Benefits and Risks of Applying the Guidelines

The statements of recommendation in these Guidelines are standard clinical indicators for CD. They support decision making of practitioners , but they neither regulate nor restrict their clinical practice. They are not intended to be a basis for a legal judgment. With the support of specialists as needed, and with the flexible use giving sufficient consideration the patients' values, the Guidelines will promisingly contribute to the improved quality of clinical practice and patient outcomes.

In actual clinical practice, the patients' values and practitioners' sound judgment are paramount, and it would be inappropriate for these Guidelines to be used to control clinical practice, to provide a legal basis for clinical practice, or to restrain a practitioners' discretion, and these Guidelines would instead be considered harmful if used in such a manner.

Independence of Guidelines

These Guidelines have been developed for common objectives by the same members of the Committees for Developing Guidelines, established by the Japanese Society of Gastroenterology and the Project Research Sub-Group, in Research Group of Intractable Inflammatory Bowel Disease, subsidized by the Ministry of Health, Labour and Welfare of Japan. They have been developed independent of any other funding sources and without the cooperation or coordination of any other academic organizations, health care providing organizations, or patient organizations.

A comprehensive list of potential conflicts of interest between health/medical industries and members of the Committees for Developing Guidelines is dsclosed. Such relationships are related to the individual members or the institutions, and no funding has been provided for the development of these Guidelines.

Problems and Future Issues Concerning the Guidelines

For these Guidelines, the statements of recommendation were created with an emphasis on literature based evidence in response to the clinical questions (CQs) raised from the patients point of view, and were reviewed and modified by a group of experts. The recommendation grades were respectively determined on the basis of the levels of evidence and clearly integrated by formal consensus. As a result, these guidelines would thus appear to possess internal validity, and clinical applicability and flexibility. They have not, however, been evaluated for their effectiveness, in terms of actual contribution to the improved quality of clinical practice for CD, and this is an issue to be addressed.

With accumulation of new evidence, a process of review and modification of the Guidelines are necessary. These Guidelines may need to be revised and supplemented by three years or so after the publication. Assessment by the users should be considered for revision, and therefore constructive criticisms are invited.

Disclosures of Conflicts of Interest

1. Disclosure of potential conflicts of interest in relation to health/medical industries for members of the Committees for Developing Guidelines

The health/medical industries from which members of the Committees for Developing Guidelines have been provided with remuneration according to medical professional contracts, or for lectures, written contributions, supervision of publications, etc., or from which they have received research funding, are listed in Table 4 on their own declaration, regardless of their relations with CD medication. The names of the pharmaceutical businesses are those as of June 2011, and are shortened as in the *Manual of Medical Therapeutics*, 2011 (IGAKU-SHOIN, Ltd.). Publishers and non-profit organizations that adopt a position of neutrality are excluded.

Table 4 Disclosure of conflicts of interest

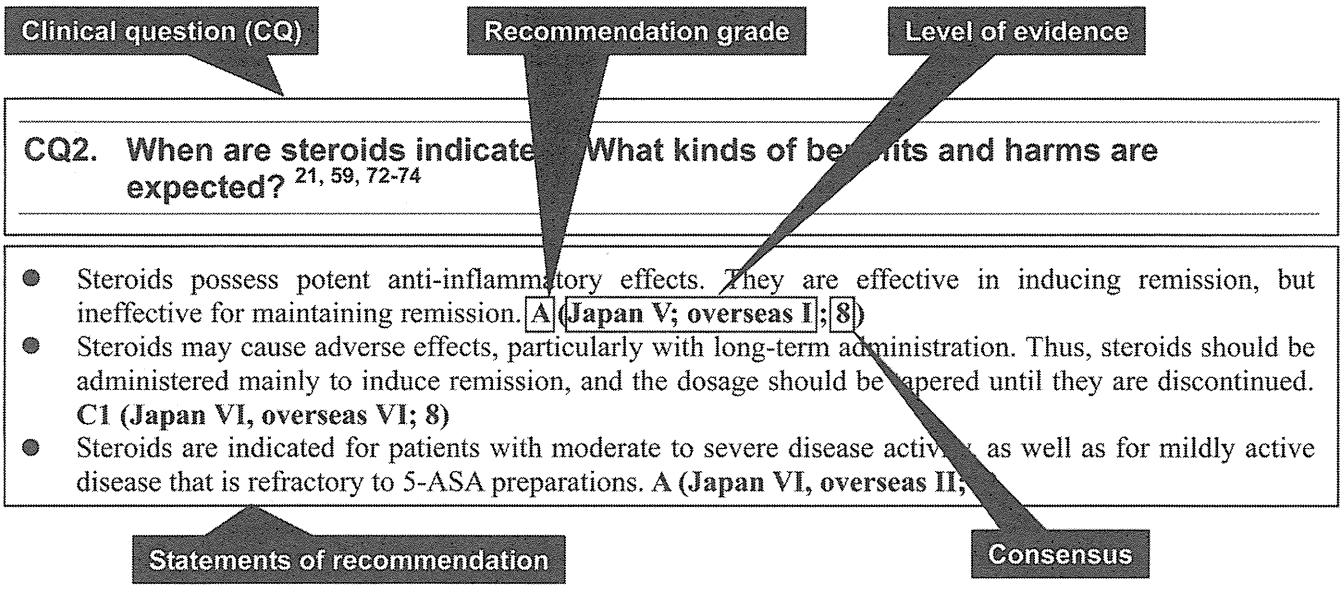
Medical professional contracts
Ajinomoto, Astellas, Abbott, Eisai, LTT Bio-Pharma, Otsuka, Kyorin, Zeria, Mitsubishi Tanabe, Chugai, FUJIFILM Medical, Bristol, Merck Serono
Remuneration for lectures, written contributions, supervision of publications, etc.
Asahi Kasei Kuraray Medical, Ajinomoto, ASKA, Astellas, AstraZeneca, Abott, EN Otsuka, Eisai, MSD, Otsuka, Otsuka Pharmaceutical Factory, Olympus Medical Systems, KAKEN, Kyorin, Kyowa Hakko Kirin, GSK, Shionogi, JIMRO, Zeria, DAIICHI SANKYO, Tyco, Dainippon Sumitomo, Taiho, Takeda, Mitsubishi Tanabe, Chugai, TSUMURA, Terumo, TORAY, Torii, NIPPON KAYAKU, Nihon Schering, Novartis, FUJIFILM Medical, Bristol, Boston Scientific Japan, Merck Serono, Yakult, Janssen, UCB
Provision of research funding
Asahi Kasei Kuraray Medical, Ajinomoto, Astellas, AstraZeneca, EN Otsuka, Eisai, MSD, Otsuka, Otsuka Pharmaceutical Factory, Olympus Medical Systems, KAKEN, Kyowa Hakko Kirin, Kyorin, KUREHA, GSK, Shionogi, JIMRO, J&J, Zeria, DAIICHI SANKYO, Tyco, Taisho Toyama, Dainippon Sumitomo, Taiho, Takeda, Mitsubishi Tanabe, Chugai, TSUMURA, Torii, Pfizer, FUJIFILM Medical, Bristol, MIYARISAN, Merck Serono, Yakult, UCB
Potential conflicts of interest though family members
Shionogi

