Review Article

Inflammatory Bowel Disease in Japan
-Is It Similar to or Different from Westerns?-

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Abstract
Ulcerative colitis and Crohn's disease, the most common types of inflammatory bowel disease, are idiopathic, intractable disease characterized by chronic inflammation in the intestine. In recent years, studies elucidating the clinical characteristics of these diseases and basic researches have suggested that the diseases are induced by the immunological abnormalities through the involvement of environmental factors with their predisposition. In Japan, significant progress of basic and epidemiological researches has been developed for these diseases and the clinical guidelines have been established. However, no fundamental treatment for these diseases has been established yet. The current number of patients in Japan continues to increase, with at least 180,000 patients suffering from ulcerative colitis and 40,000 suffering from Crohn's disease. Thus, further studies are required to understand these diseases and improve medical treatments.

Keywords
inflammatory bowel disease, ulcerative colitis, Crohn's disease

J Anus Rectum Colon 2020; 4(1): 1-13

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD), which are termed as inflammatory bowel disease (IBD), are idiopathic, intractable, chronic inflammatory diseases affecting the gastrointestinal tract. As their causes are unknown, no fundamental treatments have been established thus far. Although these diseases were previously seen mainly in Western countries, in recent years the westernization of lifestyle and dietary habits in Japan may have led to a rapid increase in the number of Japanese people affected by these diseases (Figure 1). These diseases are currently the most prevalent among all recognized intractable diseases in Japan.

Research in Japan on these diseases began in 1973 with the "Research Group on Intractable Intestinal Inflammatory Disorders" (the Research Group) of the Ministry of Health, Labour and Welfare (MHLW; known as the Ministry of Health and Welfare at that time). When the Research Group was launched, little was known about the causes and clinical characteristics of these diseases, and appropriate research methods were also insufficient. Thus, there were no studies linked to clinical practice, which meant that clinical practice focused on epidemiology and diagnostics as only a limited number of treatments were available. However, over the course of 40 years since then, there has been a rapid increase in the number of basic research and epidemiological studies conducted to identify the clinical characteristics of these diseases, establish medical guidelines, and develop new therapies, which led to major changes in the current situation. In recent years, the development of genome-wide association studies has led to the identification of susceptible genes and the realization that genetic predisposition is related to disease onset[1]. In addition, the fact that the spontaneous onset of chronic bowel inflammation does not occur in genetically modified mice in aseptic conditions indicates that environmental factors, such as dietary antigens and en-
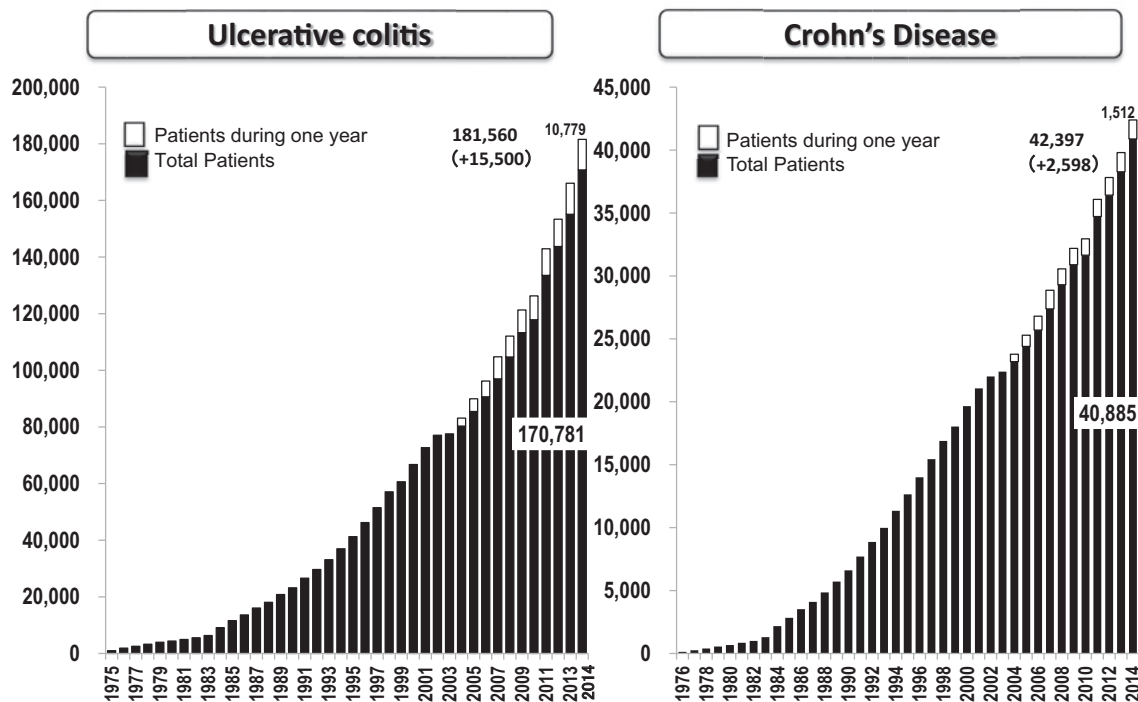
Figure 1. Accumulative Numbers of Registered Patients with IBD in Japan [42, 43]. The numbers of patients with both ulcerative colitis and Crohn's disease are increased year by year.
Quoted and modified from the materials by Japan Intractable Diseases Information Center. [Ulcerative colitis (designated intractable disease No. 97)] [Internet]. Available from: http://www.nanbyou.or.jp/entry/62. Japanese [42] and Japan Intractable Diseases Information Center. [Crohn's disease (designated intractable disease No. 96)] [Internet]. Available from: http://www.nanbyou.or.jp/entry/81. Japanese [43]

teric bacteria, play an important role in these diseases[2]. Specifically, the main clinical feature of these diseases is thought to be an abnormal immune response to enteric bacteria and dietary antigens that results from the interaction between genetic predisposition and environmental factors[3,4].

