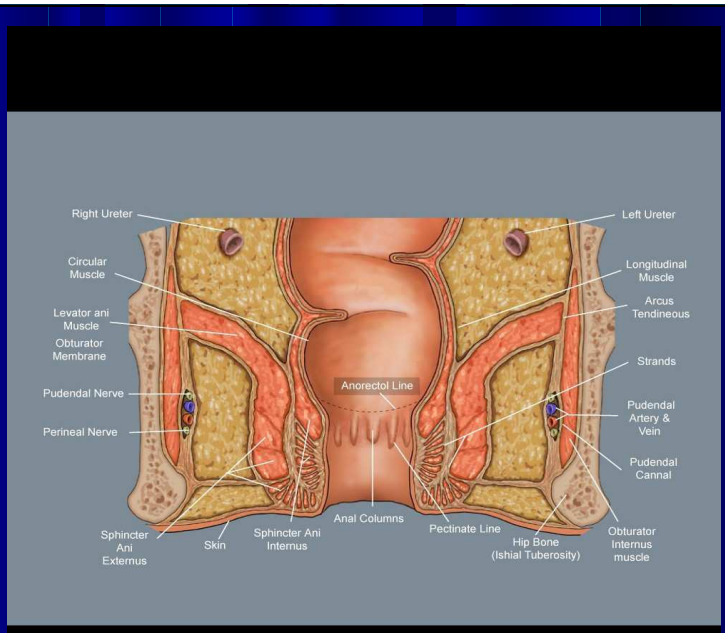
Stipsi Cronica

- Dr Giuseppe Iacono

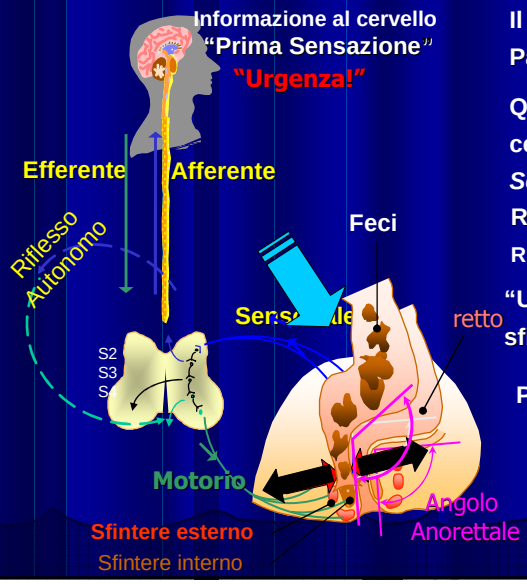
Direttore U.O Complessa di Gastroenterologia Pediatrica ARNAS (Civico Benfratelli , G.Di Cristina) Palermo

Bari 04.06.2010



CANALE ANALE

EVACUAZIONE



Il riempimento del retto espande le Pareti rettali - *stimolo continuo*

Questa *stimolazione* è trasferita al cervello ed interpretata come **una *Sensazione***

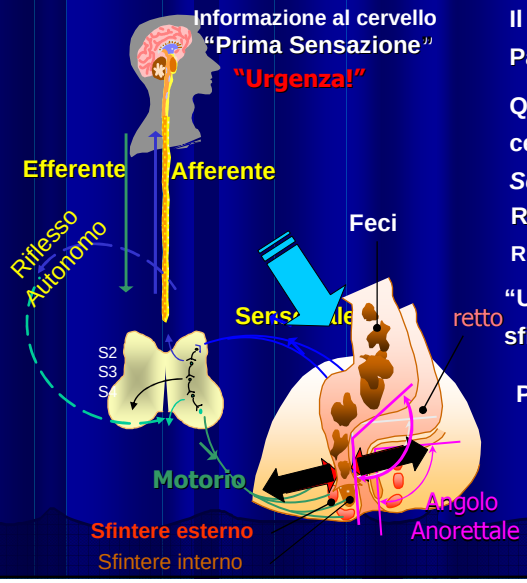
Riflesso autonomo controlla il Riflesso Inibitorio Retto Anale (RIRA)

"Urgenza" - contrazione volontaria sfintere anale esterno

Processo di defecazione

- Rilasciamento dello S.E.
- Contrazione delle pareti add.
- modifica dell'angolo anorettale

EVACUAZIONE



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Stipsi: definizione

Στύψω: restringere, condensare

E' la diminuzione della frequenza delle evacuazioni con aumento della consistenza delle feci, per riduzione del contenuto in acqua che si accompagna a defecazione dolorosa

STIPSI CRONICA: DEFINIZIONE

Table 1. Definitions of Constipation

Diagnostic criteria for constipation
At least 12 weeks, which need not be consecutive, in the preceding 12 months of 2 or more of:
Straining in >¼ defecations
Lumpy or hard stools in >¼ defecations
Sensation of incomplete evacuation in >¼ defecations
Sensation of anorectal obstruction/blockade in >¼ defecations
Manual maneuvers to facilitate >¼ defecations (e.g., digital evacuation, support of the pelvic floor) and/or
<3 defecations/week
Loose stools are not present, and there are insufficient criteria for IBS

AGA Technical Review on Constipation

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Practice Economics Committee. The paper was approved by the Committee on March 4, 2000, and by the AGA Governing Board on May 21, 2000.

Frequenza evacuazioni in età pediatrica
NASPGAN 1999

età	evac./sett
0-3 mesi (latte materno)	5-40
0-3 mesi (latte artificiale)	5-28
6-12 mesi	5-28
1-3 anni	4-21
> 3 anni	3-14

Stipsi: epidemiologia

- In età pediatrica: 20-25%
  M:F = 6:1
- In età adulta: 20-40%
  M:F = 1:2

Stipsi: epidemiologia

- 3% delle visite ambulatoriali di pediatria
- 25% delle consultazioni nei centri di gastroenterologia pediatrica

Dati generali sulla stipsi

- Frequenza minima negli USA è 2-3% della popolazione generale (4-6 milioni di individui)
- Numerosi studi epidemiologici, la stimano fra il 2% ed il 28% della popolazione generale
- 2,5 milioni di visite mediche/anno negli USA
- Costo sanitario in termini di diagnostica: 292,5 dollari / paziente
- Costo per "trattamento efficace" 11.697 dollari / paziente.

Inquadramento generale dinanzi al paziente con stipsi:

Le cause organiche.....

Condizioni mediche

Table 3. Common Medical Conditions Associated With Constipation

Drug effects
See Table 2
Mechanical obstruction
Colon cancer
External compression from malignant lesion
Strictures: diverticular or postischemic
Rectocele (if large)
Postsurgical abnormalities
Megacolon
Anal fissure
Metabolic conditions
Diabetes mellitus
Hypothyroidism
Hypercalcemia
Hypokalemia
Hypomagnesemia
Uremia
Heavy metal poisoning
Myopathies
Amyloidosis
Scleroderma
Neuropathies
Parkinson's disease
Spinal cord injury or tumor
Cerebrovascular disease
Multiple sclerosis
Other conditions
Depression
Degenerative joint disease
Autonomic neuropathy
Cognitive impairment
Immobility
Cardiac disease

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Dati generali: considerazioni

- Problema frequente.
- Elevati costi socio-sanitari.
- Di non facile soluzione: una meta-analisi che considerava 25 trattamenti in 37 trial randomizzati concludeva che fibre e lassativi sono di scarsa efficacia. (Tramonte et al: J Gen Int Med 1997;12:15-24)
- Si aggrava nel tempo

ETIOLOGY OF CONSTIPATION

Infants & toddlers	Adolescents
Unknown	Unknown
Anal fissures	Inadequate food intake
Breast feeding to bottle feeding	Anorexia nervosa
Cow's milk allergy	Slow transit constipation
Celiac disease	Diabetes mellitus
Stool withholding behaviour	Hypothyroidism
Lack of fibres	Hypercalcaemia
Cystic fibrosis	Sexual abuse
Pseudo-obstruction	Drugs (opiates, anticholinergics, antidepressants)
Hirschsprung's disease	Multiple sclerosis
Neuronal intestinal dysplasia	Scleroderma
Anorectal malformations	Amyloidosis
Spina bifida	Neoplasia
	Parkinsons disease
	Depression

Benninga M. et al. J Pediatr Gastroenterol

GASTROENTEROLOGY 2005;128:1089–1113

SPECIAL REPORTS AND REVIEWS

Gastrointestinal Food Allergy: New Insights Into Pathophysiology and Clinical Perspectives

STEPHAN BISCHOFF* and SHEILA E. CROWE*,†

*Department of Gastroenterology, Hepatology and Endocrinology, University Medical School of Hannover, Hannover, Germany; and †Digestive Health Center of Excellence, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Virginia, Charlottesville, Virginia

Table 3. End-Organ Effects of Food Allergy

Organ	Disease	IgE mediated	Afflicted age group
GI tract	Immediate GI hypersensitivity	+++	All
	Oral allergy syndrome	+++	Children, adults
	Eosinophilic gastroenteropathies	+	All
	Eosinophilic esophagitis	+	Infants, children
	Eosinophilic gastritis	+	All
	Eosinophilic enterocolitis	+	All
	Eosinophilic proctitis	+	Infants, children
	Dietary protein enterocolitis and proctitis	–	Infants
	Chronic constipation	–	Children
	Dietary protein enteropathy	–	Infants
	Celiac disease	–	Children, adults
	Irritable bowel syndrome	?	Adults
Respiratory	Rhinitis	++	All
	Asthma	++	All
	Alveolitis	+	All
Skin	Urticaria and angioedema	++	All
	Atopic eczema	+	Infants, children
	Dermatitis herpetiformis	–	Children, adults
Cardiovascular	Vasculitis	+	All
	Systemic anaphylaxis	+++	All

L'idea della relazione fra stipsi e allergia alimentare

L'idea della relazione fra stipsi e allergia alimentare

- Nasce dall'esperienza clinica e dal follow-up di pazienti pediatrici con IPLV
- "Troppi" bimbi con storia di IPLV nel corso del primo anno di vita, diventano stitici fra i 2 ed i 3 anni e negli anni successivi
- In questi pazienti, una stipsi refrattaria "sembra" risolversi drammaticamente iniziando la dieta di eliminazione.

La nostra esperienza

Persistent cow's milk protein intolerance in infants: the changing face of the same disease.

G. Iacono et al. Clin Exp. All. 1998; 28

Scopo dello Studio

Valutare la natura dei sintomi ed il loro tempo di insorgenza in soggetti , con APLV persistente , positivi ai *challenges* annuali con latte vaccino.

Schema dello Studio

- 12 bambini con APLV persistente in "follow-up";
- "challenges" annuali con latte vaccino;
- analisi della sintomatologia e **"timing"** di insorgenza.

Risultati

(sintomi e loro tempo di insorgenza)

Pzs	1°challenge	2°challenge	hrs	challenge finale	hrs
1	Diarrea	broncospasmo	>48	broncospasmo	>48
2	Diarrea	diarrea/vomito	<6	stipsi	>48
3	Diarrea/vomito	diarrea/vomito	<6	stipsi	>48
4	Dermatite	broncospasmo	24	broncospasmo	24
5	Shock	broncospasmo	24	broncospasmo	24
6	stipsi	stipsi	>48	rifiuto del cibo	>48
7	Broncospasmo	diarrea/vomito	24	diarrea	24
8	RGE	diarrea/vomito	24	dermatite	>48
9	Diarrea	diarrea/vomito	24	broncospasmo	>48
10	Dolore addom.	diarrea	24	dermatite/stipsi	>48
11	Dermatite	dermatite	24	broncosp/stipsi	>48
12	Dermatite	dermatite	24	broncosp/stipsi	>48

Riepilogo I

- comparsa degli stessi sintomi d'esordio al *challenge* diagnostico;
- comparsa di sintomi diversi al 1° *challenge* di guarigione (5/12 soggetti);
- comparsa di sintomi diversi al *challenge* effettuato al termine dello studio (12/12 soggetti);

Riepilogo II

- tempo di comparsa >6 ore al 1° *challenge* di guarigione e tempo maggiore al termine (con reazioni avverse evidenziate anche dopo 2 -3 settimane);
- stipsi presente in 5/9 soggetti

Osservazioni

- Netta familiarità per atopia nei soggetti allo studio;
- Sensibile aumento delle IgE nel tempo (probabile insorgenza di ipersensibilità verso altri allergeni);
- Patomorfosi: modificazione della sintomatologia in risposta allo stesso stimolo allergenico.

Conclusioni

- Molti casi di **stipsi cronica** in lattanti e bambini sono dovuti a **APLV**.
- Una storia di pregressa APLV o presenza di sintomi associati ad APLV aumenta la probabilità che la **stipsi** possa essere una **manifestazione allergica.**

Celiachia-like *APLV*
o
APLV cronica

S. Jorup 1952: prima segnalazione della correlazione tra esposizione al latte vaccino e coliche.

M. Davidson 1963: miglioramento clinico di soggetti con stipsi cronica alla sospensione della dieta con latte vaccino

K.C. Chin et al.
Allergy to cow's milk presenting a chronic constipation.
BMJ. 1983; 287, 1593.

J. McGrath et al.
Allergy to cow's milk presenting a chronic constipation.
BMJ. 1984; 288, 236.

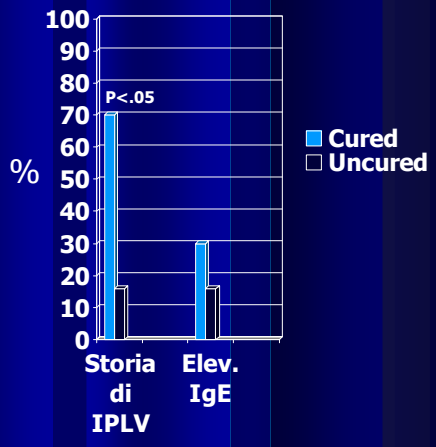
G. Iacono et al.