2. Measures to minimize conflict of interest

The statements of recommendation were created on the basis of literature based evidence. The consensus of the Assessment Committee was formally developed according to the Delphi method to avoid any particular member's dominant opinions. The recommendation grades were determined on the basis of the levels of evidence with integration by formally developed consensus, clearly indicated by the median values of Delphi rounds. In general, these Guidelines have been developed in accordance with the proposed COGS standard[1].

How to Read the Guidelines

In the text, clinical questions (CQs) are presented according to clinical categories, and each are followed by one or more corresponding statements of recommendation. Each of the statements is accompanied by a recommendation grade that indicates the strength of the recommendation. The recommendation grade, which is defined in Table 3, is followed by the levels of evidence of the literatures that are the basis for the recommendation (in Japan and overseas) and the value of the expert group consensus (i.e., the Delphi evaluation median). The comments provide a general description of the clinical practice related to each CQ. The lists of references are presented for each clinical category.



Comments: Randomized controlled trials were conducted in Europe and North America in the 1970s and 1980s to evaluate the effect of steroids, and a meta-analysis showed their efficacy in inducing remission [72]. However, efficacy in maintaining remission was not shown [73]. In the randomized controlled trials adopted in the meta-analysis, steroids were shown to be more efficacious than placebo or 5-ASA preparations in cases of disease of varying severity with CDAI scores ranging from 150 to 450 [72]. However, the indication for steroids has changed with the emergence of anti-TNF agents.

While steroids have potent anti-inflammatory effects, they may cause adverse effects, such as compromised immune functions, impaired glucose tolerance, delayed wound healing, and osteoporosis. Furthermore, they are not effective in maintaining remission. Accordingly, steroids should not be administered for prolonged periods [21]. In cases where 5-ASA preparations cannot induce remission, oral administration of steroids is recommended. When administering steroids, the dosage should be tapered down to eventual termination irrespective of the response [21, 56, 58, 59]. Daily administration of 9 mg budesonide (not yet approved in Japan), which is a steroid with reduced systemic side effects, is effective in inducing remission in mild to moderate cases [56, 57, 74].

Glossary

The text of these Guidelines includes abbreviations commonly used among health care providers. Most of these are accompanied by the full forms when they first occur. Common abbreviations are listed below in alphabetical order, with their full forms and some descriptions.

ASA: aminosalicylic acid. 5-ASA preparations include not only 5-ASA (mesalazine) but also salazosulfapyridine.
AZA: azathioprine
CD: Crohn's disease
CDAI: Crohn's disease activity index
ECCO: European Crohn's and Colitis Organisation
GMA: granulocyte-monocyte apheresis
IBD: inflammatory bowel disease
IC: indeterminate colitis
IOIBD: International Organization for the Study of Inflammatory Bowel Disease
6-MP: 6-mercaptopurine
MTX: methotrexate
NSAIDs: nonsteroidal anti-inflammatory drugs
PSC: primary sclerosing cholangitis
QOL: quality of life
SASP: salazosulfapyridine
TNF: tumor necrosis factor. Among the anti-TNF-α antibodies, only infliximab and adalimumab are currently approved for use in Japan.
TPN: total parenteral nutrition
UC: ulcerative colitis

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I. Disease Concept

I-1. Definition

CQ1: What is CD? [2]

- CD is a chronic disease of unknown causes that mainly presents as granulomatous inflammatory lesions of the gastrointestinal tract. **C1 (Japan VI, overseas VI; 8)**

Comments: CD is a chronic inflammatory disease of the gastrointestinal tract characterized by discretely distributed transmural granulomatous inflammations and fistulas. Lesions of CD may occur throughout the entire gastrointestinal tract, but they occur most commonly in the small intestine, the colon (especially the ileocecal region), and the perianal region [2]. The disease occurs at a young age, and lasts chronically, with remissions and relapses of symptoms and signs such as abdominal pain, diarrhea, hematochezia, fever, perianal symptoms, and weight loss, resulting in a reduced quality of life for the patients. Also, CD may cause extra-intestinal complications in the joints, the skin, the eyes, and other parts of the body. CD and ulcerative colitis (UC) are together referred to generically as inflammatory bowel disease (IBD). Although they have common and/or similar features, they are considered to be mutually distinct.

