Comments: If a patient does not improve with outpatient drug or nutritional therapies, and has persistent symptoms such as frequent diarrhea, abdominal pain, fever, and weight loss, and/or elevated inflammatory markers, hospitalization should be considered [57, 61]. In patients with stenosis causing bowel obstruction and those with intra-abdominal abscess formation, hospitalization and surgical treatment should be considered [57]. According to a case series study, a high proportion (50-80%) of CD patients with small-intestinal lesions require hospitalization/ surgery as the disease progresses [62].

III-4. Exercise and social activities

CQ4: Does a CD patient require rest and restriction of social activities? [31, 60, 63, 64]

- Generally, patients do not require rest or restriction of activities. **C1 (Japan VI, overseas VI; 8)**
- Patients in the active phase with severe abdominal symptoms, a finding of systemic inflammation, and exhaustion should avoid excessive exercise. **C1 (Japan VI; 8)**
- In the active phase of the disease, patients face restrictions of social activities, such as school or work, due to treatment or hospitalization. **B (Japan IVb; 8)**

Comments: In the long-term progression of CD, the QOL of the patients is generally well maintained. The number of patients with poor QOL for whom social activities are significantly restricted due to symptoms and/or treatment is limited [31, 63]

If remission is maintained, normal exercise, work, and school attendance are expected. However, in the active phase, too much exercise causing a heavy physical or mental burden is to be avoided [31, 60]. There is no evidence that bed rest or lifestyle restrictions contribute to the maintenance of remission. Rather, some reports have indicated that moderate exercise reduces CD disease activity and mental stress [64].

III-5. Diet

CQ5: Is dietary therapy necessary for the treatment of CD? [21]

- There are no specific dietary therapies to cure or improve CD. **C1 (Japan VI, overseas: VI; 9)**
- For patients in the active phase, consider inflammations in the gastrointestinal tract when selecting foods. **C1 (Japan VI, overseas VI; 8)**
- Do not allow the patient to take food orally in the presence of severe inflammation or obstruction. **C1 (Japan VI, overseas VI; 8)**

Comments: Dietary therapy denotes management in which the amounts of meals or food ingredients are adjusted, with the aim being to overcome or alleviate a disease. Unlike findings with hypertension, hyperlipidemia, and diabetes, no primary therapeutic effect of any dietary therapy in CD has been scientifically proven. Dietary guidance or advice is preferably minimal, such as cautions to avoid excessive drinking and eating or stimulants.

Although the causes of CD are unknown, it is assumed that some dietary factors are involved in the onset and the persistence of inflammation. In many cases, the oral intake of foods exacerbates the symptoms, and these patients have usually had an unbalanced diet before the onset of the disease; thus, it can be presumed that diet may have some relationship to CD. In general, patients with inflammation in the gastrointestinal tract are recommended to avoid fats, stimulants, and dietary fiber. In CD patients, this recommendation also means that the antigens in the diet are reduced to keep the intestinal tract at rest.

Nutritional deficiency is often found in CD patients due to various causes. When CD is diagnosed, the nutritional condition of the patient should therefore be assessed, and assessment should be carried out regularly during the progress of the disease, with nutritional support being provided according to the patient's pathophysiological condition [21].

CQ6: What kind of general dietary recommendations should be made? [15, 60]

- Basic recommendations during the active phase include having a low-fat, low-residue diet with low levels of stimulants, and food high in protein and calories, to improve the nutritional state while keeping the intestinal tract at rest. **C1 (Japan VI, overseas VI; 7)**
- In the remission phase, no strict dietary restrictions are necessary, but a low-fat diet is preferred. **C1 (Japan IVb; 7)**
- The response of the gastrointestinal tract to foods varies considerably from person to person. Accordingly, individual patients should avoid specific foods that make their symptoms worse. **C1 (Japan VI, overseas VI; 8)**

Comments: Dietary guidance differs according to the individual and their symptoms. Basically, no foods are absolutely restricted; however, it is advisable that CD patients maintain an orderly and regular diet, and learn which foods exacerbate their condition, and avoid such foods. Although there is little evidence to show any relationship between the diet and food ingredients and the disease activity of CD, a Japanese case-control study has indicated that fats are a risk factor for CD [15]. Low-fat, low-residue, high-protein, and high-calorie foods are basic dietary suggestions for CD [60]. When a patient undergoes a resection of the small or large intestine, the diet should be considered according to the resion that has been resected.

As evidence is lacking for the effects of health food products and popular supplements, and because their safety has not been confirmed, they are not recommended.

III-6. Smoking

CQ7: Should a CD patient refrain from smoking? [65-71]

- Upon diagnosis, the patient with CD should quit smoking. **B (overseas III; 8)**

Comments: An analytical epidemiological study showed that smoking was associated with the onset of CD [65]. It has also been reported that in infants exposed to passive smoking this has an adverse effect [66]. Case-control studies have indicated that, after remission is induced by medical or surgical treatments, the relapse rates and requirements for surgery are higher among smokers [67-69]. An interventional trial showed that a group that continued to refrain from smoking for more than 1 year had a better prognosis than continuous smokers [70]. With these lines of evidence, smoking cessation is recommended for those who have diagnosis of CD.

A multivariate analysis of the factors influencing the therapeutic effect of infliximab concluded that smoking was not an independent factor influencing the therapeutic effect; however, for the above-mentioned reasons, patients with CD are recommended to quit smoking [71].

III-7. Alcohol drinking

CQ8: Should a CD patient refrain from drinking alcohol? [60]

- It is not necessary to recommend to every patient with CD that they refrain from drinking alcohol. However, it is preferable to avoid excessive drinking and to stop drinking when the disease is in the active phase. **C1 (Japan VI, overseas VI; 7)**

Comments: There is little evidence that drinking alcohol affects the disease activity or progression of CD. However, alcohol may injure the mucosa of the intestinal tract and exacerbate the symptoms of CD. In the remission phase, drinking modest amounts of alcohol is acceptable, but it would be a good practice to advise patients to restrain themselves when drinking, as some people tend to drink excessively.

IV. Therapeutic Intervention

IV-1. Treatment options

CQ1: What are the treatment options for CD, and in what combinations? [56-58]

- Treatment strategies include drug therapies, nutritional therapies, surgical therapies, and other modalities. Select the most appropriate treatments according to the severity, extent of the lesion, and disease pattern. **C1 (Japan VI, overseas VI; 9)**
- Initially, or in a relapse, apply drug therapies and nutritional therapies as monotherapy or in combination, with the aim being to induce remission. **C1 (Japan VI, overseas VI; 8)**
- In patients with intestinal stenosis, fistulas, abscesses, and/or perianal lesions, or in cases that are resistant to medical treatment, consider surgical treatment. **C1 (Japan VI, overseas VI; 8)**
- Once remission is induced, maintain remission using drug therapies (5-aminosalicylic acid [5-ASA] preparations, immunomodulators, anti-TNF agents), and/or nutritional therapies as monotherapy or in combination. **C1 (Japan VI, overseas VI; 9)**

Comments: At present, no treatments can completely cure CD. The purposes of treatment are to control the disease activity and to improve the QOL of the patients; in other words, the aim is to maintain remission for as long as possible. For these purposes, select drug, nutritional, and surgical therapies as indicated to attenuate symptoms, to maintain nourishment, and to prevent relapse. 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 [56-58].

Both drug and nutritional therapies for CD inevitably have adverse effects. However, the benefit of each therapeutic modality outweighs the risk. Some therapies are safe in the short term, but may produce adverse effects in the long term. It is desirable that nutritional therapies and drug therapies be used to supplement each other.

