Inflammatory Bowel Disease in Children

WHAT IS NEW & IMPORTANT??

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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?

10% - 25% present during childhood

Incidence of CD 0.6 – 6.8 / 100,000 / y

Incidence of UC 0.8 – 3.6 / 100,000 / y

- Constant increase of CD
- Incidence of UC stable

Levine A et al. Inflamm Bowel Dis 2010

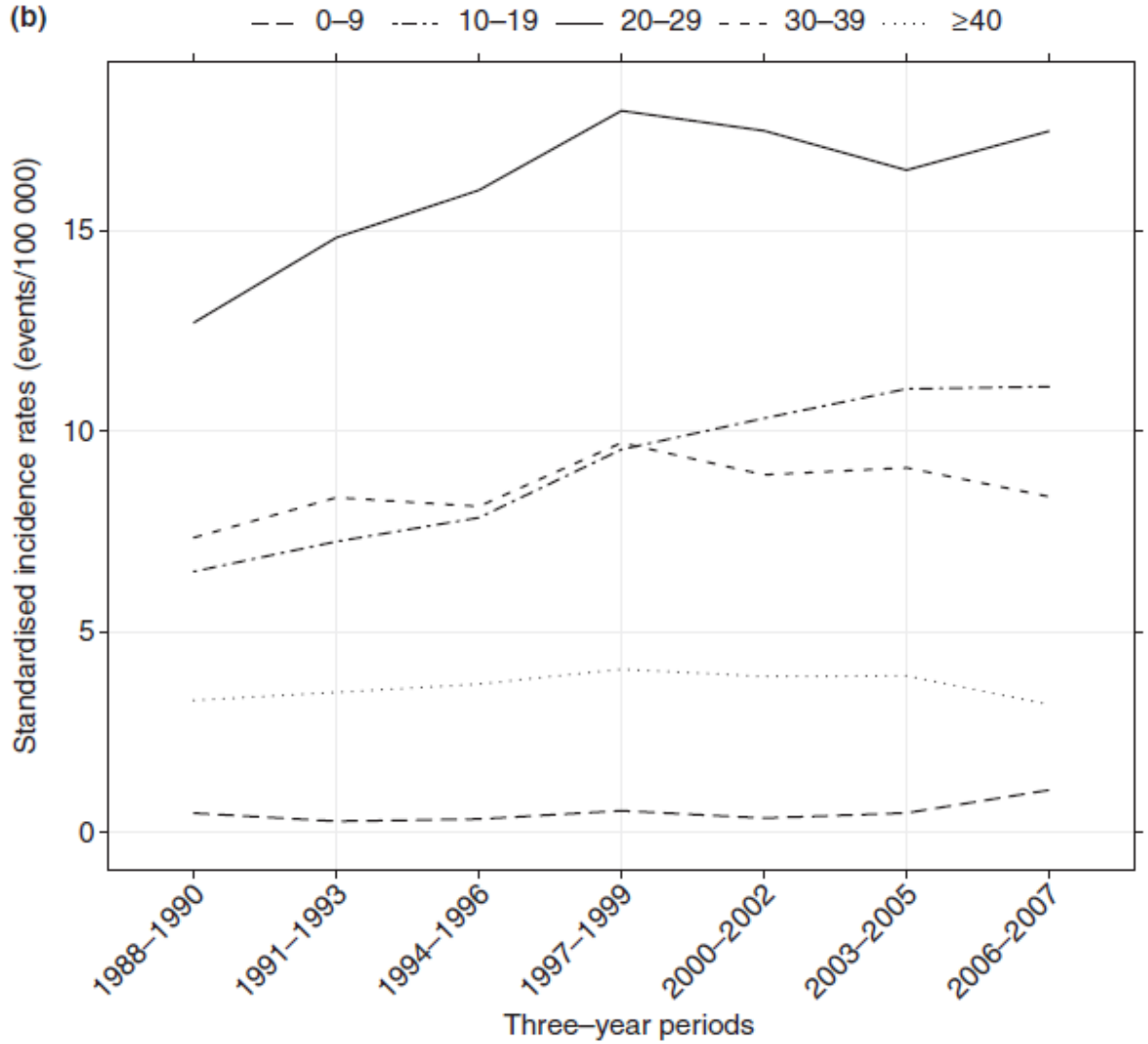


Figure 4 | (a) Evolution of the incidence of Crohn's disease in Northern France from 1988-1990 to 2006-2007 according to 20-year age groups. (b) Evolution of the incidence of Crohn's disease in Northern France from 1988-1990 to 2006-2007 according to 10-year age groups.

Chouragi et al. Aliment Pharmacol Ther. 2011;33:1133-42.

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!

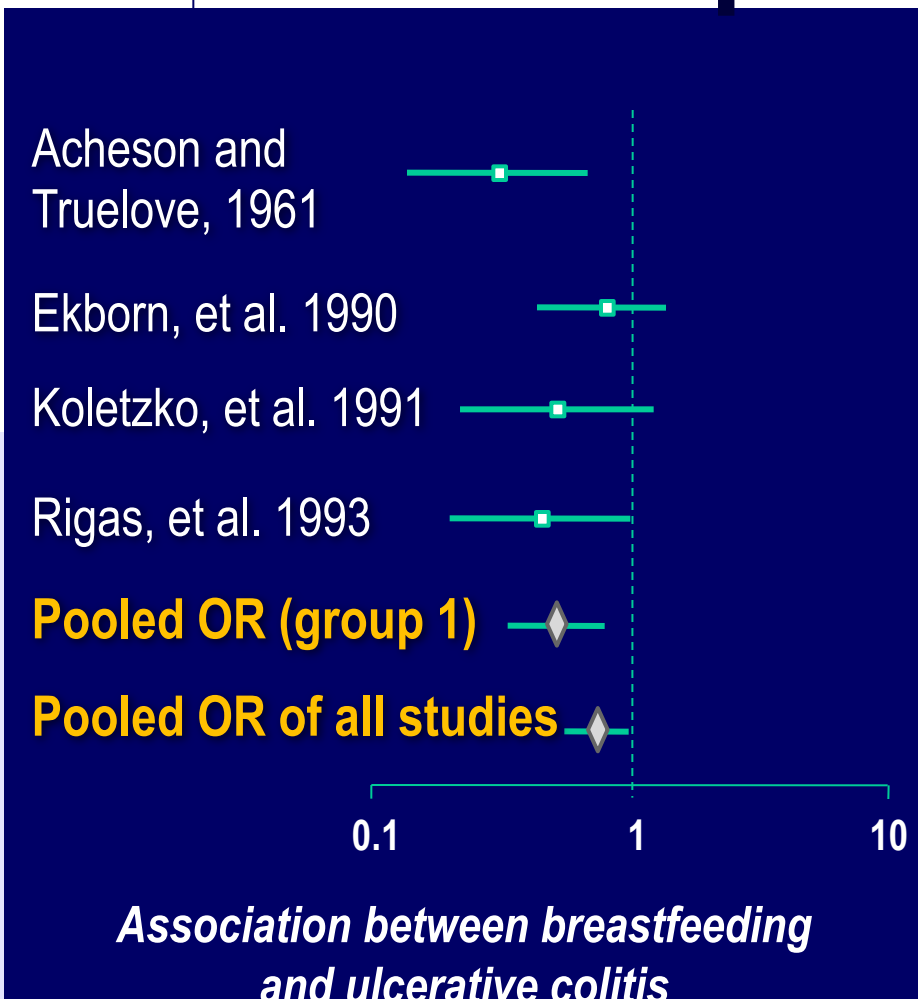
- Low intake of omega 3 LC-PUFA could be implicated in etiology of UC *(IBD in EPIC. Gut 2009)*