In addition to identifying the clinical characteristics of IBD, therapies and therapeutic goals utilized in Japan were also significantly revised. At the time the Research Group was launched, only two drugs, 5-aminosalicylic acid (5-ASA) and corticosteroids were the basic treatment for UC and nutritional therapy in addition to these drugs was the basic treatment for CD. In particular, corticosteroid has been used for over 40 years as the primary therapy for active phase, mainly in severe patients. However, the daily lives of patients with intractable diseases resistant to these drugs are largely affected. The treatment of such patients has remained a long-term issue. Since 2000, treatment options have been increasing, such as cytapheresis, immunomodulators, and biologics. Our understanding of IBD has undergone a major change since the emergence of anti-tumor necrosis factor TNF-alpha (TNFα) antibody biologics (infliximab and adalimumab). The use of anti-TNFα antibodies has led to the induction of remission in refractory diseases resistant to

conventional therapies, and continuous administration has led to improved long-term prognosis. The number of patients who were formerly hospitalized but can now be managed on an outpatient basis is also increasing. Although the development of these therapies has achieved and maintained clinical remission as therapeutic goals, recently, the goals have not been limited to just clinical remission and its maintenance. As endoscopic mucosal healing has become possible, current goals have been shifted toward maintaining a certain standard of living without morphological or functional abnormalities in the gastrointestinal tract[5].

In spite of this, there is still no fundamental therapy for IBD. Even with the use of various drugs, the number of patients with intractable diseases requiring surgery remains high. Therefore, further improvement is needed in this field.

Hereditary Predisposition

The fact that UC commonly occurs among members of the same family has been reported in both Western countries and Japan. A study on twins has demonstrated that the concordance rate of UC was 16% for identical twins and 4% for fraternal twins[6]. The closer the blood relationship, the higher the rate of the onset, suggesting that shared environ-

mental factors play a role in addition to hereditary predisposition.

Furthermore, the fact that various disease-related genes have been reported in multiple studies definitively confirms the influence of hereditary predisposition[7]. However, hereditary predisposition in Asia including Japan, is different from that in western countries.

In the 1970s, the association studies of human leukocyte antigens (HLA) had been performed to search for genetic factors in IBD. Our group reported a higher haplotype frequency of HLA-B5-DR2 in patients with ulcerative colitis than in controls[8]. However, the studies in western countries showed no relationship between HLA antigens and IBD, including the study in the British population. Around 30 years after our report, the Japanese group confirmed our study by a comparative genome-wide association study (GWAS)[9]. It was found that splits of HLA-B5 were HLA-B51 and -B52, and genotype of B52 was HLA-B*5201, and that splits of HLA-DR2 were HLA-DR15 and -DR16 serotypes. And, genotypes of DR15 were HLA-DRB1*1502. They concluded that the HLA-Cw*1202-B*5201-DRB1*1502 haplotype increases susceptibility to UC but reduces the risk for CD. The similar results were reported in Koreans. Recently in westerns, Goyete et al. reported that allele HLA-B*52:01 is indicated in Caucasian patients for ulcerative colitis[10].

In 2001, NOD2, was identified as a Crohn's disease susceptible gene by linkage analysis[11,12]. Since then, GWAS has achieved dramatic progress in IBD genetics. However, since our first report on the absence of NOD2 in the Japanese population[13], almost all genes abnormalities found in the western population, have been reported no or little association with Asian population, except for TNFSF15, FcgRII and some other genes. Recent GWAS has achieved dramatic progress in IBD genetics. At 2015, the transethnic analysis identified an additional 38 new IBD loci[14]. In total, over 200 of IBD susceptible genes have been identified so far. They observed genetic heterogeneity between divergent populations at several established risk loci. In Crohn's disease, NOD2 mutation was absent, but the effect size of TNFSF15 was higher in Asian. ATG16L1 or a combination of IL23R and IRGM was lower in Asia. In ulcerative colitis, they newly revealed HLA DQA1 and B1 in East Asians. It suggests that Caucasian and Asian populations appear to have some shared genetic risk factors, but others are distinct. These findings indicate that the genetic risk of IBD is quite different between western IBD and Japanese IBD population.

Ulcerative Colitis

The term "ulcerative colitis (UC)" was first described in 1875; in that report, Wilks and Moxon described the case of a patient with severe diarrhea as having idiopathic non-specific colitis. In Japan, UC was first reported in 1928 and was defined as "a disease that causes diffuse, localized lesions in the large intestine in the form of idiopathic, diffuse, non-specific inflammation that tends to cause mucosal erosion and ulceration." When ulcerative colitis develops, there is a repeated pattern of remission and recurrence. Lesions are mainly in the mucosa and submucosa, and in most cases result in mucosal erosion and ulceration occur during the active phase of the disease. Thus, a main characteristic symptom is blood in the stools caused by damage to the mucosa. In general, it is reported that many patients exhibit chronic onset, but a few patients exhibit, fever and bloody stools appear suddenly. In severe patients and patients in whom lesions affect a wide area, systemic symptoms such as fever, anemia, tachycardia, general malaise, poor appetite, and weight loss are observed. The disease can cause developmental delay in pediatric patients. UC is characterized by diffuse, continuous inflammation from the rectum to the proximal colon. Treatment is selected according to the extent (type) and degree (severity) of inflammation.

1. Epidemiology

In Japan, the number of patients with ulcerative colitis has been gradually increasing since the 1960s, and currently, the number is in excess of 180,000 (Figure 1). As previously mentioned, the reasons for this are thought to be environmental factors such as a shift from a high-fiber, rice-based diet to a diet with higher amounts of fat in the form of meat, dairy products, and other fatty foods, which is typical of a westernized lifestyle are thought to the main contributing factors. In addition, nowadays, a greater number of physicians and patients are aware of IBD, which increases the likelihood of detecting the disease early.

(1) Incidence and prevalence

According to a survey conducted in 2014, the incidence was 12.2 per 100,000 people and the prevalence was 133.2 per 100,000 people. Although similar increases in the number of patients have been observed in other Asian countries, the prevalence remains lower than that in Western countries.

(2) Gender differences and age at onset

Figure 2 shows the age and gender distribution of patients with UC. There is almost no difference between the onset in men and women. Additionally, it also shows that many patients experience initial onset in their 20s and 30s. However, in recent years, there has been an increase in the number of patients with UC who are in their 40s to 60s.