IV-2. Steroids

CQ2: When are steroids indicated? What kinds of benefits and harms are expected? [21, 59, 72-74]

- Steroids possess potent anti-inflammatory effects. They are effective in inducing remission, but ineffective for maintaining remission. **A (Japan V; overseas I; 8)**
- Steroids may cause adverse effects, particularly with long-term administration. Thus, steroids should be administered mainly to induce remission, and the dosage should be tapered until they are discontinued. **C1 (Japan VI, overseas VI; 8)**
- Steroids are indicated for patients with moderate to severe disease activity, as well as for mildly active disease that is refractory to 5-ASA preparations. **A (Japan VI, overseas II; 8)**

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].

IV-3. 5-ASA preparations

CQ3: When are 5-ASA preparations indicated? What kinds of benefits and harms are expected? [75-77]

- 5-ASA preparations have clinical efficacy in active CD. **A (overseas I; 8)**
- During the remission phase, 5-ASA preparations have a limited effect on maintaining remission, but harm is minimal. **A (overseas I; 8)**

Comments: According to a meta-analysis of randomized controlled trials, in cases with mild to moderate activity, mesalazine 4 g/day significantly reduced CDAI scores compared with placebo [75].

Another meta-analysis performed to evaluate the efficacy of 5-ASA preparations in remission maintenance did not show any difference between the 5-ASA preparations and placebo [76]. Another meta-analysis suggested that 5-ASA preparations were significantly efficacious in maintaining remission in CD [77].

Because the safety profiles of 5-ASA preparations are good, these preparations are frequently used in actual practice. They are also administered in the long term in many patients for the purpose of maintaining remission.

IV-4. Immunomodulators

CQ4: When are immunomodulators indicated? What kinds of benefits and harms are expected? [78, 79]

- Azathioprine (AZA) and 6-mercaptopurine (6-MP)* are effective in inducing remission in CD, but their adverse effects should be noted. **A (overseas I; 8)** *Not covered by Japanese public health insurance.
- AZA is effective in maintaining remission in CD, and has a steroid-sparing effect. **A (overseas I; 9)**

Comments: Daily administration of 2.0-3.0 mg/kg AZA, and daily administration of 50 mg (or of 1.5 mg/kg) 6-MP, are both useful in inducing remission in CD in the active phase [78].

Daily administration of 1.0-2.5 mg/kg AZA in patients with quiescent CD is effective to prevent relapse for 6 months to 2 years. The steroid-sparing effect of immunomodulators is useful for withdrawing steroids. However, it is not clear whether AZA has a long-term effect on remission maintenance [79]. A higher dose (2.5 mg/kg daily) of AZA has a more potent effect on remission maintenance than a lower dose (1.0 or 2.0 mg/kg daily). Immunomodulators are slow-acting drugs, and may cause serious side effects (e.g., myelosuppression and pancreatitis); therefore, the benefits and harms of these drugs should be carefully considered. Because Japanese have a lower ability to metabolize these drugs than Caucasian, Japanese patients are particularly susceptible to the dose-dependent adverse effects of Immunomodulators. Smaller doses (AZA 50-100 mg daily) than those used overseas are usually administered in Japan.

IV-5. Anti-TNF agents

CQ5: When are anti-TNF agents indicated? What kinds of benefits are expected? [80-85]

- Anti-TNF agents are effective to induce remission. **A (overseas I; 9)**
- In CD patients brought into remission by anti-TNF agents, these agents are also effective for fistula-closure and remission maintenance. **A (overseas I; 8)**
- When infliximab has not been successful, adalimumab may be effective in inducing remission and attenuating symptoms. **A (overseas I; 8)**

Comments: Adalimumab, a humanized anti-TNF-α monoclonal antibody agent, was approved in Japan for the treatment of CD in 2010, in addition to infliximab.

A randomized controlled trial on the remission induction effect of infliximab in patients with active CD indicated that a single administration of 5 mg/kg was efficacious in inducing remission in CD [80]. Moreover, 5 mg/kg or 10 mg/kg of infliximab given every 8 weeks to patients with CD in remission brought about by infliximab was efficacious in maintaining remission and fistula closure [81, 82]. In clinical practice, 5mg/kg of infliximab is administer at week 0, week 2, and week 6, and then at intervals of 8 weeks. If the required effect is not

obtained, consider other treatments instead of simply continuing this agent.

A randomized controlled trial on the remission induction effect of adalimumab indicated that two subcutaneous administrations of 80/40 or 160/80 mg of this drug in CD patients with moderate disease activity showed a significant remission induction effect at week 4 [83]. A trial on its remission maintenance effect indicated that administration of 40 mg subcutaneously at intervals of 2 weeks or 1 week showed a significant remission maintenance effect at week 56 [84]. In clinical practice, 160 mg of adalimumab is initially administered subcutaneously, followed by 80 mg 2 weeks later, and then 40 mg at intervals of 2 weeks in order to maintain remission.

In patients with active CD in whom infliximab was unsuccessful (due to intolerance or symptoms persisting after its administration), adalimumab had a significant effect on remission induction and had attenuated symptoms at 4 weeks after administration [85]. That trial, however, did not directly compare adalimumab with infliximab, nor did it deal with remission maintenance.

CQ6: What harms are anticipated with the use of anti-TNF agents? [81, 86-92]

- Cases of serious infections and cases of opportunistic infections have been reported among patients who received infliximab or adalimumab. **B (overseas IVa; 8)**
- Infliximab increases the chance of tuberculosis infection (including reactivation). **B (overseas IVa; 8)**
- The occurrence of malignant tumors, including lymphoma, was reported among patients who received infliximab. **B (overseas IVa; 8)**
- The incidence of cancer in general among patients who received adalimumab does not seem to be different from that in the general population. **C1 (overseas V; 8)**

Comments: A meta-analysis of studies of infliximab indicated no significant difference in the incidence of serious infections between the infliximab and placebo groups [81]. A multivariate analysis of a prospective study of more than 6,000 people in the TREAT Registry suggests that the causes of increases in serious infections in CD patients are not related to the use of infliximab, but to steroids, narcotic analgesics, and the severity of the disease [86]. In addition, the risk of opportunistic infection in patients with IBD was shown to increase due to the combined use of multiple immunomodulators with infliximab and old age [87].

However, infliximab is known to increase the reactivation and incidence of tuberculosis infection. In addition, it is known that it increases extra-pulmonary lesions and disseminated tuberculosis [88]. Screen patients with CD for tuberculosis infection before administering infliximab, and consider the prophylactic administration of anti-tuberculosis drugs, as necessary.

Analysis of the TREAT Registry indicated a worsening of intestinal stenosis in those who received infliximab, but a multivariate analysis concluded that the only risk factors were the duration and severity of the disease, small-intestinal lesions, and the initiation of steroid therapy [89]. Although few studies have indicated a relationship between infliximab and the occurrence of stenosis, patients should be informed of the risk of stenosis after taking infliximab, and surgeons should be notified if a CD patient is receiving this drug.

A further study with the TREAT Registry indicated a significant difference in the incidence of malignant tumors, including lymphoma, between groups with and without the use of infliximab [90]. A multicenter matched-pair study in Italy showed similar results [91]. However, the observation periods in these two studies were not long enough to reach definitive conclusions. Nevertheless, patients should be notified of the risk before infliximab treatment is initiated.

