Inflammatory Bowel Disease in Children

WHAT IS NEW & IMPORTANT??

Sanja Kolaček

Children’s Hospital Zagreb
Children with IBD

to be presented:

Specifics of IBD in children with regard to

- Epidemiology: prevalence, environment vs genetics
- Phenotype & diagnostics
- Clinical presentation
- Treatment
**IBD in children:** How common?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>0.6 – 6.8 / 100,000 / y</td>
</tr>
<tr>
<td>UC</td>
<td>0.8 – 3.6 / 100,000 / y</td>
</tr>
</tbody>
</table>

- Constant increase of CD
- Incidence of UC stable

Levine A et al. *Inflamm Bowel Dis* 2010
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.

**Trends in prevalence of CD**

*Chouragi et al. Changing pattern of CD in France Aliment Pharmacol Ther 2011;33:1133-1142*

**Incidence of IBD**

- 2/3 of diagnosed patients had CD

- Incidence of CD increased
  - Increase was on account of age group 10-19 from 6.5 to 11.1 (71%!!)

- Different environmental factors initiating disease at the age 10-19??
**IBD in Children: Pathogenesis**

**Environment:** Role of diet??

**Dietary factors as risk factors**
- animal fat, proteins & refined sugars in excess
- less fibres (fruits & vegetable)

**NO CONCLUSIVE EVIDENCE!**

- Low intake of omega 3 LC-PUFA could be implicated in etiology of UC *(IBD in EPIC. Gut 2009)*

**Nutrition in childhood and later IBD**
- breast feeding
- cow’s milk intake
- sucrose
The role of breast feeding in the development of IBD is illustrated in the figure below. The pooled OR of all studies is shown for the association between breastfeeding and ulcerative colitis and Crohn disease.

- 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

For 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

Role of breast feeding in development of IBD

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

Latest systematic review

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

**Multivariate Logistic regression analysis for IBD children**

<table>
<thead>
<tr>
<th>Variables Adjusted</th>
<th>OR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s degree</td>
<td>5.5</td>
<td>(2.5-11.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Breast feeding&gt; 3th month</td>
<td>4.3</td>
<td>(1.6-10.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Father’s employment</td>
<td>3.7</td>
<td>(1.2-8.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Gluten introduction &lt; 6th month</td>
<td>2.8</td>
<td>(1.5-5.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nº Siblings&lt;2</td>
<td>2.8</td>
<td>(1.5-5.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>2.7</td>
<td>(1.4-5.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pets</td>
<td>0.3</td>
<td>(0.1-0.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bed sharing</td>
<td>0.2</td>
<td>(0.1-0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low adherence to Mediterranean diet</td>
<td>2.3</td>
<td>(1.2-4.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gluten introduction &lt; 6th month</td>
<td>2.8</td>
<td>(1.6-4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nº Siblings&lt;2</td>
<td>2.0</td>
<td>(1.1-3.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pets</td>
<td>0.4</td>
<td>(0.2-0.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Family Parasitosis</td>
<td>0.07</td>
<td>(0.01-0.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Caterina Strisciuglio, et al. Impact of Environmental and Familial Factors in a cohort of pediatric patients with Inflammatory Bowel Disease. JPGN 2016, accepted for publication
Role of positive family history

Genes in childhood IBD

> 180 genes associated with increased risk

- mutations causing early & severe presentation
**IBD in children:** ROLE OF POSITIVE FAMILY HISTORY

25% - 30% of IBD patients have positive family history

**IBD will develop in:**
- 2% - 3% of siblings of CD patient
- 0.5% - 1% of siblings of UC patient

**Transmission in the family with CD is:**
- More common from mother than from father
- More common in female offspring than in male
- Most common from mother with CD to daughter

Van der Woude J et al. European evidence-based consensus on reproduction in IBD. JCC 2015
Children with IBD

to be presented:

Specifics of IBD in children with regard to

- Epidemiology: prevalence, environment vs genetics
- Phenotype & diagnostic
- Diagnostics
- Treatment
Inflammatory bowel disease

ESPGHAN IBD Working Group
PORTO GROUP

Roles

- Make diagnostic criteria & work-up
- Collect uniform phenotypic data on newly diagnosed children with IBD using PORTO criteria (start a registry !!!)
- Perform audit → new guidelines
Diagnosis of IBD

PORTO DIAGNOSTIC ALGORITHM

Ileocolonoscopy and upper GI endoscopy + histology of multiple biopsies

CD or IC or nonconclusive

UC

when diagnosis of UC is not certain

radiology: Small Bowel Follow Through (SBFT)

Porto criteria for diagnosis of inflammatory bowel disease in children.

