Unità di Pediatria ad Alta Intensità di Cura
Università degli Studi di Milano
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

34 Congresso Nazionale di
ANTIBIOTICOTERAPIA
in età pediatrica

La terapia delle malattie infiammatorie croniche intestinali

S. Martelossi, Trieste

34 Congresso Nazionale di
ANTIBIOTICOTERAPIA
in età pediatrica

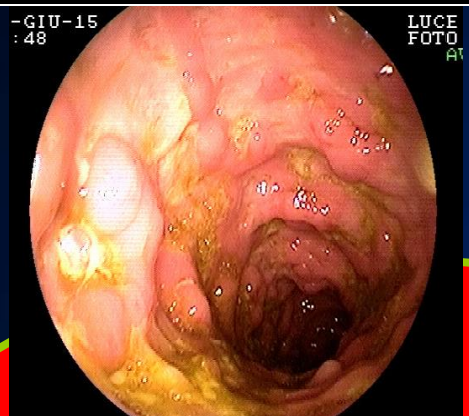
Milano, **11 - 12 - 13 novembre 2015** | Centro Congressi AtaHotel Executive

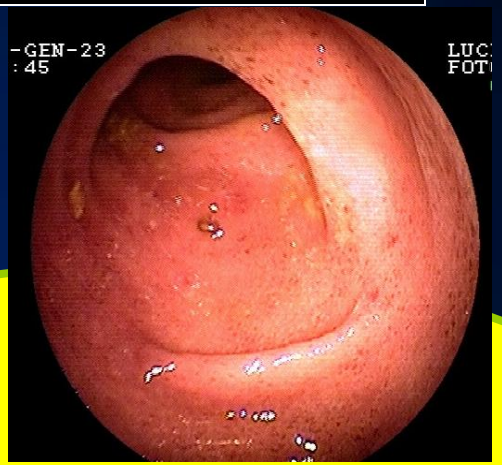
Presidenti: **Prof. Nicola Principi - Prof.ssa Susanna Esposito**

La terapia delle MICI

Stefano Martelossi
SOS Gastroenterologia e Nutrizione Clinica
IRCCS “Burlo Garofolo”
Trieste

Inflammatory bowel disease

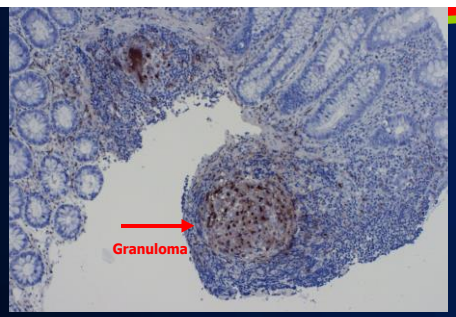


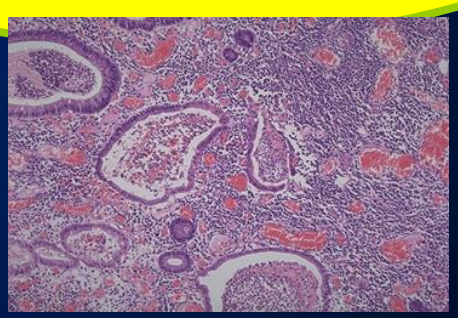


CROHN'S DISEASE

Indetermin. colitis

ULCERATIVE COLITIS

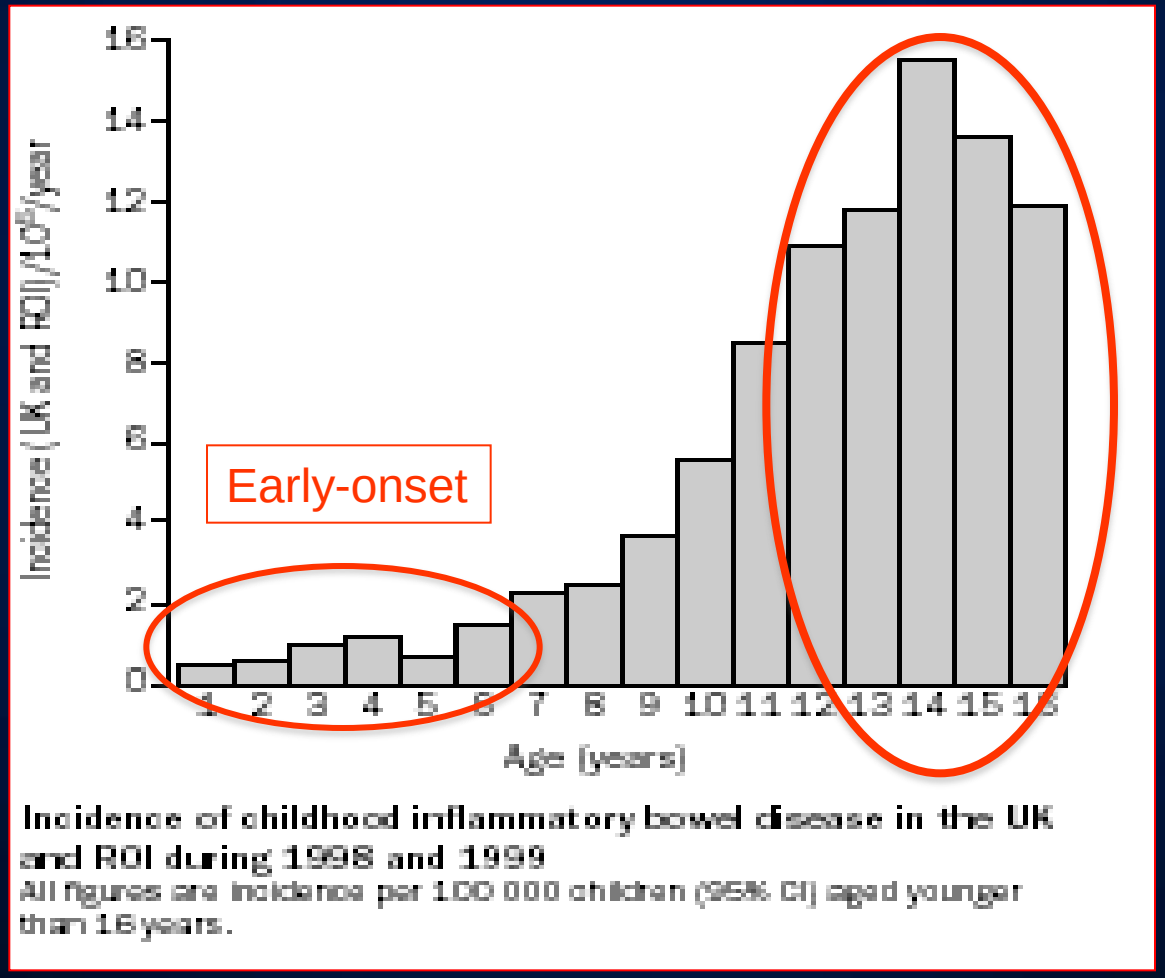




Idiopatic lifelong inflammatory destructive condition of the GI tract

Prevalence of IBD : 0.2-0.4%

25% of patients with IBD develop intestinal inflammation during chilhood or adolescence



Incidence of childhood inflammatory bowel disease in the UK and ROI during 1998 and 1999

All figures are incidence per 100 000 children (95% CI) aged younger than 16 years.

