STATEMENT

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Management of Crohn's disease in Taiwan: consensus guideline of the Taiwan Society of Inflammatory Bowel Disease updated in 2023

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Crohn's disease (CD) is a chronic, fluctuating inflammatory condition that primarily affects the gastrointestinal tract. Although the incidence of CD in Taiwan is lower than that in Western countries, the severity of CD presentation appears to be similar between Asia and the West. This observation indicates the urgency for devising revised guidelines tailored to the unique reimbursement system, and patient requirements in Taiwan. The core objectives of these updated guidelines include the updated treatment choices and the integration of the treat-to-target strategy into CD management, promoting the achievement of deep remission to mitigate complications and enhance the overall quality of life. Given the diversity in disease prevalence, severity, insurance policies, and access to medical treatments in Taiwan, a customized approach is imperative for formulating these guidelines. Such tailored strategies ensure that international standards are not only adapted but also optimized to local contexts. Since the inception of its initial guidelines in 2017, the Taiwan Society of Inflammatory Bowel Disease (TSIBD) has acknowledged the importance of continuous revisions for incorporating new therapeutic options and evolving disease management practices. The latest update leverages international standards and recent research findings focused on practical implementation within the Taiwanese healthcare system. **(Intest Res 2024;22:250-285)**

Key Words: Crohn disease; Management; Guidelines; Consensus; Taiwan

INTRODUCTION

Crohn's disease (CD) is characterized by recurring periods of active inflammation and remission, and it affects various parts of the gastrointestinal tract. In CD patients, inflammation typically presents with asymmetrical and transmural, frequently involving the terminal ileum and colon.[1]

CD poses significant risks of morbidity and mortality, with many population-based studies, including 1 conducted in Taiwan, reporting unexpectedly higher mortality rates.[2-4] The primary objectives of CD therapy are achieving and maintaining both clinical and biochemical remission, minimizing complications, enhancing the quality of life, fostering endoscopic healing, and even promoting transmural healing.[5] Despite a steady increase in the incidence and prevalence of CD in Taiwan and other Asian countries, these rates remain lower than the Western countries.[6-9] However, the severity of CD presentation appears to be similar between Asia and the West.[10]

Although guidelines for CD diagnosis and management have been established in Europe, North America, and the Asia Pacific region,[11-17] their direct applicability to clinical practice in Taiwan may be limited due to variations in endemic diseases, disease distribution and behavior, insurance coverage, and treatment accessibility. In Taiwan, the National Health Insurance (NHI) primarily provides healthcare coverage; it is a compulsory social health insurance system implemented in 1995 and currently covers more than 99% of the population.[18] Under NHI, inflammatory bowel disease (IBD), including CD, is categorized as a catastrophic illness; thus, patients receive reimbursement for treatment costs with minimal copayments, although with limitations such as a 1-year treatment period and mandatory 3-month drug holidays. Considering the disparities in the healthcare requirements between Taiwan and other countries, devising specific guidelines tailored to CD management within the Taiwanese context is essential. The first edition of diagnosis and treatment guidelines for IBD published in 2017 was established by the Taiwan Society of Inflammatory Bowel Disease (TSIBD), which convened a steering committee.[19] With the emergence of new treatment options and the implementation of treat-to-target concepts for disease monitoring in recent years, the steering committee updated the guidelines based on the most current information, aimed at guiding both young and less experienced physicians in Taiwan for improving the outcomes of patients with IBD. Therefore, a consensus was reached after a review of international guidelines and the latest literature, and the guidelines were revised to align with Taiwan's healthcare practices.

METHODS

The Scientific Committee of the TSIBD established a guideline revision panel comprising 30 experts (including gastroenterologists, pediatric gastroenterologists, surgeons, radiologists, and pathologists) in 2022. The steering committee was grouped into 10 topics (from topic 1. Epidemiology to topic 10. Management of Complications; Table 1) according to the expertise of these members. The steering committee meticulously drafted statements outlining recommendations for the clinical management of CD following an extensive review of the literature and careful consideration of the available evidence and existing guidelines, particularly those developed by the European Crohn's and Colitis Organisation (ECCO), the Asian Pacific

Table 1. Summary of the 2023 Taiwan Society of Inflammatory Bowel Disease CD Consensus Statements

1. Epidemiology
1.1 The incidence and prevalence of CD in Taiwan are increasing, and these measures are still underestimated.
1.2.1 Patients with CD in Taiwan are predominantly male, similar to most East Asian but different from Western countries' reports.
1.2.2 The genetic background of CD in Asia appears to be different from that in Western countries.
2. Diagnosis
2.1 CD is diagnosed based on a combination of clinical, endoscopic, radiological, and histological features. Infections, malignancies, and other etiologies should be excluded.
2.2 Symptoms of CD are heterogeneous but commonly include abdominal pain, chronic diarrhea, and/or weight loss.
2.3 The fecal calprotectin test helps differentiate CD from irritable bowel syndrome.
2.4 Ileocolonoscopy, with biopsies from inflamed and uninflamed areas, to identify histological evidence of CD is preferable as the first-line procedure for establishing the diagnosis.
2.5 The endoscopic features that suggest a diagnosis of CD include segmental lesions, anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance.
2.6 Intestinal TB should be excluded before the diagnosis of CD. The biopsy specimen for diagnosis of CD should also be evaluated for intestinal TB. The appropriate tests include acid-fast staining, TB culture, and TB polymerase chain reaction, alone or in combination, depending on availability.
2.7 Esophagogastroduodenoscopy is suggested for CD patients with upper gastrointestinal symptoms or to clarify the location of involvement.
2.8 Capsule endoscopy or deep enteroscopy is indicated for patients with high suspicion of CD but inconclusive ileocolonoscopy and radiological imaging results.
2.9 Cross-sectional imaging (MRI, CT, and IUS) is useful in fully assessing the disease extent and detecting possible complications. When available, enterography is preferred.
2.10 The increased risk of radiation exposure should be given consideration when selecting imaging modalities. MRI and IUS are preferred to CT in elective settings.
2.11 The major role of histopathology in the diagnosis of CD is to exclude infection, malignancy, and other etiologies.
3. Specific considerations
3.1 HBsAg, hepatitis B virus surface antibody, and anti-HBc should be routinely screened before initiating the immunosuppressive treatments.
3.2 HBV DNA quantification is recommended for patients positive for HBsAg and/or anti-HBc before the initiation of immunosuppressive treatments.
3.3 Prophylactic antiviral treatment is recommended for HBV carriers before immunosuppressive treatments.
3.4 Routine screening for latent TB infection with chest X-ray and the IGRA test is recommended before initiating advanced therapy (biologics and small molecules).
3.5 For patients diagnosed with latent TB infection, prophylactic anti-TB treatment should be started at least 4 weeks before using advanced therapy.
3.6 During advanced therapies, monitoring for signs and symptoms of active TB, with chest X-ray and IGRA performed at least annually is recommended. When active TB is diagnosed, advanced therapy must be stopped, but they can be resumed after 2 months of anti-TB treatment.
4. Evaluation and treatment goals
4.1 Clinical classification (Montreal classification) and activity scores (Crohn's Disease Activity Index for adults and Pediatric Crohn's Disease Activity Index for children) evaluation are recommended at disease diagnosis and during monitoring.
4.2 Malnutrition is common in CD patients. Comprehensive nutritional assessment and adequate support are recommended.
4.3 Time-bound treatment goals for CD include clinical remission, biomarker improvement, and endoscopic remission. Transmural healing is a potential target in the future.
5. Medical treatment
5.1 The CDED with PEN is effective in inducing remission, especially in children, with mild-to-moderate biologic-naïve luminal CD.
5.2.1 5-ASA may be used to treat mild CD. When efficacy is not satisfactory, escalated treatment is highly recommended.
5.2.2 Steroids are more effective than 5-ASA at inducing remission.
5.2.3 Systemic corticosteroids at 0.5–1.0 mg/kg (prednisolone equivalent dose, maximum dosage of 60 mg/day for a maximum duration of 28 days) are recommended for inducing remission, but not for maintaining remission.

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Table 1. Continued

5.2.4 MTX is an option for inducing remission in steroid-dependent and steroid-refractory CD. Thiopurines (AZA and 6-MP) are not recommended for inducing remission.
5.2.5 All approved advanced therapies are effective in inducing remission in patients with moderate-to-severe active CD who do not respond to or do not tolerate conventional therapy.
5.2.6 Early introduction of biologics is beneficial for patients with moderate-to-severe CD, especially high-risk patients. CD patients with poor prognostic factors need accelerated step-up or top-down therapy within the window of opportunity.
5.3.1 Thiopurines (AZA and 6-MP) and MTX are effective in maintaining remission.
5.3.2 When achieving clinical remission by advanced therapy, using the same agent to maintain remission is recommended.
5.3.3 The combination of infliximab and thiopurine is effective and safe as a maintenance treatment for CD patients.
5.3.4 The pros and cons of de-escalation have to be explained and discussed with patients, and close monitoring after de-escalation is strongly recommended.
5.4.1 Surgical resection could be a primary treatment option for isolated ileocolic CD.
5.4.2 A multidisciplinary approach is highly recommended for severe active CD.
6. Monitoring
6.1 Patient-reported outcomes are strongly correlated with well-being and should be monitored regularly throughout the course of treatment for CD.
6.2.1 Hemograms, albumin, C-reactive protein/erythrocyte sedimentation rate, and/or fecal calprotectin can be used to assess gut inflammation and disease severity in CD.
6.2.2 Fecal calprotectin is useful for evaluating treatment response and predicting clinical relapse in CD.
6.3.1 Mucosal healing is associated with better clinical outcomes. Periodic endoscopy is the gold standard for the assessment of mucosal healing.
6.3.2 Reassessment with endoscopic and/or cross-sectional imaging should be considered in cases of relapse, refractoriness, new symptoms, or when surgery is considered.
6.3.3 Endoscopic evaluation is recommended 6–12 months after surgery to diagnose postoperative recurrence in order to guide treatment decisions.
6.4 Transmural disease activity can be assessed with CT enterography, MRE, or IUS, which is adjunctive to endoscopic assessment. Due to concerns about radiation, MRE or IUS is preferred.
7. Surgery
7.1 The major role of surgery in CD is to treat medical failure and/or complications, such as fistulization, fibrotic stricture, perforation, massive bleeding, cancer and failure to thrive.
7.2 Perioperative nutritional support should be considered and provided.
7.3 Parenteral nutrition and/or enteral nutrition can reduce postoperative complications in CD.
7.4 Prednisolone at dosages greater than 20 mg daily or the equivalent for more than 6 weeks is a risk factor of surgical complications. Therefore, patients should be weaned off corticosteroids, if possible.
7.5 Regional ileocolic septic conditions resembling CD found at operation, such as appendix vermiformis, should not routinely be resected.
7.6 Active small bowel CD with a concomitant abdominal abscess should preferably be managed with antibiotics and percutaneous or surgical drainage followed by delayed resection, if necessary.
7.7 Patients with an unsuspected diagnosis of CD after IPAA have high complication and failure rates. IPAA is not recommended for patients with CD.
7.8 Medical prophylaxis and quitting smoking are crucial for reducing postoperative recurrence of CD.
8. Special populations
8.1.1 Consultation before conception is recommended. Remission status is associated with better pregnancy outcomes.
8.1.2 Modification of treatments for CD is usually not necessary for pregnant and breastfeeding patients, except MTX and Janus kinase inhibitors.
8.1.3 Live-attenuated vaccines should be avoided before 6 months of age for infants who are exposed to *in-utero* biologics, and inactivated vaccines should be applied according to local regulations.

