The role of diet in IBD

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Disclosure

- Developed educational resources: Ferring & Janssen
- Speaker fees: Takeda, Shire, Abbvie
How do we use diet in IBD?

- To ensure nutritional adequacy
- To treat inflammation
- To manage symptoms
- To manage complications
  - Bowel obstruction
  - Kidney stones
  - Fat malabsorption
- To prevent IBD in offspring

For moderate-severe IBD:
- Surgical considerations
- Stoma, pouch management
- Short bowel syndrome
Diet for inflammation
Risks for IBD development

- Cigarette smoking
  - Increased risk for CD, protective in UC
- Hygiene hypothesis – lack of early exposure to some microbial agents due to improved sanitation
- Cold-chain hypothesis – alterations of psychotropic bacteria exposure that may escape immune response as child
- Westernised environment
  - Children of migrants from low to high IBD incidence regions higher risk
- Dishwasher hypothesis – reduces residual detergent from dishes

Diet?
Pivotal change to dietary therapy – EEN

- Exclusive enteral nutrition - good efficacy for inducing CD remission in up to 80%
  - Comparable to corticosteroids in inducing clinical remission & superior for mucosal healing
  - In children, also leads to weight gain, improved vitamin D status & quality of life – first-line therapy to treat active paediatric CD
  - In adults, routinely used in Japan & China, increasing use in Europe, Australia & NZ
  - Preoperative EEN – 25% adults patients avoided surgery
- Unrelated to composition (elemental vs polymeric, fat content), but all trials use fibre-free formulas
- Partial enteral nutrition does not seem to work as well
- Great as induction therapy, but not maintenance
- Palatability & adherence big problem – particularly in adults

Heerasing et al Aliment Pharmacol Ther 2017
Wall et al Inflamm Intestinal Dis 2018
Dziechciarz et al Aliment Pharmacol Ther 2007
Day et al J Gastroenteral Hepatol 2006
Heuschkel et al J Pediatr Gastroenterol 2000
Lessons from EEN

- We can no longer say ‘diet has no role in treating disease’
- Mechanisms are unknown
  - Cannot transpose the principles of EEN into a therapeutic diet

**ADDITIONALLY  EEN doesn’t make sense:**

- EEN reduces bacterial diversity, reduces concentrations of *F. prausnitzii* (low abundance predictive of disease relapse)
  - Gatti et al *Nutrients* 2017
- Enteral formula does not fit with rationale of many diets thought to treat CD
  - No resistant starch, dairy, soy, maltodextrin, ‘processed’ foods

What do we find in EEN that we don’t in diet?
Hypotheses for pathogenically-targeted diets:

- Replicate EEN - CD
- ‘Bacterial penetration cycle’ – CD
- $\text{H}_2\text{S}$ and NO exposure to colonic epithelium – UC
- Alternative philosophies – IBD
  - Mostly internet-based diets

Specific food components:

- Emulsifiers - CD
Design of a diet based on enteral formula – CD-TREAT

- Very little detail of the diet
- Excluded:
  - Gluten, lactose (not dairy), alcohol
- Matched enteral formula for:
  - Macronutrients
  - Micronutrients
  - Fibre (????) – low fibre mean 11g/day
- *Maltodextrin is main carbohydrate of most enteral formula, but minimal found naturally in food
  - Substituted by food high in starch but low fibre
  - Because ~10% starch is resistant starch, modifies microbiota, they reduced CHO in favour of protein

Svolos et al Gastroenterology 2019
CD-TREAT diet - results

- Applied in 25 healthy adults – cross-over design
  - CD-TREAT diet for 7 days
  - EEN

- Applied in 5 children with mild-moderate active Crohn’s on stable therapy – open label
  - 4 completed CD-TREAT for 8 weeks
  - 4 responded clinically & reduced faecal calprotectin

- Safe, well tolerated
- Similar changes in microbiota

Maybe something for the future?

