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Guidelines

Guidelines for endoscopic diagnosis and treatment of inflammatory bowel diseases

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In recent years, we have seen a considerable increase in the number of patients with inflammatory bowel diseases of unknown etiology, including both Crohn's disease and ulcerative colitis. Inflammatory bowel diseases can cause intestinal lesions throughout the gastrointestinal tract, necessitating gastrointestinal endoscopy for examining all relevant aspects, especially lesion characteristics, for differential diagnosis and histological diagnosis, to select the appropriate treatment options, determine treatment effectiveness, etc. Specific guidelines are necessary to ensure that endoscopy can be performed in a safe and more tailored and efficient manner, especially since gastrointestinal endoscopy, including enteroscopy, is a common procedure worldwide, including in Japan. Within this context, the Japan Gastroenterological Endoscopy Society has formulated the "Guidelines for the Endoscopic Diagnosis and Treatment of Inflammatory Bowel Diseases" to provide detailed guidelines regarding esophagogastroduodenoscopy, enteroscopy, and colonoscopy procedures for definitive diagnosis, as well as determination of treatment effectiveness in clinical cases of inflammatory bowel diseases.

Key words: Crohn's disease, gastrointestinal endoscopy, inflammatory bowel disease, ulcerative colitis

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For Gastroenterologists and Endoscopic Surgeons

INTRODUCTION

ALTHOUGH BASIC GUIDELINES are necessary to ensure safe and reliable endoscopic treatment for all indications, including inflammatory bowel disease (IBD), there are currently no guidelines for the endoscopic treatment of IBD in Japan. Therefore, the Japan Gastrointestinal Endoscopy Society Guidelines Committee decided to develop a new basic guideline for such endoscopic procedures based on the principles of evidence-based medicine in keeping with the prevalent international standard in recent years. Specifically, the guidelines were created in accordance with the Minds Manual for Guideline Development 2020 version 3.0[1] and follow a clinical question (CQ)-based format (Table 1). As there is little high-level evidence in this area currently, the guidelines could only rely on expert consensus; it should also be noted that the contents of this guideline are intended to support general decision-making in clinical settings and not to serve as material for medical litigation. Nonetheless, we hope that they will be useful for IBD treatment in the future.

PROCEDURE OF GUIDELINE CREATION

Committee members

SIXTEEN GASTROINTESTINAL ENDOSCOPISTS were assigned with creating this guideline for the Japan Gastrointestinal Endoscopy Society. In addition, five gastrointestinal endoscopists served as members of the evaluation committee (Table 2). The collaborating institutions were tasked with proofreading.

Table 1 Strength of recommendation and evidence level

Grade of recommendation
1: Strongly recommend
2: Weakly recommend (propose)
(Nothing: Cannot make a clear recommendation or determine the strength of recommendation)
Evidence level
A (Strong): Very confident that the estimated treatment effect is sufficient to support the recommendation
B (Moderate): Moderately confident that the estimated treatment effect is sufficient to support the recommendation
C (Weak): Limited confidence that the estimated treatment effect is sufficient to support the recommendation
D (Very weak): Almost no confidence that the estimated treatment effect is sufficient to support the recommendation

Strength of recommendation, evidence level, and guideline drafting and finalization

Endoscopy procedures were categorized according to three areas: the upper gastrointestinal tract (esophagogastroduodenoscopy), colon (colonoscopy), and small intestine (enteroscopy). Diseases in each area were classified as either overall IBD, Crohn's disease (CD), ulcerative colitis (UC), and others (12 categories in total). Twenty-four draft CQs (background questions [BQ] and, future research questions [FRQ]) for each category were created. For each CQ, systematic literature searches of the PubMed and Ichushi databases were conducted for the period from April 1992 to March 2022. Missing papers were also manually searched. Articles identified based on these searches were evaluated, and the relevant papers were then used to draft the statement and explanation for each CQ. The creation committee members set the evidence level of each article in each area, as well as the strength of recommendation and evidence level of each statement according to the Minds Manual for Guideline Development 2020 version 3.0.[1] Thus, the CQ format guideline was created using the prepared statements and explanations. A total of 21 members, including the creation committee and evaluation committee, voted on the draft statements using a modified Delphi panel method—accordingly, statements that garnered seven or more votes (1–3, disagree; 4–6, insufficient; 7–9, agree) were adopted. The evaluation committee reviewed the completed draft guideline, which was then revised and presented to society members for further feedback. Thereafter, the results were discussed, and the guidelines were finalized.

Subjects

The targets of this guideline are patients with IBD undergoing endoscopic examination and diagnosis. Furthermore, this guideline is intended to be used by clinicians performing endoscopic examination and diagnosis for IBD.

This is only a standard guideline and must be flexibly adapted to suit the wishes, age, complications, social circumstances, etc. of each patient.

CONFLICTS OF INTEREST

INFORMATION REGARDING THE following was requested from each committee member involved in the creation of this guideline in order to ensure transparency regarding conflicts of interest:

Table 2 Members of the inflammatory bowel disease treatment guidelines creation committee

Japan Gastrointestinal Endoscopy Society Guidelines Committee	
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Collaborating institutions	Japanese Society of Inflammatory Bowel Disease; The Japanese Society of Gastroenterology; Research on intractable diseases from the Ministry of Health, Labour and Welfare of Japan; The Japanese Association for Capsule Endoscopy; The Japanese Gastroenterological Association; The Japan Society of Coloproctology; The Japan Society of Colon Examination

1. Companies or organizations from which individual members received any form of compensation in connection with this guideline: executive/advisory position and compensation (≥1 million yen), stock ownership and profit (≥1 million yen or ≥5% stock ownership), patent royalty fees (≥1 million yen), lecture fees, etc. (≥500,000 yen), manuscript fees (≥500,000 yen), research expenses and grants (≥1

million yen), scholarship (promotional) donations, etc. (≥1 million yen), course-related donations provided by companies, etc. (≥1 million yen), and receipt of travel expenses, gifts, etc. (≥50,000 yen).
2. Companies or organizations from which the declarer's spouse, first-degree relative, or person with whom they share income/property received any form of compensation: executive/advisory position and compensation (≥1 million yen), stock ownership and profits (≥1 million yen or ≥5% stock ownership), and patent royalty fees (≥1 million yen).
3. Institutional certificate of insurance related to the head of the research institution/department to which the declarer is affiliated (if the declarer has had or currently has a relationship as a co-investigator or sub-investigator with the head of the research institution/department to which they are affiliated): research expenses (≥1 million yen), donations (≥2 million yen), stocks, etc.

Compensation amounts were determined for each fiscal year, and committee members were asked to declare conflicts of interest for the three most recent fiscal years.

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Moreover, when voting to decide on any statement in this guideline, committee members were requested to declare "cases where individual/organizational economic conflict of interest (COI) exceeds the standard amount*" and "cases where non-economic COI (research activities, career, human relationships, conflicts of interest, etc.) is considered." However, none of these were applicable.

*The standard amount for voting rights of clinical practice guideline formulation participants established by Article 8, Paragraph 7 of the Society's COI Guidelines is as follows: lecture fees, 2 million yen; pamphlet etc. writing fee, 2 million yen; accepted research expenses, 20 million yen; and scholarship donation, 10 million yen.

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GUIDELINES FOR THE ENDOSCOPIC TREATMENT OF INFLAMMATORY BOWEL DISEASES

Esophagogastroduodenoscopy

CQ1: IS ESOPHAGOGASTRODUODENOSCOPY necessary when diagnosing IBD in a broad sense?

Statement: Esophagogastroduodenoscopy is not recommended for diagnosing broad IBD in adults. However, it is recommended in cases with suspected upper gastrointestinal lesions or when the diagnosis cannot be confirmed by colonoscopy.

Evaluation based on the modified Delphi panel method: median 8, minimum 6, maximum 9.

Strength of recommendation: 2; Evidence level: C.

Explanation: Broad IBD includes not only UC and CD but also Behçet's disease, intestinal tuberculosis, eosinophilic gastroenteritis, ischemic enteritis, microscopic colitis, drug-induced enteritis, familial Mediterranean fever, chronic enteropathy associated with *SLCO2A1* gene (CEAS), amyloidosis, vasculitis syndrome, colitis caused by immune

checkpoint inhibitors, etc. Patients with broad IBD present with lower gastrointestinal symptoms such as diarrhea and bloody stools; therefore, confirmation of diagnosis requires collecting information on the patient's medical history and the results of biochemical tests, stool culture tests, imaging tests, such as computed tomography (CT) scan and colonoscopy, and biopsies during colonoscopy. Therefore, esophagogastroduodenoscopy is generally not considered when diagnosing broad IBD, except in cases with suspected upper gastrointestinal lesions.

However, esophagogastroduodenoscopy should be performed if the above tests do not lead to a definitive diagnosis. In such cases, this procedure is performed to gather additional information for diagnosis and to rule out other diseases. In particular, esophagogastroduodenoscopy is recommended in cases where CD and UC cannot be differentiated (IBD unclassified [IBD-U]). Findings such as bamboo joint-like appearance or notch-shaped appearance suggest CD rather than UC.[2] *Helicobacter pylori* uninfected gastritis without aphthae, fragile mucosa, and granular mucosa suggest UC rather than CD.[3,4] During the procedure, multiple biopsies of the esophagus, stomach, and duodenum should be performed,[5,6] and it is helpful for the diagnosis when pathological findings such as noncaseating epithelioid cell granulomas or focally enhanced gastritis can be obtained, because such findings are characteristic of CD.

Unlike adult-onset IBD, childhood-onset IBD is associated with several atypical features that complicate the diagnosis. Upper gastrointestinal lesions are also more common in children than in adults.[7] Therefore, regardless of the presence or absence of upper gastrointestinal lesions during initial evaluation for IBD, it is suggested that all children undergo esophagogastroduodenoscopy with biopsy from multiple sites.[5,8]

CQ2: Is esophagogastroduodenoscopy recommended for the diagnosis of CD?

Statement: Esophagogastroduodenoscopy is recommended for diagnosing CD.

Evaluation by modified Delphi panel method: median 9, minimum 7, maximum 9.

Strength of recommendation: 1; Evidence level: C.

