LA COSTELLAZIONE CLINICA DEI DISORDINI FUNZIONALI GASTRO-INTESTINALI

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CONSENSUS 2015

I disordini funzionali gastrointestinali in età prescolare

LA COSTELLAZIONE CLINICA DEI DISORDINI FUNZIONALI GASTRO-INTESTINALI

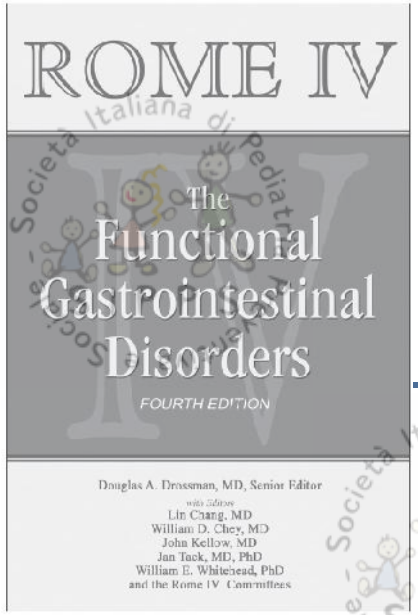
OUTLINE

- ***Definizione dei Disordini Funzionali Gastrointestinali***
- ***Epidemiologia, Costi e Qualità di vita***
- ***Patogenesi e terapia***

DISORDINI FUNZIONALI GASTROINTESTINALI

DEFINIZIONE

Combinazione variabile di sintomi gastro-intestinali cronici o ricorrenti, età-dipendenti, non spiegati da alterazioni biochimiche o strutturali.



PERCHE' I CRITERI DI ROMA?

Per effettuare una diagnosi in positivo dei DFGI, basata su un insieme di sintomi, in assenza di markers biologici specifici.

DFGI Pediatrici: Classificazione

G. Functional disorders: neonates and toddlers

G1. Infant regurgitation

G2.

G3.

G4.

G5.

G6.

G7. Functional constipation

Coliche infantili

⇩

Nessun marker!

unctional disorders: children and adolescents

.. Vomiting and aerophagia

H1a. Ac

H1b. Cy

H1c. Ae

H2. Abdor

H2a. Fu

H2b. Irr

H2c. Ab

Sindrome del colon irritabile

⇩

Nessun marker!

H2d. Childhood functional abdominal pain

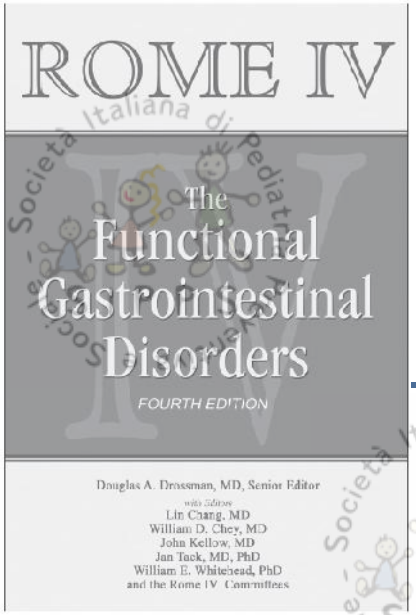
H2d1. Childhood functional abdominal pain syndrome

H3. Constipation and incontinence

H3a. Functional constipation

H3b. Nonretentive fecal incontinence

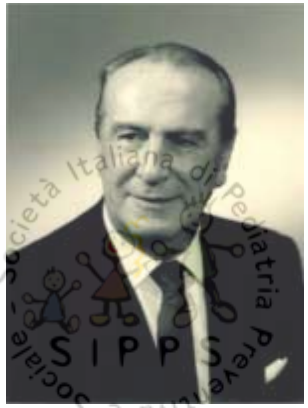
OFFICIAL JOURNAL OF THE AGA INSTITUTE



PERCHE' I CRITERI DI ROMA?

... abbiamo bisogno dei criteri di Roma per meglio definire i disordini funzionali gastrointestinali, come un insieme di sintomi quanto piu' obiettivi possibili, per parlare dello stesso disordine sia da un punto di vista diagnostico che terapeutico.

PERCHE' I CRITERI DI ROMA?



Il Prof. Aldo Torsoli per primo ha proposto di utilizzare il metodo Delphi per una serie di *committee reports* su vari argomenti di gastroenterologia che sono stati presentati al Congresso Internazionale di Gastroenterologia, a Roma nel 1988 e poi pubblicati su Gastroenterology International, come criteri di Roma I