(3) Mortality rate

According to a demographic survey conducted in 2011, 129 people died due to UC (81 males and 15 females). Using these data, the age-adjusted mortality rate was 0.046 (males: 0.068 and females: 0.029). It has been reported that the mortality rate due to UC is not different from that in the
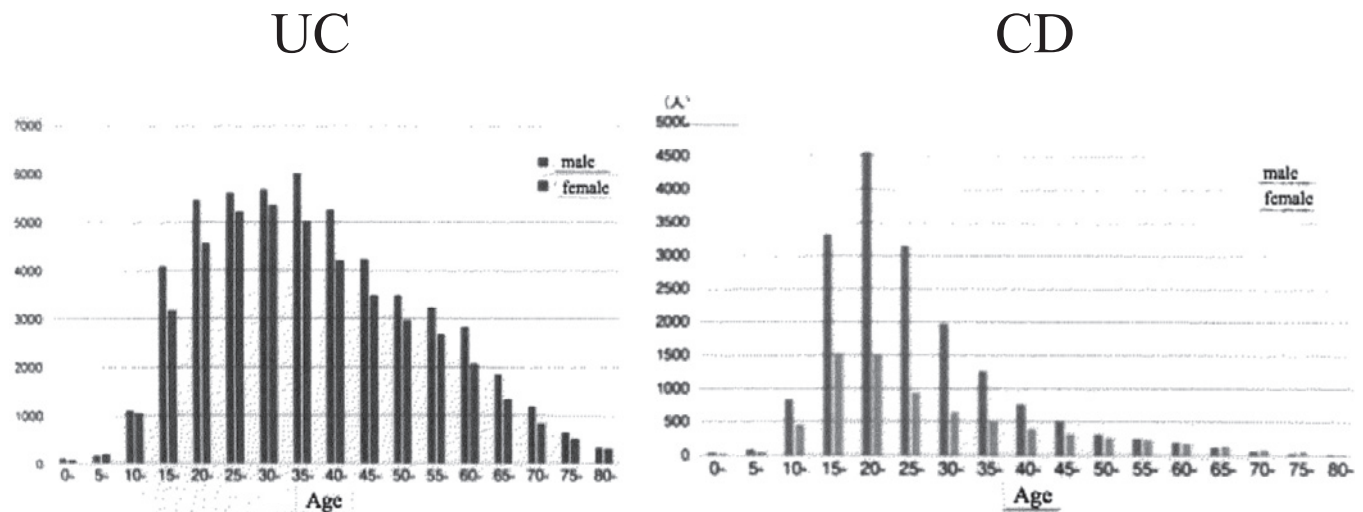
UC

CD

Figure 2. Age Distribution at Onset in UC and CD (2012) [44, 45]. The ratio of male to female in ulcerative colitis is 1:1, but that in Crohn's disease is 2:1.

Quoted and modified from the materials by Research Group on Intractable Inflammatory Bowel Disorders (Suzuki Group). [For ulcerative colitis. Basic knowledge necessary for treatment we want to know] [Internet]. Available from: http://www.ibdjapan.org/patient/pdf/01.pdf. Japanese [44] and Research Group on Intractable Inflammatory Bowel Disorders (Suzuki Group). [For Crohn's disease. Basic knowledge necessary for treatment we want to know] [Internet]. Available from: http://www.ibdjapan.org/patient/pdf/02.pdf. Japanese [45]

general population[15].

(4) Carcinogenicity

Cancer is a serious complication associated with long-term UC. In Japan, the frequency of colon cancer in patients with UC is 2.6% (123 in 4,756); onset rate is under 2% up to 10 years following onset, approximately 5% after 10 years following onset, and over 10% after 21 years following onset, which are the same rates as seen in Western countries[16]. Risk factors for carcinogenicity include a long-term course of at least 10 years, pancolitis, chronic continuous UC, and early onset.

(5) Environmental factors

UC is thought to occur as a result of environmental factors interacting with a hereditary predisposition. One of the main environmental factors is smoking, which is thought to lower the risk of onset and severity of the disease[17]. Appendectomy is also reported to be protective[18]. In addition, the Research Group has suggested that the excessive intake of sugar and processed meats, and the use of oral contraceptives are risk factors. However, their mechanisms of action remain unknown, and there is no consensus regarding the influence of each of these protective or risk factors.

2. Diagnosis

In patients showing diarrhea, mucus and blood in stools and other symptoms suggestive of UC, it is necessary to take a detailed history of the patient and perform microbial

bacteriological examinations, *Mycobacterium tuberculosis* tests (Gaffky scale, culture, or PCR), and an antiamebic antibody assessment to rule out infectious enteritis, intestinal tuberculosis, radiation enterocolitis, ischemic enteritis, drug-induced enterocolitis, and other diseases that may cause diarrhea and/or bloody stools. Next, ileocolonoscopy should be performed to obtain characteristic endoscopic findings. Particular attention is required because patients with infectious enteritis often exhibit the similar initial symptoms and endoscopic findings as those with UC. In such cases, a histopathological examination of the large intestinal mucosa is helpful for diagnosis. When necessary, a barium enema may be used to determine characteristic findings for this disease and make a diagnosis.

(1) Lower gastrointestinal endoscopy (Ileo-colonoscopy)

Characteristic findings are diffuse and continuous inflammation occurring in the mucosa from the rectum to the proximal colon. Inflammation may cause loss the vessel patterns of the mucosa, edema, mucopurulent discharge, and friability (contact bleeding). As the inflammation becomes increasingly severe, the mucosa is damaged by erosion and ulceration, and the remaining mucosa develops pseudo-polyps and exhibits an irregular mucosal surface. Endoscopy is very useful to make a diagnosis as it can identify symptoms. However, attention is required as the invasive nature of endoscopy may exacerbate symptoms and inflammation. In patients with moderate-to-severe UC, an endoscopic examination of the rectum or sigmoid colon is enough to de-

Table 1. Clinical Guidelines for the Management of Ulcerative Colitis (2016) [46].

Remission Induction therapy

	Mild	Moderate	Severe	Fulminant colitis
Extensive colitis and left-sided colitis	Oral formulations: 5-ASA Enemas: 5-ASA, Steroid ※If the inflammation is severe in moderate cases or there is no improvement by the above therapy, oral administration of prednisolone should be given. ※If there is no improvement, therapy for severe and steroid refractory colitis should be given. ※PENTASA suppositories are effective for rectal inflammation		Prednisolone intravenous infusion ※Combination therapy with the following medicines should be given according to symptoms: Oral formulations: 5-ASA Enemas: 5-ASA, Steroid ※If there is no improvement, therapy for steroid refractory colitis should be given. ※Depending on symptoms, surgery should be considered.	Emergency surgery should be considered. ※If possible, the following therapy may be applied under collaboration with surgeons: •High-dose steroid intravenous therapy •Cytaphresis •Oral tacrolimus •Cyclosporine continuous intravenous therapy* ※If there is no improvement with the above therapy, surgery is recommended.
Proctitis	Oral formulations: 5-ASA Suppositories: 5-ASA, Steroid Enemas: 5-ASA, Steroid ※Easy use of systemic steroid should be avoided.			