Chronic constipation as a symptom of cow's milk allergy

J. Ped. 1995; 126: 34

Stipsi ed allergia. La prima evidenza.

- Lo studio in "aperto" dimostra la risoluzione della stipsi nel 80% dei casi "consecutivi" (21/26).
- Le lesioni perianali "sembrano" una caratteristica importante
- Dopo 1 anno di dieta la reintroduzione del latte causa disturbi nel 50% dei casi



Iacono G. e coll: J. Pediatr. 1995; 126:34

Stipsi ed allergia: la conferma

The New England Journal of Medicine

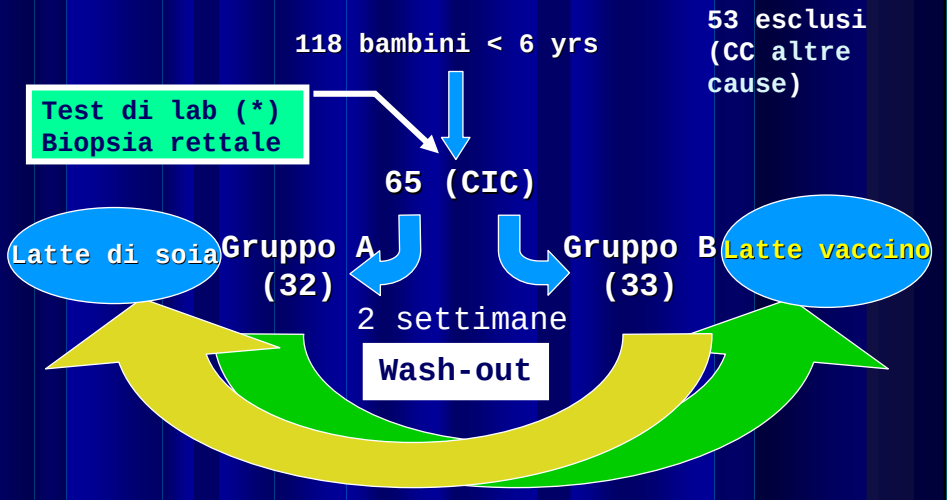
INTOLERANCE OF COW'S MILK AND CHRONIC CONSTIPATION IN CHILDREN

GIUSEPPE IACONO, M.D., FRANCESCA CAVATAIO, M.D., GIUSEPPE MONTALTO, M.D., ADA FLORENA, M.D., MARIO TUMMINELLO, M.D., MAURIZIO SORESI, M.D., ALBERTO NOTARBARTOLO, M.D., AND ANTONIO CARROCCIO, M.D.

N Engl J Med 1998;339:1100-4.)

Schema dello studio (I)

G. Iacono, et al.. NEJM. 1998. 339; 16: 1100.



(*): IgE sieriche tot, eosinofili circolanti, IgE latte-specifiche, prick tests: latte, lattalbumina, caseina, β-lattoglobulina)

Stipsi ed allergia: la conferma

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 65 PATIENTS.*

CHARACTERISTIC	VALUE
Age (mo)	34.6±17.1
Sex (M/F)	29/36
Breast-feeding at birth (no.)	35
Refused food at weaning (no.)	3
Duration of illness (mo)	8.7±3.5
Previous treatment with laxative (no.)	65
Family history of intolerance of cow's milk (no.)	26
Personal history of intolerance of cow's milk (no.)	16
Concomitant symptoms of intolerance of cow's milk (bronchospasm, dermatitis, or rhinitis) (no.)	12
Soiling or encopresis (no.)	4
Abdominal pain (no.)	27
Anal fissure and perianal erythema or edema (no.)	49
Patients with abnormal test results (no.)	
Eosinophil count	16
Serum IgE level	10
Skin tests with milk antigens	11
Specific IgE antibodies to milk antigens	20

*Plus–minus values are means ±SD.

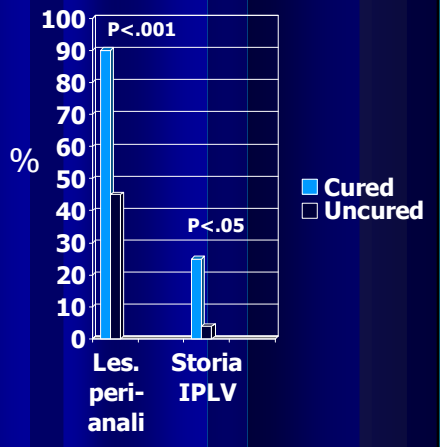
TABLE 2. NUMBER OF BOWEL MOVEMENTS AND QUALITATIVE FECAL SCORES DURING EACH STUDY PERIOD FOR THE 65 PATIENTS.

VARIABLE	OBSERVATION PERIOD	COW'S MILK*	SOY MILK	P VALUE†
No. of bowel movements				
Median	4	4	10	<0.001
25th to 75th percentile	3–5	3–5	4–12	<0.001
Qualitative fecal score‡				
1	0	0	2	<0.001
2	0	0	42	<0.001
3	65	65	21	<0.001

(N Engl J Med 1998;339:1100-4.)

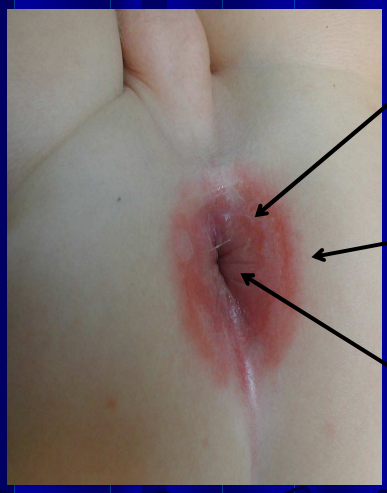
Stipsi ed allergia: la conferma

- 68% di risoluzione a dieta priva di CM (soia)
- Istologia con infiltrato eosinofilo rettale



Iacono G. e coll: N.Engl.J.Med 1998;339:1100

Aspetto macroscopico di anite



- Eritema
- Edema
- Fissurazioni e ragadi

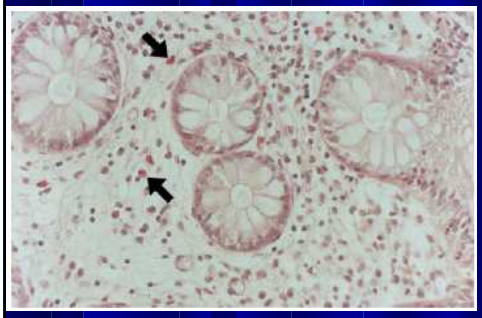
Stipsi ed allergia: la conferma

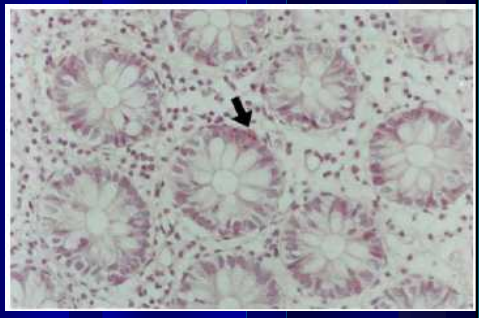
TABLE 3. HISTOLOGIC AND MORPHOMETRIC FINDINGS ACCORDING TO THE RESPONSE TO A COW'S-MILK–FREE DIET.

VARIABLE	RESPONSE (N=44)	NO RESPONSE (N=21)	P VALUE
Histologic analysis (no.)			
Abnormal crypt architecture	13	2	0.06
Depletion of goblet-cell mucin	3	0	0.32
Inflammation	15	2	0.03
Lymphoid nodules	15	3	0.08
Interstitial edema	4	0	0.26
Morphometric evaluation*			
Length of surface epithelial cells (μm)	40.4±6.2	51.3±8.1	0.001
Intraepithelial lymphocytes (per 100 deep-crypt cells)	3.4±0.8	3.1±0.6	0.21
Intraepithelial eosinophils (per 100 deep-crypt cells)	3.0±1.8	0.8±0.3	0.001
Eosinophils in the lamina propria (% of total cells)	7.15±4.31	4.21±2.31	0.009

(N Engl J Med 1998;339:1100-4.)

Stipsi ed allergia: l'infiltrato eosinofilo





(N Engl J M... 1998;339:1100-4.)

latte vaccino

predisposizione genetica

Proctite cronica da APLV

Inferenza con il SNI e muscolatura liscia

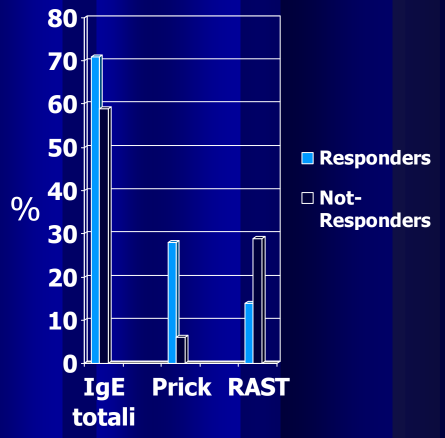
Remodeling rettale

Cellule mucipare e muco

Ipertono muscolare (ipertrofia e/o allungamento delle fibrocellule mm)

Stipsi ed allergia.
Le esperienze degli Altri

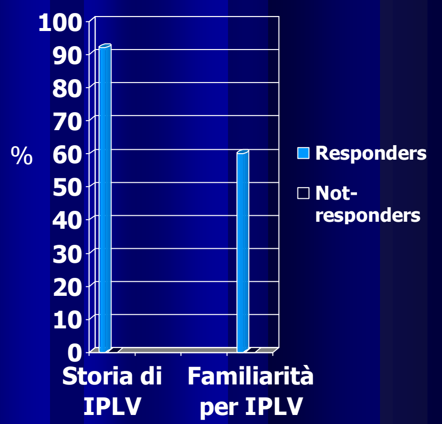
- Completa risoluzione della stipsi nel 28% dei casi "consecutivi" (7/25) durante dieta priva di latte
- Ricomparsa del sintomo 48-72 ore dopo il challenge
- Infiltrato eosinofilo della mucosa rettale



Daher e coll.: Pediatr. All. Immunol. 2001

Stipsi ed allergia.
Le esperienze degli Altri

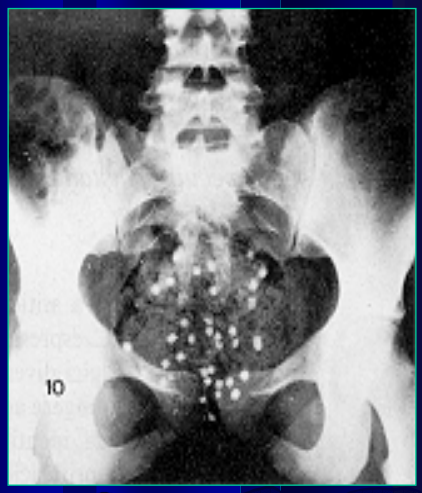
- Risoluzione della stipsi refrattaria ad altri trattamenti nel 43% dei casi (13/30)
- Nei non-responders, utile eliminare anche il frumento (2/30)
- Infiltrato eosinofilo della mucosa rettale
- Ipertono dello sfintere anale interno (valutato in 3 casi)



Shah N. e coll: N. Engl. J. Med. 1999; 340:891
Shah N e coll: J. Ped. Gastr. Nutr. 1999; 28:570

Stipsi cronica e APLV

- 14 pz., età 0.5-6.7 anni
- Stipsi refrattaria
- Atopia
- Proctite eosinofila
- Ritenzione rettale: 57%
- Tono SAI ↑
- Risposta alla dieta: 93%



Shah N, N Engl J Med 1999)

Stipsi ed allergia. Le esperienze degli Altri

- ***"CMPI is a poorly recognized cause of constipation in children"***
- ***"History of CMPI in infancy should alert the clinicians to a possible allergic constipation"***

Storia di IPLV	Certa in 7/12 Sospetta in 5/12
Eosinofili mucosa rettale	8/10 casi
Ricaduta al challenge	12/12 casi
Ricaduta dopo 1 anno	7/9 casi

Vanderhoof JA: Clin Pediatr 2001; 40: 399

Stipsi ed Allergia
le esperienze degli altri

- 18/33 pazienti rispondevano ad un trail dietetico;
- Sono stati studiati dal punto di vista istologico e funzionale;
- In particolare sono state studiate le relazioni tra i mastociti e le fibre nervose mucosali

Borrelli O. Am.J.of Gastroenterology 2008

STIPSI E ALLERGIA

Le certezze:

- Si tratta di un fenomeno molto frequente in pazienti con storia di IPLV.
- La dieta è una opzione terapeutica **"obbligatoria"** nei non responders alla terapia.

I dubbi:

- Vi è una flogosi del retto CM-dipendente ?
- Vi sono evidenze di una relazione fra flogosi e alterata motilità ?
- Vi sono altri meccanismi patogenetici ?
- Quale meccanismo immunologico è coinvolto?

STIPSI E ALLERGIA: ALCUNE RISPOSTE AI DUBBI

Scandinavian Journal of Gastroenterology, 2005; 40: 33–42

Taylor & Francis

ORIGINAL ARTICLE

Chronic constipation and food intolerance: A model of proctitis causing constipation

ANTONIO CARROCCIO[1], CALOGERO SCALICI[2], EMILIANO MARESI[3], LIDIA DI PRIMA[1], FRANCESCA CAVATAIO[2], DAVIDE NOTO[1], ROSSANA PORCASI[3], MAURIZIO R. AVERNA[1] & GIUSEPPE IACONO[2]

[1]*Department of Internal Medicine, University Hospital of Palermo, Palermo, Italy,* [2]*Department of Pediatric Gastroenterology, "Di Cristina" Hospital, Palermo, Italy,* [3]*Department Pathology, University Hospital of Palermo, Palermo, Italy*

STIPSI E ALLERGIA: ALCUNE RISPOSTE AI DUBBI

- **Scopo dello studio**:
- Esiste una "proctite da IPLV" nei pazienti con stipsi cronica ?
- **Pazienti arruolati**: 52 soggetti con stipsi refrattaria (30 F, età mediana 4 anni)
- Test allergologici all' ingresso e studio istologico all' ingresso e dopo dieta.

