Vol.45, No.2 February 2002

JMAJ

Japan Medical Association Journal

CONTENTS

Pathology and Diagnosis of Inflammatory Bowel Disease (IBD)

JMAJ 45(2): 45–54, 2002

Takashi SHIMOYAMA

Director, Department of Gastroenterology, Hyogo College of Medicine

Abstract: Intractable inflammatory bowel diseases (IBD) include ulcerative colitis ("UC" hereinafter) and Crohn's disease ("CD"). The patients with IBD are on the increase each year in Japan. In 1973, the Ministry of Health & Welfare designated 2 non-specific inflammatory bowel diseases whose causes were unknown and against which no radical treatment existed as "intractable diseases", and organized a group to study the causes of and treatment against these diseases. This is a study group to investigate "intractable inflammatory bowel disorders", so-called "diseases specified by the Ministry of Health & Welfare". So long as the number of patients remained 50,000 or less, it was decided for the government to shoulder the medical expenses of the patients who cooperated in the study. However, the number of UC patients increased from 9,193 in 1984 to about 60,000 in 1999, indicating an increase of 6 times or more within the 15 years. On the other hand, the number of CD patients increased from 2,174 in 1984 to 17,000 in the year 1999, showing an increase of 8 times or more, that is an increase by 15% each year. A significant relation between the psychological stress (worries) and the onset of UC, and that between the increased ingestion of sugar, fast food such as hamburger, etc. and CD were indicated by a study of pre-onset conditions. Furthermore, the improved health environment decreased infection with parasite, etc. and caused changes in intestinal flora. As a result, the immune response in the host has also been changed to provide a favorable environment for the onset of these diseases.

Key words: IBD; UC; CD; Individual survey card of specified disease

Intractable inflammatory bowel diseases include ulcerative colitis ("UC" hereinafter) and Crohn's disease ("CD").

The Patients with Inflammatory Bowel Disease (IBD) Are on the Increase.

Twenty-eight years ago from now, in 1973, the Ministry of Health & Welfare designated 2

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 9, 2000, pages 153–160).
The Japanese text is a transcript of a lecture originally aired on October 9, 2000, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

non-specific inflammatory bowel diseases whose causes were unknown and against which no radical treatment existed as "intractable diseases", and organized a group to study the causes of and treatment for these diseases. It was a study group to investigate "intractable inflammatory bowel disorders", so-called "diseases specified by the Ministry of Health & Welfare". So long as the number of patients remain 50,000 or less, it was decided for the government to shoulder the medical expenses of the patients who cooperate in the study. It was I 1984 when the Ministry of Health and Welfare registered the recipients of the state medical expense nationwide. However, the number of UC patients that was 9,193 in 1984 went up to about 60,000 in 1999, indicating an increase by 6 times or more within the 15 years. On the other hand, the number of CD patients increased from 2,174 in 1984 to 17,000 in the year 1999, showing an increase by 8 times or more. The extent of increase in the latter is higher than that in the former. That is, the number of CD patients is showing a 15% increase each year. As the reasons for such sharp increase will be given in detail in another report, it is simply mentioned here that a significant relation between the psychological stress (worries) and the onset of UC, and that between the increased ingestion of sugar, fast food such as hamburger, etc. and CD were indicated by a study of pre-onset conditions. Furthermore, the improved health environment decreased parasite infection cases, etc. and thereby causing changes in the intestinal flora. As a result, the immune response in the host has also been changed to provide a favorable environment for the onset of these diseases.

From the next year onward, the patients with intractable diseases including UC and CD will be electronically registered in each prefecture in the forms shown in Tables 1 and 2.

Definition, Concept

1. UC

UC is a diffuse non-specific inflammation of large intestine that mainly invades the mucosa and submucosa, frequently forming erosion or ulcer there. According to CI-MOS of WHO (1973), "Though UC frequently occurs in adults aged under 30 years old, the onset of this disease is also noted in children and those aged older than 50. The cause is unknown but the involvement of immunopathological mechanism and psychological factors is conceivable. In general, bloody stools and diarrhea occur, demonstrating various degree of systemic symptoms. When the disease invades all of large intestine for a long term, a tendency of canceration may be observed." As the complications, there are necrotic pyoderma, nodular erythema, sclerotic cholangitis, arthritis, iritis, etc.

2. CD

The study group investigating the "intractable inflammatory bowel disorders" as the diseases specified by the Ministry of Health & Welfare, partially revised the concept established by WHO and re-defined the disease as "transmular inflammatory colitis of unknown cause in young people in their teens to 20's. The symptoms include edema and ulcer as well as granular inflammation accompanied with fibrosis that mainly occur in the ileum and large intestine.

The lesion may be found in any site of digestive tract from oral cavity through stomach, duodenum, small intestine, large intestine to anus. The disease is characterized by inconsecutive longitudinal ulcer and sporadic appearance of cobble stone. The sclerosis of intestinal wall appears in asymmetrical form. Though major symptoms are abdominal pain, diarrhea and nutritive disorder, there are also fever and anemia. Systemic complications including arthritis, iritis and hepatic disorder also occur in this disease.

Clinical Symptoms

1. UC

The major symptom is bloody stools. It is said that UC is always accompanied with bloody stools but, in rare cases, patients are not aware of bloody stools because the quantity is negligible. However, the more extensive and the severer the lesion, the more bleeding generally occurs. Sometimes mucous and purulent fluid is excreted.

Diarrhea also becomes more frequent and more watery when the lesion becomes more extensive. However, constipation occurs in the initial stage of cure in the case of proctitis whose lesion is limited. Without evacuation and gas excretion, toxic megacolon results in paralytic ileus.

Abdominal pain spreads all over the abdomen in some cases but patients often complain of strong pain like the gripes in the lower left abdomen before evacuation. Fever, tachycardia, anemia and leukocytosis are the signs observed in severe cases and fulminant cases.

2. CD

Unlike UC, fever accompanied with body weight decrease occurs in addition to diarrhea and abdominal pain in CD patients.

The abdominal pain often extends all over the abdomen but gripping pain is caused if there is a stenosis.

Due to frequent diarrhea and resultant poor digestion and absorption, malnutrition is observed in the patient. Diarrhea that occurs 6 times or more a day suggests extensive lesion in the small intestine.

Fever is caused by inflammation and complicated abscess. The fever of 38°C or higher indicates severe condition.

Digestive tract bleeding and hematochezia are observed less in comparison with UC. The presence of extensive lesion or deep ulcer in the large intestine results in severe bloody stools and bloody diarrhea, causing anemia.

Sometimes tumor is tactile in the abdomen. Stenosis, fistula or abscess are often found there. In such case, tenderness is observed.

As described hereinafter, the body weight decrease and malnutrition are used as indices of severity in CD. The digestion and absorption are disturbed by the presence of an extensive lesion in the small intestine, resulting in malnutrition.

The symptoms characteristic to CD are fistula formation, and anal fistula and anal lesion. Fistula occurs between the intestines, between the intestine and bladder or vagina. Sometimes anal fistula triggers CD. The anal fistula of CD is characteristically complicated and intractable.

Pathology

1. UC

As the lesion generally becomes diffuse starting from the rectum, the pathology is classified by the spread of lesion.

1) **Spread of lesion:** Pancolitis, left sided colitis, proctitis, right sided or segmental colitis

2) **Disease stage:** Classified into active stage and remission stage. Remission refers to the disappearance of hemorrhagic tendency, erosion and ulcer in the mucosa, and improvement to a condition in which vessels are fluoroscopically observed at least in some mucosa.

3) **Endoscopic findings of active stage:** The active stage is classified into mild, moderate, and severe. Extensive ulcer formation and marked spontaneous bleeding are noted in the severe stage while the rubor and small yellow dots in the mucosa characterize the mild stage in which vessels are not detectable by fluoroscopy and the mucosa become microgranular. Other inflammatory findings indicate moderate stage. The details are described in the "Draft for revision of diagnostic criteria", pp. 96–98 released by the study group investigating the "intractable inflammatory bowel disorders", that is, the diseases specified by the Ministry of Health & Welfare.

4) **Clinical course:** The clinical course is classified into the initial onset type, acute fulminant type, recurrent remissive type, and chronically

Table 1 Individual Survey Card of Specified Disease (new/update)

Form No. 2 (12)

Name of patient		Male [1] / Female [2]	Date of birth	/ /	
Address	〒				
Occupation at the time of onset	Office worker [1] Civil servant [2] Student [3] No occupation [4] Other [5] ( )	Patient No. at the institution			
Diagnosis	Ulcerative colitis				
Estimated onset time	____ year ____ month ____ day	Date of first examination	____ year ____ month ____ day		
Treatment receiving status	Hospitalization [1] (beginning at ____ year ____ month ____ day) Regular visit to outpatient clinic [2] Irregular visit to outpatient clinic [3] No visit [4]				
Prior clinic	None [1] Yes [2] (name of medical institution / name of attending physician / Tel)	Tel:			

Pathology (for updating, indicate the current status only)	
Clinical course	Initial attack [1] Relapse, remission [2] Chronic, persistent (initial time [3], relapse [4]) Acute, fulminant [5] Unknown [6]
Frequency of hospitalization	Total ____ times (____ times at the present institution, ____ times at other institution)
Intractable or not	No [1] Yes (6 months of active stage [2] Relapse of 2 times/year [3])
Disease stage, severity (for updating, indicate the current status only)	
Severity at the time of first onset (at the first examination)	Mild [1] Moderate [2] Severe [3] Fulminant [4] Unknown [5]
Severity at the worst time ____ year ____ month ____ day	Mild [1] Moderate [2] Severe [3] Fulminant [4] Unknown [5]
Current severity ____ year ____ month ____ day	Mild [1] Moderate [2] Severe [3] Fulminant [4] Unknown [5] Remission [6]
Spread of lesion	
Site of lesion at the time of first onset (at the first examination)	Rectum [1] Colon (sigmoid [2], descending [3], transverse [4], ascending [5]) Cecum [6] Ileum [7] Unknown [8]
Site of maximum lesion ____ year ____ month ____ day	Rectum [1] Colon (sigmoid [2], descending [3], transverse [4], ascending [5]) Cecum [6] Ileum [7] Unknown [8]
Site of current lesion ____ year ____ month ____ day	Rectum [1] Colon (sigmoid [2], descending [3], transverse [4], ascending [5]) Cecum [6] Ileum [7] Unknown [8]
Intestinal complication	No [1] Yes [2] ( )
Extraintestinal complication	No [1] Yes [2] ( )
Family history of ulcerative colitis	No [1] Yes [2]
Family history of Crohn's disease	No [1] Yes [2]

Internal treatment							
At the severest time	Steroid	No [1] Yes [2]	IVH	No [1] Yes [2]	Other		
At present	Steroid	No [1] Yes [2]	IVH	No [1] Yes [2]	Other		
	5-ASA	No [1] Yes [2]	Immunosuppressant	No [1] Yes [2]			
Adverse reaction of drug		No [1] Yes [2] (symptom or finding:)					

Surgical treatment	
Reason for operation	Bleeding [1] Megacolon [2] Cancer [3] Perforation [4] Intractable [5] Extraintestinal complication [6] ( ) Other [7] ( )
Date of operation	1. ____ year ____ month ____ day 2. ____ year ____ month ____ day
Surgical technique	1. 2.
Post-operative complication	No [1] Yes [2] ( )

Table 1 Individual Survey Card of Specified Disease (new/update) *(Continued)*

Clinical symptoms and findings

Item	Recent findings	Findings obtained at the severest time	Item	Recent findings	Findings obtained at the severest time
Height	cm	cm	Body weight	kg	kg
1. Main symptoms	____ year ____ months ____ day	____ year ____ months ____ day	3. Barium enema	____ year ____ month ____ day	____ year ____ month ____ day
(1) Frequency of evacuation	time/day	time/day	Conduct of test	No[1] Yes[2]	No[1] Yes[2]
(2) Description of stools			(1) Continuous lesion	No[1] Yes[2]	No[1] Yes[2]
Bleeding	Severe[1], Moderate[2], Mild[3], None[4]	Severe[1], Moderate[2], Mild[3], None[4]	(2) Disappearance of houstra	No[1] Yes[2]	No[1] Yes[2]
			(3) Coarse surface of mucosa	No[1] Yes[2]	No[1] Yes[2]
			(4) Erosion, ulcer	No[1] Yes[2]	No[1] Yes[2]
Description	Watery[1], Muddy[2]	Watery[1], Muddy[2]	(5) Pseudopolyposis	No[1] Yes[2]	No[1] Yes[2]
(3) Abdominal pain (Spontaneous pain)	No[1] Yes[2]	No[1] Yes[2]	4. Endoscopy	____ year ____ month ____ day	____ year ____ month ____ day
(Site)	( )	( )	Conduct of test	No[1] Yes[2]	No[1] Yes[2]
(4) Body temperature	℃	℃	(1) Vascular fluoroscopy	No[1] Yes[2]	No[1] Yes[2]
(5) Pulse rate	/min	/min	(2) Hemarrhagic tendency	No[1] Yes[2]	No[1] Yes[2]
2. Blood test	____ year ____ months ____ day	____ year ____ months ____ day	(3) Microgranular mucosa	No[1] Yes[2]	No[1] Yes[2]
			(4) Erosion, ulder	No[1] Yes[2]	No[1] Yes[2]
			(5) Pseudopolyposis	No[1] Yes[2]	No[1] Yes[2]
			(6) Inconsecutive lesion	No[1] Yes[2]	No[1] Yes[2]
Conduct of test	No[1] Yes[2]	No[1] Yes[2]	5. Pathological findings of biopsy	____ year ____ month ____ day	____ year ____ month ____ day
(1) RBC	/mm^3	/mm^3			
(2) Hb	g/d*l*	g/d*l*	Conduct of test	No[1] Yes[2]	No[1] Yes[2]
(3) WBC	/mm^3	/mm^3	(1) Neutrophil infiltration	No[1] Yes[2]	No[1] Yes[2]
(4) Erythrocyte sedimentation (1 hour)	mm	mm	(2) Crypt abscess	No[1] Yes[2]	No[1] Yes[2]
(5) CRP	mg/d*l*	mg/d*l*	(3) Decreased goblet cells	No[1] Yes[2]	No[1] Yes[2]
(6) Total protein	g/d*l*	g/d*l*	(4) Abnormal glandular alignment	No[1] Yes[2]	No[1] Yes[2]
(7) Albumin	g/d*l*	g/d*l*	(5) Dysplasia	No[1] Yes[2]	No[1] Yes[2]
(8) α_2-globulin	%	%			
(9) γ-globulin	%	%			

Detection of pathogenic microorganism in stools (____ year ____ month ____ day)

No[1] Yes[2] (name of microorganism)

Other (comment of attending physician on the severity certification)

I have diagnosed the patient as in the above.

