Guidelines for the Management of Ulcerative Colitis in Japan
-Developed through Integration of Evidence and Consensus among Experts-

Principal Investigator: Toshifumi Hibi
Project Leader: Fumiaki Ueno

Research Group for Intractable Inflammatory Bowel Disease 2006
Research on Intractable Diseases, Health and Labour Sciences Research
Grants from the Ministry of Health, Labour and Welfare, Japan

Edited by Katsuyoshi Matsuoka¹ and Tsung-Chun Lee²

¹ Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine
² Division of Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University

January 2006

Reproduced with permission from the “Research Group for Intractable Inflammatory Bowel Disease”
Table of Contents

Preface ................................................................. Toshifumi Hibi (ii)
Development of Scientifically Valid and Easy to Use Guidelines for Clinical Management ................................................................. Fumiaki Ueno (iii)

I. Outline of the guidelines for the management of ulcerative colitis
1. Summary of the guidelines ................................................................. (1)
2. Objectives and focuses ........................................................................ (1)
3. Anticipated users and environments for guideline utilization .................. (2)
4. Features of the guidelines ..................................................................... (2)
5. Procedures of guideline development .................................................. (2)
6. Criteria for the selection of recommendation grades and their interpretation ................................................................. (4)
7. Applicability of the guidelines ............................................................. (5)
8. Benefits and hazards at application of the guidelines ............................. (5)
9. Independence of the guidelines ............................................................ (5)
10. Problems and open issues of the guidelines ......................................... (6)
11. Guideline development group ............................................................. (7)

II. Recommendation statements related to the management of ulcerative colitis and relevant comments
1. Disease concept, classification and risk assessment ................................ (9)
   1.1 Disease concept ........................................................................... (9)
   1.2 Classification by pathophysiology (stage, extent and severity) ........... (9)
   1.3 Etiology, pathogenesis and risk assessment .................................... (9)
2. Diagnosis: clinical examination and diagnostic tests ............................ (14)
   2.1 Medical history and physical examination .................................... (14)
   2.2 Approaches to definitive diagnosis .............................................. (14)
   2.3 Endoscopic findings .................................................................... (15)
   2.4 Differential diagnosis .................................................................... (15)
3. Remission induction therapy for active distal colitis ............................. (18)
   3.1 Basic drugs used in the treatment of active distal colitis ................. (18)
   3.2 Efficacy of oral ASA preparations against active distal colitis .......... (18)
   3.3 5-ASA enema therapy for active distal colitis ............................... (19)
   3.4 Comparison between 5-ASA enema therapy and steroid enema therapy for active distal colitis ...................................................... (19)
   3.5 Comparison between systemic therapy and topical therapy for active distal colitis ................................................................. (20)
   3.6 Significance of combined systemic and topical therapy for active distal colitis ................................................................. (20)
   3.7 Treatment of active distal colitis resistant to 5-ASA preparations ........ (21)
4. Remission induction therapy for mild to moderate total colitis and left-sided colitis ...... (23)
   4.1 Placebo effects in drug therapy for active ulcerative colitis ........................................ (23)
   4.2 Basic drugs used in the treatment of mild to moderate ulcerative colitis ............ (23)
   4.3 Efficacy of SASP against active ulcerative colitis .................................................... (24)
   4.4 Efficacy and safety of oral 5-ASA preparations in active ulcerative colitis ...... (24)
   4.5 Efficacy of 5-ASA enema therapy for active left -sided colitis............................ (25)
   4.6 Optimal dose level and dosing method of oral 5-ASA therapy for active ulcerative colitis ................................................................. (25)
   4.7 Indications of steroids in mild to moderate ulcerative colitis .................................... (26)
   4.8 Dose level and dosing method of steroids for moderate ulcerative colitis ........ (26)
   4.9 Indications of immunosuppressants (AZA/6-MP) in mild to moderate ulcerative colitis ................................................................. (27)
   4.10 Usefulness of leukocyte apheresis in active ulcerative colitis ............................ (27)
   4.11 Other drug therapy and nutrient- supplementation therapy for active ulcerative colitis ................................................ (28)

5. Treatment of severe ulcerative colitis .................................................................................................................. (32)
   5.1 Basic therapeutic strategy for severe ulcerative colitis .................................................... (32)
   5.2 Efficacy and optimal dose level of steroids in severe ulcerative colitis ............... (32)
   5.3 Usefulness and optimal dose level of cyclosporine in severe ulcerative colitis ...... (33)
   5.4 Antimicrobial drug therapy for severe ulcerative colitis ............................................. (34)
   5.5 Factors aggravating severe ulcerative colitis and countermeasures .................... (34)
   5.6 Infliximab for therapy-resistant ulcerative colitis ....................................................... (35)

6. Remission maintenance therapy for ulcerative colitis ....................................................................................................... (37)
   6.1 Dietary therapy for maintenance of remission ............................................................. (37)
   6.2 Basic drugs used in remission maintenance therapy ................................................ (37)
   6.3 SASP therapy for maintenance of remission ............................................................. (38)
   6.4 Therapy with oral 5-ASA preparations for maintenance of remission ................ (38)
   6.5 Topical 5-ASA therapy for maintenance of remission ............................................ (39)
   6.6 Immunosuppressants for maintenance of remission ................................................ (39)
   6.7 Remission maintenance therapy for severe ulcerative colitis ................................ (40)

7. Surgical treatment of ulcerative colitis ....................................................................................................................... (43)
   7.1 Indications of surgical treatment in ulcerative colitis .................................................... (43)
   7.2 Selection of operative procedure .................................................................................. (44)
   7.3 Prognosis and function after surgical treatment .......................................................... (44)
   7.4 Treatment of postoperative pouchitis .......................................................................... (45)

8. Course of ulcerative colitis and surveillance for colorectal cancer .............................................................................. (46)
   8.1 Life prognosis of patients with ulcerative colitis ........................................................ (46)
   8.2 Prediction of relapse and resistance to treatment .......................................................... (46)
   8.3 Risk of development of colorectal cancer in ulcerative colitis............................. (47)
   8.4 Significance of colorectal cancer surveillance in patients with ulcerative colitis ... (47)
   8.5 Specific protocols for colorectal cancer surveillance ................................................ (47)
Guidelines for the Management of Ulcerative Colitis in Japan
- Developed through Integration of Evidence and Consensus among Experts -

Principal Investigator: Toshifumi Hibi
Project Leader: Fumiaki Ueno

Research Group for Intractable Inflammatory Bowel Disease 2006
Research on Intractable Diseases, Health and Labour Sciences
Research Grants from the Ministry of Health, Labour and Welfare, Japan

Edited by Katsuyoshi Matsuoka¹ and Tsung-Chun Lee²
¹ Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine
² Division of Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University

January 2006

Reproduced with permission from the “Research Group for Intractable Inflammatory Bowel Disease”
Since, even at present, the precise cause of inflammatory bowel disease has not yet been identified, nor has any curative therapy been established, it is not uncommon that this disease is difficult to treat and/or surgical intervention is necessary. Many of patients suffering from this disease are young, and the disease often hampers occupation, school performance, and/or the daily life activities of the patients, leading to reduced QOL. These features, together with the recent upward trend in the prevalence of this disease have made inflammatory bowel disease a significant social problem.

We set our research group’s goals at seeking factors involved in the etiology and exacerbation of inflammatory bowel disease, primarily through clinical studies, and establishing new therapeutic methods and valid means of prevention of this disease. In addition, the research group has been endeavoring to improve the QOL of patients with this disease and to facilitate dissemination and spread of correct medical information related to this disease. Within this framework, the research group has been revising diagnostic criteria, and therapeutic guidelines for ulcerative colitis.

The project study group led by Dr. Fumiaki Ueno has developed and published Guidelines for the Management of Ulcerative Colitis in Japan. This is a practical set of guidelines that is easy to use at daily clinic, because it is based on integration of scientifically formed consensuses among experts to reflect the features of ulcerative colitis, whose clinical management requires expert knowledge and high skill levels. We have translated the Japanese guidelines into English.

I hope that this set of guidelines is referred to by many doctors and will contribute to improving the diagnosis and treatment of this disease and the QOL of the patients.
Evidence-based guidelines for clinical management have recently become popular. This trend can also not be ignored in the context of management of inflammatory bowel disease (IBD) in Japan. However, since IBD exhibits complex features and new findings related to the pathophysiology of IBD are being reported one after another, it would be essential to also take the opinions of experts into adequate account when establishing guidelines for the clinical management of patients with IBD. This view is elaborated in detail in the first half of this set of guidelines. The basic tenets of this set of guidelines is integration of evidence and consensus.

There may be objections or criticisms to the attempt at integrating evidence with consensus, which appears to basically differ in nature from each other. However, we cannot deny that the indicators recommended in all sets of currently available guidelines reflect the view of the authors who developed the guidelines, to some extent or the other, and that the developed guidelines do not clearly explain such a background. One of the striking features of the guidelines developed by us is that while the opinions and views of experts are adopted, the guidelines make recommendations with a high level of transparency through presenting evidence and consensus in a clear-cut manner.

From the early phase of development of this set of guidelines, we attempted to maintain the scientific validity while abiding by the standard rules for guidelines. The guidelines developed by us also reflect practical judgments made in the clinical setting. We therefore believe that this set of guidelines would allow a high degree of compliance in clinical practice.

Needless to say, guidelines are only a tool for assisting in the management of sick patients. If guidelines restrict the freedom of individual physicians to act at their discretion during clinical practice, it would defeat its own purpose. We hope that this set of guidelines will be utilized in a sound manner as a support tool for making the best decisions in the management of individual cases.

I take this opportunity to express my sincere thanks to the members of the guideline development group who cooperated in this difficult task of developing the guidelines for a long period of time. We owe much to Mr. Seiji Bito who advised us in detail as to the unique method called for in guideline development. Without his efforts, establishment of this set of guidelines could not have been achieved. All members of the group involved in the development of this set of guidelines wish to express their hope that this set of guidelines would be used appropriately, and that it would contribute to improving the outcomes of numerous patients with ulcerative colitis.
I. Outline of the guidelines for the management of ulcerative colitis

1. Summary of the guidelines

- **Disease covered**: Ulcerative colitis
- **Specialties covered**: Internal medicine, surgery, gastroenterology, and general care medicine
- **Users**: Physicians
- **Objectives**: Providing appropriate indicators of medical care to clinicians
- **Range of clinical care indicators covered**: Disease entity, classification, risk assessment, diagnosis, treatment, follow-up
- **Interventions**: Diagnosis (medical history, physician’s examination, laboratory tests, imaging) and treatment (drug therapy, nutritional therapy, surgical treatment, others)
- **Outcome evaluation**: Symptom alleviation, remission induction, remission maintenance, endoscopic findings, QOL, adverse effects of treatment
- **Procedure of development**: Integration of evidence (yielded from the literature) and consensus (obtained by the Delphi method among experts)
- **Rationale for recommendation**: Criteria for recommendation grades based on evidence level and the median of consensus
- **Cost-effectiveness analysis**: None
- **Confirmation of effectiveness**: Not yet confirmed
- **Guideline status**: First edition of guidelines confirmed by experts within the Project Study Group
- **Means of publication**: Printed matter and electronic information (only in Japanese)
- **Patient information**: None
- **Date of publication**: January 2006

Ulcerative colitis (UC) is a disease presenting complex features, resulting in the absence of a standard procedure for the diagnosis and treatment. Although much evidence has been accumulated in relation to the management of UC, the views and opinions of experts still have importance because of the complex management system of this disease. We have therefore developed guidelines for the management of UC through integration of currently available evidence and scientifically formed consensus among experts.