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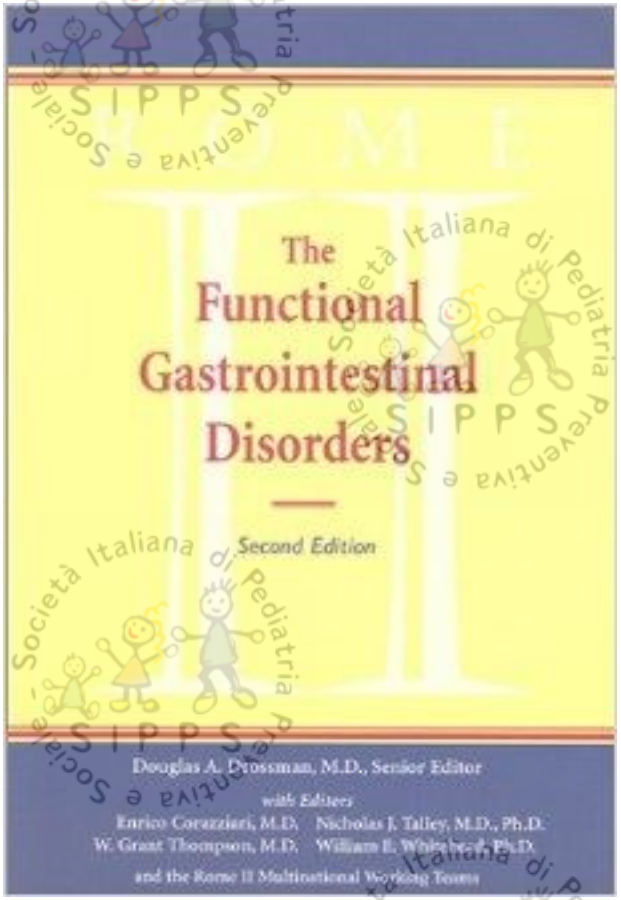
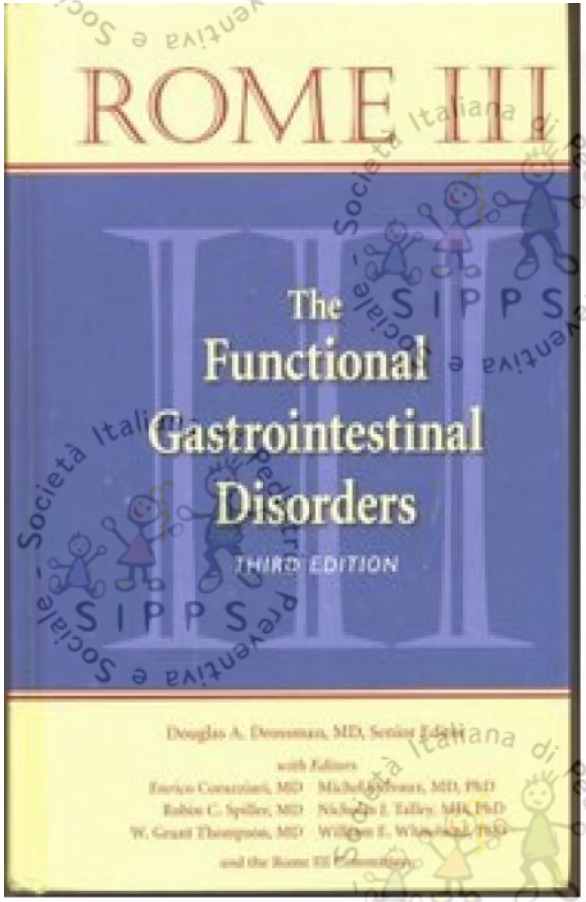
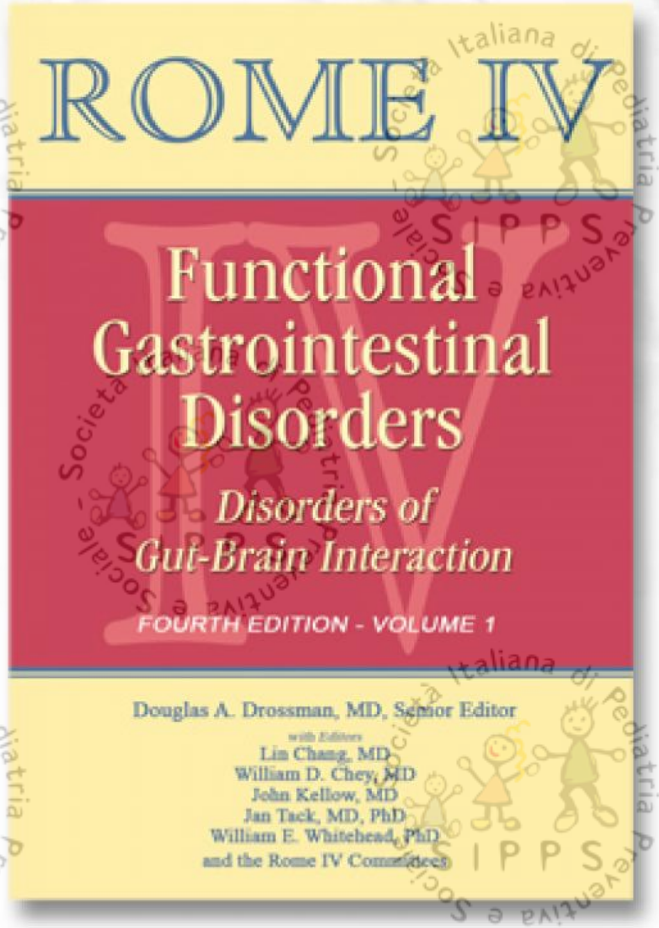


1999



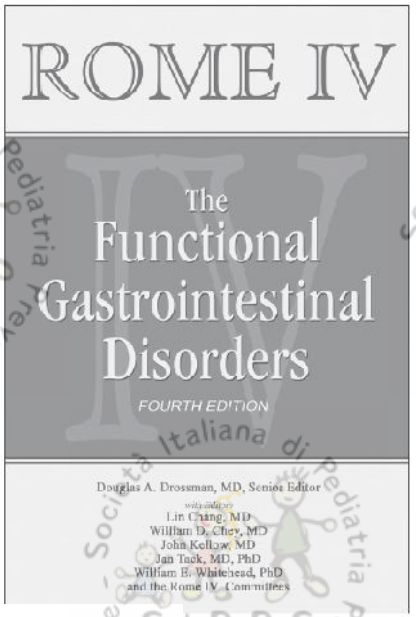
2006



2016

Childhood Functional Gastrointestinal Disorders Child/Adolescent

Carlo Di Lorenzo, MD, Chair, Jeffrey S. Hyams, MD, Co-Chair, Miguel Saps, MD, Robert J. Shulman, MD, Annamaria Staiano, MD Miranda van Tilburg, PhD



G. Childhood Functional GI Disorders: Neonate/Toddler

G1. Infant regurgitation
G2. Rumination syndrome
G3. Cyclic vomiting syndrome (CVS)
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation

H. Childhood Functional GI Disorders: Child/Adolescent

H1. Functional nausea and vomiting disorders
- H1a. Cyclic vomiting syndrome (CVS)
- H1b. Functional nausea and functional vomiting
  - H1b1. Functional nausea
  - H1b2. Functional vomiting
- H1c. Rumination syndrome
- H1d. Aerophagia

H2. Functional abdominal pain disorders
- H2a. Functional dyspepsia
  - H2a1. Postprandial distress syndrome
  - H2a2. Epigastric pain syndrome
- H2b. Irritable bowel syndrome (IBS)
- H2c. Abdominal migraine
- H2d. Functional abdominal pain—NOS

H3. Functional defecation disorders
- H3a. Functional constipation
- H3b. Nonretentive fecal incontinence