Svolos et al Gastroenterology 2019
Bacterial penetration cycle hypothesis: pathogenic model for Crohn’s disease (Levine & Wine)

- Susceptibility to Crohn’s disease
- Dietary factors
- Breakdown of epithelial barrier
- Activation of immuno-inflammatory events
- ↑ adherence, translocation, penetration of bacteria

Levine & Wine Inflamm bowel Dis 2013
Dietary factors & ‘bacterial penetration’ – based on in vitro & animal models

**Weaken barrier**
- Sodium caprate in dairy products
- Gliadin – prolamin in wheat
- Emulsifiers
  - Polysorbate 80
- Thickeners
  - Carboxymethyl cellulose

**Strengthen barrier**
- Soluble NSPs
  - Plantains

Development of the Crohn’s Disease Exclusion Diet (CDED)

Soderholm et al Dig Dis Sci 1998
Lammers et al Gastroenterol 2008
Roberts et al Gut 2010
Crohn’s Disease Exclusion Diet (CDED)

Aims to increase:
- Fruit & veg
- Resistant starch
- ‘High quality’ lean protein sources
- Complex carbs
- Healthy oils

Aims to decrease:
- Animal & saturated fat
- Taurine
- Wheat
- Haeme/iron
- Emulsifiers
- Maltodextrin
- Carrageenan
- Sulfites
- Dairy
CDED description

Daily mandatory/allowed foods:
- Unlimited fresh chicken breast
- 2 eggs
- 2 fresh potatoes, peeled, cooked & cooled
- 2 bananas
- 1 apple, peeled
- Lean fish (1/week)
- White rice, rice noodles, rice flour
- 1 avocado (limit ½/meal), 5 strawberries, 1 slice melon
- 2 tomatoes

Aims to decrease:
- Processed meat & fish
- Seafood
- Minced beef
- Soy
- Dairy
- Milk alternatives (soy, rice, almond milk)
- Wheat
- Baked goods
- Yeast
- Legumes, corn, frozen potato
- Most fruit
- Frozen veg, kale, leek, asparagus, artichoke

Diet to replace EEN

Over-restriction rather than targeted food components

Rationale fit practice?
Evidence for CDED – 2x retrospective studies

- Active Crohn’s disease – 6 weeks partial EN (50% estimated energy) + CDED or CDED alone
  - 44 children & 24 adults (8 who lost response to biologic)

- Results at week 6:
  - 46/68 (68%) achieved remission defined by HBI ≤ 3 or ≤ 5
  - Most patients had mild disease – mean HBI 6-8
  - 6/7 achieved remission with ‘whole food diet’ instead
  - 7 started on immunomodulator before week 6

References:
Sigall-Boneh et al Inflamm Bowel Dis 2014
Sigall-Boneh et al J Crohns Colitis 2017
Roediger pathogenic hypothesis for UC

1. Sulfur amino acid fermentation – more BCFA & other metabolites (amines, cresols)
2. Dysbiosis increases luminal NO
3. Impeding lipid & protein synthesis & break down epithelial barrier

Lumenal bacteria
Biochemical lesions mucosa

Diseased colonocyte
Cell death

Healthy colonocyte

Prolonged exposure $\text{H}_2\text{S} \& \text{NO}$ (protein fermentation)

5-ASA inhibit $\text{H}_2\text{S}$ production

Roediger et al Aliment Pharmacol Ther 2008
Pitcher et al Gut 2000
Roediger diet – low sulfur amino acids

- Reduce sulfide production by reducing dietary sulfur substrates
  - No
    - Eggs, cheese, whole milk, ice cream, mayonnaise
    - Cruciferous vegetable
    - Soy milk
    - Sulfated drinks (mineral water, wine, cordial)
    - Nuts
  - Limit
    - Red meat
  - Encourage
    - Chicken, fish, skimmed milk, all other vegetables

Roediger et al Lancet 1998
Other diets promoted for therapy

- Specific Carbohydrate diet
  - Crohn’s disease induction & maintenance

- IBD-Anti-Inflammatory diet (Uni of Massachusetts)
  - IBD
Specific carbohydrate diet – limits disaccharides & polysaccharides

- **Rationale:** disaccharides & polysaccharides lead to SIBO, increased CHO fermentation producing ‘toxins’, damage mucosa & impair nutrient absorption
  - Vague – not based on scientific principles

- **Restricts:** grains, dairy, starchy veg, manufactured foods, some fruits

- **Evidence - trials:**
  - 21 kids for 12 weeks - reduced mean disease activity score