Date: ____ year ____ month ____ day

Address of medical institution

Name:

Tel:

Name of physician (seal)

Table 2 Individual Survey Card of Specified Disease (new/update)

Form No. 2 (17)

Name of patient		Male [1] / Female [2]	Date of birth	/ /	
Address	〒				
Occupation at the time of onset	Office worker [1] Civil servant [2] Student [3] No occupation [4] Other [5] ( )		Patient No. at the institution		
Diagnosis	Crohn's disease				
Estimated onset time	____ year ____ month ____ day		Date of first examination	____ year ____ month ____ day	
Treatment receiving status	Hospitalization [1] (_____ times) Regular visit to outpatient clinic [2] Irregular visit to outpatient clinic [3] No visit [4]				
Prior clinic	None [1] Yes [2] (name of medical institution / name of attending physician / Tel)			Tel:	

Pathology (for updating, indicate the current status only)	
Site of lesion at the time of first onset (first examination)	Esophagus [1] Stomach [2] Duodenum [3] Jejunum [4] Ileum [5] Cecum [6] Colon [7] Rectum [8] Anus [9] Other [10] ( ) Unknown [11]
Site of maximum lesion ____ year ____ month ____ day	Esophagus [1] Stomach [2] Duodenum [3] Jejunum [4] Ileum [5] Cecum [6] Colon [7] Rectum [8] Anus [9] Other [10] ( ) Unknown [11]
Site of current lesion ____ year ____ month ____ day	Esophagus [1] Stomach [2] Duodenum [3] Jejunum [4] Ileum [5] Cecum [6] Colon [7] Rectum [8] Anus [9] Other [10] ( ) Unknown [11] None [12]
Severity at the time of first onset (at the first examination)	IOIBD scores: _____ points Refer to Note
Severity at the worst time ____ year ____ month ____ day	IOIBD scores: _____ points
Current severity ____ year ____ month ____ day	IOIBD scores: _____ points
Intestinal complication	No [1] Yes [2] ( )
Extraintestinal complication	No [1] Yes [2] ( )
Family history of ulcerative colitis	No [1] Yes [2]
Family history of Crohn's disease	No [1] Yes [2]
Hyperalimentation method	
At the severest time (kcal/day)	IVH [1] HPN [2] Enteral [3] HEN [4] Other [5]
At present (kcal/day)	IVH [1] HPN [2] Enteral [3] HEN [4] Other [5]

Drug therapy					
At the severest time (kcal/day)	Steroid	No [1] Yes [2]	5-ASA preparation	No [1] Yes [2]	
	Immunosuppressant	No [1] Yes [2]	Other	No [1] Yes [2] ( )	
At present	Steroid	No [1] Yes [2]	5-ASA preparation	No [1] Yes [2]	
	Immunosuppressant	No [1] Yes [2]	Other	No [1] Yes [2] ( )	
Adverse reaction of drug		No [1] Yes [2] (symptom or finding:)			

Surgical treatment (description from the recent operation)	
Reason for operation	Intestinal stenosis [1] Fistula [2] Anal lesion [3] Perforation [4] Extraintestinal complication [5] ( ) Other [6] ( )
Date of operation	1. ___ year ___ month ___ day 2. ___ year ___ month ___ day 3. ___ year ___ month ___ day
Surgical technique	1. 2. 3.
Post-operative complication	No [1] Yes [2] ( )

Table 2 Individual Survey Card of Specified Disease (new/update) *(Continued)*

Clinical symptoms and findings

Item	Recent findings	Findings obtained at the severest time	Item	Recent findings	Findings obtained at the severest time
Height	cm	cm	Body weight	kg	kg
1. Main symptoms	____ year ____ month ____ day	____ year ____ month ____ day	3. Barium enema	____ year ____ month ____ day	____ year ____ month ____ day
(1) Abdominal pain	No[1] Yes[2]	No[1] Yes[2]		Esophagus[1] Stomach[2] Small intestine[3] Large intestine[4]	Esophagus[1] Stomach[2] Small intestine[3] Large intestine[4]
(2) 6 times/day of diarrhea or mucous & bloody stools	No[1] Yes[2]	No[1] Yes[2]	Conduct of test	No[1] Yes[2]	No[1] Yes[2]
(3) Anal lesion	No[1] Yes[2]	No[1] Yes[2]	(1) Inconsecutive lesion	No[1] Yes[2]	No[1] Yes[2]
(4) Fistula	No[1] Yes[2]	No[1] Yes[2]	(2) Cobblestone appearance	No[1] Yes[2]	No[1] Yes[2]
(5) Other complication (content of complication)	No[1] Yes[2] ( )	No[1] Yes[2] ( )	(3) Longitudinal ulcer	No[1] Yes[2]	No[1] Yes[2]
(6) Abdominal tumor	No[1] Yes[2]	No[1] Yes[2]	(4) Aphtha, small ulcer	No[1] Yes[2]	No[1] Yes[2]
(7) Decreased body weight	No[1] Yes[2]	No[1] Yes[2]	(5) Stenosis, narrowing	No[1] Yes[2]	No[1] Yes[2]
(8) 38°C or higher fever	No[1] Yes[2]	No[1] Yes[2]	(6) Fissure	No[1] Yes[2]	No[1] Yes[2]
(9) Abdominal tenderness	No[1] Yes[2]	No[1] Yes[2]	(7) Fistula	No[1] Yes[2]	No[1] Yes[2]
2. Blood test	____ year ____ months ____ day	____ year ____ months ____ day	4. Endoscopy findings	____ year ____ month ____ day	____ year ____ month ____ day
				Esophagus[1] Stomach[2] Small intestine[3] Large intestine[4]	Esophagus[1] Stomach[2] Small intestine[3] Large intestine[4]
Conduct of test	No[1] Yes[2]	No[1] Yes[2]	Conduct of test	No[1] Yes[2]	No[1] Yes[2]
(1) Hb	g/dl	g/dl	(1) Inconsecutive lesion	No[1] Yes[2]	No[1] Yes[2]
(2) RBC	/mm^3	/mm^3	(2) Cobblestone appearance	No[1] Yes[2]	No[1] Yes[2]
(3) WBC	/mm^3	/mm^3	(3) Longitudinal ulcer	No[1] Yes[2]	No[1] Yes[2]
(4) Platelet	10^4/mm^3	10^4/mm^3	(4) Aphtha, small ulcer	No[1] Yes[2]	No[1] Yes[2]
(5) Erythrocyte sedimentation (1 hour)	mm	mm	(5) Stenosis, narrowing	No[1] Yes[2]	No[1] Yes[2]
(6) CRP	mg/dl	mg/dl	(6) Fissure	No[1] Yes[2]	No[1] Yes[2]
(7) Total protein	g/dl	g/dl	(7) Fistula	No[1] Yes[2]	No[1] Yes[2]
(8) Albumin	g/dl	g/dl	5. Istopathological findings	____ year ____ month ____ day	____ year ____ month ____ day
(9) Cholesterol	mg/dl	mg/dl	Conduct of test	No[1] Yes[2]	No[1] Yes[2]
			Non-caseous epithelioid granuloma (detected site)	No[1] Yes[2] ( )	No[1] Yes[2] ( )

Tuberculosis reaction:
Date: ____ year ____ month ____ day

$\frac{\times \quad \text{mm}}{\times \quad \text{mm}}$

Detection of pathogenic microorganism in stools (____ year ____ month ____ day)

No[1] Yes[2] (name of microorganism)

Other (comment of attending physician on the severity certification)

I have diagnosed the patient as in the above.
Date: ____ year ____ month ____ day

Address of medical institution
Name:
Tel:
Name of physician (seal)

(Note) IOIBD score: The major symptoms from (1) to (9) and Hb of 10 g/dl are calculated by giving 1 point to each item.

persistent type.

5) **Disease type classification by macroscopic finding of lesion:** The disease type is classified into pseudopolyposis type and atrophic colitis type.

6) **Clinical severity:** The severity is assessed by the 6 items including 1) evacuation frequency, 2) hematochezia, 3) fever, 4) tachycardia, 5) anemia, and 6) erythrocyte sedimentation rate as follows.

1) Evacuation frequency: Six times or more/a day — severe, 4 times or less/a day — mild
2) Hematochezia: Bloody diarrhea — severe, irregular bloody stools — mild
3) Fever: 37.5°C or higher — severe, no fever — mild
4) Tachycardia: Ninety or more beats/minute — severe, no tachycardia — mild
5) Anemia: Ten g/d*l* or less Hb — severe, no anemia — mild
6) Erythrocyte sedimentation rate: Thirty mmHg/h or higher — severe, normal rate — mild

When 1) and 2) are assessed as severe, either 3 or 4 is assessed severe, and 4 of the 6 items are assessed as severe, the case is diagnosed as severe. The condition between mild and severe is moderate.

2. CD

1) **Classified by the site of lesion**

Small intestine type: The lesion is in the small intestine. As the lesion mainly exists in the ileum, this type is also called "ileitis type".

Large intestine type: The lesion is limited to the large intestine.

Small & large intestine type: The lesion exists both in the small and large intestine. However, the lesion is mainly observed in the small intestine during the longer clinical course.

2) **Clinical severity of CD**

Crohn's Disease Activity Index (CDAI) is used in Europe and USA but assessment in Japan is often made according to the criteria of IOIBD (International Organization of Inflammatory Bowel Diseases) employed in Europe. The assessment is based on 10 items of 1) abdominal pain, 2) 6 times or more/day of evacuation, 3) anal lesion, 4. fistula, 5) complication, 6) abdominal tumor, 7. body weight decrease, 8) fever of 38°C or higher, 9) abdominal tenderness, and 10) 10 g/d*l* or less Hb. The presence of each of these items is expressed as a point and the total points are expressed as the IOIBD scores.

3) **Active stage and remission stage**

The criteria of remission are normalized erythrocyte sedimentation rate and CRP, disappearance of inflammatory finding, decrease in the above IOIBD scores to 1 point or less, and no subjective symptom.

The initial treatment of UC and CD is targeted at remission. Once remission is reached, attention is focused on the management and treatment to maintain the remission.

Diagnosis—Criteria and Procedure

When inflammatory bowel disease (IBD) is suspected from the symptom of patient, that is, when diarrhea, abdominal pain or fever is noted, it is necessary to first of all cross out the likelihood of infectious colitis. If severe bloody stools are observed, consider UC. If fistula, anal lesion, and fistula are observed, consider CD. Then cross out the possibility of infectious colitis such as bacterial or amebic dysentery, salmonella colitis, campyrobacter colitis, and intestinal tuberculosis. As the next step, it is also necessary to cross out the possibility of radiation-caused colitis, drug-caused colitis, ischemic colitis, intestinal type Bhecet's disease, intestinal lymphoid follicle proliferation. Then, the diagnosis of UC or CD is given by the following procedure depending on which is more strongly suspected.

1. Diagnostic procedure of UC

In addition to a) in the following, one of the items of b as well as c have to be satisfied for definite diagnosis of UC.

Table 3 Severity Certification Criteria (draft)

a) UC severity certification criteria (draft)
   1. Moderate and severe cases with 6 months or more of persisting active stage
   2. Cases of ileocystitis persisting for 6 months or more after radical resection of large intestine
   3. Fulminant cases
   4. Severe cases requiring operation (including severe cases with a likelihood of operation)

b) CD severity certification criteria (draft)
   1. Cases that suffer permanent small intestine function disorder due to the extensive CD lesion or extensive intestinal resection and that always require central intravenous hyperalimentation or enteral hyperalimentation of 1,200 kcal/day or more because nutritive maintenance is difficult despite the drug therapy
   2. Cases that have stoma, external fistula or intractable complex hemorrhoid and that always require central intravenous hyperalimentation or enteral hyperalimentation
   3. Cases that require intestinal operation due to intestinal complications (advanced stenosis, fistula/ulcer formation, perforation, mass bleeding, severe anal lesion, etc.) or extraintestinal complications (necrotic pyoderma, etc.)
   4. Cases that have growth disorder accompanied with secondary minor disorder

Note 1: "Nutritive maintenance is difficult" means the body weight decrease rate in the recent 3 months is 10% or more or serum albumin concentration of 3.2 g/d*l* or less despite the treatment with drugs.

Note 2: The duration for certification is limited to the year of operation.

a) **Clinical symptoms**

Presence of persistent or repeated mucous bloody stools or bloody diarrhea, or history thereof.

b) **Test findings**

(1) Endoscopy

1) Diffuse invasion of mucosa, vessels in the mucosa undetectable by fluoroscopy, coarse or microgranular mucosa. Fragile mucosa that becomes easily hemorrhagic (contact bleeding) and attachment of mucous, bloody and purulent secrete.

2) Multiple erosion and ulcer or pseudopolyposis.

(2) X-ray by barium enema

1) Coarse or microgranular changes in the surface of mucosa

2) Multiple erosion and ulcer

3) Pseudopolyposis

In addition, disappearance of houstra (lead pipe figure) as well as narrowing and curtailment of intestinal tract are observed.

c) **Histological examination by biopsy**

Diffuse inflammatory cell infiltration is noted in the whole mucosal layer in the active stage. Also observed are crypt abscess and advanced goblet cell depletion.

Abnormal alignment (undulation, bifurcation) and atrophy of glandular tube remain in the remission stage. These changes are generally observed continuously from the rectum to oral side.

2. Diagnostic procedure of CD

Please refer to the report made in 1997 by the study group investigating the "intractable inflammatory bowel disorders", the diseases specified by the Ministry of Health & Welfare.

The findings used for diagnostic criteria are as follows.

a) **Major findings**
(1) Longitudinal ulcer
(2) Cobblestone appearance
(3) Non-caseous epithelioid granuloma
b) **Auxiliary findings**
(1) Longitudinal irregular ulcer or aphtha
(2) Irregular ulcer or aphtha observed in both the superior and inferior digestive tract

A. For definite diagnosis, the following criteria have to be satisfied.
1. The cases that correspond to (1) or (2) of major findings (refer to Note 1 and 2).
2. The cases that correspond to (3) of major findings and any one of auxiliary findings.

B. Suspected cases should satisfy the following criteria
1. The cases that correspond to any one of auxiliary findings (refer to Note 3).
2. The cases that demonstrate only the major finding (3) (refer to Note 4).
3. The cases that correspond to (1) or (2) of major findings but that cannot be differentiated from ischemic colitis and ulcerative colitis.

Note 1: It is necessary to exclude the likelihood of ischemic colitis and ulcerative colitis if only (1) longitudinal ulcer is present.

Note 2: It is necessary to exclude the likelihood of ischemic colitis if only (2) cobblestone appearance is present.

Note 3: When the case is considered as a suspected case based on the auxiliary finding (2) alone, it is necessary that the finding should be persistent for 3 months.

Note 4: It is necessary to cross out the likelihood of inflammatory diseases including intestinal tuberculosis complicated with granuloma.

Lastly, for your reference, the certification criteria (draft) of severe cases established by the Ministry of Health & Welfare for the government to shoulder the whole medical expenses are summarized in Table 3 for UC and CD separately.

Surgical Treatment of Inflammatory Bowel Disease (IBD)

JMAJ 45(2): 55–62, 2002

Tetsuichiro MUTO

Vice-Director, Cancer Institute Hospital

Abstract: IBD, especially ulcerative colitis (UC) and Crohn's disease (CD), is on the increase at present and can be considered to be a common disease. Surgical treatment for UC used to involve either total proctocolectomy + ileostomy or subtotal proctocolectomy + ileorectal anastomosis. Pouch operation, in which the large bowel is completely resected and ileal pouch-anal anastomosis is performed, has recently become a safe and standardized method for treating UC. Surgery is increasingly indicated for patients with UC that is resistant to steroid therapy rather than for patients with acute disease. The increased risk of cancer and dysplasia associated in UC also presents a problem. Because of the increased risk of cancer in patients who have had IBD for at least 10 years, cancer surveillance colonoscopy must be performed once a year. The basic treatment for CD is dietary therapy, but if complications such as stenosis and fistula may occur, it is necessary to resect the affected bowel. Strictureplasty can be effective in the cases of stenosis.