- **Disegno studio**:

4 settimane di dieta CM-free.

I non-responders vanno a dieta oligoantigenica (riso, agnello, latte asina, carote, olio oliva, zucchero).

Nei pazienti con alvo normalizzato, DBPC-CM-challenge e challenge in aperto per altri antigeni alimentari.

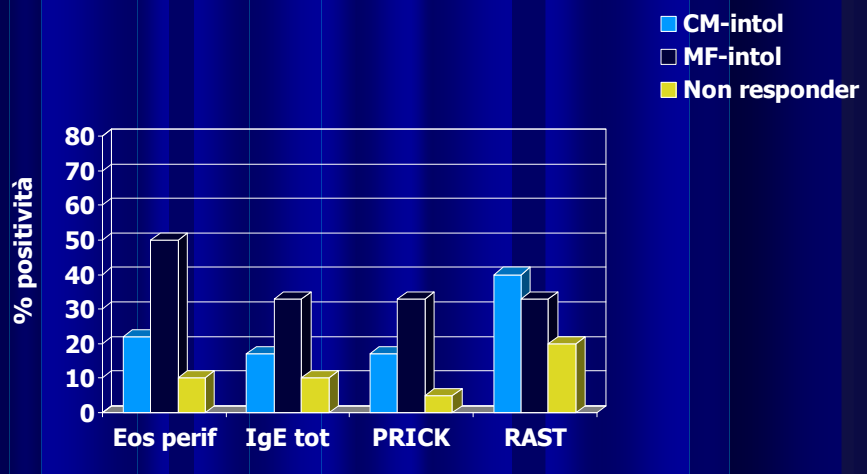
Scandinavian Journal of Gastroenterology, 2005; 40: 33–42

STIPSI E ALLERGIA: ALCUNE RISPOSTE AI DUBBI

- Risoluzione della stipsi a dieta CM-free in 24/52 pazienti (46%)
- Risoluzione della stipsi a dieta oligo-antigenica in 6/52 pazienti (12%)
- Totale dei pazienti con stipsi da intolleranza alimentare 30/52 (58%)

Scandinavian Journal of Gastroenterology, 2005; 40: 33–42

STIPSI E ALLERGIA: I TEST DI LABORATORIO



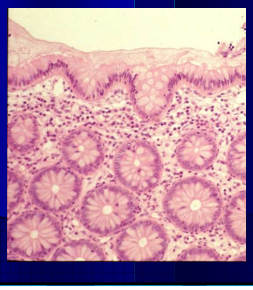
Scandinavian Journal of Gastroenterology, 2005; 40: 33–42

STIPSI E ALLERGIA: I DATI ISTOLOGICI

	Pre-dieta	Post-dieta	Non resp
Noduli linfoidi	18/30 A,B	8/30 A	4/22 B
	P<.002		
	P<.05		
IEL	4.1+1.4	3.0+0.8	3.1+1.1
	P<.0002		

PRE

POST



Scandinavian Journal of Gastroenterology 2005; 40: 33–42

I DATI ISTOLOGICI: IL RUOLO DEI LINFOCITI GAMMA/DELTA

Table III. Mean (±SD) densities of intraepithelial $CD3^+$, $\alpha\beta^+$, and $\gamma\delta^+$ T cells in mucosal samples drawn from the terminal ileum in children with chronic constipation and control subjects

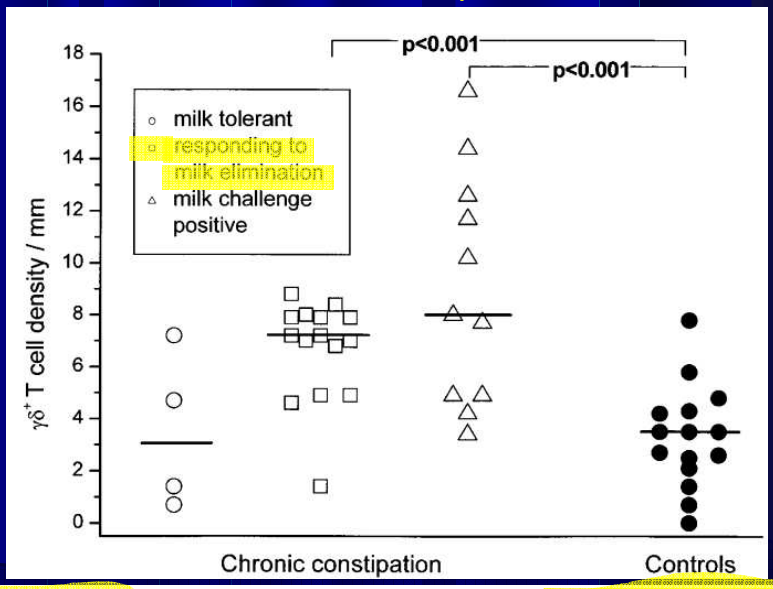
	Chronic constipation	Control subjects
$CD3^+$	26.4 ± 7.2	23.7 ± 10.6
$\alpha\beta^+$	18.6 ± 6.8	19.3 ± 8.8
$\gamma\delta^+$	7.1 ± 3.6*	3.3 ± 2.0
$\gamma\delta^+/CD3^+$	27.4 ± 12.3*	12.7 ± 4.9

*$P < .001$, study subjects compared with control subjects.

Turunen, Karttunen, and Kokkonen

The Journal of Pediatrics • November 2004

I DATI ISTOLOGICI: IL RUOLO DEI LINFOCITI GAMMA/DELTA



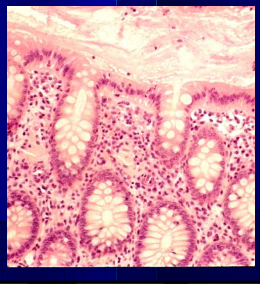
Turunen, Kantunen, and Kokkonen — The Journal of Pediatrics • November 2004

STIPSI E ALLERGIA: I DATI ISTOLOGICI

	Pre-dieta	Post-dieta	Non resp
Eos. Intra-epit.	**4.3 ± 1.1**	**1.3 ± 0.9**	**0.8 ± 0.7**
		P<.0001	
Spess muco	**130 ± 47**	**311 ± 180**	**322 ± 165**
		P<.0001	

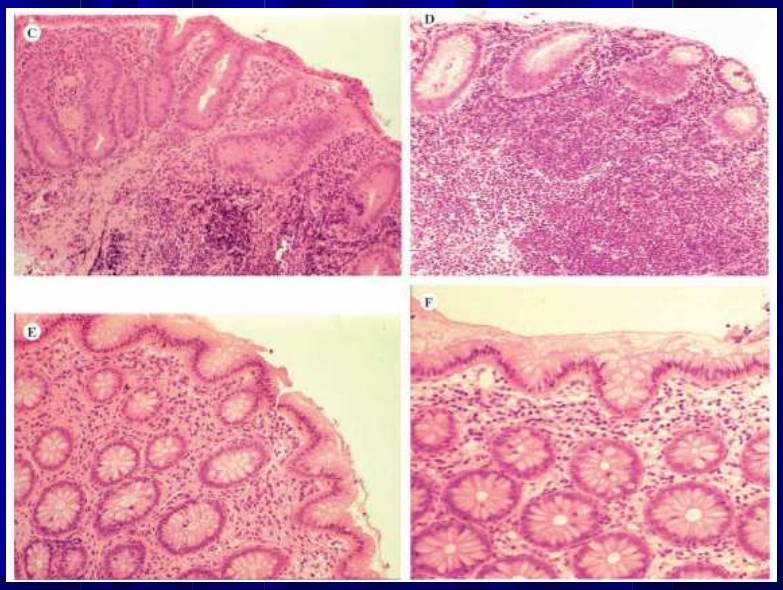
Pre

Post



Scandinavian Journal of Gastroenterology, 2005; 40: 33 - 42

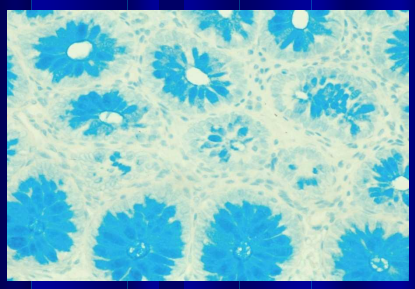
STIPSI E ALLERGIA: IL RUOLO DEL MUCO



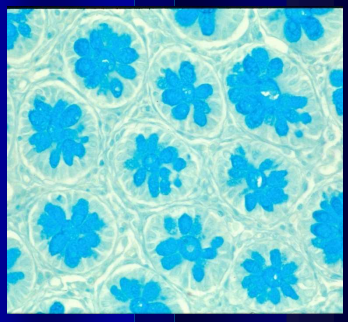
Scandinavian Journal of Gastroenterology, 2005; 40: 33–42

STIPSI E ALLERGIA: IL RUOLO DEL MUCO

Pre-dieta



Post-dieta



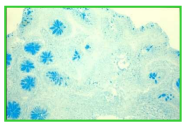
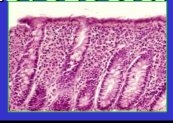
Scandinavian Journal of Gastroenterology, 2005; 40: 33–42

Iacono G, Bonventre S, Scalici C, Maresi E, Di Prima L, Soresi M, Di Gesù G, Noto D, Carroccio A.

Food intolerance and chronic constipation: manometry and histology study.

Eur J Gastroenterol Hepatol. 2006 Feb;18(2):143-50.

PRIMA

DATI CLINICI 	▪ STRAINING ▪ DOLORE ADDOMINALE ▪ < 3 EV./W. ▪ DOLORE EVACUATIVO	DATI MANOMETRICI	MRP = 88,8 ± 17,6 mmHg MVT = 58, 1 ± 13,1 ml.
DATI ISTOLOGICI 	▪ EROSIONI MUCOSE ▪ INFILTRATO EOSINOFILO LINFOPLASMACELLULARE ▪ RIDUZIONE STRATO MUCOSO RETTALE DA < SIALOMUCINE NON SULFONATE	DATI LABORATORIO (VARIAMENTE COMBINATI)	▪ EOSINOFILIA PERIFERICA ▪ > IgE ▪ PRICK + ▪ RAST + ▪ > IgG ANTIβLACTOGLOBULINA

17/36 = STIPSI ALLERGICA DA INTOLLERANZA ALIMENTARE

Iacono G, Bonventre S, Scalici C, Maresi E, Di Prima L, Soresi M, Di Gesù G, Noto D, Carroccio A.

Food intolerance and chronic constipation: manometry and histology study.

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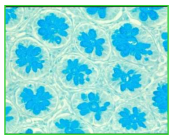
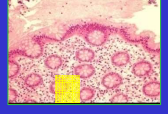
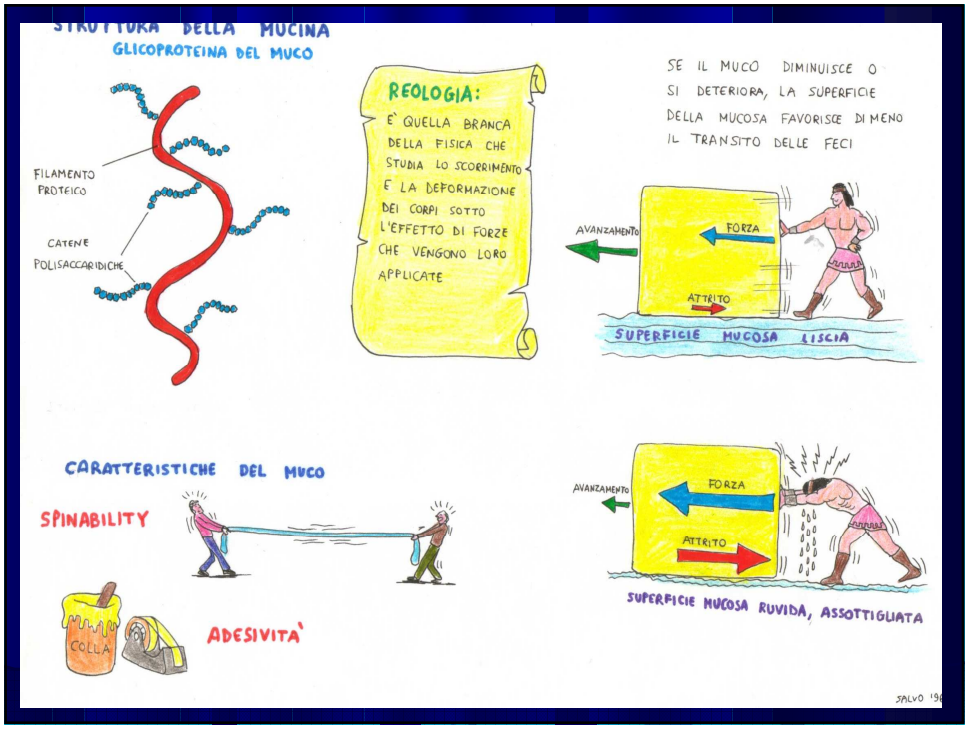
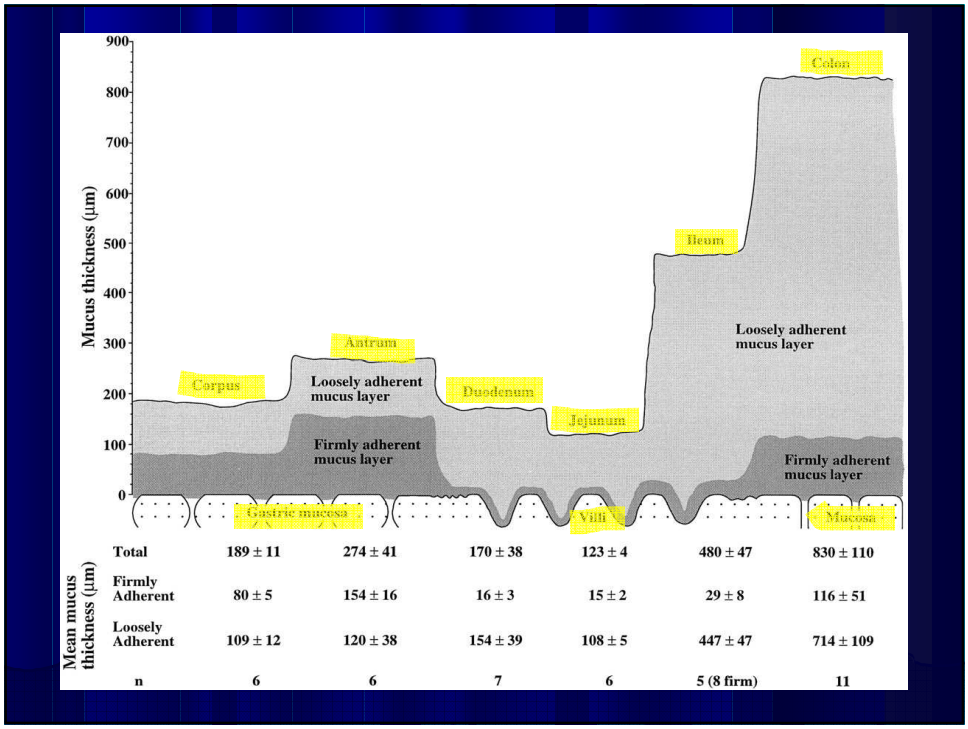
DOPO

