Dr Risch

Il vostro laboratorio – oggi e domani

RISCH.CH

Sindrome dell’intestino Irritabile (IBS)
labMed Ticino
26.09.23

Dr.Risch SA

Mauro Imperiali

Agenda

- IBS
- Calprotectina
- IBD
- IBS vs IBD
- Celiachia

Definizione di sindrome dell'intestino irritabile (IBS)

ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD, FACG[1], Mark Pimentel, MD, FACG[2], Darren M. Brenner, MD, FACG[3], William D. Chey, MD, FACG[4], Laurie A. Keefer, PhD[5], Millie D. Long, MDMPH, FACG (GRADE Methodologist)[6] and Baha Moshiree, MD, MSc, FACG[7]

Irritable bowel syndrome (IBS) is a highly prevalent, chronic disorder that significantly reduces patients' quality of life. Advances in diagnostic testing and in therapeutic options for patients with IBS led to the development of this first-ever American College of Gastroenterology clinical guideline for the management of IBS using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Twenty-five clinically important questions were assessed after a comprehensive literature search; 9 questions focused on diagnostic testing; 16 questions focused on therapeutic options. Consensus was obtained using a modified Delphi approach, and based on GRADE methodology, we endorse the following: We suggest that a positive diagnostic strategy as compared to a diagnostic strategy of exclusion be used to improve time to initiating appropriate therapy. We suggest that serologic testing be performed to rule out celiac disease in patients with IBS and diarrhea symptoms. We suggest that fecal calprotectin be checked in patients with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. We recommend a limited trial of a low fermentable oligosaccharides, disacchardies, monosaccharides, polyols (FODMAP) diet in patients with IBS to improve global symptoms. We recommend the use of chloride channel activators and guanylate cyclase activators to treat global IBS with constipation symptoms. We recommend the use of rifaximin to treat global IBS with diarrhea symptoms. We suggest that gut-directed psychotherapy be used to treat global IBS symptoms. Additional statements and information regarding diagnostic strategies, specific drugs, doses, and duration of therapy can be found in the guideline.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B755.

Am J Gastroenterol 2021;116:17–44. https://doi.org/10.14309/ajg.0000000000001036; published online December 14, 2020

Definizione IBS

La sindrome dell’intestino irritabile é una sindrome gastrointestinale caratterizzata da dolore addominale cronico e disturbi intestinali

Solo una piccola parte di persone che ne soffre si sottopone all’attenzione di un medico

Si é evidenziato che circa il 40% delle persone che sono compatibili con la diagnostica di IBD NON hanno una diagnosi formale

Questa sindrome é legata a elevati costi sanitari e anche assenze dal lavoro

Negli US, circa 25-50% dei consulti gastroenterologici solo legati a IBS

Revisionato/Rivisto lug 2022

Eziologia | Sintomatologia | Diagnosi | Trattamento | Punti chiave | Per ulteriori informazioni

La sindrome dell'intestino irritabile è caratterizzata da fastidio o dolore addominale ricorrenti con almeno due delle seguenti caratteristiche: relazione alla defecazione, associazione con un cambiamento nella frequenza delle feci o associazione con un cambiamento nella consistenza delle feci. La causa è sconosciuta e la fisiopatologia non è completamente chiara. La diagnosi è clinica. Il trattamento è sintomatico e consiste in una modificazione del regime alimentare e nell'assunzione di farmaci, inclusi anticolinergici e agenti attivi sui recettori serotoninergici.

Anatomia dell'intestino

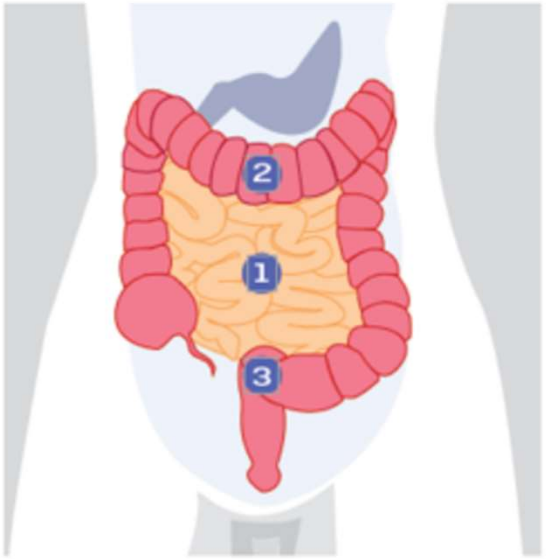
L’intestino si divide in due tratti: **intestino tenue (1) e intestino crasso. L'intestino crasso è a sua volta diviso in colon (2) e retto (3)**.

L'**intestino tenue** è lungo circa 7m e ha la funzione principale di terminare il processo di digestione cominciato dalla bocca e proseguito nello stomaco e di iniziare l’assorbimento dei nutrienti introdotti attraverso il cibo.

L’**intestino crasso** è lungo circa 1.5 m, il retto 15 cm, e ha la funzione principale di assorbire l’acqua e di consentire l’accumulo degli scarti alimentari che non possono essere digeriti.

La parete intestinale è costituita da diversi strati: quello più interno è la mucosa, rivestito da un sottile strato di sottomucosa e da robusti strati muscolari.

I tumori dell'intestino tenue sono estremamente rari. **La diagnosi precoce dei tumori intestinali si focalizza su colon e retto.**



Nozioni di fisiopatologia

- La fisiopatologia del IBS rimane ancora incerta
- tradizionalmente viene imputato un ruolo importante alla motilità intestinale e alla ipersensibilità viscerale
- Ad oggi sono emerse nuove evidenze che imputano all'infiammazione, all'alterazione della flora fecale e alla Bacterial overgrowth un ruolo importante
- viene anche considerato il ruolo della sensibilità alle derrate alimentare

Una componente genetica non può essere attualmente eclsusa

Motilità gastrointestinale

- In taluni pazienti viene associata un'anormalita nella motilità del tratto GI
  - Frequenza aumentata e irregolarità nella contrazione del lume
  - Transito prolungato nel caso di IBS con costipazione
  - Risposta motoria Esagerata in caso di assunzione di alimenti nel caso di IBS con diarrea

Ipersensitività viscerale

- Significato: percezione aumentata in risposta a stimoli di varia natura
- È il risultato della stimolazione di recettori diversi a livello della parete intestinale. Questi recettori trasmettono i segnali via neuroni afferenti direttamente al cervello
- Diversi studi mostrano una sensibilità aumentata a seguito di gonfiore e distensione intestinale

- Innervazione, rilascio di mediatori intestinali (serotoina, chinine) ipereccitabilità spinale (via NMDA receptors) può portare ad un'iperalgesia

«Infiammazione» intestinale

- Linfociti: aumento infiltrato linfatico. Queste cellule possono rilasciare mediatori (NO, hitamina, proteasi) capaci di stimolare il sistema nervoso intestinale. In modelli animali, é stato dimostrato che un trapianto fecale da pazienti con livelli elevati di serin-proteasi in topi normali, porta ad una aumento di permeabilità intestinale con dolori intestinali
- Mastociti: si nota un aumento che é correlato con il dolore cronico
- Citochine proinfiammatorie: diverse citochine proinfiammatorie sono aumentate ed inoltre é stato evidenziato che PBMC di pazienti con IBS producono piu TNF rispetto ai controlli sani

American Journal of Gastroenterology

Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2006.00654.x

CLINICAL REVIEWS CME

Postinfectious Irritable Bowel Syndrome—A Meta-Analysis

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OBJECTIVES: Irritable bowel syndrome (IBS) is a heterogeneous disorder affecting 12% of the population worldwide. Several studies identify IBS as a sequela of infectious gastroenteritis (IGE) with reported prevalence ranging from 4% to 31% and relative risk from 2.5 to 11.9. This meta-analysis was conducted to explore the differences between reported rates and provide a pooled estimate of risk for postinfectious irritable bowel syndrome (PI-IBS).

DATA SOURCES: Electronic databases (MEDLINE, OLDMEDLINE, EMBASE, Cochrane database of clinical trials) and pertinent reference lists (including other review articles).

REVIEW METHODS: Data were abstracted from included studies by two independent investigators; study quality, heterogeneity, and publication bias were assessed; sensitivity analysis was performed; and a summative effect estimate was calculated for risk of PI-IBS.

RESULTS: Eight studies were included for analysis and all reported elevated risk of IBS following IGE. Median prevalence of IBS in the IGE groups was 9.8% (IQR 4.0–13.3) and 1.2% in control groups (IQR 0.4–1.8) (sign-rank test, $p = 0.01$). The pooled odds ratio was 7.3 (95% CI, 4.7–11.1) without significant heterogeneity (χ^2 heterogeneity statistic, $p = 0.41$). Subgroup analysis revealed an association between PI-IBS risk and IGE definition used.

CONCLUSIONS: This study provides supporting evidence for PI-IBS as a sequela of IGE and a pooled risk estimate revealing a sevenfold increase in the odds of developing IBS following IGE. The results suggest that the long-term benefit of reduced PI-IBS may be gained from primary prevention of IGE.

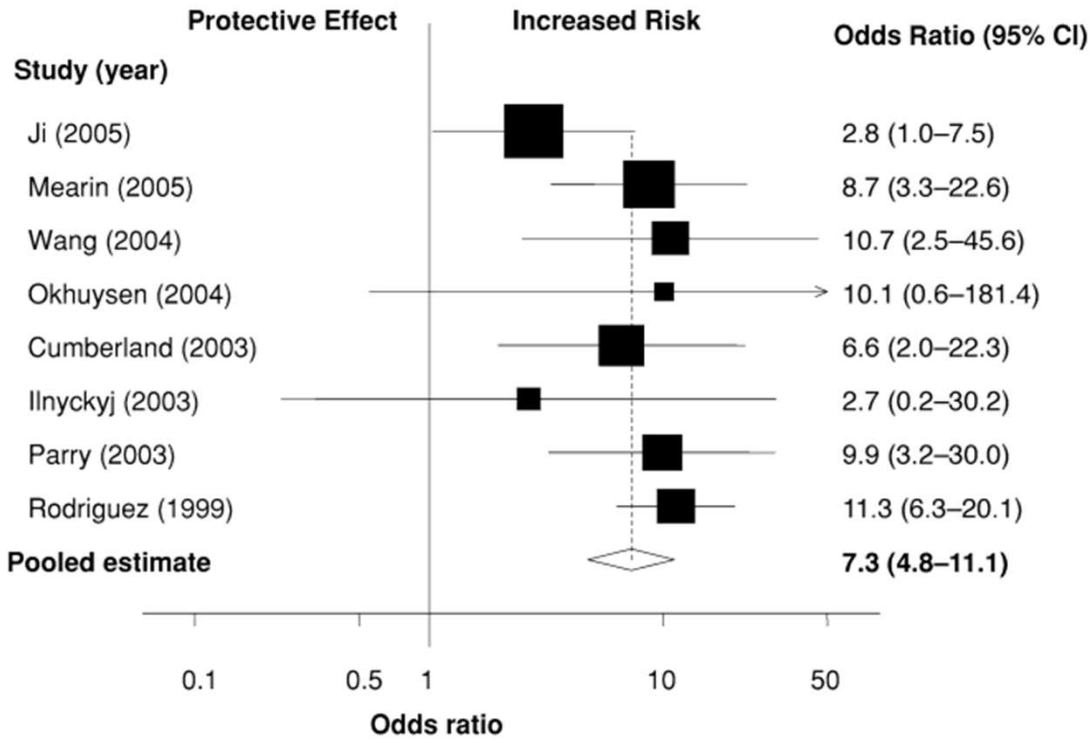
(Am J Gastroenterol 2006;101:1894–1899)

Post-infettivo con IGE si intende gastro-enterite intestinale (si veda abstract)

Table 1. Characteristics and Quality Scoring of Studies Included in Systematic Review (in Alphabetical Order)

Study	Year	Study Size	Follow-up (Months)	Location	Patient Type	Percent Male	Pathogen	IBS Diagnosis	Gastroenteritis Definition	Preexisting Excluded IBS	Mean Quality Score
Cumberland *et al.* (14)	2003	1,568	3	England	Mixed	–	Unspecified	Other	Self-report	No	5.5
Ilnyckyj *et al.* (15)	2003	109	3	Canada	Traveler	44	Unspecified	Rome I	Self-report	Yes	9.5
Ji *et al.* (16)	2005	203	12	Korea	Outbreak	31	*Shigella*	Rome II	Self-report	Yes	11
Mearin *et al.* (17)	2005	606	12	Spain	Outbreak	43	*Salmonella*	Rome II	Self-report	Yes	13.5
Okhuysen *et al.* (18)	2004	97	6	USA	Traveler	49	Unspecified	Rome II	Self-report	No	12
Parry *et al.* (19)	2003	314	6	England	Mixed	–	Bacterial NOS	Other	Clinic/lab	Yes	14.5
Rodriguez and Ruigomez (20)	1999	584,626	12	England	Mixed	52	Bacterial NOS	Other	Clinic/lab	Yes	6
Wang *et al.* (21)	2004	538	9	China	Mixed	50	Unspecified	Rome II	Clinic/lab	Yes	9

NOS = not otherwise specified.



* size of boxes denotes inverse-variance weight of each study

Figure 2. Forest plot of the odds of PI-IBS among included study with pooled estimate of risk.

Incidence and Epidemiology of Irritable Bowel Syndrome After a Large Waterborne Outbreak of Bacterial Dysentery

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[*]Department of Medicine, Division of Gastroenterology, and [†]Intestinal Diseases Research Program, [§]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada; [‖]Department of Medicine, Division of Nephrology, [¶]Department of Clinical Epidemiology and Biostatistics, [#]Department of Pediatrics, University of Western Ontario, London, Ontario, Canada

See CME Quiz on page 660.

Background & Aims: **Postinfectious irritable bowel syndrome (PI-IBS) is a common clinical phenomenon. To better define its incidence and epidemiology, a large cohort study was initiated after the contamination of a municipal water supply led to a large outbreak of acute *Escherichia coli* 0157:H7 and *Campylobacter jejuni* gastroenteritis.** ***Methods:*** **Local residents were invited to undergo structured assessments at research clinics established 2 years after the outbreak. Permanent adult residents with no prior history of inflammatory bowel disease or IBS were eligible. Standardized questionnaires defined past and current health. The cohort was divided into controls without gastroenteritis, subjects with clinically suspected gastroenteritis, and subjects with only self-reported gastroenteritis that could not be substantiated by another source. A modified Bowel Disease Questionnaire identified IBS according to Rome criteria. The incidence and epidemiology of PI-IBS was characterized. Risk factors were assessed using multiple logistic regression.** ***Results:*** **There were 2069 eligible study participants. Rome I criteria were met by 71 of 701 controls (10.1%) vs 249 of 904 subjects with self-reported gastroenteritis (27.5%) and 168 of 464 subjects with clinically suspected gastroenteritis (36.2%) (all comparisons, $P < 001$). Independent risk factors for PI-IBS included younger age, female sex, bloody stools, abdominal cramps, weight loss, and prolonged diarrhea. PI-IBS was more likely than sporadic IBS to show diarrhea-predominant features.** ***Conclusions:*** **PI-IBS is common after gastroenteritis from water contamination and often is diarrhea-predominant. Characteristics of the acute illness identify patients at increased risk for PI-IBS.**

ing pathogen.[1–8] This common clinical phenomenon of postinfectious irritable bowel syndrome (PI-IBS) was first described more than 5 decades ago.[9] However, its pathogenesis remains poorly understood and no specific therapy has been identified.