The incidence of pediatric IBD is increasing

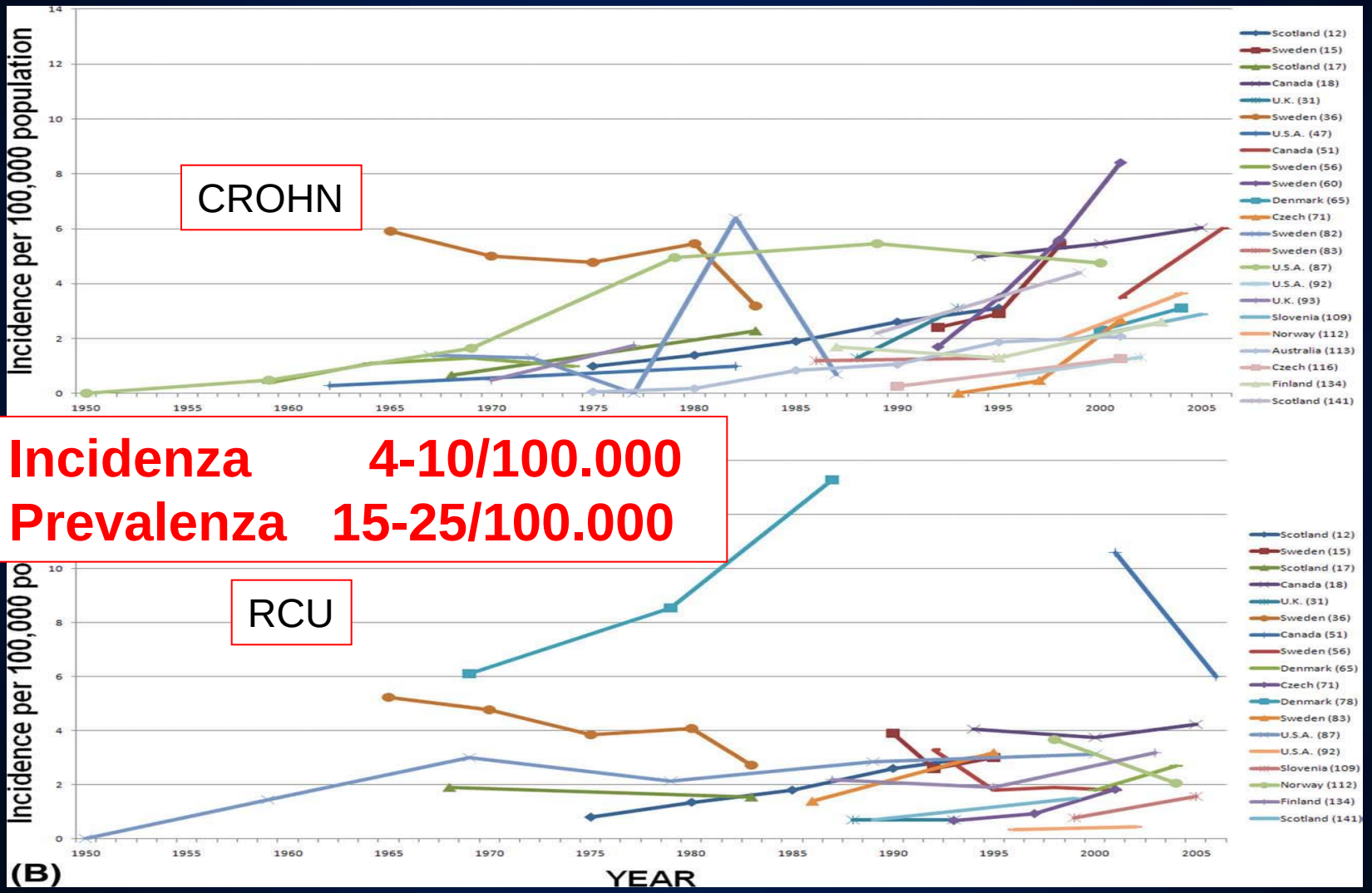


FIGURE 3. Temporal trends of incidence rates for (A) Crohn's disease and (B) ulcerative colitis in studies reporting incidence at multiple timepoints. Where a year range is reported, incidence rate is reported for the final year in the range (e.g., if incidence is reported for 1990–1999, rate is plotted as incidence for 1999).

The IBD in pediatric cases : are generally more severe than adult onset cases

Definition of Phenotypic Characteristics of Childhood-Onset Inflammatory Bowel Disease

JOHAN VAN LIMBERGEN,*·†·# RICHARD K. RUSSELL,§ HAZEL E. DRUMMOND,* MARIAN C. ALDHOUS,* NICOLA K. ROUND,*·† ELAINE R. NIMMO,* LINDA SMITH,* PETER M. GILLETT,† PARAIC McGROGAN,§ LAWRENCE T. WEAVER,‖ W. MICHAEL BISSET,¶ GAMAL MAHDI,¶ IAN D. ARNOTT,* JACK SATSANGI,* and DAVID C. WILSON†·#

416 pediatric vs 1297 adults

Table 5. Comparison of Location and [illegible] Between Childhood-Onset and Adult-Onset IBD Patients Using the Montreal Classification

	childh	At l
n		
CD phenotype: Location*		
L1		
L2		
L3		
L1 + L4		
L2 + L4		
L3 + L4		1
L4		
p		
CD phenotype: Behavior		
B1 (± p)		
B2 (± p)		
B3 (± p)		
p		
		At l
UC phenotype		
E3		
E2		
E1		
p		

*Five children had oral (n = 1)/oral+perianal disease (n = 4); 7 adults had oral (n = 4)/oral+perianal (n = 1)/perianal (n = 2) disease.

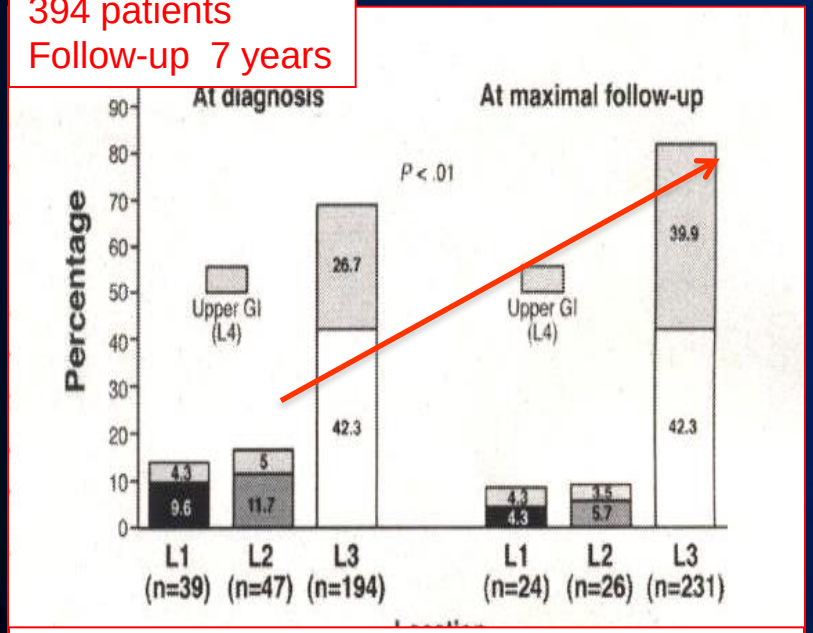
CD panenteric	**43% vs 3.2%**
CD ileo-cecal	**2,6% vs 31.5%**
CD upper GI	**23% vs 47%**
RCU pancolonic	**82% vs 47.6%**