DATI CLINICI 	▪ ASSENZA DI SINTOMATOLOGIA DOLOROSA ▪ REGOLARI EVACUAZIONI	DATI MANOMETRICI	MRP = 62,3 ± 7,1 mmHg MVT = 73, 4 ± 13,2 ml.
DATI ISTOLOGICI 	▪ ASSENZA DI LESIONI ISTOLOGICHE ▪ RICOSTITUZIONE STRATO MUCOSO CON RICOMPARSA SIALOMUCINE NON SULFONATE	DATI LABORATORIO	▪ PERSISTENTE ALTERAZIONE TESTS IMMUNOLOGICI CON MODICA RIDUZIONE LIVELLI Ig. ▪ SCOMPARSA EOSINOFILIA PERIFERICA

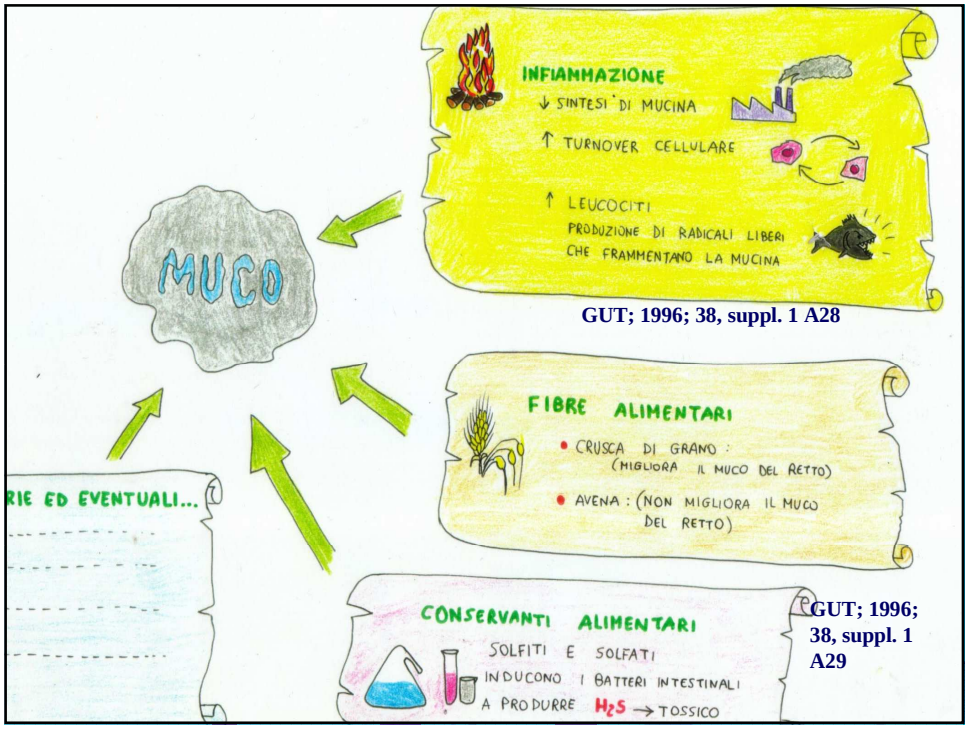
17/36 = STIPSI ALLERGICA DA INTOLLERANZA ALIMENTARE





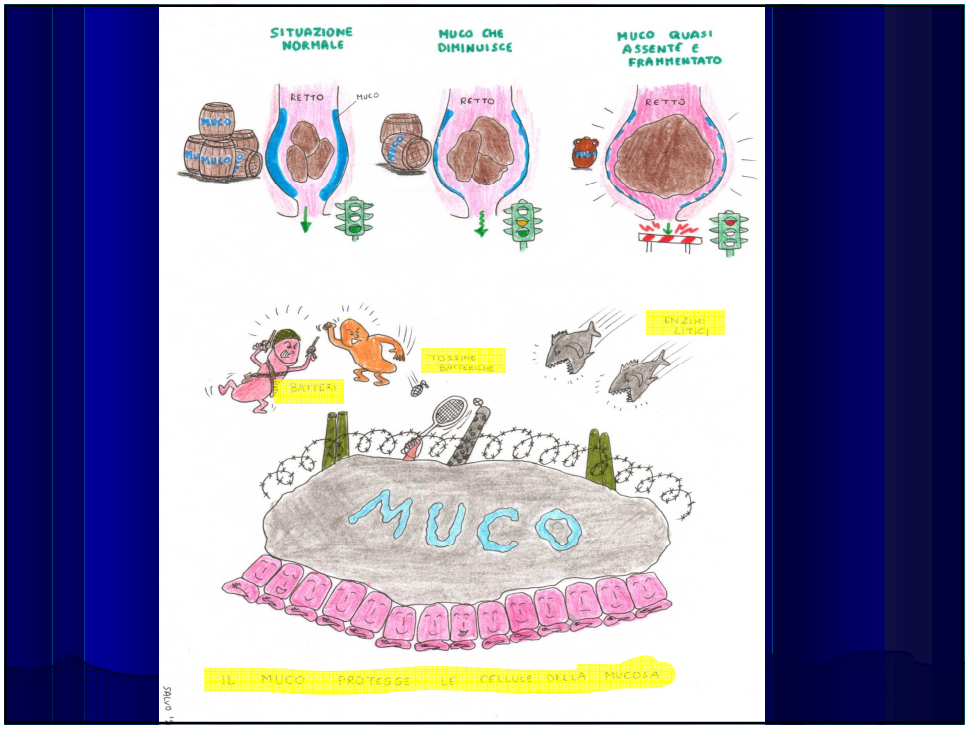
Mean mucus thickness (µm)

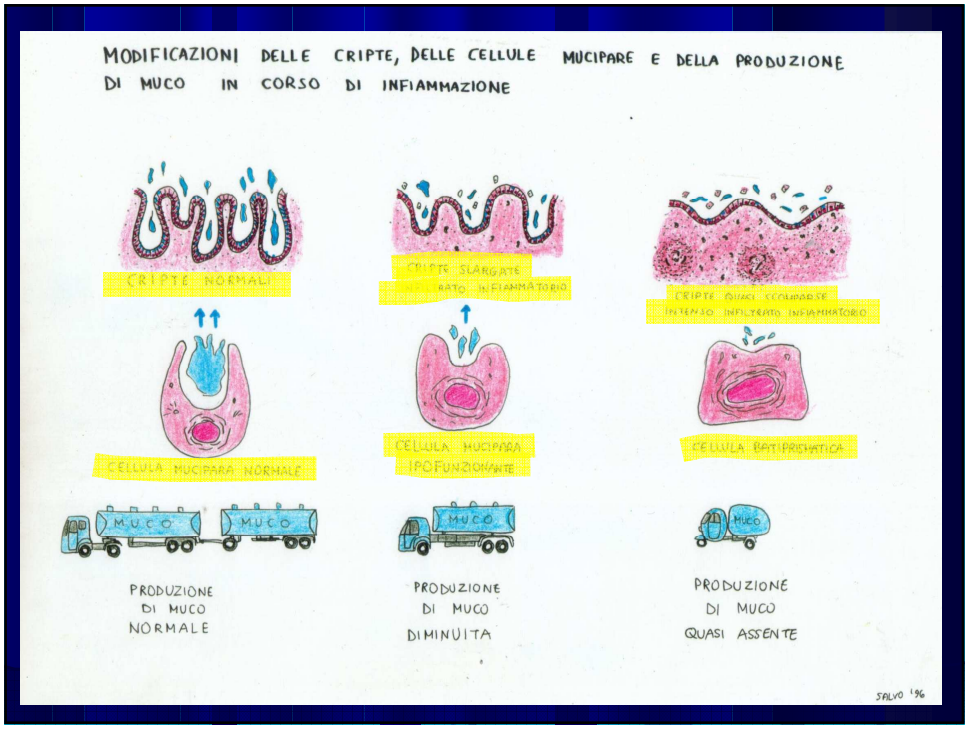
Total	189 ± 11	274 ± 41	170 ± 38	123 ± 4	480 ± 47	830 ± 110
Firmly Adherent	80 ± 5	154 ± 16	16 ± 3	15 ± 2	29 ± 8	116 ± 51
Loosely Adherent	109 ± 12	120 ± 38	154 ± 39	108 ± 5	447 ± 47	714 ± 109
n	6	6	7	6	5 (8 firm)	11



GUT; 1996; 38, suppl. 1 A28

GUT; 1996; 38, suppl. 1 A29





STIPSI E ALLERGIA: IL DATO ENDOSCOPICO

LYMPHOID NODULAR HYPERPLASIA AND COW'S MILK HYPERSENSITIVITY IN CHILDREN WITH CHRONIC CONSTIPATION

SAMI TURUNEN, MD, TUOMO J. KARTTUNEN, MD, PHD, AND JORMA KOKKONEN, MD, PHD

Objective To investigate the incidence of cow's milk allergy as evidenced by milk challenge and the findings of endoscopic and immunohistochemical examinations in children with chronic and refractory constipation.

Study design Thirty-five study subjects (mean age, 8.3 ± 3.3 years; range, 3-15 years; 17 girls) and 15 control subjects (mean age, 11.7 ± 3.2 years; range, 2-15 years; 9 girls) were studied by colonoscopy and a 4-week cow's milk elimination and challenge.

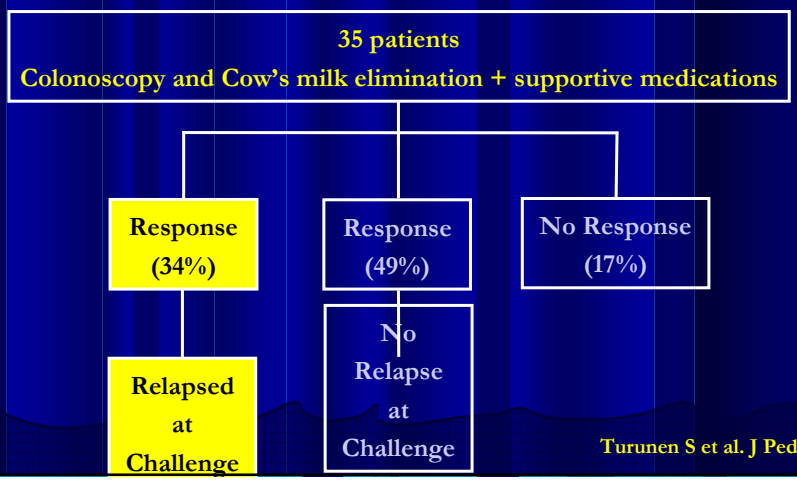
Results Lymphoid nodular hyperplasia was the most prominent endoscopic finding in half of the subjects (46%), mostly occurring patchily in the transverse colon. Histologic findings other than lymphoid accumulation and mildly increased density of eosinophils were few. During the milk elimination and with supportive medication, 83% of subjects remitted. Constipation and/or other gastrointestinal or skin symptoms relapsed only in one third (34%) during the cow's milk challenge, these having significantly higher densities of intraepithelial γδ⁺ T cells ($P < .001$) in the biopsy samples of the terminal ileum as compared with the control subjects.