Childhood Functional Gastrointestinal Disorders Child/Adolescent

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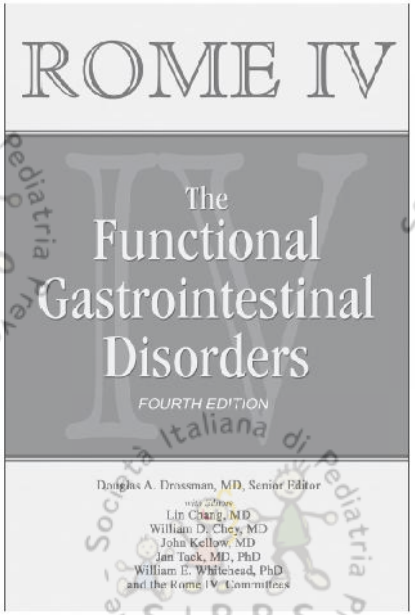
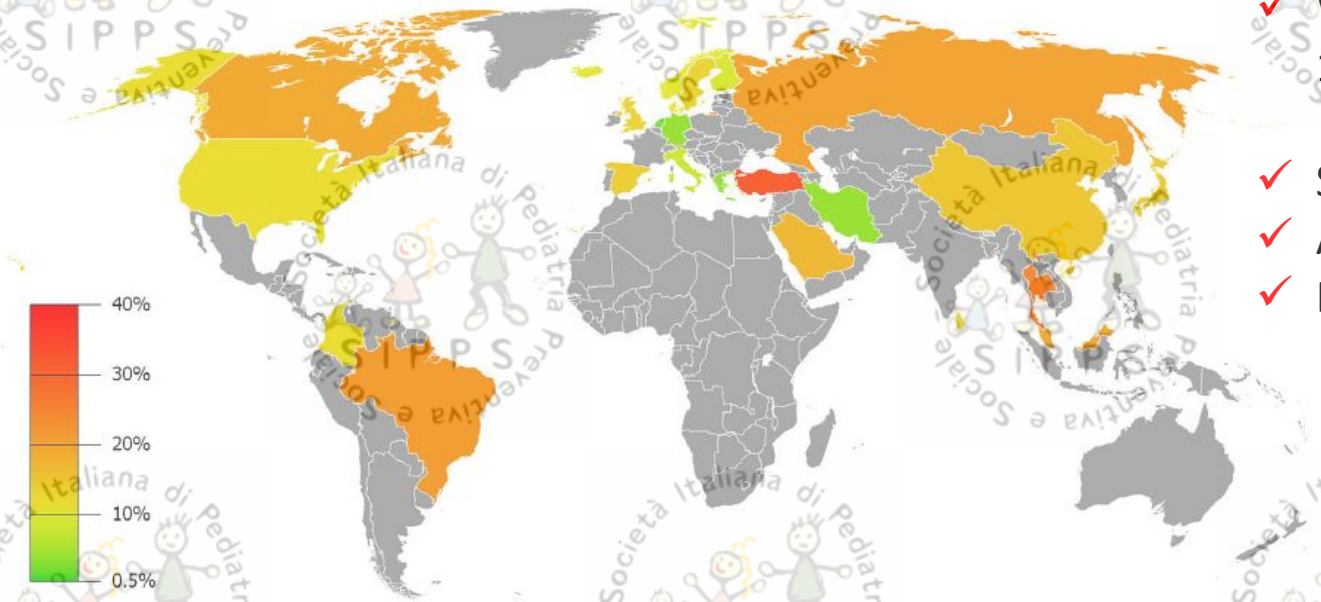


Rome III criteria emphasized that there should be "no evidence" for organic disease, which may have driven a focus on testing. Many patients received extensive and unnecessary evaluations to exclude organic disease.[3] We have now replaced the phrase "no evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms" with "after appropriate medical evaluation the symptoms cannot be attributed to another medical condition." This new statement permits selective or no testing to support a positive diagnosis rather than extensive testing to exclude many possible causes for the symptoms. Furthermore, it is important to emphasize that FGIDs can coexist with other medical conditions.

LA COSTELLAZIONE CLINICA DEI DISORDINI FUNZIONALI GASTRO-INTESTINALI

- *PREVALENZA*
- *COSTI*
- *QUALITA' DI VITA*

Epidemiology of Pediatric Functional Abdominal Pain Disorders: A Meta-Analysis



- ✓ Worldwide prevalence: 13.5%,
- ✓ South America 16.8%
- ✓ Asia 16.5%
- ✓ Europe 10.5%.

- ✓ A higher pooled prevalence was reported when using the Rome III criteria.
- ✓ Functional abdominal pain disorders are shown to occur significantly more in girls and is associated with the presence of anxiety and depressive disorders, stress and traumatic life events.

Korterink JJ et al. PLoS One. 2015 May 20;10(5):e0126982.

Prevalence of Functional Gastrointestinal Disorders in Infants and Toddlers

Table II. Percentages of subjects meeting Rome III criteria based on symptom reports by mothers

	Infants, <1 y of age	Toddlers, 1-3 y of age	Mother
Regurgitation	25.9%	N/A	N/A
Colic	5.9%	N/A	N/A
Dyschezia	2.4%	N/A	N/A
Functional constipation	4.7%	9.4%	8.6%
Functional diarrhea	2.4%	6.4%	8.3%
Cyclic vomiting syndrome	0.0%	3.4%	Not measured
Rumination	2.4%	1.9%	Not measured
Functional dyspepsia	N/A	N/A	10.9%
IBS	N/A	N/A	11.3%

- By Rome criteria, 27% of infants/toddlers qualified for FGIDs.

- Infant regurgitation was the most common disorder in infants and functional constipation in toddlers.

van Tilburg MA. J Pediatr 2015;166:684-9

Annual Costs of Care for Pediatric Irritable Bowel Syndrome, Functional Abdominal Pain, and Functional Abdominal Pain Syndrome

- Total annual costs per patient were estimated to be €2512.31.
- Inpatient and outpatient healthcare use were major cost drivers, accounting for 22.5% and 35.2% of total annual costs, respectively.
- Parental productivity loss accounted for 22.2% of total annual costs.
- No difference was found in total costs between children with IBS or FAP/FAPS.

CONCLUSIONS: Pediatric abdominal pain related functional gastrointestinal disorders impose a large economic burden on patients' families and healthcare systems. More than one-half of total annual costs of IBS and FAP/FAPS consist of inpatient and outpatient healthcare use.

Hoekman DR et al. J Pediatr. 2015 Nov;167(5):1103-8.e2

Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009

- From 1997 to 2009, the number of discharges with a FGID primary diagnosis increased slightly from 6,348,537 to 6,393,803.
- The total mean cost per discharge increased significantly from $6115 to $18,058 despite the length of stay remaining relatively stable.
- Constipation and abdominal pain were the most common FGID discharge diagnoses.

CONCLUSIONS & INFERENCES: Hospitalizations and associated costs in childhood FGIDs have increased in number and cost in the USA from 1997 to 2009

Park R et al. Neurogastroenterol Motil. 2015 May;27(5):684-92.

Health-Related Quality of Life in Pediatric Patients with Functional and Organic Gastrointestinal Diseases

- Patients with an FGID or organic GI disease demonstrated lower HRQOL than the healthy controls across all dimensions (physical, emotional, social, and school), with larger effect sizes for patients with an FGID.