The IBD in pediatric case: have a severe disease course

Natural History of Pediatric Crohn's Disease: A Population-Based Cohort Study

GWENOLA VERNIER-MASSOUILLE,* MAMADOU BALDE,† JULIA SALLERON,* DOMINIQUE TURCK,† JEAN LOUIS DUPAS,¶ OLIVIER MOUTERDE,** VÉRONIQUE MERLE,** JEAN LOUIS SALOMEZ,¶ JULIEN BRANCHE,†† RAYMOND MARTI,‡ ÉRIC LEFEBOURS,** ANTOINE CORTOT,* CORINNE GOWER-ROUSSEAU,‡ and JEAN FREDERIC COLOMBEL*

394 patients
Follow-up 7 years



Panenteric disease
Progression of disease

Natural History of Crohn's Disease: Comparison Between Childhood- and Adult-Onset Disease

Bénédicte Pigneur, MD, Philippe Seksik, MD, PhD,† Sheila Viola, MD,* Jérôme Viala, MD, PhD,‡ Laurent Beaugerie, MD, PhD,† Jean-Philippe Girardet, MD,* Frank M. Ruemmele, MD, PhD,§ and Jacques Cosnes, MD†*

Surgery :

1 every 16.6 ys ped
1 every 17.9 ys adult

At 30 years follow-up:

48% vs 14% estensive
12% vs 1% permanent stoma

The IBD in pediatric case: affect their development and growth

Natural History of Crohn's Disease: Comparison Between Childhood- and Adult-Onset Disease

Bénédicte Pigneur, MD, Philippe Seksik, MD, PhD,† Sheila Viola, MD,* Jérôme Viala, MD, PhD,‡ Laurent Beaugerie, MD, PhD,† Jean-Philippe Girardet, MD,* Frank M. Ruemmele, MD, PhD,§ and Jacques Cosnes, MD†*

TABLE 2. Anthropometric Characteristics at the Last Visit (mean ± SD) in Childhood-onset and Adult-onset CD

	Childhood-onset CD (n=206)	Adult-onset CD (n=412)	P
Height (cm)			
Males	172.8 ± 7.4	176.4 ± 6.5	<0.001
Females	162.2 ± 5.9	163.1 ± 6.0	NS
Total	167.9 ± 8.6	170.3 ± 9.1	<0.001
Weight (kg)			
Males	60.8 ± 10.1	72.9 ± 14.0	<0.001
Females	52.2 ± 7.7	59.7 ± 13.4	<0.001
Total	56.8 ± 10.1	66.8 ± 15.2	<0.001
Body mass index			
Males	20.3 ± 2.8	23.4 ± 4.3	<0.001
Females	19.8 ± 2.5	22.4 ± 4.5	<0.001
Total	20.1 ± 2.7	22.9 ± 4.5	<0.001

More 'short and more 'lean

Growth failure is present at diagnosis in up 30-80% of children with CD and persist into adulthood in 20-30%

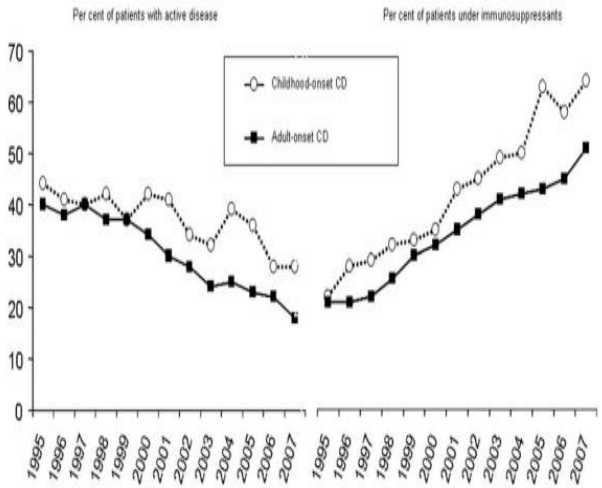
TABLE 1. *Prevalence of linear growth impairment in children with Crohn disease*

Study	Time of assessment	Patients studied	Definition of linear growth impairment	Percentage with growth impairment
Kanof et al. (3)	At diagnosis	Prepubertal (Tanner I or II) patients (n = 50)	Decrease in height velocity	88%
Kirschner (8)	At diagnosis	Early puberty to mature patients (n = 70)	Decrease in height centile >1 SD	36%
Griffiths et al. (4)	During follow-up	Prepubertal (Tanner I or II) patinets (n = 100)	Height velocity ≤2 SD for age for ≥2 years	49%
Hildebrand et al. (5)	Before diagnosis or during follow-up	Population-based cohort (n = 46)	Height velocity ≤2SD for age for 1 year	65%
Markowitz et al. (6)	At maturity	Children in tertiary care setting (n = 38)	Failure to reach predicted adult height	37%
Motil et al. (7)	Prospectively during 3-year follow-up	Children in tertiary care setting (n = 69)	Height velocity <4 cm/year, Height Z score <1.64,	24%
			Height-for-age <95% of expected at 50th percentile for age	23%
				39%

The IBD in pediatric cases : resistance or intolerance to therapy is common

Natural History of Crohn's Disease: Comparison Between Childhood- and Adult-Onset Disease

Bénédicte Pigneur, MD, Philippe Seksik, MD, PhD,† Sheila Viola, MD,* Jérôme Viala, MD, PhD,‡ Laurent Beaugerie, MD, PhD,† Jean-Philippe Girardet, MD,* Frank M. Ruemmele, MD, PhD,§ and Jacques Cosnes, MD†*



Active disease	37% vs 31%
Immunomodulators	41% vs 33%
Biologic agents	10.5% vs 3.5%

TABLE 3. Cumulative Therapeutic Requirements (Number and % of Patients) in Childhood-onset and Adult-onset CD Groups

	Childhood-onset CD (n=206)	Adult-onset CD (n=412)	P
Medical requirements			
5-aminosalicylates (%)	205 (100)	410 (100)	NS
Steroids (%)	198 (96)	376 (91)	0.03
Azathioprine or 6-mercaptopurine (%)	148 (72)	251 (61)	<0.01
Methotrexate (%)	39 (19)	41 (10)	<0.01
Anti-TNF (%)	53 (26)	55 (13)	<0.001
Enteral nutrition (%)	75 (36)	45 (11)	<0.001
Parenteral nutrition (%)	42 (20)	43 (10)	<0.001
Surgical requirements			
Intestinal resection (%)	124 (60)	250 (61)	NS
More than 1 intestinal resection (%)	50 (24)	97 (24)	NS
Permanent stoma (%)	24 (12)	30 (7)	0.07
Perianal surgery (%)	88 (43)	156 (38)	NS

Therapeutic target

Traditional :

- Inducing clinical remission
- Maintaining clinical remission
- Allowing withdrawal of corticosteroids
- Promoting growth (pediatric specificity)
- Improving patients quality of live
- Minimizing drugs complication