Explanation: CD frequently develops gastrointestinal lesions in the ileocecal region, but can develop the lesions throughout the entire gastrointestinal tract. If the patient exhibits symptoms such as chronic abdominal pain, diarrhea, fever, weight loss, or anal lesions, CD is diagnosed by obtaining information regarding the medical history, performing a physical examination and blood tests, as well as determining the sites of inflammation based on imaging tests (e.g., CT and magnetic resonance imaging [MRI]) and additional endoscopy and biopsy.

In CD, upper gastrointestinal tract lesions are frequently observed. Aphthae, erosions, and ulcers are occasionally found in the esophagus, and in addition to these, bamboo joint-like appearance is recognized in the stomach. In the duodenum, notch-shaped appearance and bead-like protrusions are considered as characteristic features. The reported incidence of upper gastrointestinal lesions is 0.2–6% in the esophagus, 24–73% in the stomach, and 21–32.1% in the duodenum.[9] Of these, characteristic gastric and duodenal lesions, such as bamboo joint-like appearance[10] and notch-shaped appearance, are also included as secondary findings in the Japanese diagnostic criteria. Therefore, it is recommended to perform esophagogastroduodenoscopy for the diagnosis of CD.

In some cases, noncaseating epithelioid cell granuloma can be confirmed based on the histologic examination from the upper gastrointestinal tract; as such, biopsies should be performed during examinations. In particular, the detection rate of noncaseating epithelioid cell granulomas may be higher in biopsies from the upper gastrointestinal tract (40–68%) than those from the colorectum (13.6–55.6%).[11] The detection rate is particularly high in biopsies from gastric lesions, bamboo joint-like appearance, and duodenal lesions.[9] Furthermore, localized neutrophil/lymphocyte infiltration in the stomach and duodenum, called focally enhanced gastritis, is specific to CD without *H. pylori* infection.[12] The presence of upper gastrointestinal tract lesions has been reported as a risk factor for requiring the use of anti-tumor necrosis factor (TNF) agents, and thus careful monitoring is recommended.[13]

As CD progresses, stenosis and fistulae may develop.[11,14,15] Therefore, patients with the upper gastrointestinal involvement should be monitored as appropriate.

CQ3: Is esophagogastroduodenoscopy recommended for the diagnosis of UC?

Statement: Esophagogastroduodenoscopy is not recommended for definitive diagnosis of UC.

Evaluation by modified Delphi panel method: median 8, minimum 7, maximum 9.

Strength of recommendation: 2; Evidence level: D.

Explanation: UC is characterized by persistent or recurrent mucous and bloody stools or bloody diarrhea. The diagnosis is confirmed based on a physical examination, blood test, and medical history, followed by a colonoscopy or biopsy to confirm the intestinal lesions characteristic of this disease.[16–19] No studies have verified the usefulness of esophagogastroduodenoscopy for diagnosing UC, and a diagnosis can be confirmed by colonoscopy; therefore, esophagogastroduodenoscopy is not recommended for the diagnosis of UC and should be limited to patients with upper gastrointestinal symptoms.

However, if a diagnosis cannot be confirmed by colonoscopy, other IBDs should be excluded by performing esophagogastroduodenoscopy and enteroscopy, among other tests. UC primarily affects the colon; however, studies have reported that 4.7–7.6% of cases of UC are complicated by upper gastrointestinal lesions.[3,20] Endoscopic characteristics of upper gastrointestinal involvement in UC include diffuse and continuous granular mucosa resembling colonic lesions, erosion, hemorrhagic/fragile mucosa, and ulcers. Histopathological findings can include diffuse inflammatory cell infiltration, cryptitis, and crypt abscesses, which are similar to those of colonic lesions. In cases where differentiation from CD is difficult, upper gastrointestinal lesions exhibiting this type of morphology may be useful for the differential diagnosis. In addition to CD, Behçet's disease and *MEFV* gene-related enteritis can result in colonic and upper gastrointestinal lesions similar to those in UC. Upper gastrointestinal lesions in Behçet's disease include oval ulcers and deep ulcers in the esophagus, and similar esophageal ulcers have been reported in UC, although this is extremely rare. Ulcerations, erosions, and aphthae in the stomach and duodenum occur in ~30% of cases of *MEFV* gene-related enteritis.[21] However, thorough systemic examination and follow-up are necessary in cases where a definitive diagnosis is not achieved.

CQ4: Is esophagogastroduodenoscopy recommended for Behçet's disease?

Statement: Esophagogastroduodenoscopy is recommended for patients with Behçet's disease who complain of upper gastrointestinal symptoms.

Evaluation by modified Delphi panel method: median 9, minimum 7, maximum 9.

Strength of recommendation: 2; Evidence level: C.

Explanation: According to the diagnostic criteria of the Japanese Ministry of Health, Labor and Welfare Behçet's disease research group,[22] intestinal Behçet's disease is classified as a special type that is diagnosed when the criteria for complete or incomplete types are met and if gastrointestinal lesions—typically, ileocecal ulcers—are observed. Behçet's disease is suspected if only gastrointestinal lesions are present; however, in Japan this is often called a simple ulcer and treated as a disease related to Behçet's disease. Endoscopy findings of Behçet's disease typically reveal deep, oval ulcers with clear borders in the ileocecal region. However, atypical lesions, such as multiple small ulcers or UC-like diffuse inflammation, can occur and require differential diagnosis from other diseases. As Behçet's disease may cause lesions in the upper gastrointestinal tract and ileocecal region, esophagogastroduodenoscopy is performed if a patient experiences epigastric pain, chest pain, or difficulty swallowing.

The reported incidence of esophageal lesions in Behçet's disease is 2.7–18%.[23–25] Furthermore, complications are uncommon in the complete type, and the incidence of esophageal lesions tends to be higher in the incomplete type or suspected cases.[26,27] Esophageal lesions occur most commonly in the middle to lower part of the esophagus. The morphological findings are characterized by single or multiple round or oval ulcers with clear borders, and there are also cases with aphthous or irregular ulcers, but little redness or edema of the intervening mucosa. Furthermore, a study has reported that a white moss-like appearance at the ulcer border and conspicuous protuberance of the ulcer border are characteristic findings in Behçet's disease.[28] Large and deep ulcerative lesions can lead to esophagobronchial fistulae, perforation, and esophageal strictures, which may exacerbate the patient's condition.

There is very little information on gastroduodenal lesions, whereas multiple and diffuse redness, aphthae, and erosion can develop in the stomach and duodenum.[24,29] In one study, upper gastrointestinal lesions were found in 30.8% (84/273) of patients with Behçet's disease.[30] However, it remains uncertain whether these lesions are related to Behçet's disease, and further investigation is necessary.

CQ5: What bowel preparation should be performed when conducting colonoscopy for IBD?

Statement 1: Bowel preparation with an oral purgative is suggested when performing colonoscopy.

Evaluation by modified Delphi panel method: median 8, minimum 7, maximum 9.

Strength of recommendation: 2; Evidence level: D.

Statement 2: Oral bowel preparation for colonoscopy is not recommended in patients with severe activity.
Evaluation by modified Delphi panel method: median 9, minimum 7, maximum 9.
Strength of recommendation: 1; Evidence level: C.

Explanation: Colonoscopy is the best option for assessing IBD activity.[31] In patients with CD, inflammation frequently occurs in the ileum and proximal colon, thus being necessary to investigate with the procedure. Inflammation of UC is generally observed continuously from the rectum, and in many cases, activity can be evaluated by sigmoidoscopy. However, the inflammation can be more severe in the proximal colon than in the rectosigmoid colon.[32,33] This means that total colonoscopy is necessary to precisely assess endoscopic activity, especially to confirm remission on endoscopy. When performing total colonoscopy, good bowel preparation allows for safer and more efficient examination. Therefore, bowel preparation with an oral purgative is suggested.

Sigmoidoscopy could be usually sufficient to assess the relapse or mucosal healing after treatment initiation in UC. In such cases, oral bowel preparation is unnecessary. In patients with a severe or fulminant state, oral purgative would rather be avoided, as bowel preparation may worsen the patient's condition.[31,34] In patients with frequent diarrhea and bloody stools during the active stage, endoscopy can often be done without bowel preparation. When choosing enema as a bowel preparation, agents that cause irritation should be avoided. Lukewarm water or physiological saline might be better if the patient experiences abdominal pain.

Furthermore, oral preparation should be applied with caution in patients with severe stenotic lesions, as they can cause intestinal obstruction or perforation. Stenosis may not be identified in some case of small bowel CD, so other imaging tests (e.g., CT) should be added.

There are only a small number of reports regarding the efficacy and safety of oral purgative for IBD patients. A prospective observational study found that the quality of bowel preparation during colonoscopy was lower in IBD patients than in patients with abdominal pain or asymptomatic patients.[35] On the other hand, a study of 100 IBD patients and 100 age- and sex-matched controls found no difference in the quality of bowel preparation; however, IBD patients had a higher visceral sensitivity index and anxiety index scores than the control group, suggesting that these may lead to increased discomfort or anxiety during bowel preparation.[36]

Many reports recommend polyethylene glycol (PEG)-based bowel cleansers as the oral purgatives.[37] This is because sodium picosulfate may cause more inflammation in the colon compared to PEG.[38] It has been reported that abdominal symptoms increase within 4 weeks after colonoscopy, but a clear relationship with oral bowel preparation has not been reported.[39] Recently, the efficacy and safety of a low volume of oral purgatives have been investigated, with good results.[40,41] Further investigations are awaited.

CQ6: Is colonoscopy recommended for pregnant IBD patients?

Statement: Colonoscopy is suggested if the benefits outweigh the risks.
Evaluation by modified Delphi panel method: median 8, minimum 6, maximum 9.
Strength of recommendation: 1; Evidence level: C.

Explanation: It has been reported that an increase in adverse events during pregnancy (preterm birth, low birth weight, etc.) in IBD patients is caused by the presence of an underlying disease and higher disease activity, rather than therapeutic drug use; as such, it is important to continue providing appropriate treatment during pregnancy to control disease activity.[42] Therefore, if symptoms suggestive of relapse occur during pregnancy, disease activity must be evaluated, and treatment should be selected appropriately. Therefore, when there is a clear indication, such as for selecting treatment at the time of relapse, it is suggested to perform colonoscopy immediately.[31,42] When performing colonoscopy, it is ideal to perform sigmoidoscopy instead of ileocolonoscopy.

