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Guidelines for the treatment of Crohn's disease in children

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Abstract

This paper shows guidelines for the treatment of Crohn's disease in children by the Working Group of the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition (Chair: Yuichiro Yamashiro) and the Japanese Society for Pediatric Inflammatory Bowel Disease (Chair: Akio Kobayashi). The points in which these guidelines differ from those for adult patients are as follows. (i) Total enteral nutrition in the form of an elemental formula is indicated as primary therapy for children with Crohn's disease at onset as well as the active stage. Oral mesalazine is used together. (ii) Total parenteral nutrition (TPN) with oral mesalazine is required for children with serious illness. The use of a corticosteroid should be withheld for at least 1 week after TPN has been started. (iii) When TPN is not considered to be effective, additional corticosteroid is used. Full doses of corticosteroid should be used for at least 2 weeks after clinical improvement has been achieved, and then the dose of the corticosteroid should be tapered carefully. (iv) When surgery is indicated in pediatric patients with stricture or fistula formation and complicated by persistent growth failure despite medical therapy, the optimum time for surgery is thought to be before epiphyseal plates have been closed.

The incidence of Crohn's disease in children has been increasing in recent years in Japan, and the age of onset has become younger. For diagnostic standards, the best current reference is in the amendment guidelines for the diagnosis of Crohn's disease in the 1995 Annual Report of the Research Committee of Inflammatory Bowel Disease by the working group for the Ministry of Health and Welfare of Japan.¹ However, the diagnosis of Crohn's disease in children may be difficult owing to initial extra-abdominal symptoms, such as anorexia, weight loss, growth failure, fever or iron deficiency anemia, that do not suggest inflammatory bowel disease.

In children, the main involved site of Crohn's disease is the ileum with or without colon, and 5–20% of cases in children involve colitis exclusively.² Pediatric patients with small bowel disease are likely to have chronic malnutrition and growth failure at the time of diagnosis (25–30% of cases).³ Since

adverse effects of corticosteroid treatment such as demineralization and growth retardation are a particular drawback to its use, long-term corticosteroid use must be avoided as much as possible, especially in childhood.

In Japan, the amendment guidelines for the treatment of Crohn's disease in the 2002 Annual Report of the Research Committee of Inflammatory Bowel Disease by the working group for the Ministry of Health and Welfare of Japan⁴ were published for adults. There is a need for guidelines for treatment of Crohn's disease in children with a focus on normal growth and pubertal development as well as induction of remission of disease activity, maintenance of remission, and prevention of relapse. Recent clinical experience of treatment with infliximab has suggested that infliximab is effective for improving symptoms and for achieving corticosteroid independence in pediatric patients. Although published clinical data for the pediatric population are limited, there is a need to specify the criteria for use of infliximab in guidelines for the treatment of Crohn's disease in children. The Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition and The Japanese Society for Pediatric Inflammatory Bowel

Disease have organized a working group to establish guidelines for the treatment of Crohn's disease in children (Fig. 1).

Treatment of Crohn's disease in children

Principles of treatment

The objective of treatment for Crohn's disease in children is to induce remission of disease activity, maintain remission and prevent relapse as well as achieve normal growth and pubertal development.

Treatment plan

Acute phase of mild-moderate disease

Generally, total elemental diets⁵ are the primary treatment in the acute phase to induce remission, especially for children with Crohn's disease. Proposed mechanisms of action are improvement of general condition, decreased gut motility, reduction of antigenic load and changes in bowel flora. Mean remission rates after enteral elemental nutrition are approximately 85%. An oral aminosalicylate (mesalazine or salazosulfapyridin) is given concomitantly. For rectal disease, mesalazine and corticosteroids (betamethasone sodium phosphate or prednisolone) are commercially available as retention enemas.

Acute phase of moderate-severe disease

The use of total parenteral nutrition (TPN)⁵ is considered when total elemental diets are ineffective. TPN is also indicated in selected patients whose disease is severe. The use of a corticosteroid should be withheld for at least 1 week after TPN has been started. A relatively large percentage of patients respond to TPN in combination with aminosalicylate because of complete bowel rest and nutritional benefits.

When TPN is not effective, patients with severe presentation are treated with a corticosteroid⁵ after confirmation of no infection or abscess. Infection or abscess requires appropriate antibiotic therapy⁵ with or without drainage. Full doses of prednisolone are to be given until 2 weeks after the symptoms have been resolved, and then doses are tapered. Corticosteroid therapy causes obvious symptomatic relief, but endoscopic improvement is not achieved concomitantly.

Nearly half of patients treated acutely with steroids will become 'steroid-dependent' or 'steroid-resistant' after the acute course. Azathioprine and 6-mercaptopurine⁵ have been effective in allowing reduction in steroid doses in patients with steroid dependence.

A novel strategy to treat Crohn's disease is offered by infliximab, a chimeric monoclonal anti-tumor necrosis factor

α antibody. Infliximab can be used for patients with severe Crohn's disease who have not responded to conventional medical treatment mentioned above and for those with fistulizing lesions. However, there are many unresolved issues regarding adverse reactions, complications and safety in the long term.

Surgical indications⁵

Although surgery is not a radical therapy for Crohn's disease, it is indicated to treat complications or refractory disease to raise the quality of life. Surgical intervention is required in the setting of massive hemorrhage, perforation, persisting or recurrent obstruction, or unresponsive fulminant disease or toxic megacolon. However, the most common indications for surgery are refractory disease such as abscess or fistula formation despite medical therapy and medication side-effects (corticosteroid dependence). Pediatric patients with growth failure who fail to improve with intensive medical management should be considered as surgical candidates. Surgical intervention might promote linear growth when it is done before the epiphyseal plates have been closed. The incidence of perianal suppuration in children is high, and incision and drainage (seton drainage) are required.

Therapy in the remission stage to prevent relapse

Remission is defined according to clinical symptoms, laboratory data and endoscopic appearance. In children, the Pediatric Crohn's Disease Activity Index,⁶ which includes evaluation of longitudinal growth, reflects disease activity. Longitudinal growth or pubertal development should also be evaluated during the course of the disease, because impairment of longitudinal growth is a sensitive marker of persistent inflammatory activity. It is noteworthy that although inflammatory disease may be in remission clinically, there may not be endoscopic or mucosal healing. In children with Crohn's disease, clinical remission and endoscopic remission are not well correlated.

Maintenance of remission has been more difficult to achieve medically. Relapse occurs once the enteral nutrition is discontinued. Pediatric patients with fibrostenosis in the small bowel require an elemental diet (at least 30 kcal/kg per day) to maintain long-term remission. Patients without stricturing lesions can be given polymeric diets instead of elemental ones and use the Crohn's disease diet (a low-fiber, fat-limited diet without stimulus) for up to 50–70% of total required energy.

Aminosalicylate therapy is used in the maintenance of remission. Azathioprine and 6-MP are used for steroid-sparing and improving maintenance of remission. The optimal duration of treatment with azathioprine or 6-MP is not known. Previous studies have shown that there may be no serious adverse effects for up to 3–5 years.

Conclusion

In this paper, a clinical diagram for treatment of Crohn's disease in children, made by the working group of The Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition and The Japanese Society for Pediatric Inflammatory Bowel Disease was introduced. The most suitable treatment should be selected after fully considering the disease condition of each patient.

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