The clash of generations: children are not small adults
*S. Kolacek (HR)*
Role of Nutrition in Children with CD

“Child is NOT a Little Adult”

Sanja Kolaček
Children’s Hospital Zagreb
Role of nutrition in pediatric CD

To be presented:

- Nutrients / diets in childhood as the cause of IBD
- Nutritional status in children with CD
- Role of nutrition in the treatment of CD in children
CHRONIC INFLAMMATORY BOWEL DISEASE - IBD

Crohn’s disease
- Can affect any part of GIT
- Transmural inflammation
- Discontinued inflammation

Indeterminate colitis

Ulcerative colitis
- Inflammation only in colon
- Only in mucosa
- Continuous inflammation
Crohn’s disease
Ulcerous colitis
IBD in children: A serious problem

Disease more extensive & severe

Gloomy prognosis

- 15-20% constantly active
- 60-70% chronic relapsing

Increasing incidence

- 6-8 / 100,000 <18 years of age
- CD doubled in last 10 years

Levine A et al...IBD Working Group. Revised Porto Criteria. JPGN 2014
Figure 4 | (a) Evolution of the incidence of Crohn’s disease in Northern France from 1988-1990 to 2006-2007 according to 20-year age groups. (b) Evolution of the incidence of Crohn’s disease in Northern France from 1988-1990 to 2006-2007 according to 10-year age groups.

Chronic inflammatory bowel disease

WHY DOES IT HAPPEN

Etiopathogenesis???

Immune mediated inflammation

to luminal content

in genetically predisposed individuals

Torres MI et al. The immunopathogenesis and therapy in IBD. World J Gastroenterol 2008
Chronic inflammatory bowel disease

WHY DOES IT HAPPEN?

Lee et al, Gastroenterology, 2015
Microbial flora in IBD

Figure 4. Distribution of predominant bacterial phylotypes in the human intestinal tract

taken from: Korboziev I et al.
Free Radic Biol Med 2014
Importance of intestinal microbiota development

- Way of delivery
- Exposure to antibiotics
- Early Diet
- Early infection
- Infant’s genotype

Because of improved hygiene, transfer of bacteria from the maternal gut has been reduced (X), with opportunists (+) from the nonliving environment and the parental skin taking their place.

Role of dietary factors in the development of IBD

Nutrition in childhood and later IBD

- breast feeding
- cow’s milk intake
- sucrose
The duration of breast feeding in Crohn’s disease patients and control subjects. The mean length of the breast-feeding period was significantly (P<0.01) shorter among CD patients (4.59 months) compared to controls (5.76 months).

Role of breast feeding in development of IBD

Acheson and Truelove, 1961
Ekborn, et al. 1990
Koletzko, et al. 1991
Rigas, et al. 1993

Pooled OR (group 1)
Pooled OR of all studies

Association between breastfeeding and ulcerative colitis

Bergstand and Hellers, 1961
Koletzko, et al. 1989
Ekborn, et al. 1990
Rigas, et al. 1993

Pooled OR (group 1)
Pooled OR of all studies

Association between breastfeeding and Crohn disease

Role of breast feeding in development of IBD

Latest systematic review

- A possible protective effect for early onset IBD, but quality of data poor


However

- Breast feeding was a risk factor for CD with an OR of 1.6 in another study

Role of pediatric nutrition in development of IBD:

Take home message

- No conclusive evidence for the cause-effect relationship
- More good quality studies needed!
Role of dietary factors in the development of IBD

Dietary factors as risk factors in adults

- Proteins & refined sugars in excess & emulsifiers & less fibres (fruits & vegetable)

- Animal fat intake
  - high intake of saturated & monounsaturated fatty acids
  - low in take of Ω3; high Ω6/Ω3

  *in patients with certain cytokine genotype*

  **NO CONCLUSIVE EVIDENCE!**

# Nutritional status at dg

## in children with IBD

<table>
<thead>
<tr>
<th></th>
<th>Crohn</th>
<th>U.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>15-60%</td>
<td>10-30%</td>
</tr>
<tr>
<td>Growth failure</td>
<td>30-50%</td>
<td>0-10%</td>
</tr>
<tr>
<td>Delay in sex. maturation</td>
<td>30%</td>
<td>0-20%</td>
</tr>
<tr>
<td>Decreased bone mineralization</td>
<td>20-43%</td>
<td>20%</td>
</tr>
<tr>
<td>Decreased growth before GIT symptoms</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>
Growth in IBD children: EPIMAD reg

Vasseur F, et al.
Nutritional status and growth in pediatric CD: population based study
*Am J Gastroenterol* 2010;105

N= 261 CD children
Minimum follow-up: 2 y
Medium follow-up: 73 m

At diagnosis < – 2 SD:
- for height 9.5%
- for weight 27%
- for BMI 32%
Growth in IBD children: EUROKIDS

de Bie CI, et al.
Height and BMI in pediatric IBD
(2015, in press)