Adverse effects over a period of 10 years were reported in 20,000 patients from 36 clinical studies on six immune-mediated diseases [92]. In patients with CD, abscesses in the abdominal cavity or the gastrointestinal tract and opportunistic infections were found, but in general, no risk of major infections was found. The incidence of cancer in these CD patients was equivalent to that in the general population.

The harmful effects noted above are considered to be common to all anti-TNF agents.

IV-6. Antimicrobial drugs

CQ7: When are antimicrobial drugs indicated, and what kinds of benefits and harms are expected? [93-97]

- Antimicrobial drugs* are sometimes effective in attenuating the clinical symptoms of CD. **A (overseas I; 8)** *Antimicrobial drugs are not covered by the Japanese public health insurance system when used for the treatment of CD.
- These drugs are more effective for colonic lesions than for small-intestinal lesions. **A (overseas II; 8)**

Comments: In some cases, antimicrobial drugs such as metronidazole and ciprofloxacin are used for the treatment of CD. Multiple randomized controlled studies have been conducted to evaluate the efficacy of antimicrobial drugs for treating active CD, and the drugs showed efficacy in attenuating the clinical symptoms [93-96]. They were more efficacious for colonic lesions than for small-intestinal lesions [96]. Another report indicated that the administration of antimicrobial drugs was efficacious in preventing the postoperative recurrence of CD [97]. However, the indications and the specific treatment strategies for antimicrobial therapies for CD have not yet been established.

When antimicrobial drugs are used for a long period of time, caution should be exercised regarding potential adverse effects. Metronidazole, in particular, may cause peripheral neuropathy.

IV-7. Enteral nutrition

CQ8: When is enteral nutrition indicated, and what kinds of benefits and harms are expected? [98-105]

- The efficacy of enteral nutrition for inducing remission in active CD is equivalent or slightly inferior to that of corticosteroids. **A (Japan III, overseas I; 8)**
- Elemental diet therapy is effective in maintaining remission in CD. **A (Japan II; 8)**
- Although enteral nutrition is safe, maintenance of the patient's acceptance is often difficult. **C1 (Japan VI; 8)**

Comments: The results of several randomized controlled studies have indicated that the efficacy of enteral nutrition for remission induction in active CD is equivalent or slightly inferior to that of corticosteroids [98-102]. A Japanese report indicated that enteral nutrition with an elemental diet had a higher rate of remission, induction than prednisolone and was particularly effective for attenuating intestinal lesions [102]. This therapy is safer than corticosteroids.

Enteral nutrition is effective for the maintenance of remission. It was reported that enteral nutrition with an elemental diet for half of the total intake of calories was efficacious in maintaining remission [103]. It was also reported that continuing an elemental diet of 30 kcal per kilogram per day was efficacious in preventing CD relapse [104, 105]. However, it is frequently difficult to continue enteral nutrition for an extended period because its acceptability to the patient decreases.

CQ9: Are there differences in the therapeutic effect between oligomeric and polymeric nutrients? [98, 99, 106, 107]

- There are no significant differences between oligomeric and polymeric nutrients in terms of their efficacy in remission induction for active CD. **A (Japan III, overseas I; 7)**

Comments: Oligomeric nutrients are enteral formulas which have amino acids and oligopeptides as a nitrogen source, with a low content of fats, and these formulas are therefore easily digested and assimilated. Among oligomeric nutrients, an elemental diet has amino acids as a nitrogen source, and contains little fat. Polymeric nutrients have proteins as a nitrogen source and contain some fats. Polymeric nutrients contain various nutrients in a good balance, and are easily taken orally. Many randomized controlled studies have been conducted to examine the differences among various enteral nutrients in terms of their therapeutic efficacy for active CD. The results have indicated no significant differences in the effect of remission induction between oligomeric and polymeric nutrients [98, 99, 106, 107]. In Japan, there are some opinions that oligomeric nutrients are clinically superior to polymeric nutrients.

CQ10: When is it necessary to administer enteral nutrients through a nasogastric tube?

- A nasogastric tube is necessary in cases where enteral nutrients should be given at a fixed rate, the oral intake of such nutrients is difficult, or such nutrients need to be given to patients at home during sleep at night. **C1 (Japan VI, overseas VI; 8)**

Comments: Enteral nutrients for patients with CD are taken orally, or through a nasogastric tube inserted into the stomach or duodenum. Unpalatable oligomeric nutrients are difficult to take orally, and in many cases are given through a nasogastric tube. Enteral nutrient feeding through a nasogastric tube at a fixed rate, using an enteral feeding pump, causes fewer side effects (such as diarrhea or abdominal pain) than orally taken enteral nutrients. For home enteral feeding, it is possible to give enteral nutrients to a patient through a nasogastric tube at night, while the patient is sleeping.

IV-8. Parenteral nutrition

CQ11: When is parenteral nutrition indicated, and what kinds of benefits and harms are expected? [58, 107-110]

- Total parenteral nutrition (TPN) is indicated for patients with active CD who have serious malnutrition, frequent diarrhea, and/or a critical disease state with extensive small-intestinal lesions, or in patients who have severe stenosis in the intestinal tract, fistulas, abscess formation, massive hemorrhage, and/or severe perianal lesions. The patient must be fasting when parenteral nutrition is administered. **C1 (Japan VI, overseas VI; 8)**
- Total parenteral nutrition (TPN) is efficacious in inducing remission in active CD, and has a therapeutic effect equivalent to that of enteral nutrition. **B (Japan III, overseas III; 8)**
- When carrying out TPN, watch for complications such as sepsis and hepatic disorders. **C1 (overseas V; 8)**

Comments: The indications for TPN through a central venous line are described in the proposed revision of the clinical practice guidelines for Crohn's Disease published by Research Group of Intractable Disease subsidized by the Ministry of Health, Labour and Welfare of Japan [58]. However, in practice, it is necessary to select a feeding method according to the individual's condition. The results of several randomized controlled studies have shown that TPN, among other parenteral feeding methods, has a remission induction effect for active CD equivalent to that of the enteral feeding of elemental nutrients [107, 108]. TPN can also attenuate intestinal lesions [108, 109]. When the CD patient's condition becomes stable on TPN, the TPN can be switched to enteral feeding.

If TPN is provided through a central venous line, catheter-related complications such as sepsis and hepatic disorders could occur. Particularly in patients undergoing parenteral nutrition at home through a central venous line, an infected feeding port is likely to progress to sepsis [110].

IV-9. Cytapheresis

CQ12: When is cytapheresis indicated, and what kinds of benefits and harms are expected? [111]

- Cytapheresis is indicated in patients with active CD with colonic involvement in whom drug and/or nutritional therapies are ineffective or inapplicable; the addition of granulocyte-monocyte apheresis (GMA) may accelerate induction of remission. **C1 (Japan V; 7)**

Comments: Cytapheresis has become an established therapeutic modality for UC in Japan. For CD, the effects of GMA in combination with other therapies were studied in 21 cases refractory to existing drug and/or nutritional therapies. The results showed remission (i.e., CDAI less than 150) in 27.8%, and improvement (i.e., reduction of CDAI by 50 or more) in 16.7% [111]. GMA was approved for clinical use in CD with colonic lesions in Japan in 2010. Although some adverse events, such as headache, dizziness, palpitation, and minor nonspecific abnormal laboratory test results have been reported, these therapies are generally considered to be safe.