Key words: Inflammatory bowel disease (IBD); Ulcerative colitis; Crohn's disease; Pouch operation; Strictureplasty

Introduction

IBD is the abbreviation for inflammatory bowel disease, which includes various conditions such as ulcerative colitis and Crohn's disease. Although other diseases tend to be overlooked when considering IBD, there are many inflammatory bowel diseases. These include infectious enteritis (e.g., amoebic dysentery and intestinal tuberculosis), ischemic enteritis that is common in the elderly, drug-induced hemorrhagic enteritis occurring after antibiotic therapy, pseudomembranous enterocolitis, radiation enteritis after radiotherapy, ulcers of unknown etiology, and the solitary rectal ulcer syndrome (recently called mucosal prolapse syndrome). Diverticulosis can lead to diverticulitis, which is also included in IBD.

Not only is the etiology of ulcerative colitis and Crohn's disease unclear, but treatment is also difficult. These diseases are considered to be representative types of IBD, so this article

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 2, 2001, pages 175–180).
The Japanese text is a transcript of a lecture originally aired on October 12, 2000, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Table 1 Surgical Indications in Patients with Ulcerative Colitis

A. Absolute indications
1) Acute progressive disease: Severe form resistant to intensive intravenous therapy and fulminant form not showing rapid improvement
2) Serious acute complications: Perforation and acute peritonitis, toxic megacolon, and massive bleeding
3) Colorectal cancer

Note: In terms of timing, emergency or urgent operations are indicated for 1) and 2). Emergency operations are performed when surgery must be done immediately, while urgent operations are performed as soon as possible when surgery is required under close monitoring.

B. Relative indications
1) Patients with refractory disease who require frequent, repeated admission and have marked deterioration of QOL (e.g., requiring hospitalization at least once in 10 months or at least twice in 20 months)

Note: Refer to the Diagnostic Criteria* for the definition of refractory disease.

2) Patients with serious side effects to steroid treatment

Note: Diabetes, femoral head necrosis, osteoporosis, steroid withdrawal syndrome, myopathy, nephropathy, neuropathy, deafness, cataracts, glaucoma, adrenal insufficiency, immune deficiency, thrombosis, etc.

3) Extracolonic complications: Patients with skin involvement (erythema nodosum, pyoderma gangrenosum, etc.) or children with growth retardation that are difficult to treat conservatively
4) Colonic complications: Patients with stenosis, fistulas, ulcers, severe inflammatory polyps, or dysplasia, especially plaque-like lesions and depressed lesions

* "Diagnostic criteria" of the Ministry of Health and Welfare Study Group on Designated Diseases, "Refractory Inflammatory Bowel Disease" (cited from Reference 1).

deals mainly with ulcerative colitis and Crohn's disease. In discussing cases where surgical treatment is necessary, other diseases will be also described.

Surgical Treatment of Ulcerative Colitis (UC)

The prevalence of UC has been increasing in recent years, and the current estimate is more than 80,000 patients registered in Japan. About 15% require surgery, but the mortality can be close to zero in specialist hospitals. In Japan, the overall mortality rate is 3% or less, and surgery is very safe. Comparatively few patients undergo surgery from 10 years after the onset of UC and most operations are carried out within 5 years. Therefore, if the patients can be well controlled with medication for 5 years after the onset, the need for surgery will be reduced.

Surgery is performed for two types of indications in patients with UC (Table 1). One is absolute indications requiring emergency surgery and the other is relative indications requiring elective surgery.[1)]

The indications for emergency surgery include massive bleeding, perforation, and toxic megacolon, as well as acute aggressive disease with rapid deterioration. When the response to medical treatment is poor in severe cases, operation should be considered. Medical treatment includes Truelove's intensive regimen, in which high doses of steroids are given for 5 days or 1 week. However, if no response such as a reduction of diarrhea or fever is obtained even with such a regimen, the patient needs emergency surgery. When symptoms do not improve with high-dose steroids (1.5 mg/kg), surgical treatment should be considered with a surgical team. In such cases, it is important not to miss the proper timing for operation by

performing unnecessary tests.

When UC is suspected, the first test should be a plain abdominal X-ray. If the lesions are extensive and dilation of the colon is confirmed, high-dose steroids therapy should be immediately started before toxic megacolon develops. If potent therapy is given at the stage of colonic dilation, toxic megacolon can be prevented. Because of the high operative mortality in patients with toxic megacolon, every effort should be made to prevent its onset.

The most recent trend is an increase of surgery for refractory UC. This includes chronic persistent disease that cannot be brought to remission, disease that recurs when steroids are reduced (often at about 15 to 20 mg/day), patients who cannot be weaned off steroids, and patients with early relapse following remission in whom the disease remains active for at least 6 months. Recent data indicate that early surgery tends to lead to a better final QOL, because it is now clear that refractory disease will require surgery at some point in the future. Other reasons for the increase of surgery are the progress made in operative methods and the improvement in safety.

Another indication for surgery is development of cancer or precancerous lesions, i.e., dysplasia (atypical epithelium). A further indication is growth retardation in childhood, and surgery should be considered before the appearance of side effects caused by long-term steroid therapy.

Surgical Procedures for UC (Fig. 1)

1. Total proctocolectomy + ileostomy

This classical operation for UC, consisting of total resection of the large bowel and creation of an ileal stoma, is rarely used recently because the burden of the ileostomy is too great.

2. Total colectomy + ileorectal anastomosis

Ileorectal anastomosis can be performed in patients with mild or no rectal inflammation. However, since the rectum remains, there is a risk of recurrent proctitis and also a risk of developing rectal cancer in the future. For these reasons, ileorectal anastomosis is not performed very often. However, in cases where an early return to social life is necessary, the procedure using mechanical anastomosis can be performed even under steroid therapy. Therefore, this surgical option should not be completely rejected. When the surgeon is not accustomed to perform ileoanal anastomosis, as described below, ileorectal anastomosis can be applyed instead.

3. Total colectomy + ileal pouch-anal anastomosis (pouch operation)

The newest operative method is called "pouch operation" where the large bowel is completely resected with creating ileal pouch, and ileal pouch-anal anastomosis is performed to preserve anal function. This is an ideal method for UC since all of the colorectal mucosa, the site of the disease, can be excised while preserving the anal function and it has now become the standard operative treatment.

There are two methods of ileal pouch-anal anastomosis: 1) the rectal mucosa is completely removed and hand-sawn anastomosis between pouch and anus is performed (ileoanal anastomosis), and 2) about 1 cm of rectal mucosa is left *in situ* and mechanical anastomosis is performed (ileoanal canal anastomosis). It has not yet been determined which method is superior, but ileoanal canal anastomosis using a autosuture device is a simpler technique and postoperative anal function seems to be better. When patients are under steroids, a two-stage operation is required. The first stage involves total colectomy and mucus fistula formation, which is followed by the second operation at the time when steroids are completely withdrawn and adrenal functions return normal (usually after about 6 months). At the second operation, pouch-anal anastomosis will be created.

Because both operations are complex, there is a high risk of complications when the surgeon lacks experience, so these procedures should

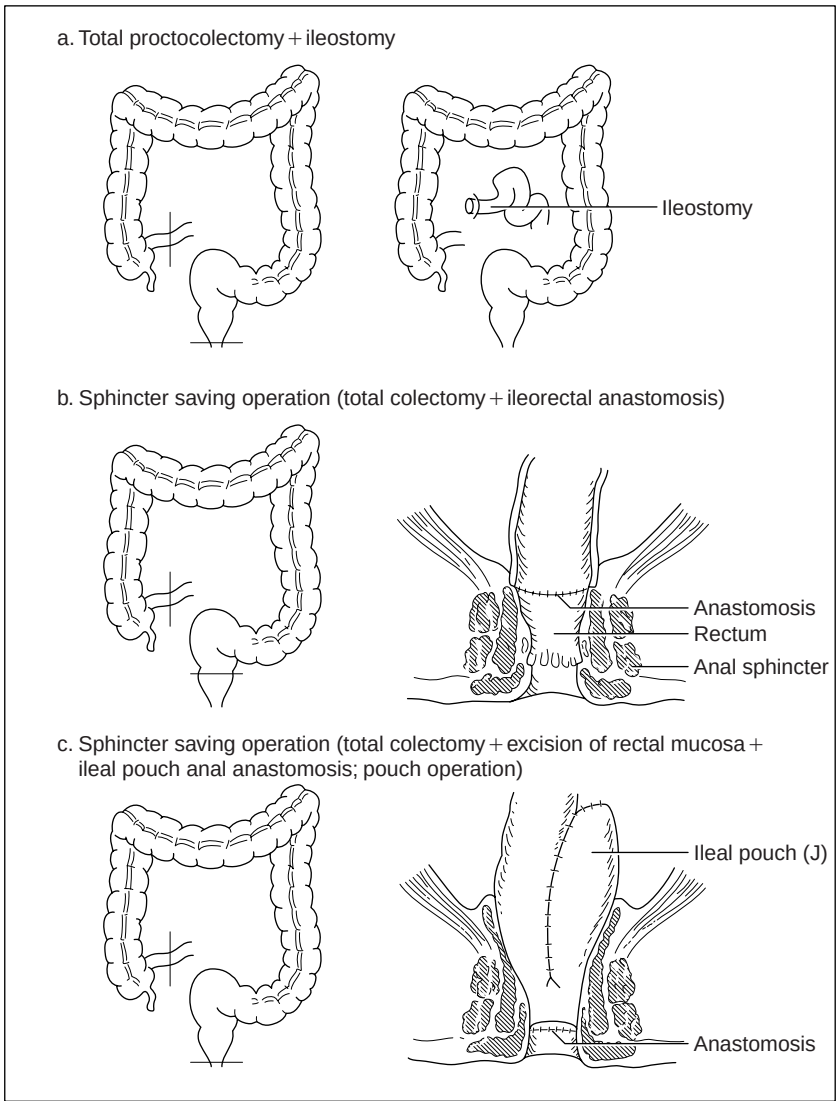

Fig. 1 Typical operative methods for ulcerative colitis
(Sugimachi Keizo: TEXT Surgery, Nanzando, 1998)

be performed in specialist hospitals. During resection of the rectum, there is a risk of damage to the pelvic autonomic nerves, so the operation should be performed by surgeons specialized in rectal cancer surgery capable of nerve preservation, which is essential particularly in young patients.

4. Surgery for dysplasia and cancer

The overall incidence of cancer in UC is about 3%, reaching 6% in total colitis, 1% in left-sided colitis (Table 2). Since this is Western data, the risk may be lower in Japan. It is known that the risk of cancer development increases with time in total colitis for at least 10 years. Therefore, these patients should undergo total colonoscopy once a year, with biopsies from any nodules if present. Dysplasia is more likely to be diagnosed if there is abnormal growth, dysplasia associated lesion or mass (DALM). Since dysplasia can also occur in the flat mucosa, it is recommended to also take biopsies at 10 cm

Table 2 Relationship between the Extent of Disease and Cancer in Ulcerative Colitis

Year	Investigator	No. with cancer	Total proctocolitis	No. with cancer	Left-sided colitis
1959	Dawson	13	264	3	399
1964	Edwards	17	236	5	388
1964	MacDougall	9	196	1	291
1966	de Dombal	7	210	0	218
1979	Greenstein	21	158	5	109
Total		67	1,064 (6.3%)	14	1,405 (1.0%)

(Dobbins WO III, *et al.*: 1984)

Table 3 Characteristics of Reported Cases of Ulcerative Colitis Developing Cancer in Japan*

No. of patients	227
Male/Female ratio	0.92
Age	40 ± 15 years
Total proctocolitis/Feft-sided proctocolitis	6.0
Duration	14 ± 8 yrs
Rectal and sigmoid colon carcinoma	72%
Poorly-differentiated mucinous carcinoma	42%
Multiple carcinoma	29%
Dysplasia association	82%

* Reported cases up to 1995 Cited from reference 1)

intervals from the flat mucosa regardless of the presence or absence of plaque-like lesions.

The distribution of colorectal cancer in UC patients is similar to that of ordinary colorectal cancer, but an increase of multiple cancer and signet-ring cancer is characteristic[2] (Table 3). The poor prognosis is caused by the characteristic pathology of this disease. Another characteristic is that atypical dysplastic epithelium, called dysplasia develops in 70 to 80% of patients with cancer. Dysplasia is considered to be a precancerous lesion. Once progressive cancer in UC is detected because of symptoms, it is most likely to be a far advanced disease and there is no way to cure the patients. So surveillance colonoscopy for dysplasia is important.

The presence of dysplasia means that the entire colonic mucosa has a high risk of developing cancer. This should not be treated as a localized lesion, but requires total resection of the large bowel as a preventive measure. Examination of the resected specimen may reveal the presence of invasive cancer away from the site of dysplasia. Histologic diagnosis of dysplasia is extremely difficult, so it is important to obtain second opinions of several pathologists specialized in gastroenterology. In the West, dysplasia is classified as high and low grade, but a classification employing four grades has been proposed in Japan (Table 4).

Differentiation between adenomas and dysplasia is important because adenomas can be treated by polypectomy, while dysplasia requires total resection of the large bowel. For

Table 4 Histopathological Classification of "Refractory Inflammatory Bowel Disease" by the Designated Disease Study Group of the Ministry of Health and Welfare

UC-I. Inflammatory changes
UC-II. Inflammatory neoplastic changes
UC-IIa. Suspicion of inflammatory changes
UC-IIb. Suspicion of neoplastic changes
UC-III. Neoplastic changes, but not cancerous
UC-IV. Cancer

Notes: 1) These criteria include the concept of "dysplasia" of Riddell *et al.*
2) Hyperplasia must be described when diagnosed as such.
3) Lesions impossible to differentiate from ordinary adenomas must be entered as such.

Table 5 Operative Indications for Crohn's Disease

	Small bowel type ($n=130$)	Small/Large bowel type ($n=225$)	Large bowel type ($n=127$)
Resistance to treatment	9%	7%	26%
Toxic megacolon	0	2	20
Fistulas/Ulcers	32	44	23
Obstruction	55	35	12
Perianal disease	5	12	19

(Farmer, R.G. *et al.*: Gastroenterology 1976; 71: 245)

differential diagnosis, it is important to obtain the opinions of several specialists, but p53 staining is also useful to distinguish these conditions. Many adenomas are negative for p53 staining, while dysplasia is often positive even when the lesion is small, so this test can be useful in some doubtful cases.

Although the postoperative frequency of defecation varies, almost all patients can lead a normal life and dietary restrictions are not required. With the advent of ileoanal (canal) anastomosis, the results of surgery have improved markedly. The indications for surgery in refractory disease have expanded as a result and surgical treatment tends to be performed earlier than before, freeing many patients from long-term steroid therapy.

Surgical Treatment of Crohn's Disease (CD)

CD has completely different operative indications as compared to those for UC. Unlike UC, CD cannot be cured by surgery alone because the pathogenesis is different from that of UC. CD is caused by abnormal responses of the body to some substances ingested orally, and relapse almost always occurs even if the diseased site is resected. It has been reported that the cumulative operative rate is 30% after 5 years and 70% after 10 years, so it is essential to reduce the reoperation rate by strict dietary therapy after surgery.