For the most part, previous studies of the epidemiology of PI-IBS have assessed relatively small population cohorts with limited power to define risks and factors that modify the effect.[1–8] To access larger populations, researchers have relied on large databases with inherent limitations.[10] Furthermore, only a few studies have assessed the long-term natural history of PI-IBS.[11]

Walkerton is a small rural town in Ontario, Canada. In May 2000, heavy rainfall washed livestock fecal residue from nearby farms into inadequately chlorinated drinking water supplied from a shallow well.[12] Contamination of the regional water supply with *Escherichia coli* 0157:H7, *Campylobacter jejuni*, and other pathogens led to a large outbreak of acute bacterial gastroenteritis that affected at least 2300 local residents, with 27 recognized cases of the hemolytic uremic syndrome and 7 deaths.[12,13] Since then, many residents have described continued abdominal discomfort and altered bowel habit. A large cohort study was undertaken in this population to define the nature and epidemiology of PI-IBS.

Materials and Methods

The Walkerton Health Study (WHS) was initiated 2 years after the outbreak to study the epidemiology and long-term health outcomes of the municipal water contamination that occurred in May 2000, and to facilitate local residents' access to specialty clinical care. Some details of its methodology have been reported elsewhere.[14–16] The WHS is directed

Post-infettivo: possibili cause, fattori di rischio

- Malassorbimento: Malassorbimento idiopatico degli acidi biliari che porta a steatorrea cosi come a malassorbimento die nutrienti (es vitamine)

- Aumento del numero di cellule/linfociti che possono produrre serotonina aumentando la motilità intestinale cosi come la ipersensitività

- Uso di antibiotici

Medline ® Abstract for Reference 62 of 'Pathophysiology of irritable bowel syndrome'

62 PubMed

TI Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome.

AU Nobaek S, Johansson ML, Molin G, AhrnéS, Jeppsson B

SO Am J Gastroenterol. 2000;95(5):1231.

OBJECTIVE: The influence of the gastrointestinal (GI) microflora in patients with irritable bowel syndrome (IBS) has not been clearly elucidated. This study was undertaken to see if patients with IBS have an imbalance in their normal colonic flora, as some bacterial taxa are more prone to gas production than others. We also wanted to study whether the flora could be altered by exogenous supplementation. In a previous study we have characterized the mucosa-associated lactobacilli in healthy individuals and found some strains with good colonizing ability. Upon colonization, they seemed to reduce gas formation.

METHODS: The study comprised 60 patients with IBS and a normal colonoscopy or barium enema. Patients fulfilling the Rome criteria, without a history of malabsorption, and with normal blood tests underwent a sigmoidoscopy with biopsy. They were randomized into two groups, one receiving 400 ml per day of a rose-hip drink containing 5 x 10(7) cfu/ml of Lactobacillus plantarum (DSM 9843) and 0.009 g/ml oat flour, and the other group receiving a plain rose-hip drink, comparable in color, texture, and taste. The administration lasted for 4 wk. The patients recorded their own GI function, starting 2 wk before the study and continuing throughout the study period. Twelve months after the end of the study all patients were asked to complete the same questionnaire regarding their symptomatology as at the start of the study.

RESULTS: All patients tolerated the products well. The patients receiving Lb. plantarum had these bacteria on rectal biopsies. There were no major changes of Enterobacteriaceae in either group, before or after the study, but the Enterococci increased in the placebo group and remained unchanged in the test group. Flatulence was rapidly and significantly reduced in the test group compared with the placebo group (number of days with abundant gas production, test group 6.5 before, 3.1 after vs 7.4 before and 5.6 after for the placebo group). Abdominal pain was reduced in both groups. At the 12-month follow-up, patients in the test group maintained a better overall GI function than control patients. There was no difference between the groups regarding bloating. Fifty-nine percent of the test group patients had a continuous intake of fermented products, whereas the corresponding figure for the control patients was 73%.

CONCLUSIONS: The results of the study indicate that the administration of Lb. plantarum with known probiotic properties decreased pain and flatulence in patients with IBS. The fiber content of the test solution was minimal and it is unlikely that the fiber content could have had any effect. This type of probiotic therapy warrants further studies in IBS patients.

AD Department of Surgery, Lund University, Lund University Hospital, Sweden.

PMID 10811333

Bacterial overgrowth (SIBO)

- I Dati tra una possibile associazione tra SIBO e IBS non sono ancora del tutto chiari

Food Sensitivity

- Allergia alimentare (IgE)
- Processi infiammatori legati agli alimenti (IgG)
- Malassorbimento die carboidrati (Fruttosio, lattosio..)
- Senbilità al glutine

Genetica

Familial studies and studies on select gene polymorphisms suggest a genetic susceptibility in some patients with irritable bowel syndrome (IBS).

Familial studies suggest a modest contribution of genetics to the development of IBS [91]. Data from studies of twins are contradictory; some studies show a higher concordance rate for IBS in monozygotic twins compared with dizygotic twins [92-95], with concordance rates for IBS in monozygotic twins ranging from 2 to 22 percent and rates in dizygotic twins ranging from 1 to 9 percent. However, in a study of 5032 twins (888 monozygotic pairs and 982 dizygotic pairs) the concordance rate did not significantly differ between monozygotic and dizygotic twins (17 versus 16 percent) [96]. In addition, one study found that having a parent with IBS was a greater independent predictor of IBS than having an affected twin, suggesting that the familial nature of IBS could be due to social learning, as well as genetics [92].

Associations between specific genes and IBS are under investigation. Some genotyping studies have shown an association between IBS and polymorphisms in the serotonin transporter gene, resulting in altered serotonin reuptake efficacy that affects intestinal peristalsis [97,98]. However, other studies have not confirmed an association of serotonin transporter gene polymorphisms and IBS [99,100]. Another study suggested that some patients with IBS may be genetically predisposed to an altered pattern of anti-inflammatory cytokine interleukin production [101].

Psicosociale e IBD

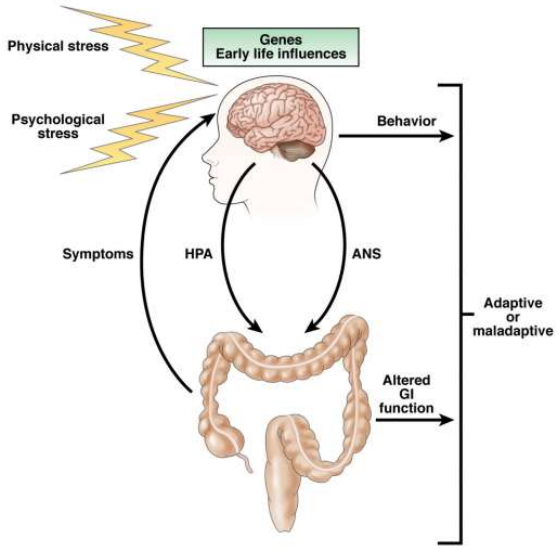

Figure 1. Physiologic and pathologic responses to stress
An adult's resilience or vulnerability to stress can be determined by genetic inherence and early life experiences. Activation of the central stress response sets in motion the HPA axis, ANS and other adaptive systems. Stress-induced changes in GI function occur and these can in turn result in perceived symptoms of IBS. (Adapted from Lightman, 2008[84])

Published in final edited form as:
Gastroenterology. 2011 March ; 140(3): 761–765. doi:10.1053/j.gastro.2011.01.032.

The Role of Stress on Physiological Responses and Clinical Symptoms in Irritable Bowel Syndrome

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Abstract

Studies support the concept that irritable bowel syndrome (IBS) is a biopsychosocial disorder that can be explained by a neurobiological model which postulates stress-induced alterations in central stress and arousal circuits and activation of parallel motor outputs from brain regions that can affect bodily function and behavior. Sustained stress can result in chronic overactivity or underactivity of allostatic (or adaptive) systems, including the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, metabolic, and immune systems, can occur. Animal and human studies have demonstrated that chronic or sustained stress is associated with the onset and exacerbation of symptoms of IBS. Chronic stress is also an independent predictor of developing post-infectious IBS. IBS patients specifically show stress-induced alterations in gastrointestinal motility, rectal perception, autonomic tone and HPA axis responses, although these findings are not entirely consistent among studies. This can be in part due to differences in study methodology or to various factors that can affect these physiologic responses. A greater recognition and understanding of the effects of stress in IBS may help identify targets for future drug development and also help guide more effective management of IBS symptoms.

Keywords

irritable bowel syndrome; stress; early adverse life events; corticotropin-releasing factor; hypothalamic-pituitary-adrenal (HPA) axis; cortisol; autonomic nervous system

Introduction

Stressors can be acute or chronic and range from daily hassles to life-threatening situations, such as natural disasters and violence that trigger the "fight or flight" response. Over time, chronic or recurrent stress results in an increase demand on physiologic systems. The wear and tear on the body, termed "allostatic load," set in motion long-term behavioral patterns, physiological reactivity, and other changes in the body that can lead to disease and health-damaging behaviors.[1] Chronic overactivity or underactivity of allostatic (or adaptive) systems can occur.[2] Allostatic systems include the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and cardiovascular, metabolic, and immune systems. Allostatic load clinically manifests as undue fatigue, irritability, and feelings of

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Psychosocial risk markers for new onset irritable bowel syndrome – Results of a large prospective population-based study

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Received 2007 Mar 22; Revised 2007 Aug 14; Accepted 2007 Aug 21.

Abstract

Irritable bowel syndrome (IBS) affects up to 22% of the general population. Its aetiology remains unclear. Previously reported cross-sectional associations with psychological distress and depression are not fully understood. We hypothesised that psychosocial factors, particularly those associated with somatisation, would act as risk markers for the onset of IBS. We conducted a community-based prospective study of subjects, aged 25–65 years, randomly selected from the registers of three primary care practices. Responses to a detailed questionnaire allowed subjects' IBS status to be classified using a modified version of the Rome II criteria. The questionnaire also included validated psychosocial instruments. Subjects free of IBS at baseline and eligible for follow-up 15 months later formed the cohort for this analysis (n = 3732). An adjusted participation rate of 71% (n = 2456) was achieved at follow-up. 3.5% (n = 86) of subjects developed IBS. After adjustment for age, gender and baseline abdominal pain status, high levels of illness behaviour (odds ratio (OR) = 5.2; 95% confidence interval (95% CI) 2.5–11.0), anxiety (OR = 2.0; 95% CI 0.98–4.1), sleep problems (OR = 1.6; 95% CI 0.8–3.2), and somatic symptoms (OR = 1.6; 95% CI 0.8–2.9) were found to be independent predictors of IBS onset. This study has demonstrated that psychosocial factors indicative of the process of somatisation are independent risk markers for the development of IBS in a group of subjects previously free of IBS. Similar relationships are observed in other "functional" disorders, further supporting the hypothesis that they have similar aetiologies.

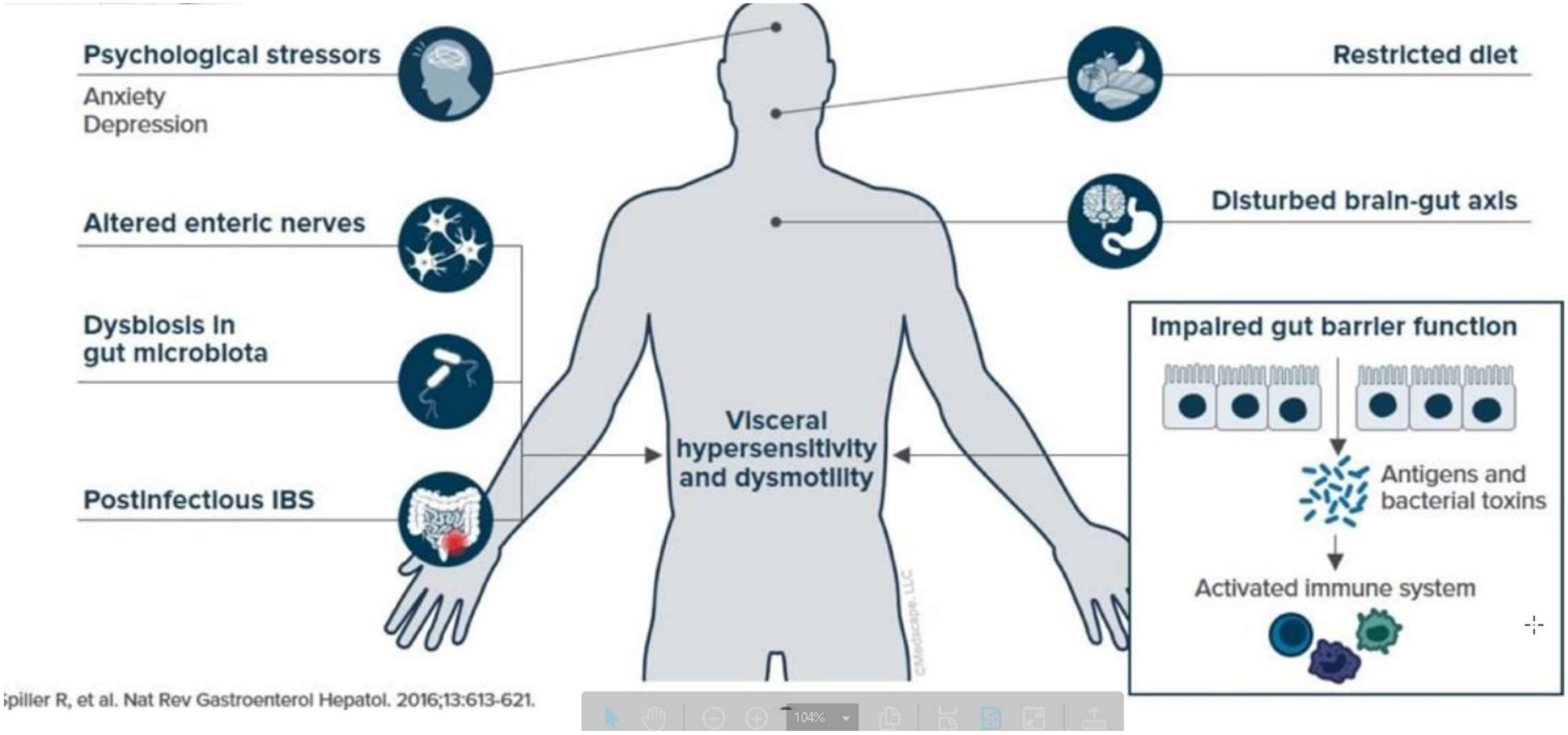
Psicosociale vs. IBS

Table 1

Summary of stress -induced physiologic changes in IBS

Function	Findings in IBS vs. controls
GI motility	Suppressed antral and small bowel motor activity and enhanced colonic motor activity
Visceral perception	Decreased rectal non-painful and pain thresholds to distension and electrostimulation during psychological stress in IBS but not in controls Higher stress, anxiety and anger ratings higher in IBS vs. controls
Intestinal permeability and secretion	Increased small intestinal and colonic permeability demonstrated in IBS but not measured in response to stress Net water flux was significantly lower in healthy women with moderate stress compared to those with low stress. Chloride secretion was lower and albumin was higher in moderate stress vs. low stress but not statistically significant
Autonomic tone	Increases in blood pressure and heart rate and shift to lower cardiosympathetic/vagal balance after mental stress in IBS and controls but no group differences
HPA axis	Increased basal levels of cortisol in IBS vs. controls Two studies show increased HPA axis response and one shows blunted response to hormone stimulation in IBS vs. controls Most studies report lack of a response to a meal and/or mental stressor in IBS HPA axis response varies depending on the type of physical stressor

IBS: sommario di patofisiologia



Spiller R, et al. Nat Rev Gastroenterol Hepatol. 2016;13:613-621.

