, Burra P, Sturmiolo GC, Russo FP, Murugesan R, D'Incá R. Inflammatory

- Bowel Disease Therapies Adversely Affect Fertility in Men- A Systematic Review and Meta-analysis. *Endocr Metab Immune Disord Drug Targets* 2019; **19**: 959-974 [PMID: [30864530](#) DOI: [10.2174/1871530319666190313112110](#)]
- 278 **Hammami MB**, Mahadevan U. Men With Inflammatory Bowel Disease: Sexual Function, Fertility, Medication Safety, and Prostate Cancer. *Am J Gastroenterol* 2020; **115**: 526-534 [PMID: [32022719](#) DOI: [10.14309/ajg.0000000000000515](#)]
- 279 **Velayos FS**, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; **100**: 1345-1353 [PMID: [15929768](#) DOI: [10.1111/j.1572-0241.2005.41442.x](#)]
- 280 **O'Connor A**, Packey CD, Akbari M, Moss AC. Mesalamine, but Not Sulfasalazine, Reduces the Risk of Colorectal Neoplasia in Patients with Inflammatory Bowel Disease: An Agent-specific Systematic Review and Meta-analysis. *Inflamm Bowel Dis* 2015; **21**: 2562-2569 [PMID: [26296062](#) DOI: [10.1097/MIB.0000000000000540](#)]
- 281 **Bonovas S**, Fiorino G, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017; **45**: 1179-1192 [PMID: [28261835](#) DOI: [10.1111/apt.14023](#)]
- 282 **Qiu X**, Ma J, Wang K, Zhang H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: a systematic review with meta-analysis. *Oncotarget* 2017; **8**: 1031-1045 [PMID: [27906680](#) DOI: [10.18632/oncotarget.13715](#)]
- 283 **Lyakhovich A**, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. *Aliment Pharmacol Ther* 2010; **31**: 202-209 [PMID: [19891667](#) DOI: [10.1111/j.1365-2036.2009.04195.x](#)]
- 284 **Flores BM**, O'Connor A, Moss AC. Impact of mucosal inflammation on risk of colorectal neoplasia in patients with ulcerative colitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2017; **86**: 1006-1011. e8 [PMID: [28750838](#) DOI: [10.1016/j.gie.2017.07.028](#)]
- 285 **Saxena AP**, Limdi JK, Farraye FA. Zeroing in on endoscopic and histologic mucosal healing to reduce the risk of colorectal neoplasia in inflammatory bowel disease. *Gastrointest Endosc* 2017; **86**: 1012-1014 [PMID: [29146080](#) DOI: [10.1016/j.gie.2017.08.029](#)]
- 286 **Ungaro RC**, Limketkai BN, Jensen CB, Allin KH, Agrawal M, Ullman T, Colombel JF, Jess T. Stopping 5-aminosalicylates in patients with ulcerative colitis starting biologic therapy does not increase the risk of adverse clinical outcomes: analysis of two nationwide population-based cohorts. *Gut* 2019; **68**: 977-984 [PMID: [30420398](#) DOI: [10.1136/gutjnl-2018-317021](#)]
- 287 **Henriksen M**, Jahnsen J, Lygren I, Aadland E, Schulz T, Vatn MH, Moum B; Ibsen Study Group. Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). *Scand J Gastroenterol* 2007; **42**: 602-610 [PMID: [17454881](#) DOI: [10.1080/00365520601076124](#)]
- 288 **Ricart E**, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Successful management of Crohn's disease of the ileoanal pouch with infliximab. *Gastroenterology* 1999; **117**: 429-432 [PMID: [10419926](#) DOI: [10.1053/gast.1999.0029900429](#)]
- 289 **Turner D**, Mack DR, Hyams J, LeLeiko N, Otley A, Markowitz J, Kasirer Y, Muise A, Seow CH, Silverberg MS, Crandall W, Griffiths AM. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? *J Crohns Colitis* 2011; **5**: 423-429 [PMID: [21939916](#) DOI: [10.1016/j.crohns.2011.05.003](#)]
- 290 **Geboes K**, Ectors N, D'Haens G, Rutgeerts P. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease? *Am J Gastroenterol* 1998; **93**: 201-206 [PMID: [9468242](#) DOI: [10.1111/j.1572-0241.1998.00201.x](#)]
- 291 **Marshall JK**, Cawdron R, Zealley I, Riddell RH, Somers S, Irvine EJ. Prospective comparison of small bowel meal with pneumocolon vs ileo-colonoscopy for the diagnosis of ileal Crohn's disease. *Am J Gastroenterol* 2004; **99**: 1321-1329 [PMID: [15233672](#) DOI: [10.1111/j.1572-0241.2004.30499.x](#)]
- 292 **Schoepfer AM**, Beglinger C, Straumann A, Trummel M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169 [PMID: [19755969](#) DOI: [10.1038/ajg.2009.545](#)]
- 293 **Ferreiro-Iglesias R**, Barreiro-de Acosta M, Lorenzo-Gonzalez A, Dominguez-Muñoz JE. Usefulness of a rapid fecal calprotectin test to predict relapse in Crohn's disease patients on maintenance treatment with adalimumab. *Scand J Gastroenterol* 2016; **51**: 442-447 [PMID: [26595391](#) DOI: [10.3109/00365521.2015.1115546](#)]
- 294 **Ferreiro-Iglesias R**, Barreiro-de Acosta M, Otero Santiago M, Lorenzo Gonzalez A, Alonso de la Peña C, Benitez Estevez AJ, Dominguez-Muñoz JE. Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. *J Clin Gastroenterol* 2016; **50**: 147-151 [PMID: [25811118](#) DOI: [10.1097/MCG.0000000000000312](#)]
- 295 **Molander P**, Färkkilä M, Ristimäki A, Salminen K, Kemppainen H, Blomster T, Koskela R, Jussila A, Rautiainen H, Nissinen M, Haapamäki J, Arkkila P, Nieminen U, Kuusma J, Punkkinen J, Kolho KL, Mustonen H, Sipponen T. Does fecal calprotectin predict short-term relapse after stopping TNF $\alpha$ -blocking agents in inflammatory bowel disease patients in deep remission? *J Crohns Colitis* 2015; **9**: 33-40 [PMID: [25052347](#) DOI: [10.1016/j.crohns.2014.06.012](#)]
- 296 **Tremaine WJ**, Hanauer SB, Katz S, Winston BD, Levine JG, Persson T, Persson A; Budesonide CIR United States Study Group. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002; **97**: 1748-1754 [PMID: [12135030](#) DOI: [10.1111/j.1572-0241.2002.05835.x](#)]
- 297 **Kane SV**, Schoenfeld P, Sandborn WJ, Tremaine W, Hofer T, Feagan BG. The effectiveness of budesonide therapy for Crohn's disease. *Aliment Pharmacol Ther* 2002; **16**: 1509-1517 [PMID: [12182751](#) DOI: [10.1046/j.1365-2036.2002.01289.x](#)]
- 298 **Bar-Meir S**, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G, Reshef R, Odes S, Moshkovitz M, Bruck R, Eliakim R, Maoz E, Mittmann U. Budesonide vs prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology* 1998; **115**: 835-840 [PMID: [9800000](#) DOI: [10.1053/gast.1998.0000000000000000](#)]

- 9753485 DOI: 10.1016/s0016-5085(98)70254-9]
- 299 **Dignass A**, Stoyanov S, Dorofeyev AE, Grigorieva GA, Tomsova E, Altortay I, Tuculanu D, Bunganić I, Pokrotnieks J, Kupčinskas L, Dilger K, Greinwald R, Mueller R; International Budenofalk Study Group. Once vs three times daily dosing of oral budesonide for active Crohn's disease: a double-blind, double-dummy, randomized trial. *J Crohns Colitis* 2014; **8**: 970-980 [PMID: 24534142 DOI: 10.1016/j.crohns.2014.01.021]
  - 300 **Coward S**, Kuenzig ME, Hazlewood G, Clement F, McBrien K, Holmes R, Panaccione R, Ghosh S, Seow CH, Rezaie A, Kaplan GG. Comparative Effectiveness of Mesalamine, Sulfasalazine, Corticosteroids, and Budesonide for the Induction of Remission in Crohn's Disease: A Bayesian Network Meta-analysis: Republished. *Inflamm Bowel Dis* 2017; **23**: E26-E37 [PMID: 30052985 DOI: 10.1097/MIB.0000000000001158]
  - 301 **Rezaie A**, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, Kaplan GG, Seow CH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015; **(6)**: CD000296 [PMID: 26039678 DOI: 10.1002/14651858.CD000296.pub4]
  - 302 **Moja L**, Danese S, Fiorino G, Del Giovane C, Bonovas S. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. *Aliment Pharmacol Ther* 2015; **41**: 1055-1065 [PMID: 25864873 DOI: 10.1111/apt.13190]
  - 303 **Ford AC**, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, Moayyedi P. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 617-629 [PMID: 21407190 DOI: 10.1038/ajg.2011.71]