- Patients with an FGID manifested lower HRQOL than those with an organic GI disease.

- Patients with an FGID or organic GI disease missed more school, spent more days in bed and needing care, had greater healthcare utilization, and had parents who missed more workdays with greater work impact, with larger effect sizes for the patients with an FGID.

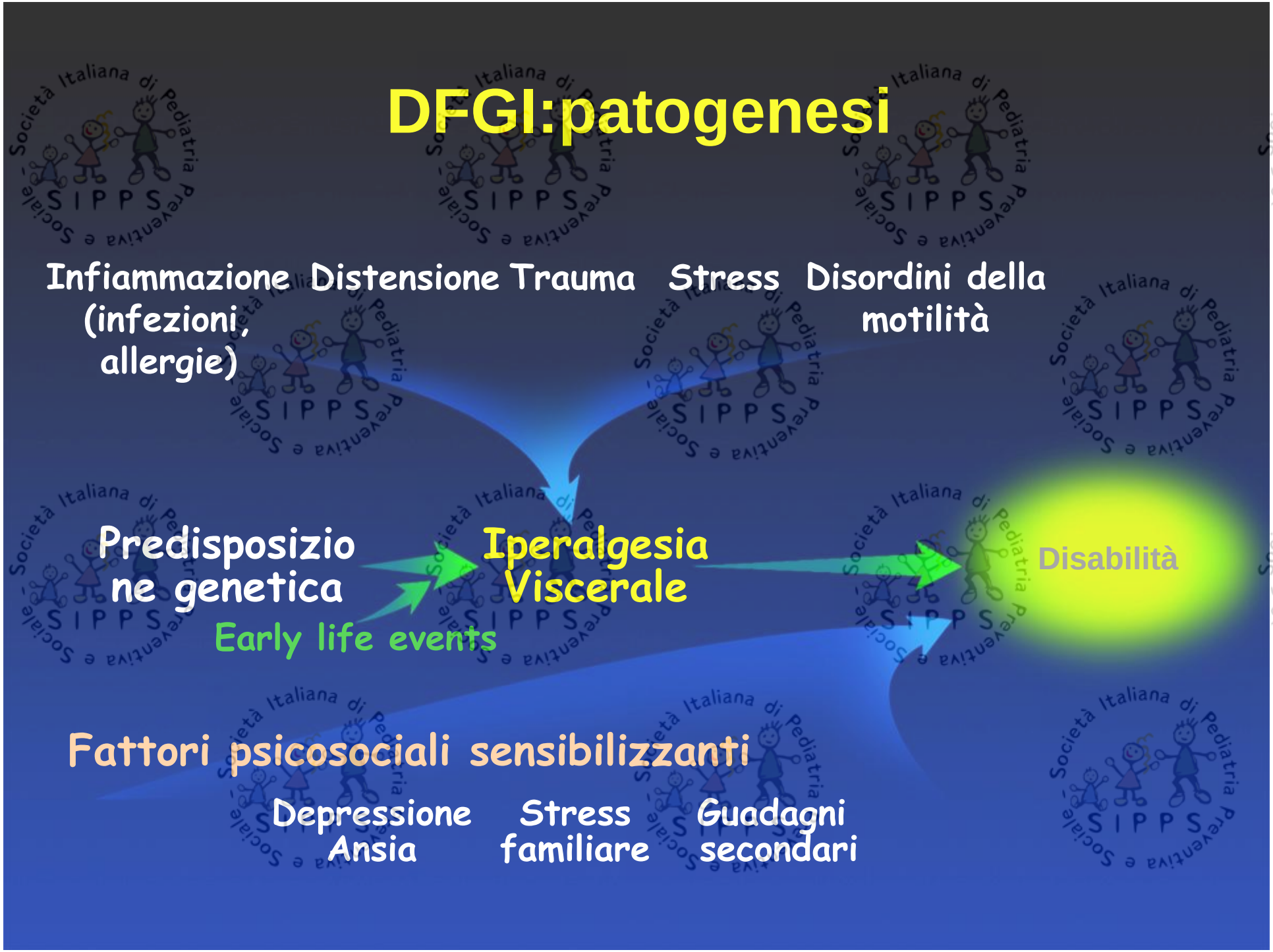
Conclusion: Patients with an FGID or organic GI disease demonstrate impaired HRQOL compared with healthy children. HRQOL can be used as a common metric to compare patient outcomes in clinical research and practice both within and across groups of patients with FGIDs and organic GI diseases.

Varni JW et al. J Pediatr 2015;166:85-90

LA COSTELLAZIONE CLINICA DEI DISORDINI FUNZIONALI GASTRO-INTESTINALI

- *PATOGENESI*
- *TERAPIA*

DFGI:patogenesi



Irritable bowel syndrome in childhood: visceral hypersensitivity and psychosocial aspects

Children with IBS had:

- Lower threshold for discomfort and higher cumulative perception score
- Higher emotional instability
- More sleep disturbance
- Higher anxiety
- Cumulative perception score was related to emotional instability

Iovino P et al. Neurogastroenterol Motil 2009;21:940-74

Post-Infectious Functional Gastrointestinal Disorders in Children

- Popolazione di studio: 4-17 anni, 44 con colture fecali positive per batteri, 44 controlli
- Batteri riscontrati: Salmonella 26, Campylobacter 13, Shigella 5
- Follow-up a 6 mesi: 16/44 di coloro che avevano le colture positive e 5/44 dei controlli riportavano dolori addominali ricorrenti ($p \leq 0.01$)
- 13/16 dei pazienti con coltura positiva e dolore addominale riportavano anche alterazioni dell'alvo associate ai dolori addominali, compatilibili con il fenotipo della sindrome del colon irritabile

Saps M et al. J Pediatr 2008;152:812-6

Postinfectious Functional Gastrointestinal Disorders in Children: A Multicenter Prospective Study

Table II. FGIDs diagnosed in exposed group within 1 month and 3 and 6 months after an acute diarrhea

	FGIDs within 1 month from acute diarrhea, exposed % (M, F)	FGIDs 3 months after acute diarrhea, exposed % (M, F)	FGIDs 6 months after acute diarrhea, exposed % (M, F)
Functional constipation	15.7% (3M, 2F)	25% (5M, 3F)	15.7% (2M, 3F)
IBS	6.3% (2M)	3.1% (1M)	9.4% (2M, 1F)
Nonretentive fecal incontinence	3.1% (1F)	3.1% (1F)	3.1% (1F)
Functional dyspepsia	3.1% (1F)	3.1% (1F)	3.1% (1F)
Functional abdominal pain	3.1% (1F)	12.5% (2M, 2F)	6.2% (1M, 1F)
Aerophagia + Functional constipation	3.1% (1M)	-	-
Abdominal migraine	-	3.1% (1M)	-
IBS + abdominal migraine	3.1% (1M)	-	-
Functional dyspepsia + Abdominal migraine	3.1% (1F)	-	-
Functional abdominal pain + Functional constipation	-	3.1% (1M)	6.2% (1M, 1F)
IBS + nonretentive fecal incontinence	-	-	3.1% (1M)

F, female; *M*, male.