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Table 1. Continued

8.2.1 EEN is recommended as the first-line induction therapy for children with active mild-to-moderate luminal CD, and the CDED plus PEN may serve as an alternative with better tolerance.
8.2.2 Long-term use of corticosteroids should be avoided, and children's growth curves should be monitored.
8.3 All CD patients with a history of cancer should be managed with multidisciplinary support. Thiopurines and anti-tumor TNFα agents should be avoided for CD patients with a history of nonmelanoma skin cancer.
8.4 Elderly patients with CD have a higher risk of serious adverse events associated with prolonged use of corticosteroids, thiopurines, or anti-TNFα agents.
9. Cancer surveillance
9.1 Patients with CD are at increased risk of bowel neoplasia. Regular cancer surveillance, including biopsy as needed, should be undertaken.
9.2 The persistence of chronic fistulas in long-standing CD has been identified as a potential risk factor of malignant transformation of fistula.
9.3 The risk of lymphoma and nonmelanoma skin cancer of CD patients treated with thiopurines is higher.
10. Management of complications
10.1 Infliximab, adalimumab, surgical treatment, or combined treatment can be used to treat anorectal fistulas in CD.
10.2.1 Intestinal strictures can be assessed with cross-sectional imaging and endoscopy.
10.2.2 Anti-inflammatory therapies, including corticosteroids, immunosuppressive drugs, and biologic agents, should be considered for stenoses with an inflammatory component.
10.2.3 Endoscopic and surgical interventions are treatment options for symptomatic fibrotic strictures.
10.3.1 Anemia can affect quality of life. Therefore, the etiology of anemia should be worked up and corrected.
10.3.2 Attention should be paid to micronutrient and electrolyte imbalances, especially after surgery for CD.

CD, Crohn's disease; TB, tuberculosis; MRI, magnetic resonance imaging; CT, computed tomography; IUS, intestinal ultrasound; HBsAg, hepatitis B virus surface antigen; anti-HBc, hepatitis B virus core antibody; HBV, hepatitis B virus; CDED, CD exclusion diet; PEN, partial enteral nutrition; 5-ASA, aminosalicylates; MTX, methotrexate; AZA, azathioprine; 6-MP, 6-mercaptopurine; MRE, magnetic resonance enterography; IPAA, ileal pouch-anal anastomosis; EEN, exclusive enteral nutrition; TNF, necrosis factor.

Association of Gastroenterology, the American Gastroenterological Association (AGA), and the American College of Gastroenterology. The members of these 10 groups then generated the initial statements, 73 statements were generated during the first step. After that, a total of 4 face to face meetings were hosted to provide time and space for statement clarification and fine-tuning then voting. During meetings among all members of the expert panel, the evidence in support and opposition of each statement as well as any proposed modifications were openly deliberated. The panel members expressed their level of agreement with each finalized statement on a scale ranging from "strongly agree" and "agree" to "disagree." Only the statements achieved ≥90% agreement would be listed as the final statements. As a result, 67 statements were approved by the steering committee. The extent of agreement indicated the strength of the recommendation for each statement.

The panel emphasized that these guidelines serve as advisory tools and should not replace clinical judgment. Practitioners should consider individual patient variables as well as the resources and treatments available at their institutions in the clinical decision-making process while prioritizing patient safety and welfare.

RESULTS

1. Epidemiology

Statement 1.1
The incidence and prevalence of CD in Taiwan are increasing, and these measures are still underestimated. Level of agreement: Strongly agree, 92.9%; agree, 7.1%; disagree, 0.0%.

In Taiwan, the incidence and prevalence of CD have consistently and significantly increased across 3 periods: 2001–2005, 2006–2010, and 2011–2015. This trend is supported by the results of the analysis of data from the population-based Taiwan National Health Insurance Research Database (NHIRD).

The incidence of CD in Taiwan has increased from 0.17 per 100,000 person-years in 2001 to 0.47 per 100,000 person-years in 2015, whereas the prevalence increased from 0.6/100,000

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person-years in 2001 to 3.9/100,000 person-years in 2015.[20] However, these incidence and prevalence rates are potentially underestimated due to the stringent criteria for catastrophic illness registration, coupled with the reluctance of some patients to be registered in Taiwan. In contrast to studies in other countries that primarily rely on clinical diagnosis data's registration process requires a thorough evaluation of clinical records, endoscopic images, cross-section images, and pathology results.[20,21]

Numerous factors contribute to the increasing incidence of CD in Taiwan and other Asian countries. These factors include the enhancement of socioeconomic status, the adoption of Westernized dietary habits, the increased awareness of CD, and advancements in diagnostic accuracy facilitated by the broader use of cross-sectional imaging techniques such as magnetic resonance (MR) or computed tomography (CT) enterography as well as innovations in endoscopic technologies such as capsule endoscopy and deep enteroscopy.[20,22,23]

Statement 1.2
Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

Statement 1.2.1
Patients with CD in Taiwan are predominantly male, similar to most East Asian but different from Western countries' reports.

Statement 1.2.2
The genetic background of CD in Asia appears to be different from that in Western countries.

The analysis of data from the population-based NHIRD revealed a consistent male-predominant trend in CD in Taiwan across the 3 periods (2001–2005, 2006–2010, and 2011–2015) with an overall male-to-female ratio of 2.19.[20] A similar male predominance (61.4%) was observed in population-based analyses of CD incidence in China, Hong Kong, Indonesia, Macau, Malaysia, Singapore, Sri Lanka, and Thailand.[10] Furthermore, in South Korea, 67% of CD cases exhibited male dominance, whereas male dominance was found in an even higher proportion of 70% of cases in Japan.[24,25] Conversely, the incidence of CD exhibited a female predominance in Europe and North America, whereas other studies have not identified any significant gender difference.[26-30] The etiology of this disparity in gender distribution is unknown, but the disparity might be attributed to genetic differences between Asian and Western populations.[31]

2. Diagnosis

Statement 2.1
CD is diagnosed based on a combination of clinical, endoscopic, radiological, and histological features. Infections, malignancies, and other etiologies should be excluded. Level of agreement: Strongly agree, 92.9%; agree, 7.1%; disagree, 0.0%.

The diagnosis of CD relies on the comprehensive assessment of stool samples and cross-sectional images as well as clinical examinations, biochemical laboratory tests, endoscopy, and histological investigations.[32] Initially, ruling out malignancy and infectious etiologies is crucial. Conditions such as intestinal tuberculosis (TB) and infectious colitis, including *Clostridioides difficile* and amoebic infections, can manifest symptoms resembling those of CD.[32,33] For differentiation from functional disorders such as irritable bowel syndrome, specific biochemical laboratory tests, including those for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin, and fecal lactoferrin, are performed,[33-35] followed by appropriate endoscopic and cross-sectional image studies. Small bowel assessment is recommended for patients with a new diagnosis of CD and those with prior indications of small bowel involvement.[16,32] Histological features such as granulomas and focal crypt architectural abnormalities are diagnostic of CD.[19,32]

Statement 2.2
Symptoms of CD are heterogeneous but commonly include abdominal pain, chronic diarrhea, and/or weight loss. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

The typical clinical presentation of CD involves chronic diarrhea, abdominal pain, and weight loss, which are commonly observed in younger patients.[36] Diarrhea and abdominal pain are primary symptoms frequently reported by patients with CD.[11] These symptoms are as prevalent as prodromal symptoms of CD compared with ulcerative colitis (UC).[37] Body weight loss is another common symptom in CD patients, and is typically absent in UC.[37] Additional common symptoms of CD include rectal bleeding, fever, and fatigue.[38] When diarrhea persists for at least 4 weeks along with increased stool frequency and altered consistency, it is unlikely to be caused by self-limiting infection. In such cases, chronic noninfectious etiologies should be considered.[11] Younger age is associated with a higher risk of perianal disease, and CD should be sus-

pected in young patients with perianal swelling and purulent discharge.[39] According to the recent findings of Weng et al.,[40] the prevalence of perianal CD among Taiwanese patients with CD from 2000 to 2017 was 14.8%, with approximately half of the patients receiving the perianal CD diagnosis at least 6 months before a CD diagnosis. Thus, a history of perianal disease should raise suspicion of CD. Measuring the body weight and calculating the body mass index are recommended. Moreover, the frequency of bowel movements and the presence of bloody stools should be carefully recorded. Furthermore, patients should be evaluated for nocturnal symptoms, extraintestinal manifestations (involving the mouth, skin, eye, or joints), perianal abscess, and anal fissure.[11]

Statement 2.3
The fecal calprotectin test helps differentiate CD from irritable bowel syndrome. Level of agreement: Strongly agree, 75.0%; agree, 21.4%; disagree, 3.6%.

Chang et al.[41] described that fecal calprotectin is a potential, valuable marker for distinguishing between IBD and irritable bowel syndrome. Notably, a previous study reported a significant difference between patients with CD in remission and controls.[42] The combination of the Red Flags Index score and noninvasive biomarkers such as fecal calprotectin appears to be highly accurate for screening patients with underlying IBD, their further diagnostic evaluation, and early implementation of effective treatment strategies.[43] Furthermore, fecal calprotectin level is correlated well with endoscopic severity in both UC and CD in previous report.[44]

Statement 2.4
Ileocolonoscopy, with biopsies from inflamed and uninflamed areas, to identify histological evidence of CD is preferable as the first-line procedure for establishing the diagnosis. Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

The first-line diagnostic procedure for CD is ileocolonoscopy with multiple mucosal biopsies.[11,13] Biopsies from 5 segments (the terminal ileum, ascending colon, transverse colon, sigmoid colon, and rectum) are recommended. This approach involves sampling from both visually normal and abnormal areas.[13,45] Further evaluations are recommended to assess the location and extent of CD in the upper gastrointestinal tract and/or small bowel, irrespective of the findings from ileocolonoscopy,[11] particularly in cases presenting with related symptoms.

Statement 2.5
The endoscopic features that suggest a diagnosis of CD include segmental lesions, anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance. Level of agreement: Strongly agree, 71.4%; agree, 25.0%; disagree, 3.6%.

The earliest and most distinctive endoscopic finding in CD is the presence of aphthous ulcers, which are small, punched-out ulcers within an otherwise normal-looking mucosa.[46,47] With the increasing severity of CD, these ulcers tend to enlarge, coalesce, and deepen. In CD, inflammation typically manifests in a segmental pattern, with discontinuous affected areas adjacent to normal tissue.[32] The presence of cobblestone appearance arises when ulcers longitudinally traverse either normal or inflamed tissue is also common in CD.[46,47] Rectal involvement and circumferential continuous inflammation are less commonly observed in CD than in UC.[36] Although CD has no specific histological features, characteristic microscopic findings include focal crypt irregularity (discontinuous crypt distortion), non-crypt-related granulomas, focal chronic inflammation (discontinuous), and irregular villous architecture in the terminal ileum.[45] Following the diagnosis or suspicion of CD from ileocolonoscopy, the Crohn's Disease Endoscopic Index of Severity or the Simple Endoscopic Score for Crohn's Disease (SES-CD) is recommended for assessing disease activity. SES-CD is considered more clinically practical and is the preferred choice.[5] Atypical endoscopic features, particularly in posttreatment situations, may complicate the endoscopic diagnosis.

Statement 2.6
Intestinal TB should be excluded before the diagnosis of CD. The biopsy specimen for diagnosis of CD should also be evaluated for intestinal TB. The appropriate tests include acid-fast staining, TB culture, and TB polymerase chain reaction (PCR), alone or in combination, depending on availability. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

CD and intestinal TB present a diagnostic challenge due to their similar clinical presentations and endoscopic features, particularly in countries where intestinal TB is prevalent and CD incidence is increasing.[48,49] Considering Taiwan's status as an endemic area for TB, intestinal TB should be included as a potential differential diagnosis.[50] Misdiagnosis of intestinal infections as CD can worsen the condition if treatment with cor-

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ticosteroids, immunosuppressants, or advanced therapy is initiated.[49,51] Certain clinical indicators, such as concomitant pulmonary TB, ascites, night sweats, involvement of fewer than 4 bowel segments, patulous ileocecal valve, transverse ulcers, scars, or pseudopolyps, strongly suggest the possibility of intestinal TB.[52]

Diagnostic tests for identifying *Mycobacterium tuberculosis* in tissue samples often have low sensitivity.[53] Therefore, the use of smear tests for acid-fast bacillus, PCR-based assays, and interferon-gamma release assay (IGRA) can assist in differential diagnosis.[13,36]

Statement 2.7
Esophagogastroduodenoscopy (EGD) is suggested for CD patients with upper gastrointestinal symptoms or to clarify the location of involvement. Level of agreement: Strongly agree, 67.9%; agree, 32.1%; disagree, 0.0%.