IV-10. Surgical treatment

CQ13: What kind of benefits and harms are expected with surgical treatment? [112-114]

- Surgical treatment for the complications of CD is expected to attenuate the symptoms and improve the QOL. **B (overseas IVa; 9)**
- Surgical treatment reduces the doses of therapeutic drugs and thus the possibility of adverse effects. **C1 (Japan V, overseas IVa; 7)**
- Surgical treatment involves the risk of postoperative complications such as short-bowel syndrome and anastomotic leaks. **C1 (Japan V, overseas V; 8)**

Comments: There are no therapies that can cure CD completely. The purpose of surgical treatment is to attenuate the symptoms due to complications that are the causes of the patient's disability, and to improve the patient's QOL [112]. If the symptoms are attenuated, the doses of therapeutic drugs such as steroids can be reduced, thus preventing possible adverse effects (such as growth retardation) [113]. However, reoperation becomes necessary in some cases (the rate of reoperation in Japan was reported to be as high as 28-30%) [114]. Short-bowel syndrome due to repeated bowel resections can compromise the patient's QOL; resection should therefore be kept to the minimum necessary.

IV-11. Endoscopic treatment

CQ14: When is endoscopic balloon dilation indicated, and what kinds of benefits and harms are expected? [115, 116]

- Endoscopic balloon dilation is indicated for benign stenosis with bowel obstruction in the gastrointestinal tract without accompanying deep ulcers or fistulas. **C1 (Japan VI, overseas VI; 7)**
- This therapy may alleviate bowel obstruction and may avoid a surgical operation. **C1 (Japan V, overseas V; 8)**
- Care must be taken with regard to complications such as perforation or restenosis. **C1 (Japan V, overseas V; 9)**

Comments: The major of endoscopic treatment for CD is endoscopic balloon dilation (EBD). In CD, EBD is indicated for benign stenosis of comparatively short length with few flexures producing clinical features of bowel obstruction, without deep ulcers or fistulas. Accordingly, it is necessary to employ endoscopy or contrast imaging to observe the stenosis well before EBD is performed. The effectiveness of EBD for CD has been reported from many medical institutions in Japan and overseas [115, 116]. It is particularly effective for stenosis of a comparatively short length, such as 4 cm or less [115]. The incidence of complications involved in EBD was 2%, and perforation accounted for most of the cases [116]. Other than perforation, care must be taken with regard to hemorrhage, fistulas, abscess formation, and further restenosis.

V. Active Phase Treatment

V-1. Mild to moderate

CQ1: How is treatment initiated for mildly to moderately active CD? [56, 75, 98, 99, 102, 117-124]

- Administer salazosulfapyridine (SASP) in patients with mildly to moderately active CD with colonic lesions. **A (overseas II; 8)**
- SASP is not effective for small-intestinal lesions. **B (overseas III; 8)**
- The effect of 5-ASA preparations is limited, but they lack serious side effects and are easy to administer. In practice, they are often chosen as a first-line drug. **A (overseas I; 8)**
- Daily administration of 1,000 mg ciprofloxacin* is expected to have an effect similar to that of 5-ASA preparations for colonic lesions in CD. **B (overseas III; 7)** *Not covered by Japanese public health insurance for treatment of CD.
- The remission induction effect of enteral nutrition for active CD is equivalent or slightly inferior to that of corticosteroids. **A (Japan III, overseas I; 8)**

Comments: As described in section II-9, there are no practical criteria to determine the severity of CD, and thus it is determined on the basis of a comprehensive assessment of clinical findings [56]. In these guidelines, mild to moderate cases are assumed to be those in which the patient is capable of visiting a hospital on an outpatient basis and of taking food orally, without findings including dehydration, fever, abdominal tenderness, bowel obstruction, or weight loss of 10% or more [56].

A meta-analysis and several randomized controlled trials have shown that SASP is effective for colonic lesions in mildly to moderately active CD [117, 118], but that it is not effective for small-intestinal lesions [119]. Some studies have also shown that mesalazine is effective for CD [75, 120-122]. A recent meta-analysis indicated that the CDAI score in the mesalazine group was significantly reduced in comparison with that in the placebo group [119]. In Japan, where treatment options are limited, mesalazine is widely used for ileal and colonic lesions because of its safety profile and ease of administration.

A randomized controlled trial has indicated that for mildly to moderately active CD, 1 g ciprofloxacin administered daily has an effect similar to that of 4 g mesalazine administered daily [123].

Meta-analyses that compared enteral nutrition with steroid therapy concluded that steroids were more efficacious [98, 99]. However, a randomized controlled small-size study has indicated that nutritional therapy using elemental nutrients has effect of remission induction similar to that of steroids (prednisolone 0.5 mg/kg daily), and provides better nutritional status than steroids [124]. Furthermore, a Japanese report indicated that enteral feeding of elemental nutrients exhibited a higher rate of remission induction than prednisolone treatment, particularly for intestinal lesions [102]. In Europe and North America, budesonide, a steroid with reduced systemic adverse effects, is used for lesions in the ileum to the right side of the colon. Budesonide exhibited a higher rate of remission induction than mesalazine.

V-2. Moderate to severe

CQ2: How is treatment initiated for moderately to severely active CD? [56, 73, 111, 119, 125-128]

- Administer oral steroids (prednisolone, approximately 40 mg daily). **B (overseas III; 8)**
- In cases where steroids are not effective, consider administering an anti-TNF agent. **A (overseas II; 8)**
- The remission induction effect of enteral nutrition for active CD is equivalent or somewhat inferior to corticosteroids. **A (Japan III, overseas I; 8)**
- In active CD with colonic lesions for which drug and/or nutrition therapies are ineffective or inapplicable, the addition of GMA may be helpful. **C1 (Japan V; 7)**

Comments: In these guidelines, moderate to severe cases are assumed to be those in which therapies for mild to moderate cases are not effective, or those in which the patient exhibits symptoms that include weight loss of 10% or more, anemia, abdominal pain, and/or nausea/vomiting without bowel obstruction [56].

Randomized controlled trials have shown that steroids are efficacious in inducing remission in CD [73, 119]. However, steroids are not effective in maintaining remission [73]. In patients in whom symptoms have worsened during the tapering of steroids, or those in whom there was a relapse shortly after withdrawal from steroids, or in those with repeated relapses, consider using an immunomodulator such as AZA or 6-MP in combination with steroids. In patients in whom AZA or 6-MP cannot be used because of adverse effects, methotrexate (MTX) is considered to be effective and is used overseas [125, 126].

Anti-TNF agents, both with single administration and with scheduled successive administrations, were shown to be efficacious in cases refractory to steroids and/or immunomodulators. [127, 128].

The addition of GMA was approved for clinical use in Japan in 2010 for active CD with colonic lesions not responsive to existing drug and/or nutrition therapies [111].

V-3. Severe to fulminant

CQ3: How is treatment initiated for severe to fulminant CD? [56, 129]

- The patient is generally hospitalized; as necessary; consider complete fasting, infusion of fluid, and/or blood transfusion, and administer an antimicrobial drug if the patient shows signs of infection. **C1 (Japan VI, overseas VI; 8)**
- Exclude infections, and intravenously administer steroids (prednisolone equivalent to 40-60 mg daily). **C1 (Japan VI, overseas VI; 8)**
- In cases resistant to steroids, consider administering an anti-TNF agent. **C1 (overseas V; 8)**
- In cases where the patient's general condition is poor, or unresponsive to medical therapies, consult with surgeons at an early opportunity. **C1 (Japan VI, overseas VI; 8)**

Comments: In these guidelines, severe to fulminant cases are assumed to be those in which the patient's symptoms persist after oral administration of steroids, or those in which the patient presents with high fever, persistent vomiting, bowel obstruction, rebound tenderness, cachexia, and/or abscess [56].