Caso Clinico – I- costipazione da 4 anni

- Pz di 27 anni
- BMI normale
- Nessuna gravidanza
- Nessuna terapia medicamentosa
- Nessun parente con malattie intestinali
- Studentessa PhD
- Pasti irregolari, poco sport
- Nega uso di tabacco
- 2-4 Oh/mese
- I sintomi con il tempo peggiorano limitando la sua capacità lavorativa➔ si reca dal medico

Caso Clinico – I- costipazione da 4 anni

- Feci dure ogni 2-4 giorni
- Dolore addominale generalizzato
- I sintomi migliorano dopo l’evaquazione
- Flatulenza
- Scala di Bristol 1-2

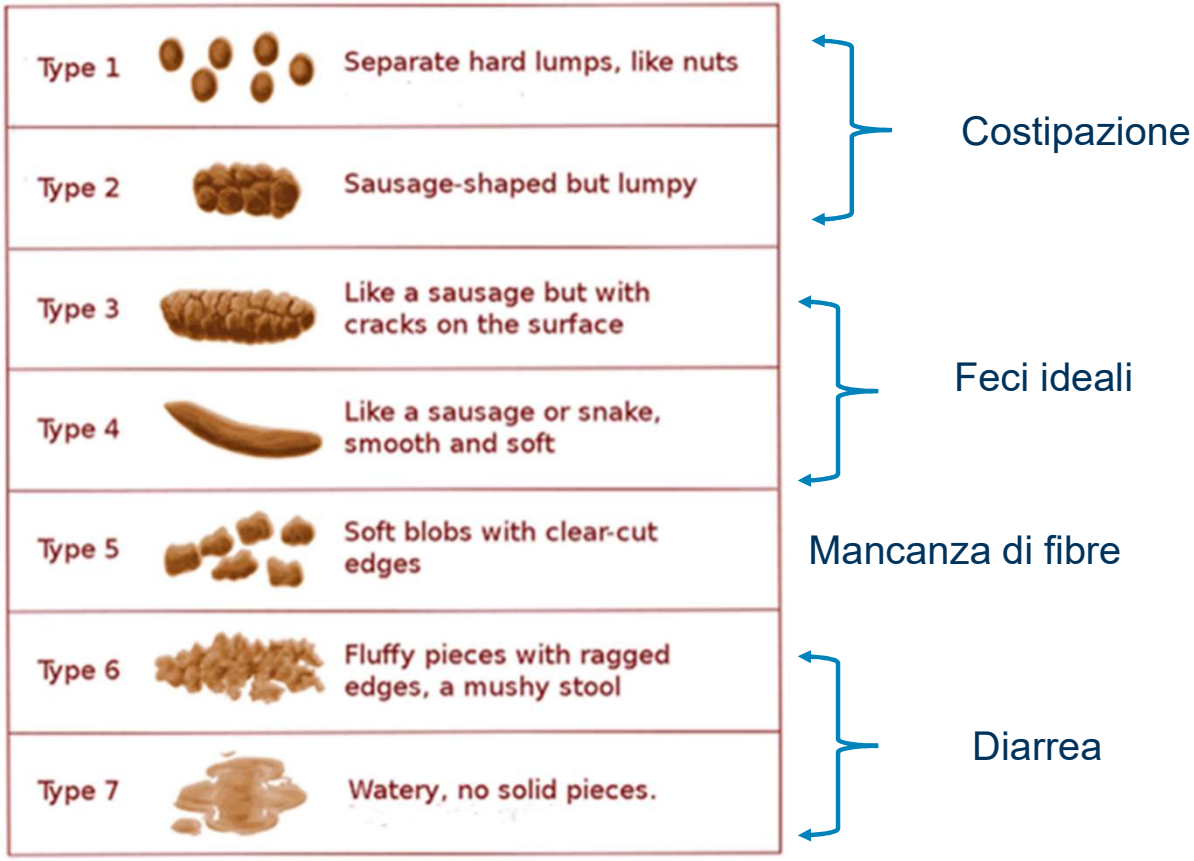


Figure 1. Bristol Stool Form Scale. Copyright 2000 © by Rome Foundation. All Rights Reserved.

form and consistency. The relevance of this scale is that it shows the patient drawings illustrating stool shapes together with precise descriptions regarding form and consistency, and using easily recognizable examples (for instance, in type 1, by a color illustration of feces as separate balls, a legend explains: "Hard, separate balls. Like nuts"). The patient has only to select the type that, according to the drawing and description, more closely resembles his or her own stools. The scale is structured from 1 to 7 according to form and consistency, from the hardest (type 1) to the fluid kind (type 7). The method used for scale validation is difficult to assess, as findings were only reported as an abstract (3).

Bristol has been home to the one study analyzing stool form and consistency in the general population (838 males and 1059 females) (4). This study shows that type 4 ("smooth, soft, long, sausage-like feces") is most common (for both genders), whereas hard stools (types 1 and 2) predominate in women (25.3 *vs*. 17.1% in males), and soft-fluid stools (types 5 and 6) are more common in males (11,9 *vs*. 8%). In addition, a majority of the population reports that defecation is normal (with no urgency or effort or rectal tenesmus) for type-3 and type-4 feces, while mushy, fluid stools are associated with defecatory urgency in 80% of cases.

This scale has shown that fecal shape correlates to total bowel transit time as measured with scintigraphy or radio-opaque markers (3,5-7), both in patients with irritable bowel syndrome (6) and healthy subjects (5,7); thus, types 1, 2 and 3 correlate with a slow transit, and types 6 and 7 correlate with a fast transit. In 1997 Lewis and Heaton (8) demonstrated in healthy volunteers a significant correlation between Bristol scale values and bowel transit time, both under baseline conditions and after laxative or constipative drug administration; that is, the Bristol scale was highly sensitive to drug-induced bowel transit changes. From the results of these studies Haeton et al. (6) concluded that the Bristol scale was a very useful tool for clinical practice, epidemiological studies, and clinical trials, as it easily and with no radiation allowed to rapidly differentiate individuals with a fast transit time (loose stools) from those with a slow transit time (hard stools).

	Normal colonic transit (n = 1662)	Slow colonic transit (n = 411)	Fast colonic transit (n = 197)
Age (mean ± s.d.; years)	62 ± 12	63 ± 13	61 ± 12
Male gender (%)	50	38	43
BMI (mean ± s.d.)	29.6 ± 7.5	28.2 ± 6.8	32.5 ± 9.9
SSC score (mean ± s.d.)	1.6 ± 0.50	1.7 ± 0.53	1.8 ± 0.57
Smoking (%)	8	7	12
Alcohol (%)	45	48	41
Marital status			
Married (%)	80	77	76
Education level			
Less than high school (%)	5	5	7
High school/some college (%)	53	52	58
College graduate or higher (%)	41	42	36
Cholecystectomy (%)	11	12	19
Appendectomy (%)	28	31	35
Family history			
Stomach cancer (%)	12	11	15
Bowel cancer (%)	16	14	15
Birth control pill (% of females)	3	5	3

BMI, body mass index; SSC, Somatic Symptom Checklist.

Table 2. Distributions of risk factors by the three colonic transit subgroups based on stool form assessment

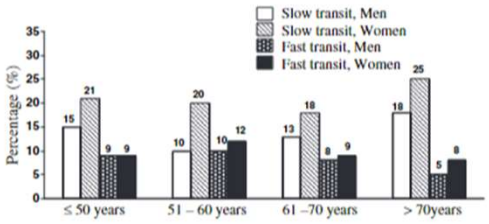


Figure 1. Proportions of slow and fast colonic transit group by age and gender, among a random sample of residents in Olmsted County, MN (n = 2268).

In the multiple variable analysis (considering age, gender, BMI, SSC score, smoking history, alcohol use, marital status, educational level, family history of stomach and, separately, colon cancer, history of appendectomy and history of cholecystectomy), the backward elimination approach identified the significant predictors for slow or fast colonic transit shown in Table 5. Significantly increased odds for fast colonic transit compared to normal colonic transit were observed with increasing BMI, increasing SSC score and a history of cholecystectomy. There were significantly decreased odds for fast colonic transit with increasing age. A significantly increased odds for slow

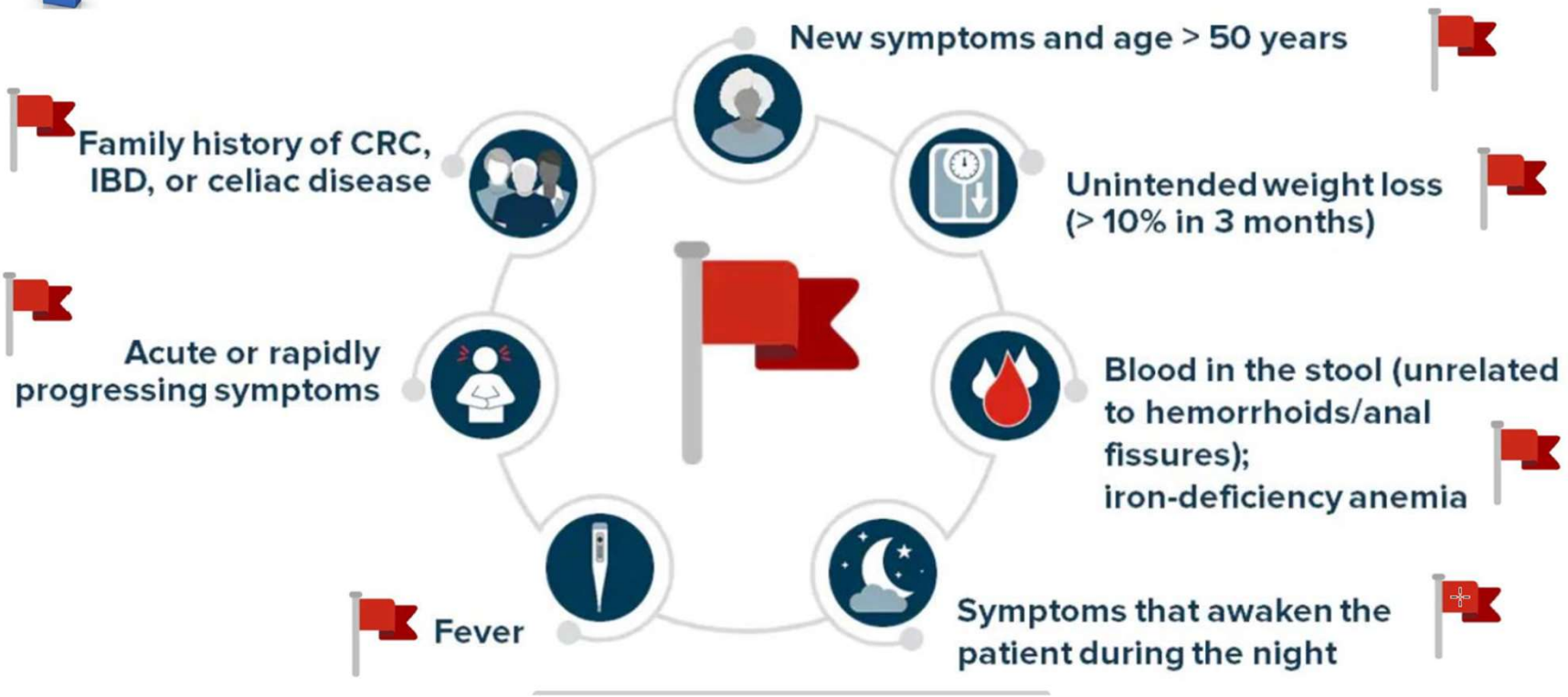
Diagnosi differenziale della costipazione

- IBS
- Costipazione cronica-idiopatica
- Carcinoma colorettale
- Malattie croniche infiammatorie
- Celiachia
- Diverticoli
- Ischemia intestinale
- Problemi di motilità intestinali
- Problematiche ginecologiche (sopratutto carcinoma ovarico)

Diagnostica della costipazione

- Anamnesi: RED FLAGS
- Visita medica completa con indagine rettale
- Laboratorio di base: CBC+Diff/autoimmunità celiachia/Calprotectina
- Sonografia addominale
- Visita ginecologica specialistica

Alarmsymptome = *red flags*



Indagine ano-rettale

Rectal Exam: Yes, it can and should be done in a busy practice!

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Am J Gastroenterol https://doi.org/10.1038/s41395-018-0006-y

"Dr, I am constipated and feel tied to the bathroom" said Mrs. Smith during an office consultation. "Let's arrange a colonoscopy to check your colon", said her gastroenterologist. At follow-up, "Mrs. Smith, good news, your colonoscopy is normal". "But Dr, I am very constipated". "Well, I suggest you take polyethylene glycol daily". And that was it! 1 year later, she was referred to another specialist, who performed a digital rectal examination (DRE), whose findings (summarized below) changed the course of her management.

Dyssynergic defecation, fecal incontinence (FI), and other anorectal disorders are common problems that affect one third of the US population [1]. DRE is a key component of physical examination [2, 3], but is rarely performed, except for perhaps a cursory exam prior to colonoscopy [4]. This problem is further compounded by a lack of knowledge on how to perform a comprehensive DRE.

A survey of 256 final-year medical students revealed that 17% had never performed a DRE, and 48% were unsure of their findings [5]. Furthermore, in another survey of 652 faculty, fellows, residents, and students, DRE was significantly underutilized [4]. While most students felt they were inadequately trained, most physicians reported lack of confidence in performing DRE or making a diagnosis [4]. The reasons for not performing DRE included concerns such as "patient's modesty", "too invasive", "limited value", "convenience", and "gender/chaperone". Thus, both training and utilization of DRE remains a challenge [4–6], and underscores the need for education and training at all levels. Training with mannequins significantly enhanced confidence for performing DRE [7, 8].