  - 304 **Hanauer SB**, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; **2**: 379-388 [PMID: 15118975 DOI: 10.1016/s1542-3565(04)00122-3]
  - 305 **Singleton JW**, Hanauer SB, Gitnick GL, Peppercorn MA, Robinson MG, Wruble LD, Krawitt EL. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993; **104**: 1293-1301 [PMID: 8482443 DOI: 10.1016/0016-5085(93)90337-c]
  - 306 **Malchow H**, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984; **86**: 249-266 [PMID: 6140202]
  - 307 **Summers RW**, Switz DM, Sessions JT Jr, Beckett JM, Best WR, Kern F Jr, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; **77**: 847-869 [PMID: 38176]
  - 308 **Khan KJ**, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 661-673 [PMID: 21407187 DOI: 10.1038/ajg.2011.72]
  - 309 **Sutherland L**, Singleton J, Sessions J, Hanauer S, Krawitt E, Rankin G, Summers R, Mekhjian H, Greenberger N, Kelly M. Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991; **32**: 1071-1075 [PMID: 1916494 DOI: 10.1136/gut.32.9.1071]
  - 310 **Levine A**, Kori M, Kierkus J, Sigall Boneh R, Sladek M, Escher JC, Wine E, Yerushalmi B, Amil Dias J, Shaoul R, Veereman Wauters G, Boaz M, Abitbol G, Bousvaros A, Turner D. Azithromycin and metronidazole vs metronidazole-based therapy for the induction of remission in mild to moderate paediatric Crohn's disease: a randomized controlled trial. *Gut* 2019; **68**: 239-247 [PMID: 29420227 DOI: 10.1136/gutjnl-2017-315199]
  - 311 **Selby W**, Pavli P, Crotty B, Florin T, Radford-Smith G, Gibson P, Mitchell B, Connell W, Read R, Merrett M, Ee H, Hetzel D; Antibiotics in Crohn's Disease Study Group. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology* 2007; **132**: 2313-2319 [PMID: 17570206 DOI: 10.1053/j.gastro.2007.03.031]
  - 312 **Iowa Digestive Disease Center**. LB06-A Phase III Randomized, Double Blind, Placebocontrolled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Fixed-dose Combination RHB-104 in Subjects with Moderately to Severely Active Crohn's Disease. Crohn's and Colitis Foundation [Internet]. Available from: <https://site.crohnscolitisfoundation.org/research/participate-in-research/find-studies-and-clinical-trials/red-hill-2/a-phase-iii-randomized-29.html>
  - 313 **Rutgeerts P**, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, Reinisch W; EXTEND Investigators; Kumar A; Lazar A; Camez A; Lomax KG; Pollack PF; D'Haens G. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012; **142**: 1102-1111. e2 [PMID: 22326435 DOI: 10.1053/j.gastro.2012.01.035]
  - 314 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]
  - 315 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859 DOI: 10.1053/j.gastro.2006.11.041]
  - 316 **Sandborn WJ**, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, D'Haens G, Li J, Rosenfeld MR, Kent JD, Pollack PF. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007; **146**: 829-838 [PMID: 17470824 DOI: 10.7326/0003-4819-146-12-200706190-00159]
  - 317 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
  - 318 **Sokol H**, Seksik P, Carrat F, Nion-Larmurier I, Vienne A, Beaugerie L, Cosnes J. Usefulness of co-

- treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010; **59**: 1363-1368 [PMID: 20587545 DOI: 10.1136/gut.2010.212712]
- 319 **Schröder O**, Blumenstein I, Stein J. Combining infliximab with methotrexate for the induction and maintenance of remission in refractory Crohn's disease: a controlled pilot study. *Eur J Gastroenterol Hepatol* 2006; **18**: 11-16 [PMID: 16357613 DOI: 10.1097/00042737-200601000-00003]
- 320 **Grossi V**, Lerer T, Griffiths A, LeLeiko N, Cabrera J, Otley A, Rick J, Mack D, Bousvaros A, Rosh J, Grossman A, Saeed S, Kay M, Boyle B, Oliva-Hemker M, Keljo D, Pfefferkorn M, Faubion W, Kappelman MD, Sudel B, Markowitz J, Hyams JS. Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children With Crohn's Disease. *Clin Gastroenterol Hepatol* 2015; **13**: 1748-1756 [PMID: 25911120 DOI: 10.1016/j.cgh.2015.04.010]
- 321 **Kawalec P**, Moćko P. An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients. *J Comp Eff Res* 2018; **7**: 101-111 [PMID: 29115855 DOI: 10.2217/ceer-2017-0041]
- 322 **Crooks B**, Barnes T, Limdi JK. Vedolizumab in the treatment of inflammatory bowel disease: evolving paradigms. *Drugs Context* 2020; **9**: 2019-10 [PMID: 32180822 DOI: 10.7573/dic.2019-10-2]
- 323 **Feagan BG**, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johans J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI-IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2016; **375**: 1946-1960 [PMID: 27959607 DOI: 10.1056/NEJMoa1602773]
- 324 **Harris KA**, Horst S, Gadani A, Nohl A, Annis K, Duley C, Beaulieu D, Ghazi L, Schwartz DA. Patients with Refractory Crohn's Disease Successfully Treated with Ustekinumab. *Inflamm Bowel Dis* 2016; **22**: 397-401 [PMID: 26752468 DOI: 10.1097/MIB.0000000000000624]
- 325 **Khorrami S**, Ginard D, Marín-Jiménez I, Chaparro M, Sierra M, Aguas M, Sicilia B, García-Sánchez V, Suarez C, Villoria A, Taxonera C, Velasco-Guardado A, Martínez-González J, Gisbert JP. Ustekinumab for the Treatment of Refractory Crohn's Disease: The Spanish Experience in a Large Multicentre Open-label Cohort. *Inflamm Bowel Dis* 2016; **22**: 1662-1669 [PMID: 27306072 DOI: 10.1097/MIB.0000000000000842]
- 326 **Kopylov U**, Afif W, Cohen A, Bitton A, Wild G, Bessissow T, Wyse J, Al-Taweel T, Szilagyi A, Seidman E. Subcutaneous ustekinumab for the treatment of anti-TNF resistant Crohn's disease--the McGill experience. *J Crohns Colitis* 2014; **8**: 1516-1522 [PMID: 24996483 DOI: 10.1016/j.crohns.2014.06.005]
- 327 **Ma C**, Fedorak RN, Kaplan GG, Dieleman LA, Devlin SM, Stern N, Kroeker KI, Seow CH, Leung Y, Novak KL, Halloran BP, Huang VW, Wong K, Blustein PK, Ghosh S, Panaccione R. Long-term Maintenance of Clinical, Endoscopic, and Radiographic Response to Ustekinumab in Moderate-to-Severe Crohn's Disease: Real-world Experience from a Multicenter Cohort Study. *Inflamm Bowel Dis* 2017; **23**: 833-839 [PMID: 28328624 DOI: 10.1097/MIB.0000000000001074]
- 328 **Ma C**, Fedorak RN, Kaplan GG, Dieleman LA, Devlin SM, Stern N, Kroeker KI, Seow CH, Leung Y, Novak KL, Halloran BP, Huang VW, Wong K, Blustein PK, Ghosh S, Panaccione R. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. *Aliment Pharmacol Ther* 2017; **45**: 1232-1243 [PMID: 28252210 DOI: 10.1111/apt.14016]
- 329 **Lenaerts C**, Roy CC, Vaillancourt M, Weber AM, Morin CL, Seidman E. High incidence of upper gastrointestinal tract involvement in children with Crohn disease. *Pediatrics* 1989; **83**: 777-781 [PMID: 2717294]
- 330 **Danzi JT**, Farmer RG, Sullivan BH Jr, Rankin GB. Endoscopic features of gastroduodenal Crohn's disease. *Gastroenterology* 1976; **70**: 9-13 [PMID: 1245289]
- 331 **Turner D**, Griffiths AM. Esophageal, gastric, and duodenal manifestations of IBD and the role of upper endoscopy in IBD diagnosis. *Curr Gastroenterol Rep* 2009; **11**: 234-237 [PMID: 19463224 DOI: 10.1007/s11894-009-0036-0]
- 332 **Mottet C**, Vader JP, Felley C, Froehlich F, Gonvers JJ, Juillerat P, Stockbrügger R, Angelucci E, Seibold F, Michetti P, Pittet V; EPACT II Study Group. Appropriate management of special situations in Crohn's disease (upper gastro-intestinal; extra-intestinal manifestations; drug safety during pregnancy and breastfeeding): Results of a multidisciplinary international expert panel-EPACT II. *J Crohns Colitis* 2009; **3**: 257-263 [PMID: 21172284 DOI: 10.1016/j.crohns.2009.03.008]