I-2. Epidemiology

CQ2: How common is CD, in what age group does it occur, and in Japan, are there any differences from other countries? [2-7]

- The number of CD patients in Japan is steadily increasing, with a current estimate of more than 30,000. CD is more prevalent among men then women, at an approximate ratio of 1.8:1.0. **B* (Japan V; 9)**
- CD occurs at comparatively young ages, more commonly from the late teens to the early 30s. **B* (Japan V; 9)**
- The prevalence and incidence of CD in Europe and North America are higher than those in Japan, and female preponderance in those areas is noted. **C1 (overseas V; 8)**

Comments: A Japanese nationwide epidemiological survey in 1991 reported that the prevalence of CD was 5.85 per 100,000 (7.94 among men and 3.83 among women) and that the incidence of CD was 0.51 per 100,000 (0.71 among men and 0.32 among women) [3]. The figures were clearly lower than those in Europe and North America. Although no such survey has been conducted since then, the estimated number of CD patients has steadily increased in Japan [4], and more than 30,000 received registered medical services for CD in 2009.

The onset of CD is usually in young people, commonly in the early third decade among men and in the late second decade among women [2-4]. According to the Japanese national registration record for medical services, it is estimated that CD occurs more commonly in the third and early fourth decades among men and in the late second decade among women [5].

The incidence in countries overseas is usually higher than that in Japan, although it varies from region to region; there are a substantial number of regions with a CD incidence rate of around 10 per 100,000 in Europe and North America. It has been shown that the prevalence of this disease has been increasing globally from year to year [6]. In general, CD is more common in women in Europe and North America, unlike in Japan [7]. At present, Japan is ranked in the middle for the prevalence and incidence rates of CD, together with South Korea, Oceanic countries, and South Africa [4].

I-3. Etiology

CQ3: What causes CD? Is it inherited? What are the risk factors? [8-19]

- The causes of CD have not been identified. **C1 (Japan VI, overseas VI; 8)**
- A tendency for familial occurrence is noted. **B (overseas IVa; 8)**
- Some causal relationships between diet and CD have been reported, though the evidence is not conclusive. **B (Japan IVb, overseas IVb; 8)**

- Smoking is a risk factor for CD. **B (overseas III; 8)**
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives are potential factors for the exacerbation of CD. **C1 (overseas IVb; 7)**

Comments: The causes of CD have not yet been identified. The current international consensus is that the intestinal inflammation is caused by a disordered immunomodulatrory mechanism, with exposure to various environmental factors in an individual with genetic susceptibility [8-10]. A somewhat higher incidence of CD is reported among relatives [11, 12], and reports of familial clustering indicate the presence of a genetic mechanism. Studies are underway to find the disease susceptibility genes for CD.

Regional differences in the incidence of CD suggest a causal relationship between diet and CD, and many clinical and epidemiological studies have been reported. Some overseas reports found a causal relationship between CD and high intakes of carbohydrates (particularly sugar) [13, 14], and some reports from Japan showed a causal relationship between CD and "fast foods" with high contents of fats and sugar [15]. However, no food has been concluded to be a risk factor for CD.

Smoking is considered to be a risk factor for CD. Reports have shown that smoking is not only related to the onset, relapse, and exacerbation of CD, but also that smoking cessation lowered the postoperative recurrence rate [16]. Smoking also affects the efficacy of infliximab treatment [17].

Among many drugs evaluated, NSAIDs and oral contraceptives have been shown to be associated with the onset and exacerbation of CD [18, 19].

I-4. Pathophysiology, classification, and disease activity

CQ4: What kind of pathophysiological conditions are present in CD, and how are they recognized? [20]

- To provide appropriate treatment, it is necessary to exactly recognize the disease extent, disease pattern, and degree of disease activity. **B* (Japan VI, overseas: VI 9)**

Comments: The pathophysiological conditions of CD are complex, but correct recognition is the first step for appropriate management. It is important to identify the distribution of the lesions, to recognize the disease pattern, and to assess disease activity/severity.

The lesions are often found in the small intestine, the colon (particularly in the ileocecal region), and the perianal region, and are classified as the ileal, colonic, and ileo-colonic types. Note, however, that lesions can occur at any site in the gastrointestinal tract; moreover, CD may have extra-intestinal complications causing systemic involvement. Treatment plans differ according to the sites of involvement.

According to an international proposal, the disease patterns can be classified as "Inflammatory", "Penetrating", and "Stricturing" [20]. Recognition of the disease pattern is also important for appropriate treatment.

Furthermore, it is necessary to assess the disease activity. Treatment during the remission phase when the symptoms have abated or are absent is different from treatment during the active phase when various symptoms interfere with daily life. For the objective evaluation of the disease activity and severity, the Crohn's Disease Activity Index (CDAI) is available, but it is not suitable for daily clinical practice. The Index of Inflammatory Bowel disease (IOIBD) is simple, but it does not assist in the selection of appropriate treatment options. At present, there is no universal classification of CD severity available for use in Japan. In general clinical practice, the disease activity can be assessed by the comprehensive evaluation of subjective symptoms, clinical findings, and laboratory investigations.

I-5. CD progression

CQ5: How does CD progress in the long term? Is there an increased risk of cancer? Is life expectancy shortened? [21-29]

- CD persists, with remissions and relapses, for a long period of time. **C1 (Japan VI, overseas VI; 9)**
- During disease progression, the daily life of CD patients is often disturbed. **C1 (Japan V, overseas V; 8)**
- The incidence of cancer among CD patients is slightly elevated. **B (Japan V, overseas IVb; 8)**

- The life expectancy of CD patients is slightly shorter than that of healthy individuals. **C1 (Japan V, overseas IVb; 7)**

Comments: CD is a disease that persists for a long period of time, with repeated active phases and remission phases. The symptoms and complications in the active phase make it difficult for patients to live a normal daily life. In countries overseas, 15% of CD patients become unable to work 5-10 years after the diagnosis [21]. According to a cross-sectional study in Japan, fewer than 30% of CD patients are able to work in full-time employment throughout the year [22]. Intra- and extra-intestinal complications are considered to have the most negative impact on the activities of daily living (ADL) among CD patients [23].