In general, the patient should be hospitalized to receive intensive general supportive care. Orally administered steroids are not as well assimilated as intravenous steroids, and intravenous administration is advantageous in terms of pharmacokinetics [129] and preferred for severe cases.

For fulminant cases not responsive to other medical treatments, there is only limited evidence on the effects of anti-TNF agents; however, they can still be a treatment option. They should be used only when the presence and/or risk of infectious complications such as abscesses are ruled out. Severe cases in which the patient has unstable hemodynamics, or those with peritoneal irritation, may be indications for surgical treatment, and therefore it is desirable to consult with surgeons at an early opportunity.

V-4. Therapies according to disease extent

CQ4: Are different therapies used for lesions in the small intestine, the colon, and both? [117, 118]

- Treatment options vary according to the disease extent. **C1 (Japan VI, overseas VI; 8)**
- SASP is effective only for colonic lesions. **A (overseas II; 8)**
- Antimicrobial drugs* are more effective for colonic lesions than for small-intestinal lesions. **B (overseas III; 8)** *Not covered by Japanese public health insurance for treatment of CD.
- Enteral nutrition is more effective for small-intestinal lesions than for colonic. **A (Japan III, overseas I; 8)**

Comments: Consideration of the mechanisms and sites of action of therapeutic drugs for CD indicates the appropriate use of these drugs depending on the sites of the lesions, and it is actually confirmed in some cases. SASP is effective only for mild colonic lesions [117, 118]. Antimicrobial drugs, particularly metronidazole, are known to be generally effective for colonic and perianal lesions. Enteral nutrients are significantly more effective for small-intestinal lesions than for colonic lesions. Mesalazine is effective for both small-intestinal and colonic lesions; and systemic steroids, immunomodulators, and anti-TNF agents are not selective with respect to lesion sites.

CQ5: What is the treatment for CD lesions in the upper gastrointestinal tract? [56, 57]

- In cases of CD with upper-gastrointestinal lesions, administer a proton pump inhibitor (PPI).* **C1 (overseas VI; 7)** *Not covered by Japanese public health insurance for treatment of CD.
- Administer steroids and/or immunomodulators, such as AZA or 6-MP, as necessary. **C1 (overseas VI; 7)**
- In cases refractory to steroids, consider administering anti-TNF agents. **C1 (overseas: VI; 8)**
- In patients with upper-gastrointestinal lesions with bowel obstruction, consider endoscopic dilation or surgical treatment. **C1 (overseas VI; 8)**

Comments: Evidence is not sufficient with regard to the treatment for upper-gastrointestinal lesions of acute CD. PPIs are often used for inflammatory lesions in the upper gastrointestinal tract, in combination with other therapies, as in the treatment for lesions at other sites [56, 57]. 5-ASA preparations in their original forms do not act on the mucosa of the upper gastrointestinal tract, and therefore attempts have been made to administer these agents orally by crushing and grinding the tablets. However, the effectiveness and safety of these preparation have not been sufficiently studied.

V-5. Perianal lesions

CQ6: What is the treatment for the perianal lesions of CD? [36, 82, 130-132]

- Treat the intestinal lesions first, and wait to see if the perianal lesions are attenuated. **C1 (Japan VI, overseas VI; 8)**
- Anti-TNF agents are effective as medical therapy for anal fistulas. **A (overseas II; 8)**
- Antimicrobial drugs and immunomodulators are effective therapies for anal fistulas. **A (overseas I; 8)**
- The Seton procedure is an effective surgical treatment for anal fistulas. In severe cases, consider a stoma. **B (Japan V, overseas V; 9)**

Comments: Perianal lesions in CD include primary lesions (fissures and cavitating ulcers), ulcerated piles with longitudinal ulcers, and secondary refractory lesions (perianal abscesses, anal fistulas). In patients with perianal lesions specific to CD, first employ medical therapies and/or surgical treatment for the intestinal lesions, and wait to see if the perianal lesions are attenuated. Among the secondary perianal lesions in CD, the Seton procedure is effective for anal fistulas; for common lesions, use ordinary treatments [130, 131]. An overseas randomized controlled trial indicated that an anti-TNF agent was effective for anal fistulas [82]. Anti-TNF agents should be used after confirmation that any infection is under control. There are no randomized controlled studies on antimicrobial drugs (such as metronidazole) for perianal lesions; however, limited evidence and clinical experience indicate that these drugs have some efficacy. For immunomodulators (such as AZA), several randomized controlled trials and meta-analyses have shown effectiveness for anal fistulas [36, 132].

V-6. Refractory cases

CQ7: What is the treatment for cases refractory to various medical treatment? [57, 133]

- Consider surgical treatment in cases refractory to medical treatment without attenuation of complications. **B* (Japan VI, overseas VI; 9)**
- The indication for surgical treatment should be determined with mutual communications among the gastroenterologist, the surgeon, and the patient. **B* (Japan VI; 9)**

Comments: Medical treatment is the primary therapy for CD, and surgical treatment remains as secondary. However, in cases refractory to medical treatment, in which the patient has extremely impaired QOL, with serious adverse reaction to drugs, or with a fibrous stenosis not expected to be improved by medical treatment, surgical treatment should be considered [57, 133]. The indication for the surgical treatment should not be determined only by the surgeon, but by thorough discussions involving the relevant healthcare providers together with the patient.

V-7. Fistulas

CQ8: What is the treatment for fistulas? [82, 132, 134]

- Immunomodulators are effective for treating fistulas, but their onset of the action is delayed. **A (overseas I; 8)**
- Anti-TNF agents are effective for treating fistulas. **A (overseas II; 9)**
- Surgical treatment is indicated in patients with internal fistulas causing severe malabsorption. **B (Japan VI, overseas VI; 8)**
- Consider surgical treatment for fistulas with abscess formation. **B*(Japan VI, overseas IV:9)**

Comments: Some cases of CD are complicated with internal fistulas such as intestinal fistulas and external fistulas such as intestinal-cutaneous fistulas. No consensus has been reached with regard to either treatments for fistulas without symptoms or treatments for internal fistulas [134].

As a medical treatment for fistulas, a meta-analysis of overseas randomized controlled studies has indicated that immunomodulators are effective [132], although the onset of action of these drugs is delayed. An overseas large randomized controlled study (ACCENT II) demonstrated that infliximab was useful [82]. A study of the effect of adalimumab on remission maintenance showed a significant effect in closing external fistulas completely at week 26 and week 56.

Consider surgical treatment in patients in whom where medical therapies have been unsuccessful. The indications for surgery include patients with internal fistulas causing severe malabsorption, patients in whom fistulas are spread over a broad area in the healthy bowel, patients with repeated urinary tract infections, patients with external fistulas with excessive leakage of intestinal juices, and patients with painful involving perianal external fistulas complicated with abscess formation [134].

V-8. Stenosis

CQ9: What is the treatment for an intestinal stenosis due to CD? [115, 135, 136]

- Administer steroids in patients with severe inflammation. **C1 (Japan VI, overseas VI; 7)**
- Consider endoscopic dilation in patients in whom there has been no improvement with drug therapies or decompression. **C1 (Japan V, overseas V; 7)**
- Consider surgery in patients whose condition has not been improved improving with medical treatment. **B*(Japan V, overseas V; 9)**

Comments: Intestinal stenosis occurs with mucosal edema due to acute inflammation or transmural fibrotic changes in the intestine. Patients with stenosis mainly due to inflammation may improve with medical treatment such as steroids [135]. In patients that do not show improvement with anti-inflammatory treatments, suspect stenotic due to fibrosis, and consider the possibility of endoscopic dilation on the basis of the length of the stenosis, the number of stenosis sites, and the presence of ulcers. It is advisable to use endoscopic dilation when the inflammation and ulcers have disappeared or become reduced with enteral nutrition or other therapies. In a report overseas, endoscopic dilation brought about favorable results in 40% of the subject [136]. A report from Japan showed the 5-year operation-free rate after endoscopic dilation was 58% [115]. Whether or not anti-TNF agents are indicated for cases of CD with stenosis has not yet been determined.