Conclusions We were able to find formal evidence for the presence of cow's milk allergy in children with chronic constipation. (*J Pediatr 2004;145:606-11*)

ENDOSCOPICAL FINDINGS AND COW'S MILK ALLERGY IN CHILDREN WITH CHRONIC CONSTIPATION

Open-label study

35 patients (age range 3 – 15 yrs) and 15 healthy controls (age range 4 – 15 yrs)

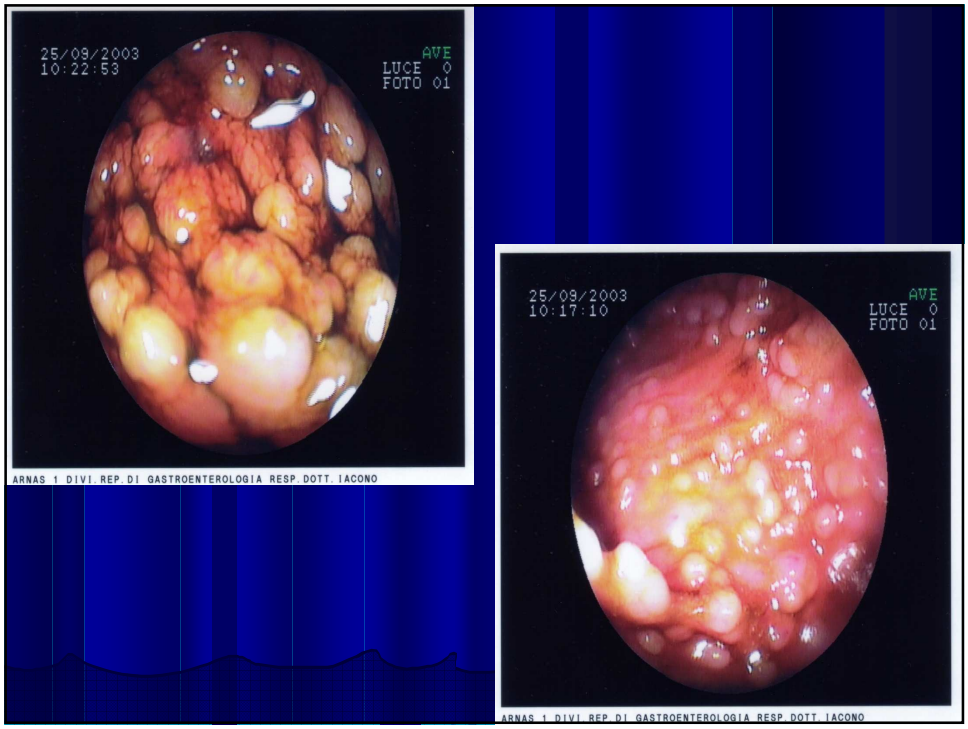


Turunen S et al. J Pediatr 2004

ENDOSCOPICAL FINDINGS AND COW'S MILK ALLERGY IN CHILDREN WITH CHRONIC CONSTIPATION

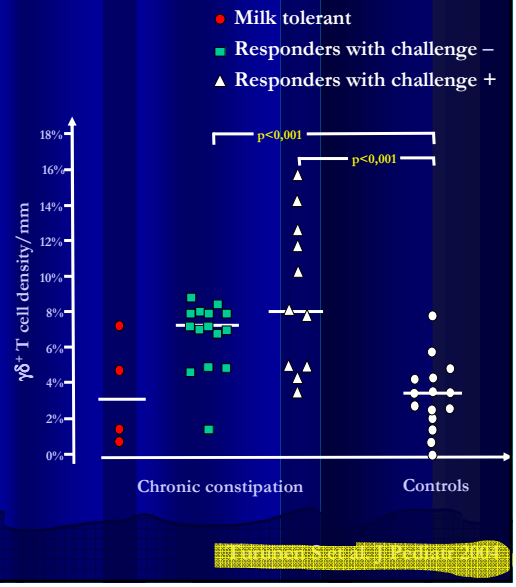
Lymphoid Nodular Hyperplasia (LNH) as an Endoscopic Findings

	Study subject (n = 35)	Control subject (n = 15)	*p* value
Terminal Ileum	26 (71%)	3 (20%)	$p < 0{,}001$
Colon anywhere	20 (57%)	1 (7%)	$p = 0{,}001$
Rectum	9 (26%)	0 (0%)	$p = 0{,}043$
Sigmoid colon	12 (34%)	0 (0%)	$p = 0{,}01$
Transverse colon	16 (45%)	1 (7%)	$p = 0{,}009$
Cecum	14 (40%)	0 (0%)	$p = 0{,}002$



ENDOSCOPICAL FINDINGS AND COW'S MILK ALLERGY IN CHILDREN WITH CHRONIC CONSTIPATION

	Study subjects	Control subjects	χ^2	*P* value*
Rectum	n = 35	n = 15		
Lymphatic follicles	8	5	0.513	NS†
Germinal centers	8	2	0.666	NS
Eosinophils ≥80/mm²	7	1	1.477	NS
Mononuclear cells	13	2	3.039	NS
Melanosis	2	1	0.011	NS
Transverse colon	n = 35	n = 15		
Lymphatic follicles	19	4	2.964	NS
Germinal centers	11	4	0.066	NS
Eosinophils ≥80/mm²	23	5	4.160	.041
Mononuclear cells	20	7	0.314	NS
Melanosis	5	4	1.251	NS
Cecum	n = 34	n = 15		
Lymphatic follicles	10	3	0.401	NS
Germinal centers	11	6	0.344	NS
Eosinophils ≥80/mm²	26	9	1.020	NS
Mononuclear cells	29	12	0.058	NS
Melanosis	14	4	0.81	NS
Terminal ileum	n = 32	n = 15		
Lymphatic follicles	27	9	1.521	NS
Germinal centers	23	5	4.468	<.05
Eosinophils ≥80/mm²	32	7	12.26	<.001
Mononuclear cells	24	11	0.113	NS
Pigmentation	12	3	1.020	NS



STIPSI E ALLERGIA: I DATI MANOMETRICI

Food intolerance and chronic constipation: manometry and histology study

Giuseppe Iacono[a], Sebastiano Bonventre[b], Calogero Scalici[a], Emiliano Maresi[c], Lidia Di Prima[d], Maurizio Soresi[d], Giuseppe Di Gesù[b], Davide Noto[d] and Antonio Carroccio[d]

Background Chronic constipation in children can be caused by cows' milk intolerance (CMI), but its pathogenesis is unknown.

Aims To evaluate the histology and manometry pattern in patients with food intolerance-related constipation.

Patients and methods Thirty-six consecutive children with chronic constipation were enrolled. All underwent an unrelated to food intolerance. Both histology and manometry abnormalities disappeared on the elimination diet.

Conclusions Food intolerance-related constipation is characterized by proctitis. Increased anal resting pressure and a reduced mucous gel layer can be considered to be contributory factors in the pathogenesis of constipation. *Eur J Gastroenterol Hepatol* 17:000–000 © 2005 Lippincott Williams & Wilkins.

STIPSI E ALLERGIA: I DATI MANOMETRICI

Table 3 Anorectal manometry results in patients with food intolerance-related chronic constipation at entry to the study and after 12 weeks of elimination diet, and in patients with chronic constipation not related to food intolerance

	Patients with food intolerance before elimination diet (n=17)	Patients with food intolerance on elimination diet (n=17)	Patients with constipation unrelated to food intolerance (n=19)	P-value
Anal sphincter resting pressure (mmHg)	88.8+17.6 A, B	62.3+7.1 A	69.8+14.7 B	A<0.01 B<0.05
Critical volume (ml)	58.1+13.1 A, B	73.4+13.2 A	69.5+17.3 B	A<0.01 B<0.05

No difference was observed between the 14 patients with cows' milk intolerance and the three patients with multiple food intolerance for any of the manometry parameters considered, either at baseline or on the elimination diet. Normal range values were: for anal sphincter resting pressure 50–70 mmHg, for critical volume 60–100 ml.

STIPSI E ALLERGIA: I DATI MANOMETRICI

Table 5 Correlation between histology and manometry data in all cases included in the study

	Critical volume	Intra-epithelial lymphocytes	Inta-epithelial eosinophils	Lamina propria eosinophils	Mucous layer thickness
Anal sphincter pressure	$r=0.286$ $P=0.05$	$r=0.425$ $P<0.001$	$r=0.630$ $P<0.0001$	$r=0.625$ $P<0.0001$	$r=-0.351$ $P=0.002$
Critical volume		$r=0.78$ NS	$r=-0.371$ $P=0.001$	$r=-0.381$ $P<0.001$	$P=0.172$ NS
Intra-epithelial lymphocytes			$r=0.633$ $P<0.0001$	$r=0.586$ $P<0.0001$	$r=-0.513$ $P<0.0001$
Intra-epithelial eosinophils				$r=0.703$ $P<0.0001$	$r=-0.639$ $P<0.0001$
Lamina propria eosinophils					$r=-0.501$ $P<0.0001$

Spearman's r coefficient of correlation was calculated.

STIPSI E ALLERGIA: I DATI MANOMETRICI

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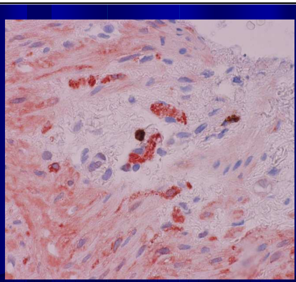
Intra-epithelial eosinophils				$r=0.703$ $P<0.0001$	$r=-0.639$ $P<0.0001$
Lamina propria eosinophils					$r=-0.501$ $P<0.0001$

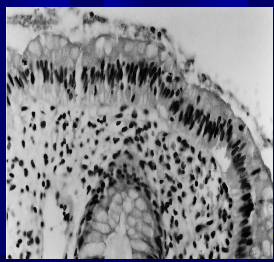
Spearman's r coefficient of correlation was calculated.

European Journal of Gastroenterology & Hepatology 2005, Vol 17

ALLERGIC COLITIS: A MIMIC OF HIRSCHSPRUNG DISEASE

Patient	Age	Clinical symptoms
1	7 days	Abdominal distention, low stool output, guaiac-negative stool
2	3 weeks	Constipation, history of bloody stools, perirectal abscess, guaiac-positive stool
3	3 weeks	Irritable, poor feeding, constipation, guaiac-positive stool
4	5 weeks	Abdominal distention, decreased stool output, nonbilious emesis, guaiac-negative stool





Bloom D. et al. Pediatr Radiol 1999

Scandinavian Journal of Gastroenterology, 2006; 41: 498–504

Taylor & Francis
Taylor & Francis Group

CASE REPORT

Multiple food hypersensitivity as a cause of refractory chronic constipation in adults

ANTONIO CARROCCIO[1], LIDIA DI PRIMA[1], GIUSEPPE IACONO[2], ADA M. FLORENA[3], FRANCESCO D'ARPA[4], CARMELO SCIUMÈ[5], ANGELO B. CEFALÙ[1], DAVIDE NOTO[1] & MAURIZIO R. AVERNA[1]

- <2 evacuazioni settimanali e mancata risposta a fibre e lassativi
- Dieta di eliminazione a base di riso, agnello, latte di asina, carote, olio di oliva
- DBPC con proteine del latte (15g/die) e proteine del frumento (20 g/die)
- Challenge “in aperto” per altri alimenti

STIPSI ED ALLERGIA NELL'ADULTO: CARATTERISTICHE CLINICHE

Table I. Clinical characteristics at baseline of the 4 patients suffering from refractory chronic constipation due to food hypersensitivity (Group A) and of 13 patients with refractory constipation unrelated to food hypersensitivity (Group B). (Plus-minus values are means ± SD).

	Group A ($n=4$)	Group B ($n=13$)	p-value
Age (years)	40.2±11.5	41±19.1	NS
Sex (males/females)	0/4	6/7	NS
Body mass index	21.1±1.15	26.7±4.31	0.03
Duration of illness (years)	39.2±7.2	24.9±10.5	0.03
Self-reported food intolerance (number)	4/4	0/13	0.01
Family history of food intolerance (number)	2/4	0/13	NS
Previous personal history of food intolerance (number)	4/4	0/13	0.01
Concomitant symptoms of food intolerance (bronchospasm, dermatitis, urticaria, rhinitis) (number)	4/4	0/13	0.01
Allergy to medications	3/4	1/13	0.04
Soiling (number)	0/4	1/13	NS
Nocturnal abdominal pain (number)	4/4	0/13	0.01
Fecal mass on rectal examination	4/4	13/13	NS
Anal itching	4/4	0/13	0.01
Dyspepsia	4/4	10/13	NS

Body mass index was calculated as patient's weight (in kg)/height^2 (in meters); normal range is 20–25.

Dietary protein proctitis/proctocolitis ……..I dati più recenti……

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:361–366

Colonic Lymphoid Nodular Hyperplasia in Children: Relationship to Food Hypersensitivity

GIUSEPPE IACONO,* ALBERTO RAVELLI,‡ LIDIA DI PRIMA,§ CALOGERO SCALICI,* STEFANIA BOLOGNINI,‡ SARA CHIAPPA,‡ GIUSEPPE PIRRONE,§ GIUSEPPINA LICASTRI,* and ANTONIO CARROCCIO§

245 bambini (età media 8,5 anni) consecutivamente sottoposti a colonscopia presso 2 centri.

Presentazione clinica: dolore addominale ricorrente (n=205), stipsi refrattaria (n=111), anemia sideropenica (n=91), diarrea con sangue (n=70), ritardo di crescita (n=45), ematochezia (n 40)

Sono state eseguite biopsie, IgE totali e specifiche, PRICK per allergeni alimentari.
I pazienti con LNH sono stati sottoposti a dieta di eliminazione (priva di LV, frumento, pesce, pomodoro, cioccolato, soia) **e successivo DBPC challenge.**

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:361–366

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Table 1. Number and Percentage of Final Diagnoses According to the Colonoscopy and Mucosa Histology Findings in the 245 Patients Who Completed the Study

	Center of Palermo (N = 142)	Center of Brescia (N = 103)	Total (N =245)
Crohn's disease	26	11	37
Ulcerative colitis	14	6	20
Indeterminate colitis	6	2	8
Allergic colitis	14	11	25
Other findings	5	5	10
Isolated LNH	30	22	52
Normal colonoscopy	47	46	93

Figure 1. Colonoscopy finding showing dense LNH in the ileum.

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:361–366

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Nei pazienti con LNH come unico dato endoscopico (n = 52), la dieta di eliminazione risolve la sintomatologia entro 3-10 giorni in 43 casi (83%).

Dopo DBPC challenge, in tutti i casi i sintomi si ripresentano entro 3-7 giorni.

La successiva ripresa della dieta di eliminazione risolve nuovamente la sintomatologia.