An overseas meta-analysis report indicates that the relative risks of cancer in the colon and the small intestine in CD patients are 2.4 and 28.4, respectively [24]. Although the relative risk of small-intestinal cancer is conspicuously higher than that of the colon, its significance is not clear because the absolute number of these cancer cases is very small. According to a Japanese report on the association of CD and cancer in the colon, the small intestine and the anal canal in CD patients, most cases of such cancers are discovered at an advanced stage. Most reports on the incidence of cancer in CD patients in Japan are based on case-series studies, but some controlled studies suggest that the incidence in Japan is similar to that in Europe and North America [25, 26].

Six of seven overseas area cohort studies estimate that the mortality in CD patients has been greater than 1.0, and has been stable in the past 40 years [27]. Two reports from Japan showed different conclusions: one reported that mortality among CD patients was higher, while the other reported that mortality was similar to that of the healthy population [28, 29]. In general, CD does not seem to significantly reduce the life expectancy of the patients.

II. Diagnosis

II-1. Clinical symptoms

CQ1: What are clinical symptoms of CD? [30]

- Abdominal pain and diarrhea are the most common symptoms. Symptoms due to perianal lesions and hematochezia are also commonly encountered. **C1 (Japan VI, overseas V; 8)**
- Although systemic symptoms and signs such as weight loss, fever, general malaise and anorexia, and oral aphthous ulcerations are often observed, they are not highly specific for CD. **C1 (Japan VI, overseas V; 8)**

Comments: Abdominal pain (70%) and diarrhea (80%) are commonly encountered at the time of diagnosis. Hematochezia is observed in 30% of patients, but is usually not massive. Generally, abdominal pain is more common in the small-intestinal type, whereas hematochezia and diarrhea are more common in the colonic type. In the course of the disease progress, perianal lesions are observed in more than 50% of patients, and fistulas and abscesses manifest approximately 15% of patients [30].

Systemic symptoms and signs such as weight loss and fever are found in 40-70% of patients at the time of diagnosis. Weight loss is more common in the small-intestinal type. Systemic symptoms such as general malaise and anorexia, aphthous stomatitis, and shallow ulcers in the oral cavity are often observed during the progress of the disease, but they are not highly specific for CD [30]. Extra-intestinal complications such as lesions in the joints, skin, and eyes are observed in approximately 2-10% of patients [30].

CQ2: What are the complications associated with CD? [30-35]

- Intestinal complications of CD include stenosis, fistulas (internal and external), abscess formation, massive hemorrhage, and colorectal cancer. **B* (Japan V, overseas V; 9)**
- Extra-intestinal complications of CD include joint lesions (e.g., joint pain, acute peripheral arthritis, and reactive arthritis), skin lesions (e.g., erythema nodosum, Sweet's disease, and pyoderma gangrenosum), eye lesions (e.g., iritis and episcleritis), and primary sclerosing cholangitis (PSC). **C1 (Japan V, overseas V; 8)**
- Complications to which children are susceptible include growth returdation, osteoporosis, and angitis. **C1 (Japan V, overseas V; 7)**

Comments: Intestinal complications of CD include stenosis, internal and/or external fistulas, and abscess formation, any of which are not infrequently candidates for surgical interventions. Complications increase with the disease progress [31]. CD with intestinal complications is known as the disabling type [31], and thus it is important to prevent these complications or treat them appropriately in order to maintain the patients' QOL. Massive hemorrhage occurs in 0.6–5% of patients, and it usually arises from anastomotic sites and the small intestine [30].

Signs of joint lesions include joint pain or acute peripheral arthritis (type 1: fewer than five joints, mainly in the large joints, associated with the CD activity) and reactive arthritis (type 2: polyarthritis in the small joints, not associated with the CD activity) [32]. Joint symptoms are found in 30% or more (arthralgia, 14.3%; type 1 arthritis, 6%; type 2 arthritis, 4%; and axial arthropathy, 9.9%) [32]. The reported association of CD with skin lesions, including erythema nodosum, Sweet's disease, and pyoderma gangrenosum, has been increasing. According to an overseas report, approximately 2.2% of IBD patients have skin symptoms [33, 34]. The frequency of erythema nodosum is about three times as high as that of pyoderma in IBD patients. Both skin conditions are more likely to manifest as a complication of CD rather than UC. Sweet's disease is rarely found in CD patients (30 reported cases in Europe and North America) [35]. Nonspecific skin eruptions are more often seen among CD patients than in healthy people, but they are not correlated with the disease activity.

Iritis and episcleritis are found in 1–2% of IBD patients [34]. PSC as a complication of CD is found at a rate of 1–3%, which is lower than that in UC. Psoriasis is more common in CD patients and their siblings than in the general population.

Complications more often found in children include growth retardation, osteoporosis, and angitis [30]. The frequency of extraintestinal complications is higher among children with IBD than in adults with IBD, and some reports indicate that the rate of such complications in children is as high as 35% [30, 32, 34].

CQ3: What kind of perianal lesions are caused by CD? [36-38]

- Perianal lesions include anal fissures, anal ulcers, skin tags, anal fistulas, perianal abscesses, anovaginal fistulas, cavitating ulcers, piles, and anal canal cancer. **C1 (Japan V, overseas V; 8)**

Comments: Perianal lesions are found in more than 50% of patients with CD, and often precede other symptoms (36-81%). The frequency of perianal lesions as complications is significantly higher in cases of CD with rectal stenosis than in those without such stenosis [36-38].

Hughes [37] classified perianal lesions according to the pathological conditions, as follows: primary lesions, i.e., deep ulcers (deep anal fissures and anal ulcers) caused by CD itself; secondary lesions, i.e., secondary lesions originating from the primary lesions via infection or other causes; and incidental lesions, i.e., lesions not related to CD. Recently, cases of anal canal cancer as a complication have also been reported in Japan. It is necessary to survey these lesions carefully in patients with long-term progression of the disease.

