

**Convegno "Allergie, intolleranze e celiachia: tra  
verità scientifiche e falsi miti"**

**20 maggio 2016 ISS Roma**

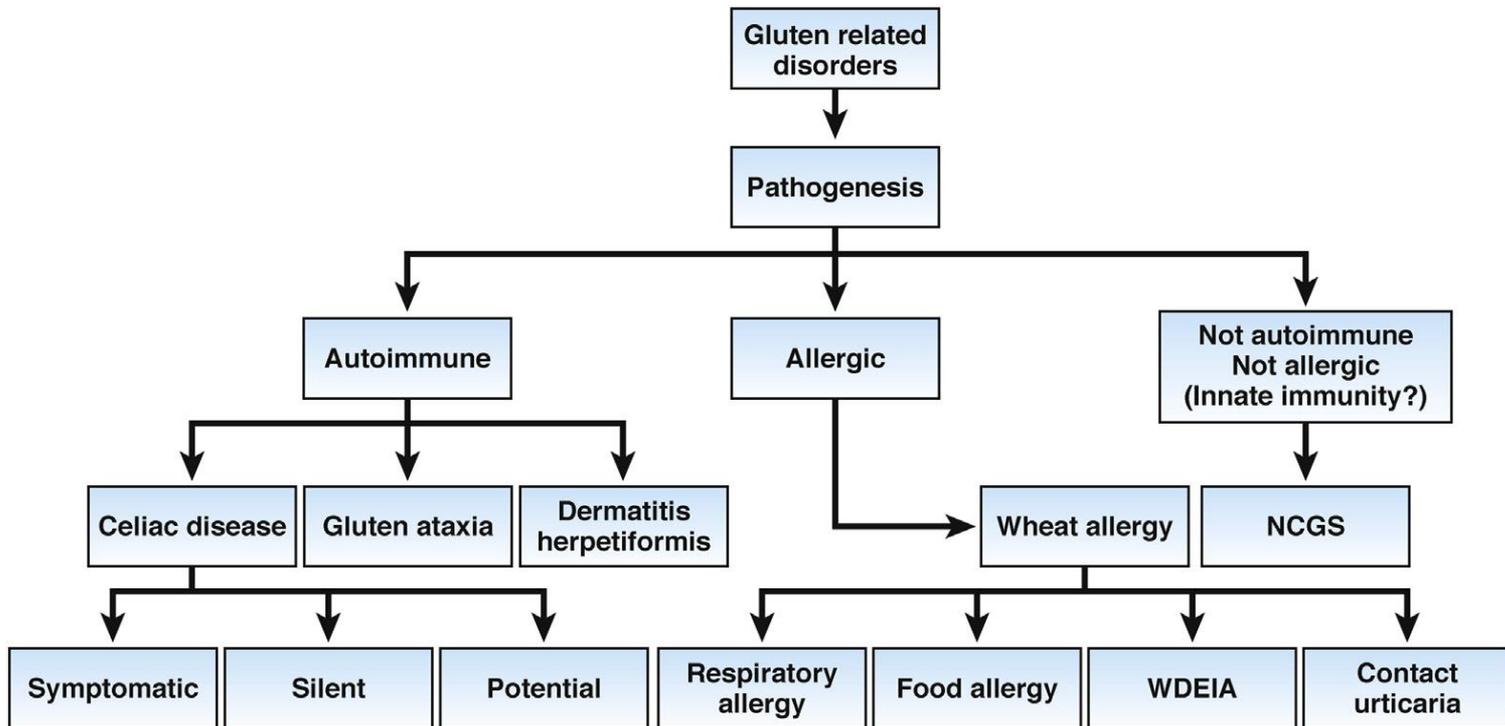
# ***GLUTEN SENSITIVITY***

***Marco Silano***



***Reparto di Alimentazione, Nutrizione e Salute  
Dipartimento di Sanità Pubblica Veterinaria e Sicurezza Alimentare***

# Patologie glutine - dipendenti



# Definizione

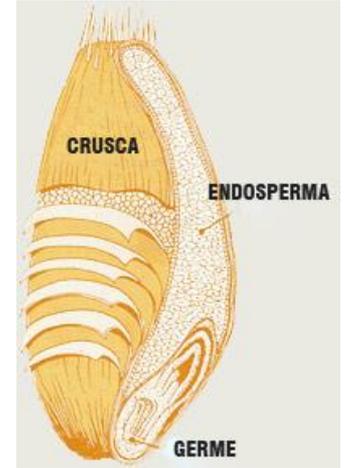
**Non-Celiac Gluten Sensitivity (NCGS) is a syndrome characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food, in subjects that are not affected by either celiac disease (CD) or wheat allergy (WA)**

**Table 1.** The clinical manifestations of Non-Celiac Gluten Sensitivity (NCGS).

<b>Frequency</b>	<b>Intestinal</b>	<b>Extra-Intestinal</b>
Very Common	Bloating	Lack of wellbeing
	Abdominal pain	Tiredness
Common	Diarrhea	Headache
	Epigastric pain	Anxiety
	Nausea	Foggy mind
	Aerophagia	Numbness
	GER	Joint/muscle pain
	Aphthous stomatitis	Skin rash/dermatitis
	Alternating bowel habits	
	Constipation	