New target

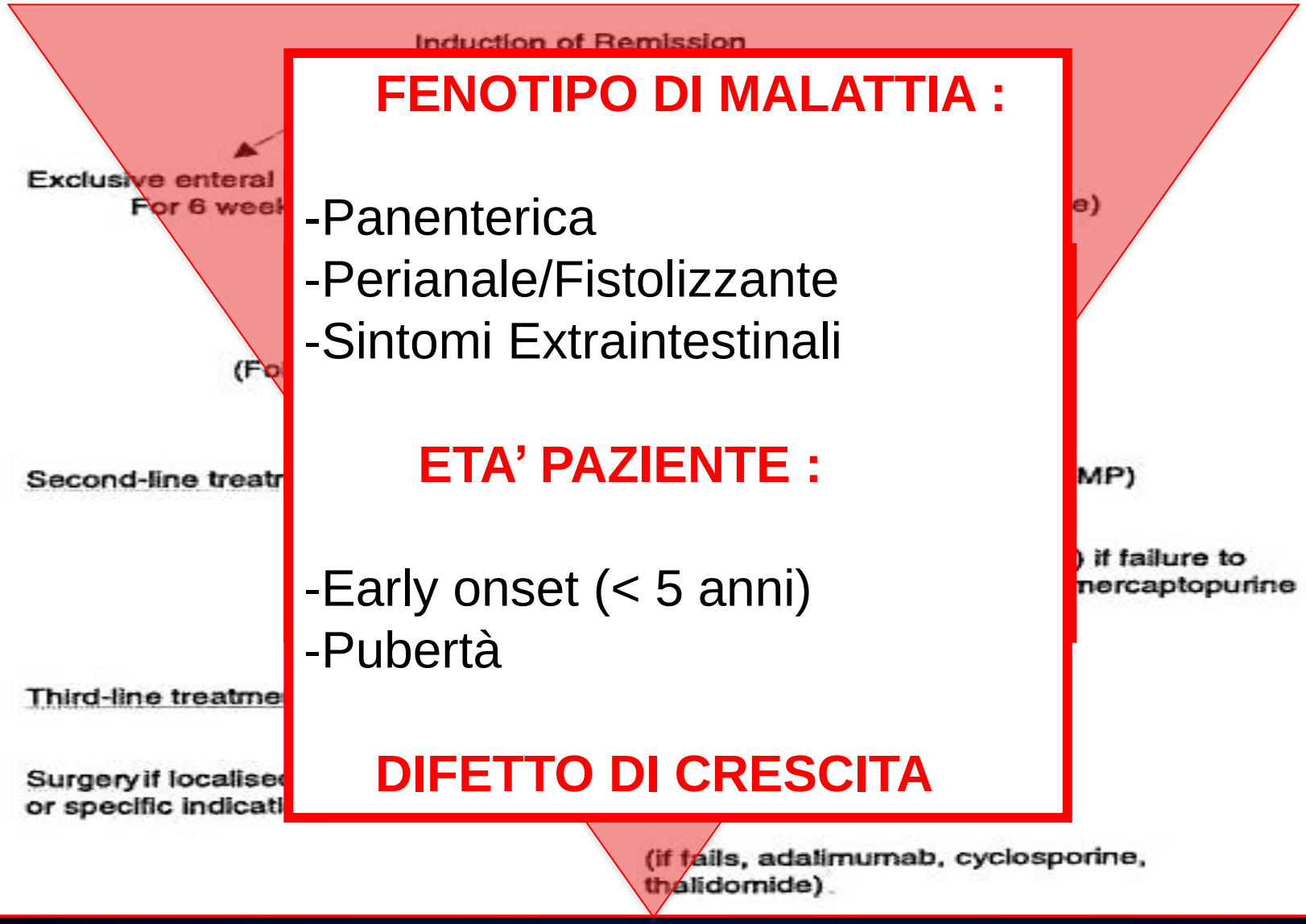
- Prevent surgery
- Prevent disability
- Inducing mucosal healing
- **Altering the natural course**

Mucosal healing are associated with a significantly better clinical outcomes : more durable clinical response, optimize growth, restored quality of live, reduced resource utilisation and finally prevent bowel damage and surgery.

	Growth	Mucosal healing	Remission	Mantainig remission
Steroids	-	-	+++	-
Nutrition	+++	+	++	+
5-ASA	(only UC)	-	-	+/- +
Azathioprine	+	+	-	+++
Thalidomide	++	++	+++	+++
Biologics	++	++	+++	++

Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom

*Bhupinder K. Sandhu, †John M.E. Fell, ‡R. Mark Beattie, §Sally G. Mitton, ||David C. Wilson, and ¶Huw Jenkins, on Behalf of the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition



FENOTIPO DI MALATTIA :

-Panenterica
-Perianale/Fistolizzante
-Sintomi Extraintestinali

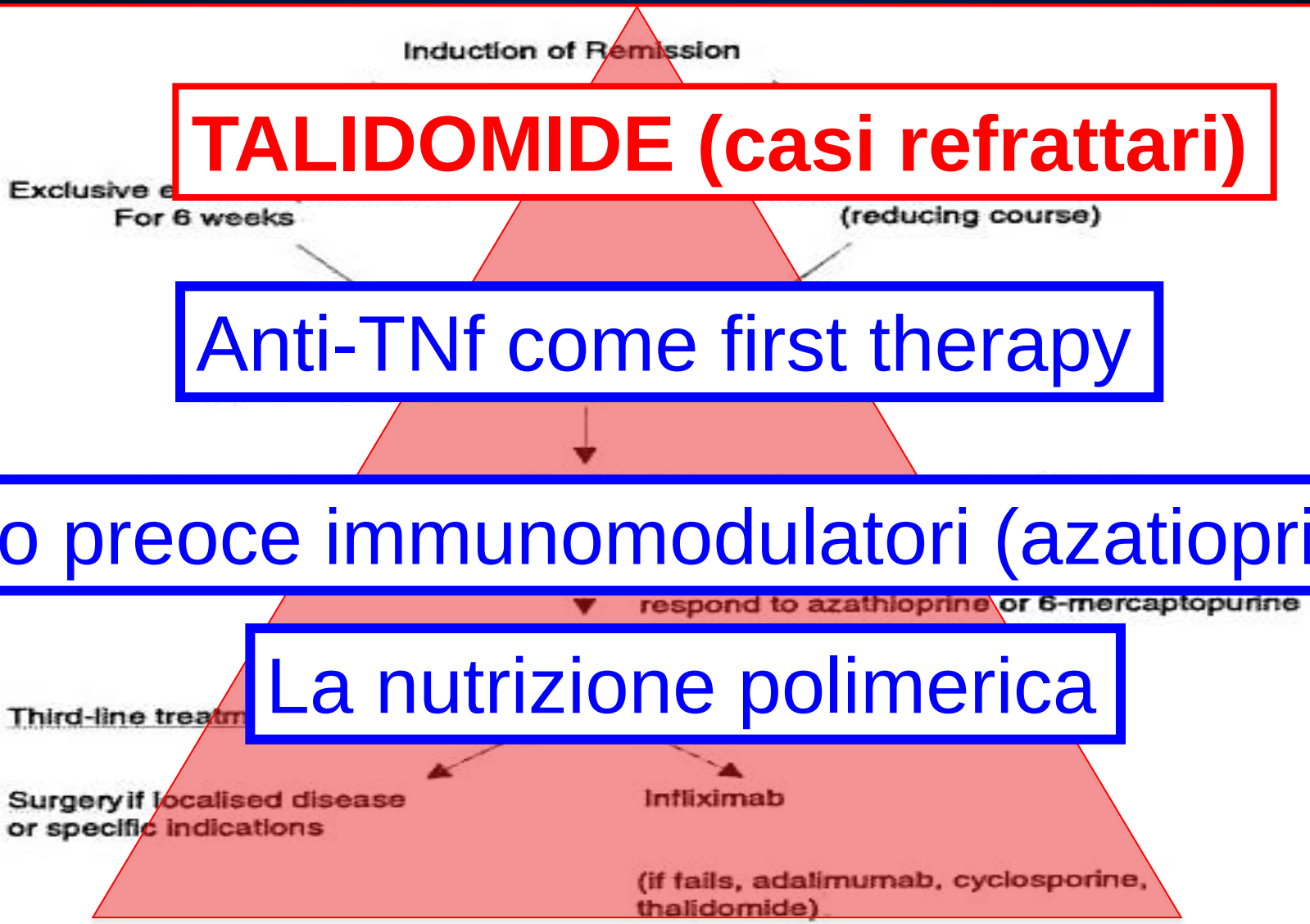
ETA' PAZIENTE :

