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SYNERGISTIC EFFECT OF EXCLUSIVE ENTERAL NUTRITION FORMULA IN ADDITION TO CORTICOSTEROIDS THERAPY TO INDUCE CLINICAL REMISSION IN PATIENTS WITH CROHN'S DISEASE: A PILOT STUDY INVOLVING A MULTIDIMENSIONAL ASSESSMENT OF POTENTIAL MECHANISMS

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Lay Abstract

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by diarrhea, abdominal pain and bleeding. There are several treatment options but the most-widely used for acute therapy are corticosteroids (CS); unfortunately, CS are often associated with severe side effects. The administration of a formula for exclusive feeding (EEN) is well-established as an alternative to CS in children with Crohn's disease (CD). However, this intervention is not routinely used in adults, in part because of uncertainty regarding the magnitude of the benefit of EEN reported in previous studies. In fact, few studies have examined the effects of EEN in adult patients with active CD. We propose that a polymeric formula, provided orally, may help decrease gut inflammation and improve nutritional status through modulation of gut bacteria. We will therefore investigate the effect of exclusive formula feeding therapy in addition to different regimes of CS therapy compared to CS alone in adult patients with active CD, on symptoms and inflammation after 6 weeks of treatment. We will collect information through questionnaires that assess gut symptoms, quality of life, mood changes and dietary patterns. To investigate potential mechanisms, we will collect stool samples to characterize gut bacterial profiles, blood to determine inflammatory markers and evaluate gut movements (motility) before, and after the treatment. We hope that our results will lead to better understanding of the beneficial effect of exclusive formula feeding in addition to CS as a more efficacious alternative than CS alone, and to understand the mechanisms of this therapy.

BACKGROUND

Crohn's disease (CD) is characterized by inflammation of the gastrointestinal (GI) tract, diarrhea, pain and rectal bleeding[1]. Canada has one of the highest prevalences of CD in the world with an estimated incidence rate of 16.3 per 100,000[2]. The pathophysiology of CD is not well understood, but a dysregulated immune response to altered microbiota may play a key role[3]. Treatment of CD requires a multi-disciplinary approach involving medical therapy, surgery and dietary changes. Corticosteroids (CS) are the first line therapy to induce remission; however, they have adverse effects and 30% of patients can prove to be steroid resistant or dependent[4]. Therefore, alternative therapies that can effectively induce and maintain disease remission without short and long-term side effects are needed[5].

Exclusive enteral therapy (EEN) involves a liquid diet of elemental or polymeric formula (PF), given exclusively over a prolonged period[6]. Elemental formula contains individual amino acids, while PF is providing intact proteins[7]. Although exclusive enteral nutrition (EEN) is used in children as an alternative to CS to induce remission due to its excellent safety profile[7], it is not routinely used in adults.

The beneficial effects of EEN in CD were first demonstrated over two decades ago, when O'Morain et al[8] demonstrated in a controlled study that an elemental diet was as effective as CS in achieving remission in adults with active CD. In particular, EEN was shown to induce the expression of growth factors, promote changes in intestinal permeability and stimulate mucosal healing[8, 9]. Since then, several studies aimed to investigate this area. Meta-analyses of EEN versus CS have found that, although CS are superior to EEN in

inducing remission, EEN is also efficacious with expected remission rates of up to 60% and provides additional nutritional benefit[5,10,20]. Although several studies have demonstrated effectiveness of elemental EEN in children, the effect of EEN in adult CD remain controversial[5,7,20].

Potential mechanisms by which EEN might act include relative bowel rest, reduced antigenic load, provision of trophic amino acids, local anti-inflammatory effects, and modification of gut microbiota[11,20]. However, there is no strong evidence to fully support any one of these mechanisms. A recent meta-analysis[20] showed that the effects of the therapeutic formula on specific bacterial strains were variable and inconsistent among studies, possibly due to small sample sizes and methodological limitations. Our preliminary data showed that short term dietary changes improve motility in patients with low-grade gut inflammation[21]. However, the effects of EEN on gastrointestinal transit in adults has not been yet investigated.

Evidence for the effect of EEN on quality of life, an essential patient reported outcome, is particularly scarce. Guo *et al*[30] found an improvement of quality of life in 13 patients with CD receiving EEN for 6 weeks. However, it is currently unknown whether EEN is more effective than CS in improving quality of life in adults with CD.