***GLUTINE***

# GLUTINE



## ALBUMINE

idrosolubili

## GLOBULINE

solubili in sol. salina

## GLIADINA $\alpha$ $\beta$ $\gamma$ $\omega$

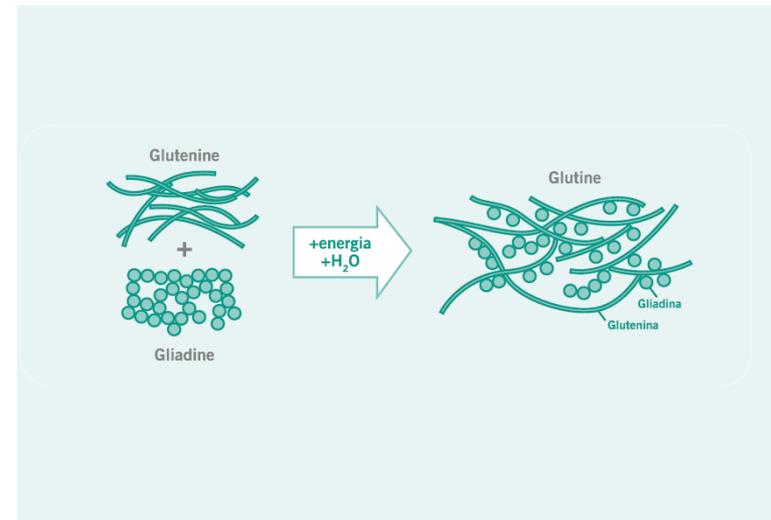
solubili in etanolo

## GLUTENINE

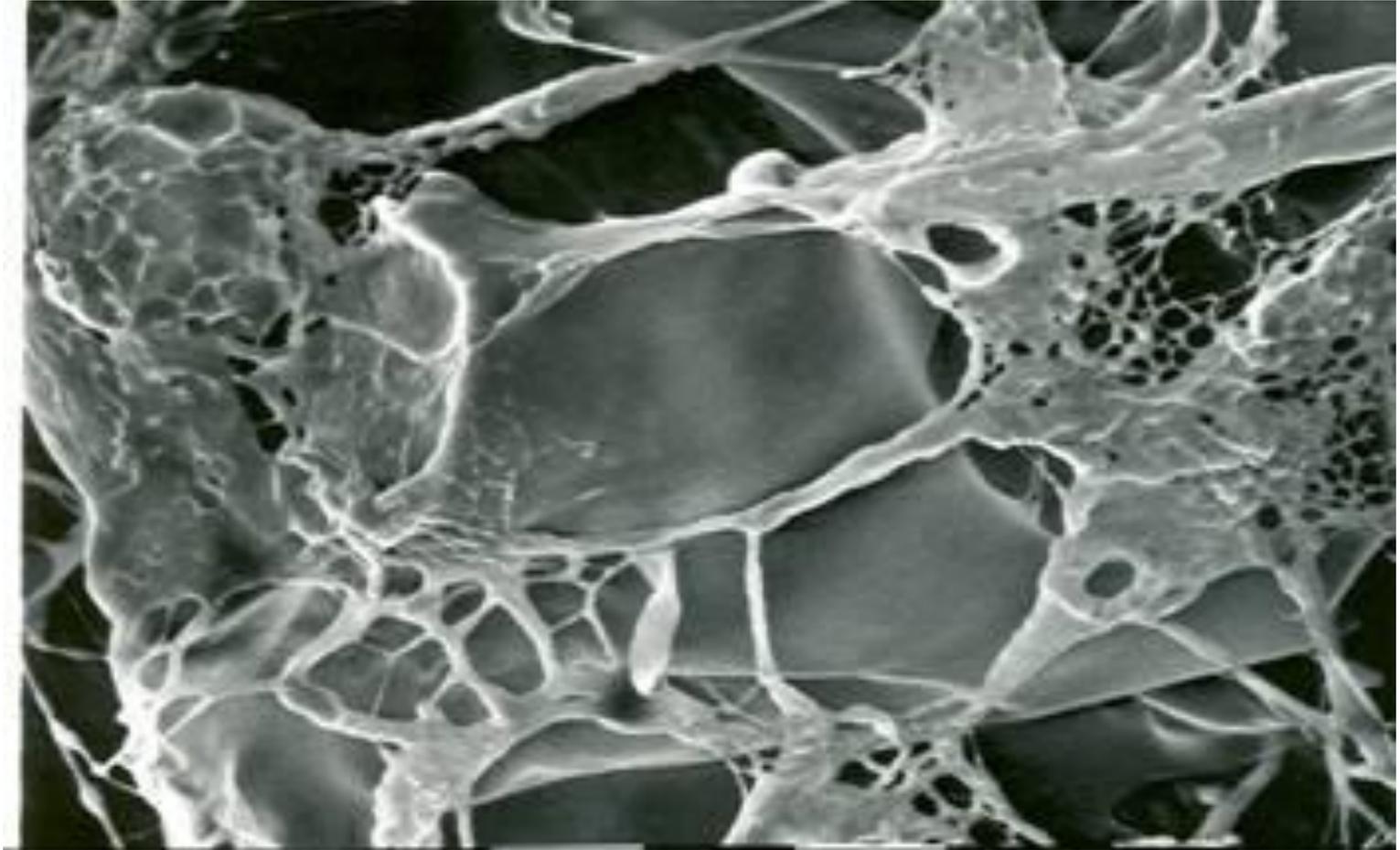
HMW LMW

solubili in acido acetico

### Proteine di riserva



# GLUTINE





**Alveografo di Chopin**



*Lo sai che il glutine è dannoso per tutti?*

sab 19 MILANO - via Stilicone, 37  
 dom 20 MILANO - via Cottolengo, 12  
 sab 26 NOVARA - viale Dante, 27A  
 27 INVERUNO - via Marcora, 39

da noi trovi tutto, anche i nostri prodotti esclusivi che altri non hanno



Dr. Stephen Wangen

# PIÙ SANI SENZA GRANO

NUOVE PROSPETTIVE E CONOSCENZE SU: ALLERGIE AI PRODOTTI DERIVATI DAL GRANO, CELIACHIA E INTOLLERANZA AL GLUTINE.

la biblioteca del benessere

**GRANO EDIZIONE**

**10 giorni senza glutine**

RIZA Perdi subito 3 chili!