CD typically affects the terminal ileum, but any segment of the gastrointestinal tract can be involved in CD. Upper gastrointestinal involvement can occur in patients with CD, irrespective of the presence of upper gastrointestinal symptoms.[54] EGD can reveal various characteristics of CD, including bamboo joint-like appearance, notch-shaped appearance, cobblestone appearance, multiple aphthous ulcerations, erosions, irregularly shaped ulcers, bead-like protrusions, nodular folds, granular mucous membrane, and stenosis.[16] The use of EGD to examine asymptomatic patients with CD is under debate. A prospective study reported an unexpectedly higher prevalence of upper gastrointestinal involvement in asymptomatic patients with CD, suggesting the utility of standard EGD for CD diagnosis.[54]

Statement 2.8
Capsule endoscopy or deep enteroscopy is indicated for patients with high suspicion of CD but inconclusive ileocolonoscopy and radiological imaging results. Level of agreement: Strongly agree, 60.7%; agree, 39.3%; disagree, 0.0%.

The small bowel involvement, which is reported in at least 70% of patients with CD, presents diagnostic challenges due to its limited accessibility during standard ileocolonoscopy.[7] In such scenarios, small bowel capsule endoscopy has proven effective with high sensitivity for detecting mucosal inflammation in the small bowel.[55-57] However, before capsule endoscopy, a patency capsule or radiographic imaging is recommended to rule out the presence of bowel strictures, which can cause capsule retention.[58] When other diagnostic modalities, including small bowel capsule endoscopy, yield inconclusive results, device-assisted enteroscopy, such as single- or double-balloon enteroscopy, can provide histopathologic confirmation.[59,60] However, this approach should be reserved when other tests fail to provide conclusive results or the primary objective is therapeutic intervention.[61] Device-assisted enteroscopy is a more invasive and labor-intensive procedure than small bowel capsule endoscopy, but it enables biopsy acquisition and facilitates therapeutic interventions.[8,62]

Statement 2.9
Cross-sectional imaging (magnetic resonance imaging [MRI], CT, and intestinal ultrasound [IUS]) is useful in fully assessing the disease extent and detecting possible complications. When available, enterography is preferred. Level of agreement: Strongly agree, 89.3%; agree, 10.7%; disagree, 0.0%.

A combination of cross-sectional imaging and endoscopy provides a more comprehensive assessment of the intestines, facilitating the identification of both mural and extramural involvement and penetrating lesions.[32] The primary imaging techniques include MRI, CT, and IUS. Oral contrast may be administered during CT and MRI examinations to enhance small bowel enterography. Ensuring adequate luminal distension is essential for acquiring high-quality images because collapsed bowel loops can hinder visualization and compromise diagnostic accuracy.[31,62] Both the MR enterography (MRE) and CT enterography (CTE) exhibit high and comparable diagnostic accuracies. However, MRI is preferred over CT in non-emergency situations due to the lack of radiation exposure.[32,63] Typical imaging findings of intestinal inflammation on MRE and CTE encompass segmental mural hyperenhancement, wall thickening, intramural edema, ulcerations, and restricted diffusion.[64] IUS is another valuable diagnostic tool for visualizing the terminal ileum and colon without prior preparation.[65] However, IUS highly relies on operator proficiency, necessitating thorough IUS training.

Statement 2.10
The increased risk of radiation exposure should be given consideration when selecting imaging modalities. MRI and IUS are preferred to CT in elective settings. Level of agreement: Strongly agree, 71.4%; agree, 25.0%; disagree, 3.6%.

Individuals with CD typically undergo repeated imaging examinations from a young age, which may increase the risk of radiation-induced malignancy over their lifetime.[66,67] Among

imaging modalities, CT significantly contributes to the overall radiation dose received by patients with IBD.[68] Despite being more expensive and time-consuming, MRI is the preferred imaging modality, particularly for patients requiring frequent follow-ups, as it eliminates the risk of ionizing radiation exposure.[69] In patients with CD, IUS is a noninvasive, radiation-free approach that can be employed as a point-of-care tool for disease monitoring.[70]

Statement 2.11
The major role of histopathology in the diagnosis of CD is to exclude infection, malignancy, and other etiologies. Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

Biopsy samples should be assessed for architectural changes and inflammatory infiltrates. The key diagnostic features of CD are discontinuous chronic inflammation, focal crypt architectural distortion, and non-crypt-related granulomas.[71] Histologic assessment is conducted mainly to rule out malignancy, infection, and other potential non-IBD etiologies (such as ischemic bowel, diverticulum, and graft versus host disease). Employing a checklist during histological assessment and reviewing previous biopsy slides are recommended for a comprehensive evaluation and precise diagnosis. In the histopathological diagnosis of CD, clinical findings and treatment history should be considered given the intermittent nature of inflammation, sampling bias, and posttreatment effects.[72]

3. Specific Considerations

Statement 3.1
Hepatitis B virus surface antigen (HBsAg), hepatitis B virus surface antibody (anti-HBs), and hepatitis B virus core antibody (anti-HBc) should be routinely screened before initiating the immunosuppressive treatments. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

Taiwan is an endemic area for chronic hepatitis B virus (HBV) infection, with a prevalence of 10.3% in the general population in a recent analysis.[73] HBV reactivation is commonly observed in patients undergoing immunosuppressive therapy and can have fatal consequences.[52] Therefore, before initiating immunomodulating or immunosuppressive treatment for CD, HBV screening with necessary antiviral prophylaxis is strongly recommended, as it significantly reduces the risk of HBV reactivation.[74,75] For patients testing negative for HBsAg, anti-HBs, and anti-HBc, HBV immunization is recommended. Additionally, before treatment with corticosteroids or immunomodulators and advanced therapy, screening for hepatitis C virus, HIV, and syphilis is recommended for patients with CD.

Statement 3.2
HBV DNA quantification is recommended for patients positive for HBsAg and/or anti-HBc before the initiation of immunosuppressive treatments. Level of agreement: Strongly agree, 85.7%; agree, 14.3%; disagree, 0.0%.

Patients who test positive for anti-HBc but negative for HBsAg may have occult HBV infection. However, the reactivation of this latent HBV with the use of immunosuppressive therapy in CD is rare.[74] Liver dysfunction has been reported in 25%–36% of HBsAg-positive patients with CD.[76,77] Notably, HBV reactivation mostly occurs in HBV-infected patients with CD who undergo 2 or more long-term immunomodulating treatments, test positive for HBV DNA, or do not receive prophylactic antiviral treatment.[74] Reactivation in patients negative for HBsAg but positive for anti-HBc is defined by the reappearance of HBsAg or the detection of HBV DNA.[78] Serial monitoring of HBV DNA titers can aid in the early identification of HBV reactivation and the prompt initiation of antiviral treatment.

Statement 3.3
Prophylactic antiviral treatment is recommended for HBV carriers before immunosuppressive treatments. Level of agreement: Strongly agree, 85.7%; agree, 14.3%; disagree, 0.0%.

HBV carriers who are HBsAg-positive or have detectable HBV DNA should undergo prophylactic antiviral treatment with nucleotide/nucleoside analogues. Entecavir and tenofovir are preferred options for patients with CD due to their rapid onset of action, high antiviral potency, and low incidence of resistance during long-term use.[74] This treatment should be initiated before immunomodulatory therapy and continued for 6–12 months following its cessation.[52,79] Regularly monitoring alanine aminotransferase and HBV DNA is advised throughout antiviral treatment.[52]

Statement 3.4
Routine screening for latent TB infection (LTBI) with chest X-ray and the IGRA test is recommended before initiating advanced therapy (biologics and small molecules). Level of agreement: Strongly agree, 85.7%; agree, 14.3%; disagree, 0.0%.

Taiwan is an endemic area for TB, with a prevalence of 30 cas-

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es per 100,000 population in 2021.[80] Patients with IBD have an increased risk of active TB infection compared with the general population, primarily due to their use of immunomodulating treatments.[74] In Taiwan, approximately 5.8% of extrapulmonary TB cases involve the gastrointestinal tract.[50] Screening protocols, including physical examination, chest radiography, and either the tuberculin skin test (TST) or IGRA for LTBI, are mandatory for all patients with CD before the initiation of anti-tumor necrosis factor alpha (TNFα) therapy and other novel CD medications.[19,79] TST results may be influenced by prior Bacillus Calmette–Guérin (BCG) vaccination, whereas IGRA results remain unaffected by this vaccination.[81] Therefore, TST is typically reserved for individuals younger than 5 years or for those unable to undergo the IGRA. Since 2016, IGRAs have been implemented for all individuals aged >5 years to minimize the false-positive results caused by cross-reactivity with the BCG vaccine and to avoid unwarranted treatment for LTBI.[82] Novel skin-based recombinant antigen tests for TB infection appear to perform comparably to IGRA and TST, but further research is required to ascertain their applicability in specific populations.[83]

Statement 3.5
For patients diagnosed with LTBI, prophylactic anti-TB treatment should be started at least 4 weeks before using advanced therapy. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

Before initiating advanced therapies, particularly anti-TNFα, and Janus kinase (JAK) inhibitors, anti-TB treatment is mandatory for patients suspected of having latent or active TB.[79] Chemoprophylaxis has been demonstrated to significantly reduce the risk of reactivation in patients with LTBI. The treatment protocol for LTBI should adhere to the guidelines established by the Taiwan Centers for Disease Control.[82] Before initiating biologic therapy, anti-TB treatment should be administered for a minimum of 4 weeks. Moreover, collaborating with a specialist in infectious diseases or chest medicine is recommended for ensuring comprehensive, multidisciplinary care.[19] Anti-TNFα treatment should be delayed until after the completion of anti-TB treatment; alternatively, the treatment should be initiated until at least 2 months after the commencement of TB treatment.[74] Although recommendations regarding LTBI management with small-molecule therapies are currently lacking, previous clinical trials conducted for other diseases recommend 4 weeks of LTBI treatment before initiating JAK inhibitors and 3 weeks of treatment before administering calcineurin inhibitors.[84]

Statement 3.6
During advanced therapies, monitoring for signs and symptoms of active TB, with chest X-ray and IGRA performed at least annually is recommended. When active TB is diagnosed, advanced therapy must be stopped, but they can be resumed after 2 months of anti-TB treatment. Level of agreement: Strongly agree, 60.7%; agree, 39.3%; disagree, 0.0%.

A systematic review identified candidiasis (oropharyngeal or other locations) and TB as the most common opportunistic infections following the administration of biologics and small-molecule drugs.[85] Notably, TB presentation in patients treated with anti-TNFα is often atypical, extrapulmonary, and disseminated, which complicates diagnosis.[74] Regular monitoring for signs and symptoms of active TB should be conducted for patients with CD on biological treatment. Additionally, the Taiwan Centers for Disease Control suggested regular chest X-ray or IGRA test every 6–12 months in patients treated with biologics or small molecules.[82]

4. Evaluation and Treatment Goals

Statement 4.1
Clinical classification (Montreal classification) and activity scores (Crohn's Disease Activity Index [CDAI] for adults and Pediatric Crohn's Disease Activity Index [PCDAI] for children) evaluation are recommended at disease diagnosis and during monitoring. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

The accurate classification of IBD is crucial for the implementation of effective patient counseling and prognosis assessment as well as the selection of appropriate therapeutic interventions. The Montreal classification, a revision of the Vienna classification, is widely adopted in clinical practice. It involves the evaluation of the age of onset (A1–A3), disease location (L1–L4), and disease behavior (B1–B3 and p).[86] The CDAI serves as a key tool for evaluating disease severity in adult patients, with CDAI scores of <150 indicating remission, 150–220 indicating mild CD, 221–450 indicating moderate CD, and >450 indicating severe CD.[87] In pediatric patients, the PCDAI is employed, adopting an 11-item physician-based index with scores ranging from 0 to 100.[88] A prospective study established cutoff values for PCDAI as follows: scores of <10 indicate remission, 10–27.5 indicate mild disease, 30–37.5 indicate moderate disease, and ≥40 indicate severe disease.[89] To

select the initial therapeutic strategy, a comprehensive evaluation of prognosis, patient characteristics (such as age and smoking status), disease features (including duration, disease location, and endoscopic findings), and laboratory markers (such as CRP, fecal calprotectin, serum albumin, and hemoglobin levels) should be conducted.[36]

Statement 4.2
Malnutrition is common in CD patients. Comprehensive nutritional assessment and adequate support are recommended. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

Malnutrition is prevalent among individuals with CD, particularly in those who have undergone gastrointestinal tract resection surgery; malnutrition is prevalent among 65% to 75% of patients. Deficiencies in folate, vitamin A, and vitamin D are common, along with potential deficiencies in essential elements such as magnesium, zinc, and iron.[90] A previous study revealed that patients who received nutritional support before surgery exhibited lower complication rates than patients who did not receive such therapy (odds ratio [OR], 0.26; 95% confidence interval [CI], 0.07–0.99; $P<0.001$).[90] Oral iron is considered the first-line treatment for patients with mild anemia.[91] Prioritizing enteral nutrition over parenteral nutrition is recommended.[92] For patients who cannot tolerate oral iron, intravenous (IV) iron supplements may be considered.

