VIII. Follow-up

VIII-1. Routine follow-up schedule

CQ1: How are CD patients followed, and what kind of examinations are required? [180, 181]

- Advise patients to have regular examinations, and observe changes in the clinical symptoms (abdominal pain, diarrhea, fever, and others). **C1 (Japan VI, overseas VI; 8)**
- CRP, ESR, complete blood counts, and serum albumin level correlate with the disease activity. **C1 (Japan VI, overseas VI; 8)**
- If changes in disease activity are noted, employ imaging examinations to observe the lesions. **C1 (Japan VI, overseas VI; 8)**

Comments: Blood tests are convenient and are the first-line examination to observe progress. CRP and ESR in particular were reported to correlate with the disease activity. Anemia and hypoalbuminemia can be indices of broadly spread lesions or highly active lesions, and hypoproteinemia is often found, particularly in patients with small-intestinal lesions. When changes in the disease activity are noted (clinical relapse, bowel obstruction, abscess, fistula), it is advisable to conduct examinations according to the previous pathophysiological conditions (the disease extent and possibility of complications) [181]. To determine the activity of intra-abdominal inflammation and the extent of active lesions, abdominal and pelvic CT and MRI are useful.

To evaluate diffuse small-intestinal lesions, radiographic examinations are often more advantageous than endoscopy or capsule endoscopy [180].

VIII-2. Morphological examination

CQ2: When is endoscopy or contrast radiography necessary? [150]

- When changes in disease activity or pathophysiological conditions are noted (clinical relapse, or complications such as bowel obstruction, abscesses, and fistulas), it is advisable to perform diagnostic imaging such as endoscopy and contrast radiography to assess the disease. **C1 (Japan VI, overseas VI; 8)**

Comments: A study of the long-term prognosis of CD indicates that even in patient with the non-stricture and non-penetrating type without complications in their initial stage, approximately 30% progressed to having stenosis or fistulas [150]. It is not unlikely that the lesions progress even in patients with stable disease, and therefore, annual endoscopic examinations or contrast radiographic examinations, as far as possible, would be helpful in assessing the pathological conditions.

VIII-3. Cancer surveillance

CQ3: Is the risk of cancer increased in CD, and can it be prevented? [25, 26, 182-185]

- Both colonic and ileocolonic CD have a higher risk of colorectal and/or anal cancer than that in the general population. **B (Japan IVb, overseas IVa: 8)**
- The incidence of small-intestinal cancer in patients with CD is low, but the relative risk is high in such patients. **C1 (oversea IVa;7)**
- There is no evidence that the administration of immunomodulators increases the incidence of malignant tumors. **C1 (overseas IVa; 7)**
- Preventive measures against the occurrence of cancer in patients with CD are not known, but control of the intestinal inflammation is considered to be important. **C1 (Japan VI, overseas VI: 7)**
- There is no data to clearly show that 5-ASA reduces the risk of colorectal cancer in CD. **C1 (overseas VI; 7)**

Comments: A meta-analysis of analytical epidemiological studies indicated that the relative risk of colorectal cancer was 2.5 in all types of CD, and significantly higher, at 4.5, in colonic-type CD; the relative risk of small-intestinal cancer was extremely high, at 33.2, in all types of CD [182]. Another epidemiological study indicated similar results [183]. Although Japanese data on these risks are sparse, some studies of the colorectal/anal canal cancer and small-intestinal cancer complications of CD indicate that most cases are found as advanced cancer, but the incidence is not different from that in Europe and the United States [25, 26].

A meta-analysis of analytical epidemiological studies has reported that there was no significant difference in the occurrence of malignant tumors between groups with and without administration of immunomodulators [184]. The TREAT study presents no evidence that a group in which infliximab was administered had an increased occurrence of malignant tumors. However, it has been reported that 13 cases of hepato-splenic T-cell lymphoma (HSTCL) occurred in a group in which infliximab and AZA were administered in combination [185]. No causal relationship has been established between such drugs and cancer.