- **Evidence – retrospective reviews:**
  - 33 kids on SCD for 3-48 mo reduced mean disease activity score or symptoms
Pros & cons of SCD

Pros
- Small amount evidence
- Anecdotally works in some

Cons
- Extremely restrictive (fibre, prebiotics, calcium ....)
- Nutritionally inadequate
- No flexibility to adapt diet
  - e.g., when eating out
- No specified timeframe for its use
  - Ongoing?
Rationale: certain carbohydrates provide pathogenic bacteria substrate on which to proliferate and lead to dysbiosis & their restriction will treat active inflammation

Evidence:
- Retrospective review of 40 patients with active IBD
  - 33% did not attempt the diet (n=13)
  - 60% had self-reported symptomatic response (n=24)
  - Remaining had no symptomatic response (n=3)
- No objective markers of inflammation measured

Olendzki et al Nutr J 2014
IBD-AID diet description – 4 phases

- IBD-AID aims to:
  - ‘Modify carbohydrates’
  - Include foods containing pro- & prebiotics
  - ‘Modify fats’
  - Review dietary pattern for detection of intolerances
  - Modify food texture
# IBD-AID diet description – 4 phases

## Phase I
- **Soft, well-cooked or cooked then pureed foods, no seeds**
- **Vegetables**
  - Butternut Squash, Pumpkin, Sweet Potatoes, Onions
  - Pureed vegetables: Mushrooms, Phase II vegetables (pureed)
- **Fruits**
  - Banana, Papaya, Avocado, Pawpaw
- **Meats and fish**
  - All fish (no bones), Sardines (small bones ok), Turkey and ground beef, Chicken, Eggs
- **Non dairy unsweetened**
  - Coconut milk, Almond milk, Oat milk, Soy milk
- **Dairy, unsweetened**
  - Yogurt, Kefir
- **Nuts/Oils/Legumes/Fats**
  - Miso (refrigerated), Tofu, Olive oil, Canola oil, Flax oil, Hemp oil, Walnut oil, Coconut oil
- **Grains**
  - Ground flax or Chia Seeds (as tolerated)

## Phase II
- **Soft Textures: well-cooked or pureed foods, no seeds, choose floppy or tender foods**
- **Vegetables**
  - Carrots, Zucchini, Eggplant, Peas, Snow peas, Spaghetti squash, Green beans, Yellow beans, Microgreens (2 week old baby greens), Watercress, Arugula, Fresh flat leaf parsley and cilantro, Seaweed, Algae
  - Pureed vegetables: all except cruciferous
- **Fruits**
  - Watermelon (seedless), Mangoes, Honeydew, Cantaloupe, May need to be cooked: Peaches, Plums, Nectarines, Pears.
  - (Phase III fruits are allowed if pureed and seeds are strained out)
  - Scallops
- **Meats and fish**
  - All fish (no bones), Sardines (small bones ok), Turkey and ground beef, Chicken, Beans
- **Non dairy unsweetened**
  - Coconut milk, Almond milk, Oat milk, Soy milk
- **Dairy, unsweetened**
  - Yogurt, Kefir
- **Nuts/Oils/Legumes/Fats**
  - Miso (refrigerated), Tofu, Olive oil, Canola oil, Flax oil, Hemp oil, Walnut oil, Coconut oil
- **Grains**
  - Ground flax or Chia Seeds (as tolerated)

## Phase III
- **May still need to avoid stems, choose floppy greens or other greens depending on individual tolerance**
- **Vegetables**
  - Butter lettuce, Baby spinach, Peeled cucumber, Olives, Leeks Bok Choy, Bamboo shoots, Collard greens, Beet greens, Sweet peppers, Kale, Fennel bulb
  - Pureed vegetables: all from Phase IV, Kimchi
- **Fruits**
  - Strawberries, Cranberries, Blueberries, Apricots, Cherries, Coconut, Lemons, Limes, Kiwi, Passion fruit, Blackberries, Raspberries, Pomegranate (May need to strain seeds from berries)
- **Meats and fish**
  - Lean cuts of Beef, Lamb, Duck, Goose
- **Non dairy unsweetened**
  - Coconut milk, Almond milk, Oat milk, Soy milk
- **Dairy, unsweetened**
  - Yogurt, Kefir
- **Nuts/Oils/Legumes/Fats**
  - Miso (refrigerated), Tofu, Olive oil, Canola oil, Flax oil, Hemp oil, Walnut oil, Coconut oil
- **Grains**
  - Ground flax or Chia Seeds (as tolerated)

