

Supplementary enteral nutrition maintains remission in paediatric Crohn's disease

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Abstract

Background—Liquid diets given enterally combined with 'bowel rest' are efficacious in the treatment of active Crohn's disease, but rapid recrudescence of gastrointestinal symptoms after resumption of a normal diet is common.

Aims—This study examined whether continuation of enteral nutrition as a nocturnal supplement to an ad libitum daytime intake of a normal diet increased the length of remission of Crohn's disease in children.

Patients and methods—Children and adolescents with active Crohn's disease treated successfully with exclusive enteral nutrition were classified retrospectively according to whether they continued supplementary enteral nutrition or not. Time to relapse and linear growth were compared between the two cohorts.

Results—Between January 1986 and December 1992, 65 patients aged 7-17 years (mean (SD) 13.6 (2.1) years) (36 males, 29 females) with Crohn's disease in exacerbation were treated for \geq four weeks by bowel rest and nasogastric tube feeding of an oligopeptide or amino acid based formula. At first follow up visit, remission (fall in Paediatric Crohn's Disease Activity Index, PCDAI to \leq 20) was achieved in 47 of 65 (72%) patients. Subsequently, 20 of these 47 (43%) relapsed by six months and 28 of 47 (60%) by 12 months. Patients who continued nasogastric supplementary feeding (n=28) after resumption of an otherwise normal diet remained well longer than those who discontinued nocturnal supplements completely (n=19) ($p < 0.02$). Furthermore, continued use of nasogastric supplements before completion of puberty was associated with improved linear growth.

Conclusion—After successful treatment of active Crohn's disease by exclusive enteral nutrition, supplementary enteral nutrition without restriction of normal diet is associated with prolongation of remission and improved linear growth in children and adolescents.

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Keywords: paediatric Crohn's disease, nutrition treatment, growth.

Corticosteroids remain the most effective available medical treatment for acute exacerbations of Crohn's disease.^{1,2} Their use in the

paediatric population is limited by the adverse effect of longterm daily use on linear growth. Therefore, alternative treatments have been sought. Exclusive enteral nutrition using formulated food has been increasingly used as primary treatment of active Crohn's disease.^{3,4} Efficacy has been shown in controlled clinical trials, but symptoms recur in a high percentage of patients within several months of stopping the diet treatment.⁵ Longterm exclusive enteral nutrition and avoidance of a normal diet is an unreasonable therapeutic option. Compliance is much better, however, when normal food is permitted during the day. Such supplementary nocturnal nasogastric tube feeding is often used in children as a means of improving growth.⁶ We have found that patients using such supplementary feeding regimens also experience fewer relapses of gastrointestinal symptoms. To examine this question formally, we reviewed our experience with enteral nutrition as primary treatment of active Crohn's disease in children and adolescents. We designed a historical cohort study to discover if continued supplementary enteral nutrition without other dietary restrictions is associated with prolongation of remission.

Methods

Patients

The medical records of all patients with active Crohn's disease treated by exclusive nasogastric tube feeding of an elemental or semi-elemental liquid diet at the Hospital for Sick Children, Toronto, between January 1986 and December 1992 were reviewed. The formula used varied according to the time period, but otherwise all patients were treated with an identical protocol as outlined below.

Patients were admitted to hospital to learn the techniques of nasogastric tube insertion and formula infusion. Infusion rates of formulated food were increased in a stepwise fashion to provide the recommended dietary allowance (RDA)⁷ of total energy and protein during a 10 to 14 hours overnight infusion. Only clear fluids were permitted by mouth during the day. Patients were discharged from hospital when comfortable with the regimen, usually after five to seven days. Exclusive enteral nutrition was then continued at home. The child removed the feeding tube each morning to facilitate normal daytime activities and reinserted it each evening. Oral corticosteroids being given at the start of the liquid diet treatment were tapered and discontinued. Other medications, with the exception of metronidazole for perianal disease, were discontinued. In all patients

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TABLE I Baseline characteristics of the patients