The potentially synergistic effects of adding EEN to CS therapy have not been explored before. Therefore, we designed a randomized controlled trial with the objective to investigate the effect of EEN in addition to different regimes of CS therapy (ECS) compared to CS alone (CS), for decreasing disease activity and improving quality of life in adult patients with CD. We also propose to investigate potential mechanisms underlying any beneficial effect of EEN in CD in the context of concomitant CS therapy.

Hypotheses:

1- Six weeks of ECS will be more effective than CS in inducing clinical remission in patients with active CD
2- Six weeks of EEN in addition to a short course of CS (ECSC) will have similar efficacy than ECS and reduced number of adverse events
3- Six weeks of ECS will lead to beneficial changes in the composition and/or metabolic activity of the intestinal microbiota, gastrointestinal transit and inflammatory burden.

Because the effect size of ECS has not been investigated before, we will perform a pilot study to assess feasibility and calculate estimates of effect size in order to plan a larger trial. Based on the significant number of patients, if the study is feasible, we will consider the sample size estimated through this pilot study for the full trial to minimize the possibility of recruiting additional patients.

General aim and endpoint: To assess study feasibility and provide estimated effect sizes (point estimates with confidence intervals) for all measures of interest in order to plan an adequately powered study. We will assess recruitment rates and acceptability of treatment in arms involving exclusive enteral nutrition.

Primary outcome and endpoint: To assess the efficacy of 6 weeks of ECS in inducing remission (CDAI <150) compared to treatment with CS in adult patients with active CD (CDAI >220 and either CRP >5 or fecal calprotectin >250 mg/l).

Secondary outcomes and endpoints: To determine the beneficial effect of 6 weeks of ECS as compared to CS in inducing:

1. Clinical disease improvement (drop in CDAI >70 or 100)
2. Improvement in quality of life (using the Inflammatory Bowel Disease Questionnaire (increase IBDQ scores))
3. Biochemical remission (normalization of either serum CRP and/or fecal calprotectin)
4. Changes in microbiota composition (16S sequencing Illumina)
5. Normalization of colonic transit (SHAPE 0-5 markers at day 5)[34] among those with altered transit at baseline
6. Decrease in anxiety and/or depression scores (decrease >2 points HAD-A and/or HAD-D scores)
7. Increase in body weight and improvement in nutritional status (increased levels of micronutrients)
8. Decrease of indirect markers of mucosal integrity (IFABP2)
9. Changes in bacterial fermentation profile (SCFAs: acetate (acetic acid), propionate (propionic acid), and butyrate (butyric acid) [26,27].
10. Decreased number of adverse events

METHODS

Study design

Randomized control trial; 3 arms of treatment: EEN plus standard or short course of CS (ECS, ECSC) vs CS alone (CS) conducted at McMaster University Medical Centre (Figure 1). The study will last 10 weeks and will involve 4 visits. At the screening visit, we will assess clinical history and symptoms, perform a physical exam and complete bloodwork after the informed consent is signed. Randomization will occur at the second visit (pre-treatment), when the inclusion and exclusion criteria and symptoms will be re-assessed, and baseline stool and urine samples will be collected. In addition, we will perform a SHAPE study and patients will be assessed by a dietitian or clinical nutrition support specialist to assess dietary factors and estimate energy needs using the Harris Benedict equation as detailed below.

Patients will be instructed to take the allocated treatment and to collect empty bottles/ blisters of medication to assess the compliance at the next visit. Six weeks later (visit 3), their symptoms will be re-assessed, blood, urine and stool samples collected and SHAPE study performed. Patients will be instructed to stop the EEN or decrease the dose of CS, as detailed in the section "Follow up after treatment". In the last visit (4^{th} visit; 10 weeks after enrollment) we will collect information on symptoms, stool samples and urine.

The study protocol will be submitted by the investigator for approval by the Hamilton Integrated Research Ethics Board (HiREB).

Randomization process

The sequence of the treatments will be randomly generated using a computer-based pseudo-random number generator (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA) Patients will receive one of challenges A,

B, or C consisting of CS, ECS or ECSC. A third person not involved in the study will perform the randomization to preserve treatment allocation concealed from participants and study staff. A block randomization will stratify patients by disease location (colonic/ small bowel involvement). Each treatment will be assigned a number according to the randomization sequence. On recruitment, the patient will be assigned into one of three strata and given the next consecutive randomization number available for that stratum. Treatment will be not blinded for patients or study staff.