- 333 **Decker GA**, Loftus EV Jr, Pasha TM, Tremaine WJ, Sandborn WJ. Crohn's disease of the esophagus: clinical features and outcomes. *Inflamm Bowel Dis* 2001; **7**: 113-119 [PMID: 11383583 DOI: 10.1097/00054725-200105000-00006]
- 334 **Hazlewood GS**, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015; **148**: 344-54. quiz e14-5 [PMID: 25448924 DOI: 10.1053/j.gastro.2014.10.011]
- 335 **Chande N**, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015; **(10)**: CD000067 [PMID: 26517527 DOI: 10.1002/14651858.CD000067.pub3]
- 336 **Feagan BG**, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297 [PMID: 7816064 DOI: 10.1056/NEJM199502023320503]
- 337 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; **342**: 1627-1632 [PMID: 10833208 DOI: 10.1056/NEJM200006013422202]
- 338 **Patel V**, Wang Y, MacDonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in



- Crohn's disease. *Cochrane Database Syst Rev* 2014; (8): CD006884 [PMID: 25157445 DOI: 10.1002/14651858.CD006884.pub3]
- 339 **Kappelman MD**, Farkas DK, Long MD, Erichsen R, Sandler RS, Sørensen HT, Baron JA. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. *Clin Gastroenterol Hepatol* 2014; 12: 265-73. e1 [PMID: 23602821 DOI: 10.1016/j.cgh.2013.03.034]
- 340 **Kotlyar DS**, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, Loftus EV Jr, Peyrin-Biroulet L, Blonski WC, Van Domselaar M, Chaparro M, Sandilya S, Bewtra M, Beigel F, Biancone L, Lichtenstein GR. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol* 2015; 13: 847-58. quiz e48-50 [PMID: 24879926 DOI: 10.1016/j.cgh.2014.05.015]
- 341 **Limdi JK**, Farraye J, Cannon R, Woodhams E, Farraye FA. Contraception, Venous Thromboembolism, and Inflammatory Bowel Disease: What Clinicians (and Patients) Should Know. *Inflamm Bowel Dis* 2019; 25: 1603-1612 [PMID: 30877770 DOI: 10.1093/ibd/izz025]
- 342 **Gutierrez JC**, Hwang K. The toxicity of methotrexate in male fertility and paternal teratogenicity. *Expert Opin Drug Metab Toxicol* 2017; 13: 51-58 [PMID: 27590039 DOI: 10.1080/17425255.2017.1230198]
- 343 **Feagan BG**, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, Bourdages R, Macintosh DG, Dallaire C, Cohen A, Fedorak RN, Paré P, Bitton A, Saibil F, Anderson F, Donner A, Wong CJ, Zou G, Vandervoort MK, Hopkins M, Greenberg GR. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014; 146: 681-688. e1 [PMID: 24269926 DOI: 10.1053/j.gastro.2013.11.024]
- 344 **Singh S**, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative Risk of Serious Infections With Biologic and/or Immunosuppressive Therapy in Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2020; 18: 69-81. e3 [PMID: 30876964 DOI: 10.1016/j.cgh.2019.02.044]
- 345 **Bonovas S**, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. *Clin Gastroenterol Hepatol* 2016; 14: 1385-1397. e10 [PMID: 27189910 DOI: 10.1016/j.cgh.2016.04.039]
- 346 **Lichtenstein GR**, Rutgeerts P, Sandborn WJ, Sands BE, Diamond RH, Blank M, Montello J, Tang L, Cornillie F, Colombel JF. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol* 2012; 107: 1051-1063 [PMID: 22613901 DOI: 10.1038/ajg.2012.89]
- 347 **Colombel JF**, Reinisch W, Mantzaris GJ, Kornbluth A, Rutgeerts P, Tang KL, Oortwijn A, Bevelander GS, Cornillie FJ, Sandborn WJ. Randomised clinical trial: deep remission in biologic and immunomodulator naïve patients with Crohn's disease - a SONIC post hoc analysis. *Aliment Pharmacol Ther* 2015; 41: 734-746 [PMID: 25728587 DOI: 10.1111/apt.13139]
- 348 **Schreiber S**, Reinisch W, Colombel JF, Sandborn WJ, Hommes DW, Robinson AM, Huang B, Lomax KG, Pollack PF. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis* 2013; 7: 213-221 [PMID: 22704916 DOI: 10.1016/j.crohns.2012.05.015]
- 349 **Faleck DM**, Winters A, Chablaney S, Shashi P, Meserve J, Weiss A, Aniwan S, Koliani-Pace JL, Kochhar G, Boland BS, Singh S, Hirtten R, Shmidt E, Kesar V, Lasch K, Luo M, Bohm M, Varma S, Fischer M, Hudesman D, Chang S, Lukin D, Sultan K, Swaminath A, Gupta N, Siegel CA, Shen B, Sandborn WJ, Kane S, Loftus EV Jr, Sands BE, Colombel JF, Dulai PS, Ungaro R. Shorter Disease Duration Is Associated With Higher Rates of Response to Vedolizumab in Patients With Crohn's Disease But Not Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2019; 17: 2497-2505. e1 [PMID: 30625408 DOI: 10.1016/j.cgh.2018.12.040]
- 350 **Honap S**, Cunningham G, Tamilarasan AG, Irving PM. Positioning biologics and new therapies in the management of inflammatory bowel disease. *Curr Opin Gastroenterol* 2019 epub ahead of print [PMID: 31021925 DOI: 10.1097/MOG.0000000000000546]
- 351 **Yang YX**, Lichtenstein GR. Corticosteroids in Crohn's disease. *Am J Gastroenterol* 2002; 97: 803-823 [PMID: 12003413 DOI: 10.1111/j.1572-0241.2002.05596.x]
- 352 **Lichtenstein GR**, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol* 2018; 113: 481-517 [PMID: 29610508 DOI: 10.1038/ajg.2018.27]
- 353 **Kopylov U**, Al-Taweel T, Yaghoobi M, Nauche B, Bitton A, Lakatos PL, Ben-Horin S, Afif W, Seidman EG. Adalimumab monotherapy vs combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014; 8: 1632-1641 [PMID: 25067824 DOI: 10.1016/j.crohns.2014.07.003]
- 354 **Matsumoto T**, Motoya S, Watanabe K, Hisamatsu T, Nakase H, Yoshimura N, Ishida T, Kato S, Nakagawa T, Esaki M, Nagahori M, Matsui T, Naito Y, Kanai T, Suzuki Y, Nojima M, Watanabe M, Hibi T; DIAMOND study group. Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial. *J Crohns Colitis* 2016; 10: 1259-1266 [PMID: 27566367 DOI: 10.1093/ecco-jcc/jjw152]
- 355 **Kawalec P**, Mikrut A, Wiśniewska N, Pilec A. Tumor necrosis factor- $\alpha$  antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease: systematic review and meta-analysis. *Arch Med Sci* 2013; 9: 765-779 [PMID: 24273556 DOI: 10.5114/aoms.2013.38670]
- 356 **Kennedy NA**, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, Thomas A, Nice R, Perry MH, Bouri S, Chanchlani N, Heerasing NM, Hendy P, Lin S, Gaya DR, Cummings JRF, Selinger CP, Lees CW, Hart AL, Parkes M, Sebastian S, Mansfield JC, Irving PM, Lindsay J, Russell RK, McDonald TJ, McGovern D, Goodhand JR, Ahmad T; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naïve patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019; 4: 341-353 [PMID: 30824404]

- DOI: [10.1016/S2468-1253\(19\)30012-3](https://doi.org/10.1016/S2468-1253(19)30012-3)]
- 357 **Sands BE**, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885 [PMID: [14985485](https://pubmed.ncbi.nlm.nih.gov/14985485/) DOI: [10.1056/NEJMoa030815](https://doi.org/10.1056/NEJMoa030815)]
  - 358 **McDonald JW**, Feagan BG, Jewell D, Brynskov J, Stange EF, Macdonald JK. Cyclosporine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2005; CD000297 [PMID: [15846602](https://pubmed.ncbi.nlm.nih.gov/15846602/) DOI: [10.1002/14651858.CD000297.pub2](https://doi.org/10.1002/14651858.CD000297.pub2)]
  - 359 **McSharry K**, Dalzell AM, Leiper K, El-Matary W. Systematic review: the role of tacrolimus in the management of Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 1282-1294 [PMID: [21999607](https://pubmed.ncbi.nlm.nih.gov/21999607/) DOI: [10.1111/j.1365-2036.2011.04873.x](https://doi.org/10.1111/j.1365-2036.2011.04873.x)]
  - 360 **Damião AOMC**, de Azevedo MFC, Carlos AS, Wada MY, Silva TVM, Feitosa FC. Conventional therapy for moderate to severe inflammatory bowel disease: A systematic literature review. *World J Gastroenterol* 2019; **25**: 1142-1157 [PMID: [30863001](https://pubmed.ncbi.nlm.nih.gov/30863001/) DOI: [10.3748/wjg.v25.i9.1142](https://doi.org/10.3748/wjg.v25.i9.1142)]