DRE SET-UP

DRE requires a good light source to illuminate the perineum,

HOW I APPROACH IT

Table 1 Components of the digital rectal examination, technique, expected findings and grading of responses

Exam component	Technique	Findings and grading of response(s)
I. Inspection of the anus and surrounding tissue	Place patient in the left lateral position with hips flexed to 90°. Inspect perineum under good light	Skin excoriation, skin tags, anal fissure, scars or external hemorrhoids, gaping anus, prolapsed hemorrhoids or rectum, condyloma
II. Testing of perineal sensation and the anocutaneous reflex	Stroke the skin around the anus in a centripetal fashion (towards anus), in all four quadrants, by using a stick with a cotton bud	Normal: brisk contraction of the perianal skin, the anoderm and the external anal sphincter
		Impaired: no response with the soft cotton bud, but anal contractile response seen with the opposite (wooden) end
		Absent: no response with either end
III. Digital palpation	Slowly advance a lubricated and gloved index finger into the rectum and feel the mucosa and surrounding muscle, bone, uterus, prostate, and pelvic structures	Tenderness, mass, stricture, or stool and the consistency of the stool (BSFS).
		Examine prostate for nodules, mass, tenderness
		Evaluate for retroverted uterus, rectocele
IV. Maneuvers to assess anorectal function and dysfunction		
Resting tone	Assess strength of resting sphincter tone	Normal, weak (decreased), or increased
Squeeze maneuver	Ask the patient to squeeze and hold as long as possible (up to 30s)	Normal, weak (decreased), or increased
Sphincter defects	Palpate anal sphincter muscle for defects during rest or squeeze maneuver	Describe as present or absent and degree of sphincter loss using a clock or in quadrants
Push and bearing down maneuver	In addition to the finger in the rectum, place the other hand over the patients' abdomen. Ask the patient to push and bear down as if to defecate and assess changes in abdominal muscle tightening, perineal descent and contraction or relaxation of anal sphincter and puborectalis	(i) Abdominal push effort: normal, weak (decreased), excessive
		(ii) Anal relaxation: normal, impaired, paradoxical contraction
		(iii) Puborectalis relaxation: normal, impaired, paradoxical contraction
		(iv) Perineal descent: normal, excessive, absent
		(v) Rectal mucosal intussusception/prolapse: presence or absence
Anorectal pain assessment	Palpate coccyx (bidigital) and palpate levator ani muscle in all four quadrants	Presence or absence of tenderness over coccyx and/or levator ani muscle. If present, grade intensity on a scale of 0–10, and whether sensation(s) experienced at home is reproducible

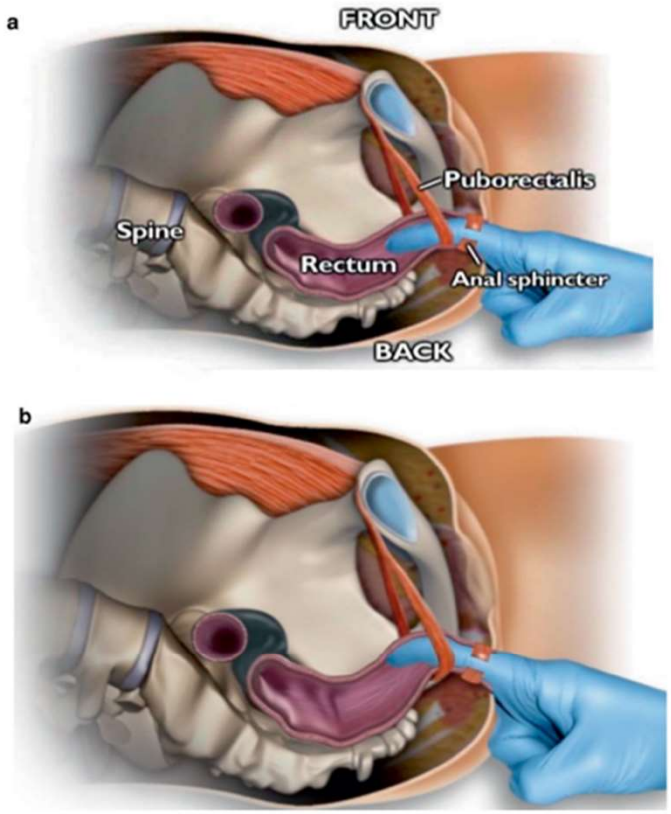


Fig. 2 **a** A schematic illustrating the anatomical components of the DRE examination in the resting state. **b** This schematic illustrates the abnormal paradoxical contraction of the external anal sphincter and puborectalis muscles with fingertip being displaced anteriorly during attempted defecation, suggesting dyssynergic defecation

Ergo…

- Viene valutato il tono sfinterico
- Presenza di dolore alla pressione
- Eventuali resistenze
- Ricerca di sangue
- Valutazione della prostata
- Dissinergie alla defecazione (difficoltà nella defecazione a causa di un alterazione funzionale o morfologica del retto)

Criteri di Roma (vedi guidelines per IBS)

Table 1. Rome IV diagnostic criteria for irritable bowel syndrome (4)

Recurrent abdominal pain on average at least 1 d/wk in the last 3 mo, associated with 2 or more of the following criteria
1. Related to defecation
2. Associated with a change in the frequency of stool
3. Associated with a change in the form (appearance) of stool
These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Adapted with permission from Bowel Disorders. *Gastroenterology* 2016;150: 1393–407.

Riprendendo il caso clinico I

- Sindrome del colon irritabile-Tipo C (costipazione)

Vengono definiti 4 tipi di IBS. La terapia é dipendente dalla classificazione

To accurately categorize a patient with IBS by subtype, we recommend the following:

1. Predominant stool consistency can be determined based on the Bristol Stool Form Scale (BSFS) (80) (Figure 1).
2. Determine patient's primary stool consistency only on the days s/he reports abnormal bowel movements. This determination should be made when patient is off of therapy(ies) that could affect bowel pattern. Daily diaries should be performed for 2 weeks for the most accurate assessment.
3. Once the pattern of stool consistency is determined, subtype decisions can be made according to the Rome IV criteria (4):
   a. IBS-C: >25% of bowel movements associated with BSFS 1 or 2 with BSFS 6 or 7 occurring less than 25%.
   b. IBS-D: >25% of bowel movements associated with BSFS 6 or 7 with less than 25% of bowel movements with BSFS 1 or 2.
   c. IBS-M: >25% of bowel movements associated with BSFS 1 or 2 and >25% of bowel movements associated with BSFS 6 or 7.
   d. IBS-U: cannot be determined.

- **Rome IV criteria for IBS** – According to the Rome IV criteria, IBS is defined as recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria [17,25]:
  - Related to defecation
  - Associated with a change in stool frequency
  - Associated with a change in stool form (appearance)
- **IBS subtypes** – Subtypes of IBS are recognized based on the patient's reported predominant bowel habit on days with abnormal bowel movements. The Bristol stool form scale (BSFS) should be used to record stool consistency [27]. Subtypes can only confidently be established when the patient is evaluated off medications used to treat bowel habit abnormalities. IBS subtypes are defined for clinical practice as follows:
  - **IBS with predominant constipation** – Patient reports that abnormal bowel movements are usually constipation (type 1 and 2 in the BSFS)
  - **IBS with predominant diarrhea** – Patient reports that abnormal bowel movements are usually diarrhea (type 6 and 7 in the BSFS)
  - **IBS with mixed bowel habits** – Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea)
  - **IBS unclassified** – Patients who meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes.

Manning criteria for the diagnosis of irritable bowel syndrome*

Pain relieved with defecation
More frequent stools at the onset of pain
Looser stools at the onset of pain
Visible abdominal distention
Passage of mucus
Sensation of incomplete evacuation

* The likelihood of irritable bowel syndrome is proportional to the number of Manning criteria that are present.

Terapia di prima linea

- Educazione al paziente: é una malattia cronica che non evolve in condizioni maligne
- Educazione alimentare: i pazienti con IBS possono beneficiare di una dieta povera di alimenti che producono gas. Dieta povera di oligo, di, ,monosaccaridi e polyoli (FODMAPS- prossime slides) ed eventualmente eliminazione di lattosio
- Eliminazione di cibi che producono gas (flatulenza): cipolle, carote, uva, banana, prugne,…
- Riduzione di lattosio: eseguire la diagnostica specifica per evitare diete restrittive inutili
- Fibre: Offrire al paziente una dieta con fibre solubili
- Testare possibili allergie alimentari
- Aumentare attività fisica

Terapia farmacologica aggiuntiva

- Costipazione (un esempio)
  - Lassativi osmotici (laxipeg…): migliorano la costipazione ma non per forza i dolori addominali
- Diarrea
  - Lorepamid (un esempio)
- Antidepressivi
  - TCA
- Antibiotici
  - Non vengono consigliati di routine ma solo in casi selezionati
- Probiotici: non consigliati di routine anche se sembrano avere effetti benefici
- Il ruolo di un trapianto fecale é ancora da analizzare anche se sembre che nel breve termine i pazienti possano trarne giovamento

Motivi per ridurre FODMAP

- Si tratta di carboidrati a catena corta che vengono assorbiti poco e sono osmoattivi nel lume intestinale dove fermentano in poco tempo

- La dieta va studiata in maniera mirata poichè é possibile che per taluni pazienti sia necessaria un’eliminazione di cibi che producono gas.

Characteristics and sources of common FODMAPs

	Word that corresponds to letter in acronym	Compounds in this category	Foods that contain these compounds
F	**F**ermentable		
O	**O**ligosaccharides	Fructans, galacto-oligosaccharides	Wheat, barley, rye, onion, leek, white part of spring onion, garlic, shallots, artichokes, beetroot, fennel, peas, chicory, pistachio, cashews, legumes, lentils, and chickpeas
D	**D**isaccharides	Lactose	Milk, custard, ice cream, and yogurt
M	**M**onosaccharides	"Free fructose" (fructose in excess of glucose)	Apples, pears, mangoes, cherries, watermelon, asparagus, sugar snap peas, honey, high-fructose corn syrup
A	**A**nd		
P	**P**olyols	Sorbitol, mannitol, maltitol, and xylitol	Apples, pears, apricots, cherries, nectarines, peaches, plums, watermelon, mushrooms, cauliflower, artificially sweetened chewing gum and confectionery

FODMAPs: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Table 2. Summary and strength of recommendations

1	We recommend that serologic testing be performed to rule out celiac disease in patients with IBS and diarrhea symptoms. Strong recommendation; moderate quality of evidence.
2	We suggest that fecal calprotectin (or fecal lactoferrin) and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. Strong recommendation; moderate quality of evidence for C-reactive protein and fecal calprotectin. Strong recommendation; very low quality of evidence for fecal lactoferrin.
3	We recommend against routine stool testing for enteric pathogens in all patients with IBS. Conditional recommendation; low quality of evidence.
4	We recommend against routine colonoscopy in patients with IBS symptoms younger than 45 years without warning signs. Conditional recommendation; low quality of evidence.
5	We suggest a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBSs to improve time to initiate appropriate therapy. Consensus recommendation; unable to assess using GRADE methodology.
6	We recommend a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBSs to improve cost-effectiveness. Strong recommendation; high quality of evidence.
7	We suggest that categorizing patients based on an accurate IBS subtype improves patient therapy. Consensus recommendation; unable to assess using GRADE methodology.
8	We do not recommend testing for food allergies and food sensitivities in all patients with IBS unless there are reproducible symptoms concerning for a food allergy. Consensus recommendation; unable to assess using GRADE methodology.
9	We suggest that anorectal physiology testing be performed in patients with IBS and symptoms suggestive of a pelvic floor disorder and/or refractory constipation not responsive to standard medical therapy. Consensus recommendation; unable to assess using GRADE methodology.
10	We recommend a limited trial of a low FODMAP diet in patients with IBS to improve global IBS symptoms. Conditional recommendation; very low quality of evidence.
11	We suggest that soluble, but not insoluble, fiber be used to treat global IBS symptoms. Strong recommendation; moderate quality of evidence.
12	We recommend against the use of antispasmodics for the treatment of global IBS symptoms. Conditional recommendation; low quality of evidence.
13	We suggest the use of peppermint to provide relief of global IBS symptoms. Conditional recommendation; low quality of evidence.
14	We suggest against probiotics for the treatment of global IBS symptoms. Conditional recommendation; very low quality of evidence.
15	We suggest against PEG products to relieve global IBS symptoms in those with IBS-C. Conditional recommendation; low quality of evidence.
16	We recommend the use of chloride channel activators to treat global IBS-C symptoms. Strong recommendations; moderate quality of evidence.
17	We recommend the use of guanylate cyclase activators to treat global IBS-C symptoms. Strong recommendation; high quality of evidence.
18	We suggest that the 5-HT_4 agonist tegaserod be used to treat IBS-C symptoms in women younger than 65 years with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues. Strong/conditional recommendation; low quality of evidence
19	We do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms. Conditional recommendation; very low quality of evidence.
20	We recommend the use of rifaximin to treat global IBS-D symptoms. Strong recommendation; moderate quality of evidence.
21	We recommend that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy. Conditional recommendation; low quality of evidence.
22	We suggest that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms. Conditional recommendation; moderate quality of evidence.
23	We recommend that tricyclic antidepressants be used to treat global symptoms of IBS. Strong recommendation; moderate quality of evidence.
24	We suggest that gut-directed psychotherapies be used to treat global IBS symptoms. Conditional recommendations; very low quality of evidence.
25	Using currently available evidence, we recommend against the use of fecal transplant for the treatment of global IBS symptoms. Strong recommendation; very low quality of evidence.

5-HT_4, serotonin type-4 receptor; FOADMAP, fermentable oligosaccharides, disaccharides, monosaccharides, polyols; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; PEG, polyethylene glycol.

conducted in North America, and these did not identify a difference in the odds of positive serological testing (1.05, 95% CI 0.21–5.15) or biopsy-proven CD (0.93, 95% CI 0.13–6.63) among patients with IBS symptoms vs controls. The increased likelihood of CD among patients with IBS symptoms was greater in studies conducted in secondary or tertiary care and less apparent in population-based studies. The meta-analysis by Irvine et al. (19) also reported the prevalence of CD in different IBS subgroups. The highest prevalence of CD was reported in IBS with diarrhea (IBS-D) (EMA or tTG 5.7%, 95% CI 3.0%–9.1%), followed by IBS with mixed or alternating bowel habits (IBS-M) (3.4%, 95% CI

Caso Clinico – II- diarrea da due anni

- 3-4 evaquazioni/giorno
- Dolori addominali
- Sovrappeso (BMI 28)
- Medicamenti
  - Loperamid contro la diarrea
  - Lorazepam per dormire
- Colonscopia 3 anni fa senza particolarità

Caso Clinico – II- diarrea da due anni

- Separato con un bambino
- Consulente per bambini problematici (molto stress)
- Problemi a dormire
- Pasti irregolari
- Niente OH
- Ninente nicotina
- Mariujana contro lo stress