-Early onset (< 5 anni)
-Pubertà

DIFETTO DI CRESCITA

Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom

*Bhupinder K. Sandhu, †John M.E. Fell, ‡R. Mark Beattie, §Sally G. Mitton, ||David C. Wilson, and ¶Huw Jenkins, on Behalf of the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition



TALIDOMIDE (casi refrattari)

Anti-TNf come first therapy

Uso preoce immunomodulatori (azatioprina)

La nutrizione polimerica

Malattia refrattaria

Assenza o perdita risposta o Aes a anti-TNF

20-40 %

Ottimizzare i biologici

"Altri" biologici

Anti-TNF :

-Golimumab

-Certolizumab

Anti-integrine :

-Vedolizumab

-Natalizumab

Anti IL12/23 :

- Ustekinumab

Chirugia

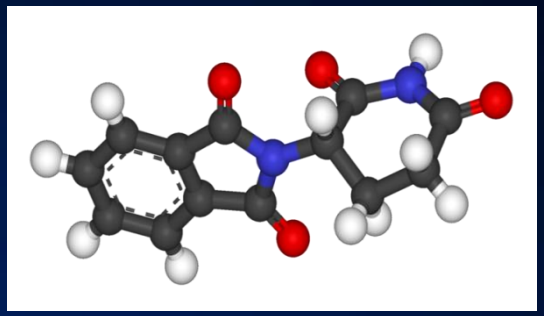
Ottimizzare terapia :

- Compliance
- Dosaggi
- Metaboliti

Talidomide

Trapianto cellule staminali

Talidomide



- Immunomodulante
- Inibizione angiogenesi

- Inibizione sintesi TNF-a
- Degradazione RNA messaggero per TNF
- Diminuzione rilascio TNF dai monociti attivati
- Switch Th1 vs Th2
- Riduce sintesi di IL-12, IFN
- Riduzione di FibroblastGF e vascular endotelial GF
- Riduzione espressione ICAM-1 e VCAM 1

Talidomide e Crohn : EFFICACIA

60-100%

20-75%

	Patients	Dose (mg)	Follow up (weeks)	Clinical Response	Remission	Steroid tapering
Adults						
Ehrenpreis 1999	22 CD	200-300	12 w	14 (63%)	9 (40%)	14/14 (100)%
Vasiliauskas 1999	12 CD	50-100	12 w	7 (58%)	2 (16%)	10/10(100)%
Bauditz 2002	10 (1 RCU)	300	12 w	6 (60%)	4 (40%)	3 *
Bariol 2002	11 (4RCU)	100-400	12 w	11 (100%)	8 (72%)	NR
Sabate 2002	15 CD	100 after Infliximab	52 w	15 (100%)	11 (73%)	3 *
Kane 2002	4 CD	200 after Infliximab	variable	3 (75%)	-	1/1 (100%)
Plamondon 2007	25 CD	50-200	52 w	15 (60%)	5 (25%)	3/7 (42%)
Children						
Facchini 2001	5 CD	1-1.5mg/kg	Long-variable	-	4(80%)	NR
Ahmed 2003	6 CD	50-200	12-36w	3/6 (50%)	NR	16/20 (80%)
Lazzerini 2007	28 CD	1.5-2.5mg/kg	78 w °	3 (10%)	21/38 (75%)	14/14 (100)%

Thalidomide in luminal and fistulizing Crohn's disease resistant to standard therapies. Aliment. Pharmacol.Ther 2007

Thalidomide for treatment of severe intestinal bleeding. Gut 2004

Disappearance of Crohn's ulcers in the terminal ileum after thalidomide therapy. Can. J. Gastroenterol 2004

Thalidomide in refractory vulvar ulcerations associated with Crohn's disease. Dermatology 2004

Thalidomide for the treatment of recalcitrant oral Crohn's disease and orofacial granulomatosis.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003 .

Fistolizzante, perianale, metastatica, granulomatosi orale
Efficace dopo anti-TNF alfa

Thalidomide as "salvage" therapy for patients with delayed hypersensitivity response to infliximab: a case series. J.Clin. Gastroenterol.2003

An open-label study of thalidomide for maintenance therapy in responders to infliximab in chronically active and fistulizing refractory Crohn's disease. *Aliment Pharmacol Ther 2002*

Thalidomide use and outcomes in pediatric patients with Crohn's disease refractory to Infliximab and Adalimumab.

JPGN 2011

Mucosal Healing With Thalidomide in Refractory Crohn's Disease Patients Intolerant of Anti-TNF-α Drugs

Report of 3 Cases and Literature Review

Maria Lia Scribano, MD, Laura Cantoro, MD,† Marzia Marrollo, MD,* Rocco Cosintino, MD,* and Anna Kohn, MD**

Thalidomide come rescue therapy (retrospettivo)

-12 pazienti (10 aa 3-14)
- follow-up 4.6 aa
- 8 ileo-colica 4 colica + gastroduodenale
- 4 malattia perianale/7 fistole/5 stenosi
- 6 pregressa chirurgia
- **12/12 IFX + 2 ADA**