Age	13.6 (2.1) years (range 7-17)
Sex	36 males, 29 females
Anatomical localisation of disease	
Small intestinal only (includes ileal ± caecal)	27
Ileocolonic disease	33
Colon only	5
Duration of diagnosed disease	2.0 (2.0) years (range 0.2-12) (9 newly diagnosed; 56 relapsed patients)
Tanner stage:	I 26, II 17, III 7, IV 6, V 9
Concurrent medications at baseline	
None	25 (9 patients in first exacerbation)
Sulphasalazine or 5-aminosalicylic acid only	13
Metronidazole	13
Prednisone (<0.5 mg/kg/day)	12
Prednisone (>0.5 mg/kg/day)	13
	(10 patients receiving ≥2 drugs)

Data shown as mean (SD).

anatomic localisation of disease had been recorded by radiological examination of the small intestine and radiological or endoscopic examination of the colon, or both. Duration of disease before the start of treatment and concurrent medications were recorded. Baseline measurements at treatment initiation included age, sex, height, weight, and Tanner stage.

After the first follow up visit, all patients who had achieved remission with exclusive enteral feeding resumed a normal an libitum daytime diet. Patients were encouraged by the consulting gastroenterologist, however, to supplement their daily intake of normal food with a lesser amount of the same liquid diet (usually 50-60% of the initial nightly amount) as a possible means of maintaining clinical remission of Crohn's disease. This was given through a nasogastric tube four to five nights weekly. Patients with growth potential were advised that such supplements could facilitate growth.⁶

For this study patients were classified retrospectively into two cohorts according to whether or not they chose to continue the nocturnal supplements after successful induction of clinical remission. Time to relapse and subsequent linear growth of patients belonging to the supplementary enteral nutrition cohort were compared with those in the control cohort. All heights were measured on a wall-mounted stadiometer.

Assessment of disease activity and response to treatment

Activity of Crohn's disease was assessed clinically at the start of treatment and at first follow up visit using the Paediatric Crohn's Activity Index (PCDAI), a multi-item score comprising clinical symptoms as well as packed cell volume, erythrocyte sedimentation rate (ESR), and albumin.⁸ Other laboratory parameters, including haemoglobin and serum orosomucoid, were also measured sequentially.

TABLE II Clinical and laboratory parameters at baseline and first follow up

	Baseline	First follow up	p Value
Body weight (kg)	36.5 (11.8)	42.1 (11.7)	<0.0001
PCDAI	40.3 (11.8)	15.4 (14.5)	<0.001
Packed cell volume	34.8 (4.3)	36.1 (3.3)	0.02
Haemoglobin (g/l)	113 (15.1)	118.4 (11.6)	0.003
ESR (mm in first hour)	28.2 (19.8)	22.6 (19)	0.05
Orosomucoid (g/l)	1.43 (0.5)	1.04 (0.5)	<0.0001
Albumin (g/l)	32.6 (4)	36.6 (4.6)	<0.0001

Data shown as mean (SD).

Success of exclusive enteral nutrition was defined as a decline in PCDAI to ≤20 at first follow up. Treatment failure was defined as the PCDAI remaining >20 or the patient being unable to tolerate the feeding regimen. Among responders relapse was defined by return of clinical symptoms necessitating additional treatment and associated rise in PCDAI to >20.

Assessment of patient acceptance

A questionnaire was given to all children who had received exclusive enteral nutrition as primary treatment. Patients were asked to report adverse effects of nasogastric tube feeding and were questioned specifically about night-time waking, nausea, vomiting, abdominal cramping, and loose stools. Patients who had previously been treated with oral corticosteroids were asked to state which, if either, of the two treatments they preferred. The questionnaire received the prior approval of The Human Subjects Review Committee at the Hospital for Sick Children, Toronto.

Statistical analysis

All data are expressed as mean (SD). Baseline values for PCDAI, age, and disease duration in the two cohorts were compared using the Student's *t* test. PCDAI and laboratory parameters at baseline and at first follow up visit and linear growth during the years before and after exclusive enteral nutrition were compared by the paired Student's *t* test. Comparisons of different anatomical locations were performed using two tailed Fisher's exact test. Rates of clinical relapse were compared using the log rank procedure. Changes in height velocity in the two groups were compared using the Student's *t* test.