Subject recruitment

Subjects will be recruited from McMaster University Medical Centre (MUMC) Digestive Diseases Clinic, identified in an ongoing database organized in 2008 and by recruitment flyers posted at McMaster University Medical Centre, Juravinski Hospital and Hamilton General Hospital. Patients in the database signed an informed consent agreeing to be contacted for future research. Patients will be contacted by study personnel and invited to participate in the study.

After the subject has provided written consent to participate, an inclusion checklist will be completed. Subjects will be enrolled after having fulfilled all inclusion criteria, and none of the exclusion criteria.

Participants

One hundred adult patients diagnosed with IBD will be recruited at McMaster University Medical Centre. This will provide 30 subjects in each treatment arm, allowing for 10% dropout rate.

Inclusion criteria:

1. Adult patients (age 18-75 years)
2. Confirmed CD diagnosis for at least 6 months
3. Clinically active disease (CDAI >220 or HBI>6) or evidence of activity in endoscopy
4. Biochemical evidence of disease activity (CRP > 5 and/or fecal calprotectin > 250),

Exclusion criteria:

1. Current treatment with EEN
2. Intestinal obstruction, perforation, toxic megacolon, massive gastrointestinal bleeding, abdominal abscess, or other criteria considered by the investigator which preclude the use of EEN;
3. Stricturing disease
4. Previous intestinal resection with a remnant bowel <180 cm
5. Treatment with prednisone in last 30 days;
6. New start or change in dose of azathioprine, 6-mercaptopurine, cyclosporine, other immunosuppressant or biologics in the last 90 days. Doses of these medications must also remain unchanged for the duration of the study.
7. New start or change in dose of 5ASA in last 30 days. 5ASA dose must remain unchanged for the duration of the study.
8. Treatment with antibiotics or probiotics use in the last 30 days.
9. Pregnancy or lactation
10. Any serious illness considered by the investigator that will interfere with the study procedure or results.

Intervention

Participants will be randomized to one of the following interventions:

1. **Exclusive enteral nutrition plus corticosteroids**

Patients randomized to ECS or ECSC arms will receive EEN defined as enteral feeds given exclusively as sole nutritional source over 6 weeks period in addition to the CS therapy. Hypercaloric polymeric formula (Modulen 1.5 kcal /ml; Nestle [22,23]) will be used for a period of 6 weeks. To increase palatability, patients will be allowed to add the "Nestle Nutrition Flavour Mix" (see Appendix). Daily volumes of formula will be prescribed based upon the patient's estimated energy requirement (EER), calculated using the Harris Benedict equation (calculator available at https://manytools.org/handy/bmr-calculator), which estimates basal metabolic rate from weight and height and then applies an activity factor which ranges from 1.2 to 2.4 (Sedentary AF 1.2; mild activity 1.375, moderate activity AF 1.55, heavy activity AF 1.7, extreme AF 1.9 For details, refer to Appendix). Actual body weight or ideal body weight for height will be used in the equation depending on whether the patient is of an appropriate weight or underweight for height. Oral administration will be encouraged wherever possible, with formula volume distributed as set meals and snacks throughout the day. Nasogastric (NG) tube insertion for delivery of formula will be discussed and offered only if oral supplementation is not possible or not tolerated by the patient. Enteral feeding will be prescribed as an exclusive therapy, with exclusion of all normal diet for the period of feeding. Patients will be reviewed after 3 weeks of therapy and, when required, energy intakes will be modified by adjusting formula volumes based upon adequacy of weight changes. Volume taken per meal and distribution during the day will be recorded in the case report form. No oral foods or fluids

(except for clear liquids including water and weak tea or coffee) will be allowed during the study period. Vitamins and supplements will be allowed if doses have been stable before entering in the study, and doses are not changed during the study.

2. Corticosteroids

Patients in ECS and CS arms will receive oral prednisone 40 mg x day for 2 weeks; with subsequent taper of daily dose by 5 mg per week. Patients randomized to ECSC arm will receive oral prednisone 40 mg x day for 3 days and taper in 16 days (Figure 1). Patients randomized to the CS arm will be asked to maintain their regular diet.

Follow up after treatment

Following the completion of the period of exclusive enteral feeding, patients receiving EEN will be instructed to gradually reintroduce foods by adding one individual item every 2 days as shown in Table 1 [32,33] and Appendix with instructions for food introduction with coincident reduction of formula volumes under the supervision of an expert in Nutrition. The accelerated introduction of foods was based on a recent study showing similar results with additional benefits of 2 days vs 4 days [33.]