Statement 4.3
Time-bound treatment goals for CD include clinical remission, biomarker improvement, and endoscopic remission. Transmural healing is a potential target in the future. Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

Short-term, intermediate, and long-term therapeutic goals should be set for the management of CD.[5] The primary goal of CD treatment is to achieve the remission of clinical symptoms. Normalization of biomarkers, including fecal calprotectin and CRP, is considered for measuring short-term to intermediate-term treatment outcomes. These biochemical analyses have high sensitivity and specificity for assessing mucosal inflammation. Endoscopic healing is regarded as a long-term treatment goal and is often associated with clinical remission, decreased risks of complications, disease flare-ups, and the need for surgery. Additionally, although formal standardization is currently lacking, transmural healing is a potential treatment objective in the future.

5. Medical Treatment

1) Nutrition

Statement 5.1
The CD exclusion diet (CDED) with partial enteral nutrition (PEN) is effective in inducing remission, especially in children, with mild-to-moderate biologic-naïve luminal CD. Level of agreement: Strongly agree, 75.0%; agree, 25.0%; disagree, 0.0%.

Dietary interventions play crucial roles in mediating remission, reducing inflammation, and promoting mucosal healing, which are key aspects of CD management. Exclusive enteral nutrition (EEN) is the primary nutritional therapy for mild-to-moderate CD in pediatric patients, and its efficacy for mediating remission is comparable to corticosteroids.[33] Another innovative dietary approach, CDED plus PEN, has been developed specifically for patients with CD. In a randomized trial, CDED alone and CDED plus PEN were demonstrated to be effective in achieving clinical remission in pediatric patients with CD, without the need of additional medications by week 6, and remission was sustained at week 24 in 80% of the patients.[93] Because malnutrition affects approximately 65%–70% of patients with CD, nutritional support has become increasingly vital in CD management, particularly in patients with weight loss and malnutrition before surgery.[1,90]

2) Induction

Statement 5.2
Level of agreement: Strongly agree, 50.0%; agree, 50.0%; disagree, 0.0%.

Statement 5.2.1
Aminosalicylates (5-ASA) may be used to treat mild CD. When efficacy is not satisfactory, escalated treatment is highly recommended.

The oral administration of 5-ASA remains under debate and is generally limited to patients with mild CD or those with ileocolonic involvement. Moreover, 5-ASA can be discontinued for patients undergoing biologic therapy, particularly because no clear benefits of long-term 5-ASA treatment have been observed in approximately one-third of patients with CD.[94] According to a meta-analysis by the ECCO, both 5-ASA and sulfasalazine are well tolerated by patients with mild-to-moderate CD. However, 5-ASA had no significant efficacy for achieving clinical remission (relative risk [RR], 1.28; 95% CI, 0.97–1.69).[95] Although the efficacy of 5-ASA is under debate, Hart et

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al.[96] suggested that its early initiation following diagnosis and dosage optimization are linked to a longer duration of 5-ASA therapy. Because of the stringent reimbursement criteria for advanced therapies in Taiwan, the committee recommends the use of oral 5-ASA as an alternative to remission therapy in patients with mild colonic CD. However, if efficacy is suboptimal, treatment escalation is highly recommended.

Statement 5.2.2
Steroids are more effective than 5-ASA at inducing remission.

Systemic corticosteroids such as prednisolone are effective in achieving remission in CD. When 5-ASA is ineffective, clinicians may consider using corticosteroids, including cortisone, prednisone, hydrocortisone, methylprednisolone, beclometasone, and budesonide.[97] However, in a systematic review of 8 trials, budesonide was found to be less effective than conventional steroids (pooled RR, 0.85; 95% CI, 0.75–0.97), although it was associated with a lower risk of corticosteroid-related adverse events.[98] Notably, in cases of more severe ileocecal CD (CDAI >300), budesonide was inferior to prednisolone for mediating remission (RR, 0.52; 95% CI, 0.28–0.95).

Statement 5.2.3
Systemic corticosteroids at 0.5–1.0 mg/kg (prednisolone equivalent dose, maximum dosage of 60 mg/day for a maximum duration of 28 days) are recommended for inducing remission, but not for maintaining remission.

Systemic corticosteroids are effective initial therapies for moderate-to-severe CD.[33] However, their use should be limited. They have limited efficacy for maintaining remission, and prolonged exposure can lead to toxicity issues.

Statement 5.2.4
Methotrexate (MTX) is an option for inducing remission in steroid-dependent and steroid-refractory CD. Thiopurines (azathioprine [AZA] and 6-mercaptopurine [6-MP]) are not recommended for inducing remission.

MTX has been demonstrated to be effective in mediating remission for steroid-dependent and steroid-refractory CD, as evidenced by retrospective analysis and randomized controlled trials studies.[99,100] However, its efficacy in the era of newer, more effective biologic therapies remains uncertain. A systematic review conducted in 2020 revealed that MTX monotherapy was not superior to placebo for inducing clinical remission in CD.[101] A more recent systematic review of 163 studies indicated that MTX at a higher parenteral dose of 25 mg/week was more effective for mediating remission in CD compared with lower oral doses.[102] Thiopurines (AZA and 6-MP) were demonstrated to provide no additional benefits compared with placebo for mediating remission. Early initiation of AZA treatment in patients with CD within 8 weeks of diagnosis was not more effective than placebo for achieving corticosteroid-free remission.[103] A 2019 review that reanalyzed 48 meta-analyses of CD yielded conflicting results regarding the effectiveness of AZA or 6-MP in comparison with placebo, with these treatments exerting impact in a small number of patients (<1,000). Therefore, larger randomized controlled trials are warranted to confirm these findings.[104] However, due to the time required for thiopurines to take effect (typically 2–3 months), their use as induction therapy alone may not be reasonable.

Statement 5.2.5
All approved advanced therapies are effective in inducing remission in patients with moderate-to-severe active CD who do not respond to or do not tolerate conventional therapy.

Several controlled trials have demonstrated the efficacy of biologics for mediating remission in patients with active CD. Anti-TNFα agents, including infliximab, adalimumab, and certolizumab pegol (the last is not approved for CD treatment by the European Union and Taiwan Food and Drug Administration), have been used for both inducing and maintaining remission in CD.[95] In a clinical trial of 108 patients in 1995, 33% of the patients receiving infliximab achieved remission at 4 weeks compared with only 4% of the patients in the placebo group (P=0.005).[105] Similarly, in the CLASSIC-I trial, 36% of the patients who were naïve to anti-TNFα therapy achieved remission at 4 weeks following adalimumab administration compared with 12% in the placebo group (P=0.001).[106] Although thiopurines have been used to maintain the remission of steroid-dependent CD, recent clinical trials have suggested that AZA may be inferior to infliximab.[107] For instance, in the SONIC trial, combination therapy with AZA and infliximab exhibited superiority over AZA or infliximab monotherapy for achieving clinical remission (56.8% vs. 30% and 44.4%, P<0.001 compared with AZA alone and P=0.02 compared with infliximab alone).[108] Anti-TNFα agents are also considered a primary treatment option for pediatric patients with CD having active perianal fistulizing disease.[109] Ustekinumab, a monoclonal antibody targeting the p40 subunit of interleukin (IL)-12 and -23, was demonstrated to exhibit efficacy in inducing remis-

sion in CD. In clinical trials, IV ustekinumab provided higher rates of clinical response and remission among patients refractory to TNF antagonists (UNITI-1 trial) or conventional therapy (UNITI-2 trial) compared with placebo. At week 6, patients receiving IV ustekinumab at a dose of 130 mg or 6 mg/kg exhibited significantly higher response rates compared with patients in the placebo group (UNITI-1: 34.3% and 33.7% with ustekinumab vs. 21.5% with placebo, $P \leq 0.003$; UNITI-2: 51.7% and 55.5% with ustekinumab vs. 28.7% with placebo, $P < 0.001$).[110] Vedolizumab, a humanized IgG1 monoclonal antibody targeting α4β7 integrin, demonstrated effectiveness in patients with moderate-to-severe active CD.[111] In the GEMINI 2 clinical trial, patients with CD who were treated with vedolizumab achieved a clinical remission rate of 14.5% compared with 6.8% in those receiving placebo at week 6 after 2 doses administered at week 0 and 2 ($P = 0.02$).

Recently, both risankizumab and upadacitinib have demonstrated efficacy for moderate-to-severe active CD. Risankizumab, an inhibitor of the p19 subunit of IL-23, has demonstrated effectiveness and safety as CD treatment in 2 clinical trials: ADVANCE involving patients with CD who had failed to respond to biologics or conventional treatment and MOTIVATE involving patients with CD who had failed to respond to biologic treatment. These trials revealed higher rates of remission at week 12 among patients receiving 600 mg (ADVANCE: 45%; MOTIVATE: 42%) and 1,200 mg (ADVANCE: 42%; MOTIVATE: 40%) of risankizumab compared with those in the placebo group (ADVANCE: 25%; MOTIVATE: 19%), with statistically significant differences.[112] Promising results have also been found for upadacitinib, an oral inhibitor of JAK1, in 2 recent phase 3 clinical trials: U-EXCEL and U-EXCEED. U-EXCEL enrolled patients with CD who had previously failed to respond to conventional or biologic therapies, and U-EXCEED enrolled patients with a history of biologic treatment failure. Treatment with 45 mg of upadacitinib for 12 weeks demonstrated superior induction of clinical remission, as measured using the CDAI, in both trials (U-EXCEL: 49.5% vs. 29.1%; U-EXCEED: 38.9% vs. 21.1% compared with placebo, $P < 0.001$ for all comparisons).[113]

Statement 5.2.6
Early introduction of biologics is beneficial for patients with moderate-to-severe CD, especially high-risk patients. CD patients with poor prognostic factors need accelerated step-up or top-down therapy within the window of opportunity.

The concept of "early" biological treatment for CD lacked a clear definition until the "Paris Definition" was established through a consensus by IBD experts. According to this definition, early CD is defined by disease duration of < 18 months.[114] Early treatment encompasses early top-down or accelerated step-up therapy for moderate-to-severe CD and the early introduction of biologics within a short disease duration, typically less than 1 or 2 years.[115] Evidence from trials such as REACT[116] and CALM[117] suggests that early intervention or a treat-to-target approach may improve outcomes.

Patients with CD with poor clinical prognostic factors or high-risk indicators, such as perianal disease, upper gastrointestinal involvement, steroid use at diagnosis, ileocolonic disease, smoking, deep ulcers, and extensive ulcer distribution, may benefit from the early initiation of biologic treatment for mitigating adverse events and complications.[95,118] A recent systemic review and meta-analysis of 16 trials involving 6,168 CD patients revealed a higher remission rate in patients with shorter disease durations.[119] Evidence from meta-analyses, prospective clinical trials, and real-world data support that the early initiation of biologic therapy improves clinical outcomes in adult and pediatric CD patients.[115,120] Moreover, the early use of biologics is evidence to reduce healthcare costs.[121] "Top-down" therapy for CD was firstly proposed by D'Haens et al. in 2008,[122] compared an infliximab plus immunosuppression group (without steroids) and a conventional treatment group (conventional step-up with steroids). The trial demonstrated "top-down" therapy with the combination of infliximab with immunosuppression was more effective than conventional step-up management for induction of remission and reduction of corticosteroid use in patients who had been recently diagnosed with CD.[122] A recent multicenter PROFILE study in a CD cohort with all patients had been treated with steroids before the enrollment.[123] Since all subjects had been treated with corticosteroid, the "top-down" and "accelerated step-up" group actually reflect the "accelerated step-up" and "conventional step-up" group according to the definition of D'Haens et al. in 2008.[122,123] The PROFILE study demonstrated the benefit of "accelerated step-up" over "conventional step-up" in CD subjects, and the intervention by biologic should be initiated at the appropriate time (early stage of CD) through strict monitoring.[123]

3) Maintenance

Statement 5.3
Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

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Statement 5.3.1
Thiopurines (AZA and 6-MP) and MTX are effective in maintaining remission.