  - 361 **Fellermann K**, Steffen M, Stein J, Raedler A, Hämling J, Ludwig D, Loeschke K, Stange EF. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14**: 171-176 [PMID: [10651657](https://pubmed.ncbi.nlm.nih.gov/10651657/) DOI: [10.1046/j.1365-2036.2000.00695.x](https://doi.org/10.1046/j.1365-2036.2000.00695.x)]
  - 362 **Kurnik D**, Loebstein R, Fishbein E, Almog S, Halkin H, Bar-Meir S, Chowers Y. Bioavailability of oral vs. subcutaneous low-dose methotrexate in patients with Crohn's disease. *Aliment Pharmacol Ther* 2003; **18**: 57-63 [PMID: [12848626](https://pubmed.ncbi.nlm.nih.gov/12848626/) DOI: [10.1046/j.1365-2036.2003.01614.x](https://doi.org/10.1046/j.1365-2036.2003.01614.x)]
  - 363 **Wilson A**, Patel V, Chande N, Ponich T, Urquhart B, Asher L, Choi Y, Tirona R, Kim RB, Gregor JC. Pharmacokinetic profiles for oral and subcutaneous methotrexate in patients with Crohn's disease. *Aliment Pharmacol Ther* 2013; **37**: 340-345 [PMID: [23190184](https://pubmed.ncbi.nlm.nih.gov/23190184/) DOI: [10.1111/apt.12161](https://doi.org/10.1111/apt.12161)]
  - 364 **To N**, Ford AC, Gracie DJ. Systematic review with meta-analysis: the effect of tobacco smoking on the natural history of ulcerative colitis. *Aliment Pharmacol Ther* 2016; **44**: 117-126 [PMID: [27193202](https://pubmed.ncbi.nlm.nih.gov/27193202/) DOI: [10.1111/apt.13663](https://doi.org/10.1111/apt.13663)]
  - 365 **Lunney PC**, Kariyawasam VC, Wang RR, Middleton KL, Huang T, Selinger CP, Andrews JM, Katelaris PH, Leong RW. Smoking prevalence and its influence on disease course and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2015; **42**: 61-70 [PMID: [25968332](https://pubmed.ncbi.nlm.nih.gov/25968332/) DOI: [10.1111/apt.13239](https://doi.org/10.1111/apt.13239)]
  - 366 **Kuenzig ME**, Lee SM, Eksteen B, Seow CH, Barnabe C, Panaccione R, Kaplan GG. Smoking influences the need for surgery in patients with the inflammatory bowel diseases: a systematic review and meta-analysis incorporating disease duration. *BMC Gastroenterol* 2016; **16**: 143 [PMID: [28003021](https://pubmed.ncbi.nlm.nih.gov/28003021/) DOI: [10.1186/s12876-016-0555-8](https://doi.org/10.1186/s12876-016-0555-8)]
  - 367 **Louis E**, Michel V, Hugot JP, Reenaers C, Fontaine F, Delforge M, El Yafi F, Colombel JF, Belaiche J. Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. *Gut* 2003; **52**: 552-557 [PMID: [12631668](https://pubmed.ncbi.nlm.nih.gov/12631668/) DOI: [10.1136/gut.52.4.552](https://doi.org/10.1136/gut.52.4.552)]
  - 368 **Gisbert JP**, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015; **41**: 613-623 [PMID: [25652884](https://pubmed.ncbi.nlm.nih.gov/25652884/) DOI: [10.1111/apt.13083](https://doi.org/10.1111/apt.13083)]
  - 369 **Cosnes J**, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001; **120**: 1093-1099 [PMID: [11266373](https://pubmed.ncbi.nlm.nih.gov/11266373/) DOI: [10.1053/gast.2001.23231](https://doi.org/10.1053/gast.2001.23231)]
  - 370 **Johnson GJ**, Cosnes J, Mansfield JC. Review article: smoking cessation as primary therapy to modify the course of Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 921-931 [PMID: [15813828](https://pubmed.ncbi.nlm.nih.gov/15813828/) DOI: [10.1111/j.1365-2036.2005.02424.x](https://doi.org/10.1111/j.1365-2036.2005.02424.x)]
  - 371 **Bornemann P**, Eissa A, Strayer SM. Smoking cessation: What should you recommend? *J Fam Pract* 2016; **65**: 22-29B [PMID: [26845161](https://pubmed.ncbi.nlm.nih.gov/26845161/)]
  - 372 **National Institute for Health and Care Excellence**. Quality standard [QS43] Smoking: supporting people to stop. 2013 Aug 28. [Internet] Available from: <https://www.nice.org.uk/guidance/qs43>
  - 373 **Winter J**, Walker A, Shapiro D, Gaffney D, Spooner RJ, Mills PR. Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; **20**: 593-599 [PMID: [15352906](https://pubmed.ncbi.nlm.nih.gov/15352906/) DOI: [10.1111/j.1365-2036.2004.02124.x](https://doi.org/10.1111/j.1365-2036.2004.02124.x)]
  - 374 **Priest VL**, Begg EJ, Gardiner SJ, Frampton CM, Gearry RB, Barclay ML, Clark DW, Hansen P. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. *Pharmacoeconomics* 2006; **24**: 767-781 [PMID: [16898847](https://pubmed.ncbi.nlm.nih.gov/16898847/) DOI: [10.2165/00019053-200624080-00004](https://doi.org/10.2165/00019053-200624080-00004)]
  - 375 **Coenen MJ**, de Jong DJ, van Marrewijk CJ, Derijks LJ, Vermeulen SH, Wong DR, Klungel OH, Verbeek AL, Hooymans PM, Peters WH, te Morsche RH, Newman WG, Scheffer H, Guchelaar HJ, Franke B; TOPIC Recruitment Team. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. *Gastroenterology* 2015; **149**: 907-17. e7 [PMID: [26072396](https://pubmed.ncbi.nlm.nih.gov/26072396/) DOI: [10.1053/j.gastro.2015.06.002](https://doi.org/10.1053/j.gastro.2015.06.002)]
  - 376 **Relling MV**, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. *Clin Pharmacol Ther* 2019; **105**: 1095-1105 [PMID: [30447069](https://pubmed.ncbi.nlm.nih.gov/30447069/) DOI: [10.1002/cpt.1304](https://doi.org/10.1002/cpt.1304)]
  - 377 **Koutsilieri S**, Caudle KE, Alzghari SK, Monte AA, Relling MV, Patrinos GP. Optimizing thiopurine dosing based on TPMT and NUDT15 genotypes: It takes two to tango. *Am J Hematol* 2019; **94**: 737-740 [PMID: [30945335](https://pubmed.ncbi.nlm.nih.gov/30945335/) DOI: [10.1002/ajh.25485](https://doi.org/10.1002/ajh.25485)]
  - 378 **Yang SK**, Hong M, Baek J, Choi H, Zhao W, Jung Y, Haritunians T, Ye BD, Kim KJ, Park SH, Park SK, Yang DH, Dubinsky M, Lee I, McGovern DP, Liu J, Song K. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nat Genet* 2014; **46**: 1017-1020 [PMID: [25108385](https://pubmed.ncbi.nlm.nih.gov/25108385/)]

- DOI: [10.1038/ng.3060](https://doi.org/10.1038/ng.3060)]
- 379 **Yip JS**, Woodward M, Abreu MT, Sparrow MP. How are Azathioprine and 6-mercaptopurine dosed by gastroenterologists? *Inflamm Bowel Dis* 2008; **14**: 514-518 [PMID: [18088072](https://pubmed.ncbi.nlm.nih.gov/18088072/) DOI: [10.1002/ibd.20345](https://doi.org/10.1002/ibd.20345)]
  - 380 **Haines ML**, Ajlouni Y, Irving PM, Sparrow MP, Rose R, Gearry RB, Gibson PR. Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 1301-1307 [PMID: [20812329](https://pubmed.ncbi.nlm.nih.gov/20812329/) DOI: [10.1002/ibd.21458](https://doi.org/10.1002/ibd.21458)]
  - 381 **Dubinsky MC**, Reyes E, Ofman J, Chiou CF, Wade S, Sandborn WJ. A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Am J Gastroenterol* 2005; **100**: 2239-2247 [PMID: [16181376](https://pubmed.ncbi.nlm.nih.gov/16181376/) DOI: [10.1111/j.1572-0241.2005.41900.x](https://doi.org/10.1111/j.1572-0241.2005.41900.x)]
  - 382 **Friedman AB**, Brown SJ, Bampton P, Barclay ML, Chung A, Macrae FA, McKenzie J, Reynolds J, Gibson PR, Hanauer SB, Sparrow MP. Randomised clinical trial: efficacy, safety and dosage of adjunctive allopurinol in azathioprine/mercaptopurine nonresponders (AAA Study). *Aliment Pharmacol Ther* 2018; **47**: 1092-1102 [PMID: [29468701](https://pubmed.ncbi.nlm.nih.gov/29468701/) DOI: [10.1111/apt.14571](https://doi.org/10.1111/apt.14571)]
  - 383 **Dassopoulos T**, Dubinsky MC, Bentsen JL, Martin CF, Galanko JA, Seidman EG, Sandler RS, Hanauer SB. Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. *Aliment Pharmacol Ther* 2014; **39**: 163-175 [PMID: [24237037](https://pubmed.ncbi.nlm.nih.gov/24237037/) DOI: [10.1111/apt.12555](https://doi.org/10.1111/apt.12555)]