Treatment compliance

The subjects will be asked to keep the cans of Modulen and blister packs of prednisone during the entire treatment period and bring them back to the investigator at the end of that period. Compliance will be recorded in the CRF. In order to improve assessment of patient's compliance, 2 copies of a paper sheet diary will be provided at Visit 1. Patients

consuming <80% of the prescribed treatment dose throughout the study, or those who interrupted therapy for more than three consecutive days will be considered as noncompliant.

Measurements before and after treatment

- Clinical data regarding demographics, disease location and activity (Harvey-Bradshaw Index), social life and habits, past and current clinical medical background, previous surgeries, nutritional status (malnourishment, weight/ height) will be collected in CRF.
- Dietitian/ Certified nutrition support clinician: Dietary habits and caloric intake will be recorded at baseline with nutritional assessment during visits
- Bloodwork to assess for inflammatory markers, CRP, fecal calprotectin, ESR, as well as CBC, platelets, micronutrients (albumin, vitamin D, B12, A , zinc, copper, chromium)
- Questionnaires: McMaster Food frequency questionnaire(Hamilton, ON), quality of life (*S*IBDQOL[13]), disease activity (CDAI), anxiety and depression (HAD score, Beck inventory), and nutritional assessment (Subjective Global Assessment[14] Braun Nutriscreen program)
- Gastrointestinal transit (colonic transit: SHAPE study and orocecal transit[24,25]: patient will take one capsule and have an x ray on day five, following R.C. Evans, et al protocol, where ≥6 markers indicate delayed transit, therefore ≤5 is normalization of colonic transit).[34]
- Stool sample (frozen samples) for microbiota composition (16S sequencing Illumina; Dr. P Bercik's lab) metabolomics and metagenomics (Britz-McKibben?) [15]

- Systemic priming to gut bacteria (Verdu Lab using Flow cytometry after incubating patients' serum with cultured fecal bacteria[16]
- First urine morning for metabolomics
- Intestinal permeability – indirect markers of mucosal integrity (FABP2)

Statistical analysis

There is no previous estimate on the effect of ECS compared to CS in inducing symptomatic improvement and associated changes in gut microbiota composition. Therefore, a sample size of 30 patients per arm[28,29] should be sufficient to estimate the results and allow us to plan for future larger study. We will recruit additional 10 patients in total, to account for drop outs rates. Results will be analyzed as intention to treat (for primary outcome) and per protocol (excluding patients non-compliant with EN). The results will be expressed as n (%), mean (SD) or median (IQR) as appropriate. We will perform logistic regression to assess the association between symptomatic response and significant changes in gut microbiota composition in each group. T test or Man Whitney U test will be used as appropriate to assess differences between means. Analysis will be performed using SPSS version 21 (San Diego, CA).

Early withdrawals:

The following criteria will be considered as reasons for early discontinuation from the study (drop outs):

- Patient's decision.

- Physician's decision in case that the continuation of the patient in the study places him/her at risk.
- Patients that that were not compliant with the unauthorized concomitant diets/treatments/medication will be considered as non-compliant and considered for the ITT analysis. If a subject's outcome measures worsen to the degree that they meet the study's Exclusion Criteria, study treatment will be withdrawn. Medical care will be provided as directed by the study physician and/or the subject's physician. If the required medical care conflicts with the study protocol, the subject will be placed in the intent-to-treat group. Study safety follow up will continue unless the subject withdraws, and/or is withdrawn by the study physician, and/or on the advice of the subject's physician.

Handling of adverse events

Reporting and documentation of adverse events

All adverse events occurring during the study will be reported and recorded whether or not they are considered to be non-serious, serious and/or related to the treatment. The following information will be required in each case:

- Subject and date
- Description of event
- Duration
- Frequency
- Intensity
- Seriousness
- Action taken

- Outcome and sequel
- Relationship to test product

Documentation of all adverse events includes completion of the appropriate section of the case report form (AE). Documentation of a serious adverse event that requires a separate form (SAE) will be completed by the investigators in each case.

If further information or examinations are required to assess the relationship between an adverse event and treatment following the occurrence of the adverse event, all examinations or laboratory findings will be noted with their results in the CRF (section UV) or attached to a follow up file. Notification of the HiREB will also be performed in the event of an SAE during the clinical trial.