- ➔ consulto per diarrea persistente e crampia addominali

Ernährungsberater:in

z.B. Low-FODMAB*-Diät

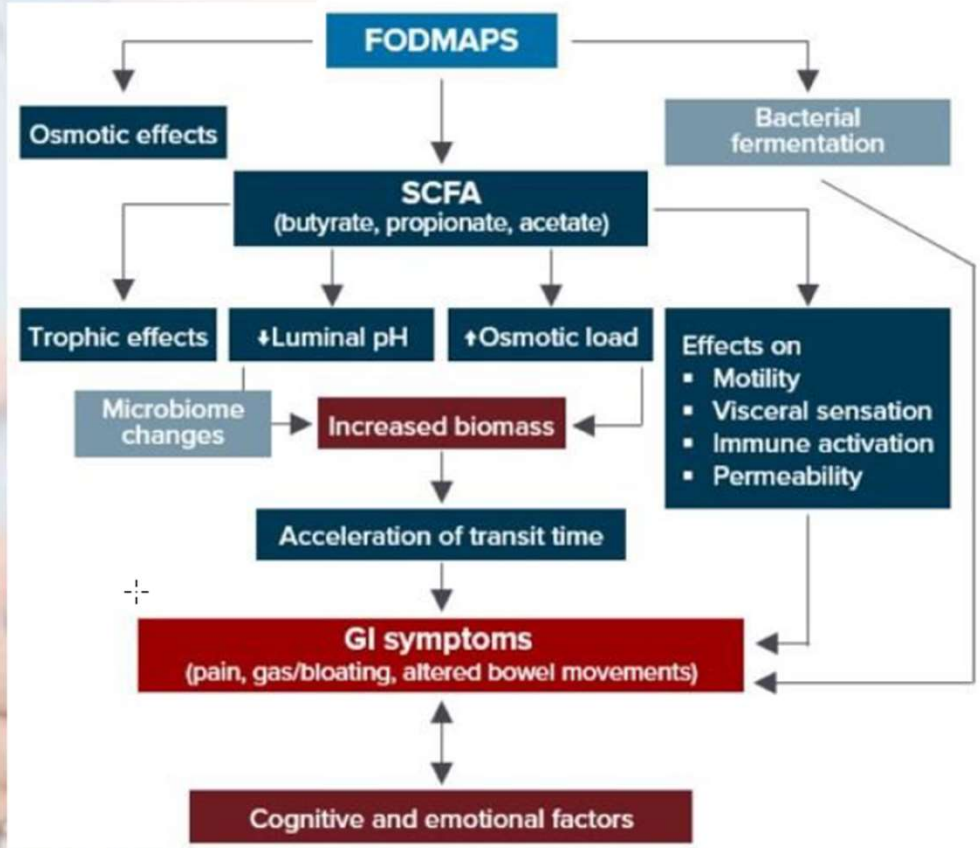
Ev. alle 3

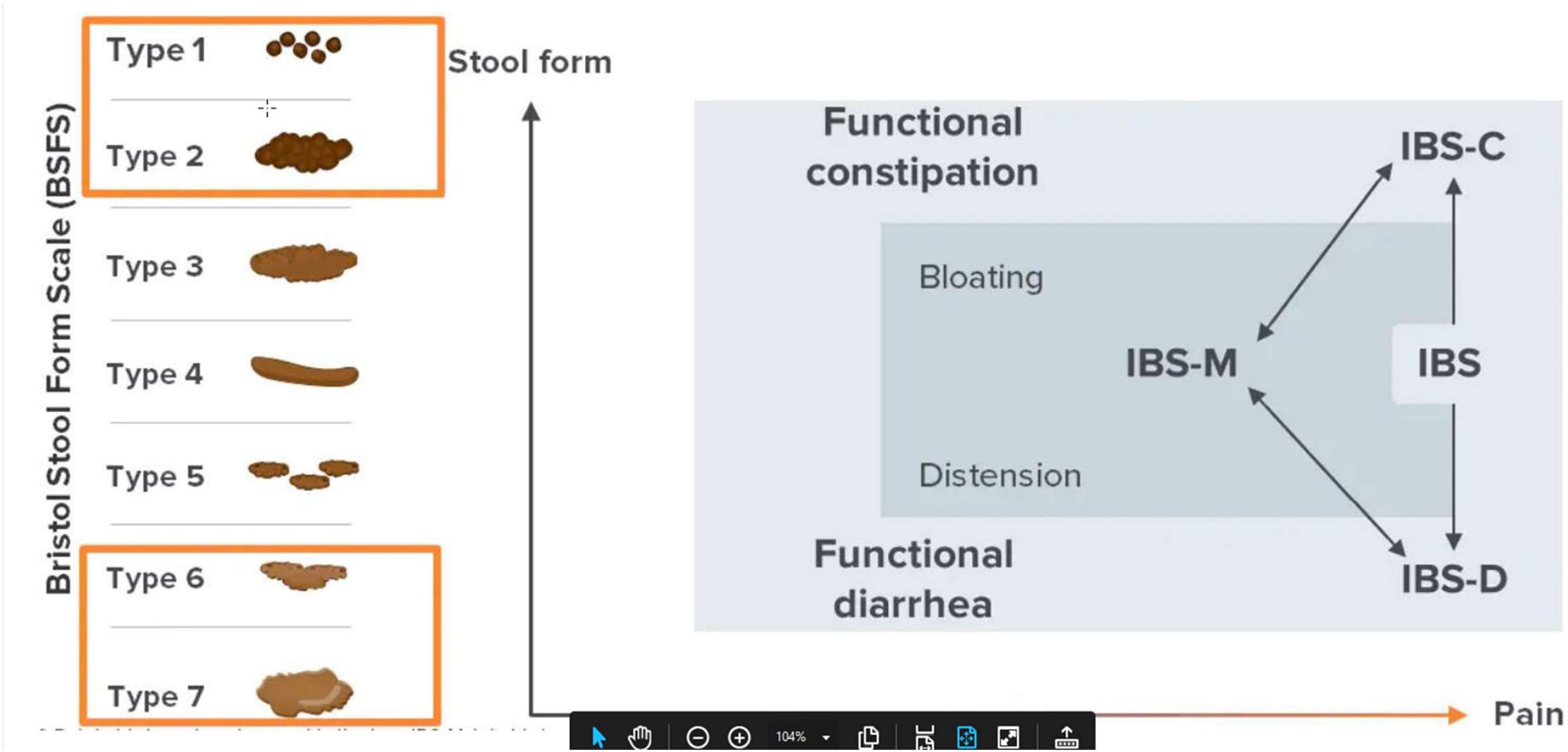
Gastroenterolog:in

z.B. Rifaximin (nicht resorbierbares Antibiotikum)

Psycholog:in

z.B. Kognitive Verhaltenstherapie




Type 1
Type 2
Type 3
Type 4
Type 5
Type 6
Type 7
Bristol Stool Form Scale (BSFS)
Stool form
Functional constipation
IBS-C
Bloating
IBS-M
IBS
Distension
Functional diarrhea
IBS-D
Pain

Il laboratorio nella diagnosi di IBS

- Emogramma completo
- Calprotectina fecale o lactofferina
- Test per la giardia
- Ricerca Celiachia
- Eventualmente CRP

Supplemental Table 1: Summary of the diagnostic accuracy of serologic and fecal testing for differentiating IBD and IBS. Results with cutoff values provided. Modified by permission (40).

Test	Test cutoff	Sensitivity, range or (95% CI)*	Specificity, range or (95% CI)*	Positive likelihood ratio, range or (95% CI)*	Negative likelihood ratio, range or (95% CI)*
ESR	10-15 mm/h	0.54-0.78	0.46-0.95	1.0-16.3	0.3-0.98
CRP	5 to 6 mg/L	0.73 (0.64-0.80)	0.78 (0.58-0.91)	3.4 (1.05-5.71)	0.35 (0.27-0.42)
FL	4.0-7.25 µg/g	0.79 (0.73-0.84)	0.93 (0.63-0.99)	11.5 (-10.7-33.8)	0.22 (0.17-0.28)
Fcal	Ranges: 24.3 to 30 µg/g 50 to 60 µg/g 100-164 µg/g	 0.92-0.98 0.81 (0.75-0.86) 0.64 (0.49-0.77)	 0.96-0.98 0.87 (0.78-0.92) 0.90 (0.72-0.97)	 28-59 6.12 (2.75-9.49) 6.23 (1.28-13.75)	 0.01-0.07 0.21 (0.14-0.28) 0.4 (0.21-0.58)

Note: This is a summary of testing for any organic disease in IBS-D and chronic diarrhea and is not limited solely to IBS-D studies

Calprotectina fecale

- È una proteina di 36kDa
- Rappresenta ca. il 60% delle proteine citosoliche die neutrofili, che rappresenta la fonte principale (fonte secondaria rappresentata da monociti e macrofagi)
- Ha proprietà antiinfiammatorie verosimilmente dovute alla capacità di chelare metalli come zinco, manganese…
- Gioca un ruolo anche nell'immunità innata
- La concentrazione nelle feci é di 6 volte maggiore rispetto al plasma➔ marcatore potenziale per infiammazione intestinale

Table 2. Examples of commercially available calprotectin assays [14,20,41].

Assay	Manufacturer	Measurement method	Measurement range (µg/g)[a]
fCAL ELISA	Bühlmann	ELISA	10–600
			30–1800
fCAL turbo	Bühlmann	PETIA	20–8000[b]
Quantum Blue fCAL	Bühlmann	LFIA	30–300
			100–1800
IB*Doc*[c]	Bühlmann	LFIA	30–1000
CalproLab	Calpro	ELISA	25–2500
Calprest	Eurospital	ELISA	15.6–2000
Calfast	Eurospital	LFIA	50–300
LIAISON Calprotectin	Diasorin	CLIA	5–8000[b]
EliA Calprotectin	ThermoFisher	FEIA	3.8–6000
Calprotectin	Euroimmun	ELISA	6.5–2100
Calprotectin	Orgentec	ELISA	15–1000
Calprosmart[c]	Calpro	LFIA	70–1500
IDK Calprotectin	Immundiagnostik	ELISA	13–840

CLIA: chemiluminescence immunoassay; ELISA: enzyme-linked immunosorbent assay; FEIA: fluoro-enzyme immunoassay; LFIA: lateral flow chromatographic immunoassay; PETIA: particle enhanced turbidimetric immunoassay.

[a]As per manufacturer.

[b]After 1:4 (Buhlmann) and 1:10 (Diasorin) dilution concentrations up to 8000 g/g can be detected.

[c]Can be used with smart phone application.

Table 3:

Intra-run and total imprecision for faecal calprotectin determinations with the tested assays.

	Intra-run imprecision[a]				Total imprecision[a]			
	Kit-controls[b]		Patient samples[c]		Kit-controls[b]		Patient samples[c]	
	Low	High	Low	High	Low	High	Low	High
EliA Calprotectin 2	9.1	8.2	5.7	8.0	10.0	9.1	5.7	8.0
Diasorin Calprotectin	3.3	4.3	2.5	2.1	3.3	7.2	4.7	2.8
Inova QUANTA Flash®	3.6	0.9	1.7	0.6	3.7	1.9	1.7	3.7
Bühlmann fCAL Turbo	5.6	1.4	4.1	2.5	5.6	1.5	8.4	2.5
Orgentec Calprotectin[d]	–	–	13.2	9.7	–	–	13.2	9.7
Euroimmun Calprotectin	10.6	19.7	16.2	7.7	10.6	23.3	16.2	18.1

[a]The results are presented as %CV (coefficient of variation). [b]Low and high kit-controls ranged from 20 to 60 µg/g and 130–270 µg/g. Kit-controls for the EliA and Inova Quanta Flash assays were analysed 10 times in duplo, for the Diasorin, fCAL Turbo and Euroimmun assays, five in duplo determinations were performed. [c]Low and high patient-sample controls ranged from 15 to 60 µg/g and 100 to 450 µg/g, respectively. The patient-sample controls were measured five times in duplo for all assays. [d]As internal kit-controls are reported as positive/negative, no data for intra-run and total imprecision for kit-controls are available for this assay.

Table 1:

Overview of the patient characteristics and faecal calprotectin concentrations (µg/g) obtained with the different methods evaluated.[a]

Final Diagnosis	n	Men/women	Age (range)[b]	EliA Calprotectin 2	Inova QUANTA Flash®	Diasorin Calprotectin	Bühlmann fCAL Turbo	Euroimmun Calprotectin	Orgente
IBD									
Crohn's disease	15	10/5	36 (14–62)	1020.0 (460.5–3168.0)	451.4 (291.7–2588.7)	278.0 (179.5–1520.0)	799.1 (483.7–1491.6)	985.5 (542.6–1829.6)	1835.2
Colitis ulcerosa	12	7/5	35 (20–76)	1167.0 (641.0–2734.0)	619.5 (396.7–1136.4)	560.5 (320.8–1025.3)	1058.0 (708.1–1844.1)	1555.9 (659.5–1985.3)	2539.(
Non-IBD									
Gastro[c]	23	10/13	53 (26–68)	98.0 (19.5–206.5)	61.6 (<16.1–140.6)	60.8 (10.9–86.8)	105.9 (<20–222.8)	137.2 (14.6–205.1)	1
Rheumato[d]	15	4/11	40 (17–59	64.0 (24.0–114.0)	37.9 (<16.1–109.0)	36.6 (15.9–57.7)	71.9 (16.2–83.8)	78.0 (33.2–218.0)	9
IBS[e]	40	13/27	29 (14–67)	14.5 (5.4–30.3)	<16.1 (<16.1)	6.1 (<5–17.3)	<20 (<20–29.9)	15.6 (3.3–42.5)	

[a]Data are presented as median (IQR). [b]Age is presented as median in years. Values in brackets indicate minimum and maximum ages. [c]Including oesophagitis, erosive gastritis, gastric ulcers, diverticulitis, microscopic colitis, colorectal cancer, hyperplastic polyps, adenomatous polyps. [d]Including spondylo-arthritis, (undifferentiated) arthritis. [e]Including patients from the gastrologic and rheumatologic disease control group with a final diagnosis of IBS. IBS, irritable bowel syndrome.

The main reasons for performing faecal calprotectin determination were diarrhoea, mucous or bloody stools, weight loss and abdominal pain and

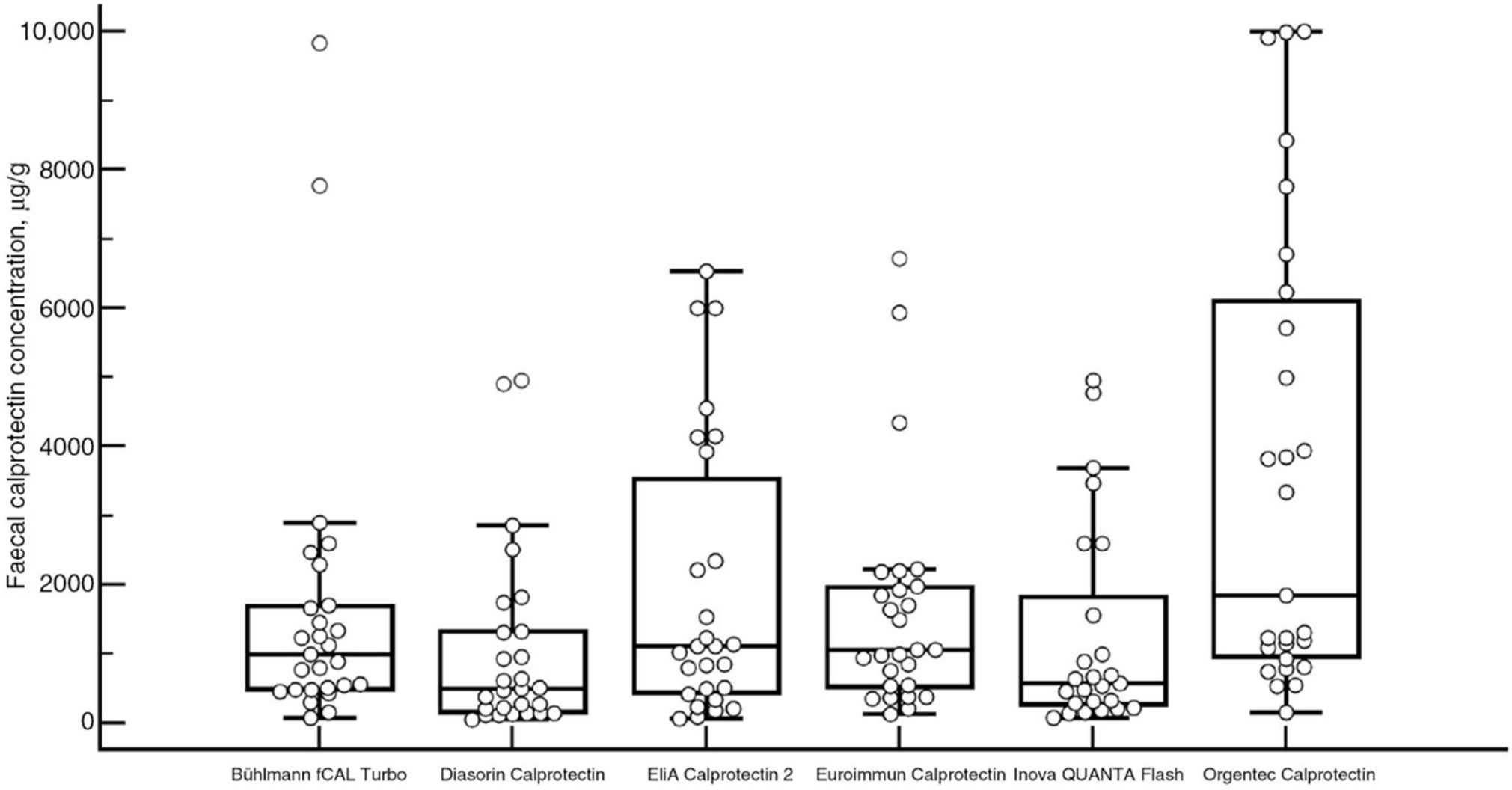

10,000
8000
6000
4000
2000
0
Faecal calprotectin concentration, µg/g
Bühlmann fCAL Turbo
Diasorin Calprotectin
EliA Calprotectin 2
Euroimmun Calprotectin
Inova QUANTA Flash
Orgentec Calprotectin

Figure 1:

Considerazioni

- Dallo studio si evince che lo stesso campione può avere valori anche molto distanti (3x) in funzione della piattaforma utilizzata.