- FGIDs were significantly more common in exposed patients compared with controls within 1 month from acute, 3 months, and 6 months later.
- Among exposed children, abdominal pain–related FGIDs were significantly more frequent compared with controls after 6 months from infection.

Conclusion **This prospective cohort multicenter study supports postinfectious FGIDs as a true entity in children. There seems to be a significant increase in abdominal pain–related FGIDs after acute diarrhea in children within 1 month and 3 and 6 months later.**

Pensabene L et al. J Pediatr 2015;166:903-7

"FAMILIAL AGGREGATION IN CHILDREN AFFECTED BY FUNCTIONAL GASTROINTESTINAL DISORDERS"

- Prevalence of FGIDs in
  - the group of parents of children with FGIDs: 64%
  - the group of parents of children without FGIDs: 30.7%

- Association between the children's type of GI disorder and their parents'disorder in 35/103 (33.9%)

- Anxiety was significally higher in the group of children with FGIDs (27.0%, vs 3, 8.3%)

Buonavolontà R. JPGN 2010; 50(5):500-505

“FAMILIAL AGGREGATION IN CHILDREN AFFECTED BY FUNCTIONAL GASTROINTESTINAL DISORDERS”

Having a mother with FGID was a stronger predictor (OR=3.5%) of FGID than having a father with FGIDs

Buonavolontà R. JPGN 2010; 50(5):500-505

Dyspeptic Symptoms in Children: The Result of a Constipation-Induced Cologastric Brake?

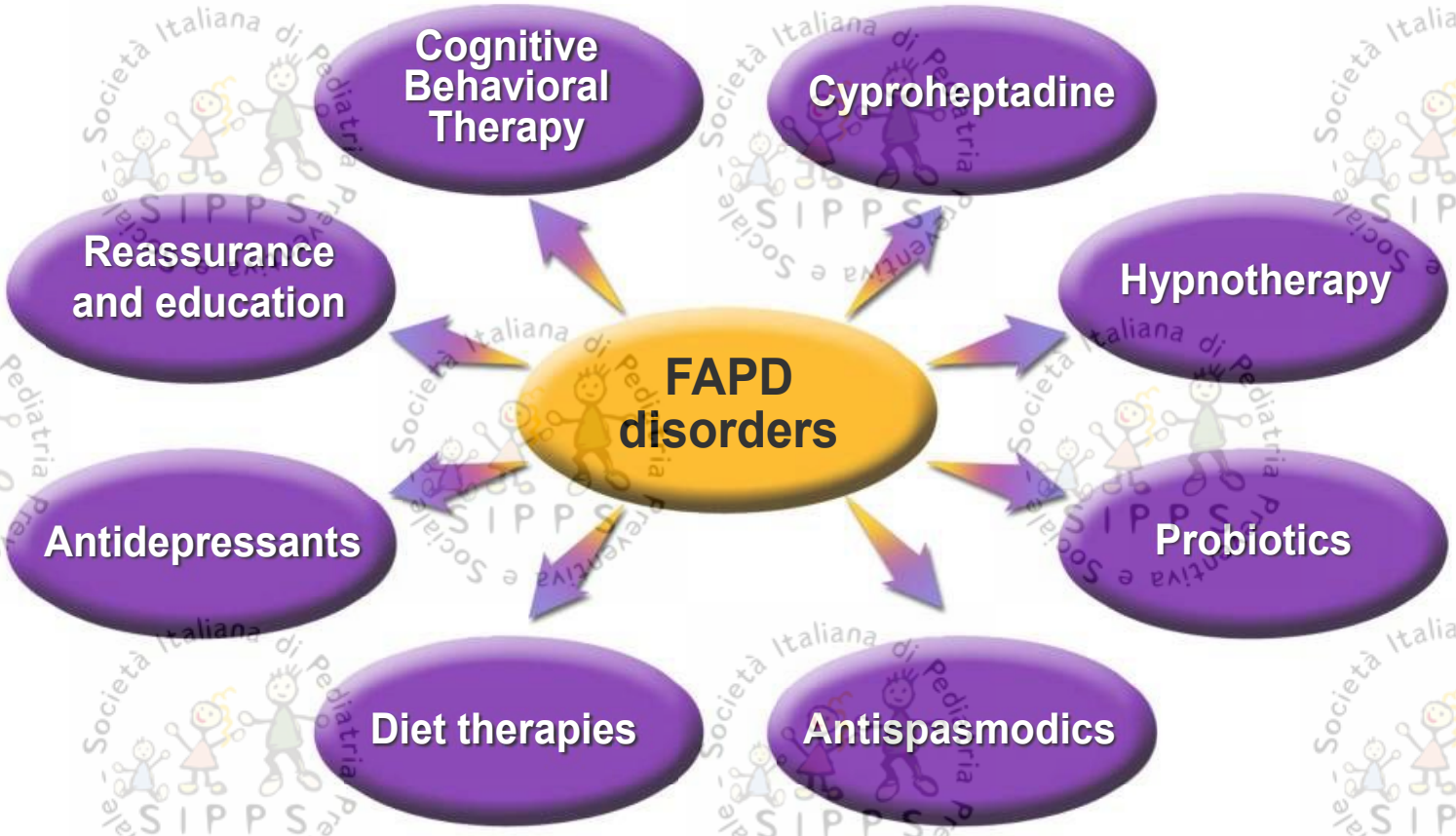
- **Sixty-six % (28/42) children with functional dyspepsia were affected by functional constipation associated with delayed gastric emptying**

- **Normalization of bowel habit improved gastric emptying as well as dyspeptic symptoms**