The indication for surgery in CD is to control complications. Common complications include stenosis and fistula, and the aim of surgery is to remove these complications, not to cure the

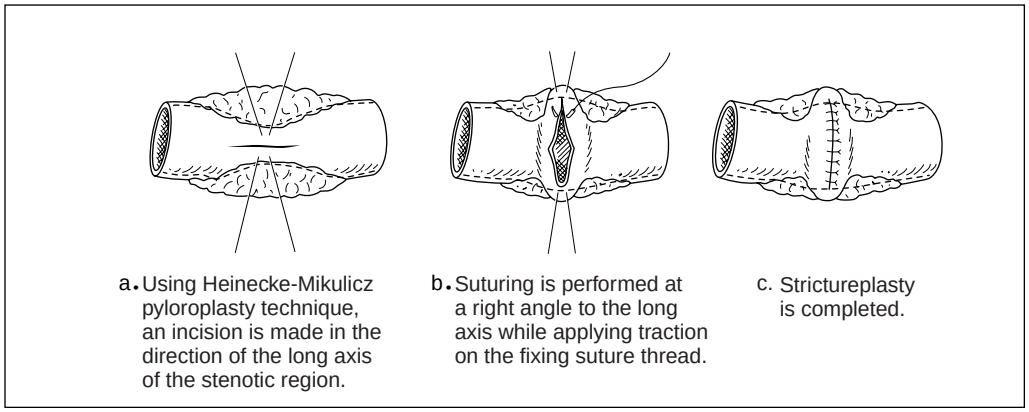

Fig. 2 Strictureplasty
(Sugimachi Keizo: TEXT Surgery, Nanzando, 1998)

underlying disease[3] (Table 5). Dietary therapy is also effective, but over-dependence on diet may cause other problems. It is important to excise the affected bowel with stenosis or fistula and adopt dietary therapy postoperatively to prevent relapses.

Some textbooks state that surgery is contraindicated for anal fistulas in CD, but more than half of these lesions are ordinary fistulas not directly related to CD itself and they can be treated safely by fistulotomy in the same manner as ordinary anal fistulas. However, such treatment is contraindicated for anal fistulas caused by CD. Specialized drainage by the Seton method is effective for these fistulas, but problems may occur when the procedures are not performed by experienced surgeons.

Removal of a small segment of stenotic bowel is a standard operation, but strictureplasty not involving bowel resection is also recommended (Fig. 2). Since postoperative treatment is much more important for CD than for UC, it should be managed by experienced physicians.

Surgical Treatment for Other Types of IBD

Surgical treatment is rarely indicated for other types of IBD, but it should be taken into consideration in selected cases. For example, surgery may be required because of bleeding or perforation in patients with amoebic dysentery, while resection is necessary when stenosis occurs in patients with ischemic enteritis. Bowel resection or colostomy may be required when bleeding cannot be controlled in patients with radiation enteritis. Resection is also indicated for stenosis caused by enteric tuberculosis and for stenosis or bleeding in patients with simple ulcers. Since straining during defecation is assumed to be the cause of solitary rectal ulcer syndrome, counseling for defecation is often effective in such cases.

Conclusion

Both UC and CD will continue to increase in the future, and these have become common diseases handled in ordinary hospitals. Medical therapy is the mainstay of treatment, but surgical treatment should be performed in properly selected patients. The existence of other types of IBD apart from UC or CD should be always kept in mind.

REFERENCES

1) Muto, T., Yao, T., Nagawa, K. and Sakurai, T. eds.: *Inflammatory Bowel Disease — Ulcerative Colitis and Crohn's Disease.* Igaku Shoin,

Tokyo, 1999. (in Japanese)
2) Riddell, R.H., Goldman, H., Ransohalf, D.F. *et al.*: Dysplasia in inflammatory bowel disease. Standardized classification with provisional clinical application. *Hum Pathol* 1983; 14: 931–968.
3) Fazio, V.W.: Conservative surgery for Crohn's disease of the small bowel: The role of strictureplasty. *Med Clin North Am* 1990; 74: 169–181.

Lifestyle Guidance and Diet for Inflammatory Bowel Disease (IBD) Patients

JMAJ 45(2): 63–68, 2002

Tadao BAMBA

Professor, Department of Internal Medicine, Shiga University of Medical Science

Abstract: Inflammatory bowel disease (IBD) reaches a peak among people in their twenties when they are most socially active. Since the disease is refractory, the patients remain under medical supervision for a long period and their quality of life (QOL) deteriorates. Measures to achieve an appropriate lifestyle are required to prevent the recurrence of IBD, maintain remission for long periods, and ensure a high QOL. IBD patients must lead a well-regulated life, avoid excessive stress, and take their medication appropriately. In Crohn's disease, dietary therapy is important and fat intake should be limited to 20 to 30 g per day. However, medium-chain fatty acids and *n*-3 polyunsaturated fatty acids, such as eisosapentaenoic acid, have an anti-inflammatory effect. Pectin, a water-soluble dietary fiber, produces butyric acid in the bowels, which is one of the sources of energy for the intestinal mucosa. Butyric acid also has an anti-inflammatory action. In dietary therapy for Crohn's disease, the appropriate constituents must be selected in accordance with the pathophysiology, and the cooperation of comedical staff is important to ensure a proper diet.

Key words: Ulcerative colitis; Crohn's disease; Elemental diet; Butyrate; Trace element

Introduction

Ulcerative colitis and Crohn's disease are both diseases of unknown etiology. These refractory forms of inflammatory bowel disease (IBD) occur in the young and show repeated episodes of remission and relapse. Since many IBD patients are young, various problems arise including those related to activities at school, advancing to higher grades and university, employment, marriage, sexual life, pregnancy, delivery, and raising children, as well as dietary problems and prejudices concerning the disease, and anxiety concerning the future for those burdened with IBD. Therefore, the patients require long-term medical care and have to live together with IBD itself. A program to enhance the quality of life (QOL) must be established in

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 2, 2001, pages 181–185).
The Japanese text is a transcript of a lecture originally aired on October 13, 2000, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

accordance with the pathophysiology of each patient.

Lifestyle Guidance

Lifestyle guidance is basically the same as that for other gastrointestinal diseases: patients should lead a regular life, avoid excessive stress, not overeat or drink too much alcohol, and abstain from fatty foods. However, IBD is common in young patients who tend to have a highly active social life and it is often difficult to comply with these restrictions. In the active stage of IBD, rest and occasionally hospitalization should be considered. However, when the symptoms start to improve, patients often become very active although they know they still have the illness and then the symptoms become worse again. In patients with Crohn's disease, maintaining a strict diet for a long time is difficult.

Ulcerative colitis and Crohn's disease are both classed as IBD, but their pathophysiology shows marked differences. The main lesions of ulcerative colitis are chronic and diffuse mucosal erosions and ulcers in the colon, and most patients have abdominal pain and diarrhea, especially bloody stools. In patients with moderate to severe ulcerative colitis, loss of plasma protein occurs in association with inflammation. Since improvement may not be achieved with oral intake of nutrients, intravenous hyperalimentation is sometimes required.

However, drug treatment is the main form of therapy and education about medication should be given with easy-to-understand explanations of the actions of the drugs. Especially when the patients are given corticosteroids, the adverse effects of steroid therapy should be explained and efforts should be made to ensure proper administration. During administration of corticosteroids, the patients are recommended to avoid strenuous physical exercise, but appropriate sports activities are acceptable during periods of remission.

In the selection of further education and employment, the patients are advised to avoid schools and careers where they must use 100% of their strength, since the disease is chronic and patients must become skilled at living with it for a long time.

Relapse of ulcerative colitis often occurs due to stress, so it is important to develop proper methods to alleviate stress.

The ideal time for pregnancy is during a 3 to 6 month remission period when no drugs are administered. However, no effect of Salazopyrin® on the fetus has been detected in the West or in Japan.

Diet

In patients with intestinal diseases, abdominal symptoms such as pain, diarrhea, and nausea often occur, and oral intake of food is generally insufficient. Also, intestinal absorption is often disturbed by lesions such as extensive inflammation, erosion, and ulceration in the bowel. Because of the loss of plasma protein from the intestines, the general condition of the patient deteriorates. Since IBD is a chronic disease, severe malnutrition with symptoms such as weight loss, anemia, and edema can occur.

In the dietary therapy of IBD patients, it is usually best to avoid foods with high levels of residue or a high fat content, as well as food that is highly stimulating. However, excessive restriction of the diet can result in the patients worrying too much about their food intake.

When the disease is active, extra energy in addition to that needed in the healthy state is required to recover from the pathological condition, i.e., it is necessary to supply additional energy for the healing erosions and ulceration. However, because the lesions affect the gastrointestinal tract, oral intake of sufficient energy from an ordinary diet is difficult. Therefore, supplemental feeding such as enteral nutrition or intravenous alimentation is used.

In patients with ulcerative colitis and Crohn's disease, the effects of nutritional therapy differ, and nutritional therapy is the treatment of the

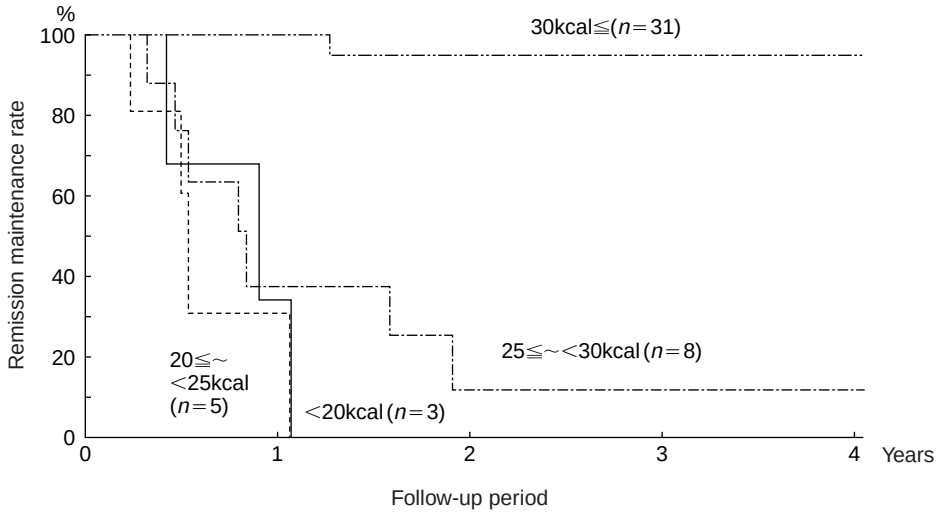

Fig. 1 Remission maintenance ratio in relation to constituent nutrients (Fukuda, Y. *et al.*, Hyogo College of Medicine)

first choice for Crohn's disease.

1. Enteral nutrition

Elemental diet therapy is placed on the primary therapy in the treatment of Crohn's disease. The parenteral nutrient Elental® contains amino acids with low antigenicity, the lipid content is very low (0.6%), and the carbohydrate consists of α-limited dextrin. All of these constituents are readily absorbed without digestion. It is not clear which constituents of this nutrient are useful for improving Crohn's disease and healing the ulcers.

It has been reported that the remission ratio does not change if the lipid intake is less than 30 g per day. However, in a study performed by the "Intractable Inflammatory Bowel Disorders" study group of the Japanese Ministry of Health, Labor and Welfare (chairman: Prof. Takashi Shimoyama), the patients with active Crohn's disease were randomly allotted to three groups, which were an Elental only group and groups receiving Elental plus 13.5 g or 27 g of lipid. When the remission ratio was compared after four weeks, the results were significantly better in the Elental only group. This is an interim report and the study is ongoing, so a conclusion should be reached about the role of lipids soon.

The nitrogen source of enteral nutrients includes peptides in addition to amino acids. The results of *in vivo* and *in vitro* studies have shown that peptides are superior to amino acids with respect to absorption and *in vivo* metabolism. Enteral nutrients containing peptides as the nitrogen source include Enterued® and Twinline®, but these preparations have a high lipid content of about 5%.

Remission can be achieved by infusing 1,800 to 2,100 kcal/day of enteral nutrients into the stomach and duodenum via a nasal tube. When at least 30 kcal per kg of body weight is provided daily using the enteral nutrient Elental®, relapse can be largely avoided (Fig. 1). However, young people find it difficult to tolerate a long-term diet of Elental® alone and its disturbs their social life, so they often stop using it or decrease its use, resulting in repeated relapses. Therefore, it is necessary to devise a richer diet to improve compliance.

2. Dietary therapy

We have prepared a diet for Crohn's disease at our hospital. During remission, an enteral

Table 1 Crohn's Disease Diet Initiation Protocol (latter half)

Main menu		Mean intake per menu							
		Energy (kcal)	Protein (g)	Lipid (g)	Carbohydrate (g)	Dietary fiber (g)	*n*-3 (g)	*n*-6 (mg)	*n*-3/*n*-6
Steamed rice 250 g	Baked egg and shrimp, boiled vegetables	542	22.1	7.6	90.6	2.2	42	445	0.09
	Salmon meniere, boiled vegetables	639	25.9	12.8	99.1	3.0	1,549	1,176	1.32
	Stickleback fish grilled with soy, boiled vegetables	577	25.4	6.6	99.8	4.8	919	1,058	0.86
	Flounder grilled with salt, boiled vegetables	610	26.2	10.5	97.4	2.2	810	1,896	0.43
	Sauteed chicken, vegetable soup	646	20.4	13.1	105.2	3.4	410	2,451	0.17
	Mackerel grilled with soy, boiled vegetables	668	28.1	11.4	107.5	4.6	1,830	1,203	1.52
	Tofu with liquid starch, boiled vegetables, miso soup	644	25.3	10.1	107.8	4.6	560	4,039	0.14
Mean nutritional content		618	24.8	10.3	101.1	3.5	874	1,752	0.50

n-3 : *n*-3 polyunsaturated fatty acids, *n*-6 : *n*-6 polyunsaturated fatty acids

Table 2 Foods Containing High Levels of *n*-3 or *n*-6 Polyunsaturated Fatty Acids

n-6 (linoleic acid)	*n*-3 (α-linoleic acid)
Safflower oil, sunflower oil	Beefsteak plant oil
Corn oil, soy oil	Perilla oil
Margarine	Fish oil
Mayonnaise	Eicosapentaenoic acid (EDA)
Dressing	Docosahexaenoic acid (DHA), etc.
Animal foods, etc.	

supplement of 600 to 800 kcal/day is given with the ordinary diet and stress is placed on maintaining a balance between taste, appetite, and nutrition. Introduction of the Crohn's disease diet has improved compliance with enteral nutrition at home and has made it possible to achieve long-term nutritional management.