Una diagnosi di ipersensibilità alimentare viene posta in 43 pazienti

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:361–366

Colonic Lymphoid Nodular Hyperplasia in Children: Relationship to Food Hypersensitivity

GIUSEPPE IACONO,* ALBERTO RAVELLI,‡ LIDIA DI PRIMA,§ CALOGERO SCALICI,* STEFANIA BOLOGNINI,‡ SARA CHIAPPA,‡ GIUSEPPE PIRRONE,§ GIUSEPPINA LICASTRI,* and ANTONIO CARROCCIO§

Table 2. Clinical Features of the Patients With Isolated LNH and Food Hypersensitivity (Group A), Compared With the Patients With Isolated LNH Not Suffering From Food Hypersensitivity (Group B) and With the Patients Who Had Normal Colonoscopy and Did Not Suffer From Food Hypersensitivity (Group C)

	Group A (N = 43)	Group B (N = 9)	Group C (N = 58)
Sex (M/F)	35/8	8/1	30/28
Age (y) (mean + SD)	7.5 ± 3.3	6.2 ± 3.6	3.8 ± 2.9
Presenting symptoms[a]	Hematochezia (29), abdominal pain (21), constipation (20), anemia (20), failure to thrive (12), chronic diarrhea (4), vomiting (4)	Abdominal pain (5), fever (2) , hematochezia (2), chronic diarrhea (2), constipation (2), anemia (2)	Abdominal pain (58), constipation (54), anemia (10), failure to thrive (2), chronic diarrhea (4)
Site of LNH	Colon and ileum, 14; terminal ileum, 10; colon, 6; rectosigmoid, 13	Colon and ileum, 3; terminal ileum, 3; colon, 3	No cases showed LNH
Symptom duration before colonoscopy (*mo*)	3.1 ± 4.1	3.5 ± 3.2	6.4 ± 8.3
Previous history of food hypersensitivity	26/43 cases (60%)	2/9 cases (22%)	8/58 cases (13%)
Elevated serum IgE	8/43 cases (19%)	1/9 cases (11%)	5/58 cases (9%)
Positive RAST results for cow's milk antigens	9/43 cases (21%)	1/9 cases (11%)	5/58 cases (9%)
Elevated serum IgG anti–β-lactoglobulin	30/43 cases (70%)	2/9 cases (22%)	3/58 cases (5%)

FH è presente in 83% dei pazienti con LNH ed in 31% dei pazienti senza LNH.
A vs C: Sesso, età, ematochezia, pregressa storia di IPLV, soggetti con IgG elevate: P<.0001

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:361–366

Colonic Lymphoid Nodular Hyperplasia in Children: Relationship to Food Hypersensitivity

GIUSEPPE IACONO,* ALBERTO RAVELLI,‡ LIDIA DI PRIMA,§ CALOGERO SCALICI,* STEFANIA BOLOGNINI,‡ SARA CHIAPPA,‡ GIUSEPPE PIRRONE,§ GIUSEPPINA LICASTRI,* and ANTONIO CARROCCIO§

CONCLUSIONI

 # In bambini d'età scolare con disturbi gastroenterologici severi LNH è un riscontro endoscopico relativamente frequente

 # La sua evidenza si associa a FH nella maggior parte dei casi

 # La presentazione clinica più frequente in questi pazienti è la rettorragia

 # La proctocolite non deve considerarsi una esclusiva della I infanzia

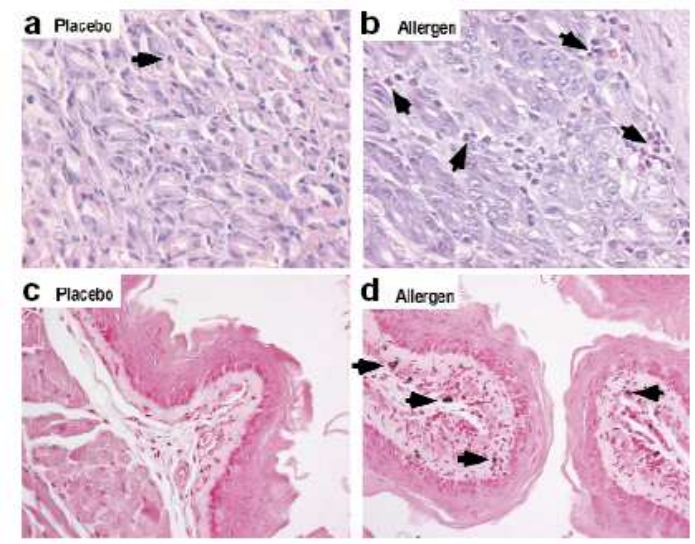
STIPSI E ALLERGIA: LE IPOTESI PATOGENETICHE

A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation

Simon P. Hogan[1], Anil Mishra[1], Eric B. Brandt[1], Michael P. Royalty[1], Samuel M. Pope[1], Nives Zimmermann[1], Paul S. Foster[2] and Marc E. Rothenberg[1]

Rothenberg et al. Nature Immunology 2001;vol 2(4)

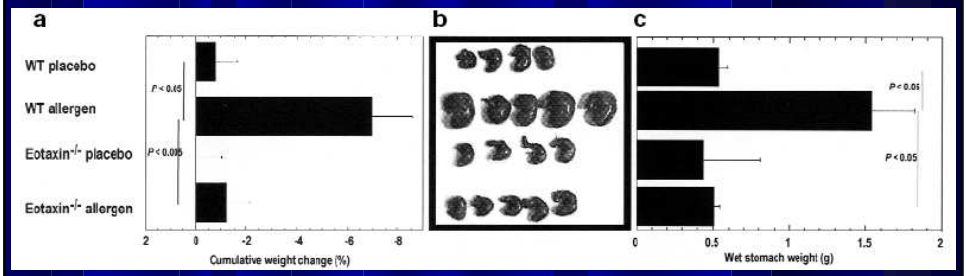
Infiltrato eosinofilo nello stomaco (**a** e **b**) e nell'esofago (**c** e **d**) di ratti sensibilizzati, trattati con somministrazione orale di placebo o dell'allergene.



Rothenberg et al. Nature Immunology 2001;vol 2(4)

STIPSI E ALLERGIA: LE IPOTESI PATOGENETICHE

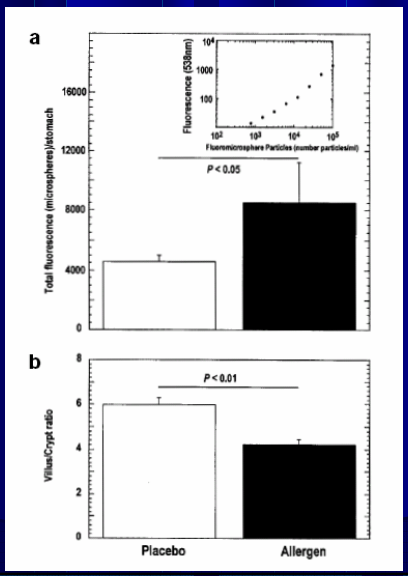
Evidenza del ruolo determinante dell'eotassina nel causare cachessia e gastromegalia in ratti sensibilizzati



IL-4, IL-5, IFN-gamma mostrano livelli comparabili in WT ed eotaxin- mice Confermando la specificità dell'eotassina nel determinare gli effetti osservati.

Rothenberg et al. Nature Immunology 2001; vol 2(4)

STIPSI E ALLERGIA: LE IPOTESI PATOGENETICHE



Fluorescenza presente nello stomaco dopo 2 ore dalla somministrazione di microsfere, al 16° giorno di challenge orale, in ratti sensibilizzati.

Villi/cripte ratio al 19° giorno di challenge orale in ratti sensibilizzati

Rothenberg et al. Nature Immunology 2001;vol 2(4)

a) Ratti non sensibilizzati
b) e c) Ratti sensibilizzati con infiltrato eosinofilo nella lamina propria (arrows)
d) A maggiore ingrandimento danno assonale

Table 1. Oral allergen-induced gastrointestinal dysmobility

	Time after challenge (h)			
Treatment of mice	6	24	48	72
Placebo	0/4	0/4	0/4	0/4
Allergen	3/3	7/9	1/4	0/4

Total number of mice with OVA beads present in the stomach per total mice at 6, 24, 48 and 72 h after allergen challenge are shown.

Rothenberg et al. Nature Immunology 2001;vol 2(4)

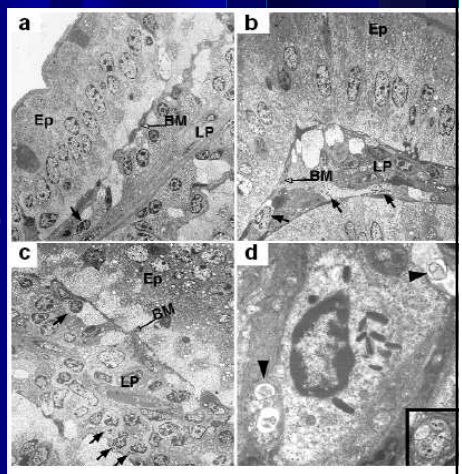
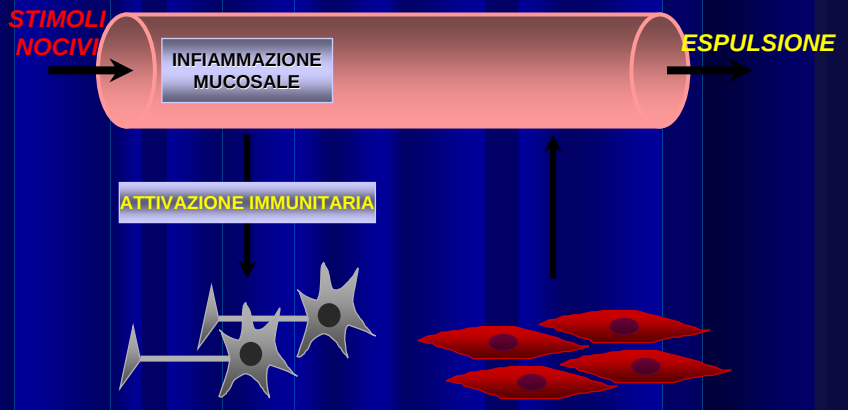


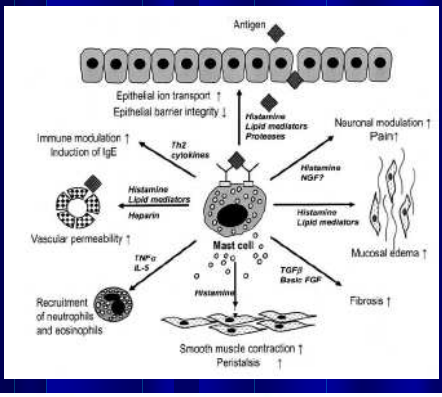
Figure 4. Electron microscopic analysis of the jejunum from oral antigen–challenged mice. Representative electron photomicrographs from the jejunum of placebo- (a) and oral allergen–challenged (b–d) mice. (a–c) Eosinophils (arrows) are observed within the lamina propria (LP) of the villi. The epithelium (Ep) and basement membrane (BM) are labeled for orientation. An increased number of eosinophils are apparent after oral allergen treatment. (d) A higher power magnification of an eosinophil with abundant granules containing the characteristic electron-dense core and matrices is shown. The eosinophil is within the reticular connective tissue of lamina propria, in close proximity to two enteric nerves. The enteric nerves are swollen, containing enlarged axonal chambers with variable loss of internal organelles, indicative of axonal necrosis (black arrowhead). Inset depicts a normal, intact enteric nerve bundle with the dense core granules of the surrounding Schwann cell from a placebo-challenged mouse. Original magnification: ×2680 (a–c) and ×16,900 (d).

Motilità e difesa gastrointestinale



IPERSENSIBILITA' E ALTERATA MOTILITA'

.....ma anche i mastociti.....



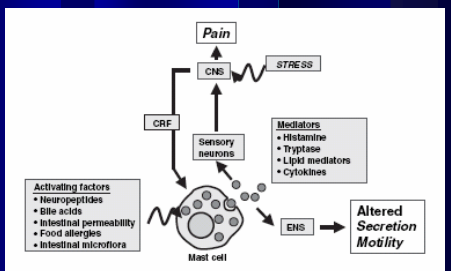


Figure 3 Schematic representation of the sequence of events involved in MC activation and the putative role that these event may have in IBS pathophysiology. CNS, central nervous system; CRF, corticotrophin releasing factor, ENS, enteric nervous system.

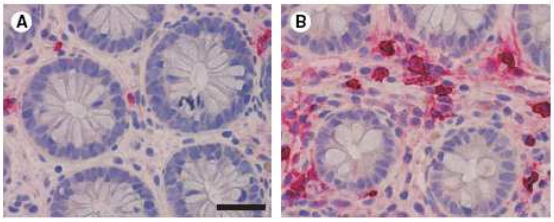
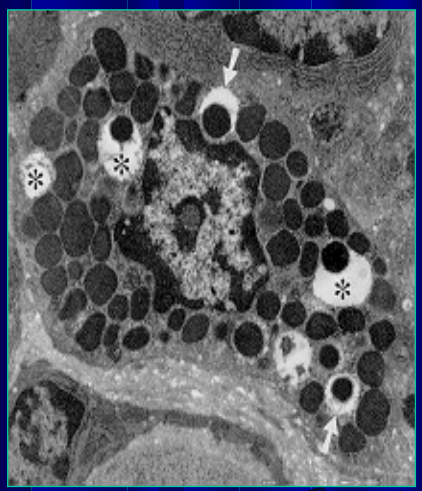
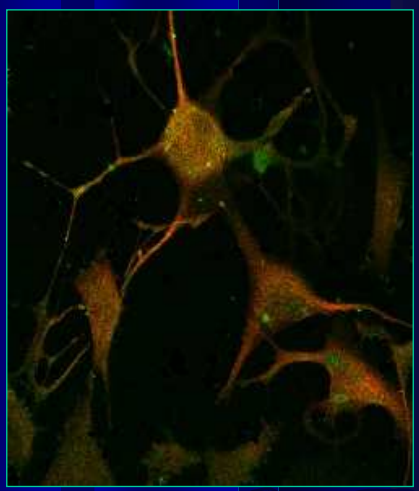


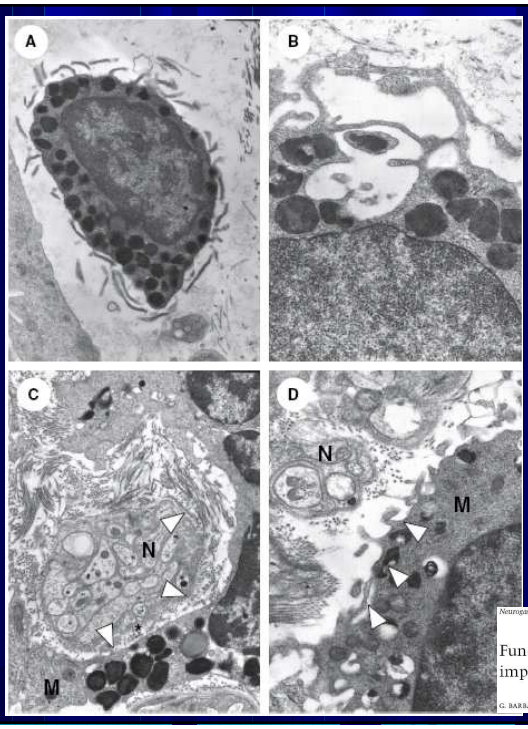
Figure 2 Representative photomicrographs showing tryptase positive MCs in the colonic mucosa of a healthy control (A) and an irritable bowel syndrome patient (B). Note the higher number of positive MCs in the IBS patient as compared with the control. Calibration bar: 25 μm.