II-2. Medical interview and physical examination

CQ4: What kind of symptoms and physical findings make CD suspected? [39]

- Chronic abdominal pain and/or diarrhea in young individuals suggest the possibility of CD, especially when accompanied by weight loss and fever. **C1 (Japan VI, overseas VI; 8)**
- On physical examination, characteristic perianal lesions (preferably checked by colorectal surgeons familiar with CD), findings similar to appendicitis, bowel obstruction, and rectal bleeding indicate CD. **C1 (Japan VI, overseas VI; 7)**
- Although the onset of CD is usually at young ages, it is not rare in the elderly. **C1 (Japan VI, overseas VI; 7)**

Comments: According to the Proposed Diagnostic Criteria for Crohn's Disease [39], this disease presents with initial symptoms of "abdominal pain, diarrhea, weight loss, fever, perianal lesions, symptoms particularly similar to appendicitis, bowel obstruction, intestinal perforation, and/or massive hemorrhage. Furthermore, it may occur with perianal lesions and/or fever (of unknown causes), without abdominal symptoms."

II-3. Diagnostic strategies

CQ5: If CD is suspected, how do physicians proceed to the diagnosis? What kind of investigations are required? [40, 41]

- Obtain blood tests to check for inflammatory activity, malnutrition, and iron-deficiency anemia. **C1 (Japan VI, overseas VI; 8)**
- Use imaging procedures to check for morphological findings characteristic of CD. **C1 (Japan VI, overseas VI; 8)**
- Exclude infectious enterocolitis (including tuberculosis), if necessary, by stool culture and other tests. **C1 (Japan VI, overseas VI; 8)**
- Apply tests to check for intestinal complications according to the symptoms. **C1 (Japan VI, overseas VI; 8)**

Comments: Apply blood tests to examine for abnormal inflammatory responses (in terms of white blood cell count, C-reactive protein [CRP], platelet count, and erythrocyte sedimentation rate [ESR]), malnutrition (low serum total protein and albumin, and/or low total cholesterol), and anemia.

Employ lower gastrointestinal endoscopy (including histological evaluation), barium enema, and/or small-intestinal contrast radiography as imaging examinations. Check for longitudinal ulcers, a cobblestone-like appearance, stenosis, and fistulas, which are characteristic of CD in such examinations. Use upper gastrointestinal endoscopy with biopsy as much as possible to detect multiple aphthous ulcerations, ulcers, stenosis, and a cobblestone-like appearance as lesions of CD in the upper gastrointestinal tract [40, 41]. Imaging procedures are usually used to exclude similar disorders. Stool cultures and serum antibodies are utilized to check for infectious enterocolitis.

Regarding intestinal complications, use computed tomography (CT) and/or magnetic resonance imaging (MRI) to check for the presence and the severity of perianal abscesses, anal fistulas, and intra-abdominal abscesses.

CQ6: What morphological examinations are necessary to make a diagnosis of CD? [40, 41]

- Lower-gastrointestinal endoscopy, barium enema radiography, small-intestinal radiography, upper-gastrointestinal endoscopy, upper-gastrointestinal contrast radiography, and histopathological examination are necessary. **B* (Japan VI, overseas VI; 9)**

Comments: The common sites of involvement by CD are the colon and the distal ileum; therefore, barium enema radiography, lower-gastrointestinal endoscopy (including examination of the terminal ileum and histological evaluation of biopsy specimens), and small-intestinal radiography are usually conducted prior to other examinations.

Although upper-gastrointestinal endoscopy is not indispensable, it should be used in cases where a definitive diagnosis could not be made by barium enema radiography or lower-gastrointestinal endoscopy.

Small-intestinal endoscopy is helpful in cases where CD lesions are not found on the lower and upper gastrointestinal endoscopic examinations or on contrast radiography despite the clinical suspicion of CD. Although capsule endoscopy is used overseas to detect lesions in the small intestine, it has not been approved for clinical use in Japan because of potential complications at the site of a stenosis.

CQ7: What kind of laboratory markers are useful to evaluate the activity of CD? [42-44]

- Markers of inflammatory response (CRP and ESR) are considered to correlate with the disease activity. **C1 (Japan VI, overseas VI; 8)**
- Nutritional indices (serum total protein and serum albumin) also reflect the disease activity in many cases. **C1 (Japan VI, overseas VI; 7)**
- There is no single index with which to quantitate disease activity to enable an objective assessment; therefore, it is necessary to assess CD disease activity in a comprehensive manner. **C1 (Japan VI, overseas VI; 9)**

Comments: The disease activity of CD is generally assessed by the CDAI or IOIBD. The CDAI is the most commonly used assessment tool worldwide [42]. CD causes lesions at any site along the entire gastrointestinal tract, and the sites and extent of lesions are related to the disease activity. Generally, the markers of inflammatory response (CRP and ESR) are comparatively well correlated with the CDAI scores indicating the disease activity, but with occasional discrepancies. In patients with severe and extensive disease, especially those with extensive small-intestinal lesions, hypoproteinemia is often present. However, values for nutritional indices may be affected by treatments such as nutritional therapy. Accordingly, no single laboratory test can contribute to the assessment of the disease activity.

The Endoscopic Index of Severity of Crohn's Disease (CDEIS) has been proposed as an endoscopic index of disease activity [43, 44]. This index is obtained by dividing the intestinal tract into five segments (the rectum, the sigmoid/descending colon, the transverse colon, the ascending colon/cecum, and the ileum), determining scores and obtaining subtotals according to the depth and length of ulceration and the area of lesions in each segment, and then calculating an average based on the number of segments with lesions, and adding points for stenosis to the average. Calculation of values in this index is complicated and time-consuming. The index is not commonly used to evaluate disease activity in clinical practice.

II-4. Endoscopy

CQ8: When is endoscopic examination necessary to make a diagnosis of CD? [39, 40, 43-46]

- When clinical symptoms and the laboratory test results suggest CD, promptly examine the patient using lower-gastrointestinal endoscopy (including an observation of the terminal ileum) and histological evaluation of biopsy specimens. **C1 (Japan VI, overseas VI; 8)**
- Examine the patient using upper gastrointestinal endoscopy when a definitive diagnosis has not been made with lower-gastrointestinal endoscopy or when the patient complains of symptoms in the upper gastrointestinal tract. **C1 (Japan VI, overseas VI; 8)**

Comments: CD can affect the entire gastrointestinal tract, but the common sites are the colon and the distal ileum. When clinical symptoms and the laboratory test results suggest CD, promptly examine the patient using lower-gastrointestinal endoscopy including an observation of the terminal ileum, to make a definitive diagnosis, to determine the extent and severity of inflammation, and also to take a biopsy sample for histological examination [40, 43-46]. Endoscopy has recently been employed for the treatment of stenosis. Small-intestinal balloon endoscopy may be useful.