Nutrition in childhood and later IBD

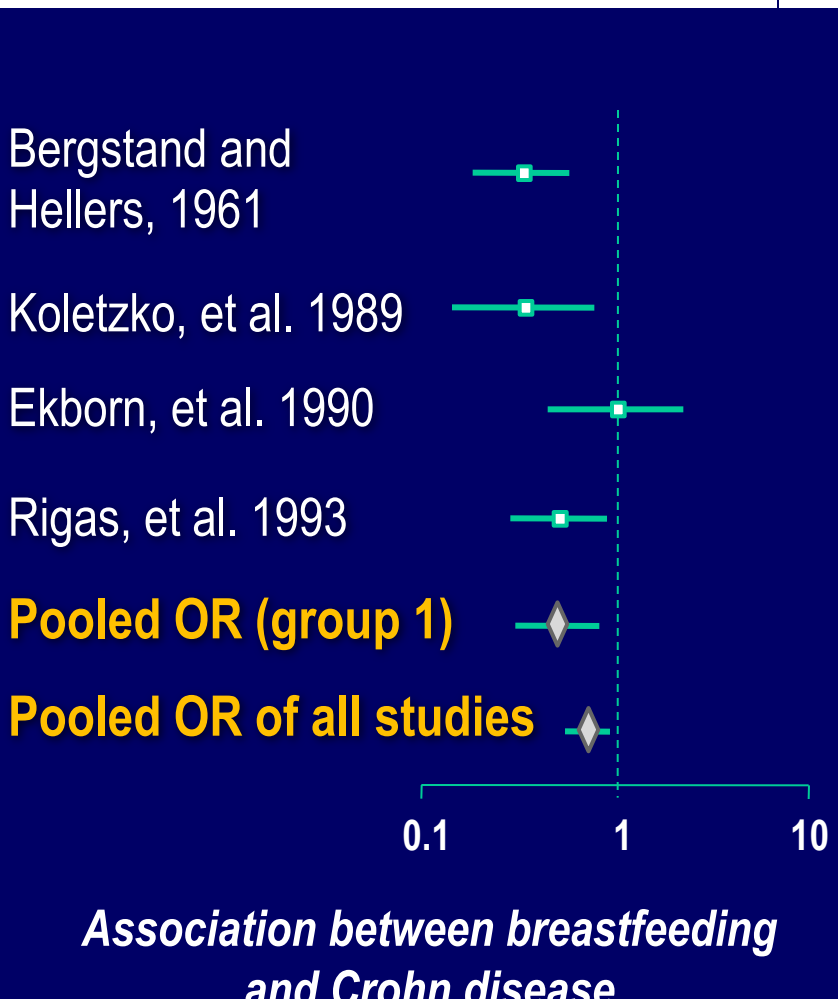
- breast feeding
- cow's milk intake
- sucrose

Role of breast feeding

in development of IBD



Association between breastfeeding and ulcerative colitis



Association between breastfeeding and Crohn disease

Klement , et al. Am J Clin Nutr 2004; 80:1342-52.

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**

  Baron S, et al.. Gut 2005; 54:357-363

Latest systematic review

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

  Barclay AR et al. A Systematic Review.. J Pediatr 2009;155:421-6.

IBD in Children: Pathogenesis

Environment: Latest data

Multivariate Logistic regression analysis for IBD children

Variables Adjusted	*OR*	*CI 95%*	*p*
Crohn's Disease			
Mother's degree	5.5	(2.5-11.6)	0.01
Breast feeding> 3th month	4.3	(1.6-10.5)	0.002
Father's employment	3.7	(1.2-8.7)	0.008
Gluten introduction < 6th month	2.8	(1.5-5.0)	0.001
N° Siblings<2	2.8	(1.5-5.3)	0.01
Autoimmune diseases	2.7	(1.4-5.3)	0.003
Pets	0.3	(0.1-0.7)	0.007
Bed sharing	0.2	(0.1-0.6)	0.001
Ulcerative colitis			
Low adherence to Mediterranean diet	2.3	(1.2-4.5)	0.01
Gluten introduction < 6th month	2.8	(1.6-4.9)	<0.001
N° Siblings< 2	2.0	(1.1-3.6)	0.01
Pets	0.4	(0.2-0.8)	0.004
Family Parasitosis	0.07	(0.01-0.4)	0.01

Caterina Strisciuglio, et al. Impact of Environmental and Familial Factors in a cohort of pediatric patients withInflammatory Bowel Disease. JPGN 2016, accepted for publication

IBD in children: pathogenesis

ROLE OF GENETICS

Role of positive family history

Genes in childhood IBD

- > 180 genes associated with increased risk
- mutations causing early & sever 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* genetis**
- **Phenotype & diagnostic**
- **Diagnostics**
- **Treatment**