## Phase IV
- **If in remission with no strictures**
- **Vegetables**
  - Artichokes, Asparagus, Tomatoes, Lettuce, Brussels sprouts, Beets, Cabbage, Kohlrabi, Rhubarb, Pickles, Spring onions, Water chestnuts, Celery, Celeriac, Cauliflower, Broccoli, Radish, Green pepper, Hot pepper
  - Grapes, Grapefruit, Oranges, Currents, Figs, Dates, Apples (best cooked), Pineapple, Prunes
- **Fruits**
  - Strawberries, Cranberries, Blueberries, Apricots, Cherries, Coconut, Lemons, Limes, Kiwi, Passion fruit, Blackberries, Raspberries, Pomegranate (May need to strain seeds from berries)
  - Lean cuts of Beef, Lamb, Duck, Goose
- **Non dairy unsweetened**
  - Coconut milk, Almond milk, Oat milk, Soy milk
- **Dairy, unsweetened**
  - Yogurt, Kefir
- **Nuts/Oils/Legumes/Fats**
  - Miso (refrigerated), Tofu, Olive oil, Canola oil, Flax oil, Hemp oil, Walnut oil, Coconut oil
- **Grains**
  - Ground flax or Chia Seeds (as tolerated)

## For whole beans and lentils
Pros & cons of IBD-AID

Pros
- Some evidence showing efficacy in reducing symptoms

Cons
- No RCT data yet
- No objective markers of inflammation measured – symptom guided
- High drop-out rate
- Developed protocols seem confusing, unstandardised & difficult to replicate
- Dependent on advising dietitian’s assessment of symptoms & needs

Multiple components of food targeted!
No clear cause-effect
Specific food components

- Common theme amongst all diets is that commercially manufactured foods are removed

Specific food components thought to drive active disease:
- Maltodextrin – ↑ adhesion of CD-associated adherent-invasive E. coli
  Nickerson & McDonald Gut 2004
- Emulsifiers – polysorbate 80 (P80) & carboxymethyl cellulose (CMC)
  - Ex vivo study - P80 increased bacterial translocation across epithelia in CD
  - Mouse study - P80 & CMC degrades mucosa in predisposed colitis
  - Mucosal simulator – P80 & CMC increase proinflammatory human microbiota
    Roberts et al Gut 2010
    Chassaing et al Nature 2015
    Chassaing et al Gut 2017

Enteral formulas contain maltodextrin (usually in larger doses)
What are emulsifiers?
Emulsifiers

- **Emulsifiers (surface activity):**
  - Surfactant – hydrophilic head (different charges) & lipophilic tail
    - Food additives & lecithin
  - Amphiphilic biopolymers – proteins, protein-polysaccharide complexes
    - Egg, gelatin & additives
- **Texture modifiers (thickeners):**
  - Modified starches, celluloses
- **Weighting agents (changes specific gravity of oils):**
  - Non-alcoholic beverages
Why are emulsifiers used?

- Enhance appearance by avoiding separation
- Improve organoleptic properties (taste, colour, odour, mouthfeel)
- Control release of or protect unstable ingredients
  - Encapsulate unpleasant aroma, or bioactive compound to improve nutritional value
- Replace O/W emulsion with W/O/W so oil content is reduced with affecting products
  - Low fat foods

Halmos et al Aliment Pharmacol Ther 2019
Common uses in food

- Baked goods - strengthening and softening dough, retaining moisture for freshness
- Fat-based spreads - provide stability, reduce water content to prevent splattering when brought to high temperatures
- Dairy desserts - reduce rate of melting and freezing time, incorporating air bubbles into aerated desserts
- Mayonnaises & salad dressings – stabilise product
- Confectionery - controlling stickiness and improve flavour release, delaying “bloom”
- Beverages - contribute to flavour of citrus and kola drinks