During the maintenance phase of CD treatment, immunosuppressives or biologics (either alone or in combination) are used to sustain remission, and they need to be tailored to meet personal needs. Steroids are ineffective for maintaining remission and can contribute to steroid dependence while increasing the risk of drug-related adverse events. A clinical trial demonstrated that patients with CD who received 6-MP or MTX achieved significantly higher remission maintenance rates than those who received 5-ASA ($P<0.001$).[124] Notably, the median time to respond to AZA treatment is 4.5 months, with some patients requiring up to 6 months to show a response,[125] rendering therapeutic drug monitoring (TDM) within this period potentially unreliable. A systematic review of 5 clinical trials evaluating MTX and other interventions or placebo for CD remission maintenance concluded that intramuscular MTX at a dose of 15 mg per week is more effective than placebo.[126] Thus, thiopurines such as AZA, 6-MP, and MTX are effective in maintaining CD remission.

Statement 5.3.2
When achieving clinical remission by advanced therapy, using the same agent to maintain remission is recommended.

In the past decades, advanced therapies have gained prominence and are increasingly being used for maintenance therapy for CD patients. The first-line advanced therapy for CD remission maintenance is anti-TNFα agents. Numerous reviews and meta-analyses have consistently confirmed the efficacy of anti-TNFα agents, including infliximab, adalimumab, and certolizumab, as maintenance treatment.[127,128] In the GEMINI 2 study, patients who received vedolizumab were more likely to achieve clinical remission at 52 weeks than those who received placebo, the remission rates were 39.0% and 36.4% for patients receiving vedolizumab every 8 weeks and 4 weeks, respectively, compared with 21.6% in patients in the placebo group ($P<0.001$ and $P=0.004$).[111] Moreover, in the long-term extension study (GEMINI LTS), patients who received vedolizumab every 4 weeks and followed up for up to 152 weeks exhibited a clinical remission rate of 74%.[129] Additionally, in the VISIBLE 2 trial, patients receiving subcutaneous vedolizumab as maintenance treatment following IV induction therapy exhibited significant clinical remission compared with those receiving placebo (48% for vedolizumab vs. 34.3% for placebo, $P=0.008$) at week 52.[130]

In the IM-UNITI trial, ustekinumab ensured the maintenance of clinical remission in patients who exhibited a clinical response at week 8 after receiving IV ustekinumab induction treatment.[110,131] At week 44, the remission rates were 53.1% and 48.8% for patients receiving injections every 8 weeks and every 12 weeks, respectively, compared with 35.9% in patients in the placebo group ($P=0.005$ and $P=0.04$, respectively). During the long-term follow-up period of up to 5 years, the remission rates were 54.9% and 45.2% for patients receiving injections every 8 weeks and every 12 weeks, respectively.[132] The effectiveness of risankizumab was demonstrated in the FORTIFY trial; patients who exhibited a clinical response to IV risankizumab in the ADVANCE or MOTIVATE induction studies were enrolled into a maintenance study and received subcutaneous risankizumab or placebo. The CDAI clinical remission rates were 55% and 52% for patients receiving 180 and 360 mg of risankizumab, respectively, compared with 41% for those receiving a placebo ($P=0.003$ for 180 mg and $P=0.005$ for 360 mg compared with placebo). Subcutaneous risankizumab was demonstrated to be effective in maintaining remission.[133] As the treat-to-target concept becomes increasingly implemented for disease monitoring and with a growing emphasis on the tight control of IBD activity, TDM for biologics is a crucial aspect of precision medicine. Reactive TDM algorithms have been proposed, and emerging evidence supports the clinical application of a proactive TDM strategy for prolonging the effectiveness of biologics and improving clinical outcomes, particularly in pediatric patients.[134]

In the maintenance trial of upadacitinib (U-ENDURE), a higher percentage of patients receiving either 15 mg (37.3%) or 30 mg (47.6%) of upadacitinib achieved clinical remission compared with those receiving placebo (15.1%). Additionally, a higher percentage of patients receiving either 15 mg (27.6%) or 30 mg of upadacitinib (40.1%) demonstrated an endoscopic response compared with those receiving compared with those receiving placebo (7.3%; $P<0.001$ for all comparisons).[113]

Statement 5.3.3
The combination of infliximab and thiopurine is effective and safe as a maintenance treatment for CD patients.

In the SONIC trial, the combination therapy of infliximab and thiopurine was more effective than monotherapy with either infliximab or thiopurine. At week 26, the rate of steroid-free clinical remission was 56.8% in the combination group compared with 44.4% in the infliximab alone group ($P=0.02$) and

30% in the AZA alone group ($P<0.001$).[108] In the DIAMOND trial, adalimumab monotherapy and combination therapy exhibited comparable efficacy at week 26, with clinical remission rates of 68.1% and 71.8%, respectively ($P=0.63$). However, the combination group exhibited greater endoscopic improvement at week 26 (84.2% vs. 63.8%, $P=0.019$).

The AGA technical review for the medical management of moderate-to-severe CD[135] suggested that combination therapy with adalimumab and thiopurines may be superior to adalimumab monotherapy for mediating and sustaining remission. However, this conclusion has very low certainty of evidence due to the risk of bias in the DIAMOND trial (open-label study and a very high rate of discontinuation due to treatment intolerance). The advantages of the combination of vedolizumab or ustekinumab with thiopurines or MTX over biologic monotherapy for remission induction and maintenance remain uncertain. This uncertainty is attributed to the lower immunogenicity relative to anti-TNFα therapies.

Statement 5.3.4
The pros and cons of de-escalation have to be explained and discussed with patients, and close monitoring after de-escalation is strongly recommended.

The considerable financial burden and potential adverse effects of therapy prompt patients in remission to consider drug de-escalation to reduce treatment intensity.[136] Because of the chronic nature of CD, the timing and approach to discontinuing combination therapy or monotherapy are of paramount importance. In a questionnaire survey, patients and physicians in the United States and Europe were found to tend to discontinue immunomodulatory more often than anti-TNFα or biologic therapy, which was driven by concerns regarding cancer risk from long-term radiation exposure and adverse effects.[137] Despite this, the standard practice still involves the continued administration of anti-TNFα therapy. However, for select patients with a low risk of recurrence, discontinuing anti-TNFα might be considered to mitigate costs and minimize side effects.[138] A meta-analysis of 27 studies that evaluated the relapse rate after the cessation of anti-TNFα therapy for CD revealed an overall risk of 44% for CD relapse (95% CI, 36%–51%; $I^2=79\%$; 912 patients).[139] Furthermore, another study revealed that 67% of patients with IBD who discontinued anti-TNFα therapy remained in clinical remission over the 12-month follow-up, 85% of whom exhibited sustained endoscopic remission.[140] Discontinuation of immunomodulators as monotherapy for CD led to relapse rates of approximately 30% within 2 years and 50%–75% within 5 years.[141] In a Taiwanese observational study involving 54 patients with CD, 59% experienced relapse within a year after discontinuing adalimumab treatment.[142] Additionally, in the VIOLET study in Taiwan, the relapse rates were 36.7% and 64.3% in patients with CD and 42.9% and 52.4% in patients with UC at 6 and 12 months after vedolizumab discontinuation, respectively.[143]

In general, the discontinuation of advanced therapy is associated with a risk of relapse, indicating the importance of careful consideration before making such decisions. Unless due to reimbursement issues in Taiwan or other economic factors, determining de-escalation based on noneconomic factors should involve shared decision-making between patients and healthcare providers. Additionally, close monitoring after the de-escalation is strongly recommended for the prompt identification of any signs of disease relapse.

4) Other Treatment Considerations

Statement 5.4
Level of agreement: Strongly agree, 64.3%; agree, 35.7%; disagree, 0.0%.

Statement 5.4.1
Surgical resection could be a primary treatment option for isolated ileocolic CD.

For some patients with CD, surgical intervention is a primary treatment option. A randomized controlled, multicenter, open-label trial (LIR!C Trial) investigated laparoscopic ileocecal resection for CD affecting the terminal ileum (<40 cm of diseased bowel) in patients who did not respond to conventional therapy. The study revealed that laparoscopic ileocecal resection is cost-effective and leads to quality of life improvement. This approach is a viable alternative to infliximab therapy for ileocecal CD.[144,145]

Statement 5.4.2
A multidisciplinary approach is highly recommended for severe active CD.

In 2018, the ECCO and the European Society of Coloproctology jointly released consensus guidelines regarding the surgical management of CD.[146] The guidelines outline a systematic approach to treating severe CD, addressing various clinical scenarios that necessitate emergency surgery, such as perfora-

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tion, peritonitis, and massive hemorrhage, which occur in approximately 6%–16% of patients with CD. To ensure appropriate management, patients with severe active disease should be regularly monitored for clinical signs and should undergo blood tests and assessments of signs of systemic toxicity. Given the complexity of the disease, a single preoperative assessment for severe active CD may not suffice for determining the appropriate surgical intervention. Conducting repeated evaluations with a radiologist interpreting preoperative images and performing thorough examinations of postoperative specimens with the assistance of a pathologist are essential Additionally, perioperative nutrition support can contribute to improved surgical outcomes.[90,91,147] Adopting a multidisciplinary approach involving gastroenterologists, a colorectal surgeon, and other relevant specialists is crucial for enhancing the outcomes of patients with CD.

6. Monitoring

Statement 6.1
Patient-reported outcomes are strongly correlated with well-being and should be monitored regularly throughout the course of treatment for CD. Level of agreement: Strongly agree, 71.4%; agree, 28.6%; disagree, 0.0%.

Patient-reported outcomes can reveal unexpressed concerns[148] and enhance the safety and efficacy of medical interventions.[149,150] The IBD Disk has 10 key domains: abdominal pain, body image, education and work, emotions, energy, interpersonal interactions, joint pain, bowel regulation, sexual functions, and sleep patterns.[151] Early and regular assessments of patient-reported outcomes, such as IBD Disk, should be conducted to monitor the progression of CD over time.[152]

Statement 6.2
Level of agreement: Strongly agree, 67.9%; agree, 32.1%; disagree, 0.0%.

Statement 6.2.1
Hemograms, albumin, CRP/ESR, and/or fecal calprotectin can be used to assess gut inflammation and disease severity in CD.

Serum markers such as CRP and ESR along with fecal markers such as calprotectin are valuable for assessing disease activity, monitoring the treatment response, and predicting relapse in CD.[153-155] The CALM study demonstrated that implementing tight control management with objective biomarkers could effectively reflect CD activity and guide treatment adjustments.[33,117] Achieving symptom relief and the normalization of biomarkers, such as CRP and fecal calprotectin, is a short- to intermediate-term goal.[152] Nonetheless, these markers should be interpreted based on the specific clinical circumstances of patients.[155]

Statement 6.2.2
Fecal calprotectin is useful for evaluating treatment response and predicting clinical relapse in CD.

The fecal calprotectin level is closely associated with the inflammatory state observed during endoscopy in patients with CD, and achieving the normalization of fecal calprotectin is associated with a reduction in the risk of CD progression.[156,157] A post hoc analysis in the CALM study revealed that a fecal calprotectin cutoff of < 250 μg/g serves as a valuable surrogate marker for mucosal healing in CD.[158] Additionally, fecal calprotectin is regarded as a noninvasive biomarker of the achievement of the intermediate treatment goal in the STRIDE II recommendation.[152]

Statement 6.3
Level of agreement: Strongly agree, 67.9%; agree, 32.1%; disagree, 0.0%.

Statement 6.3.1
Mucosal healing is associated with better clinical outcomes. Periodic endoscopy is the gold standard for the assessment of mucosal healing.

Mucosal healing is a crucial treatment goal for patients with CD due to its significant impact on long-term prognosis. Mucosal healing is associated with sustained remission, reduced rates of relapse, reduced hospital admission, and a decreased need for surgery.[159-162] Patients who achieve mucosal healing, along with clinical and biomarker remission, exhibit a higher probability of remaining disease-free compared with those with persistent mucosal inflammation.[161] Additionally, in early-stage CD, mucosal healing serves as a predictor of sustained remission, and it may be associated with a reduced likelihood of hospitalization and surgery.[162] Therefore, mucosal healing is a pivotal treatment target in CD management, and it is recommended as a long-term target in the STRIDE II guidelines.[152]

Statement 6.3.2
Reassessment with endoscopic and/or cross-sectional imaging should be considered in cases of relapse, refractoriness, new symptoms, or when surgery is considered.