The Crohn's disease diet consists of 90 g of carbohydrate, 35 g of protein, 20 g of lipid, and 5 g of dietary fiber, totalling about 700 kcal/day (Table 1). The lipids are long-chain and medium-chain fatty acids. Long-chain fatty acids are the most susceptible to digestion and absorption disorders, while medium-chain fatty acids are easily digested and absorbed and are a useful energy source. In an *in vitro* study, when the intestine 407 cell line was stimulated with IL-1β or TNF-α and medium-chain fatty acids were added, the production of IL-8 was not increased very much, but long-chain fatty acids caused IL-8 production to increase markedly. Therefore, long-chain fatty acids seem to be more likely to cause inflammation than medium-chain fatty acids. For this reason, it is better to restrict

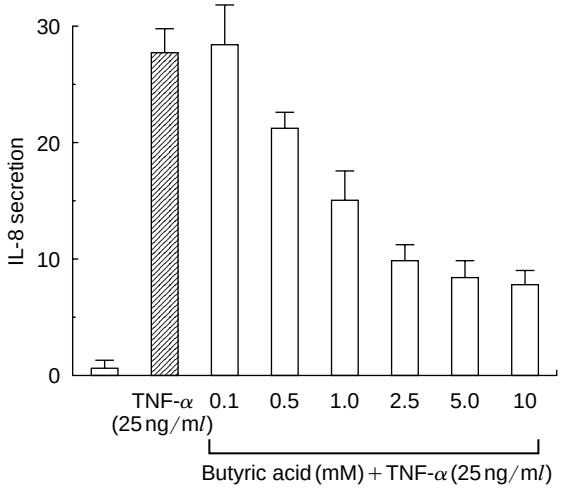

Fig. 2 Effects of butyric acid on IL-8 secretion by HT-29 cells

the lipid intake in a Crohn's disease diet.

Among the long-chain fatty acids, *n*-3 polyunsaturated fatty acids block the metabolism of *n*-6 polyunsaturated fatty acids. Leukotriene B_5, a metabolite of eicosapentaenoic acid, a typical *n*-3 polyunsaturated fatty acid, competitively binds to the receptor for leukotriene B_4, a potent leukocyte-activating factor. It also inhibits the production of cytokines such as TNF-α and eliminates free radicals. Therefore, intake of long-chain fatty acids with a high *n*-3/*n*-6 ratio (i.e., 0.8 to 0.9) is advised for patients with intestinal disease, so they are recommended to eat fish that contain high levels of *n*-3 polyunsaturated fatty acids (Table 2).

Recently, attention has been focused on butyric acid, which is produced by the intestinal flora. Pectin is a water-soluble form of dietary fiber that, is degraded by the intestinal flora to produce butyric acid, which is not only an important energy source for the intestinal epithelial cells but also has an anti-inflammatory action.

In vitro IL-8 production was increased when HT-29 cells were stimulated with TNF-α. However, when butyric acid was added to cultures, IL-8 production was reduced in a concentration-dependent manner (Fig. 2). This was also confirmed at the IL-8 mRNA level, and it was related to the inhibition of NF-KB activity by an intracellular transcription factor. In a rat colitis model produced by administration of dextran sulfate, the ulcer coefficient and inflammation score were markedly reduced by a butyric acid enema. When Clostridium bacteria were administered orally, the butyric acid level of the intestinal contents increased and the ulcer coefficient and inflammation score were both reduced. Recently, it has been found that the wheatgerm GBF diet improves fecal properties in patients with ulcerative colitis, and butyric acid is considered to be involved.

These dietary constituents are involved in tissue repair and in the suppression of inflammation. The Crohn's disease diet is a composite of such constituents. It not only helps to alleviate the pathophysiology, but also contains many foods with scientifically proven mechanisms of action and forms the basis for dietary guidance in patients with IBD.

According to dieticians, when there are abdominal symptoms such as diarrhea in the active stage of ulcerative colitis, the main diet should be about 30 g of lipid per day in the form of gruel, with protein obtained mainly from eggs, soybeans, and fish. Milk should be avoided at this stage.

In patients with active left-sided colitis and total colitis, the activity of lactase in the small intestinal mucosa is significantly reduced and the lactose contained in milk is not decomposed, which can lead to an increase of diarrhea. Foods with a high content of dietary fiber or irritant foods should also be avoided. An ordinary diet can be eaten after the symptoms subside and remission occurs.

In Crohn's disease, dietary therapy is even more important. In the active stage, enteral nutrition can lead to remission. When enteral nutrition is too difficult, intravenous hyperalimentation is used, but is switched to enteral nutrition at an early stage. About 1,200 to 1,400 kcal per day is obtained from enteral nutrition and the remainder is obtained from

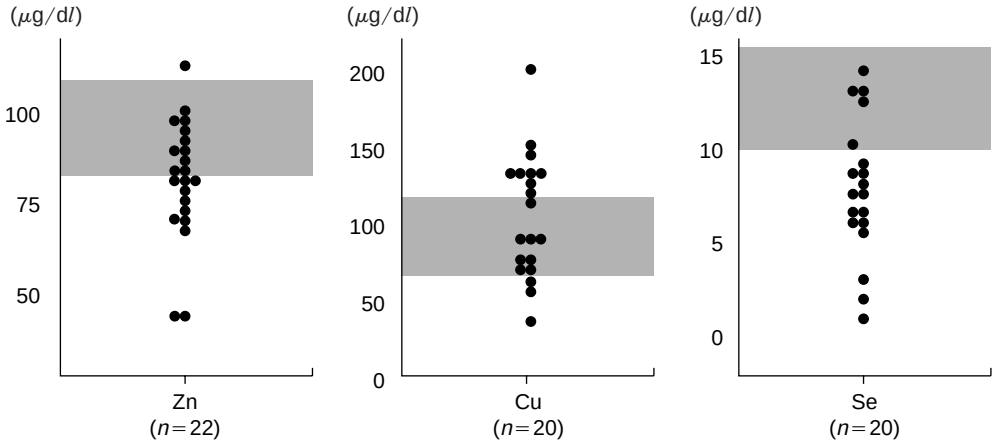

Fig. 3 Plasma levels of trace elements in patients with Crohn's disease given enteral nutrition at home

Table 3 Foods Rich in Trace Elements

Zinc	Selenium
Oysters Soybean products Sardines Liver, etc.	Fish and shellfish Eggs, etc.

the Crohn's disease diet consisting of food with high levels of *n*-3 polyunsaturated fatty acids. Long-term nutritional management not only requires certain quantities of protein, lipid, and carbohydrate to be eaten, but also involves evaluation of the quality of nutrition to ensure that there is a sufficient content of essential amino acids, essential fatty acids, vitamins, and trace elements.

When nutritional management is solely based on enteral nutrients, caution is required since trace elements such as zinc and selenium are reduced, as shown in Fig. 3, so foods with high levels of trace elements such as those shown in Table 3 are required.

Conclusion

The patients with IBD have some problems on social life as well as long-term nutritional management, so it is important to form a team consisting of a physician, nurse, dietician, and pharmacist in order to maintain a high quality of life (QOL) with the support of family members.

REFERENCES

1) Fukuda, Y., Kosaka, T., Okui, M. *et al.*: Efficacy of nutritional therapy for active Crohn's disease. *J Gastroenterol* 1995; 30 suppl 8: 83–87.
2) Belluzzi, A., Brignola, C., Campieri, M. *et al.*: Effect of enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996; 334: 1557–1560.
3) Andoh, A., Bamba, T. and Sasaki, M.: Physiological and anti-inflammatory roles of dietary fiber and butyrate in intestinal functions. *JPEN* 1999; 23 (5) suppl: S70–73.
4) Bamba, T. and Fukuda, M.: Assessment of nutrition in patients with Crohn's disease treated with home enteral nutrition. *Japanese Journal of Nutritional Assessment* 1996; 13: 419–425. (in Japanese)

Management of Viral Infection during Pregnancy

JMAJ 45(2): 69–74, 2002

Takashi KAWANA

Professor of Obstetrics and Gynecology, Teikyo University Mizonokuchi Hospital

Abstract: Viral infection during pregnancy should be handled from two main aspects, maternal management and the prevention of mother-to-child transmission. Infectious diseases in pregnant women are likely to become severe because cellular immunity is suppressed during pregnancy. Therefore, careful management is necessary in this population. The virus infecting the mother's body may be transmitted to the fetus or neonate through the following three routes: intrauterine transmission, intrapartum transmission, and transmission via breast milk. It is difficult to prevent intrauterine transmission, and therefore preventing maternal infection is prudent. Since the rubella vaccination rate has been decreasing recently, there is concern that the prevalence of antibody among pregnant women may decline as well. Maternal varicella infection in early pregnancy is said to result in congenital varicella syndrome in about 2% of infants born to infected mothers. About 10% of pregnant women who have been infected with human parvovirus B19 in early pregnancy reportedly experience miscarriage, and some of them are associated with fetal hydrops. Mother-to-child transmission of hepatitis B virus can be prevented in more than 90% of cases through the use of HBIG and HB vaccine. Mother-to-child transmission of viral infectious diseases is responsible not only for fetal or neonatal diseases but also for adult diseases. Therefore, collaborative studies involving the fields of obstetrics and gynecology, pediatrics, internal medicine, ophthalmology, and otolaryngology are required.

Key words: Mother-to-child transmission; TORCH syndrome; Preventive vaccination

Introduction

This paper discusses viral infection and maternal and child management in connection with the themes of pregnancy and interdisciplinary cooperation, and refers to new developments in the area of TORCH syndrome. TORCH is an acronym coined in the 1970s from the names of various infectious diseases that can lead to abnormal child birth if the mother is infected

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 7, 2000, pages 1013–1016).

Table 1 Infectious Diseases in Children and Adults Occurring Through Mother-to-child Transmission

Etiologic agent	Disease
Hepatitis B virus	Chronic hepatitis, cirrhosis, liver cancer
HTLV-1	Adult T-cell leukemia
Cytomegalovirus	Hearing loss, retinitis
Toxoplasma	Retinitis
Varicella-zoster virus	Pediatric zoster
Rubella virus	Diabetes mellitus, thyroiditis
HIV	Pediatric AIDS
Syphilis	Keratitis, hearing loss, dental abnormality

during pregnancy: T stands for toxoplasma, O for other (syphilis), R for rubella, C for cytomegalovirus, and H for herpes simplex virus. Subsequently, attention was given to a number of pathogens that affect the fetus through mother-to-child transmission, among them varicella virus, parvovirus B19, hepatitis B virus, adult T cell leukemia virus, Chlamydia trachomatis, and group B streptococci. Because of space limitations, this paper will focus on viruses and toxoplasma.

From the standpoint of interdisciplinary cooperation, two issues are of concern; the management of infected pregnant women and the possibility of pediatric, medical, ophthalmic, and otolaryngologic diseases of children infected through mother-to-child transmission.

Consequences of Mother-to-child Transmission

When the immunologically immature fetus or newborn is infected with a pathogen that has invaded the mother's body, various consequences may result. These consequences include a wide spectrum of abnormalities and illnesses ranging from miscarriage, stillbirth, premature delivery, deformity, congenital infection, neonatal infection, and infantile infection to diseases that manifest in adulthood. For example, infants who become carriers of the hepatitis B virus through mother-to-child transmission may develop chronic hepatitis, resulting in cirrhosis and hepatic carcinoma 30–40 years later. Adult T cell leukemia virus can also produce carriers via mother-to-child transmission, and these infants develop leukemia when they become adults. Diseases in children and adults currently known to be caused by agents transmitted from mother to child as a possible route are shown in Table 1.

Management of Infectious Diseases in Pregnant Women

First of all, the disease of the pregnant woman herself should be treated, but the presence of the fetus should always be borne in mind during such treatment, with drugs that might otherwise be used routinely administered with caution. Next, management focused on the prevention of mother-to-child transmission is necessary. For this purpose, it is necessary to know the route and time of mother-to-child transmission. Mother-to-child transmission can occur in three ways: intrauterine transmission, intrapartum transmission (transmission in the birth canal), and transmission via breast milk. Although it is often difficult to prevent intrauterine transmission, intrapartum transmission can be prevented by cesarean section and transmission via breast milk by avoiding breast feeding.

Table 2 shows the classifications of routes of major infectious diseases involving mother-to-child transmission, although not all cases of mother-to-child transmission can be classified into these three categories in such a clear-cut manner. Rubella virus infection and toxoplasma infection, which are particular problems in cases of primary infection occurring during early pregnancy, are generally transmitted in utero. In contrast, herpes simplex virus infection and hepatitis B virus infection are generally transmitted during delivery. Intrapartum transmission may occur when the fetus comes in contact with maternal blood in the parturient canal or when the maternal blood is transferred to the

Table 2 Major Infectious Diseases in Japan Mediated by Mother-to-child Transmission and Their Routes of Transmission

	Intrauterine transmission	Intrapartum transmission (transmission in the parturient canal)	Transmission via breast milk
Viruses			
Rubella virus	A	E	E
Cytomegalovirus	A′	A	A
Parvovirus B19	A′	E	E
Varicella-zoster virus	B	A	E
Herpes simplex virus	B	A	E
Coxsackievirus	C′	E	E
Hepatitis B virus	D	A	E
Hepatitis C virus	D	B(?)	E
ATL virus	D	D	A
AIDS virus	D	A	B
Chlamydia			
Chlamydia trachomatis	E	A	E
Bacteria			
Syphilis	A	A	E
Gonococci	E	A	E
Group B hemolytic streptococci	E	A	E
Fungus			
Candida albicans	E	A	E
Protozoon			
Toxoplasma	A	E	E

*Importance is graded from A to E (A denotes highest importance).

fetus as a result of labor pains. This route is important for the mother-to-child transmission of hepatitis B virus and HIV infections because the pathogens are present in the maternal blood.

Taking into consideration these mechanisms of transmission, the author has divided the practical prevention of mother-to-child transmission into four stages. In the stage of primary prevention, infection of the mother should be prevented. For instance, women who want to conceive should have established immunity to rubella in advance. In the second stage of prevention, mother-to-child transmission should be prevented by implementing treatment of the infected mother. Reduction of the amount of HIV in HIV-carrying mothers by antiviral drug therapy is an example. Tertiary prevention involves cesarean section to prevent transmission in the parturient canal and avoidance of breast feeding to prevent transmission via breast milk. The final stage of prevention involves the inhibition of clinical manifestations of disease in the infected child preemptive therapy. For instance, children born to mothers who carry hepatitis B virus will be given HBIG and HB vaccine, and children born to mothers who have had varicella during the perinatal period will be given high-titer varicella-zoster immune globulin (VZIG).

Individual Diseases

1. Rubella virus

It is well known that 30–50% of pregnant

Table 3 Time of Infection of the Mother with Varicella and Effects on the Fetus

	Time of infection	Incidence of congenital varicella syndrome	Infantile zoster
Varicella	0–12 weeks	0.4% (2/472)	
	13–20 weeks	2.0% (7/351)	0.8% (4/477) (13–24 weeks)
	21–36 weeks	0% (0/475)	1.7% (6/345) (25–36 weeks)
	VZIG therapy after exposure	0% (0/97)	0%
Zoster	0% (0/366)		

(Enders, G. *et al.*: *Lancet* 1994)

women infected with rubella during early pregnancy deliver infants with congenital rubella syndrome (CRS). To prevent the birth of infants with CRS, it is most efficient to establish immunity in women before pregnancy. Since CRS is widespread in years when rubella is common among children, it is important to suppress epidemics of rubella. In 1994, the previous preventive vaccination law was revised, and, with the new revision, the earlier procedure of mass immunization with rubella vaccine in the second year of junior high school gave way to immunization on a voluntary basis in infants up to 90 months old and male and female junior high school students. With the implementation of this procedure, epidemics of rubella, which have tended to occur every 5–6 years, are considered to have been eliminated, together with a probable decrease in the incidence of CRS. However, the change from scheduled mass immunization to voluntary immunization has caused the vaccination rate among junior high school students to fall to less than 50%. An increased proportion of seronegative individuals may be an issue when such individuals reach reproductive age. This problem may be enhanced by the fact that epidemics of rubella have been eliminated, providing less chance for these seronegative individuals to catch rubella spontaneously. Rubella vaccination has been promoted by the Japan Medical Association and the Ministry of Health, Labor and Welfare (JMA News, May 5 2000 issue). These efforts should be expanded nationwide.