Estimated length of study: 2 yrs

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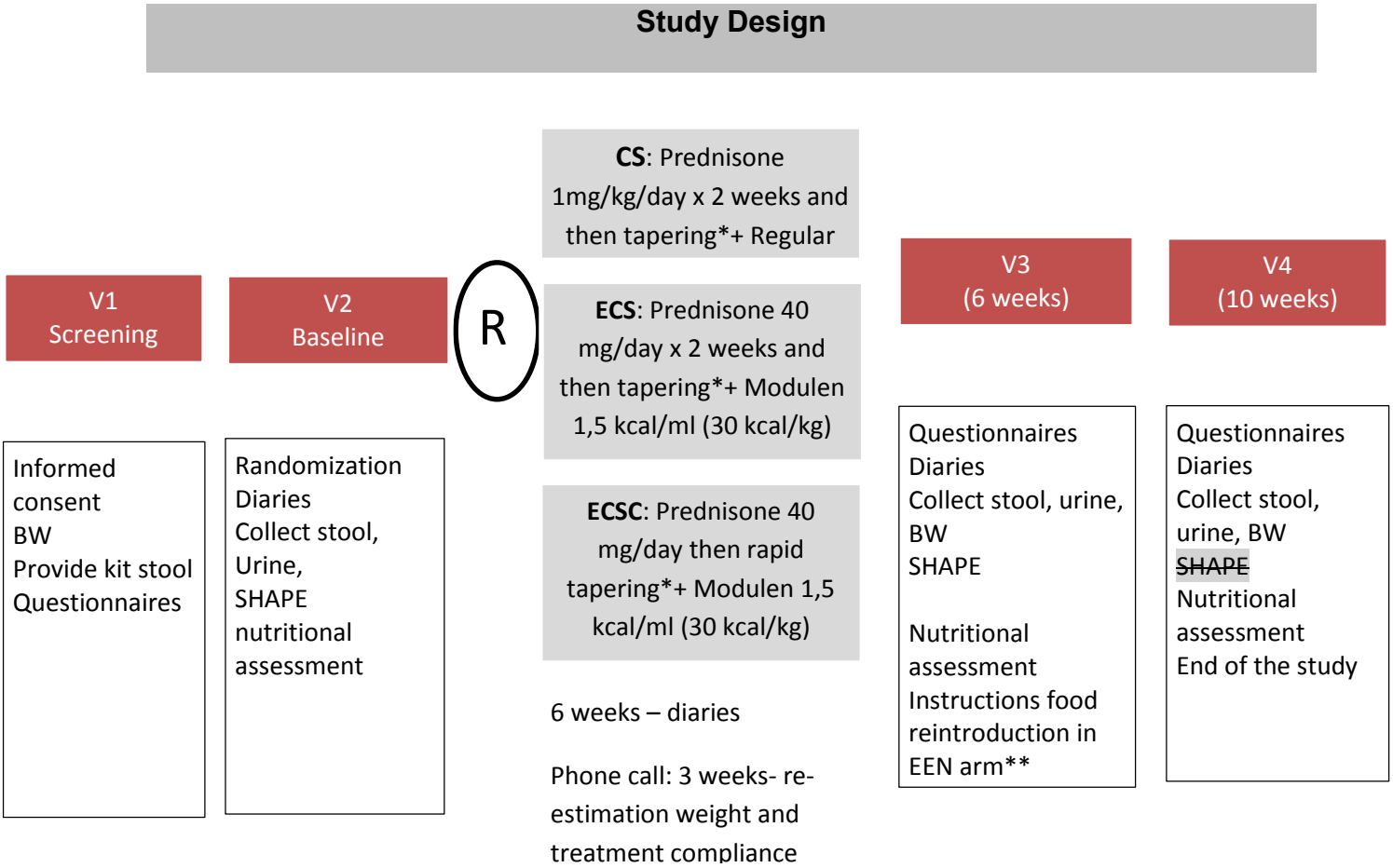
Figure 1



***Standard corticosteroids tapering regimen (ECS)**

Week	1	2	3	4	5	6	7	8	9	10
CS mg/day	40	40	35	30	25	20	15	10	5	5 mg every other day

*Short course corticosteroids tapering regimen (ECSC)