28 anni, perianale, fistolizzante.
IFX, Ada, Certolizumab

39 anni perianale, fistolizzante, artralgie.
IFX, Certolizumab

39 anni gastrico + ileocolico.
IFX

Thalidomide 50-150

Remissione 10/12
Risposta 2/12
5/7 chiusura fistole
7/12 sospendono steroide

Tutti remissione clinica

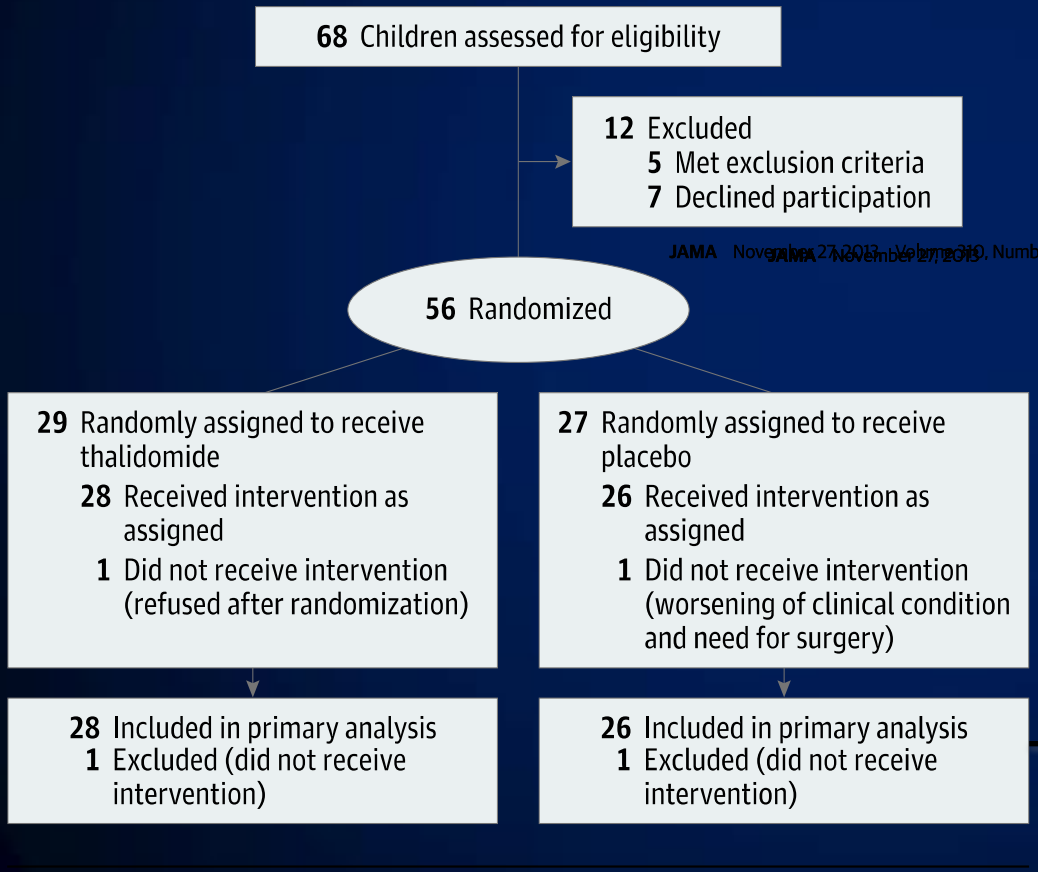
Tutti mucosal healing

Original Investigation

Effect of Thalidomide on Clinical Remission in Children and Adolescents With Refractory Crohn Disease

A Randomized Clinical Trial

Marzia Lazzerini, PhD; Stefano Martelossi, MD; Giuseppe Magazzù, MD; Salvatore Pellegrino, MD; Maria Cristina Lucanto, MD; Ari
Angela Calvi, MD; Serena Arrigo, MD; Paolo Lionetti, PhD; Monica Lorusso, MD; Francesca Mangiantini, MD; Massimo Fontana, M
Gabriella Palla, MD; Giuseppe Maggiore, MD; Matteo Bramuzzo, MD; Maria Chiara Pellegrin, MD; Massimo Maschio, MD; Vincenzo
Stefania Manenti, MD; Giuliana Decorti, MD; Sara De Iudicibus, PhD; Rossella Paparazzo, MD; Marcella Montico, MD; Alessandro V



JAMA November 27, 2013—Volume 310, Number 20

Non responders talidomide
Open label extension 8 sett.

Responders Talidomide
Follow-up minimo 52 sett.

Original Investigation

Effect of Thalidomide on Clinical Remission in Children and Adolescents With Refractory Crohn Disease

A Randomized Clinical Trial

caratteristiche 53 pazienti

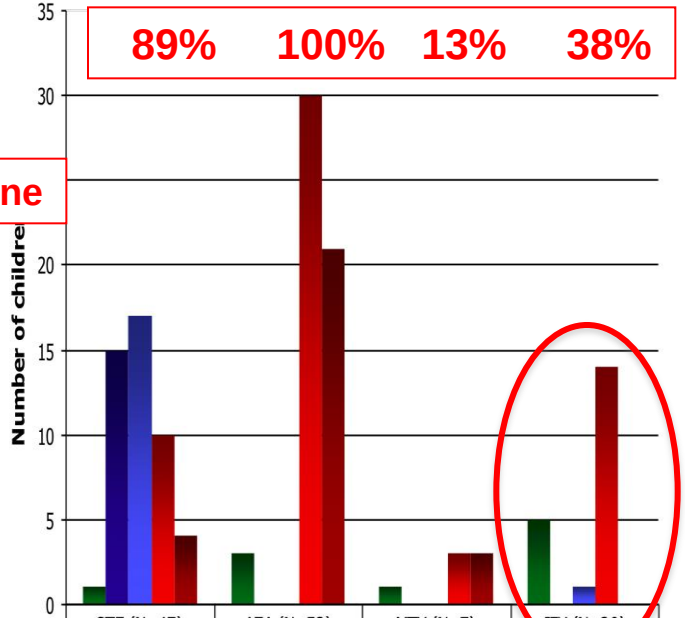
Table 1. Baseline Demographic and Clinical Characteristics of the Patients

	No. (%)[a]		
	Thalidomide (n = 28)	Placebo (n = 26)	Thalidomide After Placebo (n = 21)
Age, mean (SD), y	14.0 (3.5)	15.0 (3.0)	15.1 (2.0)
Male	15 (53.5)	17 (65.4)	13 (61.9)
Female	13 (46.4)	9 (34.6)	8 (30.1)
Disease duration, mean (SD), y	3.0 (2.2)	4.3 (3.3)	4.0 (3.1)
Median (IQR)	2 (15)	3 (2-5.7)	3 (2-5)
Involved areas			
Only ileum	3 (10.7)	2 (7.6)	1 (4.7)
Only colon	3 (10.7)	8 (30.7)	5 (23.8)
Ileum and colon	22 (78.5)	16 (61.5)	15 (71.4)
Concomitant upper tract	8 (28.5)	10 (38.4)	8 (38.1)
Concomitant perianal disease	6 (21.4)	7 (26.9)	6 (28.5)
Disease behavior			
Nonstricturing/nonpenetrating			15 (71.4)
Stricturing			5 (23.8)
Patients with fistulas[b]			2 (9.5)
Extraintestinal manifestations[c]			8 (38.1)
Previous medical therapies			
Steroids	24 (85.7)	24 (92.3)	18 (85.7)
Enteral nutrition	26 (92.8)	18 (69.2)	14 (66.7)[d]
Mercaptopurine/azathioprine	28 (100)	25 (96.1)	20 (95.2)
Methotrexate	2 (7.1)	5 (19.2)	3 (14.3)
Infliximab	9 (32.1)	11 (42.3)	8 (38.1)
Antibiotics	22 (78.5)	23 (88.4)	18 (85.7)
5-Aminosalicylates	17 (60.7)	18 (69.2)	13 (62.0)
PCDAI	30.2	30.0	27.4
PCDAI > 30	15 (53.6)	15 (57.7)	10 (47.6)
Laboratory indexes			
C-reactive protein, mean (SD), mg/dL	3.1 (2.8)	3.0 (2.8)	3.1 (2.9)
Erythrocyte sedimentation rate, mean (SD), mm/h	54.6 (27.9)[e]	41.1 (20.9)	42.7 (17.1)
C-reactive protein ≥1 mg/dL	25 (89.2)	19 (73.1)	19 (90.4)
Erythrocyte sedimentation rate ≥20 mm/h	27 (96.4)	23 (88.4)	19 (90.5)
Nutritional indicators			
Weight-for-age z score	−0.84 (1.14)	−1.36 (1.08)	−1.45 (1.26)
Height-for-age z score	−0.87 (1.05)	−1.07 (1.03)	−1.11 (1.13)
BMI z score	−0.48 (1.12)	−0.95 (1.06)	−1.11 (1.25)
Children with WAZ <−1 SD	14 (50.0)	19 (73.0)	16 (76.1)
Children with HAZ <−1 SD			
Children with BMI z score			
Physician Global Assessm			