	Steroid dependent colitis		Steroid refractory colitis	
Intractable patients	Immunomodulators: azathioprine, 6-MP* ※If there is no improvement, Cytapheresis, Oral tacrolimus, Intravenous infliximab, or Subcutaneous adalimumab could be considered.		Moderate: Cytapheresis, Oral tacrolimus, Intravenous infliximab, Subcutaneous adalimumab Severe: Cytapheresis, Oral tacrolimus, Intravenous infliximab, Subcutaneous adalimumab, Cyclosporine continuous infusion therapy* ※Combination therapy with azathioprine/6-MP* could be considered. ※If there is no improvement, surgery should be considered.	

Remission maintenance therapy

Non-refractory	Refractory
5-ASA formulations (oral, enema, suppositories)	5-ASA formulations (oral, enema, suppositories) Immunomodulators (azathioprine, 6-MP), Intravenous infliximab, Subcutaneous adalimumab**

*: not covered by insurance, **: apply when induction of remission is achieved by infliximab

Quoted and modified from the materials by Research on Intractable Inflammatory Bowel Disorders (Suzuki Group). [Diagnostic criteria and treatment strategy for neoplastic colitis and Crohn's disease]. Japan: 2017. Japanese [46]

termine the presence of lesions and the therapeutic options. As toxic megacolon associated with acute fulminant colitis often exhibits complications such as perforation, endoscopy is contraindicated in such cases.

(2) Barium enema X-ray examination

Barium enema X-ray examination is less useful than endoscopy and it is rarely performed in real practice. In case of mild inflammation, the mucosa presents a fine granular appearance, and as the disease becomes increasingly active, the mucosa exhibits a rough appearance and exhibits erosions and ulcers of varying degrees of severity. In patients exhibiting chronic inflammation, the intestinal tract exhibits the loss of the haustra, exhibiting the characteristic "lead pipe" appearance.

(3) Histological examination

During the active phase of the disease, the mucosa exhibits diffuse inflammatory cell infiltration, crypt abscesses, and decrease or loss in the number of goblet cells; since these findings are not specific for UC, making a diagnosis is based on the clinical features and a comprehensive differentiation of other diseases. During the remission phase, irregular gland architecture and atrophy are often observed.

3. Treatment

3-1. Medical treatment

In many patients, the disease is chronic, with repeated cycles of remission and relapse. Thus, it is necessary to differentiate therapy into treatments for the active phase and those for the remission phase. During the active phase, the treatment designed to swiftly inhibit the inflammation (remission induction therapy) is performed, while during the remission phase, the treatment designed to maintains the state of remission and prevent relapse (remission maintenance therapy) is performed. The treatment guidelines released in 2011 by

the MHLW Research Group are shown in Table 1. Very recently, evidence-based clinical practice guidelines for inflammatory bowel disease in Japan are published[19].

Patients with severe and moderate UC in a generally poor condition require hospitalization for rest and systemic management. For the purpose of bowel rest, some patients are required to avoid oral diet intake. Unlike CD, aggressive central venous hyperalimentation is not therapeutically useful. Surgery is performed in cases of absolute indications, such as intestinal perforation or colorectal cancer, and in cases of relative indications, such as patients who are refractory to medical treatment. However, in recent years, novel treatment options have been developed that have made it possible to avoid surgery for more refractory patients.

(1) Remission induction therapy

The treatment strategy for the active phase of UC requires estimation of the patient's general condition as well as the extent and severity of inflammation via an endoscopic examination so that remission induction therapy can be performed in accordance with a patient's specific condition.

5-ASA is the basic drug used for patients with mild-to-moderate UC[20]. It is thought to have a direct anti-inflammatory action in the local areas of the intestinal mucosa. Therefore, higher concentrations in the mucosa are associated with its better efficacy, and as a result, suppositories and enema are used as the treatment which effectively reaches the inflamed areas. As it is a safe drug with few adverse effects, most patients utilize 5-ASA, except for patients who are allergic to 5-ASA. In Japan, salazosulfapyridine (SASP) and mesalazine are the forms of the drug covered by insurance. A novel form of mesalazine, Lialda, known as MMX-5ASA, was approved at the end of 2016, in addition to Pentasa and Asacol. MMX-5ASA has a novel drug delivery system that continuously releases effective components throughout the large intestine. 5-ASA suppositories and enema are particularly effective in patients with mild-to-moderate distal colitis (proctitis and proctosigmoiditis) and also contribute to the improvement of tenesmus and the frequency of bowel movements by controlling inflammation in the distal colon.

In patients with mild-to-moderate UC in which 5-ASA is insufficiently effective, oral corticosteroid can be added to the treatment regimen[21]. Oral prednisolone is used at a dose of approximately 30 − 40 mg/day, and when necessary, it can be administered intravenously. In patients in whom this additional corticosteroid therapy remains insufficiently effective, therapy for severe or steroid-refractory patients is started.

As an alternative therapy for patients who are refractory to corticosteroid, leukocytoaoheresis therapy is commonly applied in Japan.

In severe and fulminant cases of UC, patients should be hospitalized and placed on a regimen of either oral or intra-venous prednisolone (1 − 1.5 mg/kg/day; maximum dose of 80 mg/day). Its effect should be judged within 1 week from the start of steroid, and in patients judged unlikely to be effective, general care should be initiated with the possibility of switching to calcineurin inhibitors, anti-TNFα antibodies, and surgery. If ineffective, basic treatment consists of a gradual reduction of corticosteroid (avoiding rapid dosage reduction and sudden discontinuation). However, unnecessary long-term use of corticosteroid must be avoided due to the lack of its efficacy in the remission maintenance as well as the risk of the increased frequency of adverse effects.

In patients with severe or fulminant UC refractory to steroids, either calcineurin inhibitors or anti-TNFα antibodies are considered. In patients who are refractory to these treatments with a poor general condition, colectomy is the treatment of choice.