V-9. Hemorrhage

CQ10: What is the treatment for hemorrhage from the CD lesions? [137-140]

- First apply conservative management such as supportive care and drug therapies. **C1 (Japan V, overseas V; 9)**
- Infliximab was reported to be effective in arresting hemorrhage. **C1 (Japan V, overseas V; 8)**
- If conservative management is not successful in arresting hemorrhage, surgery is indicated. **B* (Japan V, overseas V; 9)**

Comments: Massive hemorrhage may occur in CD, although it is rare. In such cases, first perform intensive conservative management, and allow nothing by mouth to keep the intestinal tract at rest. It was reported that steroids were efficacious in such cases. Try endoscopic hemostasis where it is applicable. With regard to angiography, it was reported that the intraarterial injection of vasopressin and arterial embolization were successful in arresting hemorrhage [137]. However, arterial embolization may cause intestinal ischemia leading to intestinal necrosis. It was reported that the administration of infliximab was effective for treating the hemorrhagic type of CD [138].

Surgical treatment is necessary in cases where medical treatment is unsuccessful. It was reported that the surgical operation rate for hemostasis in patients with initial massive hemorrhaging was 20-90%, and that the surgical operation rate in those with recurrent hemorrhage under medical treatment was 30-35% [139, 140].

V-10. Abscesses

CQ11: What diagnosis and treatment are used for abscesses due to CD? [141-144]

- Imaging examinations such as CT, US, and MRI are used to diagnose abscesses. **B (Japan V, overseas IVb; 9)**
- Where possible, perform image-guided (e.g., CT-guided) percutaneous drainage. **B (Japan V, overseas IV; 8)**
- In patients with abscesses in the perianal region, perform incision and drainage. **B* (Japan V, overseas V; 9)**
- In patients in whom where abscesses recur after percutaneous drainage or in those with fistulas, surgical treatment is likely to be necessary. **B* (Japan V, overseas V; 8)**

Comments: In CD, abscesses may be found to be complicated with transmural lesions in the intestinal wall. A Japanese report has indicated that the frequency of such abscesses is approximately 10% [141]. CT, MRI, and ultrasonographic examination are useful in diagnosing abscesses [142]. For treatment, percutaneous drainage should be performed where it is possible. The drainage techniques include CT-guided percutaneous drainage, US-guided percutaneous drainage, or surgical drainage via a small incision. In patients having of percutaneous drainage, administer an antimicrobial drug with a broad spectrum. Some overseas reports have indicated that percutaneous drainage avoided subsequent surgical operation in 50-69% of the patients treated [143, 144]. Patients with abscesses that cannot be controlled by percutaneous drainage require surgical treatment.

V-11. Extra-intestinal complications

CQ12: What is the treatment for extra-intestinal complications of CD? [145-147]

- In patients with active intestinal lesions, treat the intestinal inflammation. **C1 (Japan V, overseas V; 8)**
- In patients with pyoderma gangrenosum or uveitis, administer steroids. **C1 (Japan V, overseas V; 8)**
- In patients with extra-intestinal complications, the usefulness of infliximab was reported. **A (overseas II; 8)**

Comments: Extra-intestinal complications in CD include those related to the activity of the intestinal lesions (e.g., some types of peripheral arthritis, erythema nodosum, episcleritis, and intraoral aphthous ulceration) and those unrelated to the activity of the intestinal lesions (pyoderma gangrenosum, uveitis, sacral arthritis, and ankylosing spondylitis). For either category, it is necessary to intensively control the inflammation of the intestinal lesions.

In patients with arthritis, a 5-ASA preparation such as SASP is the first choice. Avoid NSAIDs because they may exacerbate the intestinal lesions. Administer steroids for serious complications such as pyoderma gangrenosum and uveitis.

Some randomized and non-randomized controlled studies, including those with non-CD patients, have indicated that infliximab was effective for treating complications such as pyoderma gangrenosum, arthritis, uveitis, and ankylosing spondylitis [145-147].

VI. Remission Maintenance Treatment

VI-1. General principles for preventing relapse

CQ1: Are there any lifestyle factors that require attention to prevent relapse? [18, 70, 148, 149]

- If the patient smokes, advise them to refrain from smoking. **B (overseas III; 9)**
- Advise the patient to avoid irregular lifestyle and eating habits, and to refrain from excessive alcohol drinking. **C1 (overseas VI; 7)**
- Advise the patient to adopt a lifestyle without excessive mental stress, to have as little as stress possible. **C1 (overseas IVb; 7)**
- Advise the patient that in using an analgesic or an antipyretic, wherever possible to avoid NSAIDs. **C1 (overseas IVb; 7)**

Comments: Although exacerbating factors common to all cases of CD cannot be specified, it has been shown that smoking contributes to the disease becoming refractory or relapsing [148], and that the disease is attenuated after smoking cessation [70]. Frequent or excessive alcohol drinking may damage the intestinal tract, and therefore drinking should be controlled. In view of the fact that nutritional therapies are beneficial for CD, irregular eating habits or unbalanced diets may precipitate relapse.

It has also been shown that mental stress has some relationship with CD relapse [149]. Patients with CD should be advised to live without mental stress as much as possible, and to adopt a lifestyle where stress does not accumulate. NSAIDs are known to cause gastrointestinal injuries, and also the relapse or exacerbation of CD. Therefore, wherever possible, they should be avoided. If analgesics or antipyretics need to be prescribed, acetaminophen would be an appropriate substitute [18].

CQ2: Are there any distinctive features of CD that make the disease likely to relapse? [31, 150]

- CD patients with fistulas, perforation, or perianal lesions, and those who have had resection of the intestinal tract, are more susceptible to relapses. **C1 (Japan V, overseas V; 7)**
- Patients with CD who have required steroids for induction of remission are more susceptible to relapses. **C1 (overseas IV; 7)**

Comments: The pathophysiology and symptomatology of CD are complex, and it is difficult to predict the variable progress of each case. However, it has been shown that patients with fistula formation or intestinal perforation are more susceptible to relapses than those with the non-perforation type [150]. Patients with CD with high disease activity who have required steroids for the induction of remission often have difficulty in withdrawing from the steroids and require immunomodulators. It has been shown that patients for whom steroids or immunomodulators are required are more susceptible to relapses than other patients [31].

VI-2. Drug treatment

CQ3: Which drugs are effective for maintaining remission of CD? [76, 79, 128, 151-153]

- AZA is effective in maintaining remission. **A (overseas I; 9)**
- In patients in whom where remission was induced by anti-TNF agents, the scheduled administration of anti-TNF agents is effective in maintaining remission. **A (overseas II; 8)**
- 5-ASA preparations are effective in maintaining remission postoperatively. **B (overseas II; 7)**

Comments: Steroids are effective for inducing remission, but ineffective for maintaining remission. It has been shown that AZA and 6-MP have steroid-sparing effects in steroid tapering and complete withdrawal, as well as having a long-term effect in maintaining remission. The standard dose of AZA is 1.0–2.5 mg/kg daily, and that of 6-MP is half of that of AZA. A high dose of these drugs exhibits a more potent effect than a low dose [79, 151]. However, both AZA and 6-MP may produce serious side effects, and the doses that may produce the required effects and the adverse reactions differ individually. The recommended doses for these agents have been determined for patients in Western countries, and it is possible that lower doses in Japanese patients would produce the required effects and/or fewer adverse effects.