  - 384 **Yarur AJ**, Kubiliun MJ, Czul F, Sussman DA, Quintero MA, Jain A, Drake KA, Hauenstein SI, Lockton S, Deshpande AR, Barkin JS, Singh S, Abreu MT. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. *Clin Gastroenterol Hepatol* 2015; **13**: 1118-24. e3 [PMID: [25562796](https://pubmed.ncbi.nlm.nih.gov/25562796/) DOI: [10.1016/j.cgh.2014.12.026](https://doi.org/10.1016/j.cgh.2014.12.026)]
  - 385 **Roblin X**, Boschetti G, Williet N, Nancey S, Marotte H, Berger A, Phelip JM, Peyrin-Biroulet L, Colombel JF, Del Tedesco E, Paul S, Flourie B. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomized clinical trial. *Aliment Pharmacol Ther* 2017; **46**: 142-149 [PMID: [28449228](https://pubmed.ncbi.nlm.nih.gov/28449228/) DOI: [10.1111/apt.14106](https://doi.org/10.1111/apt.14106)]
  - 386 **Hanauer SB**, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323-33; quiz 591 [PMID: [16472588](https://pubmed.ncbi.nlm.nih.gov/16472588/) DOI: [10.1053/j.gastro.2005.11.030](https://doi.org/10.1053/j.gastro.2005.11.030)]
  - 387 **Colombel JF**, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, Thakkar RB, Robinson AM, Chen N, Mulani PM, Chao J. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 414-22. e5 [PMID: [23856361](https://pubmed.ncbi.nlm.nih.gov/23856361/) DOI: [10.1016/j.cgh.2013.06.019](https://doi.org/10.1016/j.cgh.2013.06.019)]
  - 388 **Beaugerie L**, Itzkowitz SH. Cancers Complicating Inflammatory Bowel Disease. *N Engl J Med* 2015; **373**: 195 [PMID: [26154801](https://pubmed.ncbi.nlm.nih.gov/26154801/) DOI: [10.1056/NEJMc1505689](https://doi.org/10.1056/NEJMc1505689)]
  - 389 **Mackey AC**, Green L, Liang LC, Dinndorf P, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44**: 265-267 [PMID: [17255842](https://pubmed.ncbi.nlm.nih.gov/17255842/) DOI: [10.1097/MPG.0b013e31802f6424](https://doi.org/10.1097/MPG.0b013e31802f6424)]
  - 390 **Lemaitre M**, Kirchgessner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA* 2017; **318**: 1679-1686 [PMID: [29114832](https://pubmed.ncbi.nlm.nih.gov/29114832/) DOI: [10.1001/jama.2017.16071](https://doi.org/10.1001/jama.2017.16071)]
  - 391 **Cosnes J**. What Should Be Done in Inflammatory Bowel Disease Patients with Prior Malignancy? *Dig Dis* 2017; **35**: 50-55 [PMID: [28147366](https://pubmed.ncbi.nlm.nih.gov/28147366/) DOI: [10.1159/000449083](https://doi.org/10.1159/000449083)]
  - 392 **Axelrad J**, Bernheim O, Colombel JF, Malerba S, Ananthakrishnan A, Yajnik V, Hoffman G, Agrawal M, Lukin D, Desai A, McEachern E, Bosworth B, Scherl E, Reyes A, Zaidi H, Mudireddy P, DiCaprio D, Sultan K, Korelitz B, Wang E, Williams R, Chen L, Katz S, Itzkowitz S; New York Crohn's and Colitis Organization. Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents. *Clin Gastroenterol Hepatol* 2016; **14**: 58-64 [PMID: [26247164](https://pubmed.ncbi.nlm.nih.gov/26247164/) DOI: [10.1016/j.cgh.2015.07.037](https://doi.org/10.1016/j.cgh.2015.07.037)]
  - 393 **Annese V**, Beaugerie L, Egan L, Biancone L, Bolling C, Brandts C, Dierickx D, Dummer R, Fiorino G, Gornet JM, Higgins P, Katsanos KH, Nissen L, Pellino G, Rogler G, Scaldaferrri F, Szymanska E, Eliakim R; ECCO. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *J Crohns Colitis* 2015; **9**: 945-965 [PMID: [26294789](https://pubmed.ncbi.nlm.nih.gov/26294789/) DOI: [10.1093/ecco-jcc/jjv141](https://doi.org/10.1093/ecco-jcc/jjv141)]
  - 394 **Sandborn WJ**, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: [23964933](https://pubmed.ncbi.nlm.nih.gov/23964933/) DOI: [10.1056/NEJMoa1215739](https://doi.org/10.1056/NEJMoa1215739)]
  - 395 **Sands BE**, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, Ben-Horin S, Xu J, Rosario M, Fox I, Parikh A, Milch C, Hanauer S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014; **147**: 618-627. e3 [PMID: [24859203](https://pubmed.ncbi.nlm.nih.gov/24859203/) DOI: [10.1053/j.gastro.2014.05.008](https://doi.org/10.1053/j.gastro.2014.05.008)]
  - 396 **Sands BE**, Sandborn WJ, Van Assche G, Lukas M, Xu J, James A, Abhyankar B, Lasch K. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naïve to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. *Inflamm Bowel Dis* 2017; **23**: 97-106 [PMID: [27930408](https://pubmed.ncbi.nlm.nih.gov/27930408/) DOI: [10.1097/MIB.0000000000000979](https://doi.org/10.1097/MIB.0000000000000979)]
  - 397 **Vermeire S**, Loftus EV Jr, Colombel JF, Feagan BG, Sandborn WJ, Sands BE, Danese S, D'Haens GR, Kaser A, Panaccione R, Rubin DT, Shafraan I, McAuliffe M, Kaviya A, Sankoh S, Mody R, Abhyankar B, Smyth M. Long-term Efficacy of Vedolizumab for Crohn's Disease. *J Crohns Colitis* 2017; **11**: 412-424 [PMID: [27683798](https://pubmed.ncbi.nlm.nih.gov/27683798/) DOI: [10.1093/ecco-jcc/jjw176](https://doi.org/10.1093/ecco-jcc/jjw176)]
  - 398 **Vermeire S**, Loftus EV, Colombel JF, Feagan BG, Sandborn WJ, Sands BE, Danese S, D'Haens GR, Kaser A, Panaccione R, Rubin DT, Shafraan I, O'Byrne S, Geransar P, Previtali A, Khalid JM, Kaviya A. Long-Term Effectiveness and Safety of Vedolizumab in Patients with Crohn's Disease: 5-Year Cumulative Exposure of Gemini 2 Completers Rolling Into the Gemini Open-Label Extension Study. *Gastroenterology*

- 2017; **152**: S601 [DOI: [10.1016/S0016-5085\(17\)32147-9](https://doi.org/10.1016/S0016-5085(17)32147-9)]
- 399 **Schreiber S**, Dignass A, Peyrin-Biroulet L, Hather G, Demuth D, Mosli M, Curtis R, Khalid JM, Loftus EV Jr. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol* 2018; **53**: 1048-1064 [PMID: [29869016](https://pubmed.ncbi.nlm.nih.gov/29869016/) DOI: [10.1007/s00535-018-1480-0](https://doi.org/10.1007/s00535-018-1480-0)]
- 400 **Dulai PS**, Singh S, Jiang X, Peerani F, Narula N, Chaudrey K, Whitehead D, Hudesman D, Lukin D, Swaminath A, Shmidt E, Wang S, Boland BS, Chang JT, Kane S, Siegel CA, Loftus EV, Sandborn WJ, Sands BE, Colombel JF. The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe Crohn's Disease: Results From the US VICTORY Consortium. *Am J Gastroenterol* 2016; **111**: 1147-1155 [PMID: [27296941](https://pubmed.ncbi.nlm.nih.gov/27296941/) DOI: [10.1038/ajg.2016.236](https://doi.org/10.1038/ajg.2016.236)]
- 401 **Danese S**, Sandborn WJ, Colombel JF, Vermeire S, Glover SC, Rimola J, Siegelman J, Jones S, Bornstein JD, Feagan BG. Endoscopic, Radiologic, and Histologic Healing With Vedolizumab in Patients With Active Crohn's Disease. *Gastroenterology* 2019; **157**: 1007-1018. e7 [PMID: [31279871](https://pubmed.ncbi.nlm.nih.gov/31279871/) DOI: [10.1053/j.gastro.2019.06.038](https://doi.org/10.1053/j.gastro.2019.06.038)]
- 402 **Wils P**, Bouhnik Y, Michetti P, Flourie B, Brixi H, Bourrier A, Allez M, Duclos B, Grimaud JC, Buisson A, Amiot A, Fumery M, Roblin X, Peyrin-Biroulet L, Filippi J, Bouguen G, Abitbol V, Coffin B, Simon M, Laharie D, Pariente B; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif. Subcutaneous Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti-Tumor Necrosis Factor Agents. *Clin Gastroenterol Hepatol* 2016; **14**: 242-50. e1-2 [PMID: [26432476](https://pubmed.ncbi.nlm.nih.gov/26432476/) DOI: [10.1016/j.cgh.2015.09.018](https://doi.org/10.1016/j.cgh.2015.09.018)]