N = 459 CD; 12.8 y
475 UC; 11.9 y

- In CD ≤ 1.96 SDS height / age:
  - 9% using national charts
  - 5% using WHO standards

- In UC ≤ 1.96 SDS height / age:
  - 6% using national charts
  - 5% using WHO
Growth in IBD children: long-term outcome

**Sawczenko A, et al.**
Clinical features affecting final adult height in patients with ped. onset CD.
*Pediatrics* 2006; 118:124

- Mean final height 2.4 cm lower
- 20% had final height more than 8.0 cm below target height

Final height remains below 5th centile in 15-30% of CD patients with pediatric disease onset
Growth in IBD children: long-term outcome

PEAK BONE MASS
Most rapid bone mineral accrual: in girls 11 – 14 y; in boys 13 – 17 y
Peak bone mass is decreased in 50% of children with CD

RISK OF FRACTURES
- in children with IBD < 12 y of age is increased
- vertebral fractures in children with CD increased;
  in adults with IBD in up to 22%

Peak bone mass decreased
Fracture risk increased
Take home messages

- Nutritional status is seriously impaired in ped. IBD, particularly in children with CD, having long-term implications

- Nutritional status should be monitored on every check-up & nutritional deficiencies be timely corrected
ECCO/ESPGHAN Consensus guidelines on medical management of pediatric CD

„Growth and bone density restoration can be considered a marker of disease control and of successful therapy in children”

Nutrition in CD

- Role as primary therapy for acute CD??
- Role in prevention of relapses??
- How does it work??
Enteral nutrition as primary treatment for CD

How to use it?

1. Content of diet: ONLY enteral formula + water

2. Duration: 6-8 weeks

3. Introduction: stepwise increasing the volume and the strength during 3-5 days

4. Application:
   - orally
   - naso-gastric tube
   - PEG

EN in active CD
How effective is it?

4 meta-analyses in adults:
--- steroids more effective ---
(Fernandez-Banares, et al. JPEN 95;19:356-64
Messori S, et al. Scand J Gastroenterol 96;31:267-72

2 meta-analyses in children:
--- equal efficacy (no difference) ---
Small number of patients & remission criteria poorly defined, etc.
**Review:** Enteral nutrition  
**Comparison:** 01 Remission rate  
**Outcome:** 01 Enteral nutrition vs. corticosteroids

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borelli</td>
<td>15/19</td>
<td>12/18</td>
<td></td>
<td>1.18 (0.79, 1.77)</td>
</tr>
<tr>
<td>Seidman 1991</td>
<td>6/10</td>
<td>9/9</td>
<td></td>
<td>0.60 (0.36, 1.00)</td>
</tr>
<tr>
<td>Terrin</td>
<td>9/10</td>
<td>5/10</td>
<td></td>
<td>1.80 (0.94, 3.46)</td>
</tr>
<tr>
<td>Seidman 1993</td>
<td>26/34</td>
<td>31/34</td>
<td></td>
<td>0.84 (0.68, 1.04)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>73</td>
<td>71</td>
<td></td>
<td>0.97 (0.68, 1.40)</td>
</tr>
</tbody>
</table>

Total events: 56 (Treatment), 57 (Control)  
Test for heterogeneity: Chi²=9.40, df=3 (P=0.02, I²=68.1%)  
Test for overall effect: Z=0.15 (P=0.88)
Efficacy of EN in children with CD

Bannerjee K et al. JPGN 2004;38:270-4

**Significant improvement in:**

- ESR & IL6 by day 3
- PCDAI, CRP and IGF-I by day 7
- Nutritional/anthropometry by day 14

FIG. 1. PCDAI and CRP in individuals during the course of treatment with enteral feed.
GF in IBD children: Treatment Does EN improve growth?


- compared to steroids, EN significantly improves growth velocity

### Analysis 2.1. Comparison 2 Elemental feed versus prednisolone, Outcome 1 Height velocity standard deviation scores.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Elemental feed</th>
<th>Prednisolone</th>
<th>Mean Difference Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
</tr>
<tr>
<td>Sanderson 1987</td>
<td>9</td>
<td>0.3 (2.03)</td>
<td>7</td>
</tr>
<tr>
<td>Thomas 1993a</td>
<td>12</td>
<td>0.32 (3.32)</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0%
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

Newby EA al. Cochrane Database 2008
Enteral nutrition in CD

EN induces mucosal healing
76% with EN vs. 33% with steroids shown in the RCT in children

Enteral nutrition in CD

**DURATION OF REMISSION**

Kaplan–Meier curve showing duration of survival without relapse influenced by induction therapy—exclusive enteral nutrition (*line*) or corticosteroids (*dashed line*)

Hoj sak et al, Eur J Pediatr, 2014
Role of EN in relapse prevention?


Akobeng AK, et al. EN for maintenance of remission in CD. Cochrane Review 2009

EN in maintenance:
- may sustain remission
- prevents post-operative relapse
- postpones requirements for steroids

HOWEVER, more studies needed!!
Type of formula – does it matter?