Boccia et al. Clinical Gastroenterol Hepatol 2008

DISORDINI FUNZIONALI GASTROINTESTINALI

Treatment Options



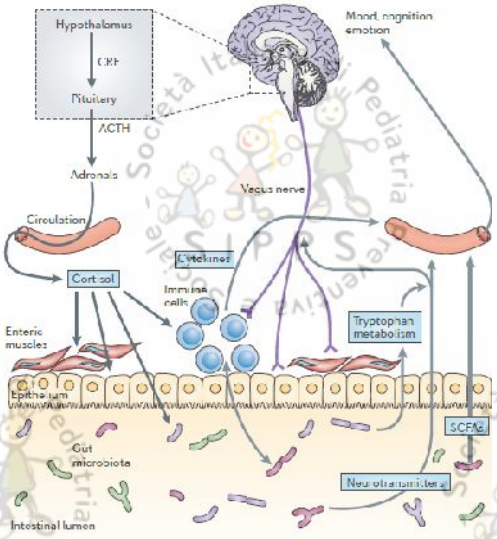
Nonpharmacologic Treatment of Functional Abdominal Pain Disorders: A Systematic Review

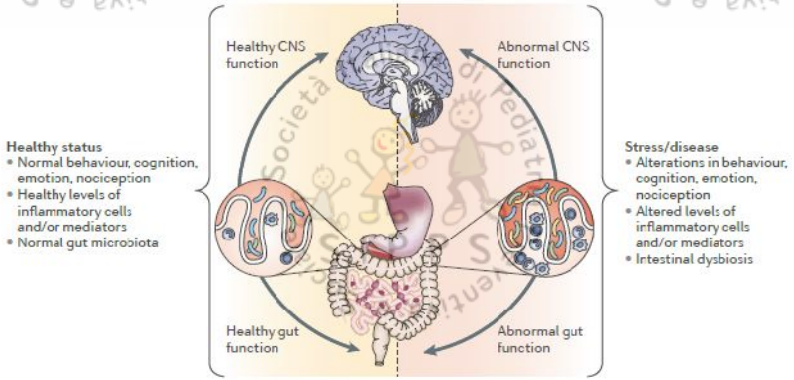
- Significant improvement of abdominal pain was reported after hypnotherapy compared with standard care/wait-list approaches and after cognitive behavioral therapy compared with a variety of control treatments/wait-list approaches.
- Compared with placebo, Lactobacillus rhamnosus GG (LGG) and VSL#3 were associated with significantly more treatment responders.
- Guar gum significantly improved irritable bowel syndrome symptom frequency; however, no effect was found for other fiber supplements or a lactose-free diet.
- Functional disability was not significantly decreased after yoga compared with a wait-list approach.
- No studies were found concerning lifestyle interventions; gluten-, histamine-, or carbonic acid– free diets; fl uid intake; or prebiotics.
- The quality of evidence was found to be very low to moderate.

CONCLUSIONS: Although high-quality studies are lacking, some evidence shows efficacy of hypnotherapy, cognitive behavioral therapy, and probiotics (LGG and VSL#3) in pediatric AP-FGIDs. Data on fi ber supplements are inconclusive.

Rutten JM et al. Pediatrics. 2015 Mar;135(3):522-35.

Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour



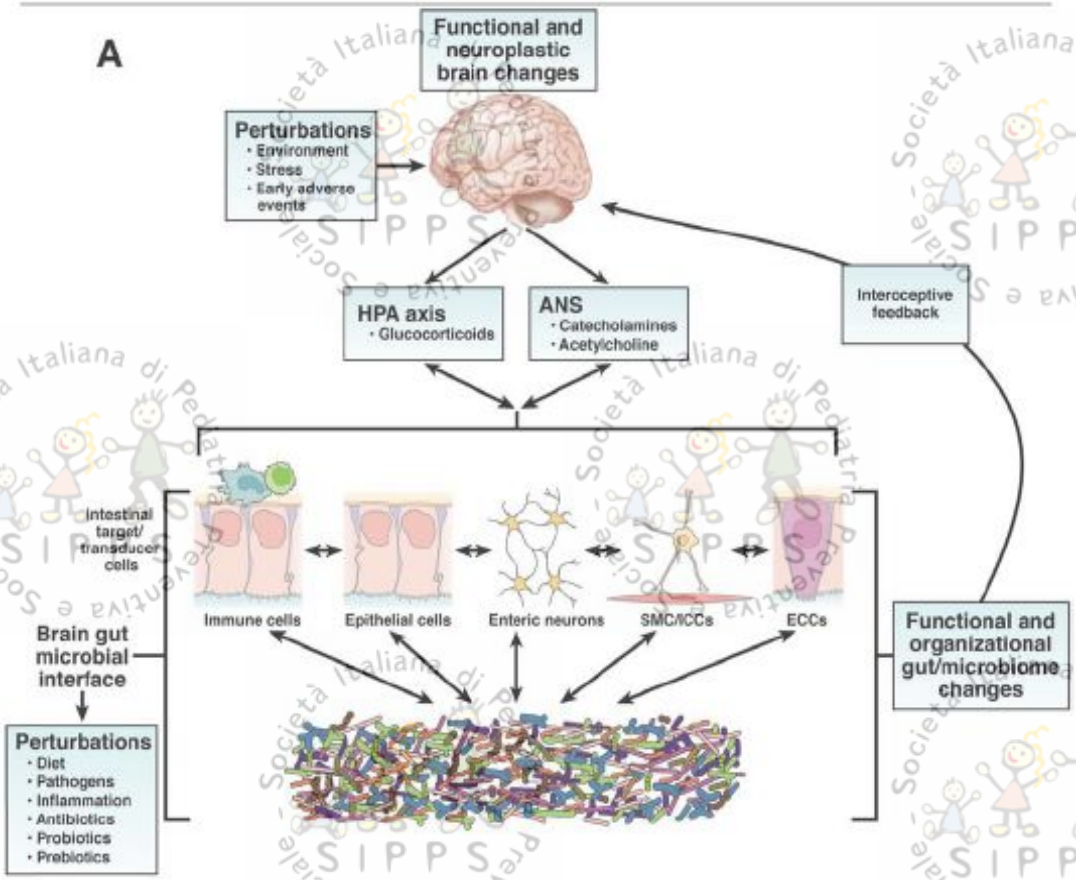


- The gut microbiota communicates with the CNS — possibly through neural, endocrine and immune pathways — and thereby influences brain function and behaviour.
- Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain.
- The emerging concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders, as well as for FGIDs.