Results

Between January 1986 and December 1992, 65 children and adolescents received exclusive elemental or semi-elemental liquid diets by nocturnal nasogastric infusion to treat active Crohn's disease. The formulated food used was either Vital HN (Abbott Laboratories, n=51), Vivonex (Sandoz Nutrition, n=8), or Peptamen (Clintec Nutrition, n=6). Table I summarises the characteristics at baseline. The study excluded an additional seven growth impaired patients without overt symptoms of intestinal inflammation, who were treated with enteral nutrition as a supplement to a normal diet but without an initial period of bowel rest. Another two patients with active Crohn's disease given with liquid diet treatment combined with bowel rest were excluded because immunosuppressive drugs were started simultaneously and may have contributed to disease control.

The PCDAI had fallen to <20 in 47 of 65 children (72%) at first follow up examination 1.5 (0.4) months (range 0.5-2.5 months) after the start of exclusive enteral nutrition. Of the 18 treatment failures, only three were

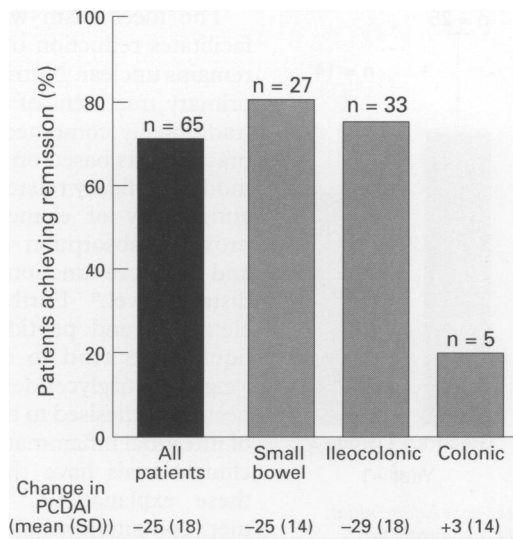


Figure 1: Percentage of patients achieving remission with exclusive enteral nutrition according to anatomical localisation of disease.

attributable to intolerance to or non-compliance with the nasogastric tube feeding. Table II shows mean values for PCDAI, weight, and laboratory parameters for all 65 patients at initial and first follow up assessments. As shown in Fig 1, fewer patients with isolated colonic Crohn's disease achieved clinical remission (one of five, 20%) compared with the other anatomical sites ($p < 0.03$).

Of the 47 patients who achieved remission, 20 (43%) children had relapsed by six months and 28 (60%) by 12 months. Those continuing nocturnal supplements ($n=28$) did not differ significantly from those declining to do so ($n=19$) with respect to age, site or duration of Crohn's disease, PCDAI at baseline or growth parameters. As Fig 2 shows, however, the cumulative probability of maintaining clinical remission was greater when supplementary feeding was continued during the year after

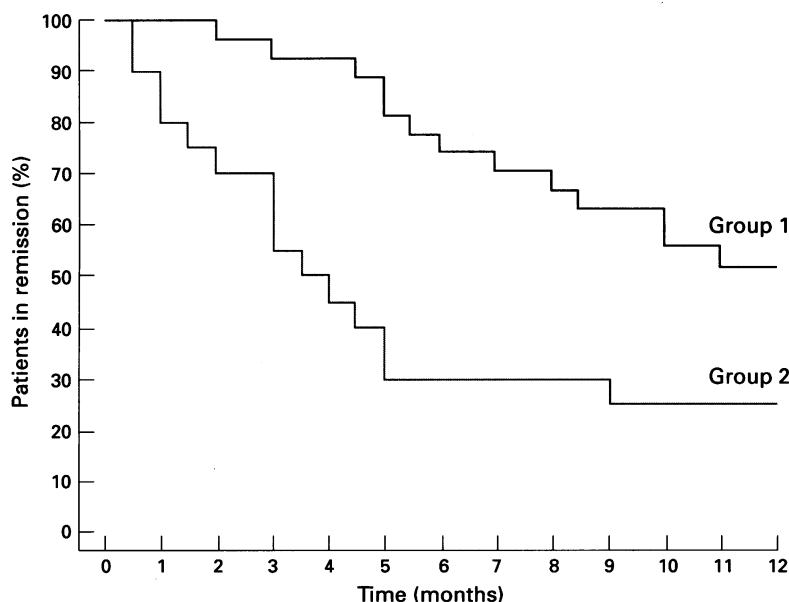


Figure 2: Cumulative percentages of patients remaining in clinical remission after resumption of ad libitum daytime diet. Group 1: cohort with nocturnal nasogastric liquid diet supplements ($n=28$), group 2: cohort without supplements ($n=19$) (log rank $p=0.005$).

exclusive enteral nutrition. Relapse rates at both six months (15 of 19 *v* five of 28, $p < 0.001$), and 12 months (15 of 19 *v* 12 of 28, $p < 0.02$) were higher in the control cohort compared with the cohort receiving nocturnal supplements.