However, there is limited evidence regarding the efficacy and safety of endoscopy in pregnant women. A cohort study in Sweden compared the delivery outcomes between pregnant women with (n = 3052) and without (n = 1,589,173) endoscopy, and demonstrated an increased risk of preterm birth and small for gestational age and low birth-weight infants, but no increased risk of congenital malformations or stillbirth.[43] The risk of preterm birth and low birth weight was also higher in pregnant women with IBD; however, these risks are thought to be related to disease activity. de Lima *et al.*[44] investigated the clinical impact of colonoscopy on 42 women with IBD suspected of having recurrence during pregnancy. Endoscopy led to treatment initiation or alteration in 24 out of 32 patients with recurrence. Furthermore, age, medication, and an activity-matched comparison between patients with and without colonoscopy revealed no difference in the frequency of events such as spontaneous abortion, preterm birth, and

low birth-weight infants. According to a study by Ko *et al*. of 48 pregnant women who underwent sigmoidoscopy (including three colonoscopies) due to suspicion of IBD or IBD recurrence, 78% had additional changes in treatment based on the endoscopy results.[45] However, none of the patients required hospitalization within 4 weeks after endoscopy.

As for the timing of the examination, the procedure was often conducted during the second trimester.[44–46] This timing may have been selected based on the risk of spontaneous abortion in the early stages and taking into account the risk of intestinal and venous compression by an enlarged uterus in the later stages. Before the procedure, consultation with an obstetrician to confirm the patient's pregnancy status is recommended.

Bowel preparation

Bowel preparation in pregnant patients with UC should be limited to less irritating enemas such as lukewarm water or physiological saline.[46] Moreover, it would be ideal to observe in the distal part of the colorectum where inflammation is most likely to occur and use transabdominal ultrasonography if there is a need to evaluate the proximal part of the colon. If it is necessary to examine the entire colon, bowel preparation may improve the safety and efficiency of colonoscopy. As for the type of oral preparation, PEG is considered to be appropriate, as has been reported to be safe for pregnant women. Oral sodium phosphate preparations should be avoided, as their use is associated with potential risks such as kidney damage due to dehydration.[43] Adverse events of sodium phosphate include acute phosphate nephropathy and electrolyte disturbances, and not only due to dehydration. Thus, its use has been limited for elderly or patients with chronic kidney disease.

Points to note during examination

The procedure should be performed with the pelvis tilted to the left or in the left lateral position, particularly after the second trimester of pregnancy to avoid supine hypotension syndrome (compression of the vena cava by the uterus).[43] When using sedatives, excessive sedation should be avoided. Several studies have reported that midazolam and analgesics such as pethidine are commonly used during the procedure.[31,43–46] The duration of the procedure should be minimized; if the procedure takes longer due to treatments, etc., the patient should be managed in collaboration with obstetricians and obstetric anesthesiologists.[43]

Enteroscopy

BQ1: Is enteroscopy recommended for the differential diagnosis of IBD?

Statement: Small bowel enteroscopy is recommended for the differential diagnosis of IBD.

Explanation: The reported diagnostic accuracy of device-assisted enteroscopy (DAE) in suspected cases of CD is ~75% (where 25–50% were confirmed cases of CD), indicating the usefulness of DAE in diagnosing CD.[47–51] Endoscopic biopsies may improve diagnostic performance by providing endoscopic findings to the pathologists.[4,49,51] DAE has a high ability to detect stenoses that require surgery.[52] For CD, the retrograde route is usually recommended, whereas the antegrade needs be considered when it is difficult[53] (refer to CQ12 for more details).

Lesion detectability under small bowel capsule endoscopy (SBCE) in CD is over 80%. It contributes to the confirmation of diagnosis in suspected CD by detecting typical lesions of CD, such as a cobblestone appearance and longitudinal ulcers, as well as linear erosions and erosions arranged longitudinally or circumferentially.[54,55] The reported diagnostic ability of SBCE is higher than those of ileocolonoscopy, MRI, CT, and gastrointestinal contrast-enhanced radiography.[56–65] The diagnostic sensitivity of SBCE increases in cases of suspected CD with anemia and high inflammatory response levels.[66,67] It has also been reported that the detectability of CD findings is higher with DAE than with SBCE[49] (refer to CQ14 for more details).

When diagnosing IBD-U, it is expected that repeated DAE with biopsies or SBCEs can confirm a definitive diagnosis.[68–73]

DAE and SBCE can be used to differentiate between CD and other conditions, such as Behçet's disease,[74] nonsteroidal antiinflammatory drug (NSAID)-induced ulcers,[75–79] tuberculosis,[80–82] ischemic enteritis,[82–85] eosinophilic enteritis,[86] radiation enteritis,[82,85,87] vasculitis syndrome,[88] CEAS,[89–91] amyloidosis,[92,93] connective tissue diseases,[94,95] polyposis,[96–99] malignant tumors (malignant lymphoma, etc.), and functional gastrointestinal disorders.

When performing SBCE, bowel preparation using bowel purgatives improves visibility; however, there is no evidence that demonstrates the improvement of IBD diagnosis.[100–103] Intestinal peristalsis promoters are reported to have limited effects on second- or third-generation SBCE.[104–106]

The retention rate of SBCE is higher in suspected and confirmed IBD cases than in non-IBD cases.[71,107–109]

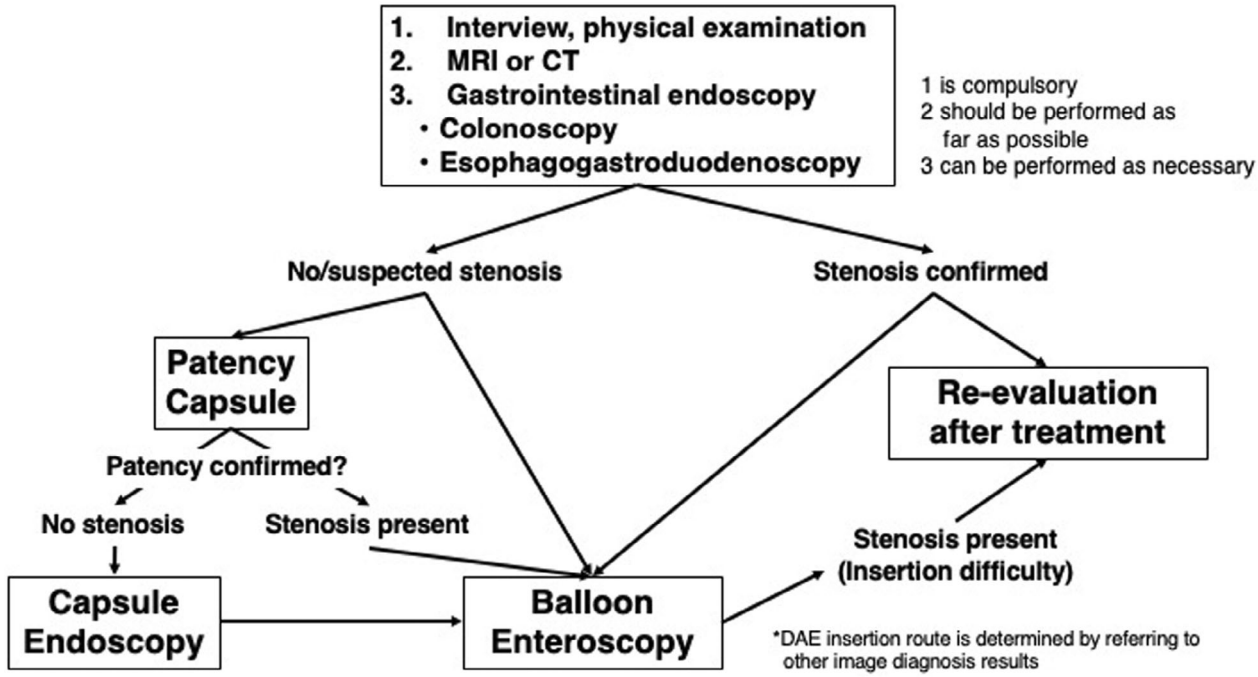

Figure 1 Enteroscopy algorithm for confirmed and suspected inflammatory bowel disease cases. CT, computed tomography; DAE, device-assisted enteroscopy; MRI, magnetic resonance imaging.

Small bowel capsule endoscopy is not recommended if there is existing stenosis or symptoms of stenosis. A thorough interview is important to prevent retention. Patency capsules have a very high patency diagnostic ability and safety and are recommended to exclude the risk of retention before examination in CD.[80,110–113] Additionally, performing SBCE after CT or MRI reduces the risk of retention.[114,115]

In summary, when enteroscopy is indicated for IBD, a thorough interview followed by an MRI or CT scan should be necessary to improve the diagnostic ability and safety. When using SBCE, the preceding patency capsule is recommended to assess the possible retention. DAE should be performed if more detailed observations and biopsies are required. If bowel patency cannot be confirmed by patency capsule, DAE should be selected, or re-evaluation should be conducted after treatment (Fig. 1).

FRQ1: Is enteroscopy recommended for diagnosing IBD in children?

Statement: Small bowel enteroscopy is recommended in children for the diagnosis of IBD, especially in cases of suspected CD.

Explanation: The reported diagnostic ability of SBCE in suspected CD cases is 50–61%.[116–119] The diagnostic ability of DAE is equivalent to that of SBCE, at 57–87%.[120–122] In a direct comparison, the diagnostic abilities of DAE and SBCE were 70.7% and 77.7%, respectively, and this difference was not significant.[122] Even when routine colonoscopy or SBCE is not performed, and only MRI and ultrasound are used, the diagnostic ability of DAE can be as high as 57%.[121] However, if DAE is performed after colonoscopy, esophagogastroduodenoscopy, small bowel contrast-enhanced radiography, MRI, or SBCE, the diagnostic ability increases to 66–87%.[120,122,123] The advantage of DAE lies in the fact that it allows for a histopathological diagnosis through tissue sampling.[124]

Based on previous reports, patients undergoing DAE must at least 1 year old and weigh at least 7.92 kg.[125,126] Weight and age are especially important because children have a more fragile intestinal wall and a small abdominal cavity, which affects the difficulty of the procedure. Children have a slightly shorter intestinal tract than adults, averaging 450 cm at age 5, 500 cm at age 10, and 575 cm at age 20.[118,125] The development of thinner scopes can decrease the risk of adverse events and facilitate the procedure for young children.[126]

The main differential diagnoses of small bowel inflammatory disorders in children include CD, UC, immunoglobulin A vasculitis, Behçet's disease, and eosinophilic gastroenteritis.[71,73,127,128] Unlike in adults, intestinal disorders caused by drugs such as NSAIDs are less common in children. SBCE is also useful for differentiating IBD-U. In cases where the initial diagnosis is UC or IBD-U, the final diagnosis changes to CD in ~25–61.5% of cases.[71,72,129]

The detectability of small bowel lesions of SBCE is 43–93% in suspected CD cases, which is similar to that in adults. This value is higher than those of small bowel radiography (12–23%) and CT enterography (CTE)/enteroclysis (20–36%), and is equivalent to or higher than that of magnetic resonance enterography (MRE) (45–78%).[61,130,131]

In children with suspected CD, examination methods should be selected by considering the balance of benefit and invasiveness in each procedure. Other various factors, including pathological conditions of differential diagnosis, the necessity of tissue sampling, radiation exposure, etc., should be also considered.