2. Varicella-zoster virus

The prevalence of antibody to varicella-zoster virus (VZV) seems to be approximately 90% among individuals in their 20s and 30s, and it is not uncommon for pregnant women to develop varicella. Since varicella occurring during pregnancy may be severe and is often complicated by pneumonia, due caution is necessary. If signs of pneumonia appear, early implementation of intravenous drip infusion of aciclovir is recommended.

It has become apparent that abnormalities may occur in the fetus if the mother has varicella. A large-scale German and British study revealed that the incidence of such abnormalities is 0.4% until 12 weeks of gestation, 2.0% at 13–20 weeks of gestation, and 0% after 21 weeks of gestation. The incidence of fetal abnormality is reportedly 0% if the mother develops herpes zoster. Abnormalities occurring in the fetus include scarring of the skin, ophthalmic abnormalities, and hypoplasia of the extremities. If a pregnant woman comes in contact with a varicella patient, prevention of infection is attempted by administering VZIG. No infants with abnormalities have been born to mothers who received such treatment (Table 3).[1)]

If the mother is infected with varicella at the time of delivery, neonatal varicella may develop through mother-to-child transmission of the virus. If infection with VZV takes place during

the period from 4 days before to 2 days after delivery, varicella in neonates is likely to be particularly frequent and severe. In this case, VZIG should be administered to the neonate just after birth, and aciclovir therapy should be given as needed. From the obstetric viewpoint, the onset of labor pains may be inhibited to allow birth to take place 7 or more days after the onset of varicella, by which time IgG antibody production begins in the maternal body.

3. Erythema infectiosum (fifth disease)

It was determined that parvovirus B19 causes this disease, and it soon became apparent that intrauterine transmission of the virus might cause miscarriage and premature delivery. A finding of particular interest was that fetal hydrops may occur, frequently resulting in stillbirth.[2)] Intrauterine transmission is considered to occur in about 30% of mothers infected with this virus, and about 10% suffer miscarriage or premature delivery. No vaccine against this virus is currently available. Infection in pregnant women may be mediated by their own children who have become infected in day care centers. It is also common for pregnant women who work in day care centers or nurses who work in pediatric departments to be infected via young children in the workplace. The possibility of fetal deformity as a result of intrauterine transmission of parvovirus B19 is considered almost nil.

4. Hepatitis B virus (HBV)

It has been more than 15 years since preventive measures were first taken on a national basis in response to the finding that the incidence of mother-to-child transmission is high among infants born to mothers who are HBV carriers. At first, only infants born to HBe antigen-positive mothers were given HBIG immediately and 2 months after birth, followed by three inoculations of HB vaccine thereafter, because such infants are infected with HBV at a rate of more than 90%. Later, it became apparent that the incidence of infection is about 10% among infants born to HB virus carriers who are negative for HBe antigen, and this group of infants was also subjected to similar, but somewhat simplified preventive measures. This project resulted in a marked decrease in the number of infants carrying HB virus, from 3,300 per year to 420 per year. Although the long-term benefits of this procedure initially were questioned, it has become apparent that children who underwent these preventive measures are still seronegative after 10 years, confirming the benefits of the procedure.

5. Herpes simplex virus (HSV)

HSV infection is not uncommon in pregnant women. It often takes the form of genital herpes. Fetal anomaly caused by the intrauterine transmission of HSV is extremely rare. A greater problem is the development of neonatal herpes caused by transmission in the birth canal. More than 95% of cases of mother-to-child transmission are preventable by abdominal delivery by cesarean section if herpetic lesions are found in the external genitalia or cervical canal of the uterus. It has been advocated that medication with aciclovir is feasible for the treatment of genital herpes in pregnant women.[3)] This is grounded on the recent finding that deformity does not appear to occur at a significantly higher rate in infants born to mothers who have received this drug. However, if there are only slight signs and symptoms, as in recurrent cases, topical application of an ointment containing anti-herpes virus is sufficient treatment.

Vaccination

Vaccination is contraindicated during pregnancy. Live vaccine in particular is an absolute contraindication because of the possibility of transmission to the fetus. It should be kept in mind that contraception is necessary for two months after the inoculation of rubella vaccine. However, fortunately, no cases have been reported of CRS infants born to high-risk mothers who received vaccination in the early

pregnancy period or who conceived soon after vaccination. It seems that attenuated rubella virus used for vaccination is less teratogenic.

In theory, vaccine made from inactivated virus has no effect on the fetus and, therefore, can be used in pregnant women. However, it is a general rule that inactivated vaccine should not be given to pregnant women. It is a difficult problem as to whether or not pregnant women should be inoculated with inactivated influenza vaccine when influenza is widely prevalent. In regard to the teratogenicity of influenza virus, a relationship with abnormalities of the central nervous system was previously suggested. However, this relationship is currently denied. It was also reported that mortality from influenza pneumonia would be high in pregnant women. If this is true, active use of vaccination should be considered; however, it is currently thought to be unlikely, and hence there appears to be no need for vaccination.

Conclusion

The consequences of mother-to-child transmission involve not only fetuses and neonates but also extend to older children and adults. Prospective studies of children after mother-to-child transmission are needed, particularly as collaborative research by pediatricians, ophthalmologists, otolaryngologists, and internists. Obstetric management should be reconsidered in light of the results of such studies.

The search is underway in the obstetric field for efficient strategies against rubella virus, cytomegalovirus, herpes simplex virus, and toxoplasma, all of which are transmissible via transplacental route and lead to the birth of abnormal infants even when infected mothers do not show any clinical signs and symptoms.

The decreased prevalence of antibody among pregnant women has recently been reported for some viruses. Increases in the incidence of primary infection in pregnant women and resultant increases in the incidence of fetal and neonatal anomalies are of recent concern.

REFERENCES

1) Enders, G., Miller, E., Cradoke-Watson, I. *et al.*: Consequence of varicella and herpes zoster in pregnancy: Prospective study of 1739 cases. *Lancet* 1994; 343: 1547–1550.
2) Amand, A., Gray, E.S., Brown, T. *et al.*: Human parvovirus infection in pregnancy and hydrops fetalis. *N Engl J Med* 1987; 316: 183–186.
3) Centers for Disease Control and Prevention (CDC): 1998 guidelines for treatment of sexually transmitted diseases. *MMWR* 1998; 47 (No. RR-1): 25–26.

Revision of Preventive Vaccination Law and Future Trends

JMAJ 45(2): 75–79, 2002

Hitoshi KAMIYA

Director, Mie National Hospital

Abstract: In Japan, the drastic reformation implemented in 1994 has transformed the concept of preventive vaccination. This reformation indicated a change in the vaccination system from mass vaccination to individual vaccination and from compulsory (mandatory) vaccination to recommended (effort-requiring) vaccination. At the same time, the importance of promoting understanding of the possibility that vaccination may invite an unexpected health problem was pointed out. Because this revision of the vaccination system was a substantial change, a review of the details of the revised system was scheduled for a date five years later. A review conducted in 1998 pointed out importance of educating students about the role of vaccination, which will lead to a correct understanding of infectious diseases and the role of vaccinations. The importance of the collaboration between the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology was also pointed out in the promotion of the preventive vaccination system. Since 1994, the influenza vaccine has been administered on a voluntary basis, which has resulted in a significant decrease in the rate of vaccination among Japanese. Therefore, even susceptible elderly people and those at high risk of influenza frequently forego the vaccination. Thus, the necessity of influenza vaccination was to be reconsidered in the review. The physicians responsible for vaccinations are reimbursed by the medical care system and the promotion of preventive vaccination among the public is expected in the future.

Key words: Preventive vaccination (vaccine);
Revision of Preventive Vaccination Law;
Review of revised Preventive Vaccination Law;
Guidelines for preventive vaccination

Introduction

The prevention of infectious diseases is the ultimate goal of the countermeasures instituted against them. All people, irrespective of age, sex, race, lifestyle, and socioeconomic condi-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 9, 2000, pages 1147–1149).

tions, are at risk of contracting infectious diseases. Those who contract infectious diseases where appropriate treatment has been established and those who have already received vaccinations are at lesser risk of aggravation of or death from infectious diseases.

The history of the legislation regarding infectious diseases has its roots in the Infectious Disease Prevention Act, which was enacted in 1897. The latest legislation is the "Law for the Prevention of Infectious Diseases" (New Infectious Diseases Prevention Act) which was implemented in 2000. It is aimed at promoting the prevention of infectious diseases in the 21st century. The New Infectious Disease Prevention Act naturally stipulates the details of preventive vaccinations. In this report, the author evaluates the current revisions and predicts the future trends of preventive vaccinations in the 21st century via a discussion of how the countermeasures for infectious diseases are implemented and what countermeasures are to be practically introduced to cope with conditions globally.

Necessity for Vaccination and Current Trends

The pathogens of infectious diseases such as viruses, bacteria, and the toxins produced by bacteria are used to prepare vaccines. Although their toxicity is reduced, vaccines produce immune responses against infectious agents or their toxins; the vaccines are orally administered or inoculated by injection. Methods of administration are defined by the Preventive Vaccination Law to maintain public health. The Preventive Vaccination Law was revised in October 1994.

The main points of this revision are summarized as follows. The infectious diseases covered by the law were reviewed because of changes in the prevalence of infectious diseases. The vaccination practice was changed from compulsory (mandatory) vaccination to recommended (effort-requiring) vaccination. (The penalty for not receiving vaccinations was abolished and the rule covering informed consent was rigorously enforced.) The necessity of establishing an effective and safe vaccination system was emphasized. (The switch from mass vaccination to individual vaccination indicates the change from protection of the group to protection on an individual basis, and the suppression of mass infection is anticipated as a result of the promotion of individual vaccination and increasing the percentage of those with full immunization.) The necessity of developing appropriate countermeasures for rapid relief of injury to health caused by vaccinations (medical treatment and compensation for unexpected adverse reactions) has been defined.

This revision provided for a review to be conducted in five years. The subcommittee on preventive vaccination related affairs was organized under the committee on infections, the council for public health. Since June 1998, a total of 18 meetings were held and the final report was submitted to the committee on July 5, 1999. This report was approved after its partial modification. Although the council for public health submitted the report to the Minister of Health and Welfare, the proposal was discarded as the Diet was dissolved before the initiation of discussion on the report. The proposal was to be resubmitted for discussion to the extraordinary session of the Diet scheduled in September 2000. As the discussion of the proposal requires a series of official procedures, whether or not the preparations for implementation in 2001 will be completed is of a great concern.

Main Points of the Report

1. Basic concept

Parents, physicians and the Government are all called upon to recognize that "prevention is superior to treatment," and to understand the natural course of the infectious diseases for which vaccines are prepared. In Japan, students have few opportunities to study health educa-

tion at school and their knowledge of diseases is extremely limited. Therefore, they seem to lack the basic understanding of the necessity of receiving preventive vaccinations. In the revision, the introduction of health education covering the importance of vaccinations into the school curriculum is expected to be discussed.

2. Types and timing of routine vaccinations

The discussions in the following sections are based on the official guidelines published by the Ministry of Health and Welfare in 1994.

(1) **Routine vaccinations and voluntary vaccinations**

There are seven routine vaccinations for poliomyelitis, diphtheria, pertussis, tetanus (diphtheria-pertussis-tetanus: DPT), measles, rubella, and Japanese encephalitis. In addition to these vaccines, BCG is administered according to the Tuberculosis Control Law. All eight vaccinations are indispensable for maintaining good health, and epidemic conditions have been surveyed according to the New Infectious Disease Prevention Act.

In 1994, the Preventive Vaccination Law was revised and appropriate agents for routine vaccinations were selected with due consideration for their potency in controlling the epidemics of specific infectious diseases, their prophylactic effects on those at high risk of severe complications from primary disease and their role as a measure to protect individuals from certain aspects of society.

Based on these basic principles, mass vaccination against influenza, which has rarely produced a consistent immune response and controlled epidemics, was excluded from routine vaccinations for elementary school and junior high school students. Since the revision, influenza vaccinations are administered on a voluntary basis and indicated only for the adults aged 65 years and older, patients with bronchial asthma and/or heart disease and individuals at high risk of immunodeficiency from primary diseases or drug administration. At the time of the discussion, other vaccinations such as varicella, mumps and Haemophilus influenza were included. After the exclusion of the influenza vaccination from routine vaccinations, people have less awareness of the seriousness of influenza as well as vaccination. This lack of awareness of the necessity of individual prophylaxis and the prevention of development and aggravation among the public has been pointed out.

Due to the recent increase in mass influenza infection and mortality from influenza during the winter among the elderly living in nursing homes, in addition to the increase in child morbidity from encephalitis and encephalopathy during a period of widespread influenza, experts point out the relationship between influenza and these phenomena. In the recent review of the vaccination system, the routine administration of influenza vaccination to adults aged 65 years and older was proposed together with its adoption under the Preventive Vaccination Law. During the discussion, it became clear that a categorization of preventive vaccination should be implemented in the revision of the law, because while the influenza vaccination was administered to adults with the diseases and was effective to prevent the development of influenza on individual basis, it was not done to control the epidemics of the virus. Under the proposed categorization, the specified infectious diseases were divided into two groups: the seven infectious diseases were in group 1, and influenza was in group 2.

While vaccination for infectious diseases in group 1 are strongly recommended, this is not the case for group 2. Therefore the relief of injury to health by vaccination differs depending on this classification of infectious diseases. Individuals are to be compensated for adverse reactions attributable to vaccine at the level which is similar to that defined by the Law of the Organization for Drug ADR Relief, R&D Promotion and Product Review. The proposed system, which defines the compensation for victims under Preventive Vaccination Law, appears to have been welcomed by the physicians responsible for vaccinations.

Regarding infant influenza, the implementation of a survey on the effectiveness of influenza vaccination sponsored by the Ministry of Health and Welfare has been recommended and the necessity of discussing appropriate countermeasures based on the results obtained from the survey was pointed out.

(2) **Timing of routine vaccinations**

Although special consideration is given to routine vaccinations so that they may be completed within 90 months after birth, the heads of cities, wards, towns, and villages responsible for vaccinations often shorten the periods of routine vaccinations because of specific local conditions. The revision of the vaccination system stated that while individuals who require vaccination are advised to receive them within a standard period determined according to the epidemic conditions of infectious diseases and it stated that patients who fail to receive them during the standard period can still receive them within the period specified by the Preventive Vaccination Law.

The establishment of one or two preventive vaccination centers per prefecture has been proposed and, as of this year, several centers have started to provide various services including vaccinations and counseling. These preventive vaccination centers can be used by children with underlying diseases who are unable to receive vaccinations at general clinics, individuals who fail to receive routine vaccinations, foreigners and those returning to Japan or living overseas who are unable to receive vaccinations at general clinics. The final goal of the establishment of these centers are to enable all individuals to receive the necessary vaccinations under the same conditions as to the standards established in their residential prefectures. While the number of those who visit these centers outside their residential prefectures are few, (cases such as babies born in the prefectures of their maternal grandparents, individuals returning to their hometowns, businessmen on temporary postings outside his or her original residents), the idea of this simple but important service was added to the proposal.