- Questo non é nuovo ma suggerise che i valori degli assay non sono intercambiabili in assenza di un calibratore standard

- Il paziente va monitorato sempre con lo stesso metodo

Age-related faecal calprotectin, lactoferrin and tumour M2-PK concentrations in healthy volunteers

Shilpa Joshi [1], Stephen J Lewis, Siobhan Creanor, Ruth M Ayling

Affiliations + expand

PMID: 19740914 DOI: 10.1258/acb.2009.009061

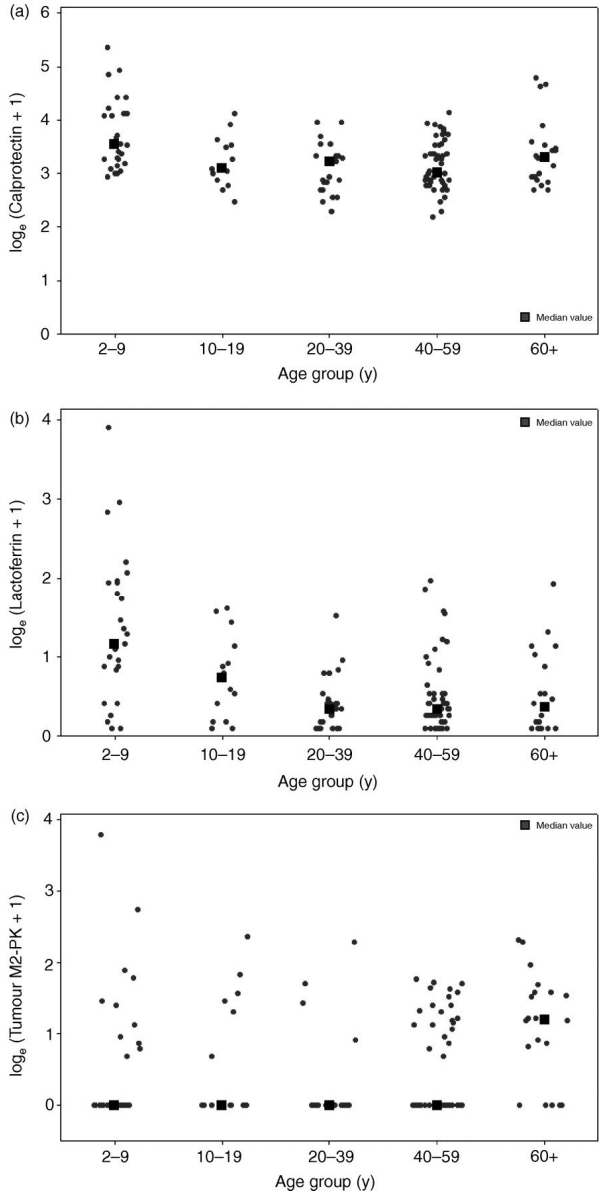
Abstract

Objective: Measurement of the faecal markers calprotectin, lactoferrin and tumour M2-PK has been reported to be useful in the diagnosis and management of a range of gastrointestinal disorders in both children and adults. The aim of this study was to investigate the requirement for age-related reference ranges.

Methods: Faecal samples were obtained from 132 healthy subjects and analysis of calprotectin, lactoferrin and tumour M2-PK performed using commercially available enzyme-linked immunosorbent assay.

Results: In the healthy subjects median concentrations were as follows: for calprotectin - 2-9 y, 34 microg/g, 10-59 y, 22 microg/g and > or =60 y, 27 microg/g; for lactoferrin - 2-9 y, 2.2 microg/g, > or =10 y, 0.5 microg/g; and for tumour M2-PK all subjects <1 U/mL. Significant differences between age groups for different markers resulted in the following age-related reference ranges: calprotectin - 2-9 y, <166 microg/g, 10-59 y, <51 microg/g, > or =60 y, <112 microg/g; lactoferrin - 2-9 y, <29 microg/g, > or =10 y <4.6 microg/g.

Conclusion: In healthy individuals, we found there to be variation in the faecal inflammatory markers calprotectin and lactoferrin with age. For both calprotectin and lactoferrin children aged 2-9 y had significantly higher concentrations than subjects aged >/=10 y. For calprotectin but not lactoferrin, adults > or =60 years had a higher concentration than those aged 10-59 y. There was no change with age in the metabolomic marker faecal tumour M2-PK in healthy subjects. The knowledge of age-related reference ranges in healthy subjects is important to fully interpret changes in gastrointestinal disease.


(a)
log$_e$ (Calprotectin + 1)
Median value
2–9
10–19
20–39
40–59
60+
Age group (y)
(b)
log$_e$ (Lactoferrin + 1)
Median value
2–9
10–19
20–39
40–59
60+
Age group (y)
(c)
log$_e$ (Tumour M2-PK + 1)
Median value
2–9
10–19
20–39
40–59
60+
Age group (y)

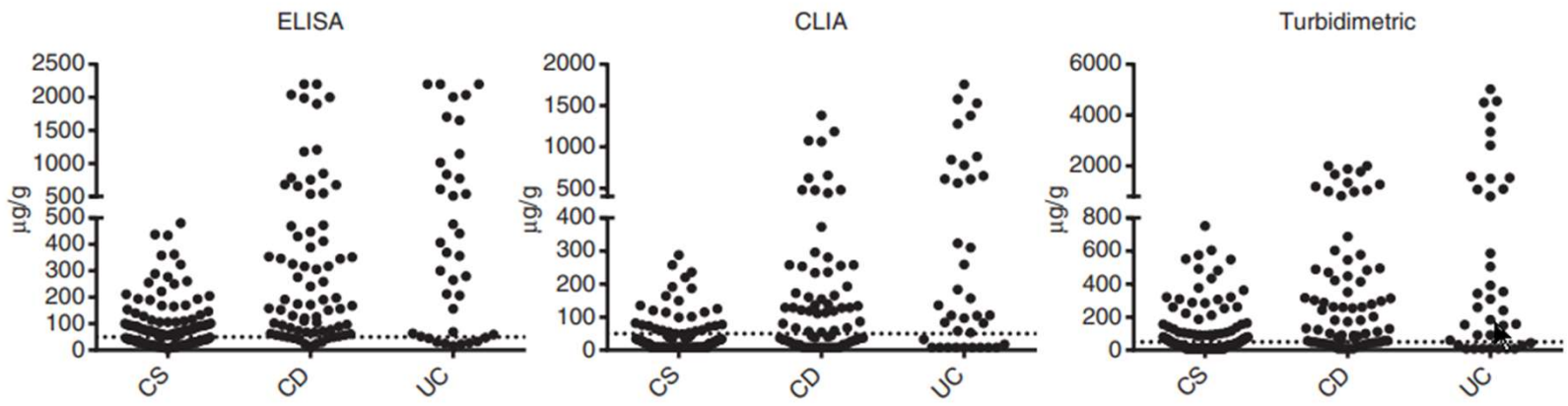


Figure 3: Individual fCal results obtained with ELISA, CLIA and turbidimetric assay in controls (CS) and patients with Crohn's disease (CD) and ulcerative colitis (UC).

Table 3: fCal biological variation, individuality index and reference change value.

	fCal ELISA	fCal CLIA	fCal turbidimetry
Intra-individual (CVi)	37.7%	31.4%	32.3%
Inter-individual (CVg)	78.0%	72.1%	84.3%
Individuality index (II)	0.54	0.52	0.56
Reference change value (RCV)	118%	104%	131%

Intra- and interindividual biological variations were calculated by Nested ANOVA according to Fraser et al. [23]. Analytical variability (CVa) value was also obtained from the same analysis. The individuality index was calculated using the following formula: $(CV_A^2 + CV_I^2)^{1/2}/CV_G$. The bidirectional reference change value was calculated using the following formula: $1.96 \times 2^{1/2} \times (CV_A^2 + CV_I^2)^{1/2}$.

Interpretazione calprotectina

- Variabilità analitica moderatamente elevata
- Variabilità individuale elevata

- ➔ utilizzare la RCV per valutare il livello di significatività tra due misurazioni seriali. Indicativamente un aumento pari ad al meno il 100% é biologicamente significativo, anche nel caso in cui le concentrazioni di calprotettina (che variano anche in funzione dell'età) sono nei limiti di normalità

Table 4. Factors associated with elevated fecal calprotectin [103].

Infectious
Infectious diarrhea (viral, bacterial, parasitic)
Helicobacter pylori gastritis
Neoplastic
Intestinal lymphoma
Colorectal cancer
Gastric cancer
Colonic/gastric polyps
Drug-related
Non-steroidal anti-inflammatory drugs (NSAIDs)
Proton pump inhibitors
Allergic
Food allergy (untreated)
Age-related
Young age (<5years)
Inflammatory
Inflammatory bowel disease
Autoimmune enteropathy
Diverticulitis
Eosinophilic gastroenteritis
Microscopic colitis
Celiac disease (untreated)
Peptic ulcer
Gastroesophageal reflux disease
Cirrhosis
Cystic fibrosis
Juvenile polyp

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Clinical Biochemistry

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Ruling out IBD: Estimation of the possible economic effects of pre-endoscopic screening with F-calprotectin

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ARTICLE INFO

Article history:
Received 15 July 2011
received in revised form 10 October 2011
accepted 14 October 2011
Available online 26 October 2011

Keywords:
Calprotectin
Colonoscopy
Cost
Faeces
Health economics
Inflammatory bowel disease
Laboratory test

ABSTRACT

Objectives: To estimate the possible economic effects of a sequential testing strategy with F-calprotectin to minimize colonoscopies.

Design and methods: Retrospective study in a third party payer perspective. The costs were calculated from initial F-calprotectin test results of 3639 patients. Two cut-off levels were used: 50 μg/g feces and 100 μg/g feces, respectively. The cost-effectiveness of the testing strategy was estimated through the short-term cost avoidance and reduction in demand for colonoscopies.

Results: The estimated demand for colonoscopies was reduced by 50% with the 50 μg/g cut-off and 67% with the 100 μg/g cut-off. This corresponded to a cost avoidance of approximately €1.57 million and €2.13 million, respectively.

Conclusions: The use of F-calprotectin as a screening test substantially could reduce the number of invasive measurements necessary in the diagnostic work-up of patients with suspected IBD, as well as the associated costs.

Introduction

Differentiating patients with inflammatory bowel disease (IBD) from patients without intestinal pathology, in particular those with irritable bowel syndrome (IBS), poses a diagnostic challenge. Gastrointestinal problems such as diarrhoea and constipation are frequently occurring among primary care patients and primary care physicians in our county has estimated that approximately 15% of their patients have gastrointestinal problems. The mean annual incidence of IBD in a Danish population was $8.6/10^5$ for Crohn's disease, $13.4/10^5$ for ulcerative colitis, and $1.1/10^5$ for indeterminate colitis [1]. Though IBD is organic and IBS functional in character, the key symptoms are common to both of these chronic gastrointestinal disorders, making differential diagnosis based on clinical assessment alone very difficult [2]. The gold standard for diagnosing IBD is endoscopy, primarily colonoscopy, with histological assessment of biopsy specimens [3]. The difficulties in distinguishing between IBD and IBS result in many patients in the IBS category being unnecessarily investigated extensively with invasive imaging techniques, such as endoscopy, to reach a diagnosis of exclusion. Endoscopies are not only invasive, but also resource intensive, require patient preparations [4], and are associated with the inherent risks of such invasive procedures [5] as well as a hesitancy of patients to undergo them [6]. Endoscopies are thus not suitable for frequent use, especially not in children, where general anesthesia is often required. There is, consequently, a need for a reliable, non-invasive, simple, and cheap test that could provide objective evidence of whether the underlying disease is organic or functional. A test that will effectively rule out IBD, a condition which requires further investigations, could aid clinicians in deciding which invasive investigations to request, or possibly avoid, in cases where the diagnosis indicated is IBS.