Perianale 25%
Extraintestinale 35%

89% 100% 13% 38%

83% Nutrizione

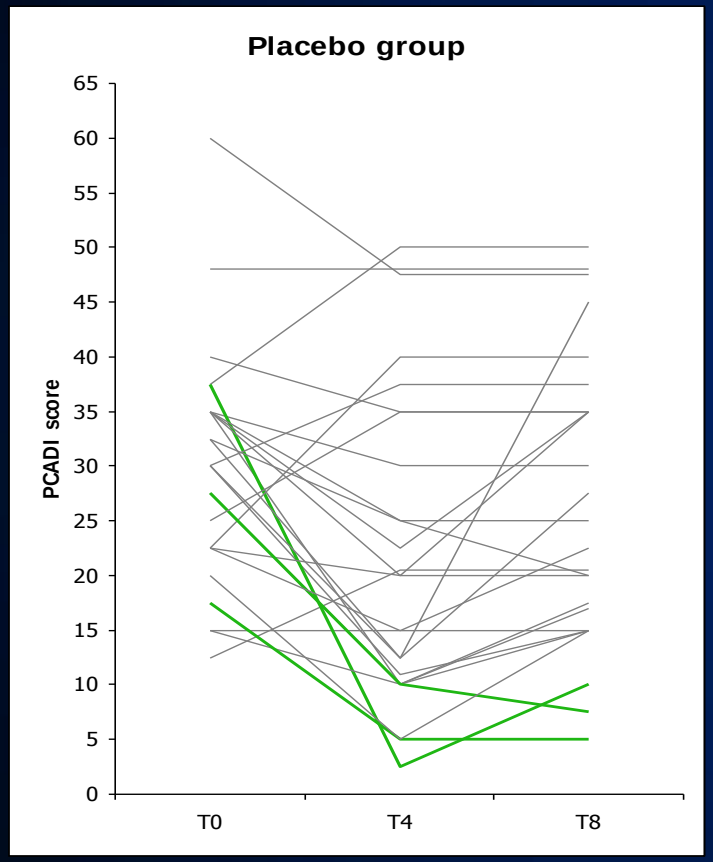


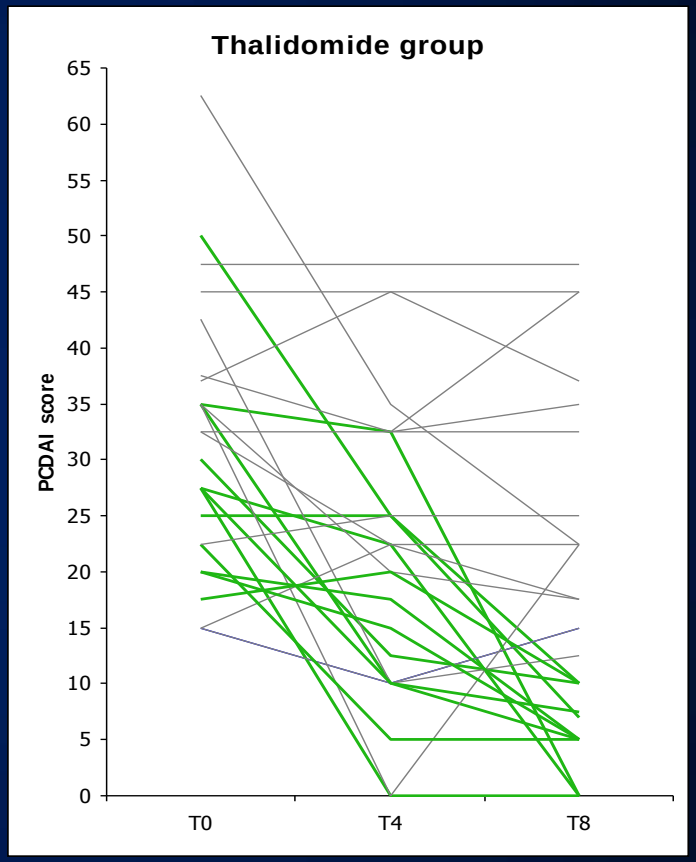
	STE (N=47)	AZA (N=53)	MTX (N=7)	IFX (N=20)
Reponder- but adverse effects that required drug suspension	1	3	1	5
Dependent without AEs	15	0	0	0
Dependent with AEs	17	0	0	1
Resistant without AEs	10	30	3	14
	4	21	3	0

Malattia moderata- refrattaria

Efficacia (remissione) 8 settimane :