Day	1	4	7	10	13	16				
CS mg/day	40	30	20	10	5	5 every other day	0	0	0	0

INSTRUCTIONS FOR FOOD REINTRODUCTION AFTER 6 WEEKS OF EXCLUSIVE ENTERAL NUTRITION

https://www.qegateshead.nhs.uk/sites/default/files/users/user1/leaflets/IL382%20Modulen%20IBD%20-%20Reintroduction%20of%20foods.pdf

After 6 weeks on exclusive formula feeding, it is time to reintroduce all of the food you have removed during the program. The purpose of doing this very slowly is to give time to the gut to adapt to the diet. Transition to normal foods must be done with care, foods should be gradually reintroduced over a period of two to four weeks, however, it may be necessary to reintroduce foods more slowly.
In order to accomplish this, please introduce each of the following food groups for the period of time suggested in each stage, ideally respecting the order. If you do have a reaction, such as headache, rash, brain fog, fatigue, digestive reaction or other symptom you are familiar with, write it down in the food reintroduction chart below or a food journal so you don't forget later. If you discover a particular food isn't good for you, remove it again. The food reaction should go away within a day or 2. If you are not used to take any of the foods from the list, it is ok to skip it. When you have finished reintroducing all the foods from the list, a free diet is allowed.

Start date: .....

Stage 1: (Two days) with ½ of IBD formula
Initially fluids not containing dairy, eg tea or coffee black or with soya milk, fruit juice, fruit squash, Oxo, carbonated drinks, sieved soup, jelly or ice lollies.

Stage 2: (Five days) with ½ of IBD formula
Introduction of a few soft foods eg fish, chicken, egg, rice and potato. Small frequent snacks should be encouraged instead of one or two larger meals.

Stage 3: (Five days) with ¼ of IBD formula
Gradually increase the variety of foods in the diet continuing to keep the fibre and fat content low, eg red meat, stewed or peeled fruit, very well-cooked vegetables. The portion size of meals should be gradually increased with the number of snacks reduced.

Stage 4: (Three days) with ¼ IBD formula
Addition of bread and other gluten containing foods ie pasta, cereal, bread, biscuits, crackers, cakes, sausages.

Stage 5: (Three days) No IBD formula
Inclusion of milk or milk derivatives (if you are not lactose intolerant) ie margarine, butter, milk, cream, ice cream, yoghurts, fromage frais, milk pudding, custard.

Stage 6: Gradually increase dietary fibre, fried and spicy food if desired. It may be an idea to keep a food and symptom diary recording the food you eat. See below for an example.

If you have any reaction to any food or food group, avoid adding anymore new foods. After three days you may return to the food reintroduction avoiding any suspect foods

FOOD REACTION LOG

Date	Food/drink	Symptoms	Severity (1-5)

Table : Food reintroduction (Sanderson et al, Arch Dis Child 1987; 61:123-127)

Table 3 *Food reintroduction programme six weeks after starting Flexical*

Each new food is reintroduced into the diet four days after the previous food in the following order:

Potatoes
Lamb
Pears
Chicken
Yeast (Breweres Yeast Tablets)
Wheat (spaghetti)
Bread (wholemeal)
Cabbage
Rice
Apple
Carrot
Beef
Milk
Butter
Cheese
Eggs

A free diet is allowed once these foods have been started

Rationale for rapid introduction of foods vs standard (Faiman A, et al. Standard versus rapid food reintroduction after exclusive enteral nutritional therapy in paediatric Crohn's disease. Eur J Gastroenterol Hepatol. 2014 Mar;26(3):276-81)

Appendix 2-Steroids adverse events assessment (visit 2)

	Yes/no	**Comments**
1. Moon face		
2. Bloating		
3. Swelling		
4. Weight gain		
5. Increase appetite		
6. Hair loss		
7. Acne		
8. Stretch marks		
9. Insomnia, restlessness and or trouble sleeping		
10. Anxiety or nervousness		
11. Depression		
12. Anger/irritability		
13. Generalized weakness or fatigue		
14. Joint pain		
15. Hot flushes		
16. Visual problems (light sensitivity, decreased visual acuity)		
17. Nausea, vomiting		
18. Diarrhea		
19. Dizziness		
20. Headaches		
21. Hypertension		
22. High glucose levels		

Nestlé Nutrition Flavour Mix

Description

Nestlé Nutrition Flavour Mix is a flavouring powder formulated for use with Peptamen® Vanilla Cup and Modulen® IBD.