It is assumed that controlling the intestinal inflammation is effective in preventing cancer in CD, as it is in UC. It has been suggested that 5-ASA has a suppressive effect on inflammatory carcinogenesis in UC, but there are no such data for CD.

CQ4: How is cancer surveillance conducted? [25, 186]

- There is no effective cancer surveillance program at present. **C1 (Japan VI, overseas VI; 8)**

Comments: In patients with long-term disease, it is advisable to conduct endoscopic and contrast imaging examinations, as appropriate, as well as to check the condition of anal fistulas. However, there are patients in whom it is difficult to conduct examinations to evaluate the small intestine in detail in the presence of stenosis. Appropriate determination of a high-risk group and an effective screening program are awaited.

In observing the progression of CD, it should be noted that the risks of small-intestinal cancer and colorectal cancer are high, particularly in the long-term progression of the disease, and that anal fistula cancer with diagnostic difficulty does occur, although the frequency is unknown. It was reported that surveillance endoscopy, like that for UC, was helpful in finding colorectal cancer [25, 186]. However, several issues remain unsolved, such as how to conduct surveillance in patients with stenotic lesions, and therefore surveillance colonoscopy has not yet become a general practice.

CQ5: Does CD increase the risk of extra-intestinal malignant tumors, and how is surveillance for such tumors conducted? [185, 187, 188]

- A combination of infliximab and immunomodulators may increase the risk of malignant lymphoma. **C1 (overseas V; 7)**
- There is no established program for the surveillance of malignant tumors in regions other than the intestinal tract. **C1 (Japan VI, overseas VI; 8)**

Comments: In patients with rheumatoid arthritis (RA), a study reported that it was unlikely that a combination of an anti-TNF agent with MTX raised the risk of lymphoma; on the other hand, another study indicated that the long-term use of a combination of an anti-TNF agent with an immunomodulator (AZA or 6-MP) did not raise the risk of solid cancer, but did raise the risk of malignant lymphoma [187, 188]. In particular, it has been reported that HSTCL, which is extremely rare, occurred in CD groups receiving combination therapy [185]. The pathophysiology of CD is different from that of RA, and the concomitant therapeutic drugs used and the clinical courses are different; because of these problems, no conclusion has been reached in regard to the risk of lymphoma with combination therapy in CD.

IX. Pregnancy

IX-1. Pregnancy

CQ1: Is CD exacerbated during pregnancy or in relation to the menstrual cycle? [189]

- There is no evidence that CD is exacerbated by either pregnancy or the menstrual cycle. **C1 (Japan VI, overseas V; 8)**

Comments: Not many studies have been carried out to evaluate the effect of pregnancy on CD. A study involving a small number of pregnant CD patients (12 patients; 18 pregnancies) indicated that pregnancy was unlikely to be a factor exacerbating CD [189]. Adherence with taking medications, however, may get worse due to the fear of taking drugs during pregnancy. It is necessary to explain the need for the medications to pregnant patients, so that the patients have a good understanding of the benefits and harms of the drugs.

There are no reports on the relationship between the menstrual cycle and exacerbation of CD, and clinical experience indicates that the cycle has no significant effect on CD. However, there is a possibility that variations in estrogen secretion have some effect on the immune system, and this requires further study.

CQ2: Do CD patients have different fertility rates from those of healthy individuals? [190-193]

- Many reports indicate that patients with CD have reduced fertility; on the other hand, some other reports show no significant differences from fertility rates in the general population. **B (overseas IVb; 8)**

Comments: Many reports have indicated that both male and female patients with CD have fewer children than the general population [190-192]. It was reported that the frequency of sexual intercourse was lower in female patients with CD because they were afraid of abdominal pain or fecal leaks [193]. There is a possibility that men who are administered SASP have reduced fertility [191].