- 403 **Götestam Skorpen C**, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, da Silva J, Nelson-Piercy C, Cetin I, Costedoat-Chalumeau N, Dolhain R, Förger F, Khamashta M, Ruiz-Irastorza G, Zink A, Vencovsky J, Cutolo M, Caeyers N, Zumbühl C, Østensen M. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016; **75**: 795-810 [PMID: [26888948](https://pubmed.ncbi.nlm.nih.gov/26888948/) DOI: [10.1136/annrheumdis-2015-208840](https://doi.org/10.1136/annrheumdis-2015-208840)]
- 404 **Venturin C**, Nancey S, Danion P, Uzzan M, Chauvenet M, Bergoin C, Roblin X, Flourie B, Boschetti G. Fetal death in utero and miscarriage in a patient with Crohn's disease under therapy with ustekinumab: case-report and review of the literature. *BMC Gastroenterol* 2017; **17**: 80 [PMID: [28629323](https://pubmed.ncbi.nlm.nih.gov/28629323/) DOI: [10.1186/s12876-017-0633-6](https://doi.org/10.1186/s12876-017-0633-6)]
- 405 **Papp K**, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, Fakhrazadeh S, Chevrier M, Calabro S, Langholff W, Krueger G. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol* 2015; **14**: 706-714 [PMID: [26151787](https://pubmed.ncbi.nlm.nih.gov/26151787/)]
- 406 **Vande Casteele N**, Ferrante M, Van Assche G, Ballet V, Compernelle G, Van Steen K, Simoons S, Rutgeerts P, Gils A, Vermeire S. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; **148**: 1320-9. e3 [PMID: [25724455](https://pubmed.ncbi.nlm.nih.gov/25724455/) DOI: [10.1053/j.gastro.2015.02.031](https://doi.org/10.1053/j.gastro.2015.02.031)]
- 407 **Roblin X**, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Paul S. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; **12**: 80-84. e2 [PMID: [23891927](https://pubmed.ncbi.nlm.nih.gov/23891927/) DOI: [10.1016/j.cgh.2013.07.010](https://doi.org/10.1016/j.cgh.2013.07.010)]
- 408 **Steenholdt C**, Brynskov J, Thomsen OØ, Munck LK, Fallingborg J, Christensen LA, Pedersen G, Kjeldsen J, Jacobsen BA, Oxholm AS, Kjellberg J, Bendtzen K, Ainsworth MA. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomized, controlled trial. *Gut* 2014; **63**: 919-927 [PMID: [23878167](https://pubmed.ncbi.nlm.nih.gov/23878167/) DOI: [10.1136/gutjnl-2013-305279](https://doi.org/10.1136/gutjnl-2013-305279)]
- 409 **Velayos FS**, Kahn JG, Sandborn WJ, Feagan BG. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. *Clin Gastroenterol Hepatol* 2013; **11**: 654-666 [PMID: [23357488](https://pubmed.ncbi.nlm.nih.gov/23357488/) DOI: [10.1016/j.cgh.2012.12.035](https://doi.org/10.1016/j.cgh.2012.12.035)]
- 410 **Paul S**, Del Tedesco E, Marotte H, Rinaudo-Gaujous M, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Roblin X. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; **19**: 2568-2576 [PMID: [24013361](https://pubmed.ncbi.nlm.nih.gov/24013361/) DOI: [10.1097/MIB.0b013e3182a77b41](https://doi.org/10.1097/MIB.0b013e3182a77b41)]
- 411 **Kopylov U**, Mantzaris GJ, Katsanos KH, Reenaers C, Ellul P, Rahier JF, Israeli E, Lakatos PL, Fiorino G, Cesarini M, Tsianos EV, Louis E, Ben-Horin S. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. *Aliment Pharmacol Ther* 2011; **33**: 349-357 [PMID: [21118397](https://pubmed.ncbi.nlm.nih.gov/21118397/) DOI: [10.1111/j.1365-2036.2010.04523.x](https://doi.org/10.1111/j.1365-2036.2010.04523.x)]
- 412 **Vande Casteele N**, Gils A, Singh S, Ohrmund L, Hauenstein S, Rutgeerts P, Vermeire S. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol* 2013; **108**: 962-971 [PMID: [23419382](https://pubmed.ncbi.nlm.nih.gov/23419382/) DOI: [10.1038/ajg.2013.12](https://doi.org/10.1038/ajg.2013.12)]
- 413 **Ben-Horin S**, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, Awadie H, Weiss B, Chowers Y. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 444-447 [PMID: [23103905](https://pubmed.ncbi.nlm.nih.gov/23103905/) DOI: [10.1016/j.cgh.2012.10.020](https://doi.org/10.1016/j.cgh.2012.10.020)]
- 414 **Bartelds GM**, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Dijkmans BA, Tak PP, Wolbink GJ. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. *Ann Rheum Dis* 2010; **69**: 817-821 [PMID: [19581278](https://pubmed.ncbi.nlm.nih.gov/19581278/) DOI: [10.1136/ard.2009.112847](https://doi.org/10.1136/ard.2009.112847)]
- 415 **Akobeng AK**, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2016; **9**: CD003715 [PMID: [27681657](https://pubmed.ncbi.nlm.nih.gov/27681657/) DOI: [10.1002/14651858.CD003715.pub3](https://doi.org/10.1002/14651858.CD003715.pub3)]
- 416 **Lim WC**, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2010; **(12)**: CD008870 [PMID: [21154400](https://pubmed.ncbi.nlm.nih.gov/21154400/) DOI: [10.1002/14651858.CD008870](https://doi.org/10.1002/14651858.CD008870)]
- 417 **Lim WC**, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in



- Crohn's disease. *Cochrane Database Syst Rev* 2016; **7**: CD008870 [PMID: [27372735](#) DOI: [10.1002/14651858.CD008870.pub2](#)]
- 418 **Subramanian S**, Ekbom A, Rhodes JM. Recent advances in clinical practice: a systematic review of isolated colonic Crohn's disease: the third IBD? *Gut* 2017; **66**: 362-381 [PMID: [27802156](#) DOI: [10.1136/gutjnl-2016-312673](#)]
- 419 **Steinhart AH**, Feagan BG, Wong CJ, Vandervoort M, Mikolainis S, Croitoru K, Seidman E, Leddin DJ, Bitton A, Drouin E, Cohen A, Greenberg GR. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology* 2002; **123**: 33-40 [PMID: [12105831](#) DOI: [10.1053/gast.2002.34225](#)]
- 420 **Arnold GL**, Beaves MR, Pryjduin VO, Mook WJ. Preliminary study of ciprofloxacin in active Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 10-15 [PMID: [11837933](#) DOI: [10.1097/00054725-200201000-00002](#)]
- 421 **Greenberg GR**, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* 1996; **110**: 45-51 [PMID: [8536887](#) DOI: [10.1053/gast.1996.v110.pm8536887](#)]
- 422 **Ferguson A**, Campieri M, Doe W, Persson T, Nygård G. Oral budesonide as maintenance therapy in Crohn's disease--results of a 12-month study. Global Budesonide Study Group. *Aliment Pharmacol Ther* 1998; **12**: 175-183 [PMID: [9692692](#) DOI: [10.1046/j.1365-2036.1998.00285.x](#)]
- 423 **Gross V**, Andus T, Ecker KW, Raedler A, Loeschke K, Plauth M, Rasenack J, Weber A, Gierend M, Ewe K, Schölmerich J. Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. *Gut* 1998; **42**: 493-496 [PMID: [9616309](#) DOI: [10.1136/gut.42.4.493](#)]
- 424 **Cortot A**, Colombel JF, Rutgeerts P, Lauritsen K, Malchow H, Hämling J, Winter T, Van Gossum A, Persson T, Pettersson E. Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. *Gut* 2001; **48**: 186-190 [PMID: [11156638](#) DOI: [10.1136/gut.48.2.186](#)]
- 425 **Hanauer S**, Sandborn WJ, Persson A, Persson T. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. *Aliment Pharmacol Ther* 2005; **21**: 363-371 [PMID: [15709986](#) DOI: [10.1111/j.1365-2036.2005.02338.x](#)]
- 426 **Löfberg R**, Rutgeerts P, Malchow H, Lamers C, Danielsson A, Olaison G, Jewell D, Ostergaard Thomsen O, Lorenz-Meyer H, Goebell H, Hodgson H, Persson T, Seidegård C. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. *Gut* 1996; **39**: 82-86 [PMID: [8881815](#) DOI: [10.1136/gut.39.1.82](#)]
- 427 **Papi C**, Luchetti R, Gili L, Montanti S, Koch M, Capurso L. Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* 2000; **14**: 1419-1428 [PMID: [11069312](#) DOI: [10.1046/j.1365-2036.2000.00867.x](#)]
- 428 **Sandborn WJ**, Löfberg R, Feagan BG, Hanauer SB, Campieri M, Greenberg GR. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. *Am J Gastroenterol* 2005; **100**: 1780-1787 [PMID: [16086715](#) DOI: [10.1111/j.1572-0241.2005.41992.x](#)]