Cryan JF et al. Nat Rev Neurosci 2012;13:701–12

Brain–Gut Microbiome Interactions and Functional Bowel Disorders

Bi-directional interactions between brain and gut

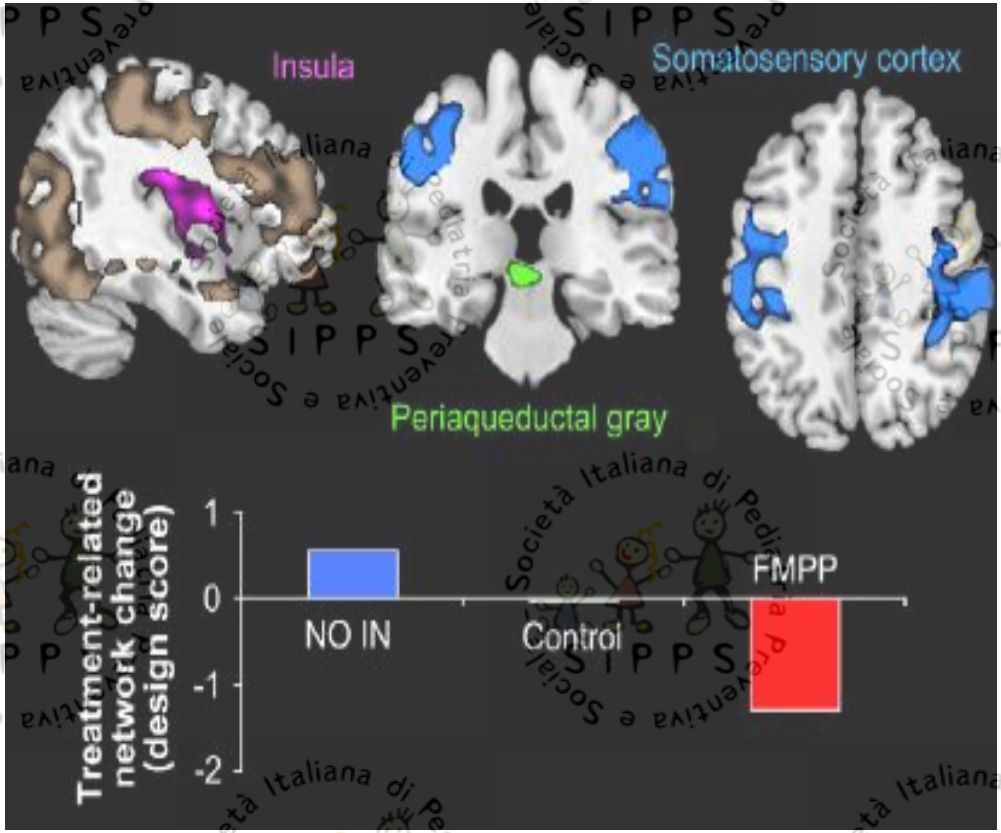


The microbiota is in constant bidirectional communication with this interface via multiple signaling pathways, and this communication is modulated in response to perturbations of the microbiota, or the brain.

The integrated output of the brain gut microbial interface is transmitted to the brain via multiple afferent signaling pathways, including endocrine and neurocrine (vagal, spinal afferents) pathways.

Mayer EA et al. Gastroenterology 2014;146:1500-12

Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity



A distributed network of brain regions showing decreases in the FMPP group during the emotional faces attention task is shown in the shaded regions.

Three regions of interest selected from the network for study in the resting state are highlighted in *pink (insula), green (periaqueductal* gray), and *blue (somatosensory regions). The change in* network strength with intervention is depicted graphically.

Tillisch K et al. GASTROENTEROLOGY 2013;144:1394–1401

Pharmacologic Treatment in Pediatric Functional Abdominal Pain Disorders: A Systematic Review

- 6 studies evaluating antispasmodic, antidepressant, antireflux, antihistaminic, and laxative agents.
- Overall quality of evidence was very low.
- Compared with placebo, some evidence was found for peppermint oil in improving symptoms and for cyproheptadine in reducing pain frequency.
- Compared with placebo, amitriptyline showed 15% improvement in overall quality of life score and famotidine only provides benefit in global symptom improvement.
- Polyethylene glycol with tegaserod significantly decreased pain intensity compared with polyethylene glycol only.
- No serious adverse effects were reported.
- No studies were found concerning antidiarrheal agents, antibiotics, pain medication, anti-emetics, or antimigraine agents.

CONCLUSIONS: Because of the lack of high-quality, placebo-controlled trials of pharmacologic treatment for pediatric AP-FGIDs, there is no evidence to support routine use of any pharmacologic therapy. Peppermint oil, cyproheptadine, and famotidine might be potential interventions, but well-designed randomized controlled trials are needed.

Korterink JJ et al. J Pediatr. 2015 Feb;166(2):424-31.e6.

Gut-directed hypnotherapy for functional abdominal pain or irritable bowel syndrome in children: a systematic review

- Three RCT comparing HT to a control treatment were included with sample sizes ranging from 22 to 52 children.
- Two studies examined HT performed by a therapist, one examined HT through selfexercises on audio CD.
- All trials showed statistically significantly greater improvement in abdominal pain scores among children receiving HT.
- One trial reported beneficial effects sustained after 1 year of follow-up.
- One trial reported statistically significant improvement in quality of life in the HT group.
- Two trials reported significant reductions in school absenteeism after HT.

Conclusions: Therapeutic effects of HT seem superior to standard medical care in children with FAP or IBS. It remains difficult to quantify exact benefits. The need for more high quality research is evident.

Rutten JMTM, et al. Arch Dis Child 2013;98:252–257.

Ruolo del Placebo nei Disordini Funzionali GI

- Nei bambini con disordine funzionale gastrointestinale dolore-correlato sono stati osservati tassi di successo per il placebo fino al 53%

- Un approccio di ascolto attivo e un atteggiamento incoraggiante verso la terapia aiuta a migliorare le risposte dei soggetti sia al trattamemto terapeutico che al placebo