- 46% talido random
- 52% talido open-label

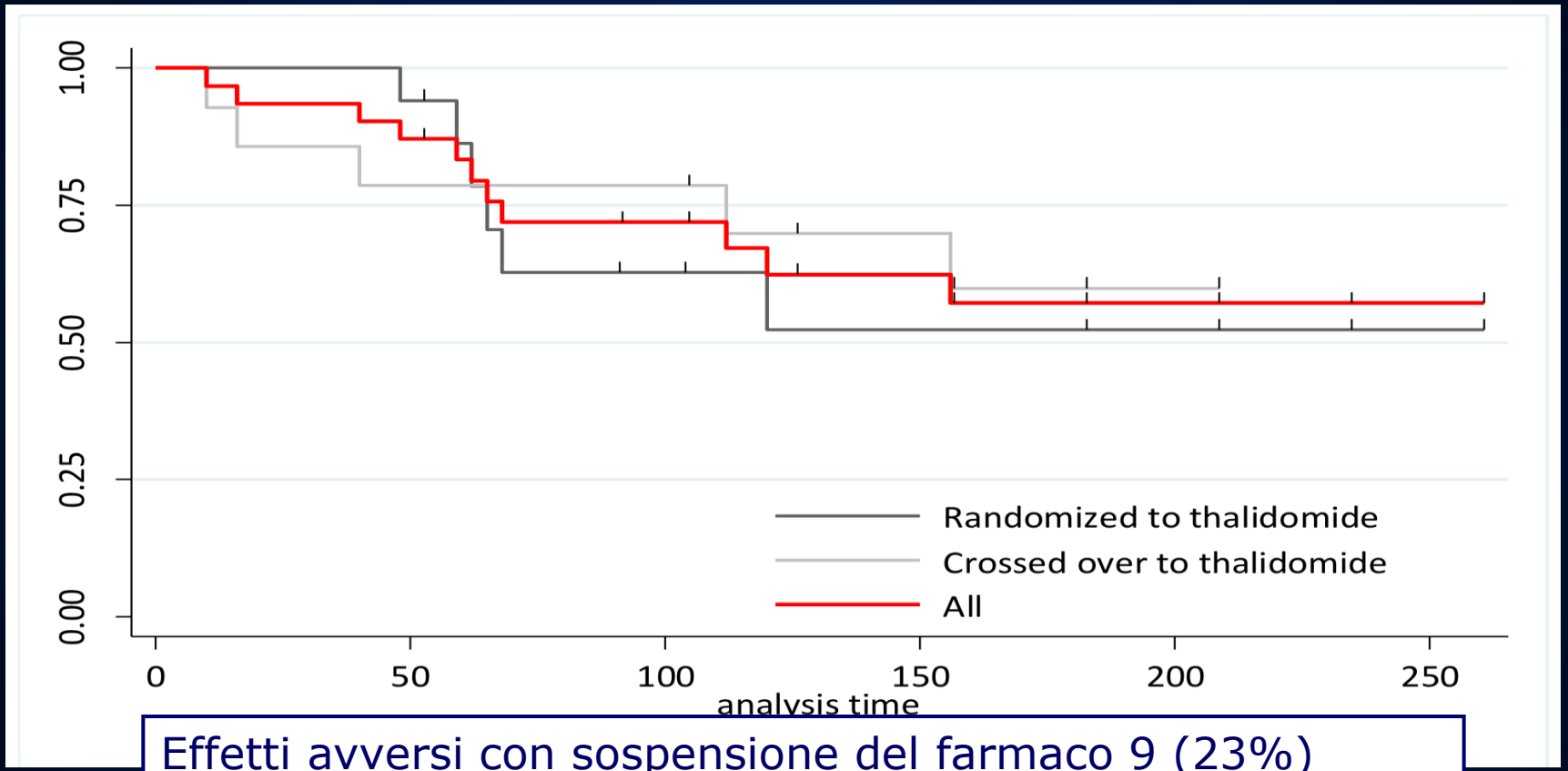




Effetti avversi : 1 sospensione per epilessia (diagnosi di epilessia idiopatica)
Cefalea, sonnolenza, vertigini, difficoltà concentrazione dermatiti, stipsi, bradicardia

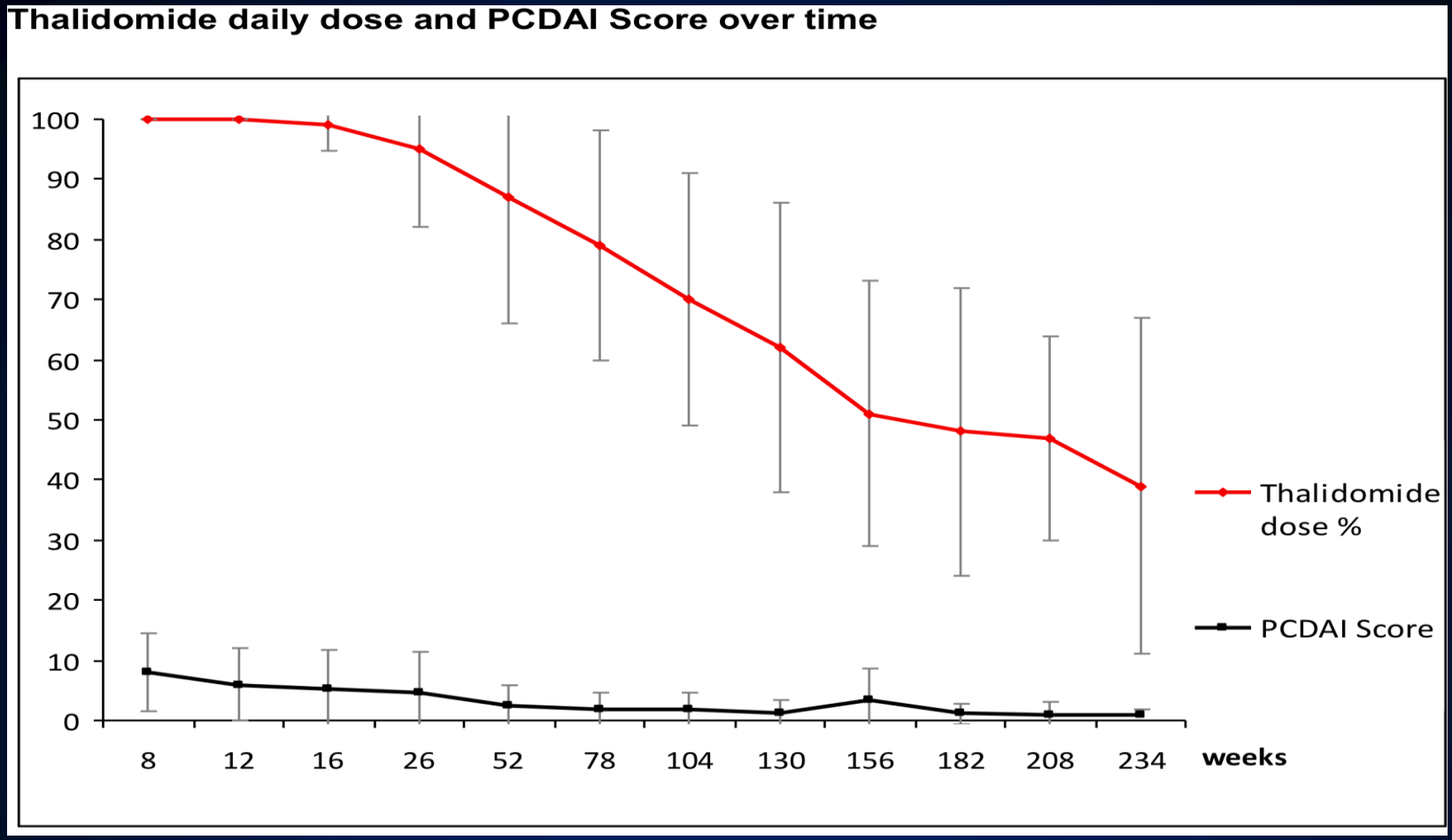
Follow-up lungo termine :

Durata media remissione 3 anni



Effetti avversi con sospensione del farmaco 9 (23%)

-7 neuropatia periferica (reversibile)
-1 amenorresa ipergonadotropa (reversibile)
-1 “attacco acuto neurologico” (TIA o emicrania?)



Modulazione dosaggio permette riduzione neuropatia

Neuropatia : dose minima 380 mg/kg (10 mesi terapia)

Se alterazioni solo EMG senza clinica : riduzione Talidomide

Talidomide

Thalidomide and Refractory Crohn's Disease
What is in the Future?

- La Talidomide è in grado di indurre e mantenere la remissione nel 50% di pazienti con Morbo di Crohn pediatrico **refrattario** a immunomodulatori e **anti-TNF**
- Può essere utilizzata per il mantenimento anche a lungo termine monitorando l'insorgenza di neuropatia (scalo se alterazioni solo EMG)
- La Talidomide può essere distribuita solo attraverso un sistema di controllo del rischio teratogeno obbligatorio.

Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease

C. Yang*, P. Singh*, H. Singh†, M.-L. Le* & W. El-Matary*

Conclusions
One high quality RCT showed that thalidomide is effective for inducing remission in paediatric CD. The current evidence is insufficient to support