2. Objectives and focuses

The purpose of developing this set of guidelines is to provide appropriate indicators for UC management and to contribute to improving patient outcomes. The statements contained in the guidelines range from standard concepts on the disease and its pathophysiology to medical interventions for diagnosis, treatment, and follow-up. The guidelines deal with the intestinal disease in adult patients, but do not refer to specific conditions such as systemic complications, extraintestinal diseases, and UC during pregnancy. The guidelines also do not provide special accounts of UC among children and elderly people.
3. Anticipated users and environments for guideline utilization

The guidelines are expected to be used by physicians involved in the clinical management of UC. Not only gastroenterologists, but also all other physicians who would have opportunities to see patients with UC in daily clinical practice are expected to use the guidelines. At present, we do not intend for patients with UC to use these guidelines.

4. Features of the guidelines

In line with internationally accepted principles for the development of clinical management guidelines, we attached importance to existing clinical evidence while preparing these guidelines. Since decisions in clinical practice are not only based on evidence, but also often depend on other factors, and because evidence is not always easy to obtain in some specific conditions, we developed guidelines through integrating evidence with the consensus of experts. The procedure for the development of the guidelines is explained in detail in the next section.

The major differences of this set of guidelines from the previous guidelines by the Research Group for Intractable Inflammatory Bowel Disease are: (1) published evidence served as the basis for recommending indicators, while also utilizing experts’ views and opinions to evaluate and supplement evidence from literature; (2) the rationale for each recommendation and the strength of the recommendation are shown; (3) the guidelines are designed to be used not only by gastroenterologists, but also by general practitioners; (4) Both the applicability and limitations of the guidelines are specified.

5. Procedures of guideline development

<Organization of the “Evaluation Panel” and preparation of statements related to clinical management>

An “Evaluation Panel” comprising 5 members (internist, gastroenterologist, general practitioner, clinical epidemiologist, and so on) was constituted. Papers related to the management of UC published between 1985 and 2004 were searched, primarily through MEDLINE and the Cochrane Library. Among the papers thus collected, we selected papers which showed the usefulness of the medical interventions which can be taken in Japan (regardless of coverage by health insurance) with level III or higher evidence and are expected to affect patient outcomes. Structured abstracts of these selected papers were prepared. Furthermore, through manual search, information on currently available guidelines and review papers related to the management of UC was collected. Statements contained in published papers, without quotation of evidence, were considered as an opinion of the author(s) and were rated as evidence level V. On the basis of these pieces of information derived from the literature, statements on the management of UC were prepared.
Table 1. Evidence level of literature-derived information used in the development of guidelines

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Meta-analysis of randomized comparative studies</td>
</tr>
<tr>
<td>Ib</td>
<td>One or more randomized comparative studies, all-or-none type case series studies</td>
</tr>
<tr>
<td>Ila</td>
<td>Well-designed non-randomized comparative studies</td>
</tr>
<tr>
<td>Iib</td>
<td>Well-designed quasi-experimental studies</td>
</tr>
<tr>
<td>Ila</td>
<td>Well-designed cohort studies</td>
</tr>
<tr>
<td>Ilib</td>
<td>Other observational epidemiological studies, such as case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Descriptive study such as case reports and case series</td>
</tr>
<tr>
<td>V</td>
<td>Reports from expert committees and views/opinions of individual experts not based on patient data</td>
</tr>
</tbody>
</table>

<Organization of Expert Panel and evaluation of statements related to clinical management>

An “Expert Panel” consisting of 10 members, i.e., 5 internists/surgeons specializing in inflammatory bowel disease (IBD), 2 general internists and 3 hospital administrators (concurrently also IBD specialists) was constituted. Statements on clinical management prepared by the Evaluation Panel were circulated by e-mail to each member of the Expert Panel, together with the structured abstracts of the papers serving as the basis for these statements, as well as other literature information and evidence level of each paper. The appropriateness of each statement was rated on a 9-category scale (1: most inappropriate to 9: most appropriate) (Delphi evaluation). The Expert Panel held meetings to discuss the issues with the first Delphi evaluation, to correct the statements, and to add new statements through exchange of views and opinions. The statements reconstructed thus were circulated again among the members of the Expert Panel. The final results of 3 sessions of Delphi evaluation were adopted as the consensus of the Expert Panel.

Selection of recommendations>

The recommendation grade for each statement was determined on the basis of the evidence level of the paper serving as the basis for a given statement and the final median rating from the 3 sessions of Delphi evaluation (Table 2 and 3). A total of 182 statements were subjected to the selection procedure, and the statements with recommendation grades of A, B and I were adopted as the recommendations for standard clinical management.

Table 2. Criteria 1 for recommendation grade rating through integration of evidence and consensus (statements related to treatment)

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Median Delphi rating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 ≥</td>
</tr>
<tr>
<td>I</td>
<td>A A I</td>
</tr>
<tr>
<td>II</td>
<td>A B C</td>
</tr>
<tr>
<td>III</td>
<td>B I C</td>
</tr>
<tr>
<td>IV, V</td>
<td>I I C</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>A A I C</td>
</tr>
<tr>
<td></td>
<td>4 ≤</td>
</tr>
<tr>
<td></td>
<td>C C C D</td>
</tr>
</tbody>
</table>
Table 3. Criteria 2 for recommendation grade rating through integration of evidence and consensus (statements related to disease concept, risk, diagnosis and follow-up)

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Median Delphi rating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥8</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>II</td>
<td>A</td>
</tr>
<tr>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>IV, V</td>
<td>I</td>
</tr>
</tbody>
</table>

6. Criteria for the selection of recommendation grades and their interpretation

Recommendation grades were determined through integration of evidence and consensus among experts. Recommendation grades determined by both the evidence level of the literature-derived information serving as the basis for a given statement and the median score of Delphi evaluation were given for individual statements (Tables 2 and 3). In the case of a statement based on information derived from multiple papers, the highest evidence level among these papers was adopted as the evidence level for the statement. Statements with a high quality of evidence and high rating by experts were given Recommendation Grade A (the highest grade). Statements with a slightly lower quality of evidence or slightly lower rating by experts were given a one level lower rating of Recommendation Grade B.

The Recommendation Grade was set at I for statements given a high rating by experts despite the lack of high-quality evidence or statements receiving a low rating by experts despite the presence of high-quality evidence. The current system for evidence level evaluation is designed to evaluate clinical studies on treatment. Thus, while it fits the indicators of treatment well, it is not entirely suitable for disease concepts, diagnosis, follow-up, etc. Bearing in mind that the ranking of the quality level of evidence is not easy with the use of such a system, we separately appended a Recommendation Grade to individual statements attaching greater importance to the views and opinions of experts (Table 3).

Table 4 shows how each Recommendation Grade was interpreted. Statements or indicators assigned Recommendation Grade C or D were not adopted in the development of this set of guidelines. Statements assigned Recommendation Grade I despite having been given a high rating by experts should be interpreted as statements for which the evidence level is not adequate, rather than statements that cannot be recommended. One should understand that statements assigned Recommendation Grade I are not necessarily inferior to statements assigned Recommendation Grade A or B, because collection of evidence is sometimes impossible, depending on the contents of the statements.
The literature-derived information serving as the basis for the statements was selected based on the criterion of “applicable to Japan.” Therefore, the medical interventions cited in the guidelines can be basically practiced during routine clinical care and do not require modification of the current system or organization. Thus, the guidelines can be applied without the addition of many medical resources.

Although, when the guidelines were developed, we did not take into account whether or not the individual medical interventions would be covered under health insurance, most of the medical interventions recommended in the guidelines happened to be those that are routinely practiced in Japan. Nonetheless, it is individual clinical users to check whether or not a given action would be covered by insurance.

### Table 4. Recommendation Grades for statements related to clinical management and their interpretation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strongly recommended as a standard medical intervention</td>
</tr>
<tr>
<td>B</td>
<td>Recommended as a standard medical intervention</td>
</tr>
<tr>
<td>C</td>
<td>Not recommended as a standard medical intervention</td>
</tr>
<tr>
<td>D</td>
<td>Should not be practiced as a standard medical intervention</td>
</tr>
<tr>
<td>I</td>
<td>Difficult to recommend as a standard medical intervention because of discrepancy between the strength of evidence and the opinions/views of experts</td>
</tr>
<tr>
<td></td>
<td>1: Evidence is inadequate although there is consensus among experts</td>
</tr>
<tr>
<td></td>
<td>2: Rating by experts is not high even though there is strong evidence</td>
</tr>
</tbody>
</table>

### 7. Applicability of the guidelines

The literature-derived information serving as the basis for the statements was selected based on the criterion of “applicable to Japan.” Therefore, the medical interventions cited in the guidelines can be basically practiced during routine clinical care and do not require modification of the current system or organization. Thus, the guidelines can be applied without the addition of many medical resources.

Although, when the guidelines were developed, we did not take into account whether or not the individual medical interventions would be covered under health insurance, most of the medical interventions recommended in the guidelines happened to be those that are routinely practiced in Japan. Nonetheless, it is individual clinical users to check whether or not a given action would be covered by insurance.

### 8. Benefits and hazards at application of the guidelines

The recommendation statements contained in this set of guidelines suggest standard indicators for the clinical management of UC. These are intended to support the decisions of individual physicians during clinical practice, but not to control their practice. The guidelines are not designed to be utilized as the rationale for judicial judgments as to individual medical care interventions. If the guidelines are utilized flexibly, while receiving support from specialists depending on the clinical situation, and taking the patients’ preferences into account, these guidelines will improve the quality of clinical management and the patient outcome.

Since sound judgments by physicians are important in the clinical management of individual patients, it is inappropriate and possibly hazardous to utilize the guidelines for control of clinical management, the rationale for judicial judgments, restriction of physicians’ discretion, and so on.

### 9. Independence of the guidelines

The guidelines were developed within the framework of a research project conducted by the Research Group for Intractable Inflammatory Bowel Disease, Research on Intractable Diseases funded by the Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan. The group preparing the guidelines was independent of any other particular source of funding and had no collaboration or coordination with any organizations including professional societies, research groups,
medical associations or patient organizations. The guidelines are an outcome of academic research, with no known conflict of interests.

The name of each enterprise with which the guideline development group may have an interest is disclosed comprehensively in a separate section. These enterprises are related to individual members of the guideline development group or to the facilities to which the members belong, and none of them provided any funding for the development of the guidelines.