(2) Remission maintenance therapy

Remission maintenance therapy during the remission phase of UC is important to prevent relapse. The basic medication used for remission maintenance is 5-ASA, which has been confirmed by multiple studies to be effective[20], although adherence is extremely important. The combination of oral and topical (suppositories or enema) 5-ASA as well as monotherapy can be continued for long-term unless it develops any side effects. Topical therapy may involve either monotherapy or combined therapy, depending on the symptoms and disease extent. In general, the long-term administration of corticosteroid is not recommended for remission maintenance.

Immunomodulators such as 6-mercaptopurine (6-MP) or azathioprine (AZA) should be considered as maintenance therapy for patients who have difficulty in discontinuing steroids, those with adverse drug effects, and refractory patients who experience a repeated relapse. However, genetic background regarding the response to thiopurines is different in Asia. Thiopurines induce leukopenia and alopecia more often and rapidly than Caucasians. Why the incidence of thiopurine-induced leukopenia is higher in Asians than Europeans. Recently, Korean group clearly demonstrated that a common missense variant in NUD15 is highly related to susceptibility to thiopurine-induced leukopenia[22]. In patients with homogenous abnormal genes, leukopenia is induced within a few days after administration of 6MP or AZA. It suggests that the study of pharmacogenetics must become important before the introduction of new therapies from westerns.

(3) Refractory patients

Although corticosteroids are highly effective for UC, there are a certain proportion of patients who do not respond despite its appropriate use (steroid-resistant), and others with difficulty in discontinuing steroids because disease relapses upon dose reduction[21]. In such refractory patients, it is necessary to utilize different drugs for the induction and

maintenance of remission.

a. Steroid-resistant patients

Apheresis is recommended in patients who do not demonstrate fulminant flare-up. It removes some leukocytes (granulocytes, lymphocytes, and monocytes), and is used in patients with UC in whom an immunological abnormality is thought to be involved in the pathogenesis. A randomized, double-blind, sham-controlled study performed in the USA did not demonstrate clear efficacy as in primary, while it proved the safety[23]. There might be some differences in clinical phenotypes or mechanisms of colonic inflammation between Japanese UC patients /and Western ones. However, by post hoc subscale analysis with Riley Score, which reflect severe mucosal inflammation, significant effect of Adacolumn therapy was demonstrated in patients who had erosions or ulcers histologically in colonic mucosa, suggesting that patients with active inflammation may respond well to leukocytapheresis therapy. Recently, a large-scale, prospective, observational study of leukocytapheresis for 847 patients with UC, revealed that any concomitant medications, including infliximab and tacrolimus, did not increase the incidence of adverse events[24]. It suggests that leukocytapheresis is a safe and effective therapeutic option for active ulcerative colitis. This therapy has fewer serious adverse effects than corticosteroid and immunosuppressants and is effective for refractory patients. However, problems include the high medical cost and the fact that it has not been proved to be effective overseas. Recently, the single-arm, open-label, multicentre trial [ART] was conducted at 18 centers across the UK, France, and Germany for moderate-to-severe, steroid-dependent active ulcerative colitis with insufficient response or intolerance to immunosuppressants and/or biologics. In all, 86 patients, 33/84 [39.3%] of patients achieved clinical remission at week 12, with 47/84 [56.0%] achieving a clinical response. Clinical remission was achieved in 30.0% of patients with previous immunosuppressant and biologic failure. These results are consistent with previous studies in Japan[25].

In refractory patients who are extremely severe, calcineurin inhibitors or anti-TNFα antibodies are recommended. Calcineurin inhibitors used in Japan are tacrolimus and cyclosporine. Calcineurin inhibitors achieve their immunosuppressive, anti-inflammatory effects by inhibiting calcineurin within the nuclei of immune cells. Although it also has a relatively high remission induction rate[26], relapse after remission induction is common, and it has been linked to adverse drug effects such as infection, renal dysfunction, and neurological symptoms (tremors and numbness). As there is a narrow range between therapeutic and toxic blood levels, renal toxicity and other adverse drug effects are caused relatively frequent, requiring the regular monitoring of blood levels.

An antibody for the inflammatory cytokine TNFα was re-cently developed[27]. This extremely effective drug led to an increased number of refractory patients being treated as outpatients rather than being hospitalized undergoing surgery as used to be common in the past. In Japan, the anti-TNF-alpha antibodies available for use in patients with UC include infliximab (Remicade) and adalimumab (Humira). Infliximab is a chimeric antibody with mouse-derived amino acid sequences. It is intravenously administered three times (at 0 weeks, after 2 weeks, and after 6 weeks) for induction, flowed by the continuous maintenance administration every 8 weeks in patients who respond In contrast, adalimumab is a fully humanized antibody. As it is subcutaneously administered every 2 weeks, it can be self-administered in an out-of-clinic setting. Adverse drug effects include infusion reaction, infection, and liver dysfunction. Particular attention is required to prevent tuberculosis and viral infections (herpes zoster, herpes, and hepatitis B).

In addition, anti-a4b7 integrin antibody and JAK inhibitor is in the market last year. They are useful for steroid-refractory patients.

b. Steroid-dependent

In patients who have difficulty in discontinuing steroids, such as those who relapse upon dose reduction, the administration of the immunomodulators, AZA or 6-MP is recommended. These drugs are metabolized in the body to form 6-thioguanine nucleotides, which have an immunomodulatory effect. In addition to having increased remission induction effectiveness when used in combination with anti-TNFα antibody[28], they have also been reported to suppress the production of antibodies that neutralize anti-TNFα antibodies.

3-2. Surgery

(1) Surgical treatment

In patients with severe, acute complications such as intestinal perforation, toxic megacolon, or massive bleeding, surgery is an absolute indication. Surgery is also recommended in patients who are refractory to medical treatments and in patients who are diagnosed to have colorectal cancer (or dysplasia) by the regular surveillance colonoscopy. Currently, the standard surgical procedures are total colectomy with ileal anal-pouch-anastomosis that preserves the anus and sphincter. There are also patients in whom total (partial) colectomy, permanent ileostomy, and ileoproctostomy are selected. Depending on risk factors, such as the patient's general condition, medical treatment, and the presence of complications, surgery may be performed in a single-stage or divided into two or three stages.