Patients are recommended to refrain from food and fluid intake except clear water and bowel purgatives for 8 h before SBCE. As with adults, pretreatment with a bowel-cleansing agent improves the visual field, but there is no evidence that demonstrates the improvement of the diagnostic ability for IBD.[132–134]

Retention is the most significant adverse event in SBCE. Its incidence in CD is 2.5% (0.5% in the stomach, 1.9% in the small intestine). This is approximately the same as in adults (2.6%), but the risk is higher in malnourished children.[63,135,136] At present, the patency capsule is most reliable to evaluate bowel patency if the patient is able to ingest it.[114]

Both SBCE and patency capsule have been approved for children aged 2 years or older since 2009. The intestinal diameter is 10–15 mm in newborns and the required diameter for both SBCE and patency capsule is 11–13 mm, which means age is not associated with the risk of retention. Although SBCE is a noninvasive procedure, the incidence of difficulty in swallowing the capsule increases in younger age. Although the AdvanCE-J study reported that the height was better predicted in swallowing the capsule rather than weight or age, children of ~10 years of age or older can generally swallow the capsule.[137] However, the capsule should be placed in the duodenum using a special device with the assistance of an endoscope if the patient cannot swallow it.[118,119,128,138]

BQ2: Are there any adverse events specific to DAE for IBD?

Statement: There are no adverse events specific to DAE for IBD patients, but the risk of perforation is higher in patients with ulcerative lesions and postoperative adhesions.

Explanation: The frequency of all adverse events related to the diagnostic DAE is around 1%, and there are no adverse events specific to IBD.[49,139–141] Typical adverse events (and their incidences) are perforation (0.06–0.5%), acute pancreatitis (0.09–3%), bleeding (0.1%), and aspiration pneumonia (0.07%). The incidence rates of adverse events, excluding perforation, in diagnostic endoscopy for

Table 3 Comparison of cases of perforation during enteroscopy in inflammatory bowel disease (IBD) and non-IBD

Authors	Year reported	Procedure	Diseases	Total no. of cases	Perforation cases (%)	Additional details
Mensink *et al.*[140]	2007	DBE	Non-IBD	1728	1 (0.06)	–
Gerson *et al.*[142]	2009	DBE	CD	33	1 (3.00)	Postoperative anastomosis
			Non-IBD	1274	7 (0.50)	
Möschler *et al.*[143]	2011	DBE	Non-IBD	1572	3 (0.19)	–
Xin *et al.*[139]	2011	DBE	IBD	180	5 (2.70)	3 cases; history of surgery
			Non-IBD	5435	15 (0.20)	
Odagiri *et al.*[144]	2014	DBE	IBD	4431	11 (0.25)	–
			Non-IBD	24,637	21 (0.08)	
			IBD (steroid use)	636	4 (0.63)	
Rahman *et al.*[49]	2015	DBE	CD	98	1 (1.00)	Anastomosis with ulceration

CD, Crohn's disease; DBE, double-balloon endoscopy.

Table 4 Report of perforation cases during enteroscopy in Crohn's disease

Authors	Year reported	Total no. of cases	Perforation cases (%)
Fukumoto *et al.*[145]	2007	23	0
Ohmiya *et al.*[84]	2009	16	0
Hirai *et al.*[146]	2010	25	0
Hirai *et al.*[147]	2014	65	1 (1.5)
Sunada *et al.*[148]	2016	85 (475 treatments)	4 (4.7/case, 0.8/treatment)
Hirai *et al.*[149]	2018	95	0

IBD are similar to those for non-IBD; however, the reported incidence of perforation in IBD, especially CD, is 0.25–2.7%, which is considered high.[49,139,140,142–144] There are also reports that IBD and steroid use are the risk factors of perforation,[144] and that the risk of perforation may be higher in cases with inflammatory adhesions, a history of surgery, or postoperative anastomotic ulcers (Table 3). Perforation is the most noteworthy adverse event during endoscopic balloon dilation (EBD) for CD, and the incidence of perforation in Japan is reportedly 0–4.7% (Table 4).[84,145–149] The risk of hyperamylasemia and acute pancreatitis, which are adverse events specific to DAE, are higher with the oral approach than with the anal approach. It has been reported that this risk is related to the procedure time, and that the physical load on the pancreatic tissue during the procedure can be the trigger.[150,151] Advanced age has been reported to be a patient background-related risk factor and clockwise insertion as a procedure-related risk factor.[152] There is no reported difference in adverse events depending on other aspects of the procedure, such as the choice of single-balloon endoscopy (SBE) or double-balloon endoscopy (DBE).[153,154] The rate of complete small bowel examination is higher in DBE (18–66%) than in SBE (0–22%),[155,156] whereas the rate is lower in CD because of the stenosis and adhesion caused by intestinal inflammation (0–12.9%).[53,157,158]

In a large-scale study in Japan,[126] the incidence of adverse events related to DAE in children was ~5.4% (14 out of 257 cases). The incidence increases with younger age, and the frequency increases to ~10% (7 out of 67) among patients under 10 years of age. However, most adverse events occurred during therapeutic endoscopy, including retrograde cholangiography, and no adverse event was found in 30 cases with IBD. The reported frequency of adverse events occurring with diagnostic DAE is 0–1.7%.[125,126,159] Weight and age are the factors associated with adverse events in pediatric patients, because they correlate with the fragility of the intestinal wall and the size of the abdominal cavity. Indication for DAE should be decided based on the factors as well as the experience at each institution. The major adverse events are the same as in adults, with an increased risk of perforation and bleeding after therapeutic DAE and with increased risks of post-procedure pancreatitis and elevated pancreatic enzyme levels after antegrade DAE.[125,126,159]

FRQ2: Is enteroscopy recommended after UC surgery?

Statement: Follow-up DAE or SBCE after UC surgery is not recommended.

Explanation: It has been reported that 13–57% of UC patients have small bowel lesions and that SBCE can be used to identify these lesions.[160–162] However, the presence of small bowel lesions in UC has not been shown to be correlated with postoperative outcomes.[163] Pathological examination of the resected specimens in UC revealed that ileitis was present in 22–33% of the pancolitis type of UC.[161,164] However, the presence of ileitis on the resected specimen was not associated with the development of postoperative pouchitis.[165] Based on the aforementioned findings, the clinical significance of small bowel lesions in UC remains unclear.

In one study, SBCE found diffuse ulcerative lesions in the upper part of the small bowel, which could not be detected by contrast radiography, in a patient with postoperative chronic pouchitis; however, there did not appear to be any correlation between the lesion and the postoperative clinical course.[166]

Studies reported from Western countries revealed that CD can occur in postoperative patients of UC.[165,167,168] Another study reported that inflammatory lesions were found in 1–50 cm from the ileal pouch opening in ~3% of cases during follow-up after UC surgery, while no case developed CD.[169] In Japan, the modification of diagnosis to CD after UC surgery is quite rare, except for cases with fistula formation.[170–172] However, multicenter studies in Japan show that ileal pouch dysfunction often developed in cases in which the diagnosis was changed to CD after UC surgery, emphasizing a precise preoperative diagnosis.[170,171,173]

One study reported that SBCE could identify the cause of anemia in 9.4% of cases with ileal pouch after UC surgery;

thus, SBCE may be useful in patients with anemia of unknown origin after UC surgery.[174]

In summary, a certain proportion of patients with UC have small bowel lesions before or after surgery. However, there is no clear evidence that follow-up enteroscopy contributes to the prediction of the postoperative clinical course or to the modification to the diagnosis of CD. SBCE may be useful when patients develop clinical findings suggestive of small bowel lesions (e.g., unexplained anemia) after UC surgery.

CQ7: Is DAE recommended for definitive diagnosis of CD?

Statement: DAE is recommended for making a definitive diagnosis of CD in patients with suspected CD without abnormal findings in the ilecolonoscopy.

Evaluation by modified Delphi panel method: median 8, minimum 6, maximum 9.

Strength of recommendation: 1; Evidence level: C.

Explanation: In addition to clinical symptoms, diagnoses are based on combining various laboratory findings, including blood test, endoscopy, gastrointestinal contrast-enhanced radiography, histological, and even cross-sectional imaging findings.[16,31,175] Among these, endoscopic findings are most important for CD diagnosis. According to the Japanese diagnostic criteria, longitudinal ulcers and a cobblestone appearance are listed as major criteria for CD diagnosis.[16] If CD is suspected, colonoscopy (ileocolonoscopy), which includes observation of the terminal ileum, is recommended as the first-line endoscopy.[176] However, it has been reported that in 10–30% of CD cases, lesions are found in the deeper part of the small bowel that cannot be accessed using colonoscopy.[177,178] Therefore, if colonoscopy does not yield positive findings, further assessment should be considered to evaluate small bowel lesions. According to several guidelines in other countries, if no abnormal colonoscopy findings are observed in patients with suspected CD, SBCE is recommended in cases without obstructive symptoms or known stenotic lesions, and cross-sectional imaging tests, such as MRE or CTE, are recommended in cases with obstructive symptoms or known stenotic lesions.[31,176] However, it is not always easy to determine whether the patient has morphological findings characteristic of CD under these procedures. DAE can directly visualize mucosal lesions in the deeper part of the small bowel that cannot be reached by colonoscopy, and it is possible to detect characteristic endoscopic findings (morphological characteristics such as longitudinal ulcers and cobblestone appearance, positional relationships with mesentery attached side, etc.) that can be useful to determine the diagnosis of CD. Furthermore, even if a definitive diagnosis cannot be obtained by endoscopic findings alone, the combination of histological examination of biopsy specimens may lead to a definitive diagnosis. However, DAE is a relatively invasive and specialized procedure that requires a relatively longer procedure, while it does not always allow the evaluation of the entire small intestine. Thus, several guidelines and statements in other countries propose that DAE should not be used as a first-line test for patients with suspected small-bowel CD.[179] However, it has been also suggested that DAE is preferable to avoid the risk of SBCE retention in patients suspected of having stenosis.[179] In recent years, the usefulness of DAE in diagnosing small-bowel CD has been reported both in Japan as well as in other countries.[48,51]

CQ8: Is SBCE recommended for diagnosing CD?