Upper-gastrointestinal lesions are not rare and may occur at a high rate (17-75%) in patients with CD, with or without related symptoms. The Japanese proposed diagnostic criteria for Crohn's disease [39] refer to irregular-shaped ulcers and aphthous ulcerations found in both the upper and lower gastrointestinal tract as minor findings. Accordingly, to make a definitive or differential diagnosis of CD, it is useful to explore lesions using upper-gastrointestinal endoscopy and by examining biopsy samples for histological evaluation (to check for the presence of noncaseating epithelioid cell granuloma).

CQ9: What endoscopic findings are characteristic of CD? [46, 47]

- Lower-gastrointestinal endoscopic findings characteristic of CD include discrete or segmental lesions (so-called skip lesions), a cobblestone-like appearance, longitudinal ulcers, irregular-shaped ulcers, multiple aphthous ulcerations, abnormal narrowing and/or stenosis, and fistulas (internal and/or external fistulas). **B* (Japan V, overseas VI; 9)**
- Upper-gastrointestinal endoscopic findings characteristic of CD include a bamboo joint-like appearance, a notch-shaped appearance, cobblestone-like appearance, multiple aphthous ulcerations, erosion, irregular-shaped ulcers, bead-like protrusions, nodular folds, granular mucous membrane, and stenosis. **C1 (Japan V, overseas VI; 8)**

Comments: It was reported that lower-gastrointestinal endoscopic findings make it possible to differentiate 89% of CD cases from UC among suspected cases of IBD [46]. Findings helpful in differentiating CD from UC are discrete lesions, cobblestone-like appearance, aphthous ulcerations and longitudinal ulcers, and perianal lesions [47].

Frequently encountered upper-gastrointestinal lesions of CD are a bamboo joint-like appearance in the stomach, gastric and duodenal erosions and/or ulcers, and duodenal notch-like protrusions and/or longitudinal erosions.

CQ10: Is examination of the entire gastrointestinal tract necessary in the diagnosis of CD? [40, 41, 47]

- Examinations of the lower gastrointestinal tract (using endoscopy or barium enema radiography) are almost indispensable for making a diagnosis of CD. **B* (Japan VI, overseas VI; 9)**
- Even after a definitive diagnosis has been made, it is preferable to examine the patient using small-intestinal contrast radiography and upper-gastrointestinal endoscopy. **C1 (Japan VI, overseas VI; 8)**

Comments: For the definitive diagnosis of CD, use lower-gastrointestinal endoscopy with biopsy for histopathological evaluation before undertaking other investigations. Even after the diagnosis is made, it is preferable to investigate the entire gastrointestinal tract, using small-intestinal contrast radiography and upper-gastrointestinal endoscopy, in order to determine the disease type, as determination of the type will contribute to the selection of the appropriate treatment and scheduling of the follow up. In cases where the results of a lower-gastrointestinal endoscopic examination do not produce a definitive diagnosis, it is absolutely necessary to explore lesions in the small intestine and the upper gastrointestinal tract [40, 41, 47].

If lesions are not found using small-intestinal contrast radiography or upper-and lower-gastrointestinal endoscopy despite clinical suspicions of CD, exploration of the small-intestinal lesions using capsule endoscopy may be useful in some cases; however, this procedure is not yet approved for clinical use in Japan for suspected cases of CD. The usefulness of small-intestinal endoscopy in the diagnosis of CD has not been established clearly, although it is useful in some cases of diagnostic difficulty.

II-5. Contrast radiography

CQ11: When is contrast radiography necessary to make a diagnosis of CD? [47-49]

- As CD may be complicated with intestinal stenosis, fistulas, abscess, and/or adhesions, the addition of barium enema radiography to colonoscopy would be advisable. **C1 (Japan VI, overseas VI; 8)**
- Even if a diagnosis of CD is made by barium enema radiography, small-intestinal contrast radiography is valuable to determine the extent of the lesions and to establish treatment strategies. **C1 (Japan VI, overseas VI; 8)**

Comments: Barium enema radiography is helpful to overview the entire colon and rectum, and small-intestinal contrast radiography can be performed safely if there is no severe stenosis in the colon. To explore small-intestinal lesions, contrast radiography is still useful, with sensitivity of 85-95% and specificity of 89-94% to detect typical lesions of CD [47-49].

CQ12: Which findings of contrast radiography are characteristic of CD? [49-52]

- Longitudinal ulcers (asymmetric sclerotic appearance), cobblestone-like appearance, stenosis, aphthous ulcerations, irregular-shaped ulcers, fissures, and fistulas are typically found. **B* (Japan V, overseas VI; 9)**

Comments: A longitudinal ulcer is an ulcer 5cm or longer that runs along the longitudinal direction of the gastrointestinal tract on the mesentery side in the small intestine and along the teniae coli in the colon, varying in width from a wide band to a thin line. Shortening of the mesentery side of the small intestine due to longitudinal ulcers produces an asymmetric sclerotic appearance, which is found in approximately 84% of CD cases [49-52].

A cobblestone-like appearance is where scattered polyp-like protrusions are formed in an area of mucous

membrane surrounded by a longitudinal ulcer and with smaller ulcers running transversely. It is assumed that mucosal edema, shortening of mucosal muscle, inflammatory cell infiltration, and fibrosis produce such a distinctive feature [52].