Crohn's Disease

CD was first reported in 1932 as regional ileitis by Crohn and his colleagues at Mount Sinai Hospital in New York. They identified a subacute or chronic intestinal inflammation as regional ileitis that affected the terminal ileum, which

was previously thought to be intestinal tuberculosis. Subsequently, it was found that the disease induces lesions throughout the gastrointestinal tract from the mouth to the anus. Although the etiology remains unknown, it is known as a granulomatous inflammatory disease that might be related to immunologic and other abnormalities. Clinical characteristics include transmural lesions of the gastrointestinal wall, chronic inflammation accompanied by erosions and ulcers mainly in the small and/or large intestines, potentially causing intestinal stenosis and fistulae. In addition to diarrhea, abdominal pain and bloody stools are main gastrointestinal symptoms. It may induce systemic symptoms such as fever, weight loss, and malnutrition as well as anal lesions such as anal fistulae and anal abscesses. It may also involve developmental retardation when it occurs in children. The disease progression is characterized by repeat of relapse and remission. In many patients, multiple symptoms lead to resistance to treatment, and some patients experience negative effects on their ability to have normal daily lives due to hospitalization and frequent surgery. Diagnosis and treatment of CD require a detailed examination of the entire gastrointestinal tract using various imaging techniques.

1. Epidemiology

Since the 1970s, the number of patients with Crohn's disease in Japan has rapidly increased, and the current number of patients is in excess of 48,000 (Figure 1). Nonetheless, the etiology remains unknown, but it is thought to be related to the combination of abnormal immune response against the environmental factors and underlying genetic factors seen in UC.

(1) Incidence and prevalence

According to a survey conducted in 2014, the incidence of the disease was 2.0 per 100,000 people and the prevalence was 31.9 per 100,000 people in Japan. As seen in UC, the incidence and prevalence rates in Japan are lower compared with those in Western countries. While the rates in such Western countries have become plateaued, the rates in Japan are continuing to increase.

(2) Gender differences and age at onset

The age distribution of patients with CD is shown in Figure 2b. Although no gender-based differences are observed in Western countries, in Japan, the male-to-female ratio is 2:1 that are also observed in Asian countries including Korea and China. The most common age at initial onset is between late teens and early 20s; however, in recent years, there has been an increase in the number of patients whose initial onset occurred at 40s to 60s.

(3) Mortality rate

According to a survey conducted in 2011, the number of deaths attributed to CD was 43 (28 males and 15 females). Using this data, the age-adjusted mortality rate was calculated at 0.026 (males: 0.037 and females: 0.016). Unlike UC, the mortality rate in patients with CD is reportedly higher than that in the general population[15].

(4) Carcinogenicity

Cancer is a serious complication of CD, although the incidence of colorectal cancer in CD is much lower than in UC. According to a study conducted abroad, the relative risk of colorectal cancer in patients with CD is 2.5-fold for all patients with CD and 5.6-fold for those with CD localized in the large intestine[29]. Anorectal cancer as a complication of CD is commonly seen in young patients with long disease duration. It is also characterized by a high percentage of mucinous carcinomas[30]. Other reported complications include small intestinal cancer and anal fistula cancer.

(5) Hereditary predisposition

The relative degree of risk of onset in siblings is 15- to 35-times higher in patients with CD than in the general population. A study on twins reported that the rate of concordance in patients with CD was 50% for identical twins and 10% for fraternal twins, indicating that the rates are higher than those in UC[6]. It has been reported that various disease-related genes are involved, including the gene for nucleotide-binding oligomerization domain-containing protein[31]. However genetic background of Japanese population is quite different from Westerns, as discribed above. It is also believed that common environmental factors are involved.

(6) Environmental factors

An important environmental factor related to enhancing inflammation in CD is smoking. Smoking is reported as a risk factor for the onset and relapse of CD[32]. Although various factors may be related to the pathogenesis of CD, there is no clear consensus regarding other environmental factors similar to UC.

2. Diagnosis

Patients with CD commonly present symptoms such as chronic abdominal pain, diarrhea, and fever, but they present a variety of clinical symptoms. Repeated anal pain by anal fistula or perianal abscess in young patient is a symptom suspicious of CD. In Japan, diagnostic criteria are based on the macroscopic findings and microscopic identification of characteristic gastrointestinal lesions. In particular, the terminal ileum and the cecum are most commonly affected areas for gastrointestinal lesions[33]. As it is necessary to differentiate the disease from other inflammatory intestinal diseases such as infectious enteritis, UC, simple ulcer, and intestinal Behcet's disease, as well as intestinal tuberculosis, ischemic colitis, and ulcers caused by non-steroidal anti-inflammatory drugs, its diagnosis should be made via a bacteriological examination and tuberculosis testing to rule out infection in combination with an endoscopic examination.

(1) Endoscopic examination

a. Colonoscopy

Lesions associated with CD are mainly found in the small intestine particularly in the terminal ileum. Thus, ileocolonoscopy is the most important diagnostic examination for patients with CD. Typical findings are longitudinal ulcers and "cobblestone" appearances. Non-classical findings such as aphthous-like lesions and irregular ulcers are also observed occasionally. Other characteristic findings include anal fistula.

b. Balloon-assisted enteroscopy

In many patients with CD, lesions occur in the small intestine; therefore, they are often found at sites that cannot be observed by conventional colonoscopy. Balloon-assisted enteroscopy allows the direct observation of the mucosa of these small intestinal lesions that would otherwise be impossible with other modalities and also enables physicians to obtain biopsy samples of mucosal tissue. Other advantages of balloon-assisted enteroscopy include endoscopic hemostasis for bleeding ulcers and balloon dilatation for intestinal stenosis.

c. Small intestinal capsule endoscopy

Small intestinal capsule endoscopy has been reported to be effective in patients with CD[34]. An advantage of this examination is its non-invasiveness as a screening method of the small intestine. However, attention is required as there is a risk of capsule retention due to the stenosis in the small intestine, which is commonly associated in patients with CD.

(2) Small-bowel barium study

In patients with CD having lesions in the small intestine, small-bowel barium studies allow the observation of the distribution of lesions and provide plenty of information including stenosis and dilation of the small intestinal tract, fistula formation, and adhesions. In particular, the accessibility of fistulae can be more accurately judged with this method than with other modalities. However, this study is not popular in westerns because of radiation exposure and lack of experience in experts of IBD.