2087 newly diagnosed (prospectively)

United Kingdom
Surrey
Chelsea
Bristol
Birmingham

Denmark

Switzerland

Poland
Cracow, Warsaw

Germany
Dresden, Munich, Bonn

Czech Republic

Croatia

France

Italy
Rome, Florence

Portugal

NL

Israel
Tel Hashomer
Tel Aviv
<table>
<thead>
<tr>
<th>N = 2087</th>
<th>N %</th>
<th>Mean Age</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>1221</td>
<td>12.5</td>
<td>59% male</td>
</tr>
<tr>
<td>UC</td>
<td>670</td>
<td>11.6</td>
<td>50% male</td>
</tr>
<tr>
<td>IBD-U</td>
<td>196</td>
<td>11.0</td>
<td>60% male</td>
</tr>
<tr>
<td>All IBD</td>
<td>2087</td>
<td>12.1</td>
<td>56% male</td>
</tr>
</tbody>
</table>
Pediatric Modification of the Montreal Classification for Inflammatory Bowel Disease: The Paris Classification

Arie Levine, MD,* Anne Griffiths, MD,† James Markowitz, MD,‡ David C Wilson, MD,§ Dan Turner, MD, PhD,¶ Richard K Russell, MD, PhD,‖ John Fell, MD,** Frank M Ruemmele, MD, PhD,†† Thomas Walters, MD,† Mary Sherlock, MD,† Marla Dubinsky, MD,‡‡ and Jeffrey S Hyams, MD§§
# Paris vs Montreal classification

**Levine A et al. Inflamm Bowel Dis 2011;17**

## CROHN’S DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Paris</th>
<th>Montreal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at dg</strong></td>
<td>A1a &lt; 10</td>
<td>A1 &lt; 17 y</td>
</tr>
<tr>
<td></td>
<td>A1b 10-16</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>L4a (upper proximal to Treitz)</td>
<td>L4  upper disease</td>
</tr>
<tr>
<td></td>
<td>L4b (distal of Treitz to</td>
<td></td>
</tr>
<tr>
<td></td>
<td>distal 1/3 of ileum)</td>
<td></td>
</tr>
<tr>
<td><strong>Behaviour</strong></td>
<td>B2B3 Both stricturing &amp;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>penetrating</td>
<td></td>
</tr>
<tr>
<td><strong>Growth</strong></td>
<td>G0 no evidence of delay</td>
<td>not applicable</td>
</tr>
<tr>
<td></td>
<td>G1 growth delay</td>
<td></td>
</tr>
</tbody>
</table>
## Paris vs Montreal classification

*Levine A et al. Inflamm Bowel Dis 2011;17*

### Ulcerative Colitis

<table>
<thead>
<tr>
<th>Extent</th>
<th>Paris</th>
<th>Montreal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E4  pancolitis (proximal to hepatic flexure)</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>S0  Never severe*</td>
<td>S0  clinical remission</td>
</tr>
<tr>
<td></td>
<td>S1  Ever severe*</td>
<td>S1  mild</td>
</tr>
<tr>
<td></td>
<td>S2  moderate</td>
<td>S2  moderate</td>
</tr>
<tr>
<td></td>
<td>S3  Severe</td>
<td>S3  Severe</td>
</tr>
</tbody>
</table>

*Pediatric UC Activity Index – PUCAI ≥ 65*
DISEASE PHENOTYPE AT DIAGNOSIS IN PAEDIATRIC CD

De Bie C et al. Inflamm Bowel Dis 2013

N=1221, mean age 12.5 y, 59% male

DISEASE BEHAVIOUR

- 82% inflammatory (B1) - younger patients more B1 (p<0.003)
- 12% stricturing (B2)
- 5% penetrating (B3)
- 2% stricturing & penetrating

- 9% perianal disease male 12%, female 6%, p=0.002
  most common in B1
- 20% extraintestinal symptoms

PRESENCE OF GRANULOMA: in 43% of patients in 19% in macroscopically normal-looking mucosa
DISEASE PHENOTYPE AT DIAGNOSIS IN PAEDIATRIC UC – ATYPICAL PHENOTYPES

Levine A et al. Inflamm Bowel Dis 2013

N= 670, mean age 11.6 y, 50% male

DISEASE EXTENT
- E1 in 5%
- E2 in 18%
- E3 in 9%
- E4 in 69%

PRESENCE OF ATYPICAL PHENOTYPES
- Cecal patch 2% (more common in younger, p=0.02)
- Rectal sparing 5% (frank ulcerations in 0.4%)
- Upper GI 4% (frank ulcerations in 0.4%)
- Backwash ileitis 10% of patients with E4 (more common in males)
DISEASE LOCATION OF UC AT DIAGNOSIS ACCORDING TO AGE

FIGURE 2. Disease location in newly diagnosed pediatric UC patients according to age at diagnosis.