CQ3: Is modification of the treatment necessary for pregnant patients with CD? [194-202]

- Devise treatment strategies according to the disease activity, considering the benefits and harms of the drugs. **C1 (Japan VI, overseas VI; 8)**
- Dominant overseas opinions are to treat pregnant CD patients similarly to non-pregnant patients. **C1 (overseas VI; 8)**
- In Japan, 5-ASA preparations, small to medium dose of steroids, and nutritional therapies are considered to be relatively safe in pregnant patients, but it is desirable to avoid immunomodulators. **C1 (Japan VI; 7)**
- When using nutritional therapies in pregnant patients, avoid excessive administration of vitamin A. **C1 (Japan VI, overseas VI; 8)**
- There is a possibility that the administration of AZA or 6-MP is associated with pre-term delivery, low birth weight, and fetal malformation. **C1 (overseas IVa; 7)**
- Infliximab has been reported to be relatively safe, but the relevant data are not sufficient. **B (overseas IVb; 8)**

Comments: Experts in Japan and overseas have different opinions concerning drug therapies for pregnant patients. Japanese specialists are cautious about using drugs because of the possibility of adverse effects, while overseas specialists assign priority to the benefits of the drugs unless they are confirmed to be harmful.

Several reports have indicated that the relative risks of pre-term delivery, low birth weight, and fetal deformation were high in groups administered AZA and 6-MP [194]; however, this does not exclude the possibility that other factors, such as high CD disease activity, were involved in these patients. Moreover, CD itself could pose such risks [195-197]. Recently, the number of reports overseas that have emphasized the safety of AZA has increased [198, 199].

Some reports have emphasized that the administration of infliximab or adalimumab in pregnancy was not associated with abnormal births; however, these reports were based on studies with a small number of subjects, and thus the safety of these drugs in pregnant patients could not be guaranteed [200, 201]. It has been reported that 5-ASA preparations are comparatively safe in pregnancy [202].

CQ4: What is the treatment for CD exacerbation during pregnancy? [198, 199, 201-203]

- Devise treatment strategies according to the disease condition, considering the benefits and harms of the drugs. **C1 (Japan VI, overseas VI; 8)**
- First increase the does of a 5-ASA preparation, and reinforce nutritional therapy. **C1 (Japan VI; 8)**
- If the result of the above is not sufficient, use steroids, an immunomodulator, and/or an anti-TNF agent, considering their benefits and harms. **C1 (Japan VI; 7)**

Comments: According to the FDA's pharmaceutical categories for safety in pregnancy, 5-ASA preparations and infliximab are in category B, oral prednisolone is in category C, and AZA and 6-MP are in category D [203]. A study of 131 pregnant women (with RA or CD) who were treated with infliximab indicated that 15% experienced birth abnormalities, and therapeutic abortion was induced in 19%; these findings correspond to the expected values for the general American population [201].

Despite the information mentioned above, many overseas textbooks recommend that the risk of such drugs be compared with the risk of CD relapse if their administration is terminated. Specifically, many overseas opinions appear to consider the risk of relapse or exacerbation of CD to pose a greater risk to pregnancy. As a result, many consider that AZA and 6-MP are relatively safe, and that they should continue to be administered when the patient becomes pregnant [198, 199]. On the other hand, MTX is contraindicated for pregnant women [202].

IX-2. Lactation

CQ5. What is the treatment for CD during a period of lactation? [202, 204, 205]

- Only a few drugs have been proven to be safe during breastfeeding, but nutritional therapy is considered safe. **C1 (Japan VI, overseas VI; 8)**
- Devise treatment strategies according to the disease activity, considering the benefits and harms. **C1 (Japan VI, overseas VI; 8)**

Comments: Date are sparse on the transfer of therapeutic drugs for CD into breast milk and potential exposure to breastfed infants. It has been found that 5-ASA is transferred into breast milk [204, 205]. However, there are many opinions that suggest it is safe in normal use. It is advisable to avoid administering a high dose of 5-ASA to lactating women. There are no relevant data with respect to AZA and 6-MP; on the other hand, MTX and cyclosporine are contraindicated in lactating women [202].