Inflammatory bowel disease

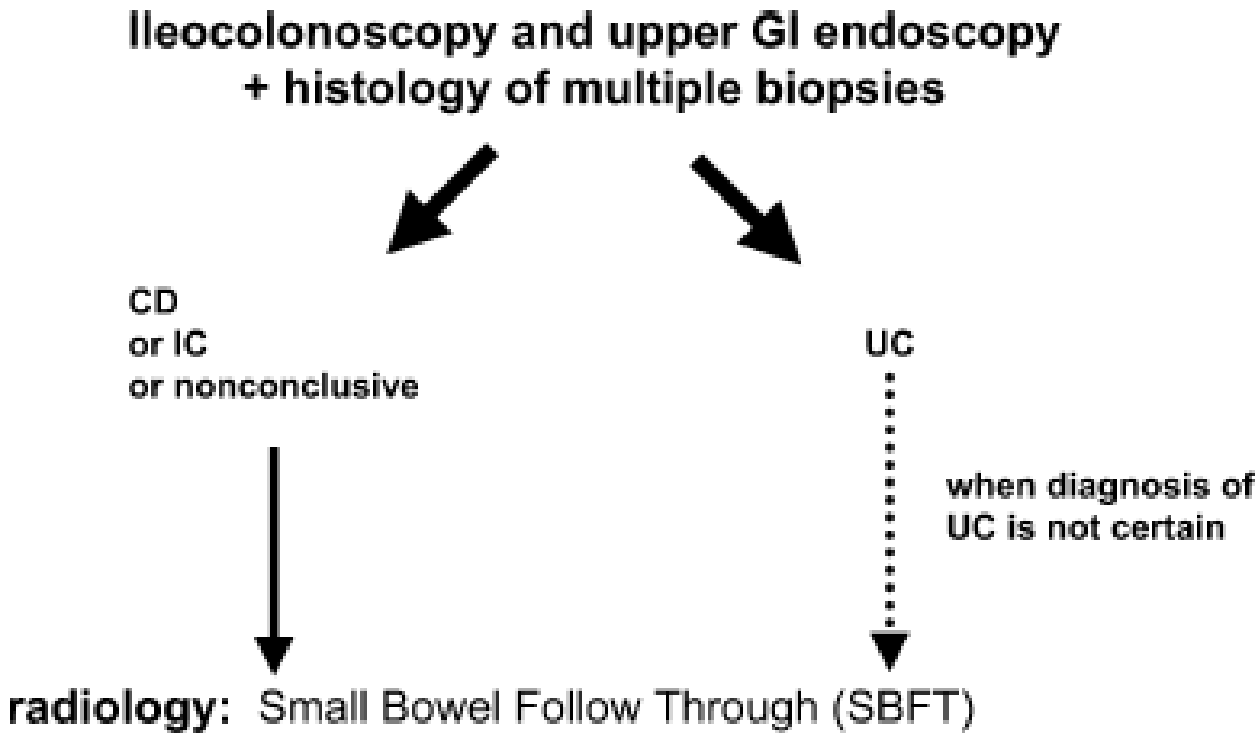
ESPGHAN IBD Working Group
PORTO GROUP

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

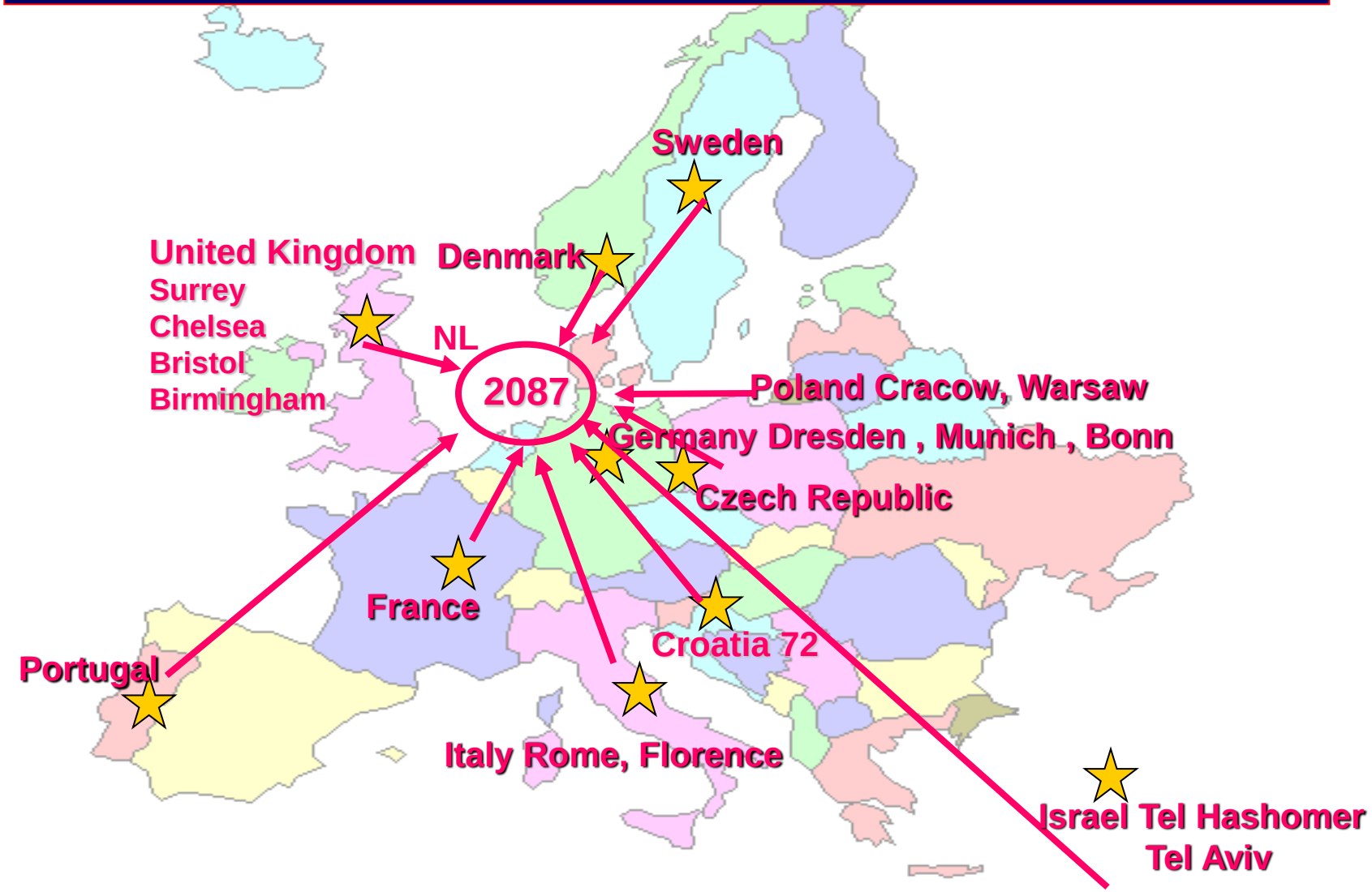
PORTO DIAGNOSTIC ALGORITHM



Porto criteria for diagnosis of inflammatory bowel disease in children.

JPGN 2005; 41:1-7.

EUROKIDS REGISTRY May 2004 - April 2009: 2087 newly diagnosed (prospectively)



ESPGHAN EUROKID registry

N = 2087	N %	Mean Age	Gender
CD	1221 (59%)	12.5	59% male
UC	670 (32%)	11.6	50% male
IBD-U	196 (9%)	11.0	60% male
All IBD	2087	12.1	56% male

ORIGINAL ARTICLE

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§§*

Inflamm Bowel Dis. 2011;17:1314-21.

Paris *vs* Montreal classification

Levine A et al. Inflamm Bowel Dis 2011;17

CROHN'S DISEASE

	Paris	Montreal
Age at dg	A1a < 10 A1b 10-16	A1 < 17 y
Location	L4a (upper proximal to Treitz) L4b (distal of Treitz to distal 1/3 of ileum)	L4 upper disease
Behaviour	B2B3 Both stricturing & penetrating	
Growth	G0 no evidence of delay G1 growth delay	not aplicable

Paris *vs* Montreal classification

Levine A et al. Inflamm Bowel Dis 2011;17

ULCERATIVE COLITIS

	Paris	Montreal
Extent	E4 pancolitis (proximal to hepatic flexure)	
Severity	S0 Never severe* S1 Ever severe*	S0 clinical remission S1 mild S2 moderate S3 Severe

* 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% infammatory (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 LOCATION AT DIAGNOSIS IN PAEDIATRIC CD