One patient who continued supplementary feeds and two patients who did not were Tanner stage 5 and had completed their linear growth before treatment with enteral nutrition. Height velocity of the remaining patients with linear growth potential is displayed in Fig 3 for the year after initial administration of formulated food and the preceding year. Reliable height data from the year before treatment were lacking for newly diagnosed patients ($n=2$ in supplemented cohort, $n=6$ in control cohort) and for one other non-supplemented patient with Crohn's disease of long duration previously treated elsewhere. One control group patient emigrated temporarily so that height at 12 months could not be recorded. Follow up growth data from another two patients in each cohort were censored, because all four had intestinal resection at time of symptomatic relapse within the year after treatment with exclusive enteral nutrition. Hence change in linear growth velocity could not be attributed solely to nutritional intervention. The mean height velocity of the remaining 24 patients receiving supplementation with complete before and after treatment data was greater during the treatment year (6.1 (4.2 cm)) than during the previous year (3.2 (1.6 cm)) ($p < 0.001$). For the seven non-supplemented patients with complete before and after treatment measurements, the mean height velocity during the second year (4.2 (4.5 cm)) did not differ significantly from that recorded during the previous year (3.8 (1.2 cm)). Comparing paired data between the two cohorts, the mean change in height velocity was 2.87 cm/year among those continuing supplements versus 0.4 cm/year among those who did not ($p=0.057$).

Results of questionnaire

Questionnaires concerning acceptance of enteral nutrition were returned by 52 of 65 patients (80%). As Table III shows, untoward symptoms including sleep disturbance and gastrointestinal complaints were common. Nevertheless, of 44 patients who had experience with both oral corticosteroid treatment and enteral nutrition, 20 (45%) reported a preference of liquid diet treatment, whereas, 12 (27%) had no preference and 12 (27%) favoured the drug treatment.

Discussion

Active Crohn's disease successfully treated with exclusive enteral nutrition has been reported to relapse by one year after its discontinuation in 60 to 70% of patients.^{5 9 10} This was confirmed in our study among patients electing not to continue supplementary feeding. Our retrospective analysis suggests that continuation of liquid diet treatment as a

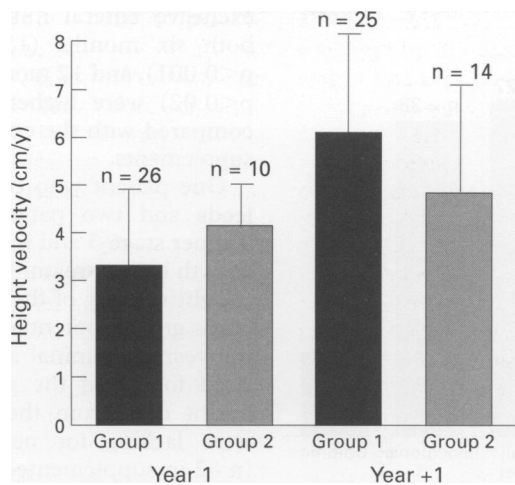


Figure 3: Height velocity during the year before initial exclusive enteral nutrition (year 1) and during the following year (year +1). Bar graphs represent mean (SD). Patients ($n=3$) whose linear growth was complete before short-term treatment with exclusive enteral nutrition are excluded. Group 1: patients with growth potential belonging to the supplementary nocturnal enteral nutrition cohort. Group 2: patients with growth potential belonging to the control cohort.