II-6. Other imaging procedures

CQ13: How can imaging procedures such as CT and abdominal ultrasonography (US) contribute to making a diagnosis of CD? [53]

- CT and US are useful for evaluating the extent and severity of gastrointestinal inflammation, and for the detection of abscess formation. **C1 (Japan VI, overseas VI; 8)**

Comments: CT and US can be used to assess intestinal inflammation, based on thickening of the intestinal walls and the increased density of surrounding fatty tissues. Contrast CT and MRI are helpful in detecting abscess formation. CT colonography, although is useful in assessing lesions proximal to a stenosis is not universally available [53].

II-7. Histopathological examination

CQ14: What pathological findings are characteristic of CD? [52, 54]

- Findings for a definitive diagnosis of CD include: (1) noncaseating epithelioid cell granuloma, (2) transmural inflammation, (3) fissure, and (4) ulcers. **C1 (Japan VI, overseas VI; 8)**

Comments: Abnormal alignment of crypts and basal cell plasmacytosis are found in the biopsy specimen, and these are findings in common with those of IBD. A key to differentiating CD from UC is focal inflammation. Granuloma is composed of such cell as epithelioid cells, macrophages, lymphocytes, and multinucleate giant cells. Although noncaseating epithelioid cell granuloma is a principal basis for a diagnosis of CD, it is detected in 40-60% of surgical specimens, and in only 15-36% of biopsy specimens [54]. Multiple biopsy specimens for serial sections may improve the rate of detection of granuloma. Note, however, that multinucleate giant cells may be found in foreign-body granulomas, and that noncaseating epithelioid cell granulomas may be found in tuberculosis [52].

In transmural inflammation, focal aggregations, mainly of lymphocytes, are found to be transmurally distributed unevenly. Lymphangiectasis, edema, and fibrosis are also found. Disproportionate inflammation, manifested more strongly in the submucosa than in the lamina propria, is a convincing key to the biopsy diagnosis of CD. Fissure formation is a vertical tissue defect along a lymphatic duct.

II-8. Definitive diagnosis

CQ15: How can a definitive diagnosis be made? What diagnostic criteria are used? [39]

- If CD is suspected based on medical interview, physical examination, and laboratory test results, gastrointestinal investigations should be conducted. **C1 (Japan VI, overseas VI; 9)**
- The Japanese *proposed diagnostic criteria for Crohn's disease* [39] (Table 5) consist mainly of morphological findings of the gastrointestinal tract. **C1 (Japan VI; 8)**

Comments: Among major findings, longitudinal ulcers in CD can be differentiated from those in UC or ischemic colitis by the presence of protrusions due to inflammatory edema. The cobblestone-like appearance in CD involves dense protrusions of mucous membrane of uneven sizes, large or small, surrounded by a longitudinal ulcer and smaller ulcers. This appearance may be seen in ischemic colitis, but in ischemic colitis the protrusions are less dense and hyperemia is more intense.

Table 5 Diagnostic Criteria of Crohn's Disease in Japan (as revised in February 2011) [39]

(1) Major findings
A. Longitudinal ulcer [Note 1]
B. Cobblestone-like appearance
C. Noncaseating epithelioid cell granuloma [Note 2]
(2) Minor findings
a. Irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal tract [Note 3]
b. Characteristic perianal lesions [Note 4]
c. Characteristic gastric and/or duodenal lesions [Note 5]
Definite
1. Major finding A or B [Note 6]
2. Major finding C, with minor finding a or b
3. All minor findings a, b, and c
Suspected
1. Major finding C, with minor finding c
2. Major findings A or B, but cannot be differentiated from ischemic colitis or ulcerative colitis
3. Major finding C only [Note 7]
4. One or two minor findings

Notes:
1. In the small intestine, it occurs more commonly on the mesentery side.
2. The rate of detection of this granuloma is improved by creating serial sections. It is advisable that a pathologist familiar with the gastrointestinal tract examine a specimen of it.
3. In typical cases, they are arranged longitudinally, but not in some cases. It is necessary that they persist for at least three months. With regard to this condition, it is necessary to exclude enteric tuberculosis, intestinal Behçet's disease, simple ulcer, NSAID-induced ulcers, and infectious enterocolitis.
4. Anal fissures, cavitating ulcers, anal fistulas, perianal abscesses, edema-like anal skin tags. Preferably, colorectal surgeons familiar with Crohn's disease are consulted to examine such lesions, referring to the atlas of visual findings of anal lesions caused by Crohn's disease.
5. Bamboo joint-like appearance, notch-like depressions. Preferably, specialists familiar with Crohn's disease are consulted to examine such lesions.
6. In cases with only longitudinal ulcers, it is necessary to exclude ischemic intestinal lesions and ulcerative colitis. In cases with only cobblestone-like appearance, it is necessary to exclude ischemic intestinal lesions.
7. It is necessary to exclude inflammatory diseases with granulomas such as intestinal tuberculosis.

CQ16: If a diagnosis of CD is not definitive, what should be done? [54, 55]

- In indeterminate colitis where it is difficult to differentiate CD from UC, choose treatment strategies for the more suspected disease, observe progress with regular check-ups, and make a definitive diagnosis as soon as the features of one or the other disorder become dominant. **C1 (Japan VI, overseas VI; 8)**
- If the diagnosis of CD is not definitive, as in patients with only aphthous ulcerations, observe progress with regular check-ups, and a definitive diagnosis of CD can be made when morphological examinations fulfill the criteria for the diagnosis. **C1 (Japan VI, overseas VI; 8)**

Comments: The number of reports of indeterminate colitis (IC), which has clinical and histopathological features of both UC and CD and is thus difficult to differentiate from either of these conditions, is increasing [54, 55]. IC accounts for approximately 4% of IBD cases in Japan [55]. Even after intestinal resection, in approximately 5% (range 1–20%) of cases, a definitive diagnosis cannot be made, because of overlapping histopathological features [54, 55]. Although the usefulness of serum anti-*Saccharomyces cerevisiae* (ASCA) and anti-neutrophil cytoplasmic antibody (ANCA) measurements has been reported, their diagnostic accuracy for IC has not been established. At present, serial observations with endoscopy and other procedures are important, and a definitive diagnosis is made when characteristic features of either UC or CD are obtained (i.e., when the criteria for diagnosis of either one are satisfied). After observing the progress of IC for 8 years, a definitive diagnosis of CD or UC was made in 80% of cases [54]. Treatment strategies are decided with a tentative diagnosis based on the clinical and imaging features.