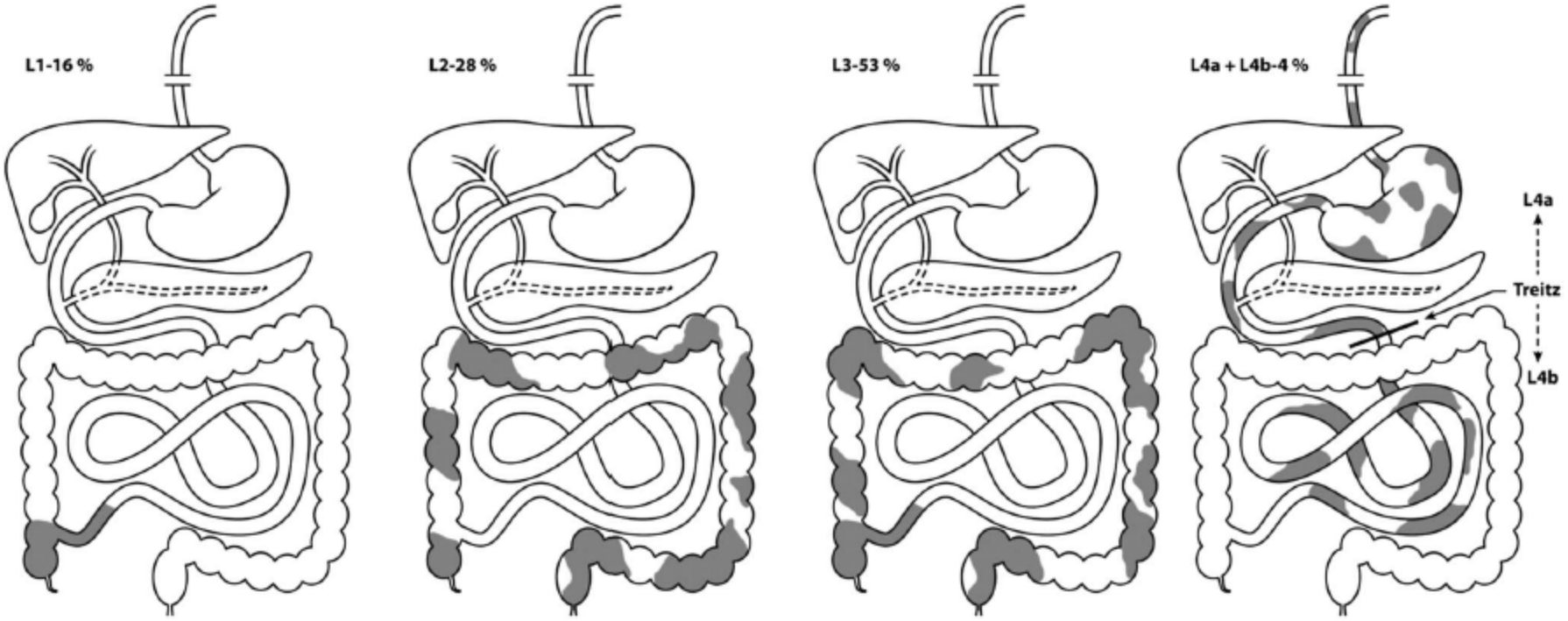


FIGURE 2. Disease location according to the Paris classification in 582 newly diagnosed pediatric CD patients who underwent a complete diagnostic workup according to the Porto criteria.[16] L1: terminal ileal disease (±limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal tract disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease.

de Bie CI et al. Inflamm Bowel Dis 2013;19:378-85

DISEASE LOCATION AT DIAGNOSIS ACCORDING TO AGE

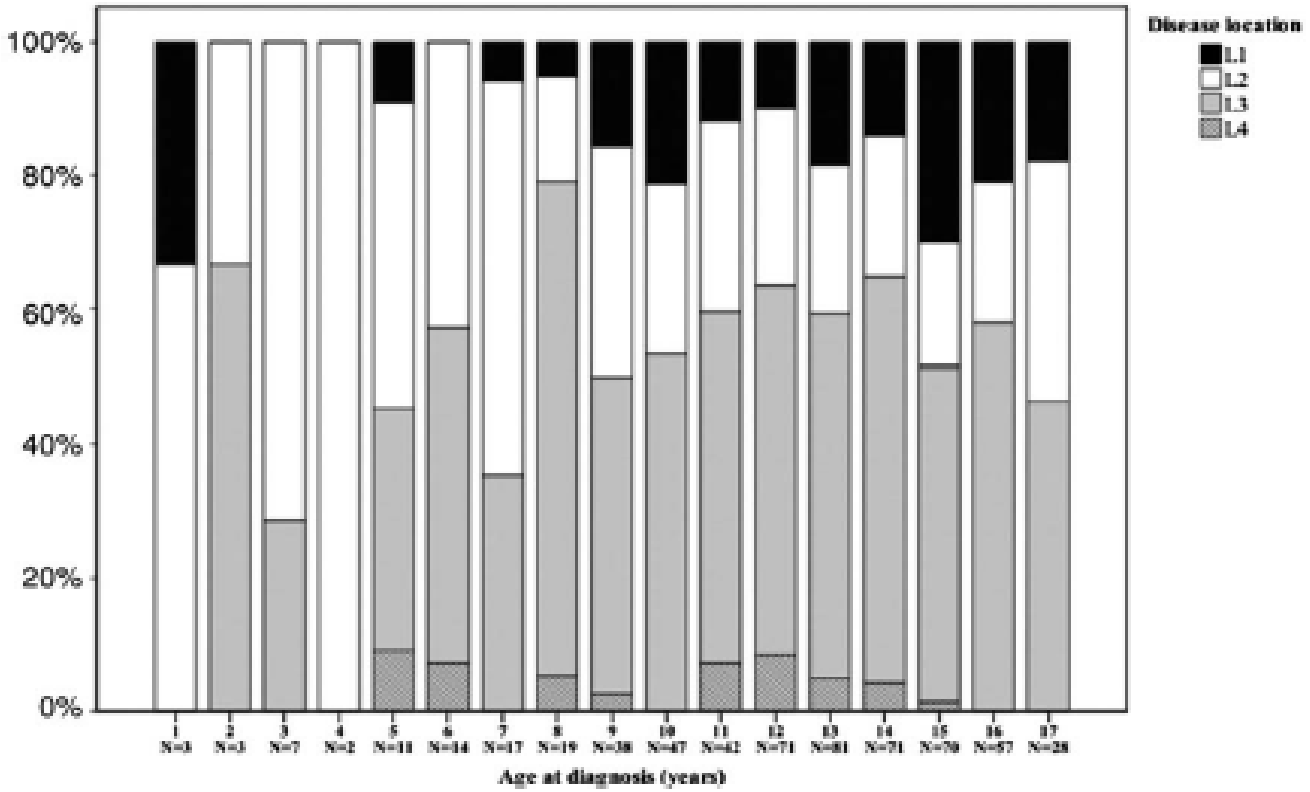


FIGURE 3. Disease location in newly diagnosed pediatric CD patients according to age at diagnosis. L1: terminal ileal disease (± limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal tract disease.

de Bie CI et al. Inflamm Bowel Dis 2013;19:378-85

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%
  - Rectal sparing 5% (more common in younger, p=0.02)
  - 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