Systematic assessment with ileocolonoscopy is recommended within 6–12 months of treatment.[12,163] When endoscopy is not feasible, cross-sectional imaging is an alternative approach. Among imaging modalities, IUS is an excellent choice for monitoring therapeutic responses because of its noninvasiveness, cost-effectiveness, and safety profile.[33,164]

Statement 6.3.3
Endoscopic evaluation is recommended 6–12 months after surgery to diagnose postoperative recurrence in order to guide treatment decisions.

Endoscopy is the gold standard for monitoring recurrence in the postoperative setting.[165] Endoscopic examinations should be performed within 6–12 months after surgery.[32] Rutgeerts score can aid in predicting postoperative recurrence and can guide treatment decisions.[166,167]

Statement 6.4
Transmural disease activity can be assessed with CTE, MRE, or IUS, which is adjunctive to endoscopic assessment. Due to concerns about radiation, MRE or IUS is preferred. Level of agreement: Strongly agree, 67.9%; agree, 32.1%; disagree, 0.0%.

Transmural healing is an indicator of symptom relief in patients with CD.[151] Because CD is a transmural inflammatory disease, endoscopic healing solely may not accurately reflect inflammation control throughout all layers. Therefore, studies have demonstrated that transmural healing, as observed through cross-sectional imaging, yields more favorable outcomes than relying solely on endoscopic findings.[168] However, due to the lack of a consensus on the standard definition of transmural healing and the absence of cost-benefit analyses, transmural healing is currently considered a potential future target rather than a formal target for CD monitoring.

7. Surgery

Statement 7.1
The major role of surgery in CD is to treat medical failure and/or complications, such as fistulization, fibrotic stricture, perforation, massive bleeding, cancer and failure to thrive. Level of agreement: Strongly agree, 71.4%; agree, 28.6%; disagree, 0.0%.

When medical interventions are ineffective, surgery is often recommended to address complications and improve patient quality of life.[169] However, considerable controversy and inconsistency exist regarding the management of multifocal disease.[170]

Statement 7.2
Perioperative nutritional support should be considered and provided. Level of agreement: Strongly agree, 75.0%; agree, 25.0%; disagree, 0.0%.

After proctocolectomy or colectomy, patients with CD must receive adequate water, electrolytes, and nutrition.[91] Appropriate nutrition can effectively alleviate inflammation, which can lead to reduced complications and mortality rates among patients with CD.[90,147]

Statement 7.3
Parenteral nutrition and/or enteral nutrition can reduce postoperative complications in CD. Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

When addressing the nutritional requirements of patients unable to receive sufficient oral intake, enteral nutrition is prioritized over parenteral nutrition.[91] If enteral nutrition alone cannot meet more than 60% of a patient's energy needs, a combination of enteral and parenteral nutrition may be necessary.[91] In acute inflammatory and gastrointestinal dysfunction cases, parenteral nutrition can serve as an alternative. However, for disease relapse or in the remission phase, enteral nutrition is prioritized.[90]

Statement 7.4
Prednisolone at dosages greater than 20 mg daily or the equivalent for more than 6 weeks is a risk factor of surgical complications. Therefore, patients should be weaned off corticosteroids, if possible. Level of agreement: Strongly agree, 71.4%; agree, 28.6%; disagree, 0.0%.

Since the 1950s, oral corticosteroids have been the primary treatment for flare-ups in patients with CD to achieve remission. However, their prescription requires careful consideration to prevent potential side effects. The prolonged use of prednisolone at a daily dose exceeding 20 mg for more than 2 weeks can increase the risk of infection.[171] Additionally, the use of perioperative/preoperative steroids may increase the risk of complications, including both infectious and noninfectious complications, such as intra-abdominal sepsis.[172-174]

Statement 7.5
Regional ileocolic septic conditions resembling CD found at operation, such as appendix vermiformis, should not rou-

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tinely be resected. Level of agreement: Strongly agree, 50.0%; agree, 50.0%; disagree, 0.0%.

The appendix is crucial in preserving intestinal homeostasis in individuals with CD. Studies on postoperative cohorts have highlighted its strong association with CD development, suggesting that appendectomy exacerbates the prognosis.[175] Although the study cohorts in Sweden and Denmark showed the increased risk of CD after an appendectomy is probably associated with diagnostic bias, there is a large cohort with 212,218 patients with appendectomy before age 50 years studies suggest the risk of CD increased after an appendectomy.[176,177] Furthermore, a recent meta-analysis in 2023 demonstrated a significant risk of developing CD following an appendectomy and persisted 5 years postoperatively.[178] Therefore, appendectomy should be avoided during this period to mitigate adverse outcomes. In addition, explore the terminal ileum to define the possible CD that would be more suitable during the operation.

Statement 7.6
Active small bowel CD with a concomitant abdominal abscess should preferably be managed with antibiotics and percutaneous or surgical drainage followed by delayed resection, if necessary. Level of agreement: Strongly agree, 71.4%; agree, 28.6%; disagree, 0.0%.

Patients with CD may develop abdominal abscesses unexpectedly, requiring percutaneous drainage as an alternative to surgery. This approach has been proven to be effective in mitigating abscesses or sepsis, thereby reducing postoperative complications and the risk of stoma formation.[179] However, a study of 36 patients with CD who underwent preoperative drainage revealed that 44.4% had postoperative morbidity, with 11.1% having anastomotic leak. Notably, patients requiring preoperative drainage before surgery demonstrated a higher rate of recurrent and penetrating disease as well as the need for preoperative total parenteral nutrition, suggesting that these patients have an elevated risk of postoperative complications.[180] Therefore, careful consideration of the optimal treatment strategy, including the need for delayed surgery, is essential, and an multidisciplinary team approach is strongly recommended.

Statement 7.7
Patients with an unsuspected diagnosis of CD after ileal pouch-anal anastomosis (IPAA) have high complication and failure rates. IPAA is not recommended for patients with CD. Level of agreement: Strongly agree, 85.7%; agree, 14.3%; disagree, 0.0%.

When considering IPAA for patients with CD, careful patient selection and counseling are crucial to minimize postoperative complications such as pelvic sepsis or pouch failure.[181] Patients with isolated colitis and no perianal disease are suitable candidates for this procedure.[182]

Statement 7.8
Medical prophylaxis and quitting smoking are crucial for reducing postoperative recurrence of CD. Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

Individuals who have undergone surgery must take proactive measures to reduce the risk of recurrence. A key measure is to quit smoking, as studies have demonstrated a significantly higher risk of both surgical recurrence and clinical recurrence of CD in smokers than in nonsmokers.[183-186] Another effective approach to preventing recurrence is medical prophylaxis with anti-TNFα or immunosuppressives (thiopurines), which has shown promising results in terms of reducing recurrence rates to 30.6% compared with 60% with placebo.[187-191] Although with less evidence compared with anti-TNFα, ustekinumab, and vedolizumab have also been reported to reduce endoscopic postoperative recurrence.[192,193]

8. Special Populations

1) Pregnant and Breastfeeding Women

Statement 8.1
Level of agreement: Strongly agree, 67.9%; agree, 32.1%; disagree, 0.0%.

Statement 8.1.1
Consultation before conception is recommended. Remission status is associated with better pregnancy outcomes.

Preconception consultation is a crucial step for all women of reproductive age with CD. The most effective and safest methods of birth control are long-acting and reversible (e.g., a hormonal or nonhormonal intrauterine device or a contraceptive implant). Having a comprehensive understanding of the impact of CD on pregnancy and planning for pregnancy is crucial, not only during pregnancy but also shortly after CD diagnosis. This knowledge helps women with CD make informed decisions about family planning.[3] According to findings from the PIANO registry, the use of corticosteroids during pregnancy is associated with an increased risk of various adverse out-

comes, including preterm birth, small-for-gestational-age infants, low birth weight, intrauterine growth restriction, and neonatal intensive care unit admission.[194] Moreover, corticosteroid use during the second or third trimester is associated with a higher risk of serious infections in infants before the age of 1 year. This indicates the importance of managing CD disease activity before and during pregnancy by using steroid-sparing therapies.[194]

Statement 8.1.2
Modification of treatments for CD is usually not necessary for pregnant and breastfeeding patients, except MTX and JAK inhibitors.

Flare-ups in pregnant women should be managed in adherence to current treatment guidelines applicable to nonpregnant patients, including 5-ASA, corticosteroids, immunomodulators, and biologic agents.[195] For pregnant women with active disease, thiopurine monotherapy or the combination of thiopurine and biologics can be continued throughout pregnancy, with the monitoring of serum anti-TNFα levels to guide treatment decisions. Concerns about fetal exposure to biologics exist; however, the discontinuation of biologics may increase the risk of relapse in pregnant women.[195] Notably, the findings from the PIANO registry revealed that the discontinuation of biologics in the third trimester was not associated with higher relapse rates at 4, 9, and 12 months postpartum.[196] The decision to discontinue biologics should be based on individual needs and should be thoroughly discussed with patients.[195] If a medication is discontinued before the third trimester, it should be resumed promptly after childbirth.[195] In previous studies on rheumatic diseases, MTX has been reported to have embryotoxic potential and is associated with a high risk of miscarriage.[197] Because MTX is contraindicated in pregnancy, both women and men are advised to discontinue MTX use 3 months before attempting to conceive as well as to avoid its use during pregnancy and breastfeeding.[197] Similarly, cyclosporin, metronidazole, and ciprofloxacin are also not recommended for breastfeeding mothers.[198] However, mesalamine, 5-ASA agents, and biologics are generally well tolerated during breastfeeding and can be safely continued.[199,200] Animal reproduction studies have suggested that upadacitinib may pose risks to fetal development. Therefore, women of reproductive age are advised to use effective contraception during upadacitinib therapy and for 4 weeks after its completion. Whether upadacitinib is present in breast milk remains unknown. Due to the potential for serious adverse reactions in breastfeeding infants, breastfeeding is not recommended during upadacitinib treatment and for 6 days after the last upadacitinib dose.[201]

Statement 8.1.3
Live-attenuated vaccines should be avoided before 6 months of age for infants who are exposed to *in-utero* biologics, and inactivated vaccines should be applied according to local regulations.

The ECCO guidelines on reproductive medicine and pregnancy recommend delaying live vaccination, including rotavirus vaccination, for at least 6 months in infants following the maternal use of biologic therapy during pregnancy.[202] A previous study revealed that infants who developed fatal disseminated BCG infection after vaccination had detectable levels of infliximab for up to 1 year after antenatal exposure.[195] The European Medicines Agency recommends avoiding live-attenuated vaccines during the first year of life in infants exposed to infliximab. Furthermore, the AGA guidelines suggest refraining from administering live vaccines within the first 6 months of age if the mother was exposed to any biologic therapy other than certolizumab during the third trimester of pregnancy.[203]

2) Pediatric Patients

Statement 8.2
Level of agreement: Strongly agree, 71.4%; agree, 28.6%; disagree, 0.0%.

Statement 8.2.1
EEN is recommended as the first-line induction therapy for children with active mild-to-moderate luminal CD, and the CDED plus PEN may serve as an alternative with better tolerance.

Meta-analyses have increasingly supported EEN as the first-line induction regimen for children with active mild-to-moderate CD.[204,205] A cross-sectional survey of 85% of specialist IBD centers in the United Kingdom revealed that polymeric feeds were used as the first-line therapy in every center, and EEN was typically recommended for 6 weeks by 70% of these centers.[206] EEN offers numerous benefits to patients, including higher remission rates (up to 80%), avoidance of steroids, correction of malnutrition and micronutrient deficiencies, and promotion of adequate growth and improved quality of life. However, EEN has some disadvantages such as low palatability, a high risk of early withdrawal, high costs related to elemental diets, and potential adverse effects (mostly diarrhea and vomiting).[207] The CDED, which combines a whole-food diet

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with PEN, was reported to be as effective as EEN for inducing remission at week 6, with superior tolerability (97.5% compared with 73.6% for EEN; $P=0.002$). Additionally, by week 12, a higher percentage of children treated with CDED plus PEN (75.6%) achieved corticosteroid-free remission compared with those treated with EEN alone (45.1%) and PEN alone ($P=0.01$; OR, 3.77; 95% CI, 1.34–10.59).[208]

Statement 8.2.2
Long-term use of corticosteroids should be avoided, and children's growth curves should be monitored.