The most striking difference between IBD and IBS is that the former is inflammatory in nature. Therefore, one possibility to differentiate between the two would be to measure surrogate markers of intestinal inflammation. Calprotectin, a calcium- and zinc-binding S100 protein released mainly from neutrophils, is a promising marker of neutrophilic intestinal inflammation [7–11]. Calprotectin is excreted in feces and can be measured using a commercially available ELISA assay at a cost of €29 per test (according to the official fee-schedule at Akademiska sjukhuset, Uppsala). The fecal (F-)calprotectin test does not require any patient preparations, and it is stable in stools for up to seven days at room temperature, enabling sample collection at home and delivery of the sample to the laboratory by ordinary mail [12]. Calprotectin measured in feces has a good overall diagnostic

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Inflammatory Bowed Disease (IBD)

- Comprende
  - Colite ulcerativa: colon
  - Malattia di Chron: colpisce il tratto gastro-intestinale dalla bocca fino all'ano

Malattia di Chron

- In genere i pazienti hanno sintomi anni prima della diagnosi
- Sintomi principali: dolore addominale, diarrea (con o senza sanguinamento), fatica, perdita di peso (malassorbimento oppure perchè il paziente sta meglio se non mangia)
- La diarrea é comune: persistente ma intermittende. La presenza di sangue é abbastanza frequente

Malattia di Chron e infiammazione transmurale

- Fistole: comunicazione tra due organi (entero-enteriche, entero-vescicali, entero-vaginali…)
- Flemmone: infiammazione della parete senza batteri
- Ascesso:

Chron e malassorbimento

- Diarrea acquosa, steatorrea➔
- Ipocalcemia, deficit di vitamine (B12, Vitamina D)
- Malattie metaboliche dell’osso

Altre manifestazioni legate alla malattia di Chron

Extraintestinal manifestations of inflammatory bowel disease

Common extraintestinal manifestations
Musculoskeletal
Arthritis – Colitic type, ankylosing spondylitis, isolated joint involvement such as sacroiliitis.
Hypertrophic osteoarthropathy – Clubbing, periostitis, metastatic Crohn disease.
Miscellaneous – Osteoporosis, aseptic necrosis, polymyositis, osteomalacia.
Skin and mouth
Reactive lesions – Erythema nodosum, pyoderma gangrenosum, aphthous ulcers, vesiculopustular eruption, cutaneous vasculitis, neutrophilic dermatosis, metastatic Crohn disease, epidermolysis bullosa acquisita.
Specific lesions – Fissures and fistulas, oral Crohn disease, drug rashes.
Nutritional deficiency – Acrodermatitis enteropathica (zinc), purpura (vitamins C and K), glossitis (vitamin B), hair loss and brittle nail (protein).
Associated diseases – Vitiligo, psoriasis, amyloidosis, epidermolysis bullosa acquisita.
Hepatobiliary
Specific complications – Sclerosing cholangitis (large-duct or small-duct), bile duct carcinoma, cholelithiasis.
Associated inflammation – Autoimmune chronic active hepatitis, pericholangitis, portal fibrosis and cirrhosis, granuloma in Crohn disease.
Metabolic – Fatty liver, gallstones associated with ileal Crohn disease.
Ocular
Uveitis iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease, retrobulbar neuritis, Crohn keratopathy.
Metabolic
Growth retardation in children and adolescents, delayed sexual maturation.
Less common extraintestinal manifestations
Blood and vascular
Anemia due to iron, folate, or vitamin B12 deficiency or autoimmune hemolytic anemia, anemia of chronic disease, thrombocytopenic purpura; leukocytosis and thrombocytosis; thrombophlebitis and thromboembolism, arteritis and arterial occlusion, polyarteritis nodosa, Takayasu arteritis, cutaneous vasculitis, anticardiolipin antibody, hyposplenism.
Renal and genitourinary tract
Urinary calculi (oxalate stones in ileal disease), local extension of Crohn disease involving ureter or bladder, amyloidosis, drug-related nephrotoxicity.
Renal tubular damage with increased urinary excretion of various enzymes (eg, beta N-acetyl-D-glucosaminidase).
Neurologic
Up to 3% of patients may have non-iatrogenic neurologic involvement, including peripheral neuropathy, myelopathy, vestibular dysfunction, pseudotumor cerebri, myasthenia gravis, and cerebrovascular disorders. Incidence equal in ulcerative colitis and Crohn disease. These disorders usually appear 5 to 6 years after the onset of inflammatory bowel disease and are frequently associated with other extraintestinal manifestations.
Airway and parenchymal lung disease
Pulmonary fibrosis, vasculitis, bronchitis, necrobiotic nodules, acute laryngotracheitis, interstitial lung disease, sarcoidosis. Abnormal pulmonary function tests without clinical symptoms are common (up to 50% of cases).
Cardiac
Pericarditis, myocarditis, endocarditis, and heart block – More common in ulcerative colitis than in Crohn disease; cardiomyopathy, cardiac failure due to anti-TNF therapy.
Pericarditis may also occur from sulfasalazine/5-aminosalicylates.
Pancreas
Acute pancreatitis – More common in Crohn disease than in ulcerative colitis. Risk factors include 6-mercaptopurine and 5-aminosalicylate therapy, duodenal Crohn disease.
Autoimmune
Drug-induced lupus and autoimmune diseases secondary to anti-TNF-alpha therapy.
Positive ANA, anti-double-stranded DNA, cutaneous and systemic manifestations of lupus.

TNF: tumor necrosis factor; ANA: antinuclear antibody; DNA: deoxyribonucleic acid.

Modified from: Das KM. Relationship of extraintestinal involvements in inflammatory bowel disease: New insights into autoimmune pathogenesis. Dig Dis Sci 1999; 44:1.

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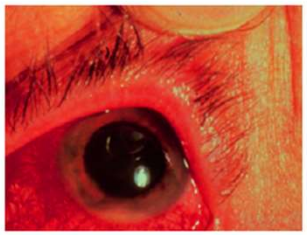
Anterior uveitis in a patient with inflammatory bowel disease



Anterior uveitis in a patient with inflammatory bowel disease is characterized by injection of the conjunctiva and opacity in the anterior chamber.

Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA.

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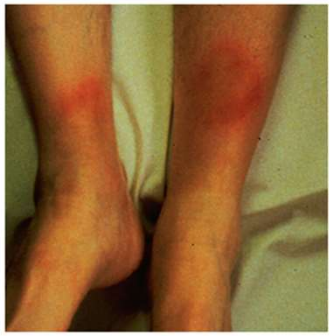
Erythema nodosum



Patient with inflammatory bowel disease with red nodular areas on the shins which are characteristic of erythema nodosum.

Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA.

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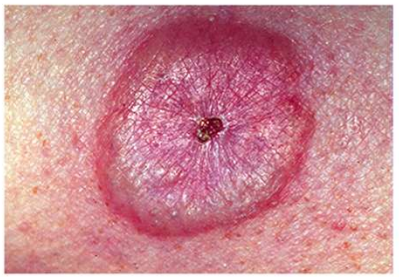
Pyoderma gangrenosum



Early lesion in pyoderma gangrenosum presenting as a pustular and violaceous plaque with incipient breakdown.

Courtesy of Cynthia Magro, MD.

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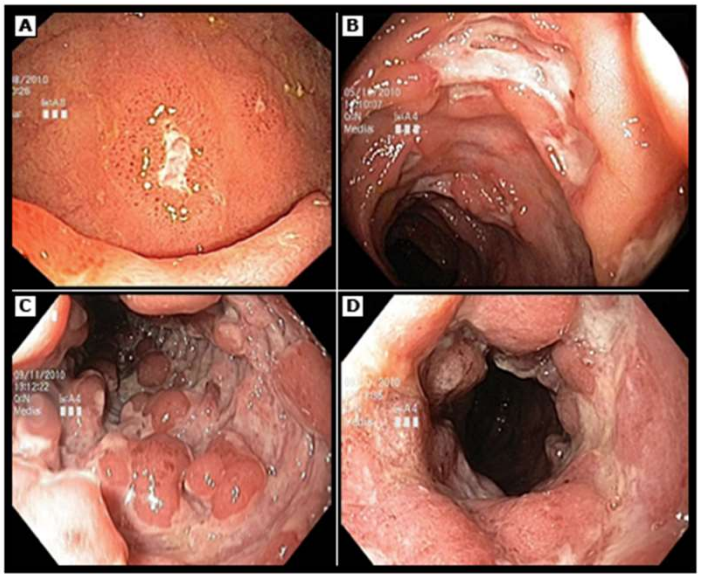
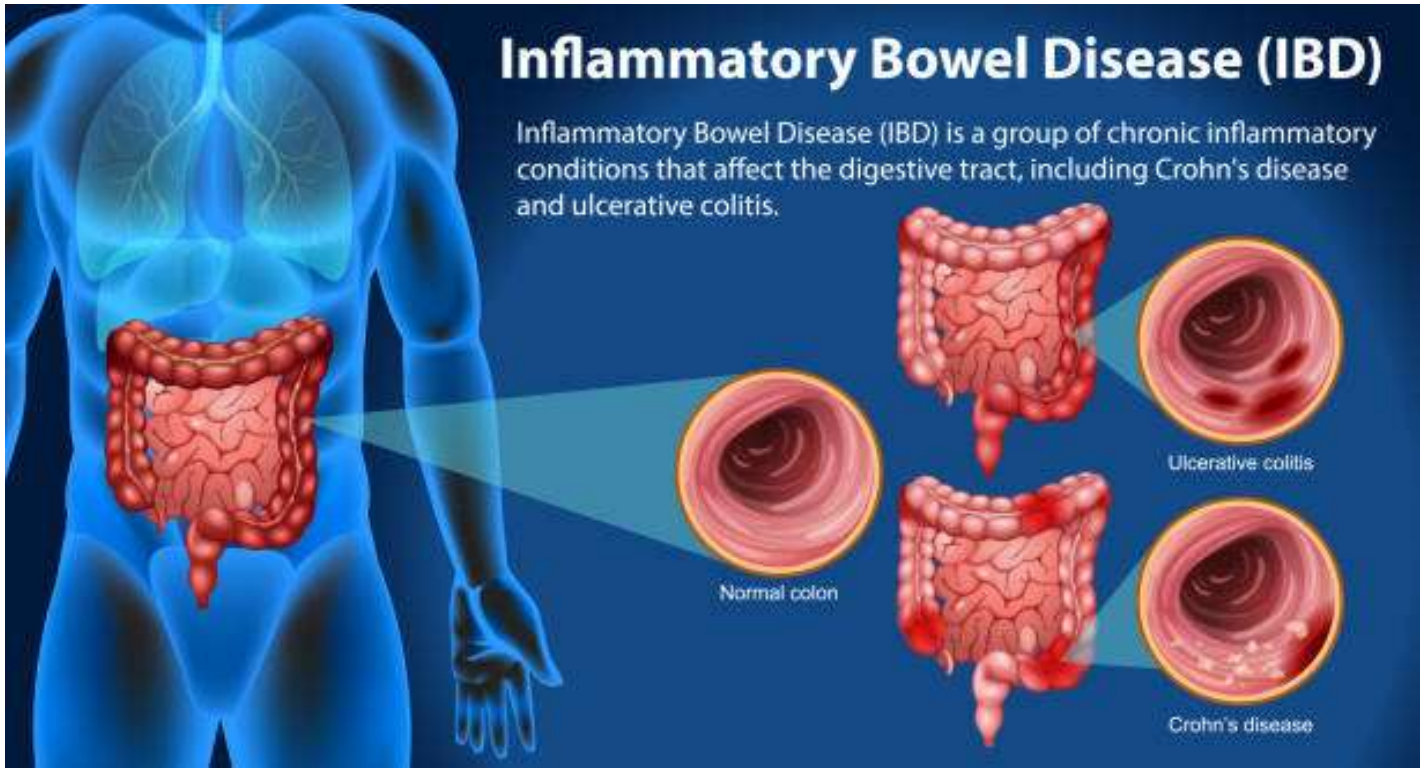
Endoscopic findings in Crohn disease



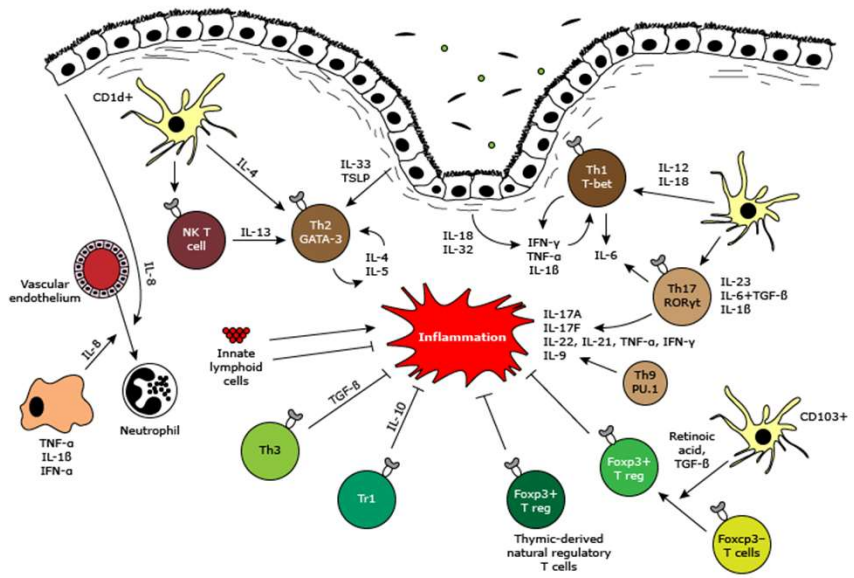
The dominant endoscopic feature in Crohn disease is the presence of ulcerations. Endoscopic findings in Crohn disease include: aphthous ulcers, which are the earliest lesions seen in Crohn disease (panel A); large ulcers interspersed with normal mucosa, which are typical for the segmental distribution of Crohn disease (panel B); a cobblestone appearance that is characterized by nodular thickening, with linear or serpiginous ulcers (panel C); and strictures due to fibrosis (panel D).

Courtesy of Paul Rutgeerts, MD, PhD, FRCP.


Inflammatory Bowel Disease (IBD)
Inflammatory Bowel Disease (IBD) is a group of chronic inflammatory conditions that affect the digestive tract, including Crohn's disease and ulcerative colitis.
Normal colon
Ulcerative colitis
Crohn's disease

IBD	IBS
Malattia	Sindrome (gruppo di sintomi)
Provoca un’infiammazione distruttiva e permanente che danneggia l’intestino	Non provoca infiammazione, raramente necessita ospedalizzazione oppure interventi chirurgici
Imaging mette in rilievo la malattia	Durante un’esame del colon non si mettono in evidenza anormalità
Rischio aumentato del tumore al colon	Non vi é un rischio aumentato di tumore al colon o di IBD
Parametri infiammatori elevati	Parametri infiammatori normali

Influence of cytokines on gut immune homeostasis



Neutrophil recruitment to the intestinal lamina propria in the early stages of inflammation is induced by IL-8, a chemokine secreted by macrophages and epithelial cells. Antigen-presenting cells including DCs and macrophages drive T helper cell (Th1), Th9, Th17, or Th2 differentiation through the secretion of IL-12 (Th1) or IL-23, IL-6, transforming growth factor (TGF)-beta, IL1 beta (Th17 or Th9 per specific combination of cytokines), or IL-4 (Th2). Epithelial cells can also secrete cytokines such as IL-33 and TSLP that can contribute to Th2 differentiation. T effector cells secrete pro-inflammatory cytokines that lead to inflammation. CD1d-restricted natural killer (NK) T cells secrete IL-13 upon activation and lead to Th2 cytokine secretion. Suppression of inflammation can occur through naturally occurring thymic-derived Foxp3+ regulatory cells (Foxp3+ Treg), IL-10 producing T cells (Tr1), or TGF-beta secreting T cells (Th3). Suppressive Foxp3+ T cells can also arise from Foxp3– T cells upon retinoic acid and TGF-beta stimulation via CD103+ DCs. T-bet, GATA-3, PU.1, ROR-gamma-t, and Foxp3 are transcription factors involved in Th1, Th2, Th9, Th17, and Treg differentiation, respectively.