10. Problems and open issues of the guidelines

When the guidelines were developed, we attempted to integrate evidence with consensus. A possible criticism is that the correlation between the evidence level and the recommendation grade is not parallel. When preparing the guidelines, we collected literature-derived information first. Then, on the basis of the literature-derived information, statements on clinical management were drafted and their appropriateness was evaluated by experts. During the evaluation, structured abstracts of each paper cited by each statement as well as the evidence level of each paper was provided to the evaluators. It is therefore unlikely that the evaluation was based solely on the view of individual evaluators without considering evidence. Furthermore, since the evidence level is involved again in the step of determination of the recommendation grade, we may say that the recommendation grade adequately reflects the evidence.

An advantage of this set of guidelines is that the recommendation grade is not based solely on the evidence level. The evidence level was set only based on the study design, without evaluating the quality of individual studies. Some medical interventions, even though based on the results of excellent studies, do not appear to be useful clinically. Conversely, medical interventions without strong evidence are sometimes useful clinically. There are even some medical interventions for which clinical studies have not been carried out, because the validity of these interventions is considered to be evident. When selecting appropriate ones from these medical interventions, it would be useful to reflect experts’ assessment into the recommendation grade. This strategy will allow the guidelines to be established without much discrepancy from clinical practice, thus improving the compliance with the guidelines.

The literature-derived information collected for development of this set of guidelines primarily pertained to English-language articles published over the past two decades. Original papers published more than 2 decades ago and papers published in languages other than English are not directly cited in the guidelines. The guidelines developed thus may therefore be criticized for: (1) not covering studies conducted more than 2 decades ago, even though some of the currently used standard medical interventions are based on such studies; and (2) not covering papers written in Japanese. To correct these shortcomings as much as possible, the guidelines refer to other guidelines and review papers related to management of UC and reflect major descriptions and quotations of such literature in the statements. Furthermore, the Expert Panel was asked to check completeness of the referral to major papers in the guidelines to ensure that the guidelines provide thorough information.

The guidelines have been examined by specialists within the Research Group for Intractable Inflammatory Bowel Disease. At present, a third party assessment is planned. Coordination with organizations which have an interest in the guidelines and the validation of the guidelines through trial application to clinical practice are also open issues.

For all clinical guidelines, it is essential to accumulate new evidence and to constantly review the guidelines. While it is unknown how clinical evidence related to the management of UC will change from now on, it is nonetheless essential to revise the guidelines by 3 years, in accordance with the principles of clinical guideline development. Assessments made by clinicians will also taken into account at the revision, and active and constructive feedback from users will be welcome.
11. Guideline development group (in alphabetical order)

1. Evaluation Panel members
   • Bito, Seiji (Division of Clinical Epidemiology, National Hospital Organization)
   • Inoue, Nagamu (Center for Comprehensive and Advanced Medicine, Keio University School of Medicine)
   • Kobayashi, Kenji (Department of Medicine, Division of General Medicine, Tokai University School of Medicine)
   • Komiya, Kenichi (Department of Gastroenterology, National Hospital Organization, Tokyo Medical Center)
   • Ueno, Fumiaki (Ofuna Chuo Hospital)

2. Expert Panel members
   • Fukushima, Tsuneo (Yokohama Stroke and Brain Center)
   • Hiwatashi, Nobuo (Iwaki Kyoritsu General Hospital)
   • Igarashi, Masahiro (Endoscopy Division, Cancer Institute Ariake Hospital)
   • Ito, Hiroaki (Division of Intestinal and Inflammatory Bowel Disease, Kitano Hospital)
   • Matsui, Toshiyuki (Department of Gastroenterology, Chikushi Hospital, Fukuoka University)
   • Matsumoto, Takayuki (Division of Lower Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine)
   • Munakata, Akihiro (First Department of Internal Medicine, Hirosaki University)
   • Noguchi, Yoshinori (Department of General Internal Medicine, Nagoya Second Red Cross Hospital)
   • Shoda, Ryosuke (Department of Gastroenterology, International Medical Center of Japan)
   • Sugita, Akira (Department of Surgery, Yokohama Municipal Hospital)

3. Project Study Group Leader
   • Ueno, Fumiaki (Ofuna Chuo Hospital)

4. Principal Investigator, Research Group for Intractable Inflammatory Bowel Disease
   • Hibi, Toshifumi (Department of Gastroenterology, Keio University)

5. Disclosure of the relationships between the guideline development group and third parties
   Table 5 lists the names of the health care-related industries, self-reported by each member of the guideline development group, with potential conflict of interest, regardless of the management of UC. The list does not cover publishing companies in a neutral position or non-profit organizations.
Table 5. Health care-related industries with which members of the guideline development group had potential conflict of interest (company names as of the date of guideline development are shown in a simplified form in alphabetical order)

<table>
<thead>
<tr>
<th>Asahi Kasei Medical</th>
<th>Abbott Japan</th>
<th>Ajinomoto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajinomoto Pharma</td>
<td>AstraZeneca</td>
<td>Banyu Pharmaceutical</td>
</tr>
<tr>
<td>Chugai Pharmaceutical</td>
<td>Daiichi Pharmaceutical</td>
<td>Dainippon Pharmaceutical</td>
</tr>
<tr>
<td>Eisai</td>
<td>Fujisawa Pharmaceutical</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Horii Pharmaceutical</td>
<td>JIMRO</td>
<td>Kyorin Pharmaceutical</td>
</tr>
<tr>
<td>Kyowa Hakko</td>
<td>LTT Biopharma</td>
<td>Medicon</td>
</tr>
<tr>
<td>Minophagen Pharmaceutical</td>
<td>Mitsubishi Pharma</td>
<td>Mochida Pharmaceutical</td>
</tr>
<tr>
<td>Nippon Sherwood</td>
<td>Nisshin Kyorin Pharmaceutical</td>
<td>Olympus</td>
</tr>
<tr>
<td>Ono Pharmaceutical</td>
<td>Otsuka Pharmaceutical</td>
<td>Sankyo</td>
</tr>
<tr>
<td>Schering-Plough</td>
<td>Sumitomo Pharmaceutical</td>
<td>Taiho Pharmaceutical</td>
</tr>
<tr>
<td>Takeda Pharmaceutical</td>
<td>Tanabe Pharmaceutical</td>
<td>Terumo</td>
</tr>
<tr>
<td>Torii Pharmaceutical</td>
<td>Yamanouchi Pharmaceutical</td>
<td>Zeria Pharmaceutical</td>
</tr>
</tbody>
</table>
II. Recommendation statements related to the management of ulcerative colitis and relevant comments

The interpretation of each recommendation grade is shown in Table 4 (Page 5).

The numerals within parentheses accompanying each recommendation grade indicate the evidence level and the median rating score assigned by the experts. Recommendation grades were determined according to the criteria given in Table 2 and 3 (Page 3, 4).

Cited papers are shown by the numbers in superscript attached to each statement. All the cited papers are listed at the end of each chapter.

1. Disease concept, classification and risk assessment

1.1 Disease concept

- Ulcerative colitis is a diffuse non-specific inflammatory disease of the large intestine of unknown cause, primarily affecting the mucosa, characterized by erosions and/or ulcerations. The disease is characterized by repeated cycles of relapses and remissions, occasionally accompanied by extra-intestinal complications. Ulcerative colitis persisting for prolonged periods of time and affecting a wide area of the large intestine is more likely to be associated with neoplastic change. Recommendation Grade I (V · 9)

Commentary:
This disease concept, based on the definition of the 1996-2001 Research Group for Intractable Inflammatory Bowel Disease (a widely accepted definition in Japan for many years) and supplemented by experts’ views and contents of overseas guidelines, has gained consensus among experts.

1.2 Classification by pathophysiology (stage, extent and severity)

- Selection of the treatment varies depending on the stage, extent and severity of the disease. Recommendation Grade I (V · 9)
- UC can be divided into two stages: (1) active stage (characterized by the presence of melena and, on endoscopy, loss of visible vascular pattern, easy bleeding, erosions, ulcerations, etc.) and (2) remission stage (characterized by disappearance of melena and the endoscopic signs observed during the active stage, and restoration of visible vascular pattern in the colonic mucosa). Recommendation Grade I (V · 9)
- UC can be divided into the following types depending on the extent of the lesions: proctitis, distal colitis (lesions extending up to the sigmoid colon), left- sided colitis (lesions extending up to the splenic flexure) and pancolitis (Table 6). Recommendation Grade I (V · 8)
The severity of this disease is rated as “mild” when the frequency of defecation is 4 times/day or less, melena is absent or minimal, and systemic symptoms are absent, as “severe” when the frequency of defecation is 6 times/day or more, severe melena is present, and systemic symptoms (fever, tachycardia, anemia, etc.) are present, and as “moderate” when the features are intermediate between “mild” and “severe” (Table 7). Recommendation Grade I (V · 9)

Commentary:
Understanding the features of UC and precise assessment of its stage, extent and severity is important for selecting the appropriate treatment. Classification of the stage and severity, as described above, is based on the criteria reported by the 1996-2001 Research Group for Intractable Inflammatory Bowel Disease. According to the International Classification, left-sided colitis is defined as the lesions confined to the area distal to the splenic flexure. This classification has taken into account the applicability of topical therapy, and gained consensus among the experts involved in the development of this set of guidelines. See Table 6 and 7 for details of these classifications.

<table>
<thead>
<tr>
<th>Table 6. Definition of the extent of the lesions used in the guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proctitis</strong></td>
</tr>
<tr>
<td><strong>Distal colitis</strong></td>
</tr>
<tr>
<td><strong>Left-sided colitis</strong></td>
</tr>
<tr>
<td><strong>Pancolitis</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7. Classification of ulcerative colitis by severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Modification of Truelove and Witts’ criteria)</em></td>
</tr>
<tr>
<td><strong>(1)</strong> Frequency of defecation</td>
</tr>
<tr>
<td><strong>(2)</strong> Apparent melena</td>
</tr>
<tr>
<td><strong>(3)</strong> Fever</td>
</tr>
<tr>
<td><strong>(4)</strong> Tachycardia</td>
</tr>
<tr>
<td><strong>(5)</strong> Anemia</td>
</tr>
<tr>
<td><strong>(6)</strong> Erythrocyte sedimentation rate</td>
</tr>
</tbody>
</table>

Notes)
- Rated as “severe” when criteria (1), (2) and one of the systemic symptoms (3) or (4) are satisfied, and at least 4 of the 6 criteria are satisfied.
- Rated as “mild” when all of the 6 criteria are satisfied.
- Among the patients with “severe” disease, those showing extremely severe symptoms are classified as having “fulminant” disease, and, depending on the rapidity of the disease onset, “fulminant” disease is subdivided into “acute fulminant” and “relapsing fulminant” disease.
Criteria for the diagnosis of fulminant ulcerative colitis: Patients satisfying all of the following criteria are classified as having "fulminant" disease

1. Satisfying the criteria for "severe" disease
2. Bloody stools occurring at a frequency of about 15 times/day or more
3. Persistent high fever (38°C or higher)
4. Increase of the leukocyte count to 10,000/mm³ or more
5. Severe abdominal pain
1.3 Etiology, pathogenesis and risk assessment