Currently, the approved treatments for mediating remission in pediatric IBD patients include corticosteroids, EEN, CDED plus PEN, MTX, and anti-TNFα agents.[209] Corticosteroids are considered the first-line therapy for mediating remission in pediatric patients with moderate-to-severe active CD, but they are not typically used as maintenance therapy. A meta-analysis that compared the efficacy of EEN and corticosteroids did not reveal a significant difference in remission induction (OR, 1.35; 95% CI, 0.90–2.10; $P=0.14$). However, EEN was found to be superior to corticosteroids for achieving short-term improvement in mucosal inflammation and the reduction of PCDAI.[210] Immunomodulators are often included in the regimen for maintaining remission. The monitoring of growth curves is recommended.

3) Cancer Patients

Statement 8.3
All CD patients with a history of cancer should be managed with multidisciplinary support. Thiopurines and anti-TNFα agents should be avoided for CD patients with a history of nonmelanoma skin cancer (NMSC). Level of agreement: Strongly agree, 75.0%; agree, 25.0%; disagree, 0.0%.

Immunosuppressive treatment is associated with reduced rates of new or recurrent cancer in patients with IBD who have experienced significant inflammation for 3 or more years.[211] The use of biologics or anti-TNFα is not associated with cancer occurrence in patients with CD.[212-215] In patients with a history of cancer, including gastrointestinal, dermatologic, hematologic, and solid tumors, the risk of subsequent cancer did not differ between groups treated with vedolizumab or ustekinumab and groups without exposure to immunosuppressive agents.[212] Similarly, in patients with a prior nondigestive malignancy, the risk of incident cancer did not vary between groups with vedolizumab treatment and anti-TNFα therapy.[213] However, caution should be exercised when considering thiopurine and anti-TNFα therapy for patients with a history of NMSC.[216-218] The prolonged use of thiopurine (adjusted OR, 4.27; 95% CI, 3.08–5.92) or the persistent use of anti-TNFα therapy (adjusted OR, 2.18; 95% CI, 1.07–4.46) in patients with IBD is associated with a higher risk of NMSC development and recurrence.[217] Notably, evidence regarding the increased incidence of non-Hodgkin's lymphoma resulting from thiopurine or anti-TNFα treatment has primarily been obtained in Caucasian populations, with limited data available for Asian populations. Therefore, the impact of differences in ethnicity should be considered in the assessment of incidence rates of malignancies in the future.[219] Comprehensive support from gastroenterologists and oncologists is crucial for managing patients with IBD having a history of cancer, and healthcare providers must be aware of the potential impact of immunosuppressants on cancer risk.[216]

4) Elderly Populations

Statement 8.4
Elderly patients with CD have a higher risk of serious adverse events associated with prolonged use of corticosteroids, thiopurines, or anti-TNFα agents. Level of agreement: Strongly agree, 89.3%; agree, 10.7%; disagree, 0.0%.

In contrast to patients diagnosed as having IBD at a younger age, those with onset in older age exhibit distinct disease characteristics, clinical presentations, natural history, and baseline immunosenescence.[220] Elderly patients with CD commonly present with rectal bleeding, whereas symptoms such as abdominal pain, fever, and weight loss are less prevalent in elderly patients than in younger patients who often have more involvement of the ileum.[221] Current evidence suggests that elderly patients are at a higher risk of adverse events due to the prolonged use of corticosteroids than younger adults.[221] Thiopurines should be prescribed for elderly patients with caution due to concerns regarding potential drug interactions, an elevated risk of lymphoma, NMSC, and serious infection.[221] Additionally, elderly patients with IBD often have a higher burden of comorbidities than younger adults, and effectively managing these comorbid conditions can mitigate the potential risks associated with IBD. Immunomodulatory treatments with a lower overall risk of infection or malignancy, such as anti-integrin, anti-IL-12/-23, or anti-IL-23 antibodies, may be more suitable for elderly patients.[222,223]

9. Cancer Surveillance

Statement 9.1
Patients with CD are at increased risk of bowel neoplasia. Regular cancer surveillance, including biopsy as needed, should be undertaken. Level of agreement: Strongly agree, 82.1%; agree, 17.9%; disagree, 0.0%.

A meta-analysis of 26 observational studies (n = 531,449 patients with IBD) revealed higher risks of both small bowel cancer and colorectal cancer (CRC) in patients with CD.[224] A recent review highlighted that the standardized incidence ratio (SIR) for small bowel cancer was 22.01 (95% CI, 9.10–53.25), and that for CRC was 2.08 (95% CI, 1.43–3.02), with a notable prevalence of anorectal cancer reported in Asian countries compared with Western countries.[225] The CD is associated with an increased risk of extraintestinal cancers (IRR, 1.43; 95% CI, 1.26–1.63), affecting various sites throughout the body.[225] In patients with CD, small bowel neoplasms primarily manifest as adenocarcinomas that typically develop in inflamed segments.[216] In a meta-analysis of 33 studies, the prevalence of small bowel adenocarcinoma (SBA) in patients with CD was estimated to be 1.15 per 1,000 patients (95% CI, 0.31–2.33), with only 11% of patients exhibiting observable radiological features. Notably, CD-associated SBA predominantly arises in the ileum (84%) in contrast to de novo SBA which primarily occurs in the duodenum. CD-related SBA is often diagnosed in stage 2 (36%), with common symptoms including obstruction, weight loss, and abdominal pain.[226] Fistulizing disease and long-standing CD are risk factors for small bowel cancer in patients with CD.[227] In addition to small bowel cancer, patients with CD are at an increased risk of various malignancies affecting the gastrointestinal tract, breast, lung, urinary system, and bladder as well as lymphoma (particularly non-Hodgkin's lymphoma) and NMSC compared with the general population.[228] Patients with CD exposed to thiopurines exhibit a higher risk of NMSC, with squamous cell and basal cell skin cancers being the most common types.[229,230]

Patients with CD exhibit a notably increased risk of postcolonoscopy CRC (RR, 3.82; 95% CI, 2.94–4.96) compared with individuals without IBD; particularly, those with missed rectal lesions exhibit the highest risk.[231] Additionally, patients with IBD at a high risk of CRC often have a poor prognosis, with low overall survival rates.[232] A meta-analysis conducted by Canavan et al. (n = 11,840)[233] demonstrated that the RR of CRC in patients with CD was 4.5 (95% CI, 1.3–14.9), with a cumulative CRC risk of 2.9% (95% CI, 1.5–5.3) at 10 years after the first diagnosis. In a nationwide register-based Danish–Swedish cohort (n = 47,035), the incidence of CRC upon diagnosis was higher among patients with CD (0.82 per 1,000 person-years) than in the referenced general population (0.64 per 1,000 person-years), with an overall adjusted hazard ratio (HR) of 1.4 (95% CI, 1.27–1.53).[234] Furthermore, in a study of 2,621 patients with IBD (1,108 CD and 1,603 UC) from Hong Kong, the risk of anorectal cancer was high among patients with CD (SIR, 4.11; 95% CI, 1.84–9.14).[235]

The presence of pediatric-onset IBD provides strong epidemiological evidence for overall cancer development and moderate evidence for CRC.[236] Despite the rarity of pediatric-onset IBD incidence, intestinal carcinoma, particularly CRC, is the most frequently reported fatal malignancy in this population.[237]

The incidence of CRC in patients with CD may be associated with various factors including disease duration, extent of disease, comorbidities such as primary sclerosing cholangitis, family history, and early onset of CD.[238] Physicians should be aware of the increased risk of the aforementioned cancers in patients with CD and should conduct regular cancer surveillance, such as biopsies, as deemed necessary.

Statement 9.2
The persistence of chronic fistulas in long-standing CD has been identified as a potential risk factor of malignant transformation of fistula. Level of agreement: Strongly agree, 71.4%; agree, 28.6%; disagree, 0.0%.

A meta-analysis of 20 studies spanning from 1965 to 2008 and involving 40,547 patients revealed a notable association between fistulas in patients with CD and the onset of carcinomas, with an incidence rate of 0.2 per 1,000 patient-years among patients with CD.[239] A systematic review of studies from 1950 to 2008 investigated 61 patients with CD having perianal fistulas. Among these patients, 61% were female, and their mean age at the initial diagnosis of cancer was significantly lower than that of male patients. Additionally, female patients exhibited a shorter average duration of CD and fistula before the detection of cancer compared with male patients.[240] In a clinical trial involving 430 patients with CD, the prevalence of perianal disease was 40.2%, with fistulas (78.6%) and abscesses (60.7%) being the most common indications. The development of these conditions was associated with the involvement of the rectum and extraintestinal manifestations. Patients with perianal disease often receive treatment with immunosuppressants and biologics, obviating the need for abdominal surgery.[241] Because fistula-related cancer does not present specif-

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ic signs and symptoms, its diagnosis is often delayed, resulting in poor prognosis. Therefore, regular surveillance for anorectal carcinoma and routine biopsy are recommended for the management of patients with perianal disease.[216]

Statement 9.3
The risk of lymphoma and NMSC of CD patients treated with thiopurines is higher. Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

A nationwide population-based study in Taiwan revealed that patients with CD were at a higher risk of hematological malignancies (SIR, 14.08; $P<0.01$), non-Hodgkin's lymphoma (SIR, 14.29; $P<0.01$), and leukemia (SIR, 19.23; $P<0.01$), particularly within the first year following diagnosis. However, the overall incidence of cancer, including NMSC, did not significantly increase. Notably, the use of immunomodulators was not associated with a higher incidence of hematological malignancies among patients in Taiwan compared with those who did not receive such treatment.[9] In Japanese patients with IBD treated with thiopurines or anti-TNFα, evidence supporting the increased risk of non-Hodgkin's lymphoma is lacking,[219,242] although an increased incidence of NMSC was noted in this population.[219] Differences in the risk of lymphoma due to thiopurines between Caucasian and Asian populations may result from racial factors rather than from differences in the drug dosage or duration.[219] In a study involving 10,777 pediatric patients with IBD, 5 patients developed lymphoma in the follow-up year, of whom 4 received thiopurine treatment. None of the patients were prescribed anti-TNFα agents.[243] Recent investigations have failed to establish an association between an increased risk of lymphoma and the use of anti-TNFα monotherapy. However, patients exposed to thiopurines or combination therapy were observed to have a higher risk of lymphoma.[244]

10. Management of Complications

1) Fistulas

Statement 10.1
Infliximab, adalimumab, surgical treatment, or combined treatment can be used to treat anorectal fistulas in CD. Level of agreement: Strongly agree, 75.0%; agree, 25.0%; disagree, 0.0%.

Various treatment modalities are available for managing complex perianal fistulas in CD, including advancement flaps, ligation of the inter-sphincteric fistula tract, and fibrin glue, but their efficacy is limited. Complicated ano- and rectogenital fistulas related to CD warrant treatment by experienced multidisciplinary teams.[95,245] Although antibiotics are recommended for controlling perianal sepsis, evidence supporting antibiotic monotherapy for perianal fistula closure is lacking.[95] Patients with concurrent fistulas and abscesses are not recommended to undergo endoscopic balloon dilation due to the potential disruption of nearby fistula tracts or abscesses during the procedure.[246] Because moderate-to-severe fistulizing CD is rare and difficult to treat, an approach involving medical and surgical management should be considered.[247] Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) have shown promising results for treating complex perianal fistulas in CD.[248] In a randomized placebo-controlled trial, 52-week treatment with Cx601 had long-term efficacy and safety in patients with CD.[249] Although the treatment options for patients with CD with complex perianal fistulas are limited, darvadstrocel, a novel minimally invasive therapy, is recommended in case of inadequate responses of fistulas to ≥1 conventional treatment or biologic therapy.[250] Additionally, the combination of surgical and medical therapy, such as anti-TNFα or immunomodulators, may yield more favorable outcomes for perianal fistula healing in patients with CD than surgery or medical therapy alone.[251]

2) Stenosis

Statement 10.2
Level of agreement: Strongly agree, 85.7%; agree, 14.3%; disagree, 0.0%.

Statement 10.2.1
Intestinal strictures can be assessed with cross-sectional imaging and endoscopy.

Strictures are common complications in CD and result from complex processes involving inflammation and fibrosis. Distinguishing between the levels of active inflammation and the extent of fibrosis within strictures by using current techniques is challenging. Currently, no reliable technique is available for the accurate determination of the extent of intestinal fibrosis in CD.[32,252] Cross-sectional imaging modalities such as IUS, CTE, and MRE are promising tools for the diagnosis of bowel strictures in patients with CD.[253]

Statement 10.2.2
Anti-inflammatory therapies, including corticosteroids, immunosuppressive drugs, and biologic agents, should be

considered for stenoses with an inflammatory component.