Statement: If ileocolonoscopy does not lead to a definitive diagnosis, we recommend using SBCE as an auxiliary method for diagnosing CD.

Evaluation by modified Delphi panel method: median 8, minimum 5, maximum 9.

Strength of recommendation: 1; Evidence level: C.

Explanation: Endoscopy plays a key role in the definitive diagnosis of CD, and longitudinal ulcers and a cobblestone appearance are listed as major diagnostic criteria for CD in Japan.[16] According to Japanese and international guidelines, ileocolonoscopy is recommended as the first-line endoscopy in cases with suspected CD.[31,175,180] Those guidelines also recommend SBCE if the examination does not find abnormal findings and if neither obstructive symptoms nor stenotic lesions under cross-sectional imaging are detected.[133,176] SBCE is less invasive, allows observation of the entire small bowel, and is also superior for detecting diminutive small-bowel mucosal lesions. In fact, a meta-analysis on the diagnostic yield of small-bowel lesions in patients with a confirmed diagnosis of CD showed the excellent diagnostic ability of SBCE.[58,130] However, strictly speaking, these results should be interpreted with caution, because the reports do not demonstrate the accuracy (diagnostic ability) of CD diagnosis, but demonstrate the detectability of small-bowel lesions (findings rate) in patients with confirmed CD.[58,130] Another report examined the sensitivity and specificity of

CD diagnosis using different combinations of four modalities (colonoscopy, CTE, SBCE, and small-bowel radiography). The results revealed that SBCE, because of its low specificity, caused a lower diagnostic accuracy for CD compared to colonoscopy, even when combined with either CTE or small intestinal radiography.[181] At present, no CD-specific SBCE findings have been established as the gold standard for CD diagnosis.[179] However, compared to small intestinal lesions found in inflammatory diseases other than CD, Esaki *et al*. reported that the cobblestone appearance, longitudinal ulcers, and irregularly shaped ulcers are frequently observed in CD, and lesions showing a circumferential or longitudinal alignment are significantly more common in the upper part of the small bowel.[55]

CQ9: Can enteroscopy be used for evaluating the activity of small-bowel lesions after a definitive CD diagnosis?

Statement: Enteroscopy using DAE or SBCE is recommended for evaluating the activity of small-bowel lesions if there were no abnormal findings on other modalities or if colonoscopy is unable to evaluate after a definitive CD diagnosis.

Modified Delphi panel method evaluation: median 8, minimum 7, maximum 9.

Strength of recommendation: 1; Evidence level: C.

Explanation: In ~30% of patients diagnosed with CD, lesions are found in areas that cannot be reached using colonoscopy (ileocolonoscopy), including the terminal ileum.[182] Therefore, if there are no abnormal findings in cross-sectional imaging tests (CT, MRE, and ultrasound) or small-bowel radiography, enteroscopy using DAE or SBCE is considered. DAE, which allows direct visualization of mucosal lesions in the small bowel, can be used to evaluate CD activity.[183] There are several reports, especially from Japan, regarding the effectiveness of DAE for small-bowel evaluation. In an observational study using DAE on patients in clinical remission, Takabayashi *et al*. reported that active lesions deep in the small bowel unreachable with colonoscopy were found to be at risk of relapse.[184] Takenaka *et al*. reported that small bowel ulcers were observed in 45% of patients who underwent DAE, even in clinical and serological remission, and that these lesions were a risk factor for relapse, hospitalization, and surgery.[157] Additionally, in a study with the evaluation by DAE, small-bowel lesions were found to be more difficult to heal than colonic lesions, and residual small-bowel lesions were a risk factor for poor patient prognosis.[185] DAE is a highly invasive procedure, but the use of a thin endoscope improves safety and allows for a less invasive method of evaluating CD lesions.[186] Furthermore, European guidelines recommend cross-sectional imaging for the evaluation of small-bowel lesions, and MRE can be used to evaluate inflammation throughout the abdomen, including intramural and extra-intestinal inflammation.[187] However, DAE has a higher diagnostic ability for intestinal damage than MRE.[53] Furthermore, small-bowel stenosis, which MRE cannot detect, is also a significant risk factor for surgery.[52] Therefore, DAE can be considered to be useful on CD patients with stenosis, and when used in conjunction with retrograde contrast imaging, enables the evaluation of the deeper portion of the small bowel where an endoscope cannot reach because of stenoses.[188]

On the other hand, there have been several reports indicating the usefulness of SBCE in confirmed CD patients. The detection rate of mucosal inflammation in the small bowel (Lewis score ≥135) by SBCE in CD patients can be as high as ~70%.[189] Furthermore, the sensitivity for detecting previously unrecognized lesions is significantly higher with SBCE than with MRE.[190] A meta-analysis on the diagnostic ability of SBCE and other tests (small-bowel radiography, CTE/enteroclysis, ileocolonoscopy, push enteroscopy, etc.) for small-bowel lesions in confirmed CD patients showed that SBCE was significantly better than other methods.[58,130] However, another meta-analysis comparing the diagnostic ability of SBCE, MRE, and/or intestinal ultrasound sonography (IUS) in patients with small-bowel CD showed that the diagnostic ability of SBCE for active small-bowel lesions was equivalent to those of MRE and IUS.[191] Other studies have reported that SBCE has a significantly higher ability to detect lesions in the proximal part of the small bowel than CTE or MRE.[191,192] Based on these reports, overseas guidelines recommend SBCE in cases with symptoms that cannot be explained based on colonoscopy findings or findings using other methods, and to confirm endoscopic healing of the small-bowel mucosa.[133] However, when performing SBCE in CD patients, the possible risk of capsule retention needs to be considered. A meta-analysis showed that patients with confirmed CD had a significantly higher risk of retention compared to those with suspected CD. However, it has also been reported that the risk of capsule retention decreases after negative intestinal stenoses are confirmed using patency capsules, MRE, or CTE.[193] Therefore, when performing SBCE in confirmed CD, it is recommended to use a patency capsule to confirm bowel patency.

CQ10: Is enteroscopy recommended for follow-up observation after CD surgery?

Statement: SBCE or DAE is recommended for evaluating the remaining part of the small bowel after CD-related surgery.

Evaluation by modified Delphi panel method: median 9, minimum 7, maximum 9.

Strength of recommendation: 2; Evidence level: C.

Explanation: Clinical relapse within 5 years after CD surgery is reported to be 30–40%.[194] The most useful predictor of clinical relapse is endoscopic activity. The current gold standard for evaluating postoperative relapse is colonoscopy (ileocolonoscopy), which includes assessment of the terminal ileum. Postoperative recurrence can be reduced by optimizing treatment based on colonoscopic findings 6 months after surgery.[195] There are several reports on MRE and SBCE for the evaluation of postoperative ileal lesions that cannot be reached by colonoscopy, but very few reports on DAE.[196] Naganuma *et al*. reported that when retrograde DAE was performed 6–12 months after surgery, active inflammation of CD was observed not only near the anastomosis but also deep on the proximal side.[197]

Several small-scale prospective studies have evaluated activity using SBCE in postoperative CD patients, and most of them compared SBCE with colonoscopy. The criteria of SBCE findings indicative of postoperative recurrence vary, but most are based on the Lewis score (≥135) or Rutgeerts score (≥i,1 or ≥i,2). Bourreille *et al*. and Biancone *et al*. reported that the detection rate of postoperative recurrence in the neoterminal ileum using SBCE was not as high as that with colonoscopy.[198,199] Nonetheless, several reports indicate that SBCE can detect postoperative recurrence more frequently than colonoscopy,[200,201] and no consensus has been established in this regard. However, small bowel lesions can be found by SBCE beyond the reach of colonoscopy in more than 50% of cases.[198,200] A retrospective observational study examined the influence of SBCE findings on clinical outcomes in asymptomatic CD patients after ileocecal resection. The results revealed that both clinical and endoscopic recurrence rates after 1 year of ileocecal resection were significantly lower in the SBCE with colonoscopy group than in the colonoscopy alone group (drug therapy is initiated for patients with recurrence confirmed by either colonoscopy or SBCE).[202] Another study prospectively examined the relationship between lesions in the residual small bowel evaluated using SBCE less than 3 months after surgery and subsequent clinical recurrence in 25 patients with CD. The results revealed that residual small-bowel lesions are common (84.0%) and that lesions in the distal part of the small bowel are particularly associated with postoperative clinical relapse in CD.[203] Collectively, these findings indicate that SBCE is useful for the early detection of residual small-bowel lesions that increase the risk of postoperative recurrence in CD. However, when performing SBCE for postoperative CD, it is desirable to use a patency capsule to confirm GI tract patency.[193]

FRQ3: Can enteroscopy be used for evaluating Behçet's disease?

Statement: Enteroscopy is suggested for evaluating Behçet's disease.

Explanation: Typical endoscopic findings in Behçet's disease include a deep, circular, or oval ulcer found mainly in the ileocecal region, and this is also a diagnostic criterion for the disease.[204] If the purpose is only to check for such a lesion, this can be accomplished using a colonoscope. However, another diagnostic criterion is to be able to differentiate Behçet's disease from CD, intestinal tuberculosis, drug-induced enteritis, etc. It has been reported that DAE can be used to differentiate between Behçet's disease and CD.[205] Therefore, diagnostic accuracy may improve by endoscopic observation not only in the ileocecal area, but also deeper in the small bowel.