- It is assumed that the onset of UC is affected strongly by environmental factors. Exposure to environmental factors predisposing to the disease is considered to occur during early life. **Recommendation Grade I (IIIb · 6)**
- The incidence of UC is lower in smokers than in nonsmokers. **Recommendation Grade B (IIIb · 7)**
- Ingestion of animal fat can increase the occurrence of UC. **Recommendation Grade I (IIIb · 6)**
- A history of appendectomy is correlated negatively with the occurrence of UC. **Recommendation Grade B (IIa · 7)**
- Nonsteroidal anti-inflammatory drugs (NSAIDs) can be associated with the onset or relapse of UC; therefore, careful use of this class of drugs is warranted. **Recommendation Grade B (IIIb · 7)**

**Commentary:**

The etiology and pathogenesis of UC still remain veiled. In general, it is considered that this disease develops under the influence of multiple environmental factors in individuals who are genetically predisposed to it. Numerous epidemiological studies have been conducted to identify factors that can influence the onset of this disease; however, no decisive findings have been obtained yet. The statements given above are those rated as recommendable on the basis of the evidence level of the cited papers and consensus among experts. Clinically, attention to smoking and use of NSAIDs seems particularly important. The risk of occurrence/relapse of UC in smokers is only 60% of that in nonsmokers, and this point must be kept in mind when patients are advised to quit smoking. It has been reported that the use of NSAIDs can be associated with relapse and emergency hospitalization.
References


2. Diagnosis: clinical examination and diagnostic tests

2.1 Medical history and physical examination

- A major symptom of UC is bloody diarrhea, occasionally accompanied by abdominal pain and/or frequent inclination for bowel movement. Recommendation Grade I (V · 9)
- UC should be suspected in cases with a history of persistent or repetitive mucous bloody stool/bloody feces. Recommendation Grade I (V · 9)
- A careful history of recent overseas travel, medication (particularly antimicrobial agents), smoking habit, family history, etc, must be obtained. Recommendation Grade I (V · 9)
- Patients with UC often have no abnormal findings on physical examination, but anemia, weight loss, abdominal tenderness and fresh bleeding on digital rectal examination are occasionally seen. Recommendation Grade I (V · 8)

Commentary:
Bloody diarrhea is often the initial symptom of UC. Depending on the disease severity, other symptoms such as abdominal pain and fever may accompany the bloody diarrhea. At the first presentation, the clinical symptoms may resemble those of self-limiting diseases such as infectious enteritis, drug-induced enteritis, etc. It is therefore important to obtain a careful history to ascertain the persistence or recurrence of symptoms, recent overseas travel, medication, etc. Physical findings are non-specific and resemble those of other acute intestinal diseases.

2.2 Approaches to definitive diagnosis

- The diagnosis of UC is usually established based on the characteristic clinical and endoscopic findings. Recommendation Grade I (V · 8)
- In cases suspicious of UC based on the clinical findings, it is recommended to perform colonoscopy. Recommendation Grade I (V · 9)
- A diagnosis of UC is made in the following steps: suspicion based on clinical findings → characteristic endoscopic and biopsy findings → exclusion of infectious enteritis by examination of the feces, etc. Recommendation Grade I (V · 9)
- As needed, total colonoscopy or a barium enema examination is performed to examine the characteristics, severity, extent, etc., of the intestinal lesions and rule out other possible diseases. Recommendation Grade I (V · 9)
- If possible, total colonoscopy should be performed, but it is essential in some cases (particularly patients with severe disease) to carefully assess the patient’s condition and postpone colonoscopy until stabilization of the symptoms. Recommendation Grade I (V · 9)
- At the same time, peripheral blood examination, urinalysis, biochemical tests, measurement of the erythrocyte sedimentation rate (or serum CRP), abdominal X-ray, etc., are carried out. Recommendation Grade I (V · 8)
- Usually, a morphological diagnosis is made based on the findings on endoscopy; however, a barium enema examination instead of colonoscopy may be performed depending on the availability at a given facility or other factors. Recommendation Grade I (V · 7)
Commentary:
The basic steps in the diagnosis of UC rely on a precise assessment of the clinical and endoscopic findings. However, since the clinical symptoms and endoscopic findings are sometimes akin to those of infectious enteritis, it is necessary to rule out infection by bacteriological and parasitological tests of the feces. Colonoscopy is also useful for determination of the extent and severity of the lesions. However, since colonoscopy or its pretreatment can aggravate the disease, particularly in patients with severe disease, early examination of the entire large intestine is not always necessary. The statements/indicators related to diagnosis of UC listed above are not supported by evidence, but the experts reached consensus on the appropriateness of these statements/indicators. Ultrasonography for assessment of the extent of lesions was assigned a low recommendation grade (Grade C). Because the sensitivity and specificity have not yet been evaluated for any of the diagnostic methods discussed above, their scientific validity remains unknown.

### 2.3 Endoscopic findings

- Typically, UC shows endoscopic findings such as loss of vascular pattern, granular mucosa, easy bleeding, and ulceration in a continuous manner. **Recommendation Grade I (V · 8)**
- The mucosa is involved diffusely, the vascular pattern cannot be observed, and a coarse or microgranular appearance is noted. Furthermore, the mucosa is fragile and easy to bleed by contact. Mucous/bloody/puriform secretions, multiple erosions, ulcers and/or pseudopolyposis are observed. **Recommendation Grade I (V · 9)**

Commentary:
The statements on the endoscopic findings were prepared on the basis of the general descriptions in overseas publications and detailed expressions contained in the reports from the 1996-2001 Research Group for Intractable Inflammatory Bowel Disease. Consensus among experts was reached about these statements. However, endoscopic diagnosis of UC is not always possible solely on the basis of these statements. The statements serve only as a standard to be referred to by gastroenterologists. One should also pay attention to the limitation that none of these endoscopic findings is specific to making a definitive diagnosis of UC.

### 2.4 Differential diagnosis

- Clinical features of infectious enteritis are sometimes indistinguishable from those of UC. In cases suspicious of UC for the first time or having a flare-up of UC, it would be advisable to conduct bacteriological tests (including for pathogenic *Escherichia coli*) and parasitological tests of the feces, along with, in suspected cases, *Entamoeba histolytica* antibody test and test for *Clostridium difficile*. **Recommendation Grade I (V · 9)**
- Infectious enteritis is a major disease that needs to be ruled out before making a definitive diagnosis of UC. Other diseases that need to be ruled out include Crohn’s disease, radiation colitis, drug-induced colitis, lymphoid follicle hyperplasia, ischemic colitis, intestinal Beçet’s disease, etc. **Recommendation Grade I (V · 9)**
- Measurement of pANCA and ASCA is useful if differentiation from Crohn’s disease is difficult. **Recommendation Grade I (IIIa · 6)**
Commentary:
Differentiation between UC and infectious enteritis is sometimes difficult, even on the basis of the clinical and endoscopic features. One should also consider the possibility that a flare-up of symptoms during the course of UC is caused by infectious enteritis, although such cases are uncommon. It is essential to rule out infection in advance, particularly if steroid therapy is planned. Differentiation from other diseases is relatively easy on the basis of the clinical history, endoscopic findings, course of the disease, etc. Measurement of pANCA (perinuclear anti-neutrophil cytoplasmic antibody) and ASCA (anti-*Saccharomyces cerevisiae* antibody) to differentiate between UC and Crohn’s disease is not widely adopted clinically and its value as a standard practice was not given a high rating by the experts.

**Disease history (1): Major symptoms**
Persistent/repetitive bloody diarrhea or mucous bloody stool

**Diagnostic test**
Colonoscopy

**Assessment of condition and differential diagnosis**
- General tests such as CBC, CRP and abdominal X-ray
- Bacteriological/parasitological tests

**Diagnosis**
Ulcerative colitis

**Other diseases**

**Extent of lesions**
- “Proctitis”, “Distal colitis”, “Left-sided colitis”, “Pancolitis”

**Severity**
- “Mild”, “Moderate”, “Severe”

**Recommendation Grade I**

**Disease history (2):**
Recent history of overseas travel, medication, smoking habit, family history, etc., are obtained

**Physical findings:**
Anemia, weight loss, abdominal examination, rectal examination

Waiting for stabilization of the clinical condition is considered in severe cases

Endoscopy may be replaced by a barium study, depending on the availability at a given facility

Fig. 1. Diagnostic approaches of ulcerative colitis
References

3. Remission induction therapy for active distal colitis

3.1 Basic drugs used in the treatment of active distal colitis

- The basic drugs that are used in the treatment of mild to moderate distal colitis are oral ASA preparations, topical 5-ASA preparations and topical steroids. Recommendation Grade A (Ia · 9)

Commentary:
Many randomized controlled trials (RCTs) have demonstrated the effectiveness of these drugs in inducing remission in patients with distal colitis. Comparison of these drugs and the methods of their use (including the route of administration) are described in the following sections. The cited papers deal with multiple 5-ASA preparations that differ slightly from each other. At present, only mesalazine is available for use in Japan among these 5-ASA preparations; however, the statements were prepared referring to evidence related to multiple 5-ASA preparations.

Note: In this set of guidelines, salazosulfapyridine (SASP) and mesalazine are collectively referred to as ASA (aminosalicylic acid preparations), and 5-aminosalicylic acids, such as mesalazine, are referred to as 5-ASA.

3.2 Efficacy of oral ASA preparations against active distal colitis

- Both oral SASP and 5-ASA are useful for inducing remission of UC. Recommendation Grade A (Ia · 9)

Commentary:
The effectiveness of oral ASA preparations in inducing remission of UC has been shown in numerous RCTs and their meta-analysis. Oral SASP treatment has been reported to induce remission in 50-80% of all cases. Similar effectiveness has also been shown for oral 5-ASA treatment. The dose level of SASP used for the induction of remission is 3-4 g/day. Because intolerable adverse symptoms such as headache and gastric discomfort are likely to develop if treatment with this drug is begun at this dose level, it is advisable to begin treatment at a lower dose and to increase the dose gradually. Some experts, on the other hand, have pointed out that intolerable adverse reactions to this drug are less likely to develop in Japanese patients. Collectively, 5-ASA is superior to SASP, because 5-ASA can be started at optimal doses without the risk of development of significant adverse reactions.
3.3 5-ASA enema therapy for active distal colitis *6,7,8,9,10*

- 5-ASA enema is useful for inducing remission in patients with active distal colitis. **Recommendation Grade A (Ia · 9)**
- The optimal dose level of 5-ASA enema for mild to moderate distal colitis is 1 g/day. **Recommendation Grade A (Ib · 8)**

**Commentary:**
Much high-quality evidence has been collected endorsing the effectiveness of 5-ASA enema therapy. Based on these evidences, 5-ASA enema therapy is often deemed as the therapy of first choice for inducing remission in patients with distal colitis in Western countries. Since there is no significant difference in the efficacy among the daily dose levels 1, 2 and 4 g, the dose level of 1 g/day is expected to suffice.