IBD in children: TAKE HOME MESSAGE

Unique phenotype in ped. IBD

- Extensive intestinal involvement
  CD at presentation: L3 in 50%-60% of children
  3% -20% in adults
  UC at presentation: extensive 82% of children
  48% of adults

- Progressive severity in individual child

- Progression in severity in time cohorts

---

del. Bie Cl. Inflamm Bowel Dis 2013
Chouraki V et al. Aliment Pharmacol Ther 2011;33:1133-1142
DIAGNOSTIC WORKUP OF PEDIATRIC IBD
RESULTS OF 5-YEAR AUDIT OF EUROKIDS

De Bie CI at al. et al. JPGN 2012

WORKUP

- Complete (EGD + ileocolon.+ small bowel imaging): 59%
  - 59% of CD
  - 58% of UC
  - 45% of IBD-U

- EGD + ileocolonoscopy: 64%

DIAGNOSTIC YIELD OF ILEAL INTUBATION: 13%

DIAGNOSTIC YIELD OF EGD: 7%
DIAGNOSTIC WORKUP OF PEDIATRIC IBD
RESULTS OF 5-YEAR AUDIT OF EUROKIDS

FIGURE 3. Endoscopic procedures in paediatric patients with inflammatory bowel disease during the first 5 years of the EUROKIDS registry. OGD = oesophagogastroduodenoscopy.
FIGURE 4. Small bowel imaging in paediatric patients diagnosed with Crohn disease and IBD-unclassified during the first 5 years of the EUROKIDS registry. CT=computed tomography; MRI=magnetic resonance imaging; SBFT=small bowel follow-through.
Revised ESPGHAN Porto Criteria for Diagnosis of Ped. IBD

Evaluation of Child / Adolescent with Intestinal or Extra-intestinal Symptoms Suggestive of IBD

Strong Suspicion of IBD

Tests unhelpful or Isolated extraintestinal symptoms

Test Fecal Markers (FM) (e.g. calprotectin, lactoferrin), if elevated

Ileocolonoscopy & EGD (with biopsies from all segments)

Typical UC

Atypical UC

Clear CD

Normal

IBDU

Consider MRE

MRE/WCE

MRE/WCE

MRE/WCE

Consider WCE if FM positive and MRE negative

Positive

Negative

Suggest UC

Suggest CD

Negative

Suggest CD

Negative

UC

CD

No IBD

CD

IBDU

Levine A, et al. JPGN 2015
Children with IBD

to be presented:

Specifics of IBD in children with regard to

Epidemiology: prevalence, environment vs genetics

Phenotype & diagnostic

Clinical presentation

Treatment
# Paediatric IBD: clinical presentation

<table>
<thead>
<tr>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Blood in stool</td>
</tr>
<tr>
<td>Weight loss &amp; stunted growth</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>

**CD clinical presentation vague – greater delay in diagnosis**

Presence of symptoms at diagnosis in 623 children with IBD

# Nutritional status in children with IBD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Crohn</th>
<th>U.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>75%</td>
<td>25-30%</td>
</tr>
<tr>
<td>Stunted growth</td>
<td>36%</td>
<td>0-10%</td>
</tr>
<tr>
<td>Delay in sex. maturation</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Delay in bone mineralization</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Decreased growth before GIT symptoms</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>
IBD in children & adult height

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
- Most important factors: -- presence of jejunal disease -- duration of symptoms prior dg

20 – 30% of adults with CD are stunted
“Growth and bone density restoration can be considered a marker of disease control and of successful therapy in children”

Pathogenesis of growth failure

TAKE HOME MESSAGE

Taken from: Marcovechio ML, et al. Inflammatory cytokines and growth in childhood. Curr Opin Endocrinol Diabetes Obes 2012;19

Diagram:
- Drugs, i.e. glucocorticosteroids
- Inflammation
- Disease severity, duration
- Poor nutrition
- Genetic background
- Lack of exercise

Growth failure
Growth failure in IBD children
HOW TO TREAT - CONCLUSIONS

- DECREASE INFLAMMATION: role of EN in CD biologics surgery
- LIMIT USE OF STEROIDS
- PROVIDE NUTRITION SUPPORT
- PROMOTE WEIGHT-BEARING ACTIVITY
- ACT EARLY IN PUBERTY
- CALCULATE TARGET HEIGHT (based on parents) TO AVOID UNREALISTIC EXPECTATIONS
Children with IBD

to be presented:

Specifics of IBD in children with regard to

- Epidemiology: prevalence, environment vs genetics
- Phenotype & diagnostic
- Clinical presentation
- Treatment
Paediatric IBD: treatment

- Aims of treatment
  - induce remission of active disease
  - maintain remission & prevent relapse
  - normalise growth and maturation
  - restore normal QL

Wilson DC et al. Systematic review of evidence base for the medical treatment of paediatric IBD. JPGN 2010;50
Children with IBD: TREATMENT

Special features of pediatric age:

role of nutrition
role of biologicals
EN in active CD

How effective is it?

4 meta-analyses in adults:
--- steroids more effective ---

( Fernandez-Banares, et al. JPNEN 95;19:356-64
Messori S, et al. Scand J Gastroenterol 96;31:267-72

2 meta-analyses in children:
--- equal efficacy (no difference) ---

EN vs. steroids: A meta-analysis


**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><strong>73</strong></td>
<td><strong>71</strong></td>
<td></td>
<td><strong>0.97 (0.68, 1.40)</strong></td>
</tr>
</tbody>
</table>

Total events: 56 (Treatment), 57 (Control)

Test for heterogeneity: \( \chi^2 = 9.40, \text{df}=3 \) (P=0.02, \( I^2 = 68.1\% \))

Test for overall effect: \( Z = 0.15 \) (P=0.88)
Enteral nutrition in CD

EN induces mucosal healing
--- 76% with EN vs. 33% with steroids ---


EN has NO side-effects & supports growth and bone mineralization

Enteral nutrition in CD duration of remission

EEN

Kortikosteroid

Enteral nutrition as primary treatment for CD

How to use it?

1. Content of diet
   ONLY enteral formula + water

2. Duration
   6-12 weeks

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

4. Application
   - orally
   - naso-gastric tube
   - PEG
Compared to steroids EN is equally effective, and has a good safety profile.

EN is recommended as the first line treatment in children with active CD.

Elemental formulae are not more effective than polymeric formulae.

ESPGHAN /ECCO Evidence-based consensus on diagnosis & treatment of CD. JPGN 2014
Nutrition in chronic UC in children

ECCO / ESPGHAN Consensus, JPGN 2012

EN or PN is inappropriate for primary disease treatment

Special diets or supplementations are not effective to maintain remission and carry a risk of nutritional deficiencies

--- 68% of patients with UC believe that diet influence activity of disease & modify their diet

Role of biologics in children with iBD

**ECCO / ESPGHAN Consensus on UC, JPGN 2012**

**ECCO / ESPGHAN Consensus on CD, JPGN 2014**

### Anti-TNF in children with CD (infliximab, adalimumab)
- Remission induction & maintenance for moderate to severe steroid-dependent, refractory & resistant to standard treatment including treatment with immunosuppressants

### Anti-TNF in children with UC
- Infliximab as a second line treatment in acute severe disease after failure of iv steroids
- In presistantly active, steroid- dependent, uncontrolled by 5-ASA and thiopurines
- Adalimumab only in those with lost response to infliximab
IBD in children: USE of anti-TNFs

2/3 of responsive patients require constant maintenance treatment.

> 40% of children for remission require double dose & shorter interval between doses.

After 5 y of treatment infliximab ineffectiveness in every second child despite dose adjustment.

Infliximab in IBD: Hepatosplenic T-cell lymphoma

1998 - 2013: 36 cases in IBD patients
- 24 / 27 male; 22 had CD; 17 age < 30 y
- 23 / 27 died within 1 y (in 4 outcome unknown)
- 27 / 27 received also AZA or 6-MP
- 5 / 27 also on another anti-TNF drug
- 16 patients treated ONLY with AZA

Very rare! In immunosuppressed & young male!
Very aggressive – fatal outcome within 1 y
IBD in Children: treatment

Take home messages

- Growth and QL important outcome measures
- Exclusive EN recommended as the first line treatment of active CD
- Anti-TNFs to be used as „step-up” treatment in moderate to severe disease persistently active, refractory / resistant
Meta-analysis: EN vs Steroids in pediatric CD

- **Dziechciarz, et al.**
  *Aliment Pharmacol Ther* 2007; 26:795-806

- Total 11 RCT’s, 394 children with active Crohn’s disease

- EN versus Steroids:
  - 4 RCT’s, n=144

- Remission rate:
  - no evidence for difference between EN and steroids