(3) Computed tomography/magnetic resonance imaging enteroclysis/enterography

Imaging using computed tomography or magnetic resonance imaging (MRI) with an oral contrast medium to dilate the gut lumen allows small intestinal lesions to be observed with a high diagnostic accuracy. In patients who require repeated examination of small intestine, MRI—which does not expose patients to radiation and non-invasive—is useful especially in young patients, among whom the disease is common. However, the usefulness of MRI is reduced in patients with small fistulae and when assessing the accessibility of fistulae[35]. Recently, the techniques of MR enterography have been well developed and allow us to observe the intestinal and extra-intestinal lesions easily.

(4) Histopathological examination

The characteristic histological findings in CD include the formation of non-caseating granulomas, fissuring ulcers, transmural inflammation, and obstructive lymphangitis. Among them, the most important diagnostic finding is non-caseating granulomas.

3. Treatment

3-1. Medical treatment

There is no fundamental treatment for patients with CD yet since its cause remains unknown. Therapeutic goals are to control disease activity and maintain the state of remission to avoid functional damage to the gastrointestinal tract and prevent loss of patients' quality of life (QOL). The treatment guidelines indicated by the MHLW Research Group in 2011 are shown in Table 2. Medical treatment mainly consists of a combination of nutritional, drug, and endoscopic therapies. Treatment must be determined based on the level of disease activity, complications, and the disease pattern (inflammatory, stenotic, or fistulating). Stenosis and fistulae have a significant negative impact on a patient's QOL, therefore management of these complications is important. The recent emergence of anti-TNFα antibodies has led to the possibility of changing the natural course of CD. Anti-TNFα antibodies not only rapidly induce clinical remission but also are effective in healing intestinal mucosal lesions. Thus, the timing of the use of these drugs is crucial.

In addition to anti-TNFα antibodies, the anti-IL12/23 antibody has become available in Japan and an anti-$\alpha_4\beta_7$ antibody is used in Japan as will as in western countries.

(1) Remission induction therapy

Because patients with CD present various symptoms during the active phase, it is important to use various imaging tests to ascertain the severity and pattern of the disease as well as complications to tailor treatment to the specific conditions and induce remission.

Patients with mild-to-moderate CD are treated using a regimen of 5-ASA and nutritional therapy. The types of 5-ASA approved in Japan are Pentasa, and Salazopyrin. As the drug delivery system of each form differs, they must be selected and administered in accordance with the distribution of inflammation. However, their efficacy is less for CD than for UC, and even questionable. In Japan, the main treatments for CD are drug therapy and nutritional therapy (Figure 3). In Western countries, nutritional therapy is not widely used for adult patients because its mechanism of action has not been elucidated and adherence is generally low. However, nutritional therapy can be highly effective for small intestinal lesions, and it is recommended particularly in those with pediatric CD.

In patients with CD who are difficult to be controlled with 5-ASA and/or nutritional therapy, oral steroid is considered. Oral steroids include prednisolone and budesonide. Oral budesonide is a glucocorticoid that is effective locally in the small intestine and proximal colon, recently approved

Table 2. Clinical Guidelines for the Management of Crohn's Disease (2016) [46].

Treatment in the active period
(Combined treatment with nutritional therapy and/or medication could be applied according to symptoms and patient's tolerance)

Mild to moderate	Moderate to severe	Severe (severely active or advanced complications)

Medication
  •Pentasa® sachet/tablet
  •Salazopyrin® tablet (colonic lesion)
Nutritional therapy (enteral nutritional therapy)
When patients tolerate, this therapy is applied.
  •Elemental diet (Elental®)
  •Digestable nutrients (Twinline®)
※Semi-digestion nutrition agent can be applied if low tolerance.
※If there is no improvement, therapy for moderate to severe Crohn's disease should be considered.
	Medication
	  •Oral steroids (prednoisolone)
	  •Antimicrobials (metronidazole, ciprofloxacin)
	※Intractable cases for steroid tapering/weaning: azthioprine, 6-MP
	※Non-responders to steroids and/or nutritional therapy: infliximab, adalimumab
	Nutritional therapy (enteral nutritional therapy)
	  •Elemental diet (Elental®)
	  •Digestable nutrients (Twinline®)
	※Semi-digestion nutrition agent can be applied if low tolerance.
	Cytapheresis
	  •Granulocytapheresis (Adacolumn®)
	※Apply to non-responders/intolerance with symptoms from colonic lesions to conventional therapy.
		After considering surgeries, the following medication should be given:
		Medication
		•Steroids (oral or intravenous)
		•infliximab, adalimumab (refractory to conventional therapy)
		Nutritional therapy
		•Total parenteral nutrition should be given under fasting
		※Switch to enteral nutrition therapy when improved
		※Infliximab and adalimumab can be administered patients without obstructions and abscesses.

Remission maintenance therapy	Anal lesion therapy	Stenosis therapy	Post-operative relapse prevention
Medication •5-ASA: Pentasa® sachet/tablet, Salazopyrin® tablet (colonic lesions) •azathioprine, 6-MP •Infliximab, Adalimumab (Remission achieved patients with these biologics) Home parenteral nutritional therapy •Elental®, Twinline® ※Semi-digestion nutrition agent can be applied if low tolerance. ※This therapy should be considered for patients with difficulty in nutrition management such as short-bowel syndrome patients.	Surgical treatment should be considered, first. Drainage and seton treatment Medical treatment: •Anal fistulas and perianal abscesses: metronidazole*, antimicrobials, antibiotics, infliximab •Anal fissures and perianal ulcers: same medication as intestinal lesions •Anal stenosis: transanal dilation	【Stenosis】 Surgical treatment should be considered, first. •Inflammation should be reduced with medication, then endoscopic balloon dilation can be applied after confirming healing or shrinking of ulcers. 【Fistula】 Surgical treatment should be considered, first. •Medication (external fistula): infliximab, adalimumab, azathioprine	Apply same treatment as remission maintenance therapy: Medication •5-ASA: Pentasa® sachet/tablet Salazopyrin® tablet (colonic lesions) •Azathioprine, 6-MP* Nutrition therapy •Enteral nutritional therapy ※Combination with medication can be applied.