3.4 Comparison between 5-ASA enema therapy and steroid enema therapy for active distal colitis *6,9,11,12,13*

- 5-ASA enema therapy is at least comparable to steroid enema in terms of efficacy. **Recommendation Grade A (Ib · 8)**
- When used for the treatment of active distal colitis, 5-ASA enema is superior to steroid enema in terms of improvement of the clinical symptoms, endoscopic findings and histological findings. **Recommendation Grade I (Ia · 6)**
- It is not uncommon to find that 5-ASA enema is effective even in patients with active distal colitis who do not respond to steroid enema. **Recommendation Grade A (Ib · 7)**

**Commentary:**
There is evidence in the literature suggesting that 5-ASA enema is comparable to or superior to steroid enema therapy. A meta-analysis of 7 RCTs revealed an approximately two-fold higher response rate to 5-ASA enema as compared with the response rate to steroid enema, clearly indicating the superiority of 5-ASA enema over steroid enema. However, because the dosing method, dose levels and type of drugs varied among different studies, a simple comparison might be difficult. Through evaluation of multiple candidate statements by experts, a consensus was reached for the view that it is more appropriate to consider 5-ASA enema as comparable to steroid enema than as deeming it superior. The slight discrepancy between the literature-derived evidence and experts’ consensus is possibly attributable to the lack of widespread clinical use of 5-ASA enema in Japan. Systemic adverse effects cannot be ignored when using steroid enema preparations available in Japan. For this reason, 5-ASA enema seems to be superior to steroid enema also in terms of safety. Although there is evidence supporting the effectiveness of sucralfate and epidermal growth factor (EGF) administered by enema for inducing remission in patients with distal colitis, these drugs were not adopted in this guideline, because the rating of these drugs by experts as standard therapy did not reach the levels for recommendation.
Both systemic therapy and topical therapy are useful for inducing remission in patients with active distal colitis. Recommendation Grade A (Ib · 8)

5-ASA enema is comparable to oral SASP in terms of efficacy, and furthermore, is less likely to elicit adverse reactions as compared to oral SASP. Recommendation Grade A (Ib · 7)

Steroid enema is comparable to oral 5-ASA in terms of improvement of clinical symptoms, endoscopic findings and histological findings. Recommendation Grade A (Ib · 7)

SASP suppositories are considered to be effective for some patients with proctitis and are very convenient to use, despite the lack of adequate evidence. Recommendation Grade I (V · 7)

Commentary:
In patients with distal colitis, topical therapy is theoretically superior in terms of efficacy and safety, because the drug can directly reach the lesion and act on it. Oral systemic therapy, on the other hand, is superior in terms of convenience of use, and has also shown to be effective. It is therefore difficult to simply argue about superiority/inferiority of one over the other. It seems advisable to select one of these therapies by not only considering the aspect of convenience, but also taking into account the patient’s preference. Evidence about the efficacy of SASP suppositories is scarce, but this drug has been adopted in this guideline based on the consensus among experts who assigned a rather high rating to the convenience of use of these preparations.

The efficacy of a combination of oral and topical 5-ASA therapy is superior to that of either drug alone. Recommendation Grade A (Ib · 8)

Topical therapy should be combined with oral therapy if rapid alleviation of symptoms is necessary. Recommendation Grade A (Ib · 7)

Commentary:
It has been confirmed that a combination of oral and topical 5-ASA significantly improves the efficacy of either agent alone. Therefore, the combined therapy is advisable in patients showing poor response to monotherapy or those with severe symptoms. Some guidelines recommend the combined therapy right from the beginning, with the expectation of rapid alleviation of the symptoms.
3.7 Treatment of active distal colitis resistant to 5-ASA preparations

- In cases who do not respond to oral 5-ASA therapy at an optimal dose combined with topical 5-ASA or steroid therapy, oral PSL (prednisolone) should be started at a daily dose of 30-40 mg. Recommendation Grade I (V · 7)

Commentary:
Since steroids began to be used for the treatment of UC much before strict requirements on clinical trial design were imposed, high-quality evidence is scarce regarding the effectiveness of steroids for the treatment of distal colitis. A statement similar to the aforementioned is also noted in textbooks and other guidelines. This statement was adopted in this set of guidelines on the basis of consensus among experts. There is no clear-cut evidence on the optimal dose level of PSL. In this statement, a general dose level based on experts’ consensus was adopted. Because the physical and nutritional conditions vary among individual UC patients, it would be advisable to tailor the dose level to individual cases, with the above-mentioned dose levels serving as a standard.

Fig. 2. Remission induction therapy for distal colitis (including proctitis)

- Surgical treatment needs to be considered in cases showing inadequate responses to conservative treatment and the activities of daily living are markedly disturbed.
References

4. Remission induction therapy for mild to moderate total colitis and left-sided colitis

4.1 Placebo effects in drug therapy for active ulcerative colitis

- The remission rate with placebo is about 10%, and the clinical/endoscopic improvement rate with placebo is about 30%. Recommendation Rate A (Ia · 7)

**Commentary:**
Analysis of 38 placebo-controlled studies reported to date has yielded these percentages which are not low. These rates probably reflect spontaneous improvement or remission rather than the placebo effect. These results suggest the necessity of RCT for correct evaluation of the effects of therapeutic interventions.

4.2 Basic drugs used in the treatment of mild to moderate ulcerative colitis

- Treatment is started with oral ASA preparations. Recommendation Grade A (Ia · 8)
- In patients who do not respond to ASA preparations or require rapid alleviation of symptoms, PSL is administered orally at the dose of 30-40 mg/day. Recommendation Grade I (IV · 8)

**Commentary:**
Oral ASA preparations are the drugs of first choice for the treatment of mild to moderate UC. The effectiveness of this class of preparations for inducing remission in patients with UC has been demonstrated in multiple RCTs and their meta-analysis. As described later, 5-ASA exerts dose-dependent efficacy. For this reason, it is important to confirm that the drug has been administered at optimal dose levels (2 g/day or more) before judging its effectiveness. Some experts advised to begin treatment with a combination of oral ASA and topical 5-ASA. A consensus has been reached among experts on the usefulness of additional or combined use of steroids, although high-quality evidence is scarce due to the longstanding use of these drugs. See Commentary to “3.7 Treatment of active distal colitis resistant to 5-ASA preparations” for the recommended dose level.
4.3 Efficacy of SASP against active ulcerative colitis

- When used in patients with active UC, SASP (2-6 g/day) can induce remission in 50-80% of all cases. Recommendation Grade A (Ib · 8)

**Commentary:**
The effectiveness of SASP was demonstrated in multiple clinical studies conducted in the 1960s. No marked difference was observed between SASP and 5-ASA on inducing remission. As already described in the section on remission induction therapy for distal colitis, the recommendation overseas is to begin treatment with SASP at a low dose level and to increase the dose gradually, because starting SASP at a high dose level is likely to cause intolerable adverse reactions. In Japan, however, treatment with this drug is often started at optimal dose levels based on the view that intolerable adverse reactions are less likely to occur in Japanese patients. (See Commentary to “4.4. Efficacy and safety of oral 5-ASA preparations in active ulcerative colitis”)

4.4 Efficacy and safety of oral 5-ASA preparations in active ulcerative colitis

- 5-ASA is evidently superior to placebo in terms of inducing remission in patients with active UC. Recommendation Grade A (Ia · 9)
- Oral 5-ASA at dose levels of 2 g/day or more is useful for inducing remission in patients with mild to moderate UC, regardless of the previous treatment or extent of the lesion. Recommendation Grade A (Ib · 8)
- When used in patients with mild to moderate UC, 5-ASA is comparable to SASP in terms of efficacy and superior to SASP in terms of safety. Recommendation Grade A (Ib · 9)
- SASA is, however, economically advantageous. Recommendation Grade I (V · 8)
- 5-ASA is useful for SASP-intolerant cases and male patients who desire fertility. Recommendation Grade I (V · 9)
- 5-ASA treatment can improve the QOL of patients with UC. Recommendation Grade A (Ib · 8)

**Commentary:**
The effectiveness of 5-ASA against active UC has been demonstrated in numerous clinical studies. This drug exerts efficacy in a dose-dependent manner, and needs to be administered at dose levels of over 2 g/day to induce remission. Multiple randomized comparative trials have been conducted to compare the efficacy of 5-ASA with that of SASP. The results of these studies suggest the lack of any significant difference between the two drugs. Since adverse reactions to SASP are attributable primarily to sulfapyridine bound to 5-ASA, incidence of adverse reactions is lower with 5-ASA, which contains no sulfapyridine. When SASP is used at high dose levels, it is not uncommon for patients to show poor tolerance to this drug because of adverse reactions such as headache and gastric discomfort. However, it has also been pointed out that because of ethnic differences in metabolism, intolerable adverse reactions to SASP are less likely to occur in Japanese patients.
4.5 Efficacy of 5-ASA enema therapy for active left-sided colitis

- In patients with active left-sided colitis, 5-ASA enema therapy has efficacy on clinical improvement and induction of remission. Recommendation Grade A (Ia · 8)
- In patients with active left-sided colitis, 5-ASA enema is superior to steroid enema in terms of induction of remission. Recommendation Grade I (Ia · 6)
- In patients with active left-sided colitis, 5-ASA enema is superior to oral SASP and oral 5-ASA in terms of the efficacy on clinical improvement. Recommendation Grade A (Ia · 7)

Commentary:
It has been shown in a meta-analysis of multiple RCTs that in patients with active left-sided colitis, remission can often be induced by topical 5-ASA therapy alone and this therapy is superior to oral systemic drug therapy. “Left-sided colitis” in this statement refers to patients in whom the disease involves the area distal to the splenic flexure as defined in the international classification. Comparing the efficacy between 5-ASA enema and steroid enema, many studies demonstrated superiority of 5-ASA. In Japan, where the history of clinical use of 5-ASA enema is short, the rating of 5-ASA enema by experts was not adequately high, and the Recommendation Grade remained at I.

4.6 Optimal dose level and dosing method of oral 5-ASA therapy for active ulcerative colitis

- The efficacy of oral 5-ASA is dose-dependent. Recommendation Grade A (Ia · 8)
- To induce remission, dose levels of 2 g/day or more are needed. Recommendation Grade A (Ia · 8)
- In patients with mild to moderate UC, it is acceptable to administer the drug twice daily at the same daily dose level. Recommendation Grade A (lb · 8)
- In patients with mild to moderate UC, the effect of inducing remission does not differ between oral 5-ASA monotherapy (4 g/day) and combined oral 5-ASA (2 g/day) + 5-ASA enema (2 g/day) therapy. Recommendation Grade I (lb · 6)

Commentary:
The efficacy of oral 5-ASA therapy for mild to moderate UC is dose-dependent. The results of a meta-analysis allow us to recommend that this drug be administered at a dose level of 2 g/day or more to induce remission. Although some studies failed to demonstrate a dose-response correlation, no consensus was reached among experts on these studies. According to a study designed to compare four-times daily and twice-daily treatment with 5-ASA at the same daily dose, the efficacy did not differ significantly between the two methods, and the patients preferred twice-daily treatment. In a study conducted to compare the efficacy of oral 5-ASA alone at a high dose and combined oral + enema treatment with 5-ASA at the same daily dose, the efficacy did not differ significantly between the two methods. However, according to a later report, combined high-dose oral 5-ASA + 5-ASA enema therapy yielded a higher rate of improvement and remission in patients with extensive UC than oral therapy alone.
4.7 Indications of steroids in mild to moderate ulcerative colitis

- If rapid improvement is desirable or patients fail to respond to treatment with ASA preparations at optimal dose levels, it is appropriate to administer PSL at dose levels of 30-40 mg/day. **Recommendation Grade A (II · 8)**
- The effect of steroids in achieving rapid remission was demonstrated in clinical studies conducted more than 30 years ago. **Recommendation Grade A (Ib · 8)**

**Commentary:**
Systemic steroid therapy is recommended if treatment with ASA preparations at optimal dose levels is not effective or rapid improvement of the clinical condition is desirable due to systemic symptoms, etc. The effect of steroids in inducing remission in patients with mild to moderate UC was demonstrated in multiple studies carried out more than 30 years ago. Also in comparison to SASP, steroid was shown to induce remission more rapidly in most of patients. Although steroids are useful for inducing remission, their efficacy as maintenance therapy has not been endorsed. ASA preparations, on the other hand, have been shown to be useful for both induction and maintenance of remission.