Regarding small-bowel lesions associated with Behçet's disease, there are reports that SBCE detects more lesions than in healthy subjects,[206] that lesions are observed in the jejunum in 63–80% of cases,[207,208] and that lesions increase from the jejunum onwards to the ileum.[209] These results indicate that many lesions exist in areas that cannot be accessed using a colonoscope. In addition, there are reports demonstrating the usefulness of SBCE for the assessment of endoscopic activity of small-bowel lesions,[210] and small-bowel stenosis due to Behçet's disease has also been reported.[211] Therefore, enteroscopy may be used not only for the diagnosis, but also for the assessment of disease activity or target lesions for endoscopic treatments such as EBD.

Although no reports have compared the accuracy of Behçet's disease diagnosis with and without enteroscopy, many retrospective studies have reported that this method can provide a wealth of information that complements colonoscopy. Thus, enteroscopy could be a key to making an appropriate diagnosis, provided that no contraindications or risks are involved.

Colonoscopy

CQ11: Is ileocolonoscopy recommended for diagnosing IBD?

Statement: Ileocolonoscopy is recommended for diagnosing IBD.

Evaluation by modified Delphi panel method: median 9, minimum 8, maximum 9.

Strength of recommendation: 1; Evidence level: B.

Explanation: IBD causes mucosal inflammation in the lower gastrointestinal tract—mainly from the ileocecal region to the large intestine—and direct observation of the lower gastrointestinal tract is essential for diagnosis. Crohn *et al*. first reported intestinal lesions of CD using gastrointestinal contrast radiography in 1932, when endoscopy was not yet commonplace.[212] Although the predominance of endoscopy compared to other modalities, including gastrointestinal contrast radiography, has not been proven because of the widespread use of endoscopic technologies, colonoscopy has already become the gold standard for diagnosing IBD, including UC. Since Hommes *et al*. specified the importance of endoscopy in IBD in their guidelines in 2004, many IBD treatment guidelines in Japan, Europe, and the United States clearly state that if IBD is suspected based on clinical symptoms or laboratory tests, colonoscopy should be performed for a definitive diagnosis.[11,19,180,213–215] Additionally, endoscopy with biopsy can be used to differentiate CD from UC and IBD from non-IBD, as well as determine disease activity.

Collectively, these findings suggest that it is important to perform colonoscopy to accurately diagnose IBD and decide on an appropriate treatment plan. Future evidence needs to be accumulated to determine whether chromoendoscopy, magnifying endoscopy, image-enhanced endoscopy, diagnostic aids using artificial intelligence, etc., have a better diagnostic accuracy than conventional white-light endoscopy.

CQ12: Is ileocolonoscopy necessary for evaluating CD activity?

Statement: Ileocolonoscopy is recommended to evaluate the disease activity and complications of CD lesions in the terminal ileum and the colorectum and to confirm the effectiveness of treatment and recurrence.

Evaluation by modified Delphi panel method: median 8, minimum 6, maximum 9.

Strength of recommendation: 2; Evidence level: C.

Explanation: Colonoscopy can be used to evaluate lesions in the entire colon as well as the terminal ileum and the anal region, which are the most common sites of CD lesions. Using a small-diameter scope or fluoroscopic guidance allows retrograde, selective, contrast radiographic assessment that enables the evaluation of the proximal ileum. Since CD is a chronic disease and requires repeated evaluations, it is necessary to consider sedation as well as the choice of endoscopic equipment. Anal stenosis can hinder endoscope insertion; however, the examination using a thin scope with sufficient sedation or dilation of the anal stenosis is recommended because of the high risk of perianal malignancies.[216]

Endoscopic remission is now considered a therapeutic goal in many clinical trials and in clinical practice. The International Organization for the Study of IBD (IOIBD) defines endoscopic response as a reduction of ≥50% in the Simple Endoscopic Score for Crohn's Disease (SES-CD) or the Crohn's Disease Endoscopic Index of Severity (CDEIS) and endoscopic remission as SES-CD 0–2.[217] In addition, endoscopic remission at the anastomotic site after surgery was defined as a Rutgeerts score of i0-i1 (<5 aphthous lesions).[218] Endoscopic remission is associated with improved outcomes, including sustained clinical remission, steroid-free clinical remission, lower risk of penetrating complications, lower surgical rates, and fewer hospitalizations.[217–225] In CD, patient-reported outcome (PRO) evaluation, based mainly on clinical symptoms such as abdominal pain and bowel movement frequency, has been reported to predict clinical remission 1 year after treatment intervention; however, it failed to predict endoscopic remission.[7] For this reason, it has been pointed out that there are limitations to determine treatment efficacy based solely on clinical scores, such as the Crohn's Disease Activity Index (CDAI).[31] The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) initiative proposed by the IOIBD recommended to set endoscopic remission as the treatment goal to achieve the higher-level goals, such as improving quality of life and eliminating disabilities.[226] Furthermore, endoscopic re-evaluation is recommended 6–9 months after intervention.[227]

Minimally invasive biomarker-based methods are also attracting attention as alternatives to endoscopy. The fecal calprotectin level reportedly has a moderate correlation with the SES-CD,[228] and serum leucine-rich α2 glycoprotein has also been shown to be effective in predicting endoscopic remission.[229] Nevertheless, endoscopy remains the gold standard, and the assessment combined with clinical

symptoms and biomarkers is thought to be useful in predicting disease activity and determining the timing of endoscopy.[230] Furthermore, since active lesions in the deeper part of the ileum have been shown to affect disease prognosis, ileocolonoscopy alone may be insufficient for the assessment of disease activity in CD with small-bowel involvement.[184] In this regard, colon capsule endoscopy can be a choice of endoscopic assessment because it allows the observation of the small bowel, while several issues regarding confirmation of gastrointestinal patency, total colon observation rate, and degree of bowel cleansing, being currently unapproved in Japan, remain to be addressed.[231] In addition, panenteric capsule endoscopy, PillCam Crohn's (Medtronic, Plainfield, IN, USA), has been available in foreign countries. In conclusion, colonoscopy is recommended for evaluating disease activity and complications such as intestinal stenosis of the colon including the terminal ileum in CD.

BQ3: Is ileocolonoscopy recommended for evaluating postoperative relapse in CD after surgery?

Statement: Ileocolonoscopy is recommended 6–12 months after surgery to evaluate relapse at the anastomotic site and other sites.

Explanation: CD cannot be completely cured by surgical treatment, and there is a risk of relapse after surgery. The postoperative relapse rate varies depending on various indicators (e.g., clinical, endoscopic, and surgical), and the rate of surgical relapse is the lowest and that of endoscopic relapse is the highest.[232] Colonoscopy enables identifying relapse that cannot be identified based on clinical symptoms, to differentiate between ischemic lesions on the anastomotic line and lesions due to CD relapse, and to confirm complications such as stenosis.[233] Actually, SBCE performed within 3 months after surgery has been reported to reveal residual or recurrent active lesions outside the anastomosis in 85.7% of cases.[234] Furthermore, in cases after ileocecal resection, evaluation by colonoscopy is important, because lesions in the large intestine as well as the anastomotic site or the proximal small bowel can be causative of reoperation.[235] When performing an examination, it is necessary to use sufficient sedation, if possible, to reduce the burden on the patient, and to choose an endoscope that is appropriate for the region to be observed.

The postoperative clinical course without any therapeutic intervention can be known from the data of the placebo group in a trial on postoperative remission maintenance therapy. The meta-analysis demonstrated that the median endoscopic relapse rate 1 year after surgery was 58% (95% confidence interval [CI] 51–65).[236] In a prospective study, the rate of endoscopic relapse 1 year after surgery was significantly higher in the placebo group than in the infliximab group (9.1% vs. 84.6%, $P = 0.0006$)[237]; the same was true after 18 months (22.4% vs. 51.3%, $P < 0.001$).[238] On the other hand, the cumulative reoperation rates 5 and 10 years after intestinal surgery in Japan were 23.4% and 48.0%, respectively; however, the 5-year cumulative surgery rate for patients who underwent initial surgery after May 2002 was 18.5%. The value was significantly lower than the 5-year cumulative surgery rate of 29.4% for patients who underwent surgery before April 2002 (hazard ratio [HR] 0.72, 95% CI 0.61–0.86), and it appears that the postoperative reoperation rate is decreasing with advances in medical treatment.[239]

Predictors of clinical relapse include preoperative disease activity, the indication for surgery (Montreal classification B3, penetrating type is more relevant than B2, stenotic type), and number of previous resections.[194] Smoking is the most important risk factor, with a meta-analysis showing that it increases the risk of endoscopic relapse by 2.5 times and the risk of clinical relapse by 2 times.[240] The European Crohn's & Colitis Organization (ECCO) lists active smoking, Montreal classification B2/B3, early steroid use, small-bowel lesion, and early onset as risk factors for postoperative relapse. The British Society of Gastroenterology (BSG) defines that patients with two or more factors of smoking, Montreal classification B3, history of multiple intestinal resections, anal fistulae, extensive small-bowel lesions, and residual active lesions are considered as having a higher risk of postoperative relapse.[19,232] It has been suggested that early postoperative intervention is ideal for patients with three or more of the risk factors defined by the ECCO and BSG. CD patients with these risk factors have a high need for precise assessment after surgery.[241]

Postoperative endoscopic relapse at the anastomotic site is defined as Rutgeerts score ≥i2 (the number of aphthous lesions is five or more, with normal mucosa between the lesions; skip lesions; or a lesion localized <1 cm from the ileocolic anastomosis).[194] However, in the POCER study, a randomized clinical trial of postoperative CD relapse, endoscopic assessment 6 months after surgery (for Rutgeerts score ≥i2, treatment will be stepped up based on the algorithm) contributes to the prevention of endoscopic relapse 18 months later, rather than continuing drug therapy adopted early after surgery without endoscopic assessment (relative risk [RR] 0.73, 95% CI 0.56–0.95).[195] In that study, 83% of patients received postoperative azathioprine or adalimumab due to a high risk of relapse, suggesting the

importance of postoperative disease assessment even when therapeutic intervention has been started soon after surgery. For these reasons, colonoscopy 6–12 months later is recommended to evaluate endoscopic recurrence after CD surgery. If therapeutic intervention is started, re-examination of endoscopic evaluation should be attempted at ~6 months. Evaluations other than colonoscopy include clinical disease activity and biomarkers such as fecal calprotectin (FC). However, the CDAI does not have a high concordance rate with endoscopic activity 1 year after intestinal resection ($\kappa = 0.12$).[242] The FC level has a higher negative predictive value for postoperative relapse than the CDAI.[243,244] It has also been reported that if the FC level increases by 100 μg/g, the risk of clinical relapse increases by 18%.[245] However, FC levels may be affected by the mucosal inflammation of the deeper regions of the small bowel. FC should be used as a minimally invasive postoperative assessment measure of disease activity, and colonoscopy should be performed when necessary.