Halmos et al Aliment Pharmacol Ther 2019
Translation to diet

- Many IBD experts state “emulsifiers are widespread in our diet”
- Emulsifiers are not well defined - ~60 approved for use in Australia, including:
  - Sorbitan monostearate 491
  - Mono- & di-glycerides of fatty acids 471
  - Polysorbate-80 433
  - Lecithin (soy & egg yolks) 322

May be present:
- Breads, cakes, cakes mixes, pastry
- Margarines, peanut butter, other fat spreads
- Mousse, meringue, ice cream, frozen desserts
- Mayonnaise, salad dressings
- Lollies, chocolates
- Soft drinks, wine, spirits

Limited information on where, which & amount consumed?

No comprehensive food lists

Likely differences between emulsifiers - needs classification in context of effect in IBD

Presence not always predictable in manufactured food
Diet to treat inflammation?

- EEN - only clear evidence of efficacy in inducing remission
- CDED or CD-TREAT – possibly to use with partial EN or as replacement for EEN – not maintenance diet
- SCD & other diets – needing more evidence & clear rationale
- Removing specific food components – preliminary data promising but cannot be transposed into useable diet yet
  - Needs better classification, design of diet + comprehensive food lists & evidence in humans
Diet for symptoms
Symptoms in IBD – Is it functional or is it inflammation?

- Functional gut symptoms are 3 times more common in IBD than general population
  Farrokhyar et al Inflamm Bowel Dis 2006

- Functional symptoms respond poorly to drug therapy

- Function can be affected by inflammation

- We try to distinguish between inflammatory & functional symptoms & treat accordingly

<table>
<thead>
<tr>
<th>Symptoms in IBD</th>
<th>Symptoms in IBS</th>
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<tbody>
<tr>
<td>PR bleeding</td>
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<td>Nocturnal diarrhoea</td>
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<td>Weight loss</td>
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<td>Fever</td>
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<td>Abdominal pain</td>
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<td>Bloating &amp; distension</td>
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<td>Diarrhoea &amp; urgency</td>
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<td>Constipation</td>
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<td>Altered bowel habits</td>
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Dietary therapy in IBS

- Low FODMAP diet
- Gluten free diet

Other diets:
- High fibre
  - Specific fibre supplements may alter stool form & stool passage
  - Otherwise doesn’t work & may worsen symptoms

- Gluten free/dairy free/sugar free/paleo/’clean eating’
  - Anecdotally has provided benefit to some but no evidence
  - Can be very restrictive, ongoing use
  - Philosophy not based on science…….. ‘detoxification’, ‘not designed to digest’

Bijkerk et al Aliment Pharmacol Ther 2004
Moayyedi et al Am J Gastroenterol 2014
Low FODMAP diet - efficacy

Worldwide evidence efficacy of in reducing functional gut symptoms in patients with IBS

Good symptom response in ~75% IBS patients

Staudacher et al Gastroenterol 2017
McIntosh et al Gut 2017
Eswaran et al Am J Gastroenterol 2016
Böhn et al Gastroenterol 2015
Halmos et al Gastroenterol 2014
Chumpitazi et al Aliment Pharmacol Ther 2015
de Roest et al Int J Clin Pract 2013
Staudacher et al J Hum Nutr Diet 2011
..........AND MORE
Low FODMAP diet in IBD

In those with quiescent IBD & IBS-like symptoms:

- **Australia** – improved symptoms in >50% subjects
  Gearry et al J Crohns Colitis 2009

- **Denmark** – 43% full improvement & 47% partial improvement of symptoms
  Maagaard et al World J Gastroenterol 2016

- **UK** – 78% subjects had satisfactory relief
  Prince et al Inflamm Bowel Dis 2016
RCT: low vs typical FODMAP diet

Overall symptoms – Crohn’s (n=9)

Halmos et al Clin Transl Gastroenterol 2016

Mean 13.5mm 95%CI [5.9-21.1]
24.8mm 95%CI [12.6-37.0]
P<0.001; repeated measures ANOVA
Low FODMAP targets functional symptoms