Presentation

60g tub (with a 0.6g scoop). Available in 5 flavours: Banana, Lemon & Lime, Chocolate, Strawberry and Coffee.

Indications

ACBS approved, prescribable on FP10 (GP10 in Scotland). For use with Vanilla flavoured Peptamen® and Modulen® IBD.

Ingredients

Banana Flavour
Dextrose, Flavouring (contains Maltodextrin), Maltodextrin, Anit-caking agent (Silicon dioxide), Colour (Curcumin), Sweetener (Sucralose).

Coffee Flavour
Dextrose, Soluble Coffee solids, Anti-caking agent (Silicon dioxide), Colour (Caramel E150c), Sweetener (Sucralose).

Strawberry Flavour
Dextrose, Flavouring (contains Maltodextrin), Acidity regulators (Lactic acid, Acetic acid), Stabiliser (Gum arabic), Preservative (Sulphur dioxide), Anti-caking agent (Silicon dioxide), Colour (Beetroot red), Sweetener (Sucralose).

Lemon & Lime Flavour
Dextrose, Flavouring (contains Maltodextrin), Modified starch, Antioxidant (E320), Citric acid, Anti-caking agent (Silicon dioxide), Colour (Curcumin), Sweetener (Sucralose).

Chocolate Flavour
Dextrose, Flavouring (contains Maltodextrin), Stabilisers (Glycerine, Gum arabic), Molasses, Anti-caking agent (Silicon dioxide), Colour (Caramel E150c), Sweetener (Sucralose).

All Flavours: Milk, Egg, Soya, Nut, Gluten and Lactose free.

Administration and dosage

Suggested intake: Add 2 scoops Nestlé Nutrition Flavour Mix per 100ml.

Shelf life and storage

Shelf life of 12 months from date of manufacture when stored at room temperature.

Contraindications

Not for intravenous use.
Not suitable for children under 3 year of age.

Precautions

To be used with caution in children between 3 and 5 years of age.
Suitable for use in children over 5 years of age.
Must be used under medical supervision.

Nutrition information (All flavours)

Nutrients		Nutrient content per scoop (0.6g)	Nutrient content per 100g
General			
Energy	(kcal/kJ)	2.04/8.2	340/1360
Protein	(g)	Nil	Nil
Fat	(g)	Nil	Nil
Carbohydrate	(g)	0.51	85

Osmolality information

The addition of Nestlé Nutrition Flavour Mix to Modulen® IBD or Peptamen® will increase the osmolality.

As a guide the following increases will occur (based on the addition of 2 scoops of Nestlé Nutrition Flavour Mix to 100ml Modulen® IBD standard concentration):

	Change in Osmolality (mOsm/kg)
Nestlé Nutrition Flavour Mix Strawberry	+60
Nestlé Nutrition Flavour Mix Coffee	+72

Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci USA 1918;4(12):370-3.

BMR calculation for men (metric)
BMR = 66.47 + (13.75 x weight in kg) + (5.003 x height in cm) - (6.755 x age in years)

BMR calculation for women (metric)
BMR = 655.1 + (9.563 x weight in kg) + (1.850 x height in cm) - (4.676 x age in years)

Activity factor:
Sedentary. Little to no regular exercise.
(*factor 1.2*)

Mild activity level: Intensive exercise for at least 20 minutes 1 to 3 times per week. This may include such things as bicycling, jogging, basketball, swimming, skating, etc. If you do not exercise regularly, but you maintain a busy life style that requires you to walk frequently for long periods, you meet the requirements of this level.
(*factor 1.375*)

Moderate activity level: Intensive exercise for at least 30 to 60 minutes 3 to 4 times per week. Any of the activities listed above will qualify. (*factor 1.55*)

Heavy or (Labor-intensive) activity level: Intensive exercise for 60 minutes or greater 5 to 7 days per week (see sample activities above). Labor-intensive occupations also qualify for this level. Labor-intensive occupations include construction work (brick laying, carpentry, general labor, etc.). Also farming, landscape worker or similar occupations. (*factor 1.7*)

Extreme level: Exceedingly active and/or very demanding activities: Examples include: (1) athlete with an almost unstoppable training schedule with multiple training sessions throughout the day (2) very demanding job, such as shoveling coal or working long hours on an assembly line. Generally, this level of activity is very difficult to achieve. (*factor 1.9*)
Calculator: http://www.globalrph.com/harris-benedict-equation.cgi