- 429 **Simms L**, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2001; **(1)**: CD002913 [PMID: [11279777](#) DOI: [10.1002/14651858.CD002913](#)]
- 430 **Benchimol EI**, Seow CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009; **21**: CD002913 [PMID: [19160212](#) DOI: [10.1002/14651858.CD002913.pub2](#)]
- 431 **Seastedt KP**, Trencheva K, Michelassi F, Alsaleh D, Milsom JW, Sonoda T, Lee SW, Nandakumar G. Accuracy of CT enterography and magnetic resonance enterography imaging to detect lesions preoperatively in patients undergoing surgery for Crohn's disease. *Dis Colon Rectum* 2014; **57**: 1364-1370 [PMID: [25380001](#) DOI: [10.1097/DCR.0000000000000244](#)]
- 432 **Xie Y**, Zhu W, Li N, Li J. The outcome of initial percutaneous drainage vs surgical drainage for intra-abdominal abscesses in Crohn's disease. *Int J Colorectal Dis* 2012; **27**: 199-206 [PMID: [22052039](#) DOI: [10.1007/s00384-011-1338-x](#)]
- 433 **de Parades V**, Far HS, Etienney I, Zeitoun JD, Atienza P, Bauer P. Seton drainage and fibrin glue injection for complex anal fistulas. *Colorectal Dis* 2010; **12**: 459-463 [PMID: [19210300](#) DOI: [10.1111/j.1463-1318.2009.01811.x](#)]
- 434 **Hyman N**. Endoanal advancement flap repair for complex anorectal fistulas. *Am J Surg* 1999; **178**: 337-340 [PMID: [10587195](#) DOI: [10.1016/s0002-9610\(99\)00180-4](#)]
- 435 **Sonoda T**, Hull T, Piedmonte MR, Fazio VW. Outcomes of primary repair of anorectal and rectovaginal fistulas using the endorectal advancement flap. *Dis Colon Rectum* 2002; **45**: 1622-1628 [PMID: [12473885](#) DOI: [10.1007/s10350-004-7249-y](#)]
- 436 **Nguyen DL**, Sandborn WJ, Loftus EV Jr, Larson DW, Fletcher JG, Becker B, Mandrekar J, Harmsen WS, Bruining DH. Similar outcomes of surgical and medical treatment of intra-abdominal abscesses in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2012; **10**: 400-404 [PMID: [22155562](#) DOI: [10.1016/j.cgh.2011.11.023](#)]
- 437 **Singh S**, Ding NS, Mathis KL, Dulai PS, Farrell AM, Pemberton JH, Hart AL, Sandborn WJ, Loftus EV Jr. Systematic review with meta-analysis: fecal diversion for management of perianal Crohn's disease. *Aliment Pharmacol Ther* 2015; **42**: 783-792 [PMID: [26264359](#) DOI: [10.1111/apt.13356](#)]
- 438 **Gaertner WB**, Decanini A, Mellgren A, Lowry AC, Goldberg SM, Madoff RD, Spencer MP. Does infliximab infusion impact results of operative treatment for Crohn's perianal fistulas? *Dis Colon Rectum* 2007; **50**: 1754-1760 [PMID: [17899271](#) DOI: [10.1007/s10350-007-9077-3](#)]
- 439 **Regueiro M**, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis* 2003; **9**: 98-103 [PMID: [12769443](#) DOI: [10.1097/00054725-200303000-00003](#)]
- 440 **Topstad DR**, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal

- Crohn's disease: a single center experience. *Dis Colon Rectum* 2003; **46**: 577-583 [PMID: [12792431](#) DOI: [10.1007/s10350-004-6611-4](#)]
- 441 **Hyder SA**, Travis SP, Jewell DP, McC Mortensen NJ, George BD. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. *Dis Colon Rectum* 2006; **49**: 1837-1841 [PMID: [17041753](#) DOI: [10.1007/s10350-006-0656-5](#)]
- 442 **Yarur AJ**, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, Patel A, Best K, Fox C, Idstein K, Abreu MT. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017; **45**: 933-940 [PMID: [28211593](#) DOI: [10.1111/apt.13970](#)]
- 443 **Colombel JF**, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, Enns R, Panaccione R, Schreiber S, Li J, Kent JD, Lomax KG, Pollack PF. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut* 2009; **58**: 940-948 [PMID: [19201775](#) DOI: [10.1136/gut.2008.159251](#)]
- 444 **Dewint P**, Hansen BE, Verhey E, Oldenburg B, Hommes DW, Pierik M, Ponsioen CI, van Dullemen HM, Russel M, van Bodegraven AA, van der Woude CJ. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomized, double-blind, placebo controlled trial (ADAFI). *Gut* 2014; **63**: 292-299 [PMID: [23525574](#) DOI: [10.1136/gutjnl-2013-304488](#)]
- 445 **Bernstein LH**, Frank MS, Brandt LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79**: 599 [PMID: [7429123](#)]
- 446 **Brandt LJ**, Bernstein LH, Boley SJ, Frank MS. Metronidazole therapy for perineal Crohn's disease: a follow-up study. *Gastroenterology* 1982; **83**: 383-387 [PMID: [7084615](#)]
- 447 **Jakobovits J**, Schuster MM. Metronidazole therapy for Crohn's disease and associated fistulae. *Am J Gastroenterol* 1984; **79**: 533-540 [PMID: [6741906](#)]
- 448 **Thia KT**, Mahadevan U, Feagan BG, Wong C, Cockeram A, Bitton A, Bernstein CN, Sandborn WJ. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009; **15**: 17-24 [PMID: [18668682](#) DOI: [10.1002/ibd.20608](#)]
- 449 **Kaimakliotis P**, Simillis C, Harbord M, Kontovounisios C, Rasheed S, Tekkis PP. A Systematic Review Assessing Medical Treatment for Rectovaginal and Enterovesical Fistulae in Crohn's Disease. *J Clin Gastroenterol* 2016; **50**: 714-721 [PMID: [27466166](#) DOI: [10.1097/MCG.0000000000000607](#)]
- 450 **Zhang W**, Zhu W, Li Y, Zuo L, Wang H, Li N, Li J. The respective role of medical and surgical therapy for enterovesical fistula in Crohn's disease. *J Clin Gastroenterol* 2014; **48**: 708-711 [PMID: [24457944](#) DOI: [10.1097/MCG.0000000000000040](#)]
- 451 **de la Poza G**, López-Sanroman A, Taxonera C, Marín-Jimenez I, Gisbert JP, Bermejo F, Opio V, Muriel A. Genital fistulas in female Crohn's disease patients.: clinical characteristics and response to therapy. *J Crohns Colitis* 2012; **6**: 276-280 [PMID: [22405162](#) DOI: [10.1016/j.crohns.2011.08.015](#)]
- 452 **Ravindran P**, Ansari N, Young CJ, Solomon MJ. Definitive surgical closure of enterocutaneous fistula: outcome and factors predictive of increased postoperative morbidity. *Colorectal Dis* 2014; **16**: 209-218 [PMID: [24521276](#) DOI: [10.1111/codi.12473](#)]
- 453 **Yaari S**, Benson A, Aviran E, Lev Cohain N, Oren R, Sosna J, Israeli E. Factors associated with surgery in patients with intra-abdominal fistulizing Crohn's disease. *World J Gastroenterol* 2016; **22**: 10380-10387 [PMID: [28058018](#) DOI: [10.3748/wjg.v22.i47.10380](#)]
- 454 **Gecse K**, Khanna R, Stoker J, Jenkins JT, Gabe S, Hahnloser D, D'Haens G. Fistulizing Crohn's disease: Diagnosis and management. *United European Gastroenterol J* 2013; **1**: 206-213 [PMID: [24917961](#) DOI: [10.1177/2050640613487194](#)]
- 455 **Amiot A**, Setakhr V, Seksik P, Allez M, Treton X, De Vos M, Laharie D, Colombel JF, Abitbol V, Reimund JM, Moreau J, Veyrac M, Flourie B, Cosnes J, Lemann M, Bouhnik Y. Long-term outcome of enterocutaneous fistula in patients with Crohn's disease treated with anti-TNF therapy: a cohort study from the GETAID. *Am J Gastroenterol* 2014; **109**: 1443-1449 [PMID: [25091063](#) DOI: [10.1038/ajg.2014.183](#)]
- 456 **Frolkis AD**, Dykeman J, Negrón ME, Debruyen J, Jette N, Fiest KM, Frolkis T, Barkema HW, Rioux KP, Panaccione R, Ghosh S, Wiebe S, Kaplan GG. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013; **145**: 996-1006 [PMID: [23896172](#) DOI: [10.1053/j.gastro.2013.07.041](#)]
- 457 **Greenstein AJ**, Sachar DB, Pasternack BS, Janowitz HD. Reoperation and recurrence in Crohn's colitis and ileocolitis: Crude and cumulative rates. *N Engl J Med* 1975; **293**: 685-690 [PMID: [1160935](#) DOI: [10.1056/NEJM197510022931403](#)]
- 458 **Agrez MV**, Valente RM, Pierce W, Melton LJ 3rd, van Heerden JA, Beart RW Jr. Surgical history of Crohn's disease in a well-defined population. *Mayo Clin Proc* 1982; **57**: 747-752 [PMID: [7144254](#)]