**100 ricette utili contro**

- sovrappeso
- cellulite
- psoriasi
- celiachia

PERDI FINO A 20 KG IN POCCHI MESI

# LA DIETA ZERO GRANO

DR WILLIAM DAVIS

MONDADORI **meglio**

RIZA **72**

## SALUTE NATURALE EXTRA

OGNI MESE UNA CURA VINCENTE

SEMPRE PIÙ ITALIANI SONO INTOLLERANTI E NON LO SANNO

# ELIMINA IL GLUTINE DIMAGRISCI SUBITO

IN 7 GIORNI risultati sorprendenti: vanno via gonfiori, fermentazioni e digestione lenta

**CI VOGLIONO I CEREALI GLUTEN FREE!**

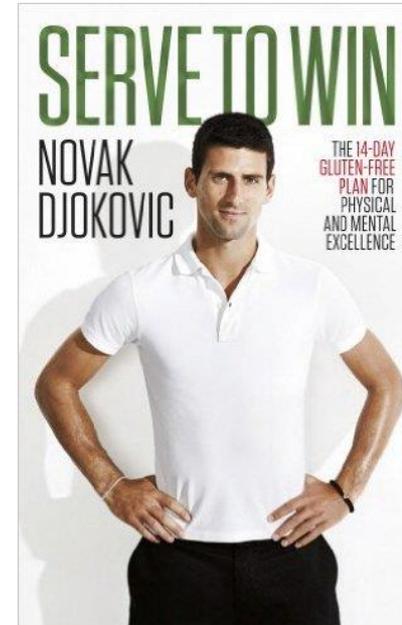
Con il miglio, il grano saraceno e il teff di Etiopia spazzi via le tossine acide che ti fanno ammalare

**SCOPRI I CIBI GIUSTI!**  
Ecco i cereali ricchi di fibre dimagranti che disinflammanno

**IL NOSTRO TEST**  
Scopri se stai assumendo troppo glutine

**IL VANTAGGIO IN PIÙ**  
Con l'amaranto fai scorta di ferro e proteine "magre"

# Il glutine fa male anche a chi non è celiaco ?



# Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Jessica R. Biesiekierski, B Appl Sci<sup>1</sup>, Evan D. Newnham, MD, FRACP<sup>1</sup>, Peter M. Irving, MD, MRCP<sup>1</sup>, Jacqueline S. Barrett, PhD, BSc, MND<sup>1</sup>, Melissa Haines, MD<sup>1</sup>, James D. Doecke, BSc, PhD<sup>2</sup>, Susan J. Shepherd, B Appl Sci, PhD<sup>1</sup>, Jane G. Muir, PhD, PGrad Dip(Dietetics)<sup>1</sup> and Peter R. Gibson, MD, FRACP<sup>1</sup>

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**OBJECTIVES:** Despite increased prescription of a gluten-free diet for gastrointestinal symptoms in individuals who do not have celiac disease, there is minimal evidence that suggests that gluten is a trigger. The aims of this study were to determine whether gluten ingestion can induce symptoms in non-celiac individuals and to examine the mechanism.

**METHODS:** A double-blind, randomized, placebo-controlled rechallenge trial was undertaken in patients with irritable bowel syndrome in whom celiac disease was excluded and who were symptomatically controlled on a gluten-free diet. Participants received either gluten or placebo in the form of two bread slices plus one muffin per day with a gluten-free diet for up to 6 weeks. Symptoms were evaluated using a visual analog scale and markers of intestinal inflammation, injury, and immune activation were monitored.