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Figure 1 Diagnostic approach in Crohn's disease

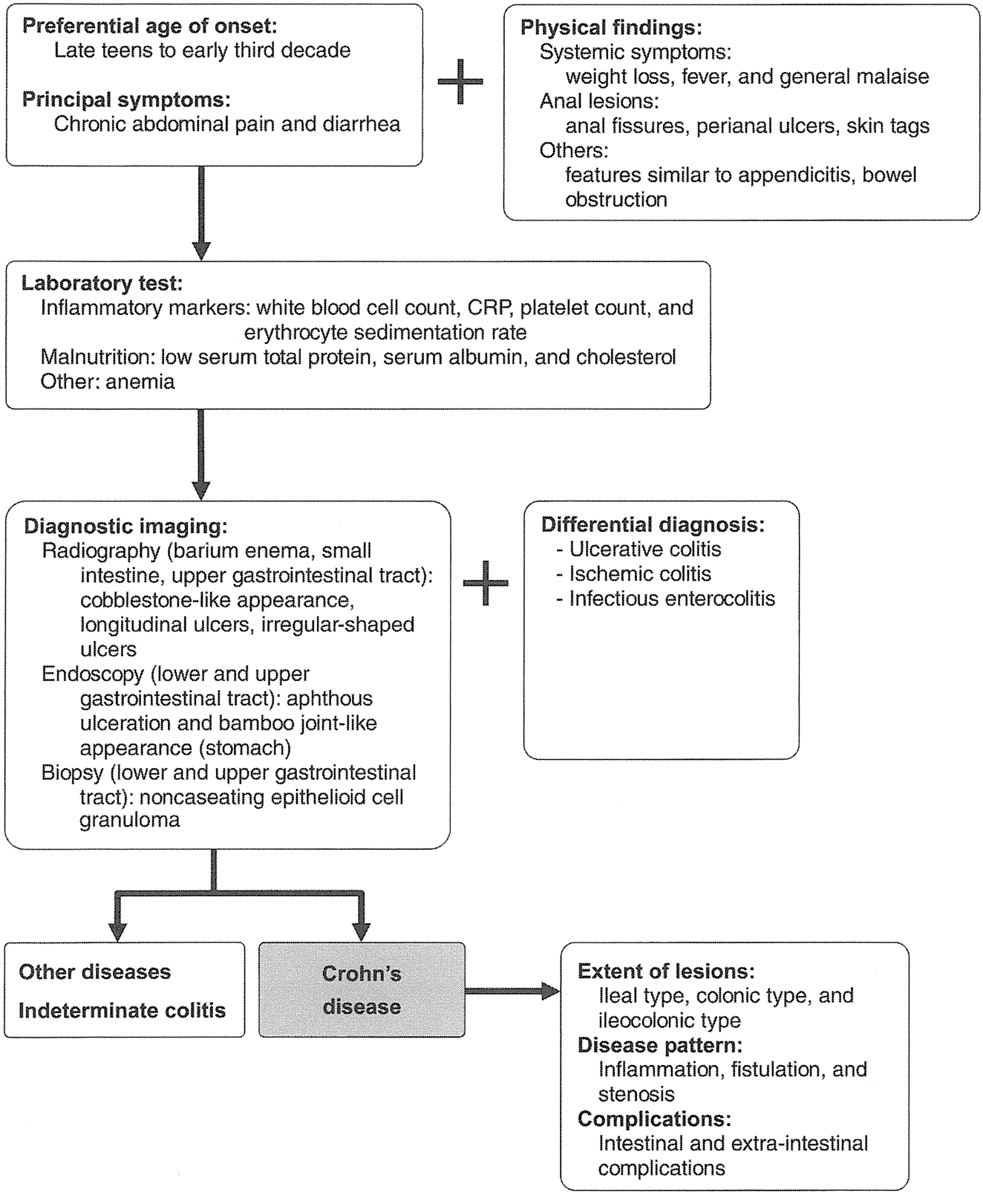
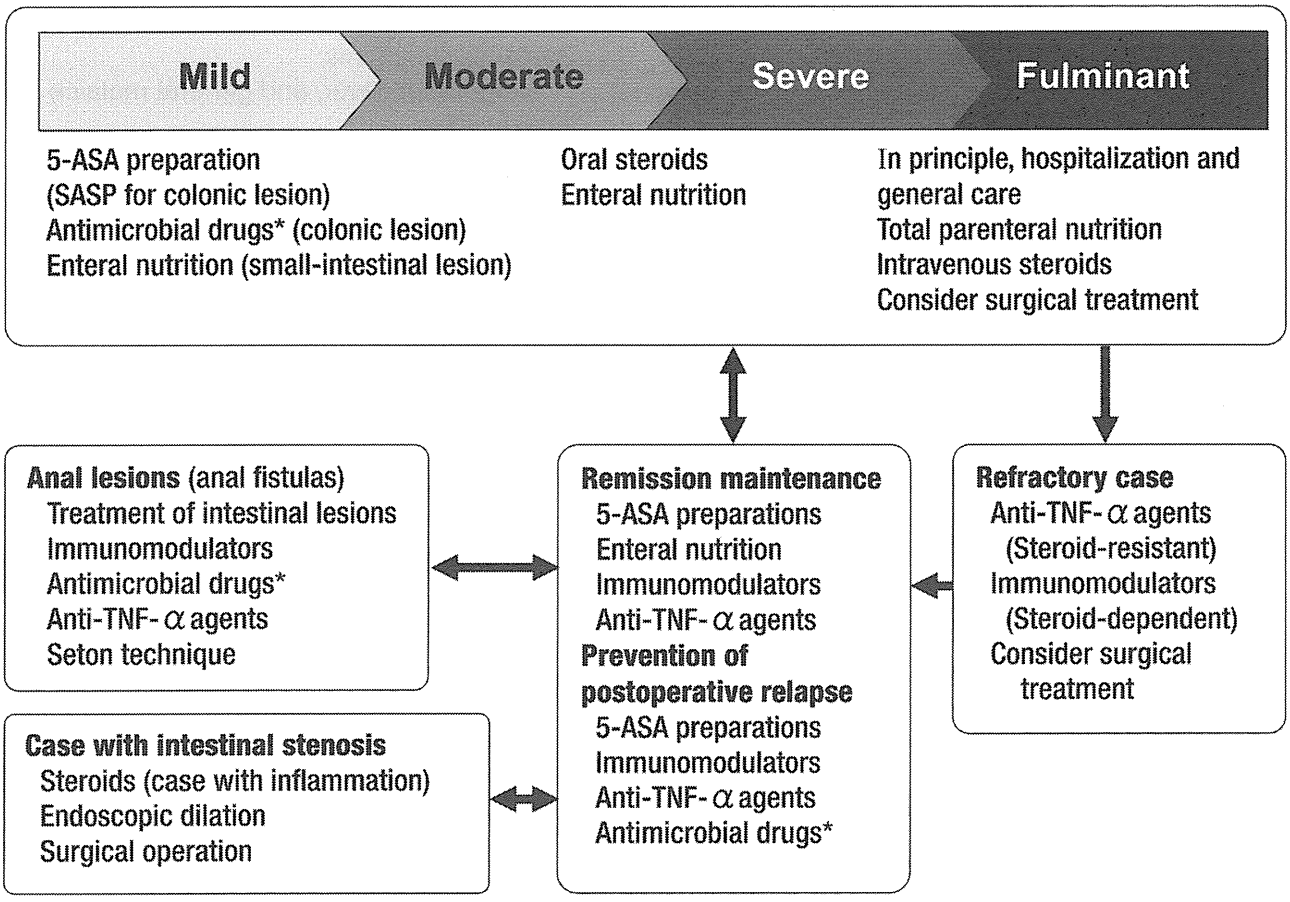


Figure 2 Treatment of Crohn's disease



Note: Medical therapies are the standard treatment for CD, but surgical treatment should always be kept in mind while performing treatment.

* Antimicrobial drugs are not covered by the Japanese public health insurance system when used for the treatment of CD.

IX. 研 究 班 構 成

難治性炎症性腸管障害に関する調査研究班

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