CQ13: Can endoscopic scoring be useful in the assessment of CD?

Statement: Endoscopic scoring is recommended for objective evaluation of CD endoscopic findings.

Evaluation by modified Delphi panel method: median 7, minimum 6, maximum 9.

Strength of recommendation: 2; Evidence level: B.

Explanation: In the treat-to-target treatment strategy for IBD, endoscopic remission is currently considered an objective and ideal long-term treatment goal.[226] However, it is well known that the evaluation of endoscopic findings may differ, depending on the endoscopist, which makes endoscopy a subjective method.[246] Several papers have shown that endoscopic scores can be used to objectify this subjectivity and provide useful data for comparison with other patients and for follow-up observations of the same patient.[247–249] It is known that there is a weak correlation between clinical disease activity and endoscopic disease activity, especially in CD with small-bowel lesions.[250] Therefore, the significance of endoscopic observation to evaluate actual CD activity has also been recognized.[226] Actually, in multicenter prospective randomized controlled trials, such as the well-known SONIC study and the DIAMOND study conducted in Japan, the effectiveness of each treatment was compared using the endoscopic score.[251,252] Thus, it is necessary to understand the representative scoring methods, including evaluation area, calculation methods, and the presence or absence of validation, etc.[253]

The oldest endoscopic score for CD is the CDEIS, which was first introduced in 1989 and has been validated.[254] However, the colorectum is scored based on four segments —the right colon, transverse colon, left colon, and rectum— whereas only one part of the small bowel, the terminal ileum, which can be observed using conventional ileocolonoscopy, is scored. Above all, the calculation formula based on multiple regression analysis is complex and has been scarcely used recently in daily clinical practice or clinical research. To compensate for the complex shortcomings of the CDEIS, the SES-CD was developed in 2004 and has since then been validated.[255] However, the evaluation sites are the same as in CDEIS. Furthermore, it has been pointed out, especially in the biologic era, that the development of stenosis caused by scarring of the ulcers due to effective treatment makes it difficult to accurately evaluate overall treatment effectiveness. Subsequently, the number of clinical studies using the modified SES-CD to compensate for these issues has been increasing.[256] In particular, the modified multiplier SES-CD (MM-SES-CD), which adds weighted coefficients to each SES-CD subscore, is attracting attention because the coefficient for the ileum, which is frequently responsible for hospitalization and surgery, is larger than for other sites.[257]

Postoperative recurrence is also an important issue in CD. In cases undergoing ileocecal resection, a common surgical procedure in CD, endoscopic recurrence has been demonstrated to frequently occur at the anastomotic site called the neo-terminal ileum before clinical recurrence.[194] Based on the findings, endoscopic evaluation 6–12 months after surgery has been considered as the appropriate postoperative management. The endoscopic score used in this study was the Rutgeerts score; while it can only evaluate the neo-terminal ileum, the score is occasionally used not only for the assessment of anastomotic site, but also for evaluating other areas. CD is theoretically a disease that can involve the entire gastrointestinal tract, but it is clinically difficult to perform periodic endoscopic examinations of the entire gastrointestinal tract. For this reason, the idea that the endoscopic evaluation of the most important parts of each CD patient can compensate that of the entire gastrointestinal tract has been recently proposed to implement the treat-to-target clinical strategy, although this remains an area of future study.[258]

From a different perspective, CD is a disease in which intestinal damage (e.g., stenosis) can progress. The issue is not only the activity of gastrointestinal mucosal lesions, but also the severity of damage due to intestinal destruction (e.g., stenosis), and the Lémann Index was developed as a

score that reflects these factors.[259] However, this scoring system requires all types of imaging modalities, including esophagogastroduodenoscopy, colonoscopy, MRE or SBCE and MRI for perianal lesions, and complicated calculations, making it difficult to use in clinical practice. Future improvements and development of other scores with the same intention are expected. Other SBCE scores include the Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI).[260,261] Although both have been validated, it is important to note that the former was not developed specifically for CD.

The definition of endoscopic efficacy and endoscopic remission, as well as indicators for treatment intensification, are also important. The IOIBD defines the endoscopic response as reduced by >50% of SES-CD and endoscopic remission as SES-CD 0–2.[217] It has been also proposed that endoscopic remission is defined as the disappearance of ulcerative lesions in the entire gastrointestinal tract.[248] The intensification of treatment should be determined by comprehensive assessment of endoscopic findings, clinical course, the difference from previous examination, etc. Recently, the modified Rutgeerts score, which subclassifies the i2 Rutgeerts score (more than five aphthous lesions with normal mucosa observed between lesions, skip lesions, or a lesion localized <1 cm from the ileocolic anastomosis), has been accepted as an easy-to-imagine endoscopic index, and i2b (more than five aphthous ulcers or large lesions with normal mucosa between the lesions, or proximal ileal lesions regardless of the presence or absence of lesions at the anastomotic site) is considered as an indication for intensifying treatment.[262] Knowledge regarding this indication is likely to increase its use in the future.

CQ14: Is endoscopic treatment effective for colonic stenosis in CD?

Statement: EBD is recommended for colonic stenosis in CD.

Evaluation by modified Delphi panel method: median 8, minimum 6, maximum 9.

Strength of recommendation: 1; Evidence level: C.

Explanation: Stenosis is a CD-related complication that can lead to hospitalization and surgery due to intestinal obstruction. Endoscopic balloon dilation (EBD) for CD stenosis is effective in avoiding hospitalization and surgery.[263] In particular, EBD for colonic stenosis, where there is a high possibility that the endoscope will reach the stenotic lesion, can be expected to have a higher success rate than for small-bowel stenosis due to a reduction in the difficulty of the procedure. Although there are no randomized controlled trials that provide evidence for the effectiveness of EBD, several meta-analyses have been reported. A meta-analysis of 141 cases of EBD found that the short-term efficacy was 87%, the incidence of complications such as perforation was 2.9%, and symptomatic relapse was observed in 70.5% cases during the 23.1-month observation period. It was reported that 59.6% of patients required re-EBD and 30.8% required surgery. It has also been reported that symptomatic relapse (HR 2.1, $P = 0.003$), Asian ethnicity (HR 2.8, $P < 0.001$), and small-bowel lesions (HR 1.9, $P = 0.004$) were risk factors for recurrent EBD, and that prestenotic dilatation (HR 1.9, $P = 0.001$) was a risk factor for surgery.[264] In a meta-analysis comparing anastomotic and nonanastomotic stenosis, the surgery rate after EBD was lower for anastomotic stenosis (18% vs. 29%); however, it did not reach statistical significance (RR 0.88, 95% CI 0.59–1.32, $P = 0.54$). A stenosis less than 4 cm in length significantly lowered the risk of requiring surgery after EBD (RR 0.48, 95% CI 0.26–0.90, $P = 0.02$).[265] Regarding the long-term prognosis, an observational study of 72 cases, including those with small-bowel stenosis, in Japan reported that the cumulative nonsurgical rate after EBD was 81.1% at 3 years and 73.5% at 5 years. The onset of CD at age 16 or younger was a risk factor for requiring surgery after EBD (HR 3.69, 95% CI 1.36–10.01, $P = 0.011$).[266]

The short-term effectiveness of CD treatment depends on procedural success, and the accurate judgment for the indication of EBD is important for procedural success. The following conditions are listed: (i) stricture length is 5 cm or less; (ii) there is no fistula or abscess in the stricture; (iii) there is no deep ulcer in the stricture; and (iv) there are no severe bends or adhesions.[149,180,267] Other procedural factors are also relevant, such as the selection of endoscopic equipment, tip attachment, and the size of the dilation balloon. On the other hand, medical treatment based on the treat-to-target approach affects long-term prognosis after EBD. A systematic review of 25 studies with drug therapy data reported that 50% of CD patients treated with anti-TNFα antibody avoided surgery over a 4-year observation period.[268] Furthermore, in a Japanese observational study of EBD for small-bowel lesions associated with CD, the cumulative surgery rate after EBD for patients with ulcerative lesions in the stenotic area was 19.2% at 1 year and 39.8% at 5 years. The surgery rate after EBD was significantly higher for patients with ulcerative lesions in the stenotic area than for patients without ulcers (31.7% vs. 11.4%, $P = 0.029$). Multivariate analysis also indicated that this was a risk factor (HR 4.84, 95% CI 1.58–14.79,

$P = 0.006$).[269] Similar results are expected for colonic stenosis. As such, evaluating the stenotic area by endoscopic examination after EBD and implementing appropriate medical treatment based on a treat-to-target strategy will likely improve the long-term prognosis after EBD.[270] Anal stenosis, which is often accompanied by anal fistulas and perianal abscesses, requires a different approach than colonic stenosis, and requires management that also takes into account the risk of cancer.

Endoscopic treatments for CD stenosis other than EBD include stent placement and endoscopic stricturotomy (ES). A meta-analysis of nine studies on 163 cases of stent placement found that seven studies used self-expanding metal stents and two studies used self-collapsing stents. The reported technical success rate was 93% (95% CI 87.3–96.3), the clinical success rate of eliminating stenosis symptoms was 60.9% (95% CI 51.6–69.5), and 9.6% of patients required re-stent placement (95% CI 5.3–16.7).[271] It is worth noting that total adverse events were observed in 15.7% of patients, proximal stent deviation in 6.4%, perforation in 2.7%, and abdominal pain in 17.9% of patients. In a prospective randomized controlled trial (the ProtDilat study) comparing self-expanding metal stent placement with EBD, a self-expanding metal stent group of 39 patients and an EBD group of 41 patients were compared. The percentage of patients who did not require any intervention after 1 year was 80% in the EBD group compared to 51% in the self-expanding metal stent placement group, indicating that EBD was significantly more effective (odds ratio 3.9, 95% CI 1.4–10.6, $P = 0.0061$).[272] Considering the pathology of intestinal stenosis in CD and the impact on surgical procedures if the stent prolapses, the effectiveness and safety of stent placement for colonic stenosis in CD have not yet been established. Furthermore, it must be kept in mind that stent placement is not covered by insurance for benign colonic stenosis in Japan.