More than one-third of patients with CD exhibit a unique fibrostenosing phenotype, characterized by the progressive narrowing of the intestinal lumen due to fibrosis.[141] Although no specific treatment exists for fibrotic intestinal strictures, patients with CD are recommended to undergo assessments to determine the extent of the inflammatory component in the stricture.[141] Both cross-sectional imaging studies and biomarkers such as CRP, ESR, and fecal calprotectin can be used to assess the inflammation level.[254] Anti-inflammatory therapies, including corticosteroids; immunosuppressive medications, such as thiopurines and MTX; and biologic agents, may alleviate inflammatory lesions and other related symptoms. However, they cannot directly prevent or reverse substantial intestinal fibrosis and strictures.[141] In a clinical investigation, approximately 39% of patients with CD having stenosis who received anti-TNFα therapy underwent abdominal surgery in the subsequent year, with a surgery incidence rate of 1.8 per 1,000 person-months.[255] In a retrospective study of 262 patients with CD, infliximab (54%) or adalimumab (46%) treatment demonstrated effectiveness in 87% and 73% of patients, respectively, over 6 and 12 months; this finding highlights the advantages of early intervention with medication in terms of treatment success.[256] In a multicenter, prospective, observational study evaluating the efficacy of adalimumab in patients with CD and symptomatic small bowel strictures, almost two-thirds of the patients achieved treatment success by week 24 of adalimumab treatment. Furthermore, more than half of the patients remained surgery-free 4 years after treatment.[257] Moreover, combination therapy with anti-TNFα agents has been demonstrated to be effective in preventing therapeutic failure in patients with CD (HR, 0.17; 95% CI, 0.4–0.71; $P=0.015$).[258]

Statement 10.2.3
Endoscopic and surgical interventions are treatment options for symptomatic fibrotic strictures.

Endoscopic balloon dilation is the first-line therapy for short strictures (typically defined as those ≤5 cm) in patients with CD.[254] Strictureplasty and resection are also viable alternative treatment options.[141,259] A systematic review of 33 studies involving a total of 1,463 patients revealed that endoscopic dilation was technically successful in 90% of cases, with a subsequent possibility of re-dilation in 73.5% of cases and surgical intervention in 42.9% of cases within 24 months.[259] Moreover, strictures with a length of ≤5 cm were significantly associated with surgery-free outcomes (HR, 2.5; 95% CI, 1.4–4.4).[141] Two prospective studies involving 95 and 35 patients with CD, respectively, demonstrated that endoscopic balloon dilatation conducted using balloon-assisted enteroscopy yielded technical success rates of >90%.[260,261] Endoscopic dilation and strictureplasty are contraindicated for stenoses associated with abscesses, phlegmons, fistulas, high-grade dysplasia, and malignancy.[141]

Patients with IBD and colonic strictures exhibit a higher risk of neoplasms due to the potential obstruction from strictures for colonoscopy screenings, which may hinder the early detection of colon cancer.[262] When endoscopic treatment is unfeasible or medical therapy fails or is contraindicated, resection is recommended.[254] Early surgical resection is suggested for patients with symptomatic strictures, ileocecal CD without signs of inflammation, or strictures >5 cm in length.[141,259,263] Timely identification and isolation of localized ileocecal disease in high-risk patients at diagnosis can prevent complications, reduce clinical recurrence rates, and reduce remission durations compared with patients receiving prolonged medical treatment.[141] The rate of emergency surgery was 6.7% within 5 years of diagnosis and 8.8% within 15 years, with the overall risk of surgical recurrence being 35.9%.[264] Strictureplasty is a viable option for cases involving fibrotic strictures.[265] Resection of the affected bowel segment can render postoperative medical therapy more effective, thereby reducing the requirement for biologic therapy among patients with limited ileocecal CD.[262,266]

3) Anemia and Micronutrient Deficiency

Statement 10.3
Level of agreement: Strongly agree, 78.6%; agree, 21.4%; disagree, 0.0%.

Statement 10.3.1
Anemia can affect quality of life. Therefore, the etiology of anemia should be worked up and corrected.

Patients with CD may present with various types of anemia caused by several conditions, including iron deficiency anemia (IDA), anemia of chronic disease, and micronutrient deficiency-associated anemia. Among these, IDA remains the predominant type in patients with IBD and can be differentiated from anemia of chronic disease based on the ferritin level of <100 μg/L when CRP levels are elevated.[267] Platelet counts also serve as an indicator of disease severity in patients with CD. A univariate analysis revealed a positive correlation be-

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tween the CD activity index and platelet count ($P<0.001$).[268] In a cohort of 72,026 patients discharged from the index hospitalization for CD, 8.1% presented with IDA, with a prolonged hospital stay (4 days, interquartile range 2–6 days vs. 3 days, interquartile range 2–5 days; $P<0.001$) compared with those without IDA.[269] In a recent study in Taiwan, the identified risk factors for persistent anemia were low body mass index, corticosteroid usage, thiopurine usage, colectomy, and small bowel resection after IBD diagnosis.[270] Patients with IBD who were anemic exhibited higher rates of hospital admission ($P<0.01$) and mortality ($P<0.01$). IDA adversely affects quality of life by causing fatigue; reduced physical performance; dizziness; headaches; dyspnea upon exertion; and pallor of the skin, nails, and conjunctiva.[267] Persistent inflammation in the intestinal mucosa leads to blood loss from the gastrointestinal tract, malabsorption, and iron deficiency.[271] In addition to microcytic anemia caused by IDA, macrocytic anemia caused by vitamin B_{12} and folate deficiencies is common in patients with CD, and it is associated with hematological and neurological abnormalities and a high risk of thrombosis.[272] Therefore, to treat anemia, appropriate dietary adjustments are recommended to rectify existing deficiencies, and iron and micronutrient supplementation should be provided when necessary.

Statement 10.3.2
Attention should be paid to micronutrient and electrolyte imbalances, especially after surgery for CD.

Micronutrient and electrolyte deficiencies are vital concerns requiring careful monitoring post-surgery in patients with IBD. A study reported that 39.0% of patients with IBD and intestinal Behcet's disease had deficiencies of micronutrients, with patients with CD constituting 83% of this deficiency group.[273] The prevalence of vitamin B_{12} deficiency among patients with CD was reported to be 15.6% (95% CI, 9.7%–20%), with 22.2% (95% CI, 16%–28%) exhibiting folic acid deficiency. Notably, in all patients with anemia, resolution occurred following supplementation with vitamin B_{12} or folic acid.[272] Ileal resection in patients with CD and bowel surgery in patients with IBD pose high risks for micronutrient deficiency, such as impaired absorption of vitamin B_{12} and folic acid and reduced levels of vitamin D and ferritin. Close monitoring with adequate supplementation is essential to avoiding complications associated with micronutrient deficiencies.

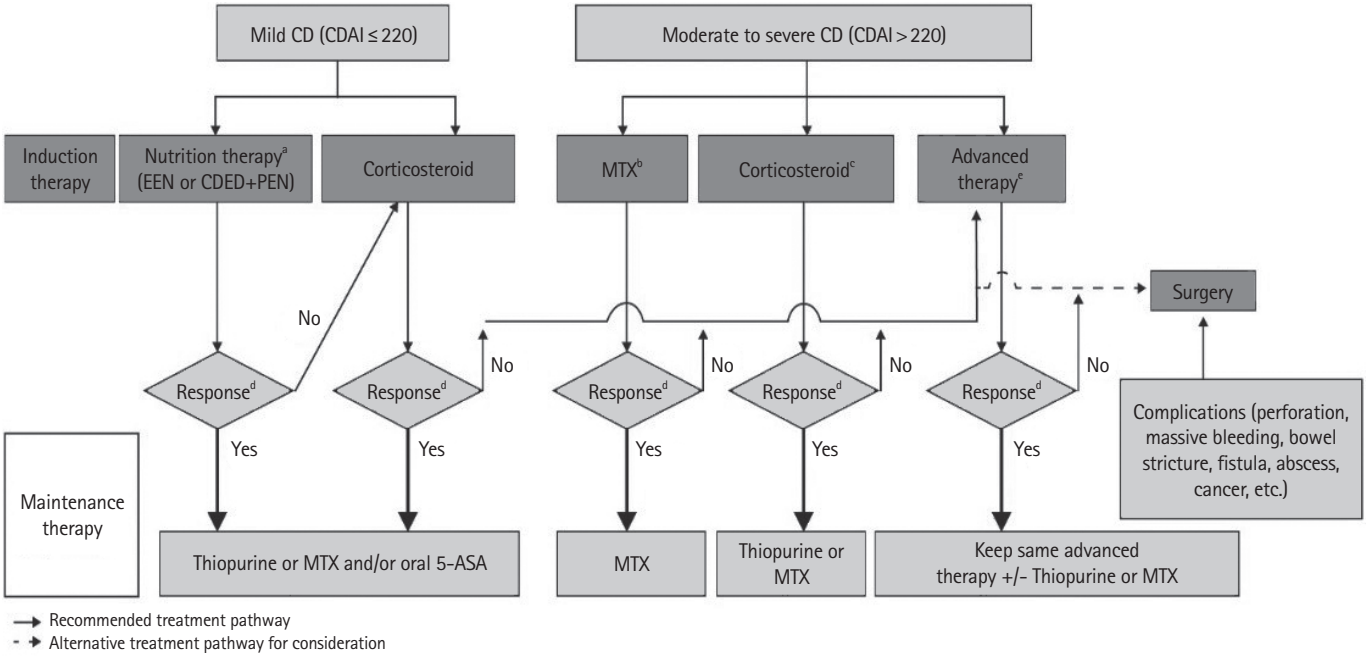

Fig. 1. A recommended algorithm for Crohn's disease (CD) treatment. [a]The majority of the studies showing the efficacy of inducing remission are conducted in the pediatric population. However, the evidence in adults is insufficient; [b]SC or IM 25 mg/wk; [c]0.5-1.0 mg/kg (max dose 60 mg/day, max duration 28 days); [d]Remission definition CDAI < 150; [e]Advanced therapeutics include infliximab, adalimumab, ustekinumab, risankizumab, and upadacitinib. CDAI, Crohn's Disease Activity Index; EEN, exclusive enteral nutrition; CDED, Crohn's disease exclusion diet; PEN, partial enteral nutrition; MTX, methotrexate; 5-ASA, aminosalicylates.

CONCLUSIONS

The guidelines for CD diagnosis and management in Taiwan were collaboratively developed by an expert panel convened by the TSIBD. The panel considered available evidence, expert opinions, and specific factors pertinent to Taiwan such as endemic diseases, treatment availability, and NHI coverage. The proposed treatment algorithm (Fig. 1) offers a straightforward and practical tool to assist clinicians in Taiwan in clinical decision-making. The 2023 TSIBD CD consensus statements are summarized in Table 1.

The accurate diagnosis of CD requires a thorough evaluation of clinical symptoms, endoscopic findings, and histological evidence along with the exclusion of other potential differential diagnoses. Treatment strategies should be tailored according to the severity of the disease, typically starting with corticosteroids to induce remission induction, followed by immunomodulators and/or advanced therapies as maintenance therapy. Surgery may be considered for patients with severe disease that does not respond adequately to medical interventions, and timely decision-making is crucial. As new data emerges on both established and innovative therapies for CD, the recommendations in the guidelines by the TSIBD require to be updated in future revisions.

ADDITIONAL INFORMATION

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Conflict of Interest

Wong JM and Wei SC are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

Not applicable.

Author Contributions

Conceptualization: Wu JF, Wang HY, Wei SC. Data curation: Wu JF, Wang HY, Wei SC. Formal analysis: Wu JF, Yen HH, Wang HY, Wei SC. Funding acquisition: Wu JF, Wei SC. Investigation: all authors. Methodology: all authors. Project administration: Wu JF, Yen HH, Wang HY, Wei SC. Resources: Wu JF, Wang HY, Wei SC. Software: Wu JF, Yen HH, Wei SC. Supervision: Wei SC, Wang HY, Chou YH, Hsu TC, Hung TI, Lin Chun-Che, Lin Chun-Chi, Lin JK, Ni YH, Shieh MJ, Shih IL, Shun CT, Wang CY, Wong JM, Wu DC. Validation: all authors. Visualization: all authors. Writing - Original draft: all authors. Writing – review & editing: all authors. Approval of final manuscript: all authors.

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