**Ludvigsson, et al.**

- Prospective randomized study, 33 children with active Crohn’s disease
- 6 weeks treatment with elemental vs. standard polymeric formula
- Elemental: remission 69%
- Polymeric: remission 82% (p=0.4) more weight gain (p=0.004)
114 children treated with EN, mean age 11.6 at dg

<table>
<thead>
<tr>
<th>Disease location (Vienna class)</th>
<th>Rate of remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term ileum (L1)</td>
<td>1 / 4 (25%)</td>
</tr>
<tr>
<td>Colonic (L2)</td>
<td>15 / 19 (79%)</td>
</tr>
<tr>
<td>Ileocolonic (L3)</td>
<td>25 / 29 (86%)</td>
</tr>
<tr>
<td>Upper GIT (L4)</td>
<td>43 / 49 (88%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease behaviour (Vienna class)</th>
<th>Rate of remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td>67 / 80 (84%)</td>
</tr>
<tr>
<td>Penetrating</td>
<td>14 / 18 (78%)</td>
</tr>
<tr>
<td>Stricturing</td>
<td>4 / 5 (80%)</td>
</tr>
</tbody>
</table>

Does it need to be exclusive?

Johnson, et al.
Gut 2006; 66:356-61

Partial vs. exclusive enteral nutrition??

- Partial EN (50% as normal diet)
  -- 15% remission

- Exclusive EN:
  -- 42% remission
  \( p < 0.035 \)
Enteral nutrition in CD

**TAKE HOME MESSAGE**

- EN is equally effective as CS
- + Induces mucosal healing significantly better than CS
- EN has NO side-effects & supports growth and bone mineralization


*Shamir R, et al. Inflamm Bowel Dis 2007*
STATEMENT 1

Exclusive enteral nutrition (EN) is recommended as first line therapy to induce remission in children with active luminal CD (EL1)
EN in Crohn’s Disease:

How does it work?

- Bowel rest:  
  --- less antigenic pressure ---

- Improves nutr. status:  
  --- better general condition ---

- Alteration of intestinal microflora  
  (persist 4 months after EN treatment)  
  modulation of immune effect

- Direct anti-inflammatory efect

Lee D et al. Gastroenterology 2015
Tilg H et al. Gastroenterology 2015
Exclusive EN: How difficult it is?
Nutrition in Ped. CD

ROLE OF EXCLUSION DIET

Why exclusion diets??
role of nutrients in microbial composition
in bacterial penetration
in epithelial barrier

Which dietary components to remove??
animal fat, high sugar, gliadin, emulsifiers....

Does it work?? Are data reliable?

Sigall-Boneh R et al. Partial EN + Crohn’s disease exclusion diet is effective for induction of remission in children and young adults with CD
Inflamm Bowel Dis 2014;20:1353-60

Cohort of 47 patients (34 children) treated with:
  6-week structured exclusion diet +
  50% of energy as partial EN

Results: - remission in 70%
  - normalization of CRP in 70%
  - 6/7 patients who used only exclusion diet achieved remission

HOWEVER, NO RANDOMIZED STUDIES YET!
**Nutrition in pediatric CD**

**TAKE HOME MESSAGES**

- Nutrition in early childhood could shape microbiome & immune response towards IBD
- Growth rate is a marker of disease severity and treatment success
- Exclusive EN to be used as the first line treatment in active CD in children
- Role of exclusion diet: to be established
THANK YOU FOR YOUR KIND ATTENTION
**ESPGHAN EUROKID registry**

**Mean age of presentation & gender**

<table>
<thead>
<tr>
<th></th>
<th>N = 2087</th>
<th>N (%)</th>
<th>Mean age</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD</strong></td>
<td>1221 (59%)</td>
<td>12.5</td>
<td>59% male</td>
<td></td>
</tr>
<tr>
<td><strong>UC</strong></td>
<td>670 (32%)</td>
<td>11.6</td>
<td>50% male</td>
<td></td>
</tr>
<tr>
<td><strong>IBD-U</strong></td>
<td>196 (9%)</td>
<td>11.0</td>
<td>60% male</td>
<td></td>
</tr>
<tr>
<td><strong>All IBD</strong></td>
<td>2087</td>
<td>12.1</td>
<td>56% male</td>
<td></td>
</tr>
</tbody>
</table>

De Bie et al. JPGN 2012
NUTRITION IN CHILDREN WITH CD
pathogenesis of growth failure

Taken from: Marcovech Ml, et al. Inflammatory cytokines and growth in childhood. Curr Opin Endocrinol Diabetes Obes 2012;19
Enteral nutrition in CD
LONG TERM OUTCOME

- Induction with EN + early thiopurine \textit{versus}
  induction with CS + early thiopurine
- N=89; followed for at least 2 years

\textbf{Induction with EC associated with}

- reduced growth failure (7 vs 26%)
- less steroid dependency (7 vs 43%)
- improved later response to IFX