- Clinically quiescent Crohn’s disease patients n = 8

Halmos et al Clin Transl Gastroenterol 2016
Pros & cons of a low FODMAP diet

Pros:
- Good evidence of efficacy
- Appears nutritionally balanced – but fibre may be compromised
- Flexible – ‘cheating’ allowed

Cons:
- Cost
Pros & cons of a low FODMAP diet

Pros:
- Good evidence of efficacy
- Appears nutritionally balanced – but fibre may be compromised
- Flexible – ‘cheating’ allowed

Cons:
- Cost
- Negative effects on microbiota
A low FODMAP diet may have negative effects on microbiota in patients with IBD, a population already at risk of dysbiosis.

Health effects?
Pros & cons of a low FODMAP diet

Pros:
- Good evidence of efficacy
- Appears nutritionally balanced – but fibre may be compromised
- Flexible – ‘cheating’ allowed

Cons:
- Cost
- Negative effects on microbiota
- Growing recognition of the diet leads to its inappropriate application
Inappropriate application

- **Mis-use**
  - Applied in patients who do not have IBS

- **Ineffective application**
  - Patients who have not sufficiently reduced FODMAP intake

- **Over-restriction**
  - Increased risk of inadequate nutrition & malnutrition
  - Risk to gut microbiome
  - Fuels food obsession
Strategies for applying a low FODMAP diet

Top-down

Bottom-up
Top-down

- Restrict most/all foods considered high FODMAP for 4-8 weeks
- If no symptomatic benefit, patients stop the diet
- If beneficial, liberalise the diet to tolerance:
  - Specific foods and dose ie. ‘challenge’ process
  - General recommendations to only limit foods of higher FODMAP content
Top-down approach

Best in patients:

- Where the success of a low FODMAP diet or type/amount of FODMAP tolerance is uncertain
- Do not normally eat a lot of FODMAPs
- Very symptomatic
- Who would prefer this approach
Bottom-up

- Start reducing foods with very large amounts of FODMAPs (or specific FODMAPs)
- Continue to reduce if necessary to tolerance
Bottom-up approach

Best in patients:
- Eat a lot of FODMAPs
- Mildly symptomatic
- Children
- Nutritionally compromised/at risk of malnutrition
- With other dietary restrictions
- Where prebiotics are important
- Who prefer this approach

IBD?
Gluten free diet in IBD

- Theoretical issues
  - Gluten may affect intestinal permeability
  - Non-gluten wheat proteins may stimulate innate immunity/injure epithelium

- Questionnaire studies:
  - North America: 8% IBD sufferers follow gluten free for symptomatic benefit
    Herfarth et al Inflamm Bowel Dis 2014
  - UK (Sheffield): n=145
    - 28% believed they were gluten sensitive
    - 13% had tried gluten free diet
    - 6% currently on gluten free diet

Aziz et al Inflamm Bowel Dis 2015
Non-coeliac gluten sensitivity

- Latest on non-coeliac gluten sensitivity
  - Studies in self-reported NCGS - condition rare or does not exist

Biesiekierski et al Gastroenterol 2013
Skodje et al Gastroenterol 2018
Pros & cons of a gluten free diet

Pros:
- Helps proportion of IBS
- Does not seem to impact nutritionally
- Probably easier than low FODMAP, but not flexible

Cons:
- Cost
- Often self-prescribed without exclusion of coeliac disease
What about fibre restriction in IBD?

- Fibre restriction (modified fibre, low fibre or low residue diets) are used to treat & prevent bowel obstruction.

**BUT**

- Historically, low fibre diets have been used to treat all IBD – sometimes advised to use at time of flare – some people feel better.

- These diets are can be restrictive & increase risk of nutritional inadequacies.

- High fibre diet during times of remission has been associated with reducing risk of flare in UC.

Not typically used in mild to moderate disease or colonic disease.
Diet to treat symptoms?

- Assess inflammatory versus functional symptoms
- In presence of functional symptoms
  - Low FODMAP or modified FODMAP diet
  - Gluten free diet?
  - Fibre restriction not really used for symptoms
- In absence of functional symptoms
  - Promote healthy eating – no specific therapeutic diet
  - High fibre during remission for flare prevention?