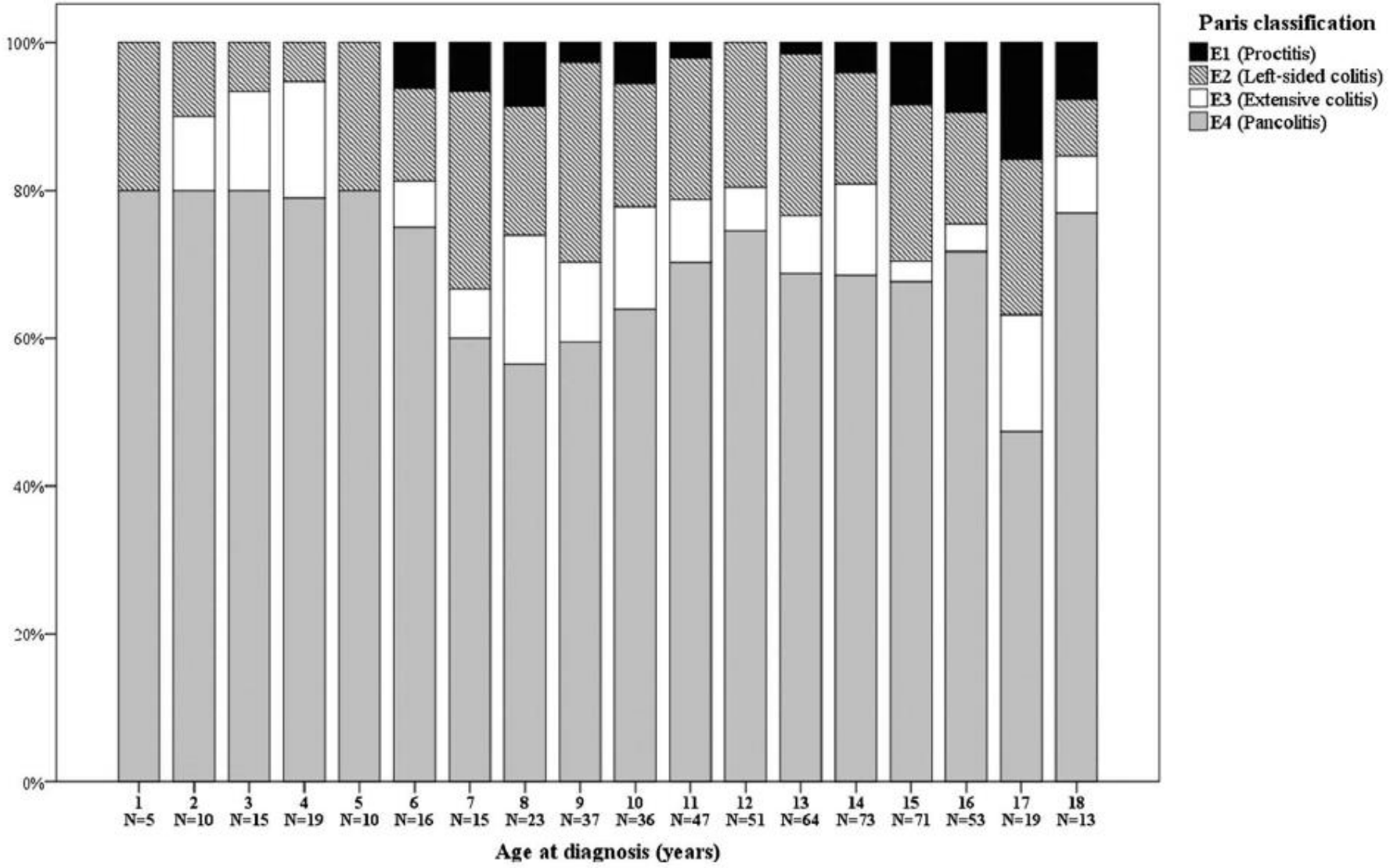


FIGURE 2. Disease location in newly diagnosed pediatric UC patients according to age at diagnosis.

Levine A, et al. Inflamma Bowel Dis 2013;19:370-7.

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

- **Progresive severity in individual child**

- **Progression in severity in time cohorts**

de Bie CI. Inflamm Bowel Dis 2013
Van Limbergen J et al. Gastroenterology 2008;135:1114-1122
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

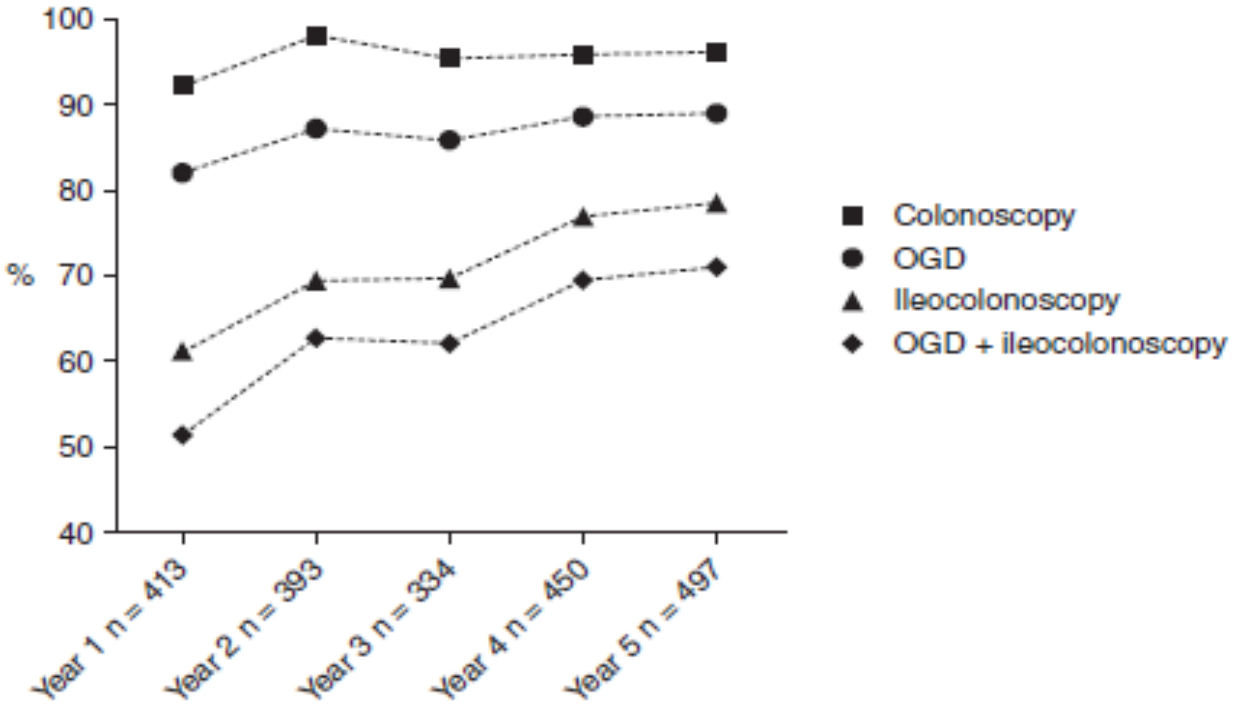


FIGURE 3. Endoscopic procedures in paediatric patients with inflammatory bowel disease during the first 5 years of the EUROKIDS registry. OGD = oesophagogastroduodenoscopy.