4.8 Dose level and dosing method of steroids for moderate ulcerative colitis

- Adequate efficacy can be expected with PSL at the dose level of 40 mg/day. **Recommendation Grade A (Ib · 8)**
- PSL 60 mg/day is slightly more effective than PSL 40 mg/day but is more likely to be associated with adverse reactions. **Recommendation Grade A (Ib · 8)**
- Once-daily PSL treatment does not differ in efficacy from that of PSL administered in divided doses at the same daily dose. **Recommendation Grade A (Ib · 8)**
- Oral treatment is expected to exhibit comparable efficacy to that of non-oral treatment. **Recommendation Grade A (Ib · 7)**

**Commentary:**
In patients with moderate UC, it is desirable to set the initial steroid dose level at around 30-40 mg/day. Because there is no evidence-based optimal dose level, the dose level needs to be adjusted depending on the disease activity and the patient’s physical and nutritional conditions. PSL at the dose of 60 mg/day is slightly more effective; however, the incidence of adverse events is also significantly higher at this dose. Although there is no evidence to support the use of divided doses, there is a view that divided doses are useful to alleviate nocturnal diarrhea. In patients who show evident improvement, it is not advisable to continue prolonged PSL therapy. Instead, one should gradually taper steroids and wean the patient from steroids while paying attention to relapse. It must be borne in mind that steroids are not effective in maintenance of remission.
4.9 Indications of immunosuppressants (AZA/6-MP) in mild to moderate ulcerative colitis 2,18,19

- This class of drugs is indicated primarily in patients refractory to steroid treatment or in whom weaning from steroids proves difficult. Recommendation Grade A (Ib · 8)
- The use of this class of drugs in combination with steroids can facilitate steroid dose reduction or weaning from steroids without aggravating the clinical symptoms or endoscopic findings. Recommendation Grade A (Ib · 8)

Commentary:
Immunosuppressants such as AZA (azathioprine) and 6-MP (mercaptopurine) are considered in patients in whom the symptoms worsen during steroid tapering, the disease relapses soon after discontinuation of steroid or frequent cycles of remission and relapse develop. This class of drugs has been demonstrated to show significant efficacy in multiple RCTs designed to analyze steroid dose reduction or weaning from steroids as the primary endpoint. Because it usually takes approximately 3 months for AZA/6-MP to exert their optimal efficacy, these drugs cannot be expected to induce rapid remission in patients with active UC. If AZA/6-MP is indicated, it is important to start these drugs before the steroid dose is reduced. Because of ethnic differences in metabolism, the blood levels of these drugs tend to be higher in Japanese patients, thus warranting caution to the dose levels. In Western countries, the most commonly used dose range is 1.5-2.5 mg/kg/day for AZA and 1-1.5 mg/kg/day for 6-MP. In Japanese patients, on the other hand, AZA is often effective at dose levels as low as about 50 mg/day. Serious adverse reactions such as flu-like symptoms, bone marrow suppression and hepatotoxicity can develop occasionally. Careful monitoring by hematological testing, etc., is essential particularly in the initial period of the treatment with these drugs. One should also be careful about patients receiving combined AZA + 5-ASA therapy, because these patients are more likely to develop adverse reactions such as bone marrow suppression due to inhibited degradation of AZA by 5-ASA. If adverse reactions do not appear during the first several weeks of the initial treatment, long-term administration is relatively well-tolerated. Studies published to date have not endorsed the concern that treatment with 6-MP/AZA is associated with an elevated risk of malignancy.

4.10 Usefulness of leukocyte apheresis in active ulcerative colitis 20,21

- In UC patients requiring PSL at dose levels of 30-40 mg/day or more due to high disease activity, it is more effective and safer to maintain or reduce the steroid dose through combined use of leukocyte apheresis than to continue high-dose steroid alone. Recommendation Grade A (Ib · 8)
- Even when used as the primary treatment of moderate to severe UC, leukocyte apheresis is expected to exert efficacy comparable to that of steroids. Recommendation Grade B (IIa · 7)
- Leukocyte apheresis often exhibits inadequate efficacy in patients with intractable disease (particularly those with chronic persistent type disease and those on prolonged steroid therapy). Recommendation Grade I (V · 7)
Commentary:
Leukocyte apheresis, developed in Japan, has been approved for clinical use in Japan, but high-quality evidence supporting this therapy is still scarce. It has been reported that in patients with moderate to severe disease requiring high-dose steroid therapy, combined use of leukocyte apheresis will be more effective than steroid alone, while also reducing the incidence of adverse reactions. Furthermore, some experts have rated leukocyte apheresis alone to be comparable to steroids as a primary therapeutic option for active UC. However, since this therapy is applied in sessions at intervals of one week, it takes longer to manifest its efficacy as compared to steroids. It has also been pointed out that the therapy is not adequately effective in patients with the chronic persistent type of UC or those requiring prolonged use of steroids.

4.11 Other drug therapy and nutrient-supplementation therapy for active ulcerative colitis

- In patients with active UC, nicotine patch therapy is inferior in efficacy to oral steroid therapy. Recommendation Grade A (Ib · 7)
- In patients with active UC, metronidazole is inferior to SASP in terms of its effect in inducing remission. Recommendation Grade A (Ib · 7)
- Food supplementation with fish oil-derived fatty acids can alleviate clinical symptoms and reduce the steroid dose requirement. Recommendation Grade I (Ib · 6)
- Oral intake of GBF can alleviate clinical symptoms without causing any adverse reactions. Recommendation Grade I (Ib · 6)

Commentary:
Epidemiological studies have shown that the activity of UC is lower in smokers than in nonsmokers. Based on this finding, some studies demonstrated the effectiveness of nicotine patch and combined use of nicotine patch with other treatment in patients with mild UC. However, this therapy as a standard treatment received a lower rating from experts than the recommendation standards. It has been reported that nicotine patch alone is inferior in efficacy to oral PSL 15 mg/day. Unlike the proven efficacy of metronidazole in the treatment of Crohn’s disease, there are no data endorsing the efficacy of metronidazole in the treatment of UC. Therefore, this drug cannot be recommended as a remission induction therapy in UC patients. Food supplementation with fish oil-derived fatty acids (EPA 4.5 g/day) can reduce the steroid dose requirement and alleviate clinical symptoms in patients with mild to moderate UC, but is not effective at maintenance of remission. GBF (germinated barley foodstuffs) has been reported to alleviate clinical symptoms of UC. However, some experts doubt its efficacy, and this therapy received a poor rating from the experts as a standard therapy. Evidence supporting the effectiveness of interferon in patients with active UC has been collected in multiple studies, but the experts did not assign a high rating for this therapy.
References


4 Stevens AC. Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease. UpToDate 2004, version 12.3.


5. **Treatment of severe ulcerative colitis**

5.1 **Basic therapeutic strategy for severe ulcerative colitis**

- Patients failing to respond to maximum oral/topical treatment or those satisfying the criteria of severe disease are generally required to be hospitalized and to receive intravenous steroid therapy and intravenous alimentation. **Recommendation Grade I (V · 8)**
- Cooperation between the gastroenterologist and the surgeon is needed even from the initial stage of the treatment. **Recommendation Grade I (V · 9)**

**Commentary:**
Hospitalization generally needs to be considered in patients with severe disease. Intravenous steroid therapy is indicated in patients with persistent symptoms despite optimal drug therapy (e.g., oral PSL 40-60mg/day, oral 5-ASA 4 g and combined topical therapy). There are no studies evaluating the benefit of combined administration of oral ASA preparations or topical therapy with intravenous steroid therapy. For this reason, combined use of these agents is only considered if oral or topical drug therapy is possible in a given case. At the same time, management of the systemic condition (dehydration, electrolyte abnormalities, anemia, hypoproteinemia, malnutrition, etc.) is a fundamental element of patient management. Although there is no evidence to support the primary efficacy of total parenteral nutrition, it is usually selected for patients with malnutrition. Management of severe cases should be assigned to specialists with much experience in the care of UC patients. It is advisable to cooperate with the surgeon even from the initial stage of the treatment, bearing in mind the possible necessity of surgery.

5.2 **Efficacy and optimal dose level of steroids in severe ulcerative colitis**

- Intensive steroid therapy can induce remission in approximately half of patients. **Recommendation Grade A (Ia · 8)**
- Intensive steroid therapy can avoid early colectomy in nearly two-thirds of cases. **Recommendation Grade A (Ia · 8)**
- In patients with persistent symptoms or severe endoscopic findings, intensive intravenous steroid therapy is less likely to be effective, and other treatment need to be considered. **Recommendation Grade I (IIIb · 7)**
- The optimal steroid dose level for intravenous administration is 1-1.5 mg/k/day on a PSL dose basis. **Recommendation Grade B (V · 8)**
- Steroid therapy at higher doses increases the risk of adverse reactions, but does not increase the efficacy. **Recommendation Grade B (IIa · 8)**
Commentary:
The effectiveness of intravenous steroid therapy in patients with severe UC has been confirmed. However, high-dose steroid therapy is likely to induce adverse reactions, sometimes leading to a poor prognosis. It is therefore essential to select the dose levels and dosing period through adequate assessment of the disease state and patient’s systemic conditions, as well as precise evaluation of the responses to the treatment. In patients showing poor response to steroid therapy, it should be considered to switch to other treatment without delay. PSL at dose of 1-1.5 mg/kg/day generally suffices for intravenous steroid therapy. Intravenous steroid therapy at higher dose levels are reported to be associated with elevated risk of adverse reactions, but not to increase the efficacy. Intra-arterial steroid therapy has been attempted in Japan, but this therapy was not taken into account during the preparation of this set of guidelines, because there are as yet no evidence-based data on this therapy.