It has been shown that infliximab exhibits a remission induction effect even in refractory or severe cases, and that administration of infliximab every 8weeks to patients in whom remission was induced by the agent had a significant effect in preventing relapses for at least 1year [128, 152]. 5-ASA preparations have only a limited remission maintenance effect [76], but they are effective in controlling postoperative relapses [153].

CQ4: How long should the treatment for remission be continued? [128, 152, 154]

- If effective, it is advisable to continue the administration of AZA or 6-MP* for 3-4 years. **C1 (overseas VI; 8)** *Not covered by Japanese public health insurance for treatment of CD.
- Scheduled administration of infliximab is effective for at least 1year. **A (overseas II; 8)**

Comments: AZA and 6-MP, thiopurine derivatives, are known to have efficacy for long-term remission, and a meta-analysis showed that they were effective in maintaining remission for at least 1 year. Furthermore, it has been reported that the continued administration of these agents for more than 2 years is effective, and therefore it is advisable that they continue to be administered for 3-4 years as long as remission is maintained without the emergence of adverse effects [154]. In a study to evaluate the effect of the scheduled administration of infliximab at 8-week intervals for 1 year in patients in whom remission was induced by infliximab, the remission maintenance effect was significantly higher in the group receiving infliximab regularly at intervals of 8 weeks compared with placebo [128, 152].

VI-3. Nutritional therapy

CQ5: Is home enteral nutrition effective in maintaining remission? [103, 155, 156]

- Replacing half of the daily caloric intake by enteral nutrients is effective in maintaining remission. **A (Japan II, overseas II; 8)**

Comments: Enteral nutrition as a long-term therapy for remission maintenance has an excellent safety profile, but often lacks acceptability and convenience. It is thus difficult for patients to receive total enteral feeding at home for a long period of time. Partial enteral feeding is more acceptable and more convenient for the patient, and the patient can enjoy eating as well. It was shown that replacing 30-50% of the normal daily caloric intake by enteral nutrients had a significantly higher remission maintenance rate than a normal daily diet only [103, 155, 156].

CQ6: How long should nutritional therapy be continued? [103, 155, 156]

- Replacing half of the daily caloric intake by enteral nutrients is effective in maintaining remission for at least one year. **A (Japan II, overseas II; 8)**

Comments: It was shown that replacing 30-50% of the daily caloric intake by enteral nutrients had a significantly higher rate of remission maintenance at 1 year than a normal daily diet only [103, 155, 156]; therefore, it is recommended to continue enteral nutrition for 1 year in patients in whom remission was induced by nutritional therapy. Although there is no evidence to favor enteral nutrition beyond 1 year, it may be advisable to continue this treatment for as long as possible, if no problems of acceptability or convenience emerge.

CQ7: When is home parenteral nutrition (HPN) necessary, and how is it performed?
157

- In patients with short-bowel syndrome for whom sufficient nutritional care by enteral feeding is not possible, supply nutrition by infusion through a central venous line. **C1 (Japan VI, overseas VI; 8)**

Comments: In CD patients with small-intestinal lesions where the remaining small intestine is short as a result of the resection of a large area or frequent resections, the bowel cannot digest and assimilate a sufficient amount of nutrition (i.e., if the remaining small intestine is 1 m or less, malabsorption is inevitable; even if the remaining small intestine is a little longer, malabsorption is likely to occur). Accordingly, to provide the patient with the required nutritional support, a catheter is placed in the central vein, and a home-based arrangement is made whereby the patient or the patient's family can manage nutrition drips [157].

VII. Surgical Treatment

VII-1. Indication for surgery

CQ1: How often is surgical treatment required for CD? [158, 159]

- In Japan, the cumulative rate of surgical intervention for CD at 5 and 10 years after the onset is 30.3 and 70.8%, respectivery. The rates vary greatly from area to area in Europe and North America. **C1 (Japan V, overseas V; 7)**

Comments: In Japan, the cumulative rates of surgical treatment for CD at 5 and 10 years after the onset are 30.3 and 70.8%, respectively. respectively (N = 361). Regarding the rate according to the disease location, there were no significant differences among the ileal, ileocolonic, and colonic types at in 5 and 10 years after the disease onset [158]. In Europe and North America, the rate of surgical treatment for CD varies from area to area [159].

CQ2: What are the absolute indications and the relative indications for surgery? [141, 160, 161]

- Surgery is absolutely indicated in patients with perforation, massive hemorrhage, development of cancer, bowel obstruction not alleviated by medical therapies, and abscesses. **B* (Japan V, overseas V; 9)**
- Surgery is relatively indicated in patients with refractory stenosis or internal and external fistulas, and in those to medical treatment, or with refractory extra-intestinal complications (e.g., growth retardation, pyoderma gangrenosum), and refractory perianal lesions. **C1 (Japan V, oversea: V; 8)**

Comments: Surgical indications in CD in percentages according to the underlying lesions or clinical situations, are as follows: bowel obstruction and stenosis: 54%; fistulas: 28%; abscesses: 7%; perforations: 4.5%; cases refractory to medical therapies: 3.5%; massive hemorrhage: 2%; and colorectal cancer: 1%. Toxic megacolon was also referred to as a surgical indication. Other surgical indications are: symptomatic fibrotic stenosis; enterocutaneous fistulas with excessive leaks of intestinal juices or with stenosis; symptoms due to bypass formation (e.g., duodenal/transverse colonic fistulas); intestinal fistulas involving a broad area of intact bowel; enterovesical fistulas refractory to medical therapies and with repeated urinary tract infection; intra-abdominal abscesses not responsive to medical therapies; and retroperitoneal abscesses [141]. The relative risks of colorectal cancer and small-intestinal cancer are significantly high in patients with CD [161]. In Japan, colorectal cancer in CD patients is more common in the form of rectal and anal fistula cancer, and small-intestinal cancer is more common in the ileum. With regard to gastric/duodenal lesions as complications of CD, surgical indications are fistulas starting at the colon or ileo-colonic anastomosis to the stomach, long duodenal stenosis, and duodenal fistulas that often occur arising from the adjacent lesions [160].

VII-2. Refractory to medical treatment

CQ3: What is the main principle guiding surgery on the intestine? [162, 163]

- As CD involves the entire intestinal tract and often recurs, the intestinal tract should be preserved as much as possible. **A (overseas II; 9)**
- Only the small portion of the intestinal tract causing stenosis or fistulas should be resected. Strictureplasty should be performed in patients with short fibrotic stenosis in the small intestine or in those with a short length of small intestine remaining. **C1 (Japan V, overseas V; 9)**

Comments: The postoperative recurrence of CD after resection of the intestine is unrelated to the distance between the lesion and the resected end [162], or to the histological residue of the lesion at the resected ends [163]. Therefore, in principle, a short segment should be resected. In patients with an intestinal fistula induced by another intestinal lesion, the intestinal area of the principal lesion is resected, and the fistulized area is wedge-resected. Strictureplasty is performed to preserve the small intestine. Bypass operations result in a high incidence of malignant tumors in the diverted residual lesion, and a high rate of reoperation. In principle, therefore, only gastrojejunostomy for duodenal stenosis is performed in patients with CD.