- 459 **Rutgeerts P**, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984; **25**: 665-672 [PMID: [6735250](#) DOI: [10.1136/gut.25.6.665](#)]
- 460 **Tytgat GN**, Mulder CJ, Brummelkamp WH. Endoscopic lesions in Crohn's disease early after ileocecal resection. *Endoscopy* 1988; **20**: 260-262 [PMID: [3168939](#) DOI: [10.1055/s-2007-1018188](#)]
- 461 **Olaison G**, Smedh K, Sjö Dahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. *Gut* 1992; **33**: 331-335 [PMID: [1568651](#) DOI: [10.1136/gut.33.3.331](#)]
- 462 **Bernell O**, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. *Br J Surg* 2000; **87**: 1697-1701 [PMID: [11122187](#) DOI: [10.1046/j.1365-2168.2000.01589.x](#)]
- 463 **Binder V**, Hendriksen C, Kreiner S. Prognosis in Crohn's disease--based on results from a regional patient group from the county of Copenhagen. *Gut* 1985; **26**: 146-150 [PMID: [3967832](#) DOI: [10.1136/gut.26.2.146](#)]
- 464 **Lautenbach E**, Berlin JA, Lichtenstein GR. Risk factors for early postoperative recurrence of Crohn's disease. *Gastroenterology* 1998; **115**: 259-267 [PMID: [9679030](#) DOI: [10.1016/s0016-5085\(98\)70191-x](#)]
- 465 **Reese GE**, Nanidis T, Borysiewicz C, Yamamoto T, Orchard T, Tekkis PP. The effect of smoking after

- surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis* 2008; **23**: 1213-1221 [PMID: [18762954](#) DOI: [10.1007/s00384-008-0542-9](#)]
- 466 **Simillis C**, Yamamoto T, Reese GE, Umegae S, Matsumoto K, Darzi AW, Tekkis PP. A meta-analysis comparing incidence of recurrence and indication for reoperation after surgery for perforating vs nonperforating Crohn's disease. *Am J Gastroenterol* 2008; **103**: 196-205 [PMID: [17900320](#) DOI: [10.1111/j.1572-0241.2007.01548.x](#)]
- 467 **Regueiro M**, Feagan BG, Zou B, Johanns J, Blank MA, Chevrier M, Plevy S, Popp J, Cornillie FJ, Lukas M, Danese S, Gionchetti P, Hanauer SB, Reinisch W, Sandborn WJ, Sorrentino D, Rutgeerts P; PREVENT Study Group. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. *Gastroenterology* 2016; **150**: 1568-1578 [PMID: [26946343](#) DOI: [10.1053/j.gastro.2016.02.072](#)]
- 468 **McLeod RS**, Wolff BG, Ross S, Parkes R, McKenzie M; Investigators of the CAST Trial. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. *Dis Colon Rectum* 2009; **52**: 919-927 [PMID: [19502857](#) DOI: [10.1007/DCR.0b013e3181a4fa58](#)]
- 469 **Pascua M**, Su C, Lewis JD, Brensinger C, Lichtenstein GR. Meta-analysis: factors predicting post-operative recurrence with placebo therapy in patients with Crohn's disease. *Aliment Pharmacol Ther* 2008; **28**: 545-556 [PMID: [18565159](#) DOI: [10.1111/j.1365-2036.2008.03774.x](#)]
- 470 **Regueiro M**, Velayos F, Greer JB, Bougatsos C, Chou R, Sultan S, Singh S. American Gastroenterological Association Institute Technical Review on the Management of Crohn's Disease After Surgical Resection. *Gastroenterology* 2017; **152**: 277-295. e3 [PMID: [27840073](#) DOI: [10.1053/j.gastro.2016.10.039](#)]
- 471 **Mowat C**, Arnott I, Cahill A, Smith M, Ahmad T, Subramanian S, Travis S, Morris J, Hamlin J, Dhar A, Nwokolo C, Edwards C, Creed T, Bloom S, Yousif M, Thomas L, Campbell S, Lewis SJ, Sebastian S, Sen S, Lal S, Hawkey C, Murray C, Cummings F, Goh J, Lindsay JO, Arebi N, Potts L, McKinley AJ, Thomson JM, Todd JA, Collie M, Dunlop MG, Mowat A, Gaya DR, Winter J, Naismith GD, Ennis H, Keerie C, Lewis S, Prescott RJ, Kennedy NA, Satsangi J; TOPPIC Study Group. Mercaptopurine vs placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomized controlled trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 273-282 [PMID: [28404197](#) DOI: [10.1016/S2468-1253\(16\)30078-4](#)]
- 472 **De Cruz P**, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, Liew D, Prideaux L, Lawrance IC, Andrews JM, Bampton PA, Jakobovits S, Florin TH, Gibson PR, Debinski H, Gearry RB, Macrae FA, Leong RW, Kronborg I, Radford-Smith G, Selby W, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Desmond PV. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. *Aliment Pharmacol Ther* 2015; **42**: 867-879 [PMID: [26314275](#) DOI: [10.1111/apt.13353](#)]
- 473 **Peyrin-Biroulet L**, Deltenre P, Ardizzone S, D'Haens G, Hanauer SB, Herfarth H, Lémann M, Colombel JF. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 2089-2096 [PMID: [19568226](#) DOI: [10.1038/ajg.2009.301](#)]
- 474 **Shen FC**, Zhang HJ, Zhao XD, Cao RS, Shi RH. Purine analogues compared with mesalamine or 5-ASA for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Int J Clin Pract* 2012; **66**: 758-766 [PMID: [22805268](#) DOI: [10.1111/j.1742-1241.2012.02965.x](#)]
- 475 **Doherty G**, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. *Cochrane Database Syst Rev* 2009; **7**: CD006873 [PMID: [19821389](#) DOI: [10.1002/14651858.CD006873.pub2](#)]
- 476 **Singh S**, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. *Gastroenterology* 2015; **148**: 64-76. quiz e14 [PMID: [25263803](#) DOI: [10.1053/j.gastro.2014.09.031](#)]
- 477 **Rutgeerts P**, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, Kerremans R. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; **108**: 1617-1621 [PMID: [7768364](#) DOI: [10.1016/0016-5085\(95\)90121-3](#)]
- 478 **Rutgeerts P**, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, Aerden I, De Hertogh G, Geboes K, Hiele M, D'Hoore A, Penninckx F. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2005; **128**: 856-861 [PMID: [15825069](#) DOI: [10.1053/j.gastro.2005.01.010](#)]
- 479 **Herfarth HH**, Katz JA, Hanauer SB, Sandborn WJ, Loftus EV Jr, Sands BE, Galanko JA, Walkup D, Isaacs KL, Martin CF, Sandler RS, Sartor RB. Ciprofloxacin for the prevention of postoperative recurrence in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2013; **19**: 1073-1079 [PMID: [23511031](#) DOI: [10.1097/01.MIB.0000428910.36091.10](#)]
- 480 **Jigaranu AO**, Nedelciuc O, Blaj A, Badea M, Mihai C, Diculescu M, Cijevschi-Prelipcean C. Is rifaximin effective in maintaining remission in Crohn's disease? *Dig Dis* 2014; **32**: 378-383 [PMID: [24969283](#) DOI: [10.1159/000358141](#)]
- 481 **Sorrentino D**, Paviotti A, Fiorino G. Anti-TNF's for postoperative recurrence in Crohn's disease: the if's and how's. *Curr Drug Targets* 2010; **11**: 219-226 [PMID: [20210769](#) DOI: [10.2174/138945010790309920](#)]
- 482 **Sorrentino D**, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. *Clin Gastroenterol Hepatol* 2010; **8**: 591-9. quiz e78-9 [PMID: [20139033](#) DOI: [10.1016/j.cgh.2010.01.016](#)]
- 483 **Sorrentino D**, Terrosu G, Avellini C, Maiero S. Infliximab with low-dose methotrexate for prevention of postsurgical recurrence of ileocolonic Crohn disease. *Arch Intern Med* 2007; **167**: 1804-1807 [PMID: [17846401](#) DOI: [10.1001/archinte.167.16.1804](#)]
- 484 **Savarino E**, Bodini G, Dulbecco P, Assandri L, Bruzzzone L, Mazza F, Frigo AC, Fazio V, Marabotto E, Savarino V. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. *Am J Gastroenterol* 2013; **108**: 1731-1742 [PMID: [24019080](#) DOI: [10.1038/ajg.2013.287](#)]

- 485 **van Loo ES**, Dijkstra G, Ploeg RJ, Nieuwenhuijs VB. Prevention of postoperative recurrence of Crohn's disease. *J Crohns Colitis* 2012; **6**: 637-646 [PMID: [22398096](#) DOI: [10.1016/j.crohns.2011.12.006](#)]





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