de Bie CI et al. JPGN 2012;54:374-380

DIAGNOSTIC WORKUP OF PEDIATRIC IBD
RESULTS OF 5-YEAR AUDIT OF EUROKIDS

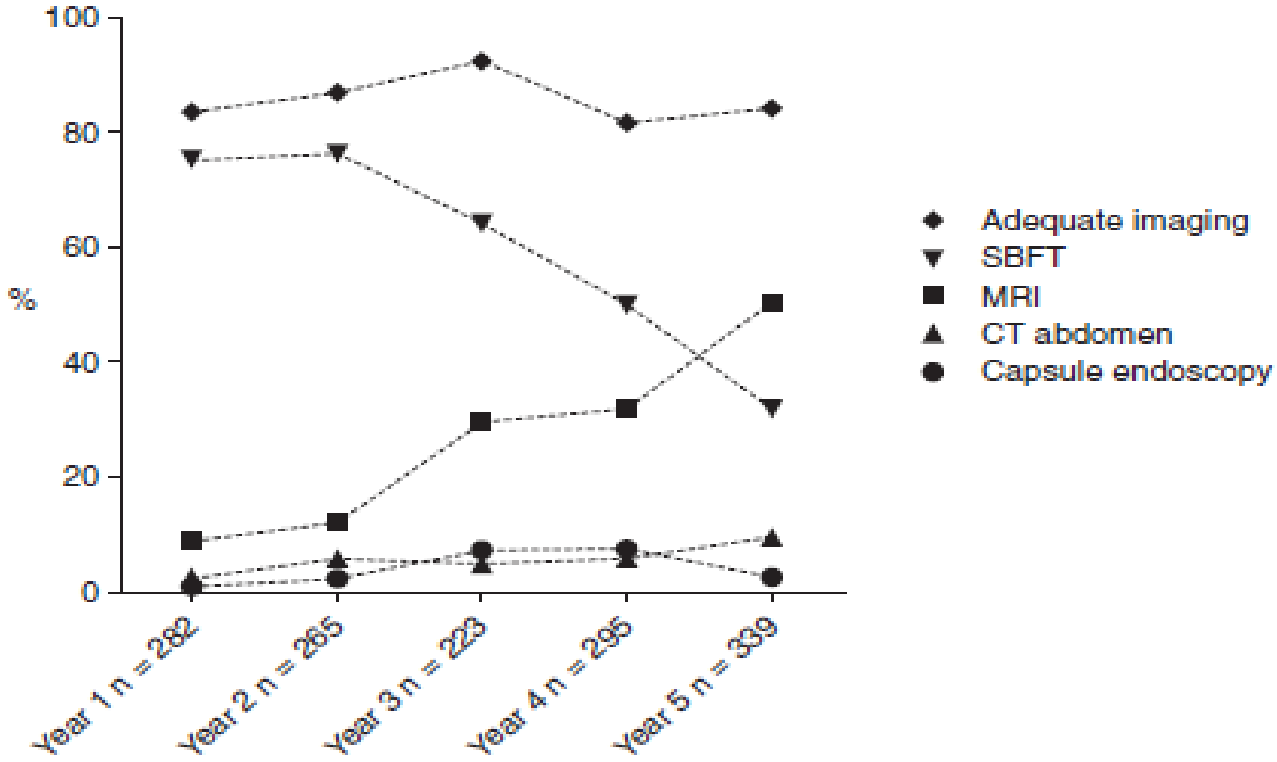
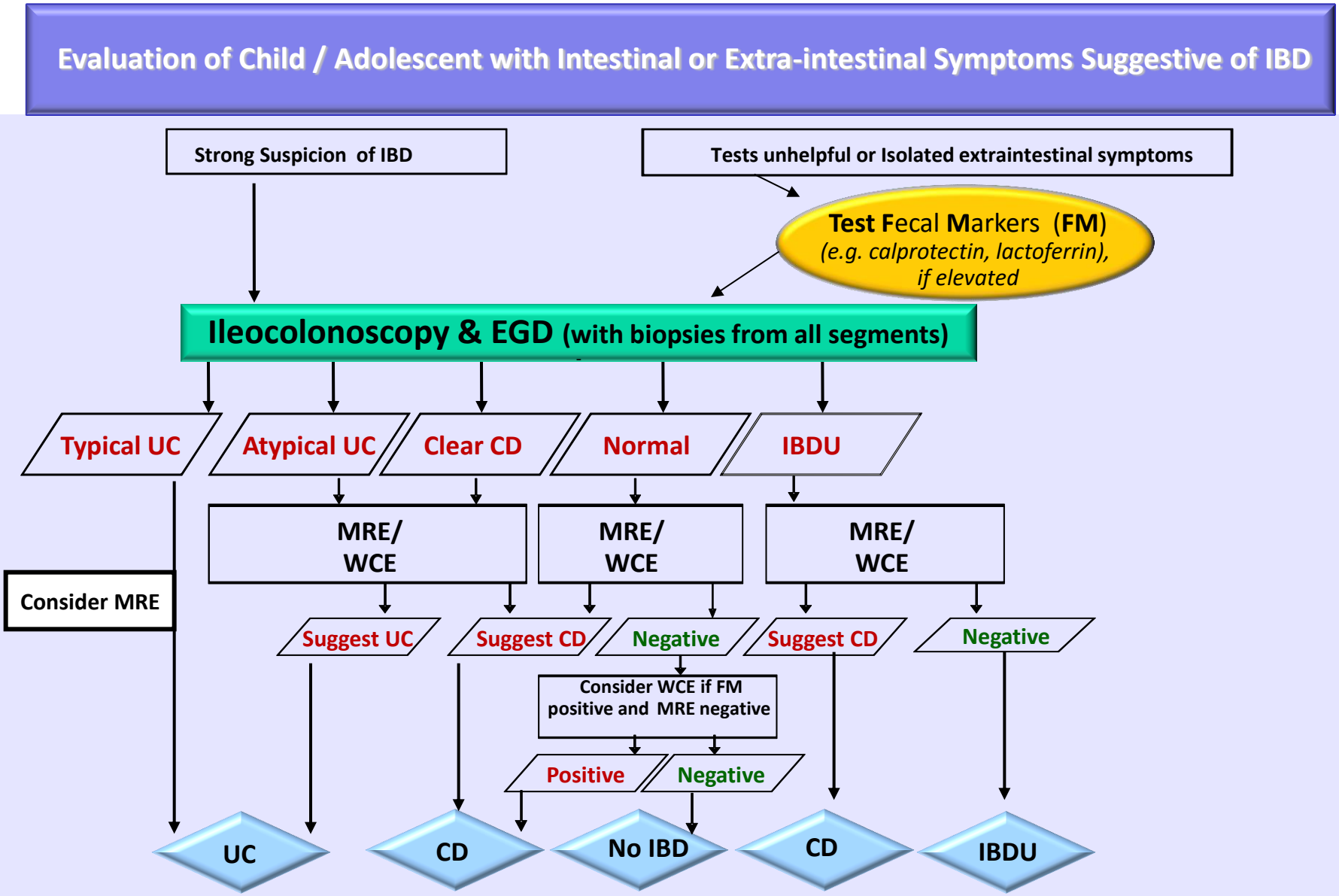


FIGURE 4. Small bowel imaging in paediatric patients diagnosed with Crohn disease and IBD-unclassified during the first 5 years of the EUROKIDS registry. CT = computed tomography; MRI = magnetic resonance imaging; SBFT = small bowel follow-through.

de Bie CI et al. JPGN 2012;54:374-380

Revised ESPGHAN Porto Criteria for Diagnosis of Ped. IBD



Levine A, et al. JPGN 2015

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Paediatric IBD: clinical presentation