3. Preventive vaccination notebook

The completion of vaccinations is currently recorded in the mother-and-baby notebook. In view of the current changes in society including the increase in the number of individuals undergoing vaccinations in foreign countries and the need to respect the privacy of divorced couples and their children, the preparation of preventive vaccination records, not as a record of mother and child but as a life-long individual record of vaccination, has been proposed.

4. Rate of preventive vaccination

Since the introduction of the individual vaccination system, the decrease in the rates of preventive vaccinations among older elementary school pupils and junior high school students, probably caused by the fact that they are now required to visit the clinics with their parents, has become a serious problem. In the case of junior high school students, the system will soon be modified. In addition, because the age range of individuals to be vaccinated has been widened since the revision, the calculation of a precise vaccination rate is becoming difficult. In view of the differences in vaccination rates created by the multiple calculation methods, the rates should be calculated according to the data obtained from routine physical examinations for infants at one and a half years and three years and the physical examination conducted at the time of entering elementary school. In this way, more consistent vaccination rates can be obtained. In cooperation with the Ministry of Health and Welfare, the heads of prefectures, cities, towns, and villages are to establish a simpler calculation method through discussion.

5. The guidelines for preventive vaccination

The first official preventive vaccination guidelines issued by the Ministry of Health and Welfare came at the time of the revision of the law in 1994. These guidelines provide the basic infor-

mation on vaccinations required by all physicians responsible for vaccinations, such as the standard for vaccinations and the appropriate treatment for adverse reactions caused by vaccinations. While the guidelines aimed to clarify some of the complicated issues in the law by referring to specific cases, some of the explanations have occasionally caused misinterpretations and confusion. Such problems may have occurred due to the limited number of pages and to the fact that it was the very first set of guidelines to be printed. Thus, the guidelines are expected to overcome these issues after the latest review and will be improved.

A more comprehensive vaccination system will therefore be established in the near future. The guidelines issued by the Ministry of Health and Welfare are regarded as the official guidelines for vaccinations although there are several personal handbooks available.

6. Future trends

In order to reduce the number of vaccinations and increase the vaccination rates, various types of multiple mixed vaccines are to be developed in the future. Pediatricians have been responsible for vaccinations. However, since vaccination rates among adults are expected to increase in the future, physicians are encouraged to become involved in administering vaccinations.

The immunizing agents indicated for adults are vaccines for tetanus, hepatitis B, hepatitis A, measles, varicella, and mumps. The latter three vaccines are indicated only for adults with no previous history of the diseases. It is necessary to implement a campaign to promote vaccination in collaboration with the Japan Medical Association.

Conclusion

In the present study, I have discussed the important aspects of the proposal, together with present conditions and future trends. This report also includes provisions which protect the physicians responsible for vaccinations. Furthermore, the comments from those involved parties throughout the country have been reflected in the proposal. The author hopes that the procedures for the official revision will soon be completed and that an effective system based on the proposal will be practically introduced. The author is keen to follow the future trends in the vaccination system.

REFERENCES

1) Kamiya, H.: *New Preventive Vaccination*. Iji Publishing Co., Ltd., Japan, 1996. (in Japanese)
2) Kamiya, H.: Review of preventive vaccination. *Almanac of Pediatrics* 1994; 14: 173–176. (in Japanese)
3) *Guidelines for Preventive Vaccinations.* The Ministry of Health and Welfare. (in Japanese)

Protein Restriction Diet as an Essential Tool in Treating Uremia: Myth or Truth?

JMAJ 45(2): 80–83, 2002

Yoshitaka MAEDA and Tatsuo SHIIKAI

Nephrology Section, Department of Internal Medicine,
Toride Kyodo General Hospital

Abstract: Protein restriction diet is not always accepted by every nephrologist, even though one century has been passed since such a nutritional therapy was introduced as one of the strategies against uremia. One reason might be that nutritional therapies, in contrast to drug therapies, require a longer observation period and are more difficult to use in a randomized controlled trial (RCT) to evaluate their effectiveness. At least, protein restriction has been revealed to be certainly effective in chronic renal failure except for polycystic kidney disease and diabetic nephropathy, based on the accumulated results obtained by meta-analysis, RCT and cohort studies. Another reason why some physicians hesitate to restrict protein, might be attributable to dialysis therapy; an already established procedure in the treatment of uremia, even though it is expensive and its availability is restricted. Another issue, which should be resolved in the future, is whether protein restriction diet before dialysis improves the overall prognosis of uremic patients. In any case, it is true that nutritional support, as well as drug therapies, is a mainstream treatment for uremia.

Key Words: Uremia; Chronic renal failure; Protein restriction diet; Nutritional therapy; Dialysis

Introduction

Almost one hundred years have passed since a protein restriction diet (PRD) was first applied to treat uremic symptoms. PRD certainly reduces the blood urea nitrogen level, and reduces nausea, anorexia, and itching. However it is still controversial whether PRD has an inhibitory effect on the progression of chronic renal failure (CRF).[1)] For uremic patients, nutritional therapy, contrary to drug therapy, requires so much effort to be learned and each meal must be prepared specially everyday. For physicians, other than the difficulty in evaluat-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 9, 2000, pages 1230–1231).

ing the compliance of patients, a longer period is needed to follow up the renal function of each patient, which disturbs the protocol of randomized controlled trials (RCT). These problems must be overcome to clarify the precise worth of nutritional therapy against uremia. Accordingly, we discuss the present issues, the limitations and the future of PRD.

Which Diseases are Responsive to Protein Restriction?

PRD has been recognized as an effective therapy for CRF, other than due to polycystic kidney disease and diabetic nephropathy, based on the results by RCT[2–9] and meta-analyses.[10–12] However, from the standpoint of careful reading, each study had some problems; in selection and exclusion of background renal diseases,[2–4,7–9] strictness of protein restriction,[7] prescription of angiotensin I converting enzyme inhibitors,[5,9] and evaluation of renal function.[2–3,7] Only one report by Ihle, *et al.*[5] had a satisfactory study design, in which PRD was concluded to be effective.

As mentioned above, it is difficult to investigate the efficacy of protein restriction by RCT. So we have continued the cohort study since 1987, which revealed that 102/348 cases (29.3 %), observed longer than one year and except for diabetic nephropathy, were non-progressive and showed less reduction of creatinine clearance (Ccr) than that estimated by aging. The amount of proteinuria in the non-progressive group was significantly less than that in the progressive group. Surprisingly, twenty-one patients (20.6%) were non-progressive even with mild PRD of more than 0.9 g/kg body weight (BW)/day.

Animal experiments showed that PRD increased the survival rate and suppressed azotemia in polycystic kidney diseases (PCKD), but did not support the inhibitory effect of PRD on progression of renal failure. MDRD study[9] was also suspicious about the effect of PRD among PCKD patients. We have some experience that PRD can be effective if introduced earlier (Ccr>70 m*l*/min) even in PCKD patients.

There is no direct evidence on the effect of PRD in diabetic nephropathy, even accumulated results obtained by animal experiments and clinical studies suggested favorable effect of PRD. It may be due to many concurrent problems, such as atherosclerosis in generalized arteries, and to renal interstitial damage caused by proteinuria.[13]

How Early Should PRD Begin, and How Much Should Protein be Restricted?

The Japanese Society of Nephrology has recommended 0.6–0.7 g/kg BW/day of PRD for the patients with Ccr less than 70 m*l*/min, which corresponds to a half of the average protein intake among Japanese. One alternative would be to start with mild PRD; 0.9 g/kg BW/day rather than with strict PRD, initially.

Several recent reports suggested that the amount of proteinuria was well correlated with the progression of CRF.[13] So mild PRD (0.9 g/kg BW/day) might be sufficient among slowly progressive CRF with proteinuria less than 1 g/day. Meanwhile, strict PRD; 0.4 g/kg BW/day might be required in critical CRF with Ccr less than 20 m*l*/min, in which supplement of calcium, vitamins (B_6, C, folate, and D), essential amino acids, and keto-acids should be considered.

Availability of Protein-restricted Foods

PRD was previously resisted by patients, because their taste was too sweet and oily, and their foods and menu were also restricted. However low protein rice, noodle, bread, side dishes and various desserts (such as jelly) were developed, which have extended the availability of PRD. Home delivery service of PRD was started by two companies in Japan. Hence

even home-bound senile patients need not be excluded from PRD treatment.

Prognosis After Dialysis

PRD, which can even succeed in extending the pre-dialysis period, would not be effective either for patients or medical costs, if such diets increase morbidity and mortality rate after dialysis is introduced. This is the main concern of most physicians about PRD. The quality of dialysis therapy has been kept high, and government aid for dialysis patients has been established in Japan, which are other reasons why PRD has not spread widely.

There are certainly some patients who have problems on the introduction of dialysis even at our facility. However most such cases have been related to calorie deficiency rather than PRD itself. With respect to the prognosis of protein-restricted patients after dialysis, only one report[14] is available, in which there was no difference on the prognosis after the initiation of dialysis therapy between the CRF patients with and without PRD. It is also important to urge the patients to learn not only PRD but also to accept it with dialysis.

Conclusion

Dialysis is certainly the established and crucial therapy for uremia, which might weaken the enthusiasm of physicians in dealing with pre-dialysis patients. However as well as nutritional therapy, newly developed drugs, such as oral adsorbent, angiotensin I converting enzyme inhibitors, angiotensin II receptor antagonists, are now available, which may suppress the progression of CRF, decrease dialysis patients, and be consecutively anticipated to reduce the healthcare spending on CRF.

REFERENCES

1) Mehrotra, R. and Nolph, K.: Treatment of advanced renal failure: Low protein diets or timely initiation of dialysis? *Kidney Int.* 58: 1381–1388
2) Williams, P.S., Stevens, M.E., Fass, G. *et al.*: A randomized trial of the effects of protein and phosphate restriction on the progression of chronic renal failure. *Nephrol.Dial.Transplant.* 7: 285, 1987
3) Jungers, P., Chauveau, P.H., Ployard, F. *et al.*: Comparison of ketoacids and low protein diet on advanced chronic renal failure progression. *Kidney Int.* 22: 67–71, 1987
4) Rosman, J.B., Langer, K., Brandl, M. *et al.*: Protein-restricted diet in chronic renal failure: a four year follow-up shows limited indications. *Kidney Int.* (suppl.)25: S96–102, 1989
5) Ihle, B.U., Becker, G.J., Whitworth, J.A. *et al.*: The effect of protein restriction on the progression of renal insufficiency. *N. Engl. J. Med.* 1989; 321: 1773–1777.
6) Bergström, J., Alvestrand, A., Bucht, H. *et al.*: Stockholm clinical study on progression of chronic renal failure-An interim report. *Kidney Int.* 36(suppl. 27): S110–114, 1989
7) Locatelli, F., Alberi, D., Graziani, G. *et al.*: the Northern Italian Cooperative Study Group: Prospective, randomized, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. *Lancet* 337: 1299–1304, 1991
8) D'Amico, G., Gentile, M.G., Fellin, G. *et al.*: Effect of dietary protein restriction on the progression of renal failure: A prospective randomized trial. *Nephrol. Dial. Transplant.* 9: 1590–1594, 1994
9) Klahr, S., Levey, A.S., Beck, G.J. *et al.* (the Modification on Diet in Renal Disease Study Group): The effect of dietary protein restriction and blood pressure control on the progression of chronic renal disease. *N. Engl. J. Med.* 330:877–884, 1994
10) Fouque, D., Laville, M., Boissel, J.P. *et al.*: Controlled low protein diets in chronic renal insufficiency: meta-analysis. *BMJ*. 304: 216–220, 1992
11) Pedrini, M.T., Levey, A.S., Lau, J. *et al.*: The

effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases. *Ann. Intern. Med.* 124(7): 627-632, 196

12) Kasiske, B.L., Lakatua, J.D.A., Ma, J.Z. *et al.*: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am. J. Kidney Dis.* 31: 954–961, 1998

13) Epstein, F.H.: Pathophysiology of progressive nephropathies. *N. Engl. J. Med.* 339(20): 1448–1456, 1998

14) Coresh, J., Walser, M. and Hill, S.: Survival on dialysis among chronic renal failure patients treated with a supplemented low-protein diet before dialysis. *J. Am. Soc. Nephrol.* 6: 1379–1385

The 2000 Guidelines for the Treatment of Hypertension

JMAJ 45(2): 84–87, 2002

Takao SARUTA

Department of Medicine, School of Medicine, Keio University

Key words: Guideline; Treatment of hypertension; Antihypertensive drugs; Lifestyle modification

Introduction

Guidelines for the treatment of hypertension in Japan, "The Manual for Treatment of Hypertension (*Koketsuatsu shinryo no tebiki*)" were published in 1990 as a result of collaboration between the Ministry of Health and Welfare and the Japan Medical Association. Since credible data from clinical studies conducted in Japan were not sufficiently available at that time, the guidelines were developed on the basis of clinical experiences of guideline committee members with reference to similar guidelines from countries outside Japan.

Since "The Manual for Treatment of Hypertension" had not been revised for 10 years and had therefore become outdated, there were growing feelings in the Japanese Society of Hypertension that the guidelines needed to be revised, which would incorporate evidence-based instructions based on studies conducted in Japan. Around that time, the development of guidelines for the treatment of various diseases was proposed by the Promotion Committee for the Evaluation of Health Care at the Ministry of Health and Welfare with due consideration to the medical economy, which first resulted in the creation of the guidelines for the treatment of essential hypertension. The Japanese Society of Hypertension began the development of the guidelines headed by Dr. Masatoshi Fujishima, (professor emeritus and former professor of the Second Department of Internal Medicine, School of Medicine, Kyushu University) as the committee chairman. The new guidelines were published in July 2000.

1. Characteristics of the new guidelines

The new guidelines took sufficient account of characteristics of hypertension among the Japanese, and they were developed by drawing upon results of clinical studies conducted in Japan as much as possible. With regard to modifications of lifestyles and usage of antihypertensive drugs, current treatment practices in Japan were well taken into consideration. The new guidelines adequately reflect results of research conducted in Japan, by setting slightly higher goals for the timing of initiating antihypertensive drug therapy, and for the target of lowering blood pressure among patients in their 60s, 70s, and 80s. The addition of a new

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 7, 2001, pages 1040–1042).

Table 1 Classification of Blood Pressure Levels in Adults

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimum blood pressure	<120	and	<80
Normal blood pressure	<130	and	<85
High-normal blood pressure	130~139	or	85~89
Mild hypertension	140~159	or	90~99
Moderate hypertension	160~179	or	100~109
Severe hypertension	≥180	or	≥110
Systolic hypertension	≥140	and	<90

Table 2 Risk Factors for Cardiovascular Diseases and Disorders of the Cardiovascular Organs/Cardiovascular Diseases

Risk factors for cardiovascular disease	Disorders of the organs/Cardiovascular diseases
Hypertension	Heart: hypertrophy of the left ventricle; history of angina/myocardial infarction; heart failure
Smoking	Brain: cerebral hemorrhage and stroke; transient ischemic attack
Hypercholesterolemia	Kidney: proteinuria; renal disorder/failure
Diabetes	Blood vessels: arteriosclerotic plaque; dissection of the aorta; occlusive arterial diseases
Elderliness (60 or older in men and 65 or older in women)	Ocular fundus: hypertensive retinopathy
Family history of premature cardiovascular disease	

chapter on hypertension among children provides another feature of the new guidelines.