5.3 Usefulness and optimal dose level of cyclosporine in severe ulcerative colitis

- In patients with severe UC, cyclosporine is superior to steroids. Recommendation Grade A (Ib · 7)
- It is not uncommon for patients with steroid-resistant severe UC to show response to intravenous cyclosporine therapy. Recommendation Grade A (Ib · 7)
- In patients who does not respond to 7-10 days of intensive steroid therapy, continuation of steroid is not expected to improve the efficacy, and surgical treatment or cyclosporine is indicated. Recommendation Grade B (II · 7)
- In patients with severe UC, the optimal cyclosporine dose is 2 mg/kg. Recommendation Grade A (Ib · 7)
- When patients with severe UC are treated with cyclosporine, the blood drug levels needs to be monitored. Recommendation Grade I (V · 8)

Commentary:
In a study designed to compare steroid monotherapy with cyclosporine monotherapy in patients with severe UC, cyclosporine was superior in terms of efficacy. However, if safety and economic factors are also considered, it is not rational to use cyclosporine as a primary therapy based solely on efficacy. One study has demonstrated that the improvement rate following cyclosporine therapy was over 80% even in patients unresponsive to intensive steroid therapy. These results suggest that in patients with severe disease who fail to response to steroid therapy, not only surgical treatment, but also cyclosporine therapy may be considered. Nonetheless, these comparisons referred to short-term outcomes, and it is not uncommon for surgical treatment to be needed in the long run. In an earlier clinical study on cyclosporine, the drug was used at a high dose level (4 mg/kg). A recent study compared a cyclosporine dose of 2 mg/kg with that of 4 mg/kg and found that the improvement rate on Day 8 was over 80% in both doses, and time to response was similar (4 days). Furthermore, the rate of avoidance of colectomy was higher in the lower dose group. Consensus was reached among experts over the view that intravenous cyclosporine should be administered at facilities familiar with this therapy and that the blood drug levels need to be monitored during this therapy.
5.4 Antimicrobial drug therapy for severe ulcerative colitis\textsuperscript{3,10,11,12}

- Combined use of antimicrobial agents such as ciprofloxacin with steroid therapy for severe UC does not improve the responses. \textbf{Recommendation Grade I (Ib \cdot 6)}
- Antimicrobial agents are used only in cases possibly complicated by infection and patients immediately before surgery. \textbf{Recommendation Grade I (V \cdot 7)}

\textbf{Commentary:}
There is no clear-cut evidence demonstrating the usefulness of combined administration of antimicrobial agents with steroids during treatment of UC. Some studies demonstrated the effectiveness of ciprofloxacin in patients with mild to moderate UC, but the drug was not effective in those with severe UC. Combined use of aminoglycosides and metronidazole also failed to exert any additional efficacy. Based on the literature-derived evidence, it is not advisable to use antimicrobial agents for all cases of severe UC. Instead, it seems better to use antimicrobial agents carefully in patients suspected to have infection or immediately prior to surgery. There is a view that when treating severe UC patients with intensive intravenous steroid therapy, short-term prophylactic use of antimicrobial agents is rational. In Japan, the effectiveness of multiple antimicrobial drug therapies (ATM therapy) against \textit{Fusobacterium} has been reported (evidence level IV), but evidence of higher quality is needed to validate it as standard therapy.

5.5 Factors aggravating severe ulcerative colitis and countermeasures\textsuperscript{1,3}

- Anticholinergics, antidiarrheal agents, NSAIDs, narcotics, etc., should be discontinued. \textbf{Recommendation Grade B (II/III \cdot 8)}
- Infection with \textit{C. difficile} or CMV needs to be checked during treatment. \textbf{Recommendation Grade I (V \cdot 8)}

\textbf{Commentary:}
Severe UC is often difficult to treat. It is necessary to eliminate iatrogenic factors that can aggravate the condition. Careless use of symptomatic treatments for diarrhea, fever, abdominal pain, etc., should be avoided since this kind of treatment is known to potentially induce toxic megacolon. In patients receiving steroids or immunosuppressants, the incidence of infectious complication is not low, and it is essential to check and treat infection promptly. Since complicating infection with \textit{Clostridium difficile} or CMV (cytomegalovirus) can sometimes aggravate UC, it is necessary to check such infections and treat them appropriately.
5.6 Infliximab for therapy-resistant ulcerative colitis

- Infliximab is not effective against moderate to severe steroid-resistant UC. **Recommendation Grade I (Ib · 6)**
- It is too early at present to consider the indication for infliximab in patients with UC. **Recommendation Grade I (V · 8)**

**Commentary:**

The effectiveness of infliximab against Crohn’s disease has been established, and this drug has been incorporated into the treatment schema for Crohn’s disease. However, the use of this drug for the treatment of UC is still under evaluation. To date, no adequate evidence supporting its use for the treatment of UC has been collected. There are reports indicating that some UC patients resistant to steroids or cyclosporine respond to infliximab. However, the rating given this drug by experts was not high enough to satisfy the criteria for recommendation in this set of guidelines. According to a recent large-scale multicenter study conducted overseas, infliximab was useful for both inducing and maintaining remission in patients with therapy-resistant moderate to severe UC. In the USA, the use of infliximab in UC patients has been approved by the FDA.

![Fig. 4. Treatment of severe ulcerative colitis](image-url)
References

6. Remission maintenance therapy for ulcerative colitis

6.1 Dietary therapy for maintenance of remission

- None of commonly employed dietary restriction has been shown to reduce the risk of relapse. Recommendation Grade B (IIla · 8)

Commentary:
The significance of dietary therapy in the management of UC is low, unlike its significance in the management of Crohn’s disease. Many patients voluntarily limit their diet even in remission, and tend to avoid intake of dairy products. However, the effect of such practices in preventing disease relapse is unknown, and, on the contrary, the risk of malnutrition arising from such practices has been pointed out. Particularly during remission, it is not advisable to suppress nutrient intake or reduce the QOL of patients through unnecessary dietary restriction. There is no evidence to support the effectiveness of elemental diet in the management of UC.

6.2 Basic drugs used in remission maintenance therapy

- All ASA preparations are effective for maintaining remission. Recommendation Grade A (Ib · 8)
- Steroids are ineffective for maintenance of remission. Recommendation Grade A (Ib · 8)
- Immunosuppressants (AZA/6-MP, etc.) are used in steroid-dependent patients or patients who are difficult to wean from steroids. Recommendation Grade A (Ib · 8)

Commentary:
UC is characterized by repeated cycles of remission and relapse. A basic strategy in the management of UC during the remission phase is to maintain a comfortable daily life for as long as possible while preventing relapse. Generally, remission maintenance therapy needs to be continued for almost lifelong period. In patients with mild disease in whom relapse seldom occurs, and who can be easily treated even in the event of a relapse, follow-up without long-term drug therapy is one possible option. If treatment needs to be continued for prolonged periods of time, drugs less likely to induce adverse reactions should be selected. The effect of ASA preparations (SASP, 5-ASA) in maintaining remission has been confirmed in many RCTs. Steroids are not likely to be useful for maintenance of remission. Prolonged use of steroids without particular necessity should be avoided from the aspect of adverse reactions. If the dose level of steroid cannot be reduced or weaning from steroid is difficult, immunosuppressants (AZA/6-MP) should be considered.
6.3 SASP therapy for maintenance of remission

- The effect of SASP in maintaining remission has been shown to be dose-dependent in the dose range of 2 and 4 g/day; however, the incidence of adverse reactions also rises in a dose-dependent manner. Recommendation Grade A (Ib · 8)

Commentary:
In a study comparing different doses of SASP (2-4 g/day), SASP exerted significant efficacy in maintaining remission at each dose level, and its effect improved significantly in a dose-dependent manner. However, as the dose level increased, the incidence of adverse reactions and intolerable symptoms also increased. It is reported overseas that about 1/4 of patients do not tolerate SASP at the dose of 4 g/day (the most effective dose). For this reason, the daily dose level is often set at about 2 or 3 g for maintenance of remission. There is evidence showing that episodic administration of SASP according to symptoms has similar efficacy for prevention of relapse compared to regular use of SASP. However, the rating of experts for this treatment method was low, and this method is not widely adopted even at present, 20 years after it was first reported to be beneficial. Therefore, this treatment method is not suggested in the recommendation.

6.4 Therapy with oral 5-ASA preparations for maintenance of remission

- Oral 5-ASA preparations provide an effective and safe means of maintaining remission in UC patients. Recommendation Grade A (Ib · 8)
- Oral 5-ASA preparations are useful for maintaining clinical and endoscopic remission of UC. Recommendation Grade A (Ia · 8)
- Oral 5-ASA therapy is comparable to SASP therapy in terms of efficacy and safety, but it is superior to the latter in terms of the incidence of dose-dependent adverse reactions. Recommendation Grade A (Ia · 8)
- 5-ASA is particularly useful in patients who do not tolerate SASP and male patients who desire fertility. A possible problem with oral 5-ASA preparations is the slightly higher cost as compared to that of SASP. Recommendation Grade I (V · 8)
- Oral 5-ASA at the daily dose of 1.5 g is effective for preventing relapse in most patients. Recommendation Grade A (Ib · 7)
- Once daily administration of oral 5-ASA improves the compliance with the drug while retaining the remission-maintenance effects. Recommendation Grade A (Ib · 7)

Commentary:
The remission-maintenance effect of oral 5-ASA therapy has been confirmed in RCTs. While no significant difference in efficacy has been observed between SASP and 5-ASA, the incidence of adverse reactions varies among reports. Studies showing that dose-dependent adverse reactions are less frequent with 5-ASA were supported and 5-ASA was rated by experts to be superior in terms of safety to SASP. Because male sterility associated with SASP has been reported, 5-ASA should be selected as the treatment agent for males desiring fertility. Dose levels over 1.5 g/day have been recommended, and there is evidence to support the use of once-daily treatment with this drug at such dose levels, although this treatment method is not widely adopted.
6.5 **Topical 5-ASA therapy for maintenance of remission**

- In patients with distal colitis, 5-ASA enema therapy shows very high efficacy in maintenance of remission. **Recommendation Grade A (Ia · 7)**
- 5-ASA enema therapy is useful for maintaining remission in patients with distal colitis. Even intermittent treatment (about one dose every 2-3 days) exerts efficacy close to that of consecutive day treatment. **Recommendation Grade A (Ib · 7)**
- 5-ASA enema therapy (1 g/day) serves as an effective and safe means for maintenance of remission in patients with left-sided colitis. **Recommendation Grade A (Ib · 7)**
- Twice-weekly 5-ASA enema therapy is comparable to oral SASP therapy in terms of its efficacy in maintaining remission in patients with left-sided colitis. **Recommendation Grade I (Ib · 6)**
- Stronger remission maintenance effect can be obtained by combining oral 5-ASA with twice-weekly 5-ASA enema. **Recommendation Grade A (Ib · 7)**

**Commentary:**
Multiple RCTs and their meta-analysis have shown that in patients with distal or left-sided colitis, 5-ASA therapy is useful not only for inducing remission, but also maintaining remission. Although enema therapy is less convenient than oral therapy, it has been reported that even twice- or thrice-weekly enema therapy exerts comparable remission-maintenance effect to consecutive day treatment. Therefore, intermittent enema therapy may serve as a valid alternative for improving the compliance with the treatment. It has also been shown that twice-weekly enema therapy is comparable in efficacy to daily SASP therapy. According to a study, daily oral 5-ASA in combination with twice-weekly 5-ASA enema can further increase the remission-maintenance effect.