Introduzione alla celiachia

- Malattia dell'intestino tenue caratterizzata da infiammazione della mucosa, atrofia dei villi

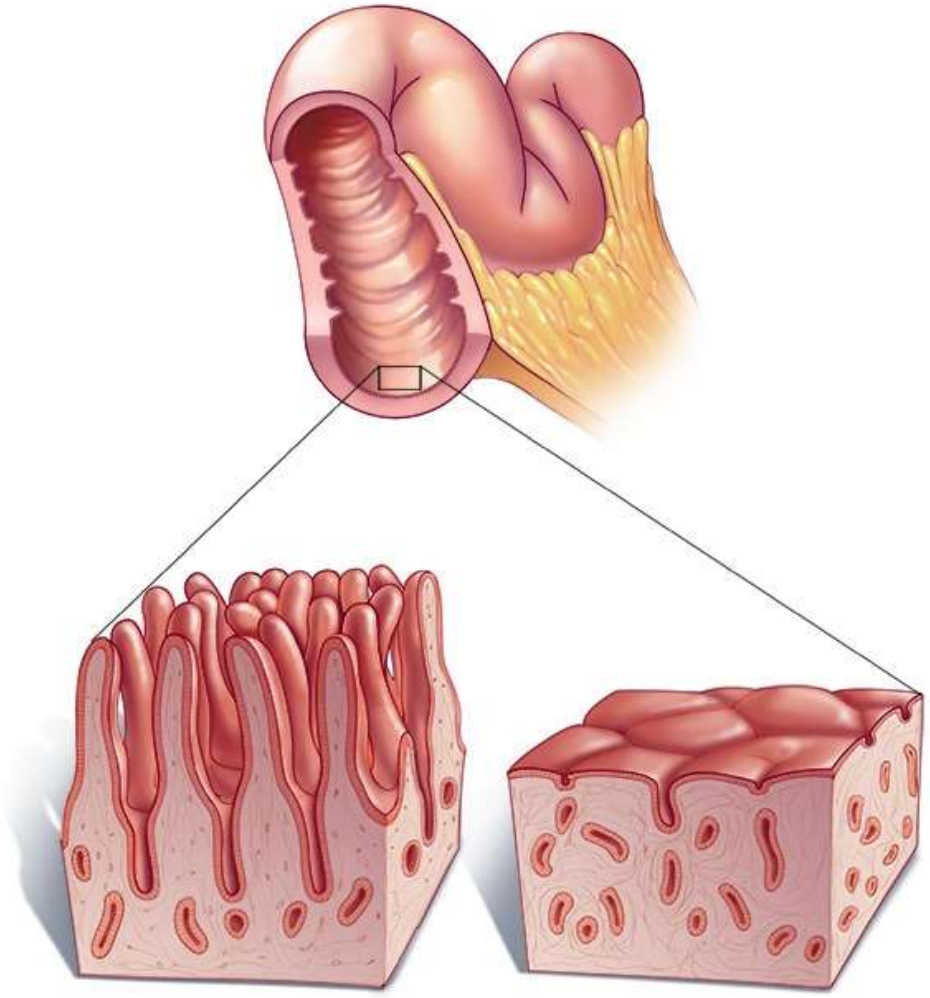
- A seguito dell'esposizione di glutine proveniente dalla dieta

La celiachia (concetti molto generali)

- Malattia infiammatoria data all'esposizione di glutine in pazienti con predisposizione genetica

- Glutine: complesso proteico insolubile in acqua le cui proteine principali sono la prolammina (=gliadina) e la gluteina. Il glutine conferisce elasticità

- A livello intestinale il glutine viene degradato dalle transglutaminasi. Nel paziente con celiachia si sviluppano anticorpi diretti contro questo enzima portando a un processo infiammatorio, congiuntamente alla produzione di peptidi che attivano i linfociti.



Chi beneficia di uno screening per celiachia

- Non si consiglia uno screening a tappeto in pazienti asintomatici
- Si consiglia lo screening in parenti di primo grado di pazienti con celiachia conclamata
- Sintomi GI per cui si consiglia lo screening
  - Diarrea o costipazone
  - Malassorbimento
  - Perdita di peso
  - Dolori addominali
  - Flatulenza
  - In pazienti con clinica suggestiva di IBS
- Segni/sintomi extra-GI suggestivi di celiachia
  - Anemia ferripriva senza motivi documentati
  - Deficit di vitamina B12 o folati
  - Aumento delle aminotrasfeasi
  - Dermatite herpetiforme
  - Stanchezza
  - Mal di testa ricorrenti
  - Poliabortività
  - Problemi di fertilità
  - Osteoporosi prematura
  - ….

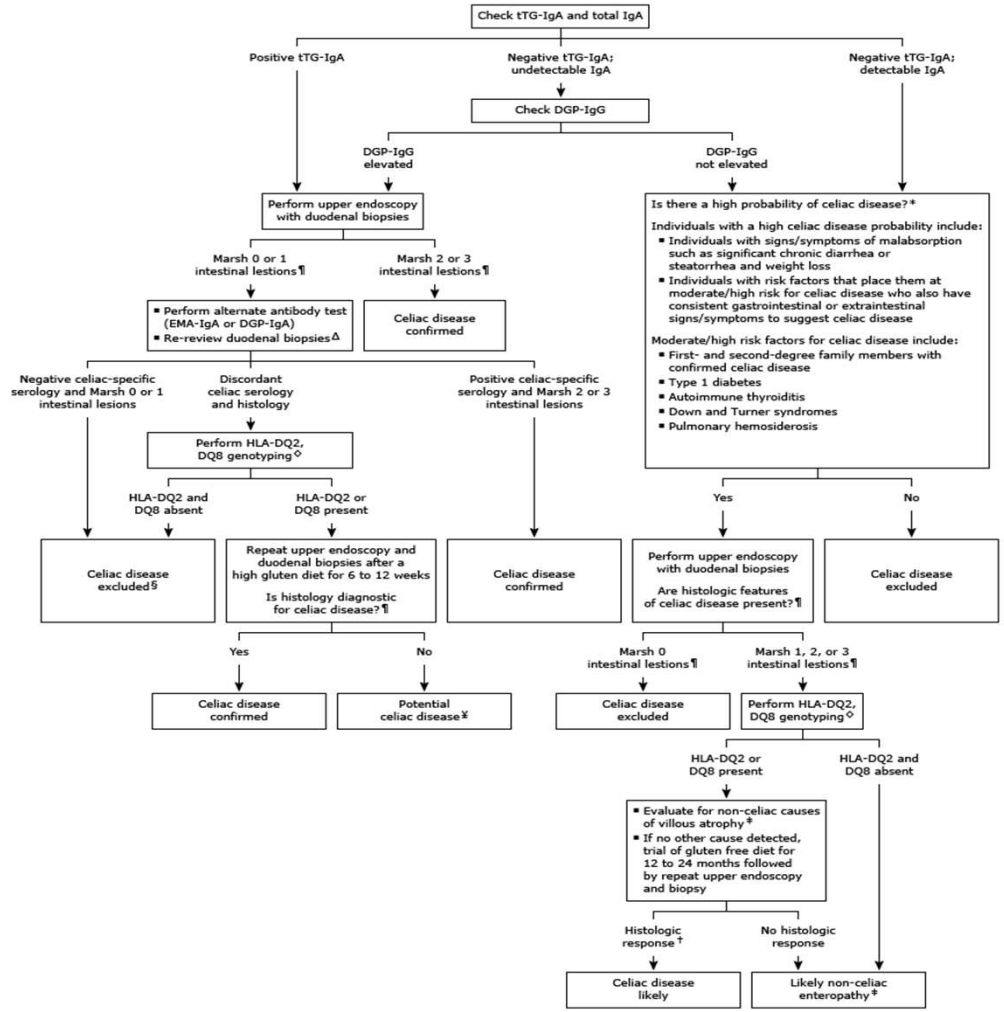
Approcio diagnostico alla celiachia

- I test sierologici andrebbero condotti quando il paziente ha una dieta con glutine

- Test sierologici e bioptici andrebbero eseguiti in pazienti con alta probabilità di avere una celiachia

  - Diarrea/steatorrea perdita di peso
  - Parenti di primo o secondo grado con casi confermati di celiachia
  - Tiroidite autoimmune
  - Sindrome di down

Diagnostic approach for suspected celiac disease in an adult patient on gluten containing diet*



This algorithm is intended for use in conjunction with additional UpToDate content on celiac disease. Refer to the UpToDate topic on diagnosis of celiac disease in adults for additional details of diagnostic testing.

tTG: tissue transglutaminase; IgA: immunoglobulin A; DGP: deamidated gliadin peptide; IgG: immunoglobulin G; EMA: endomysial antibody; HLA: human leukocyte antigen.

* Testing for celiac disease should be performed in adults with suggestive gastrointestinal or extraintestinal signs/symptoms of celiac disease. Testing for celiac disease should ideally be performed while patients are on a gluten containing diet.

¶ The histologic severity of intestinal lesions in celiac disease are graded using the Marsh-Oberhuber classification. Marsh 2 and 3 are consistent with a diagnosis of celiac disease in individuals with positive celiac-specific serology. Marsh 1 is equivocal and Marsh 0 is normal. Refer to UpToDate content on the diagnosis of celiac disease.

Δ The intestinal biopsy should be reviewed by a pathologist familiar with celiac disease to look for subtle abnormalities of celiac disease.

◇ Absence of alleles encoding DQ2 or DQ8 excludes celiac disease.

§ Other conditions associated with lymphocytic duodenosis include *Helicobacter pylori* infection, medications (eg, non-steroidal antiinflammatory drugs), small bowel bacterial overgrowth, and systemic autoimmune disorders.

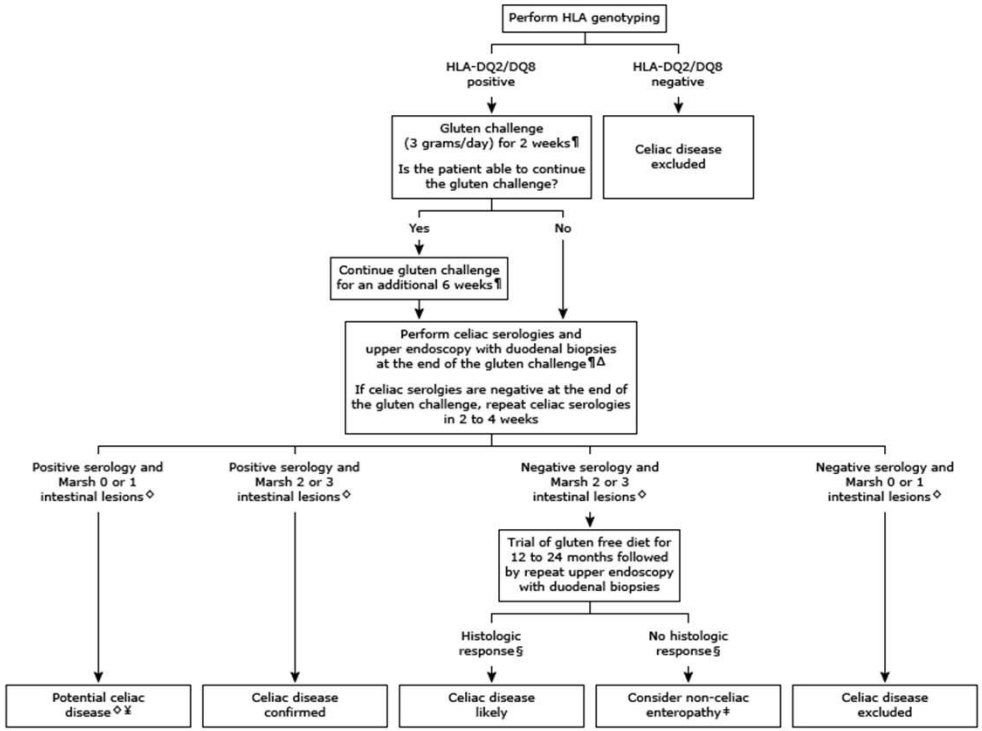
¥ Individuals with positive celiac-specific serology but Marsh 0 or 1 intestinal lesions on duodenal biopsy have potential celiac disease. Individuals with potential celiac disease should be evaluated and monitored further depending upon their clinical circumstances. Symptomatic patients with potential celiac disease are likely to benefit from treatment with a gluten free diet. Asymptomatic patients can remain on a normal diet unless clinical features of celiac disease develop.

‡ There are several causes of non-celiac enteropathy (villous atrophy in duodenum). Potential causes include giardiasis, small-bowel bacterial overgrowth, and common variable immunodeficiency. For a more comprehensive list of causes, refer to UpToDate content on diagnosis of celiac disease.

† An improvement in histology (with or without complete resolution) on a gluten free diet in patients with villous atrophy strongly supports a diagnosis of celiac disease.

This algorithm is intended for use in conjunction with additional UpToDate content on celiac disease. Refer to the

Diagnostic approach for suspected celiac disease in an adult patient on gluten free diet and negative baseline serologies*



This algorithm is intended for use in conjunction with additional UpToDate content on celiac disease. Refer to the UpToDate topic on diagnosis of celiac disease in adults for additional details of diagnostic testing.

HLA: human leukocyte antigen; tTG: tissue transglutaminase; IgA: immunoglobulin A; IgG: immunoglobulin G; DGP: deamidated gliadin peptide.

* Testing for celiac disease should be performed in adults with suggestive gastrointestinal or extraintestinal signs/symptoms of celiac disease.

¶ A two-week gluten challenge may yield false-negative results in 10% of patients. The added diagnostic sensitivity of extending the challenge to a total of eight weeks is unknown.

Δ tTG-IgA antibody is the single preferred test for detection of celiac disease in adults. In addition, we concurrently measure total IgA levels. In patients with IgA deficiency, we perform IgG based testing with DGP-IgG.

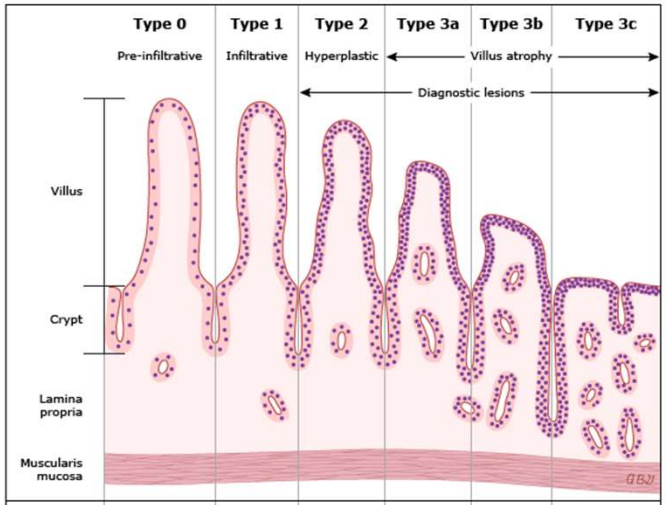
◇ The histologic severity of intestinal lesions in celiac disease are graded using the Marsh-Oberhuber classification. Marsh 2 and 3 are consistent with a diagnosis of celiac disease in individuals with positive celiac-specific serology. Marsh 1 is equivocal and Marsh 0 is normal. Refer to UpToDate content on diagnosis of celiac disease.

§ An improvement in histology, even in the absence of complete histologic resolution, is supportive of the diagnosis of celiac disease.

¥ Individuals with positive celiac-specific serology but Marsh 0 or 1 intestinal lesions on duodenal biopsy have potential celiac disease. Individuals with potential celiac disease should be evaluated and monitored further depending upon their clinical circumstances. Symptomatic patients with potential celiac disease are likely to benefit from treatment with a gluten free diet.

‡ There are several causes of non-celiac enteropathy (villous atrophy in duodenum). Potential causes include giardiasis, small intestinal bacterial overgrowth, and common variable immunodeficiency. For a more comprehensive list of causes, refer to UpToDate content on diagnosis of celiac disease.

Intestinal lesions in celiac disease



	Type 0	Type 1	Type 2	Type 3a	Type 3b	Type 3c
Villus	Normal	Normal	Normal	Mild atrophy	Moderate atrophy	Severe atrophy
Crypt	Normal	Normal	Hyperplasia	Hyperplasia	Hyperplasia	Hyperplasia
Ratio, villus height: crypt depth	3:1	3:1	<3:1	<2:1	1:1	<1:1
IEL/ 100 EC	<40	>40	>40	>40	>40	>40

Schematic drawing of the characteristic histologic changes seen in celiac disease as described by Marsh. The lesions range in severity from only increased numbers of intraepithelial lymphocytes in the early stages (Type I) to elongation of the crypts (Type II) and progressive villus atrophy (Type 3a to 3c).

IEL: intraepithelial lymphocytes; EC: epithelial cells (in villus).

Modified from: Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102:330.

Dr Risch

Il vostro laboratorio – oggi e domani

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