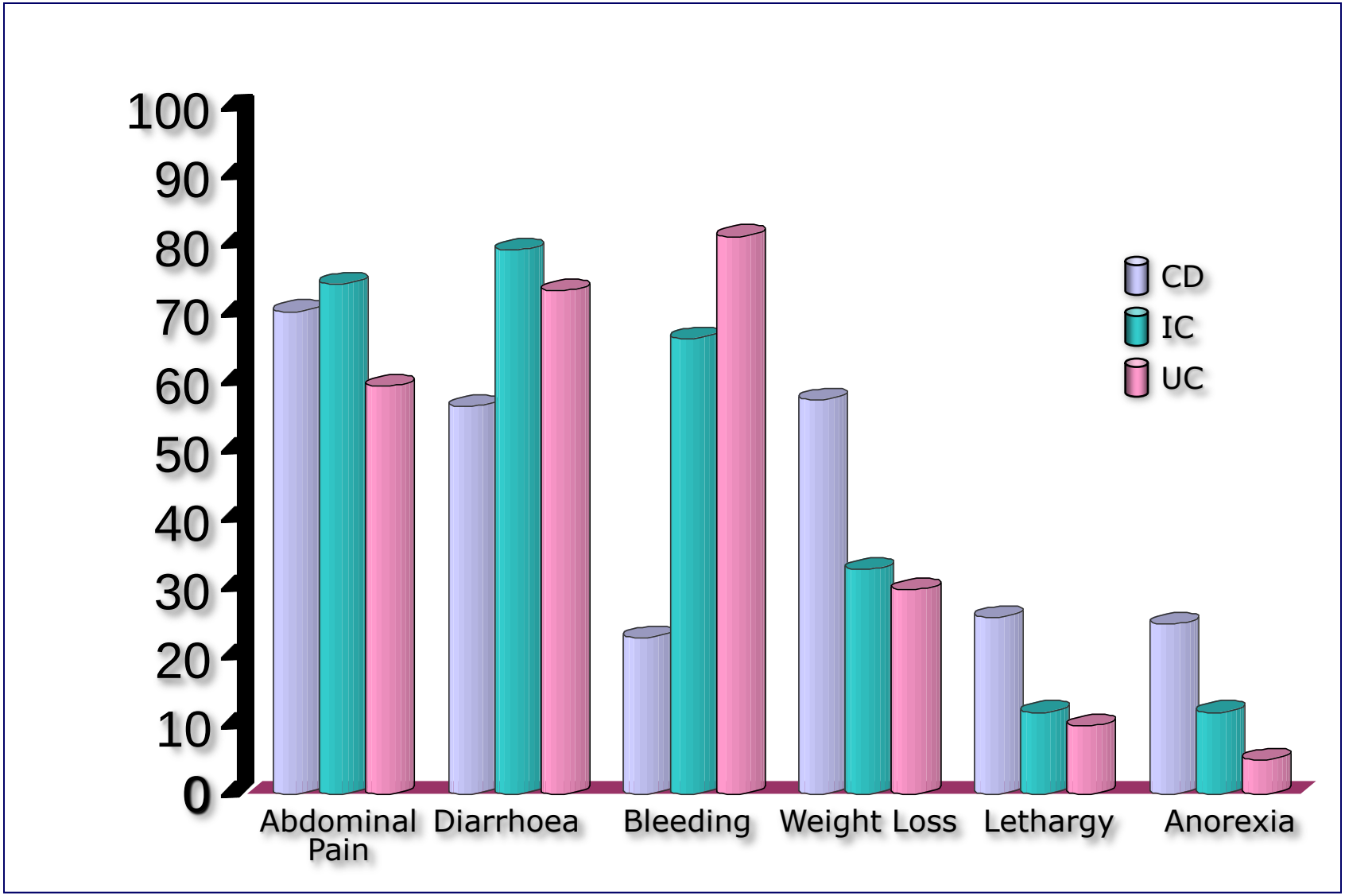
Crohn's Disease	Ulcerative Colitis
Abdominal pain	Blood in stool
Weight loss & stunted growth	Diarrhoea
Anorexia	Abdominal pain

CD clinical presentation vague – greater delay in diagnosis

Reviewed in: Sandhu B K, et al. Guidelines for the management of IBD in Children in UK. JPGN 2010; 50, Suppl 1

Presence of symptoms at diagnosis in 623 children with IBD

***Sawczenko A**, et al. Arch Dis Child 2003;88:995-1000*



Nutritional status

in children with IBD

	Crohn	U.C.
Malnutrition	75%	25-30%
Stunted growth	36%	0-10%
Delay in sex. maturation	30%	20%
Delay in bone mineralization	20%	20%
Decreased growth before GIT symptoms	50%	

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

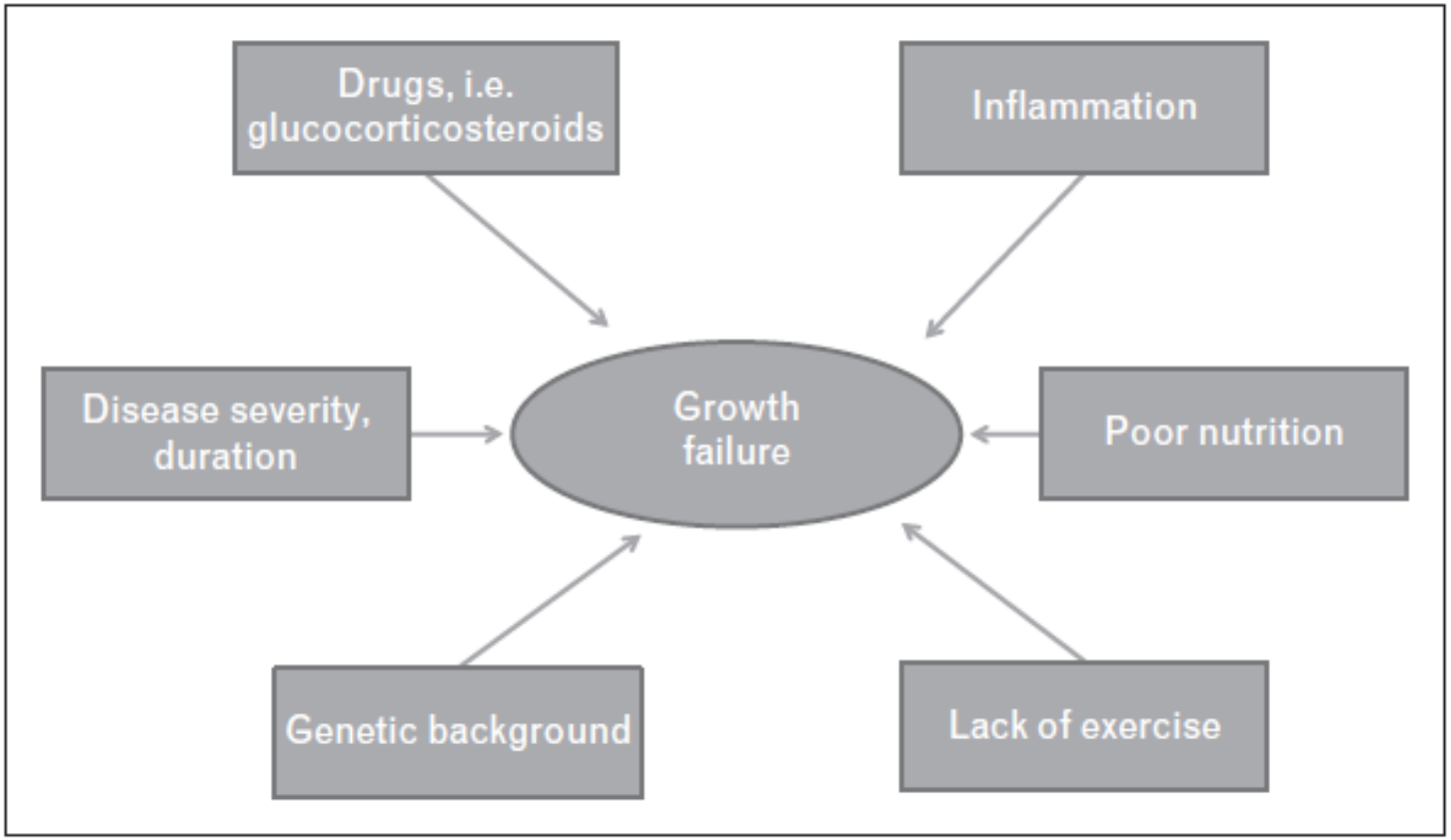
20 – 30% of adults with CD are stunted

GROWTH IN IBD CHILDREN: pathogenesis & treatment

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

Ruemmele F et al. Consensus Guidelines of ECCO/ESPGHAN on medical management of pediatric CD. JCC 2014

Pathogenesis of growth failure
TAKE HOME MESSAGE



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

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

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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. JPEN 95;19:356-64
Griffiths A, et al. Gastroenterology 95;108:1056-67
Messori S, et al. Scand J Gastroenterol 96;31:267-72
Zachos M, et al. Cochrane DatabaseSyst Rec 2007)

2 meta-analyses in children:

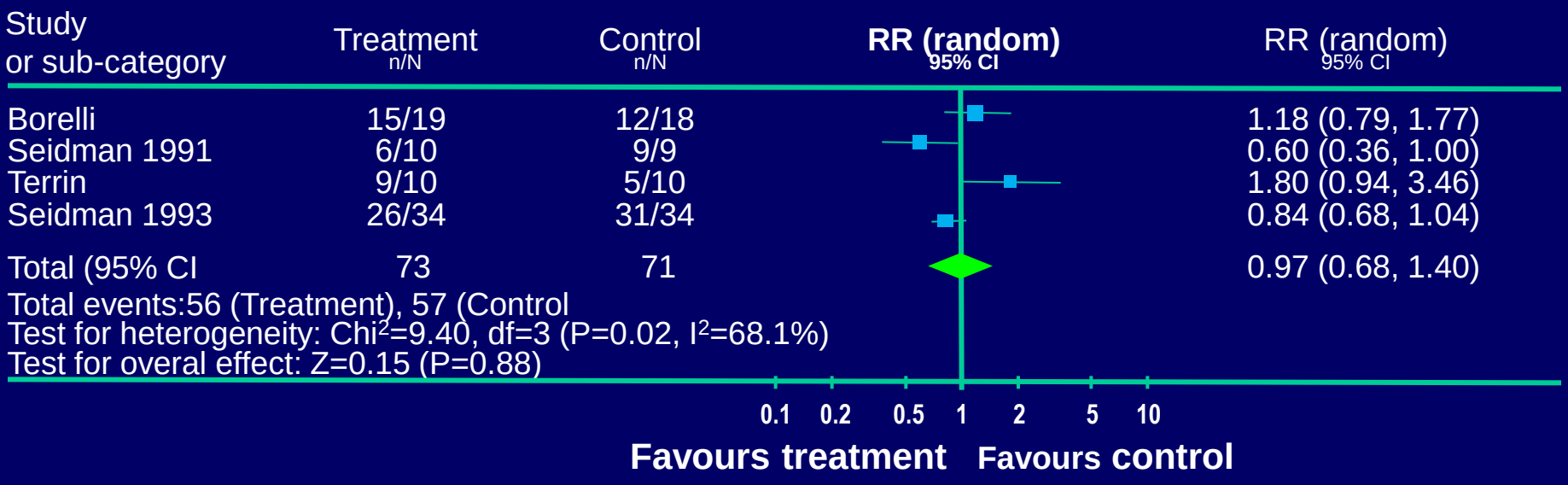
--- equal efficacy (no difference) ---

(Heuschkel RB, et al. J Pediatr Gastroenterol Nutr 2000;31:8-15
Dziechciarz et al. Aliment Pharmacol Ther 2007;26:795-803)

EN vs. steroids: A meta-analysis

Dziechciarz, et al. *Aliment Pharmacol Ther 2007*

Review: Enteral nutrition
Comparison: 01 Remission rate
Outcome: 01 Enteral nutrition vs. corticosteroids



Enteral nutrition in CD

EN induces mucosal healing

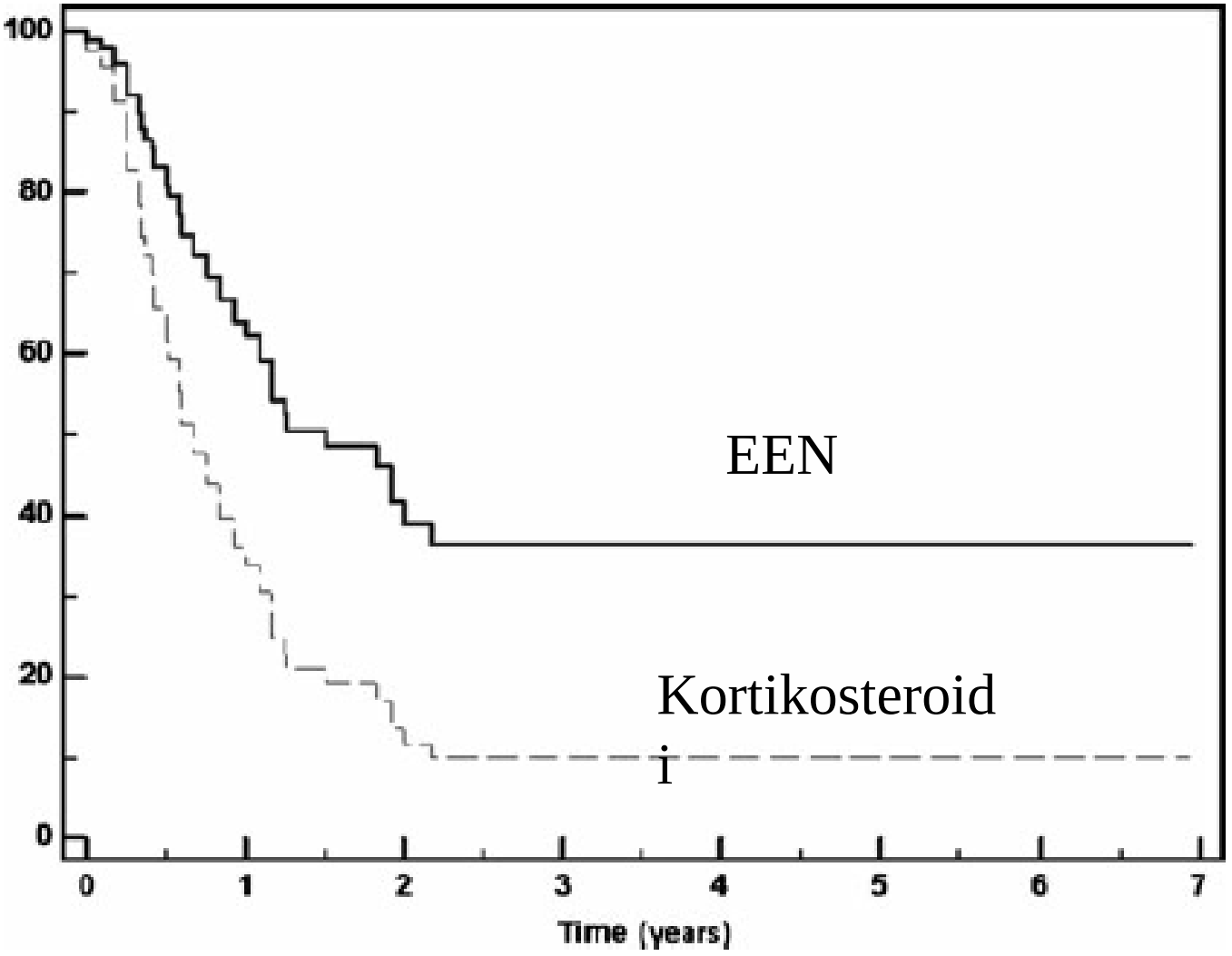
--- 76% with EN vs. 33% with steroids ---

Borelli, et al. Clin Gastroenterol Hepatol 2006; 4

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

Newby EA, et al. Cochrane Database Syst Rev 2005
Shamir R, et al. Inflamm Bowel Dis 2007

Enteral nutrition in CD
duration of remission



Hojsak I et al. Eur J Pediatr. 2015

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 strenght during 3-5 days
4. Application	▪ orally ▪ naso-gastric tube ▪ PEG

EN in active CD

Role of enteral nutrition in children with active CD

- 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 riskof nutritional defficiencies

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

Jowett SL, et al. Clin Nutr 2004

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 immunosupressants

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 in-effective in every second child despite dose adjustment

de Bie C, et al. Antitumor necrosis factor treatment for pediatric IBD. Inflamm Bowel Dis 2012;18:981-998

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 immunosupressed & young male!
Very agressive – 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 persistenly 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