Evidence regarding ES is even more scarce and consists mainly of case series. In a retrospective study comparing 21 cases of ES and 164 cases of EBD, the short-term procedural success rate was 100% for ES and 89.5% for EBD. Furthermore, ES tended to have a higher efficacy rate than EBD, with improvement in stenosis symptoms being 72.7% vs. 45.4% ($P = 0.08$).[273] The probability of requiring surgery after endoscopic treatment was significantly lower in ES (9.5% vs. 33.5% for EBD, $P = 0.03$). However, no case of EBD required blood transfusions after procedures, whereas 8.8% of ES cases required transfusions. In a historical cohort study comparing ES and anastomotic resection for anastomotic stenosis after ileocecal resection, 37 cases of ES and 147 cases of ileocecal resection were compared, and the probability of requiring surgery was 11.3% for ES and 10.2% for ileocecal resection, with no significant difference between the two groups. However, it has been reported that the rate of adverse events was significantly lower for ES (10.2%, compared to 31.9% for anastomotic resection).[274] The indications for ES are currently limited to the anastomotic stenoses after ileocecal resection and short strictures in the distal ileum. Since it requires more advanced endoscopic techniques than EBD, its effectiveness and safety have not yet been established.

CQ15: What indicators are recommended for endoscopic evaluation of UC activity?

Statement: Although the Mayo endoscopic subscore (MES) is currently the most commonly used index for UC endoscopic activity evaluation, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is also recommended to evaluate the difference in endoscopic activity before and after treatment more objectively.

Evaluation by modified Delphi panel method: median 8, minimum 6, maximum 9.

Strength of recommendation: 2; Evidence level: D.

Explanation: The popularity of the endoscopic activity score for UC has been described in the "Second Edition Collection of Activity Evaluation Indices for Inflammatory Bowel Disease" published by the Ministry of Health, Labor and Welfare.[275] This was estimated from 164 studies extracted by the literature search in PubMed using the search terms [ulcerative colitis] and [clinical trial] (English). The results showed that the Mayo score (including the MES)[276] was most frequently used (in 113 studies, 68.9%). As the MES can be used simultaneously with clinical activity indicators, it is currently the most commonly used indicator for treatment evaluations in clinical trials. The MES is a four-point index: 0, normal or inactive findings; 1, mild (redness, decreased vascular visibility, mild friability); 2, moderate (significant redness, loss of vascular visibility, friability, erosion); and 3, severe (spontaneous bleeding, ulcer). The advantage of MES lies in its simplicity due to it being a simple four-grade evaluation; however, there is often little change in scores before and after treatment.

The second-most commonly used indicator is the disease activity index (DAI) score (including the Sutherland index) at 29.9%, followed by the Rachmilewitz index at 6.7%, and the Baron index (including the modified Baron index) at 4.9%.[275] However, compared to the MES, they are quite less frequently used worldwide, including Japan.

The UCEIS[277] is a newer endoscopic score proposed by Travis *et al.* in 2012, and the one revised in 2013[278] is currently in use. This index includes three descriptors: "vascular pattern," "bleeding," and "erosions and ulcers."

The system evaluates each area with the strongest findings separately and then combines the results to obtain a final score. Therefore, changes in each finding can be easily evaluated, and the score range is relatively wide (0–8), making it possible to evaluate endoscopic change before and after medical treatment more objectively than with the MES. Validation to evaluate interobserver variation in endoscopic evaluations showed that there was a high degree of agreement between raters.[278] At present, the reported frequency of use is not high (3.7%),[275] but more studies on mucosal healing evaluated by the UCEIS are being published every year, and so it is likely that its adoption rate will increase in the future.

The above-mentioned scores are calculated by the scores of the most severe area. Thus, even if an active lesion area is clearly improved after treatment, the grade may not change. This is because these endoscopic scores were basically created on the premise of the evaluation using a sigmoidoscope. However, total colonoscopy is now widely performed worldwide, and it has been proposed that the severity of UC should be evaluated based not only on the severity of mucosal findings but also on changes in the extent of the lesions over time. The Ulcerative Colitis Colonoscopic Index of Severity (UCCIS),[279] which was first reported in 2013, considers five segments each of the cecum/ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, and scores for four items—vascular pattern, granularity, friability, and ulceration—are added. Since these four items have been demonstrated to have high interobserver agreement in previous reports, it is expected that the degree of agreement between evaluators will be high. However, this method has the disadvantage that it is not possible to compare patients with a different disease type, because the score varies significantly, depending on the lesion extent. In addition, the calculation method is complicated, possibly hindering the future adoption rate.

CQ16: What is the definition of endoscopic remission in UC?

Statement: There is no consensus on the definition of endoscopic remission in UC. Most commonly, MES 0 or 1 is considered endoscopic remission.

Evaluation by modified Delphi panel method: median 8, minimum 6, maximum 9.

Strength of recommendation: 2; Evidence level: D.

Explanation: Endoscopic remission, or mucosal healing, has long been a goal of treatment for UC, but its definition is not clear. Currently, the most frequently used endoscopic activity score in UC is the MES.[275] However, there is no consensus on whether mucosal healing is considered at MES 0 or MES 0–1. In a clinical study on infliximab use, there was no difference in the subsequent surgery rate between the MES 0 and MES 1 groups,[280] and it has generally been thought that the treatment goal for UC is to aim for MES ≤1. However, the STRIDE[281] guidelines, published in 2015, specified that the optimal treatment goal is MES 0 and that the goal should be at least MES 1. Furthermore, a Spanish longitudinal cohort study published in 2016[282] used the Kaplan–Meier method to examine clinical relapse in 187 cases of UC in which MES 0 or MES 1 was confirmed by colonoscopy. The results showed that the MES 0 group had a significantly lower clinical relapse rate (P = 0.0002, log-rank test), indicating the clinical significance of achieving MES 0. A meta-analysis of 17 clinical studies comparing MES 0 and MES 1 published in 2020 found that patients who achieved MES 0 had a 52% lower risk of clinical relapse than those with MES 1 (RR 0.48, 95% CI 0.37–0.62).[283,284] In a latest international clinical trial examining the efficacy of upadacitinib for UC, in terms of secondary end-points, MES ≤1 was defined as endoscopic improvement, whereas MES 0 was defined as endoscopic remission.[284] This suggests that we will move towards MES 0 as the criterion for endoscopic remission in the future.

On the other hand, the UCEIS, which has recently been used more frequently along with the MES, did not originally indicate any definition of endoscopic remission.[277,278] Vuitton *et al*. attempted to reach a consensus regarding the definition of endoscopic remission based on the results of two Delphi polls conducted by 15 IBD specialists. They reported that there was a high level of agreement in defining UCEIS 0 as endoscopic remission.[285] Since UCEIS has not yet been widely adopted as an evaluation item in clinical trials, future studies should be awaited before any further progress can be made.

CQ17: Is colonoscopy recommended after medical treatment for UC?

Statement 1: If clinical remission is achieved after medical treatments, we suggest colonoscopy to evaluate endoscopic activity.

Evaluation by modified Delphi panel method: median 8, minimum 4, maximum 9.

Strength of recommendation: 2; Evidence level: D.

Statement 2: If clinical symptoms do not improve after medical treatments, we suggest colonoscopy to consider alteration of medical treatment.

Evaluation by modified Delphi panel method: median 8, minimum 7, maximum 9.

Strength of recommendation: 2; Evidence level: D.

Explanation: Although multiple biomarkers have recently been available for clinical practice, endoscopy remains an important tool for evaluating disease activity. According to the ECCO endoscopic guidelines for IBD,[31,213] endoscopic re-evaluation should be performed after treatment modification in cases of treatment resistance, unexplained residual symptoms, relapse, or when considering surgery. In such cases, evaluation using a sigmoidoscope is recommended.[31]

No studies have directly examined the significance of endoscopic reassessment when clinical remission has been achieved after treatment initiation. However, the latest ECCO guidelines state that treatment efficacy after therapeutic intervention should be determined using a combination of endoscopy and biomarker analyses in addition to clinical symptoms.[31] Cohort studies[220] and a meta-analyses[286] indicate that endoscopic improvement is associated with subsequent clinical remission, steroid-free remission, and surgery. The positive correlation of endoscopic activity after treatment with clinical outcomes such as recurrence and surgery has been reported with tacrolimus,[287–289] anti-TNFα antibodies,[280,290,291] and cyclosporine.[292] Based on these findings, the STRIDE-II guidelines recommend endoscopic evaluation after therapeutic intervention in accordance with a treat-to-target algorithm.[293]

There is no evidence regarding the timing of endoscopic activity reassessment after therapeutic intervention. However, it has been suggested that if therapeutic efficacy is observed, mucosal healing should be evaluated using endoscopy or the FC level assessment ~3–6 months after treatment.[31] Of note, the time to achieve endoscopic remission varies depending on the types of medical treatments and ranges from 11 to 20 weeks according to the STRIDE-II guidelines.

FRQ4: Is colonoscopy recommended for severe UC?

Statement: We suggest sigmoidoscopy by an experienced endoscopist after thorough consideration of the indications.

Explanation: No studies have directly examined the significance of endoscopy in severe UC. However, endoscopy should ideally be performed if the situation allows and considering the necessity to assess the intensity and extent of intestinal mucosal inflammation, to differentiate other diseases such as infectious enteritis, and of histological evaluation of cytomegalovirus reactivation. In such cases, sigmoidoscopy would be the optimal procedure.[294] Due to the risk of intestinal perforation during endoscopy, it is recommended that indications of endoscopy be thoroughly considered, and that the procedure be performed in a short period of time by an experienced endoscopist. In cases of severe inflammation, insufflation should be minimized, the procedure should be performed without the use of bowel-cleansing agents, and inversion observation in the rectum should be avoided.[19]

Several studies have examined the relationship between endoscopic activity before treatment and treatment efficacy for acute severe UC. It has been reported that a C-reactive protein level ≥50 mg/L, albumin level ≤3.0 g/dL, and MES 3 are risk factors for steroid resistance in patients with acute severe UC.[295] In other studies, deep ulceration[294] and high UCEIS before treatment[296,297] were reported as factors associated with the requirement of surgery. Based on these findings, colonoscopy before treatment is considered useful for predicting disease activity and therapeutic efficacy in severe UC.

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