supplement to normal food, but without daytime dietary restrictions, prolongs the clinical remission induced by an initial period of exclusive enteral nutrition. The use of longterm dietary supplementation by nocturnal nasogastric infusion of formulated food to prevent relapse has not previously been reported. Harries *et al*¹¹ reported a beneficial effect of oral dietary supplements in maintaining remission in a crossover trial among adults with Crohn's disease. We and others have found that children and adolescents will not consistently comply with recommendations for oral supplements. Therefore, nasogastric tube feeding has become more widely used. In a study of similar design to ours, Belli *et al*¹² described improvement in clinical activity of Crohn's disease and growth among a much smaller group of children and adolescents who continued intermittent but exclusive enteral nutrition one month out of four over the course of one year, compared with those who declined to do so. The beneficial effects of such cyclical enteral nutrition combined with bowel rest on disease activity and growth were confirmed by Polk *et al*¹³ in an additional six patients who served as their own controls.

TABLE III Results of questionnaire (52 of 65 (80%) returned)

	Number (%) of patients reporting
Night-time wakening	
Always	11 (21)
Often	18 (35)
Sometimes	18 (35)
Never	2 (4)
Abdominal cramps	11 (21)
Diarrhoea	30 (58)
Nausea	23 (44)
Vomiting	22 (42)
Patients with previous experience with prednisone:	$n=44$
Patients reporting preference for:	
nutritional therapy (%)	20 (45)
prednisone (%)	12 (27)
no preference (%)	12 (27)

The mechanism whereby enteral nutrition facilitates reduction of intestinal inflammation remains unclear. Nutritional treatments used as primary treatment of active disease have been traditionally combined with 'bowel rest'. This practice was based on the hypothesis that their mode of efficacy related either to the decreased antigenicity of elemental liquid diets or to proximal absorption of predigested nutrients and therefore functional bypass of the diseased distal bowel.⁴ Further, amino acid based elemental and peptide based semi-elemental liquid diets tend to contain low amounts of longchain triglycerides. A low fat content has been hypothesised to be necessary for reduction of intestinal inflammation.⁴ However, results of clinical trials have challenged the validity of these explanations.^{5 9 14-16} Polymeric liquid diets containing whole protein and the normal 30-35% of energy as fat have been recently successfully used in the treatment of active Crohn's disease.^{5 9 14-16} In a randomised trial of adjunctive nutritional treatments, Greenberg *et al*¹⁷ found that partial parenteral nutrition plus an ad libitum oral diet was as effective in inducing clinical remission as either elemental liquid diets given by nasogastric tube or total parenteral nutrition and complete bowel rest among patients in hospital because of continuing activity of Crohn's disease despite high dose corticosteroid treatment. Furthermore, in a study comparing a semi-elemental with an elemental formula, the likelihood of attaining clinical remission correlated with an improvement in nutritional status rather than with effects on serum lipids.¹⁸ These findings support the hypothesis that the beneficial effect of enteral nutrition is primarily nutritional. It may depend on improved nutritional state in general or on the provision of an, as yet unidentified, micronutrient that facilitates healing of intestinal inflammation.

Our findings that supplementary enteral nutrition was associated with prolonged clinical remission despite resumption of regular food is consistent with a micro- or macro-nutritional effect, but not with the necessity of 'bowel rest' or avoidance of dietary antigenicity. Whether the type and amount of fat consumed by the supplementary enteral feeding group was significantly lower than that of the comparison group is not known. We did not ask patients in either group to keep daytime food diaries, and therefore cannot make definitive statements concerning the composition of their total dietary intake. The improved rate of weight gain and linear growth seen with supplementary feeding of an average 1250 calories five nights weekly, however, dictates that the unrestricted ad libitum oral intake was considerable.

Growth impairment is a common complication of childhood Crohn's disease. In our institution height velocity fell below the normal prepubertal rate (≥ 4 cm per year) for at least two individual years and bone age was accordingly delayed in 50% of a group of 100 children who were at Tanner stage 1 or 2 of pubertal development at the time of diagnosis.¹⁹ The important mechanism of the observed