Interazione neuro-immune





Schäppi M, ESPGHAN 2003; Torrente F, ESPGHAN 2003)



A) Mastocita intra-mucosale
B) Degranulazione di un mastocita
C) Mastociti attorno a neuroassone
D) Degranulazione peri-assonale

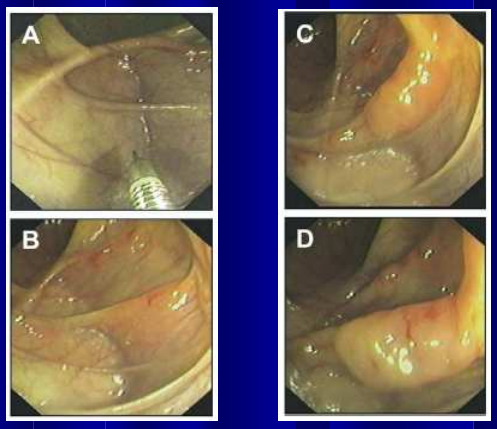
Neurogastroenterol Motil (2006) 18, 6–17 doi: 10.1111/j.1365-2982.2005.00685.x

Functional gastrointestinal disorders and mast cells: implications for therapy

G. BARBARA, V. STANGHELLINI, R. DE GIORGIO & R. CORINALDESI

Perché una reazione che <u>pare</u> di tipo Th2 non si correla con RAST e/o PRICK ??

La "Colonoscopic allergen provocation":



Reimann et al: Am J Gastroenterol 1988;83:1212
Bischoff et al: GUT 1997;40:745

Journal of Pediatric Gastroenterology and Nutrition
43:470–476 © October 2006 Lippincott Williams & Wilkins, Philadelphia

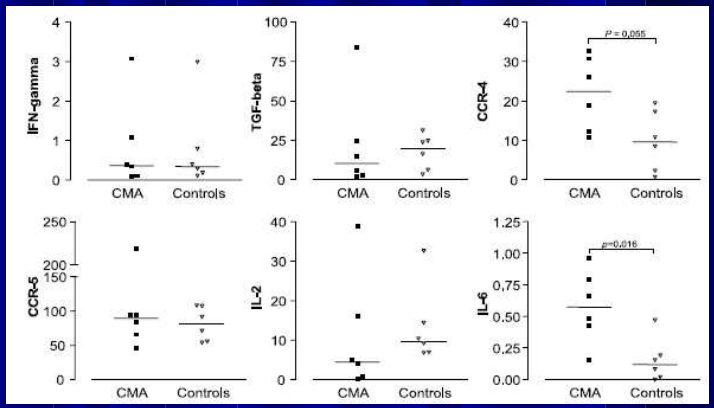
Intestinal Cytokine mRNA Expression in Delayed-type Cow's Milk Allergy

*†Laura Paajanen, ‡Jorma Kokkonen, ‡Tuomo J. Karttunen, §Tuula Tuure, *§‖Riitta Korpela, and ¶#Outi Vaarala

TABLE 1. *Clinical data on study children*

	Delayed-type CMA	Celiac disease	Controls	Total
Baseline characteristics				
n	10	6	10	26
Male/female	3/7	1/5	4/6	8/18
Age, yr (range)	10 (3–14)	10 (6–14)	10 (3–15)	10 (3–15)
Biopsies from bulb of duodenum	6	6	6	18
Biopsies from terminal ileum	6	0	6	12
Main GI symptoms				
Diarrhea	6	2	1	
Constipation	2	0	0	
Recurrent abdominal pain	1	0	4	
Other GI symptoms	1	4	5	

Espressione di citochine e recettori di chemochine nella mucosa dell'ileo terminale



CCR-4 è recettore di chemochine espresso su linfociti Th-2
IL-6 è secreta da diversi tipi cellulari inclusi i Th-2

Real-Time PCR per m-RNA
(gene target "normalizzato su controllo endogeno)

Paajanen et al. JPGN 2006

.....e anche i linfociti.....

	IBS-NI (A)	IBS-NSI (B)	CONTROLS (C)	P value
IELs	10.4±6.3	9.8±5.7	5.6±3.3	A e B vs C 0.01
CD3 Lam Pr	1112±419	1107±408	712±329	A e B vs C 0.001
Mastociti	377±175	638±291	411±152	B vs A e C 0.01

IBS-NI =IBS non- inflammed IBS-NSI=IBS with non-specific inflammation

Chadwick et al: Gastroenterology 2002;122:1778-83

I linfociti: non un ruolo da comparse.....

Enteric neuromuscular abnormalities

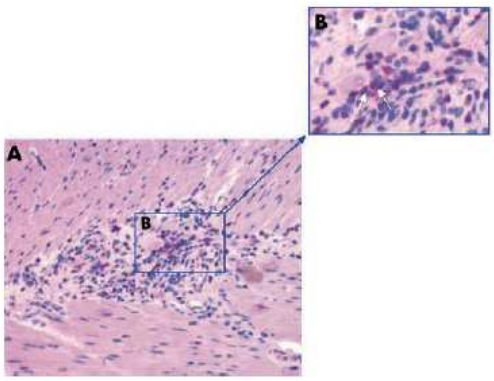


Figure 1 Representative photomicrograph illustrating a case of idiopathic lymphocytic myenteric ganglionitis. The immune infiltrate is localised within the myenteric plexus of the small bowel of a patient with chronic intestinal idiopathic pseudo-obstruction. The positive immunolabelling (light red/pink colour) identifies CD8 T lymphocytes (A). The inset selected (B) is a higher magnification of (A) showing the close proximity between CD8 positive lymphocytes and myenteric neurones (arrows). Alkaline phosphatase antialkaline phosphatase immunohistochemical technique. Original magnifications: 80×, A; 160×, B.

LEADING ARTICLE

Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction

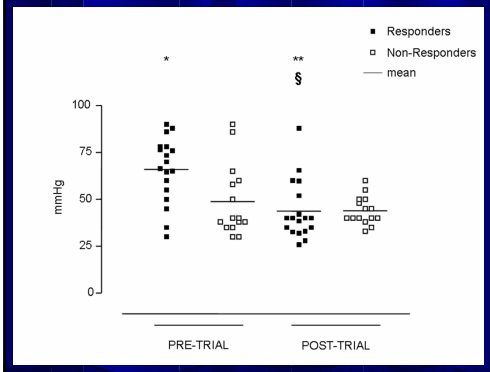
R De Giorgio, G Sarnelli, R Corinaldesi, V Stanghellini

Gut 2004;53:1549–1552. doi: 10.1136/gut.2004.043968

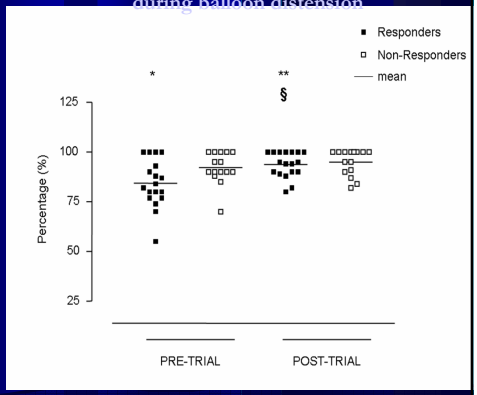
NEURO-IMMUNE INTERACTION AND ANORECTAL MOTILITY IN CHILDREN WITH FOOD-ALLERGY CONSTIPATION

18 OF 33 CHILDREN WERE RESPONSIVE (RESPONDERS) CLINICALLY TO THE ELIMINATION DIET, 15 DID NOT (NON-RESPONDERS)

Anal resting pressure



% of anal relaxation during balloon distension



Borrelli O et al Am J Gastroenteroly 20

NEURO-IMMUNE INTERACTION AND ANORECTAL MOTILITY IN CHILDREN WITH FOOD-ALLERGY CONSTIPATION

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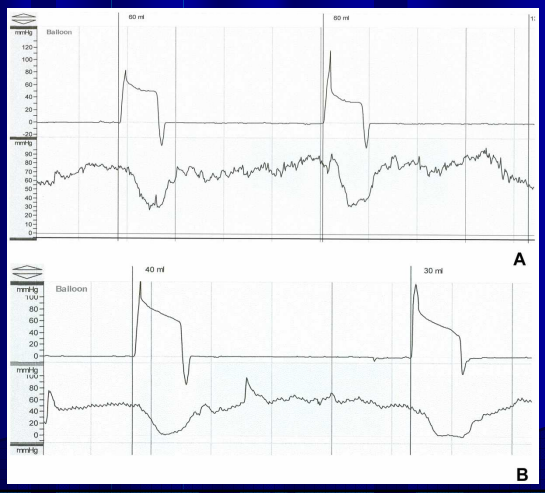
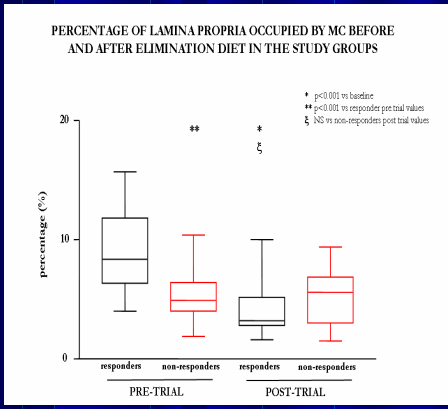
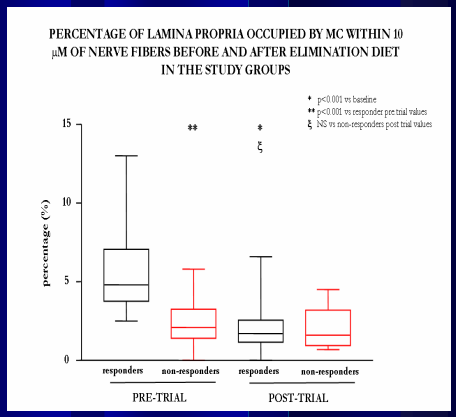


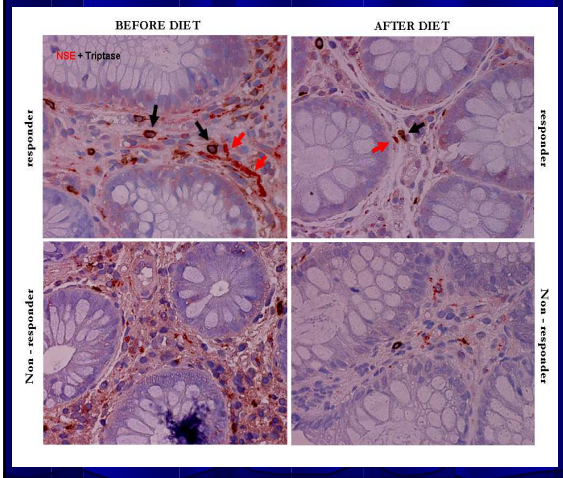
NEURO-IMMUNE INTERACTION AND ANORECTAL MOTILITY IN CHILDREN WITH FOOD-ALLERGY CONSTIPATION

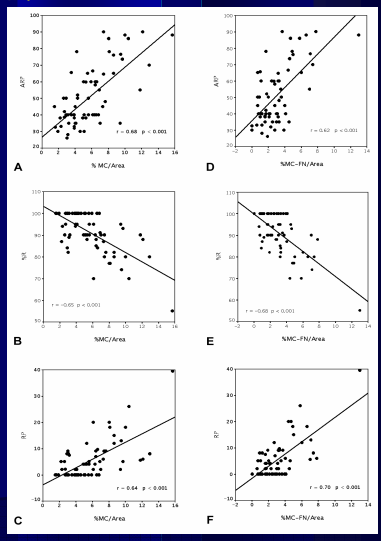




Borrelli O et al Am J Gastroenterology 2

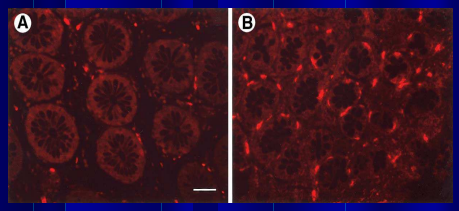
NEURO-IMMUNE INTERACTION AND ANORECTAL MOTILITY IN CHILDREN WITH FOOD-ALLERGY CONSTIPATION