When CD is suspected but without a definitive diagnosis, as in patients with aphthous ulcers that show no longitudinal arrangement and patients who do not have noncaseating epithelioid cell granuloma, regular follow up, using laboratory test results and morphological examinations is necessary to be able to make a definitive diagnosis of CD when the criteria for the diagnosis are met. Use mainly symptomatic treatments until a definitive diagnosis is made. If morphological examinations cannot confirm the diagnosis, but CD is suspected comprehensively by symptoms and laboratory test results, treatments for CD may be initiated, while observing the patient's progress and conducting follow-up examinations.

II-9. Determination of severity

CQ17: How are the severity and activity of the disease determined? [40, 56, 57]

- The severity and activity are usually determined on the basis of clinical symptoms. **C1 (Japan VI, overseas VI; 7)**
- The IOIBD and CDAI can be used to quantify the disease activity, but these indices are not easy to use in daily clinical practice. **C1 (Japan VI, overseas VI; 8)**

Comments: The IOIBD score consists of nine clinical parameters and hemoglobin, and it is a convenient index that is used in the disease datasheet of the Japanese national CD registration. Though the IOIBD data have a certain level of correlation with the CDAI scores [40], the number of items showing correlation is limited, and the IOIBD is not suitable for detailed evaluation of the long-term progress of the disease. In Europe and North America, the CDAI [40], in which eight indices are calculated, is used as a standard index for the assessment of disease activity; it is also used to assess treatment efficacy in clinical studies in Japan. However, calculation of the CDAI requires that clinical symptoms and laboratory test data are available over the 7 days immediately before the day of calculation. Thus, it is not suitable for use in daily clinical practice. Although assessment of severity is important for treatment, severity does not always correlate with disease activity [56]. In some patients, particularly those with small-intestinal lesions, the clinical symptoms are mild, and disease activity is not reflected in the CDAI scores.

In selecting treatment options, comprehensive evaluation should be made. The initial treatment might be modified during follow-up period. A recent opinion suggests that the disease pattern (whether the case is susceptible to fistulation or stenosis) and the mucosal healing of gastrointestinal lesions should be evaluated.

The European Crohn's and Colitis Organisation (ECCO) has classified disease activity in the categories of mild, moderate, and severe according to the criteria (Table 6) [57].

Table 6 Classification of disease severity

	CDAI	Complication	Inflammation (CPR)	Treatment response
Mild	150-220	None	Slight rise	
Moderate	220-450	No manifestation of complications such as bowel obstruction	Clear rise	No response to treatment for mild CD
Severe	450<	Bowel obstruction, abscess, and so on	Great rise	Poor treatment response

III. General Principles of Treatment

III-1. Outline of treatment

CQ1: If a patient has a diagnosis of CD, what will the treatments be, and how will this affect the patient's lifestyle? [56-60]

- In the active stage, the treatments are direct to induce remission; once remission is induced, the treatments are given to maintain remission for a prolonged period. **B* (Japan VI, overseas VI; 9)**
- Therapeutic modalities include medical treatments, such as drug therapies and nutritional therapies, and surgical treatments. They are selected as monotherapy or combination therapy. **B* (Japan VI, overseas VI; 9)**
- The majority of patients can live a normal daily life, with regular school life or working hours. In patients with severe or fulminant symptoms, or frequent relapses, the patient needs to be hospitalized, or requires surgical treatment, and faces dietary and lifestyle restrictions. **C1 (Japan VI; 8)**

Comments: Repeated remissions and relapses are characteristic during the course of CD. Because CD is not curable at present, the goal of the treatment is to control disease activity and to improve the QOL of the patient. For this purpose, it is important to control the symptoms, to maintain nourishment, and to prevent relapse or postoperative recurrence by combining drug therapies, nutritional therapies, and surgical treatments [58].

Treatments are selected according to the sites of lesions, the levels of inflammation, the disease pattern, the responses to treatments in the past, and the presence or absence of complications. Although there is abundant evidence in regard to the efficacy of different treatments in relation to disease severity or location, the patients should be fully instructed about the disorder, and the treatment should be chosen according to the social background and environment of the patients, as well as the individual pathological conditions [56-59].

In mild to moderate cases, remission is sufficiently attained with drug and/or nutritional therapies, and the patient can live a normal daily life with maintenance treatment and some attention to daily life. For moderate cases, the patient needs to be hospitalized during periods of relapse, but can otherwise live an almost normal life [60].

III-2. Consultation

CQ2: Should a CD patient be referred to a specialist for the treatment? [21]

- On many occasions in the management of CD, consultation with a specialist is necessary. **B* (Japan VI, overseas VI; 9)**
- Consultation is required for nutritional therapy, anti-tumor necrosis factor (TNF) therapy, failure to maintain remission, and surgical treatment. **B* (Japan VI, overseas VI; 9)**

Comments: Except for very typical cases, consultation with a specialist should be considered for any diagnostic difficulty. If the institution is not sufficient for diagnostic investigations, the patient should be referred to a specialist to establish the diagnosis and to determine the extent and severity of the disease [21].

At the initial diagnosis of CD, consultation with a specialist is preferable for education and general guidance. Quiescent cases can be managed by a general practitioner for remission maintenance and follow up.

Steroid-dependency and the administration of immunomodulators or biologic agents are indications for consultation. In cases of intestinal/extra-intestinal complications, the patient should be referred to specialists in the relevant areas.

III-3. Hospitalization

CQ3: Under what circumstances should a CD patient be hospitalized? [57, 61, 62]

- Consider hospitalization when the patient does not improve on outpatient treatment. **B* (Japan VI, overseas VI; 9)**