retardation of growth is considered to be chronically inadequate intake of energy and protein resulting from both anorexia and aggravation of intestinal symptoms by eating.^{20 21} Enteric protein leakage from the inflamed intestine,²² excessive losses of specific dietary nutrients such as zinc, corticosteroid inhibition of somatomedin production interact and may contribute to the significant growth delay in at risk children.²³ Cytokines and other inflammatory mediators, such as tumour necrosis factor α (cachetin), may have a direct negative effect on both intake and utilisation of energy.²⁴ Consistent provision of adequate nutrition either orally, enterally or parenterally is effective in restoring normal growth.^{6 12 20 21} Aiges *et al* previously reported linear growth improvement by supplementary nocturnal nasogastric tube feeding of formulated food in a comparison of children and adolescents complying with versus those refusing such treatment.⁶ We have confirmed this beneficial effect in a larger group of patients. The observed improvement in linear growth probably reflects improved nutritional intake, as well as control of intestinal inflammation without the use of daily corticosteroids. Greater use of nutritional treatment as alternative primary treatment of active Crohn's disease should reduce the frequency of growth impairment and improve the prognosis for ultimate height.

The 47 patients comprising the supplementary enteral nutrition and control cohorts in this study constituted 72% of all those in whom treatment of active Crohn's disease with exclusive enteral nutrition was attempted. This 72% rate of clinical response to exclusive enteral nutrition is very similar to the overall 78% response rate in a prospective, randomised, multicentre paediatric trial where the response rate among those treated with oral prednisone was 90%.²⁵ Exclusive enteral nutrition in other randomised controlled trials versus corticosteroids successfully induced remission as defined by clinical multi-item measures in 53% to 82% of patients.^{9 10 25-30} In all but the smallest of these,^{9 30} the percentage of patients achieving clinical remission through enteral nutrition was lower than with corticosteroids. Only in the two largest trials, however, did the difference reach statistical significance.^{26 27} Our recent meta-analysis of randomised controlled trials of enteral nutrition versus corticosteroid treatment showed a treatment benefit for drug therapy compared with nutritional therapy that was not explained merely by intolerance.³¹

Enteral nutrition still constitutes an important therapeutic option, even if less efficacious than corticosteroids. No placebo controlled trials of enteral nutrition have been conducted. Clinical response rates to placebo, however, in active Crohn's disease in controlled clinical trials of drug treatment have ranged from 18% to 42% after intervals of 14 to 17 weeks.^{1 2 32} Comparison with observed response rates to exclusive enteral nutrition in prospective studies^{9 10 25-30} suggests that it is effective. Moreover, a reduction in gastrointestinal protein loss, a decrease in intestinal permeability, and a reduction in faecal excretion of

indium labelled leucocytes have each been shown,³³⁻³⁵ suggesting a direct effect on intestinal inflammation.

Acute Crohn's disease isolated to the colon proved comparatively refractory to treatment with exclusive enteral nutrition, but the small number of such patients precludes any definite conclusion. Adult patients with Crohn's colitis also responded poorly to enteral nutrition in another retrospective report.³⁶ Prospectively accrued data from randomised controlled trials of enteral nutrition are not often reported in a site specific fashion.^{9 10 28-30} The European Cooperative Crohn's Disease Study (ECCDS) could not show a correlation between site of intestinal inflammation and rate of clinical response to enteral nutrition.^{26 27} Over 60% of a group of 30 patients treated in randomised fashion with either an elemental or a polymeric liquid diet had inflammation confined to the colon, but the response rate overall was 70%.⁵ Hence prospective studies do not support restriction of enteral nutritional treatment to patients with active small intestinal inflammation.

We have been impressed that young patients adapt to nocturnal nasogastric tube feeding better than would originally have been expected. With instruction and encouragement provided by experienced nursing staff, intolerance was infrequent in the acute phase of treatment. Reported intolerance among predominantly adults in clinical trials versus corticosteroids is 21% overall, but is much greater when oral administration of formulated food is initially attempted than when, as in our study, the nasogastric route is used from the outset.³¹ The results of our questionnaire show that enteral nutrition is accompanied by frequent adverse effects such as night-time waking, nausea, loose stools, and vomiting. However, the beneficial effects on disease activity, the improved nutritional state, and improved linear growth make enteral nutrition acceptable to young patients despite these inconveniences.

In the long term, allowing normal food at times when family and friends are eating is particularly important in achieving compliance. The findings of this historical cohort study suggest that administration of formulated food is useful in controlling activity of Crohn's disease even when dietary restrictions are not imposed. The efficacy of such supplementary rather than exclusive enteral nutrition in maintaining remission should be further studied in a randomised, controlled fashion.

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