*: not covered by insurance

Quoted and modified from the materials by Research on Intractable Inflammatory Bowel Disorders (Suzuki Group). [Diagnostic criteria and treatment strategy for neoplastic colitis and Crohn's disease]. Japan: 2017. Japanese [46]

in Japan. As it is quickly metabolized in the liver after absorption, adverse drug reactions are less than prednisolone. Although clinical remission is achieved in many patients through the use of steroids, there are many steroid-dependent patients who relapse during the reduction of the drug dose. Since it is not effective for remission maintenance, more recently, such patients are increasingly put on early introduction of anti-TNFα antibodies[36]. Anti-TNFα antibodies can achieve clinical remission; reports also point out an increasing number of patients in whom the drug has resulted in endoscopic mucosal healing.

In 2017, another kind of biologics, anti-Il12/23 antibody, has become available in Japan. These drugs could reduce issues related to steroid discontinuation, reduce the relapse rate, and enable to avoid surgery[5,37]. Furthermore, it has allowed many patients to be treated in an outpatient setting without being hospitalized.

(2) Remission maintenance therapy

During the remission phase of CD, it is important to administer maintenance therapy designed to prevent recur-
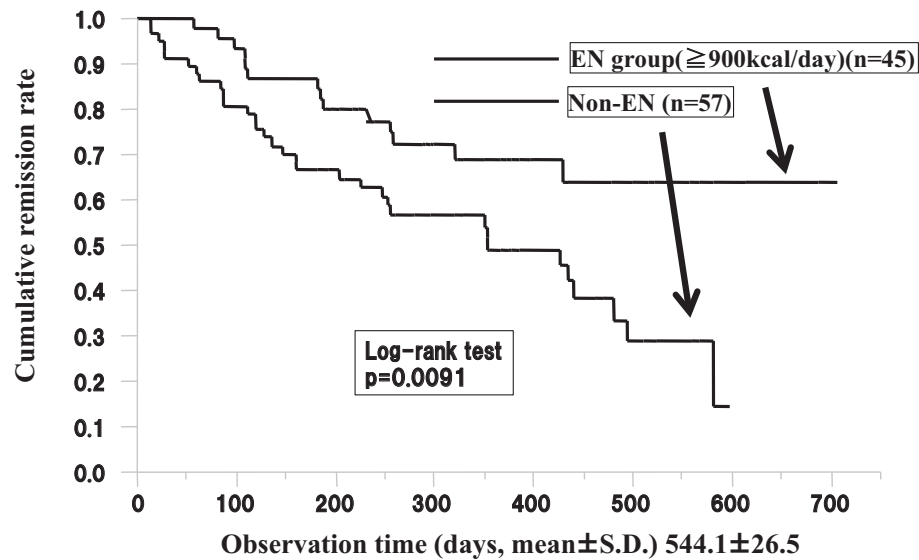
Figure 3. Effectiveness of concomitant enteral nutrition therapy and Infliximab for maintenance treatment of Crohn's disease in Adults [40].

Hirai et al. conducted a multicenter, retrospective, cohort study to determine whether enteral nutrition (EN) added to the IFX therapy regimen is effective for maintaining remission in adult CD patients. The cumulative remission rate was significantly higher in the EN group than in the non-EN group. The results demonstrated that EN combined with IFX was clinically useful for maintaining remission.

Quoted and modified from the materials by Hirai F, Ishihara H, Yada S, et al. Effectiveness of concomitant enteral nutrition therapy and Infliximab for maintenance treatment of Crohn's disease in adults. Dig Dis Sci. 2013 May; 58 (5): 1329-34 [40]

rence. The effectiveness of 5-ASA as remission maintenance therapy has not been demonstrated. There is also no evidence that steroids are effective for the maintenance and their adverse effects prevent their long-term usage. Nutritional therapy is effective in maintaining remission[38] and has also been reported to reduce the rate of repeat surgery when conducted as postoperative therapy[39]. In addition, concomitant partial enteral nutrition (more than 900 Cal) is effective for loss of response for anti-TNFα antibodies[40,41]. In patients in whom 5-ASA and nutritional therapy are insufficiently effective and in whom discontinuing steroids is difficult, the immunomodulators (6-MP or AZA) are used for the maintenance. When remission is induced using anti-TNF-alpha antibodies, it is used also for the maintenance of remission.

(3) Treatment of anal lesions

In patients who present anal lesions, it is important to control the activity of CD in addition to performing local treatment of the anus. The treatment of anal lesions includes the examination of the necessity of surgical treatment for perianal abscess and drainage by seton must be considered. Medical treatment includes the administration of immunomodulators and/or anti-TNFα antibodies after achieving the local control of anal fistulae and abscesses by antibacterial therapy (metronidazole or ciprofloxacin) or surgical drain-

age.

(4) Treatment of stenosis and fistulae

In patients complicated with stenosis and fistulae, the need for surgery should be first investigated. If stenosis is induced by active inflammation and not by fibrosis, medical treatments will be often effective. Endoscopic treatments for stenosis by fibrosis, include balloon dilatation for stenosis by ileocoloscopy or balloon-assisted endoscopy. Surgery is the first-line therapy for internal fistulae especially with infection, but depending on the clinical condition, anti-TNFα antibodies and immunomodulators may be administered. External fistulae such as skin or anal can be treated by these medications.

3-2. Surgical treatment

(1) Surgical therapy

Surgery is required in patients having various intestinal complications including intestinal perforation, massive bleeding, stenosis, fistulae, abscesses, and cancer. Among them, the most common indication for surgery is stenosis. Given that surgery cannot achieve a radical cure of CD, careful judgment has to be made when considering surgery. To reduce postoperative adhesion and in consideration of the patient's QOL, laparoscopic surgery is often performed. As CD has a high rate of relapse, minimizing the intestinal resection is required, and it is preferable to conduct minimal

resection or strictureplasty for stenosis.

Future treatment development

Recent advances in the medical therapies are remarkable and various new drugs are under clinical trials. In near future, these two disease will be controlled easily and excellent quality of life can be achieved by appropriate use of these medications.

Conflicts of Interest

Toshifumi Hibi received lecture fees from Mitsubishi-Tanabe Pharma, Kyorin Pharmaceutical, Abbvie GK, Janssen, Mochida Pharmaceutical, JIMRO, Takeda Pharmaceutical, Gilead Sciences, Kissei Pharmaceutical, Zeria Pharmaceutical, Ferring Pharmaceutical and Nippon Kayaku, advisory/consultancy fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical, EA Pharma, Janssen, Eli Lilly, Pfizer and Zeria Pharmaceutical and research grant from Abbvie GK, JIMRO and Zeria Pharmaceutical.

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