2. Classification of blood pressure levels, the timing of initiating antihypertensive drug therapy, and target of lowering blood pressure

Since classification of blood pressure levels should be universal, the new guidelines adopted the same classification scheme used in the 6th report of the Joint National Committee in the U.S. as well as in the guidelines of the World Health Organization — International Society of Hypertension (WHO-ISH) committee, although expressed in different ways. Table 1 summarizes the classification scheme. Hypertension is defined as a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, and the degree of hypertension is broken down into 3 grades. The range of normal blood pressure is also classified into 3 levels: optimum, normal, and high-normal.

The new guidelines suggest that the timing of initiating antihypertensive drug therapy should be determined not by the blood pressure level alone, but also on the presence of other risk factors for cardiovascular diseases, target organ damage, or comorbid conditions of cardiovascular diseases. As factored in the new guidelines, procedures for antihypertensive therapy should be shaped according to the severity of high blood pressure assessed in light of risk factors associated with cardiovascular disease and of disorders of cardiovascular organs or cardiovascular diseases as shown in Table 2. Taking into account the levels of blood pressure and the contents of Table 2, Table 3 shows stratification of risks of hypertensive patients. Figure 1 illustrates risk stratification according to medical examinations of hypertensive patients and

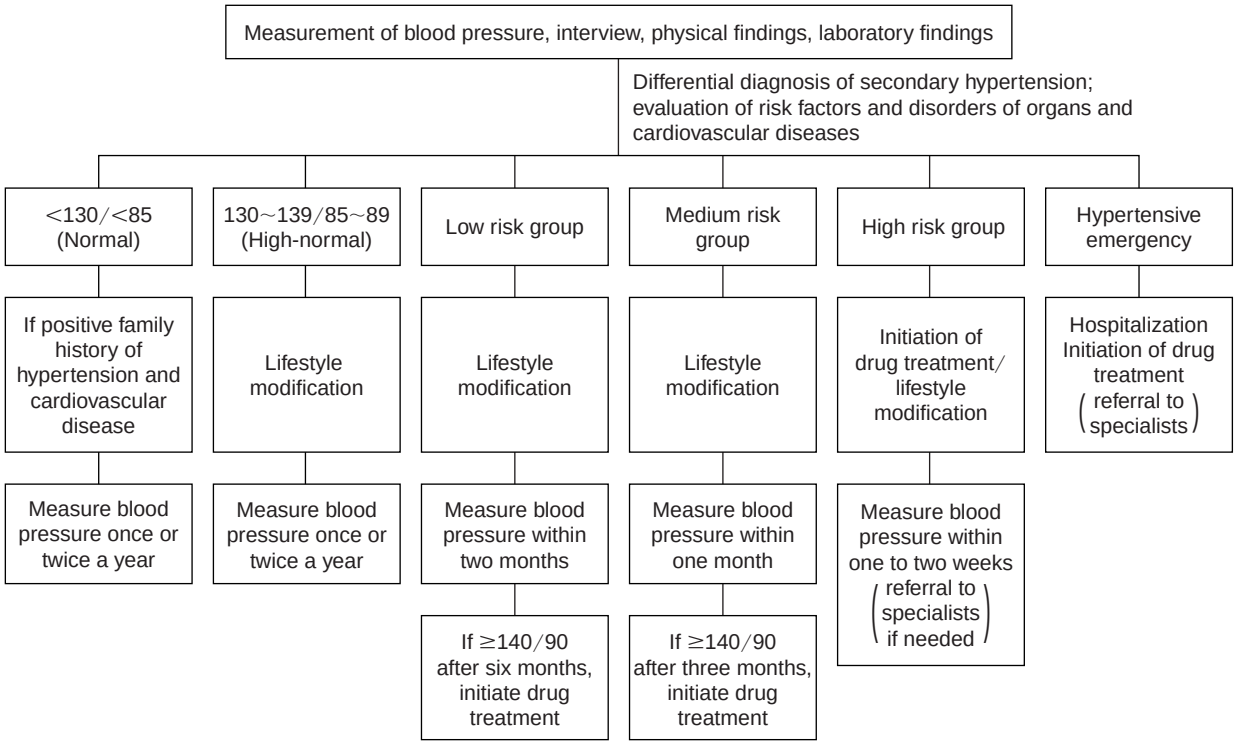

Fig. 1 Diagnosis of hypertensive patients and treatment procedures

Table 3 Risk Stratification of Hypertensive Patients

Blood pressure levels / Risk factors other than blood pressure	Mild hypertension (140~159/90~99 mmHg)	Moderate hypertension (160~179/100~109 mmHg)	Severe hypertension (≥180/≥110 mmHg)
No risk factors	Low risk	Medium risk	High risk
Risk factors present other than diabetes	Medium risk	Medium risk	High risk
Diabetes, organ damage, or cardiovascular diseases present	High risk	High risk	High risk

treatment guidelines for each group.

As indicated in Table 3 and Fig. 1, for patients in a low risk group with no risk factor and mild hypertension, the new guidelines encourage the introduction of antihypertensive drug therapy if the blood pressure level continues to exceed 140 mmHg systolic pressure or 90 mmHg diastolic pressure after 6 months during which lifestyle modification is attempted. For those in a medium risk group, the new guidelines recommend that antihypertensive drug therapy be instituted if the blood pressure level continues to be 140/90 mmHg or greater after 3 months of lifestyle modification. For hypertensive patients with blood pressure level of 180/110 mmHg or greater, with diabetes, or with disorders of target organs, immediate initiation of antihypertensive drug therapy is recommended along

with changes in lifestyle.

3. Lifestyle modification

Lifestyle modification constitutes the cornerstone of hypertension treatment. The new guidelines provide the following recommendations for modification of lifestyle: daily salt intake of less than 7 g; maintenance of appropriate body weight; moderation of alcohol consumption; limited intake of cholesterol and saturated fat; therapeutic exercises; and smoking cessation.

4. Directions for antihypertensive drug use

Drug treatment is initiated when blood pressure does not decrease to a desired level even with lifestyle modification. The new guidelines recommend the following as primary drug classes: calcium antagonists; ACE inhibitors; angiotensin II receptor antagonists; diuretics; β-blockers (including $\alpha\beta$-blockers); and α-blockers.

The general principle of antihypertensive drug use calls that primary drugs that best suit the clinical conditions of the patient should be selected. The dosage should be small at the beginning and then be gradually increased, and if desirable effects are not achieved, combination therapy with other drugs with the possibility of producing synergistic effects should be added to the regimen. Furthermore, if the primary drugs are found to be ineffective, another approach is to change class of drugs.

Blood pressure is important to be gradually reduced. Especially in elderly patients, the blood pressure levels should be slowly decreased.

5. Goals of treatment lowering blood pressure

Goals of blood pressure reductions vary slightly based on age and the presence of complications. The new guidelines set the threshold level of under 130/85 mmHg for young and middle-aged individuals with hypertension as well as for those hypertensive patients with diabetes or nephropathy. Blood pressure level of under 125/75 mmHg is recommended for patients with 1 g or greater of urine protein excretion per day.

REFERENCE

1) Organizational Committee of the Japanese Society of Hypertension for the Guidelines for the Treatment of Hypertension: *The 2000 Guidelines for the Treatment of Hypertension.* The Japanese Society of Hypertension, 2000. (in Japanese)

Future Outlook for Treatment of Chronic Hepatitis C

JMAJ 45(2): 88–90, 2002

Shiro IINO

Professor, Division of Gastroenterology and Hepatology,
Department of Internal Medicine, St. Marianna University, School of Medicine

Key words: IFN; Ribavirin; HCV genotype; HCV RNA

The basic treatment of chronic hepatitis C (CHC) worldwide is interferon (IFN) therapy. In Japan, however, IFN is perceived to have inadequate efficacy and strong side effects as well as being subject to unreasonably stringent health insurance review, and IFN therapy remains unpopular. This situation continues despite the demonstration of efficacy in CHC in many short-term and long-term clinical studies conducted in Japan as well as in other countries of the world.

Side effects may not be acceptable if the treatment is for the relief of symptoms. However, IFN therapy for CHC is aimed at treatment of the cause of the disease, and some side effects may be considered unavoidable particularly since IFN therapy only started about 10 years ago. If analogy is made to the history of tuberculosis treatment, we are now in the age of streptomycin.

Currently, the first choice of treatment of CHC in the United States and Europe is combination treatment with IFN and ribavirin. In Japan, clinical studies of this combination have been completed, and regulatory approval is expected very soon. Since very good results have been obtained, the treatment of CHC in Japan is also expected to be with the IFN and ribavirin combination.

Ribavirin

Ribavirin is an antiviral drug used against a broad spectrum of DNA and RNA viruses. Following oral administration, it is absorbed in the intestines, followed by uptake by all cells of the body. The half-life of plasma concentrations is long at 298 hours, and there is a tendency for accumulation. Steady state in plasma concentrations is reached in about one month of daily administration, and complete washout takes about 6 months. Ribavirin is not released once there is uptake by red blood cells, and therefore hemolytic anemia may occur. Ribavirin does not bind to plasma protein and is metabolized in the liver, although it is not a substrate of P450. Excretion of ribavirin and its metabolites is through the kidneys. Factors related to excretion are kidney function, body weight, sex, and age. Excretion is not affected by hepatic impairment. Although there are many unknown aspects of the mechanism of antiviral action of ribavirin, reduction of the GTP pool in cells and polymerase inhibition are known. In combination

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 9, 2001, pages 1444–1445).

Table 1 Efficacy of IFN-ribavirin Combination Therapy

U.S.	IFN + placebo		IFN + ribavirin	
	24 weeks (n = 231)	48 weeks (n = 225)	24 weeks (n = 228)	48 weeks (n = 228)
HCV RNA-negativity	6%	13%	31%	38%
ALT normalization	11%	16%	32%	36%

(Taken from Reference 1)

Europe	IFN + placebo	IFN + ribavirin	
	48 weeks (n = 278)	24 weeks (n = 277)	48 weeks (n = 277)
HCV RNA-negativity	19%	35%	43%
ALT normalization	24%	39%	50%

(Taken from Reference 2)

with IFN, however, ribavirin is thought to promote the HCV eradication effect of IFN by effect on the immune system instead of by direct antiviral effect.

IFN + Ribavirin Combination Therapy

1. Initial treatment

Many reports of clinical experience in the U.S.[1] and Europe with IFN + ribavirin combination therapy are now available. The main reports are of the two studies conducted in the United States[1] and Europe,[2] The results of which are summarized in Table 1. The IFN is IFN α-2b and the treatment regimen was 3 MIU administered 3 times a week for 24 or 48 weeks. The treatment regimen with ribavirin was 1,000 or 1,200 mg/day every day (body weight of 75 kg as cutoff point). About one-half of the patients received placebo instead of ribavirin.

In the U.S. study, at the Japanese standard duration of treatment of 24 weeks, only 6% of patients became HCV RNA-negative with IFN monotherapy. In Japan, a 29% HCV RNA negativity rate is observed since high dose induction therapy is conducted with IFN monotherapy. With IFN + ribavirin combination therapy, 31% in the U.S. study and 35% in the European study were observed to achieve HCV RNA negativity.

Two double-blind comparative clinical studies of IFN + ribavirin combination therapy were conducted in Japan, one in patients with genotype 1b and viral load of at least 1 Meq/m*l* as determined by the branched-DNA assay or 100 Kcopies/m*l* by Amplicor-monitor assay and the other in non-responders to previous IFN treatment.

Schering-Plough interim data indicate that in IFN-treatment naive patients with genotype 1b and high viral titers, 2 out of 24 patients (8%) in the IFN + placebo group and 12 out of 57 patients (21%) in the IFN + ribavirin group achieved HCV RNA negativity. The treatment regimen with IFN α-2b was 10 MIU daily for the first two weeks followed by 6 MIU three times a week thereafter for the IFN + placebo group and 10 MIU or 6 MIU daily for the first two weeks followed by 6 MIU three times a week for the IFN + ribavirin groups. No difference was observed in the results between the groups receiving 10 MIU and 6 MIU in the first two weeks.

Patients with low viral titers account for about 30% of patients with genotype 1b. About 50%

of these patients achieve HCV RNA negativity with initial treatment with IFN monotherapy as do patients with genotype 2a and 2b.

2. Re-treatment

The results obtained outside Japan with re-treatment with IFN + ribavirin in non-responders and relaspers to initial IFN therapy have been various. The most well-known of these is the study conducted by Davis and colleagues[3] in patients who achieved HCV RNA negativity during initial IFN therapy but who relapsed after the end of treatment. The treatment regimen was the same as that of the previously mentioned two comparative studies, and HCV RNA negativity was observed in 8 out of 172 patients (5%) in the IFN + placebo group and in 84 out of 173 patients (49%) in the IFN + ribavirin group.

In one of the two clinical studies conducted in Japan, retreatment of patients with genotype 1b and high viral titers resulted in HCV RNA negativity in 0 out of 60 patients with IFN + placebo and 19 out of 114 (16%) with IFN + ribavirin. In the other study conducted in Japan, retreatment resulted in 6 out of 41 (15%) patients with genotype 1b and high viral titers and 16 out of 20 (80%) patients with other than genotype 1b and high viral titers achieving HCV RNA negativity.

3. Adverse reactions with ribavirin

Ribavirin is a teratogen and patients must avoid pregnancy from the start of treatment to 6 months after the end of treatment. Hemolytic anemia has been reported as an adverse reaction during treatment with ribavirin. Hemoglobin levels are observed to decrease to minimum levels in the first month of treatment and to remain at reduced levels for the duration of treatment. The dose of ribavirin is reduced if hemoglobin reduction is marked.

Conclusion

In patients with genotype 1b and high viral titers who account for about 50% of all chronic hepatitis patients in Japan, the rate of HCV RNA eradication can be expected to be raised from 6–8% achieved with IFN monotherapy to over 20% with IFN + ribavirin combination therapy. In patients with genotype 1b and low viral titers who account for about 20% of patients, the HCV RNA eradication rate can be raised from about 50% to over 65%, and in patients with genotype 2a and 2b, an increase from about 50% to over 75% can be expected with combination therapy. Based on past results and these new results, an overall increase in HCV RNA eradication rate of at least 45% can be expected with combination therapy from the 29% achieved with IFN monotherapy. In addition, further improvement in eradication rate can be expected if treatment duration is extended to 12 months.

The future of treatment of chronic hepatitis C will remain to be based on IFN.

REFERENCES

1) McHutchison, J.G., Gordon, S.C., Schilff, E.R. *et al.*: Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998; 339: 1485–1492.
2) Poynard, T., Marcellin, P., Lee, S.S. *et al.*: Randomised trial of interferon alfa-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alfa-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; 352: 1426–1432.
3) Davis, G.L., Esteban-Mur, R., Rustgi, V. *et al.*: Interferon alpha-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N Engl J Med* 1998; 339: 1493–1499.