VII-3. Stenosis

CQ4: What kind of surgery is used to treat stenosis? [164-166]

- Only the area of the lesion causing the stenosis should be resected. Strictureplasty should be performed for a short segment of fibrotic stenosis in the small intestine or in patients with a short length of small intestine remaining. **B (Japan V, overseas IVb; 8)**

Comments: It is a general opinion that there is little difference in postoperative recurrence rates between strictureplasty and intestinal resection [164]. In patients with a stenosis in a short segment, the Heineke-Mikulicz technique is applied; in those with stenosis over a long segment, the Finney technique or the Jaboulay technique is applied; and in those with stenoses close to one another, a more complex anastomosis technique is applied [165, 166]. Furthermore, it is important to conduct a biopsy examination at the stenosis to exclude cancer. The effectiveness of strictureplasty on colonic stenosis is yet to be confirmed.

VII-4. Perianal lesions

CQ5: What kind of surgery is used to treat perianal lesions? [38, 167, 168]

- Perianal lesions in CD are classified as primary lesions (cavitating ulcerative lesions due to CD), secondary refractory lesions (secondary lesions originating from a primary lesion via infection and other causes), and incidental lesions (lesions not associated with CD). **C1 (overseas VI; 7)**
- For incidental lesions, use ordinary treatments generally appropriate for such lesions. **C1 (Japan VI, overseas VI; 7)**
- Among the secondary refractory lesions, a Seton technique is used for low intersphincteric fistulas and ischiorectal fistulas. Consider creating a stoma in cases not responsive to the Seton technique or in those with fibrotic stenosis. **C1 (Japan VI, overseas VI; 8)**

Comments: In the diagnosis of perianal lesions in CD, determine whether the lesion is a secondary refractory lesion or an incidental lesion, on the basis of the presence or absence of a primary lesion characteristic of CD in the anal canal and the fistula (e.g., whether or not there are multiple fistulas, the location, and so on [167]; refer to the Atlas of findings by visual observation of lesions in the anus of Crohn's disease [38]). The refractory fistulas most frequent in CD are secondary lesions. Cancer complications are found more commonly in the rectum and anal canal (including fistulas) in patients with long-term progression of CD [168]. For the treatment of refractory fistulas, use medical treatment (nutritional therapy, and drug therapies such as metronidazole or steroids) for the primary lesion, and try to induce remission if there are active rectal lesions. Subsequently, if no improvement is observed, use surgical treatment on the fistulas. For local treatment, as a general rule, use a Seton drainage technique to establish a drain to eventually discharge pus in the fistula contents. Consider creating stoma in patients with fistulas or rectal stenosis that cannot be controlled with the Seton technique. For lesions of rectal stenosis with fistulas, consider rectal amputation.

CQ6: Is it possible to close a stoma later? [169, 170]

- In principle, a stoma that has been created because of rectal/anal lesions in CD is not closed because the lesions tend to recur frequently if it is closed. **C1 (Japan V, overseas V; 7)**

Comments: In a report of stoma closure surgery in 16 patients with symptomatic improvement out of 42 patients who underwent undergoing colostomies for refractory rectoanal lesions as complications of CD, 75% required re-creation of the stoma [169]. It has been reported overseas that the cumulative rate of stoma closure in 5 years was 40% [170].

VII-5. Postoperative management

CQ7: What is the relapse rate after surgical treatment? [171-173]

- Relapse after intestinal resection is frequently discovered early by means of endoscopic exploration. The cumulative reoperation rates were 16-43% at 5 years and 26-65% at 10 years. **C1 (Japan V, overseas V; 8)**

Comments: Postoperative relapse has been defined separately on the basis of endoscopic or contrast imaging findings, or on the basis of reoperation, and so the reported rates of relapse vary. The rate of relapse found by means of endoscopic exploration (in an ileocolonic anastomosis) seemed to be 72% within 1 year after the operation [171], indicating that the lesions tend to recur early. It was reported that the cumulative reoperation rates were 16-43% at 5 years and 26-65% at 10 years [172, 173].

CQ8: What are the risk factors for a relapse? [164, 172, 174-176]

- Gender and the presence of granuloma are not significant risk factors. In patients who have had operations on the colonic lesions of CD, reoperation is not frequent. **C1 (overseas V; 7)**
- The length of the uninvolved area in the resection margins is not a significant risk factor. **C1 (overseas V; 7)**
- No consensus has been reached on the disease duration before the initial operation, the presence or absence of histological inflammation at the resection margins, or the types of anastomosis (end-to-end, end-to-side, or functional end-to-end) as risk factors. **C1 (Japan VI, overseas VI; 8)**
- In patients where fistulization is the surgical indication, the reoperation rate may be higher in comparison with that in patients with a non-fistulizing type. **B (overseas IVb; 8)**
- It was reported that there was little difference in terms of recurrence rates between strictureplasty and intestinal resection. **C1 (overseas IVb: 7)**

Comments: Risk factors for recurrence have not been determined. Gender and the presence or absence of granuloma are not significant risk factors. In patients who have had oprations on the colonic lesions of CD, reoperation is not frequent [172]. The length of the intact area in the resection margins is not a significant risk factor [174]. There are contradictory reports on the disease duration before the initial operation and the presence or absence of histological inflammation at the resection margins as risk factors. There is no consensus on the type of anastomosis (end-to-end, end-to-side, or functional end-to-end) as a risk factor. Reports about the types of surgical indication (perforating versus non-perforating) are also contradictory [175]; however, a meta-analysis has indicated that the perforating type shows a higher reoperation rate [176]. It was reported that there was little difference in terms of recurrence rates between strictureplasty and intestinal resection [164].

CQ9: How can postoperative relapse be prevented? [105, 177-179]

- There are no established measures to prevent relapse. **C1 (Japan VI, overseas VI; 7)**
- 5-ASA, 6-MP* and metronidazole* may be effective in preventing a postoperative relapse. **B (overseas II; 7)** *Not covered by Japanese public health insurance for treatment of CD.
- The effect of postoperative nutritional therapies to prevent relapse is unclear. **C1 (Japan V; 7)**

Comments: The effects of surgical procedures, drug therapies, and nutritional therapies on relapse have been studied. With regard to surgical procedures, there are different views on the comparison between conventional end-to-end anastomosis and functional end-to-end anastomosis (in which the anastomotic site opening is wider in order to improve the retention of intestinal contents, which is considered to be a cause of relapse).

5-ASA (3,000 mg daily) exhibited significantly better results, in terms of clinical symptoms and relapse rate defined by endoscopy and contrast radiography, in comparison with a placebo group [177]. In patients who underwent ileal resection, metronidazole (20 mg/kg) was superior to placebo in terms of endoscopic relapse at 3 months after the operation, and in regard to the relapse rate at 1 year, but the relapse rates in the two groups were similar at 2 and 3 years after the operation [178]. In subjects with ileal resection, the 6-MP group (50 mg daily) exhibited significantly lower recurrence rates, according to the clinical symptoms, and endoscopic and contrast radiographic findings, at 2 years after the operation in comparison with the 5-ASA group and the placebo group [179]. Corticosteroids do not have efficacy to prevent postoperative relapse. Studies of the effects of anti-TNF agents to prevent postoperative recurrence have not been sufficient to reach definitive conclusions on such effects.

The long-term application of nutritional therapy (approximately 1,000 kcal daily) is difficult in many cases. A report has indicated that nutritional therapies were effective in preventing postoperative relapse [105], but the issue remains controversial.