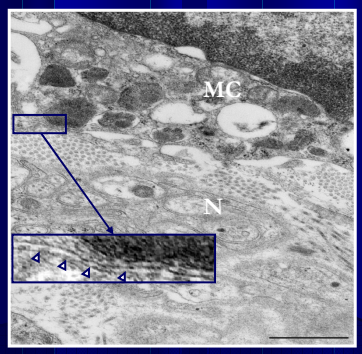


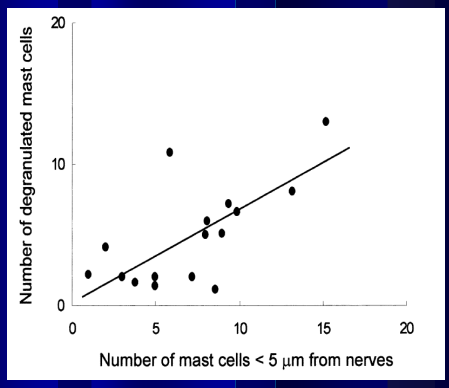


Borrelli O et al Am J Gastroenterology 2008

MASTCELLS IN IRRITABLE BOWEL SYNDROME (triptasi







	All IBS patients	IBS-D	IBS-C	*p* value
Controls	3,3 ± 0,8	-	-	NA
IBS	9,2 ± 2,5	8,6 ± 2,7	9,7 ± 2,1	*NS*

Barbara et al. Gastroenterology 200

NEURO-IMMUNE INTERACTION AND ANORECTAL MOTILITY IN CHILDREN WITH FOOD-ALLERGY CONSTIPATION

CLINICAL RESPONSE WAS SIGNIFICANTLY RELATED TO:

Personal history of atopy

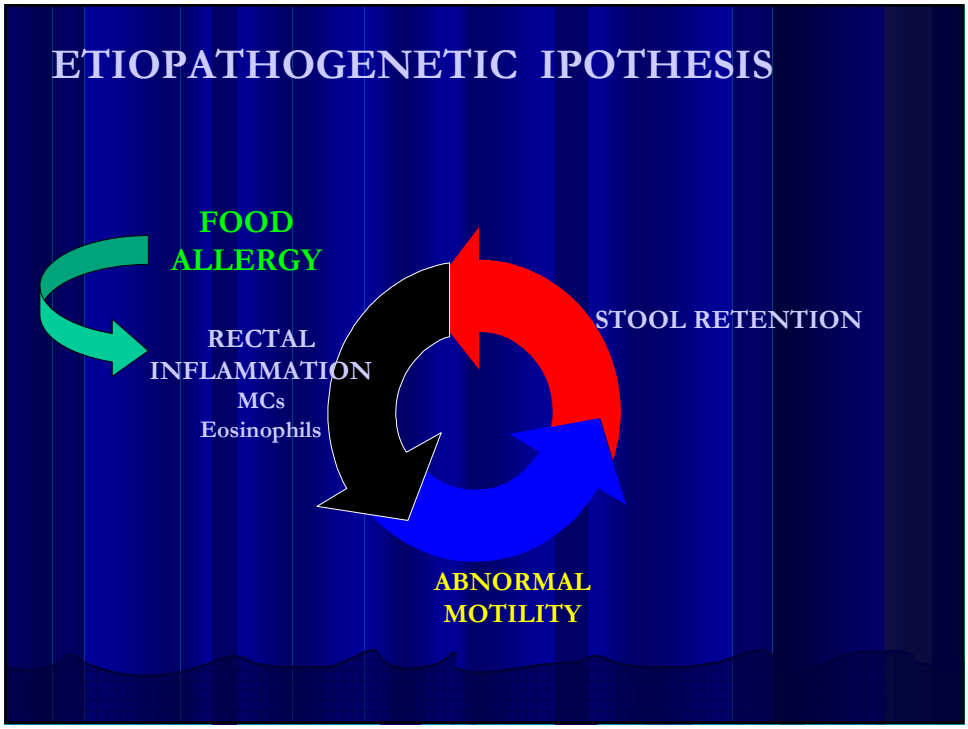
presence of 1 or more positive immunologic tests

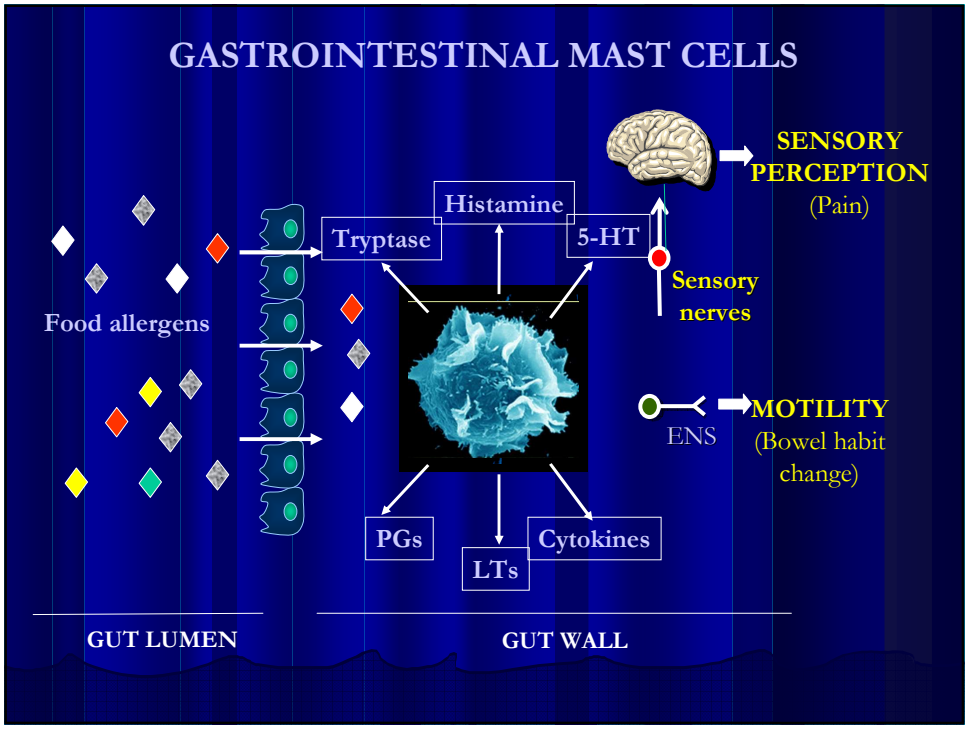
baseline values of ARP

%MC/area

%MC-NF/area

Borrelli O et al Am J Gastroenterol ogy 2008


ETIOPATHOGENETIC IPOTHESIS
FOOD ALLERGY
RECTAL INFLAMMATION
MCs
Eosinophils
STOOL RETENTION
ABNORMAL MOTILITY


GASTROINTESTINAL MAST CELLS
SENSORY PERCEPTION
(Pain)
Histamine
Tryptase
5-HT
Sensory nerves
Food allergens
MOTILITY
(Bowel habit change)
ENS
PGs
LTs
Cytokines
GUT LUMEN
GUT WALL

NEURO-IMMUNE INTERACTION AND ANORECTAL MOTILITY IN CHILDREN WITH FOOD-ALLERGY CONSTIPATION

CONCLUSIONS

IN CHILDREN WITH FUNCTIONAL CONSTIPATION RELATED TO FA

1. ANORECTAL DYSMOTILITY IS SUSTAINED BY ABNORMAL RECTAL DENSITY OF MCs AND SPATIAL INTERACTIONS BETWEEN MCs AND NERVES.
2. THESE VARIABLES ARE SIGNIFICANTLY AFFECTED BY AN ELIMINATION DIET.

Borrelli O et al Am J Gastroenterology 2008

STIPSI E INTOLLERANZA: LE ATTUALI CONCLUSIONI IN ETA' PEDIATRICA

- Si tratta di una vera proctite con chiare caratteristiche istologiche di flogosi
- Vi è una relazione fra entità della flogosi e "dismotilità" ano-rettale.
- La riduzione del "gel" di muco rettale può essere un co-fattore patogenetico.

STIPSI E INTOLLERANZA: LE ATTUALI CONCLUSIONI IN ETA' PEDIATRICA

- Si tratta di un fenomeno frequente in età pediatrica, che deve essere considerato nel trattamento dei bimbi che hanno una storia di IPLV o che non rispondono ai comuni lassativi.
- Il problema va spesso inquadrato e trattato come una polintolleranza.
- I meccanismi immunologici sono ancora da interpretare

...E NELL'ADULTO ??

Scandinavian Journal of Gastroenterology, 2006; 41: 498–504

Taylor & Francis
Taylor & Francis Group

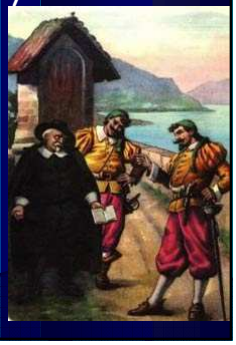
CASE REPORT

Multiple food hypersensitivity as a cause of refractory chronic constipation in adults

ANTONIO CARROCCIO[1], LIDIA DI PRIMA[1], GIUSEPPE IACONO[2], ADA M. FLORENA[3], FRANCESCO D'ARPA[4], CARMELO SCIUMÈ[5], ANGELO B. CEFALÙ[1], DAVIDE NOTO[1] & MAURIZIO R. AVERNA[1]

The Authors of this study have convinced me that there are a small number (about 5%) of adults with constipation and abdominal pain whose symptoms are based on food allergies and who may respond to dietary elimination of offending foods. Moreover, these patients would appear to have symptoms consistent with IBS, constipation predominant.....

Referee of Annals Internal Medicine



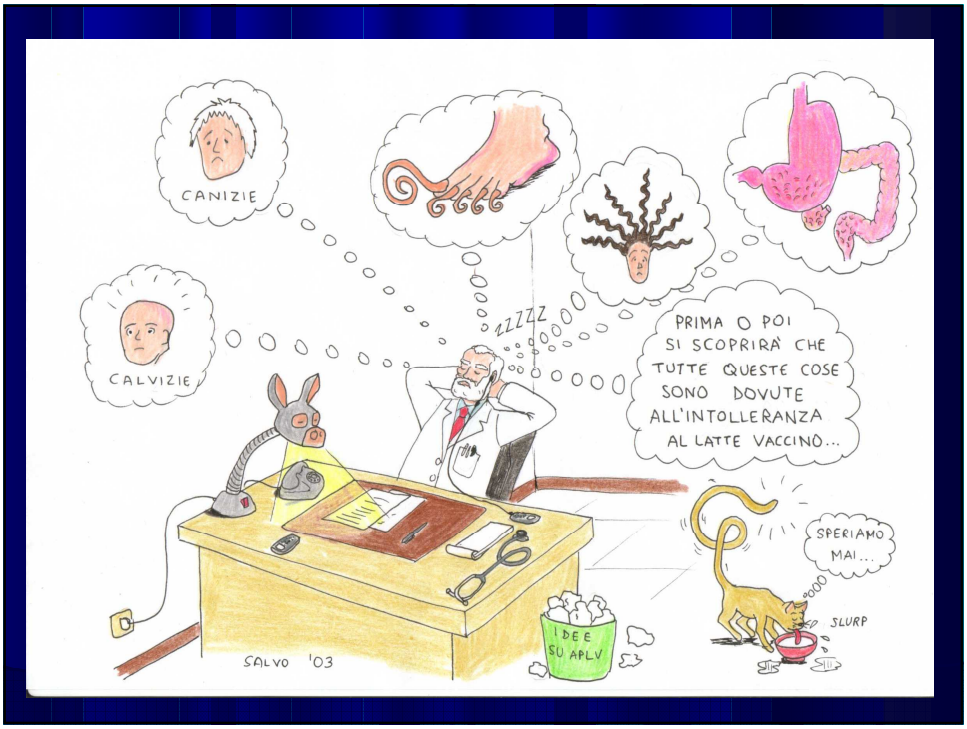
Thank you for submitting.....
I'm sorry that we won't be able to accept it for publication.....
We found the work interesting and realize that many of the reviewers' comments were positive but their comments, while very important, are only one of several factors that contribute to our decision. We thought that the findings were too preliminary.....

The Editor of Annals Internal Medicine

SUMMARY OF THE MAIN STUDIES WHICH HAVE INVESTIGATED THE RELATIONSHIP BETWEEN CHRONIC CONSTIPATION AND CMPH

Author, year	Number of cases	Type of study	Evidence of the relationship
Chin, 1983	1	Case report	Yes
McGrath, 1984	1	Case report	Yes
Iacono, 1995	27	Prospective, uncontrolled trial	Yes
Iacono, 1998	65	Prospective RCT	Yes
Iacono, 1998	1	Case report	Yes
Daher, 1999	25	Not specified	Yes
Shah, 1999	14	Prospective	Yes
Bloom, 1999	4	Case report	Yes
Daher, 2001	25	Prospective	Yes
Loening-Baucke, 2001	Not specified	Unpublished personal experience	No
Vanderhoof, 2001	12	Retrospective	Yes
Turunen, 2004	35	Prospective	Yes
Carroccio, 2005	52	Prospective with DBPC challenge	Yes
Iacono, 2006	26	Prospective with DBPC challenge	Yes
Carroccio, 2006	4	Case reports	Yes

Iacono et al Aliment Pharmacol Ther 2006;24:1295



TAKE HOME MESSAGES

A causal relationship between food allergy and chronic constipation has been clearly described at least in a subgroup of patients with functional constipation unresponsive to stool softeners

Children with chronic constipation related to food allergy show an increase in the density of rectal mucosa MCs and eosinophils

These inflammatory changes correlate with abnormalities in anorectal and colonic motility

An elimination diet can be recommended for children with refractory chronic constipation and especially those with a history of atopy and/or positivity for at least one of the commonly performed tests for food allergy

Considerazioni conclusive

- Molti disturbi di dismotilità gastrointestinale hanno una base flogistica e molti dati indicano che la flogosi allergica può essere alla base di una percentuale di essi.
- Non abbiamo test diagnostici sufficientemente accurati nella diagnosi di allergia alimentare con manifestazioni gastroenterologiche
- Le manifestazioni IgE-mediate (positività di PRICK o RAST) rappresentano la minoranza dei casi

- **La diagnosi è "un puzzle" nel quale l'evidenza clinica (dieta e challenge) ha sicuramente il ruolo più importante**