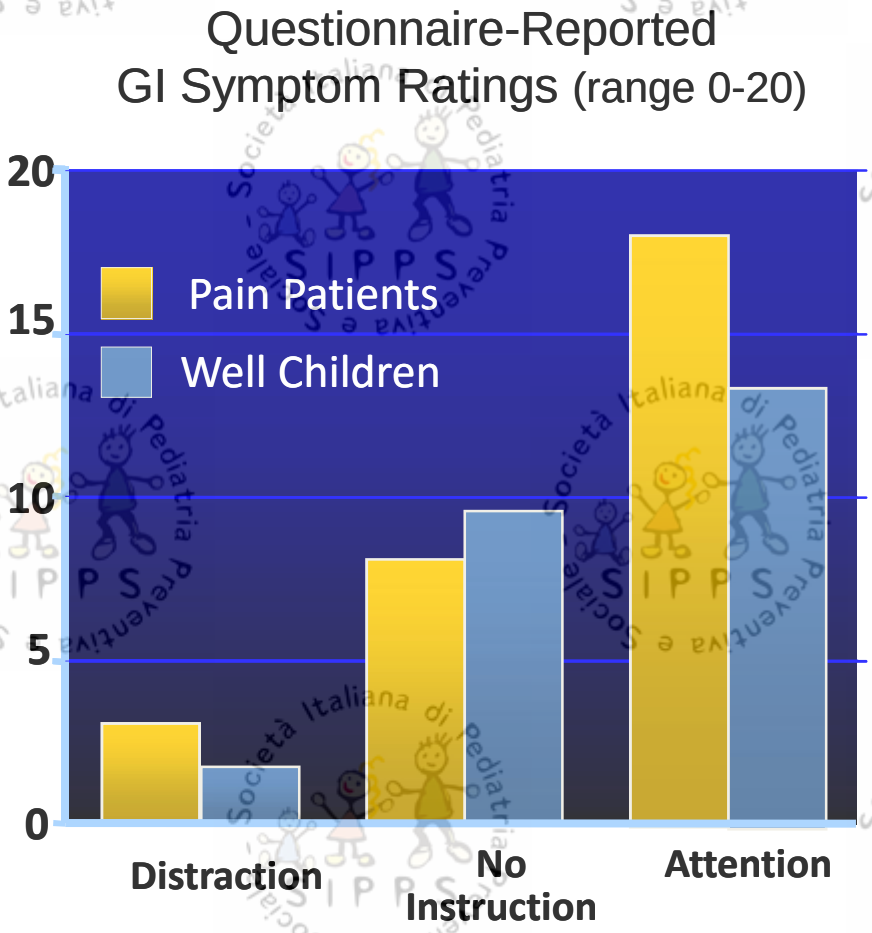
- Inoltre, l'alta risposta al placebo potrebbe essere spiegata dal naturale decorso della malattia o dalla fluttuazione dei sintomi.

Gastroenterology 2009;137: 1261-1269.
J Pediatr 2015; 166: 424–431

LA COSTELLAZIONE CLINICA DEI DISORDINI FUNZIONALI GASTRO-INTESTINALI

- Biopsychosocial Approach
- Familial Education: EXPLAIN!!!
  - Frequency
  - Organic vs Functional
  - Brain-gut interactions
- Pharmacological Therapy
- **Psychological Therapy**

Parent Attention vs. Distraction

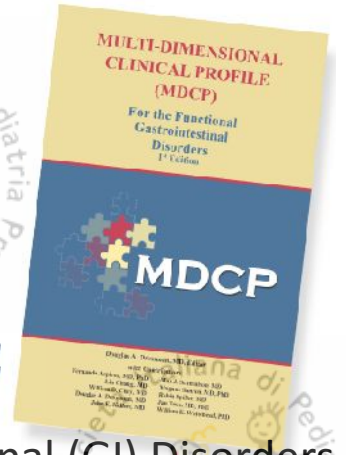


- **Pain induced by water load test**
- **Parents randomized to using distraction or attention in their interaction with children in pain**
- **All mothers felt distraction was inappropriate response to pain**

Walker LS et al. Pain 2006, 122: 43-52

Primer
to First Edition of

Multi-Dimensional Clinical Profile (MDCP)
For Functional Gastrointestinal Disorders



The Multi-Dimensional Clinical Profile (MDCP) for Functional Gastrointestinal (GI) Disorders was developed to capture the wide range of clinical features of patients with FGIDs and to present the information in a manner that is patient specific and consistent with the thinking of experts in the field.

Aim: To develop a multi-component assessment system for FGIDs that can be used to characterize the full dimensionality of the patient's illness state, and which will be applied in treatment planning and research. There are five dimensions:

- A. The categorical Rome diagnosis (Category A);
- B. Additional information that subclassifies the diagnosis leading to more specific treatments, e.g., IBS-D or IBS-C; sphincter of Oddi dysfunction (SOD) I or II; functional dyspepsia EPS; or PDS (Category B);
- C. The personal impact of the disorder on the patient (Category C);
- D. Psychosocial influences (Category D); and
- E. Physiological abnormalities or biomarkers (Category E).

MDCP: Functional nausea

A 14 year old girl reports daily nausea that is particularly severe upon awakening and often lasts until mid-morning for the past 4 months since school 9th grade started. She is unable to eat breakfast and will usually snack around 10 am and then is able to eat lunch and dinner. On the weekend when she sleeps late and arises around 10 am she has no nausea. She has lost 5 pounds over the past 6 months. There has been no abdominal pain, vomiting, diarrhea, or constipation. She states that she is anxious about her friendships and school performance and gets herself “all worked up” which worsens her nausea. She also has marked nausea before piano recitals. At least twice weekly she goes into school late because of the severity of her symptoms. The patient has seen a counselor in the past. The family could no longer afford the sessions and they were stopped. Both her mother and father have a history of anxiety and depression.

MDCP Categories

- A. Categorical diagnosis: Functional nausea
- B. Clinical modifier: weight loss
- C. Impact on daily activities: moderate, school tardiness
- D. Psychosocial modifier: anxiety
- E. Physiological modifier: n/a

MDCP: Functional nausea

Explanation of MDCP categories

A. **Categorical diagnosis**: As her symptoms are occurring on most weekdays for the past 4 months and her nausea is not associated with vomiting she meets Romve IV criteria for functional nausea.

B. **Clinical modifier:** The presence of weight loss is a significant clinical modifier as it documents the physiological impact of her nausea which has significantly impacted her nutritional status.

C. **Impact on daily activities:** The symptom is episodic and only on weekdays when she goes to school. It has caused her to be late to school on multiple occasions.

D. P**sychological modifier**: The patient has a long history of anxiety and has seen a counselor in the past. The family could no longer afford the sessions and they were stopped. Both her mother and father have a history of anxiety and depression.

E. **Physiological features and biomarkers**: none known

Overall assessment

This adolescent female has functional nausea with weight loss and a moderate impact on her daily activities. Her symptoms are clearly worsened by her anxiety.

Treatment plan

Engage psychologist to engage patient and family in discussion to elucidate the effect of anxiety on the continued symptoms. Consider cognitive behavioral therapy (CBT) as a primary therapeutic approach. Consider SSRI such as citalopram to address anxiety while CBT program is initiated to act as a bridge to improvement. Consult nutritionist to guide increased caloric intake during the latter part of the day to achieve adequate daily caloric needs.