6.6 **Immunosuppressants for maintenance of remission**

- When remission has been achieved by AZA, remission can be maintained by continued use of AZA. **Recommendation Grade A (Ib · 8)**
- In steroid-dependent UC patients in whom remission is maintained by AZA, the combined use of 5-ASA will not alter the incidence of relapse. **Recommendation Grade I (Ib · 6)**

**Commentary:**
Use of immunosuppressants is recommended in steroid-dependent patients or patients who are difficult to wean from steroids. Many studies demonstrated that continued treatment with AZA after induction of remission can increase the rate of maintenance of remission to over 50%. Results from multiple RCTs indicate that immunosuppressants play a significant role in maintaining remission and tapering steroids. The currently recommended dose levels of immunosuppressants are 1.5-2.5 mg/kg for AZA and 0.75-1.5 mg/kg for 6-MP. However, owing to ethnic differences in metabolism, the use of these drugs at the aforementioned dose levels is more likely to cause adverse reactions in Japanese patients. In general, immunosuppressants should be used at an initial dose level of about 50 mg/day and individual patients must be monitored closely for the development of adverse reactions and responses to the treatment. The remission-maintenance effect of AZA monotherapy is reported to be comparable to that of combined 5-ASA + AZA therapy; therefore, combined use of 5-ASA + AZA offers no additional benefit. However, the consensus of experts for this view is not adequate, and 5-ASA preparations are often used clinically in combination with AZA as remission maintenance therapy.
6.7 Remission maintenance therapy for severe ulcerative colitis

- In patients in remission after severe disease, the rate of remission maintenance with SASP is comparable to that obtained with AZA; and adverse reactions are fewer with SASP. Recommendation Grade I (Ib · 6)
- The remission-maintenance effect of combined SASP + AZA therapy is greater than that of SASP monotherapy. Recommendation Grade A (Ib · 7)

Commentary:
It has been reported that the efficacy of ASA preparations is comparable to that of AZA for maintaining remission in patients with severe UC. According to some reports, however, the remission-maintaining effect of combined ASA + AZA therapy was higher than that of ASA monotherapy. Experts attach greater importance to the combined therapy, possibly based on the view that intensive prevention of relapse is necessary in patients with severe disease.

Fig. 5. Remission maintenance therapy for ulcerative colitis

* Surgical treatment is considered in cases unlikely to respond to conservative treatment or cases in whom daily living has been markedly disturbed.
References


7. Surgical treatment of ulcerative colitis

7.1 Indications of surgical treatment in ulcerative colitis

- Absolute indications for surgery are massive bleeding, perforation, or complication of colorectal cancer. Recommendation Grade I (V · 9)
- Surgical treatment is considered in patients with severe colitis unresponsive to conventional medical treatment, patients with persistent symptoms interfering with dairy activities, patients with intolerable side effects, and so on. Recommendation Grade I (V · 9)
- Total colectomy is performed for treatment of extraintestinal complications in some cases. Recommendation Grade I (V · 8)
- Discussion among the gastroenterologist, surgeon and the patient is needed to determine the indications for surgery. Recommendation Grade I (V · 9)

Commentary:
Absolute indications for surgical treatment are unmistakable, while relative indications for surgery are difficult to determine, since the severity of the disease and the condition of the patient vary from case to case. Surgery should be considered promptly in patients showing failure of intensive medical treatment and patients with toxic megacolon. Cooperation between the gastroenterologist and surgeon is essential, while ensuring that the patient is informed adequately and taking into account the patient’s physical condition, social background and preferences. Although evidence supporting these indications for surgery is scarce, consensus among experts has been reached.
7.2 Selection of operative procedure

- The standard procedure for elective surgery is ileal pouch-anal anastomosis or ileal pouch-anal canal anastomosis. **Recommendation Grade I (IV/V · 9)**
- Ileal pouch-anal anastomosis is a highly radical operation, while ileal pouch-anal canal anastomosis is superior in terms of the postoperative defecation function. **Recommendation Grade I (V · 9)**
- The operative procedure for severe UC is usually total (subtotal) colectomy and sigmoid mucous fistula placement or Hartmann’s operation. **Recommendation Grade I (V · 8)**
- Ileal pouch-anal (anal canal) anastomosis allows better postoperative function than ileostomy, but is slightly more likely to be associated with complications. **Recommendation Grade I (IV/V · 7)**

**Commentary:**
The purpose of surgical treatment is to resect the colon and rectum affected by UC. It would be ideal for the surgery to be performed safely while retaining good defecation function and prognosis. The operative procedure can be divided into ileostomy (serving as a permanent stoma) and anus-preserving surgery. From the viewpoint of QOL, especially in terms of the postoperative defecation function, the anus-preserving procedure is superior and is often selected as the standard procedure for elective surgery. Depending on the condition, anal function, age, etc., of the patient, proctocolectomy + ileostomy or total colectomy + ileoproctostomy is sometimes selected. Because each procedure has both advantages and shortcomings, the selection of operative procedure should be made by an experienced surgeon, taking into account the physical condition and social background of the patient.

7.3 Prognosis and function after surgical treatment

- The course of patients after proctocolectomy + ileal pouch-anal anastomosis or ileal pouch-anal canal anastomosis is usually favorable. **Recommendation Grade I (V · 7)**
- The frequency of defecation after ileal pouch-anal (anal canal) anastomosis is usually 5-6/day. Fecal leakage sometimes occurs. **Recommendation Grade I (IV · 8)**

**Commentary:**
The prognosis and function after proctocolectomy + ileal pouch-anal (anal canal) anastomosis are usually favorable. A study revealed that the ileal pouch functioned relatively well in patients undergoing surgery for complicating colorectal cancer during the course of UC. Proctocolectomy + ileal pouch anal anastomosis (IAA) is a radical surgery that resects the complete colorectal mucosa; however, the incidence of postoperative dysfunction of defecation is higher. With proctocolectomy + ileal pouch-anal canal anastomosis (IACA), better postoperative defecation function is expected; however, the residual affected mucosa in the anal canal can lead to postoperative inflammation and/or recurrence of cancer.
7.4 Treatment of postoperative pouchitis

- Two-week treatment with oral metronidazole or ciprofloxacin is the therapy of first choice. Recommendation Grade A (Ib · 8)
- When antimicrobial drug therapy is ineffective, 5-ASA or steroid is used. Recommendation Grade I (IVN · 7)

Commentary:
Ileal pouch-anal (anal canal) anastomosis is expected to allow favorable postoperative defecation function and to improve the QOL. However, non-specific inflammation of unknown cause may develop in the ileal pouch, which serves as a reservoir to pool feces, resulting in symptoms such as diarrhea, and melena. These complications are often seen following operation with ileal pouch placement. Metronidazole, shown by RCT to reduce the frequency of defecation, is considered as a first-line drug, and ciprofloxacin and doxycycline have also been demonstrated to be effective. In cases unresponsive to antimicrobial agents, either 5-ASA or steroid is used. Since pathophysiology of this disease still remains veiled, development of diagnostic criteria and therapeutic guidelines for pouchitis is now under way in Japan.

References
8. Course of ulcerative colitis and surveillance for colorectal cancer

8.1 Life prognosis of patients with ulcerative colitis

- The life prognosis of patients with UC is almost equal to that of healthy individuals. **Recommendation Grade A (IIIa · 8)**

**Commentary:**
The death rate in UC patients is known not to differ significantly from that for the general population. The prognosis of this disease in terms of survival seems to be reasonably favorable. Considering that this disease develops during youth and is characterized by repeated cycles of remission and relapse throughout life, the goal of treatment is to allow patients to lead comfortable lives by maintaining remission.

8.2 Prediction of relapse and resistance to treatment

- The risk for relapse is high in young patients, female patients with a history of multiple relapses and patients with basal plasmacytosis in rectal biopsy specimens. **Recommendation Grade I (IIIa · 6)**
- Stress has been shown to influence time to relapse and disease activity. **Recommendation Grade B (IIIa · 7)**
- Severe diarrhea and hypoalbuminemia can serve as predictors of poor responses to medical treatment. **Recommendation Grade B (IIIb · 7)**

**Commentary:**
Numerous factors have been identified as possible predictors of disease exacerbation; however, little information that might affect the therapeutic strategy has been accumulated from such evaluations. Here, the factors reaching an adequate recommendation level are listed as reference information.
**8.3 Risk of development of colorectal cancer in ulcerative colitis**\(^7,8\)

- The risk of colorectal cancer increases with the duration of disease. **Recommendation Grade A** (IIIa · 9)
- The rate of development of colorectal cancer is 2%, 8% and 18% at 10, 20 and 30 years after diagnosis, respectively. **Recommendation Grade A** (IIIa · 8)
- The risk of colorectal cancer is particularly high in patients complicated with primary sclerosing cholangitis (PSC). **Recommendation Grade B** (IIIa · 7)

**Commentary:**
It is known that the risk of colorectal cancer is correlated with the duration and extent of the disease in patients with UC. The risk is the highest in patients with pancolitis. The risk is reported to start increasing about 10 years later in left-sided colitis as compared with pancolitis. According to some reports, the severity of inflammation and the age at onset are also correlated with the risk of colorectal cancer. In cases with PSC, cancer often develops on the right side of the colon, suggesting the possible involvement of bile acid.

**8.4 Significance of colorectal cancer surveillance in patients with ulcerative colitis**\(^9\)

- Detection of colorectal cancer at an early stage among patients with UC is possible by surveillance. Surveillance may also contribute to extend the survival period of these patients. **Recommendation Grade A** (IIIB · 8)

**Commentary:**
Periodic surveillance for colorectal cancer should increase the cancer detection rate; however, whether or not such a procedure will contribute to improving the patient outcome remains an open question. A study published in Japan indicates that the death rate from colorectal cancer is reduced by colonoscopic surveillance.

**8.5 Specific protocols for colorectal cancer surveillance**\(^10,11,12\)

- No well-designed clinical studies have been published on the surveillance protocols. **Recommendation Grade I** (V · 7)
- Annual or biannual colonoscopy with biopsies is performed, beginning 8-10 years after disease onset in patients with extensive colitis. **Recommendation Grade A** (IIib · 8)
- Proctocolectomy is usually indicated if dysplasia is found on biopsy specimen and is confirmed by another gastroenterological pathologist. **Recommendation Grade I** (V · 7)
- It is not uncommon that histological evaluation of dysplasia associated with UC varies among examiners. **Recommendation Grade A** (IIib · 8)
Commentary:
Because no studies comparing different colorectal cancer surveillance programs are available, there is no consensus over specific protocols of colorectal cancer surveillance. Consensus among experts was reached over the validity of the clinical study finding that it is useful to begin colonoscopy with biopsies 8-10 years after disease onset, i.e., when the risk of colorectal cancer begins to increase, primarily in patients with pancolitis. However, the rating of experts was not adequate for random biopsy (conducted at intervals of 10 cm) often practiced in Western countries. This practice thus failed to reach an adequate recommendation level. Discrepancies in the histological diagnosis of dysplasia have been recognized, and indicators for careful evaluation of dysplasia were adopted for recommendation. At present, a study evaluating the validity of surveillance by detailed observation and targeted biopsy rather than random biopsy is under way.

References