**RESULTS:** A total of 34 patients (aged 29–59 years, 4 men) completed the study as per protocol. Overall, 56% had human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8. Adherence to diet and supplements was very high. Of 19 patients (68%) in the gluten group, 13 reported that symptoms were not adequately controlled compared with 6 of 15 (40%) on placebo ( $P=0.0001$ ; generalized estimating equation). On a visual analog scale, patients were significantly worse with gluten within 1 week for overall symptoms ( $P=0.047$ ), pain ( $P=0.016$ ), bloating ( $P=0.031$ ), satisfaction with stool consistency ( $P=0.024$ ), and tiredness ( $P=0.001$ ). Anti-gliadin antibodies were not induced. There were no significant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2/DQ8.

**CONCLUSIONS:** “Non-celiac gluten intolerance” may exist, but no clues to the mechanism were elucidated.

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*Am J Gastroenterol* 2011; 106:508–514; doi:10.1038/ajg.2010.487; published online 11 January 2011

**EFFETTO PLACEBO/NOCEBO !!**

## No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates

JESSICA R. BIESIEKIERSKI,<sup>1,2</sup> SIMONE L. PETERS,<sup>2</sup> EVAN D. NEWNHAM,<sup>1</sup> OURANIA ROSELLA,<sup>2</sup> JANE G. MUIR,<sup>2</sup> and PETER R. GIBSON<sup>2</sup>

<sup>1</sup>Department of Gastroenterology, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia and <sup>2</sup>Department of Gastroenterology, Central Clinical School, Monash University, The Alfred Hospital, Melbourne, Victoria, Australia

**Podcast interview: [www.gastro.org/gastropodcast](http://www.gastro.org/gastropodcast). Also available on iTunes. See editorial on page 276.**

**BACKGROUND & AIMS:** Patients with non-celiac gluten sensitivity (NCGS) do not have celiac disease but their symptoms improve when they are placed on gluten-free diets. We investigated the specific effects of gluten after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates (fermentable, oligo-, di-, monosaccharides, and polyols [FODMAPs]) in subjects believed to have NCGS. **METHODS:** We performed a double-blind cross-over trial of 37 subjects (aged 24–61 y, 6 men) with NCGS and irritable bowel syndrome (based on Rome III criteria), but not celiac disease. Participants were randomly assigned to groups given a 2-week diet of reduced FODMAPs, and were then placed on high-gluten (16 g gluten/d), low-gluten (2 g gluten/d and 14 g whey protein/d), or control (16 g whey protein/d) diets for 1 week, followed by a washout period of at least 2 weeks. We assessed serum and fecal markers of intestinal inflammation/injury and immune activation, and indices of fatigue. Twenty-two participants then crossed over to groups given gluten (16 g/d), whey (16 g/d), or control (no additional protein) diets for 3 days. Symptoms were evaluated by visual analogue scales. **RESULTS:** In all participants, gastrointestinal symptoms consistently and significantly improved during reduced FODMAP intake, but significantly worsened to a similar degree when their diets included gluten or whey protein. Gluten-specific effects were observed in only 8% of participants. There were no diet-specific changes in any biomarker. During the 3-day rechallenge, participants' symptoms increased by similar levels among groups. Gluten-specific gastrointestinal effects were not reproduced. An order effect was observed. **CONCLUSIONS:** In a placebo-controlled, cross-over rechallenge study, we found no evidence of specific or dose-dependent effects of gluten in patients with NCGS placed diets low in FODMAPs. [www.anzctr.org.au](http://www.anzctr.org.au). ACTRN12610000524099

gluten-containing products continues to increase worldwide.<sup>2</sup> The clinical entity of non-celiac gluten sensitivity (NCGS) has been defined as those without celiac disease but whose gastrointestinal symptoms improve on a gluten-free diet (GFD).<sup>3,4</sup> Since its original description in 1980,<sup>5</sup> reports of NCGS have not taken into account the presence of other components of wheat, particularly fructans, that might have been pathogenically responsible for the symptoms. The first evidence that gluten might specifically induce symptoms in patients with IBS derived from a randomized, placebo-controlled trial of a single dose of carbohydrate-deplete gluten in 36 patients remaining on their habitual GFD in parallel groups.<sup>6</sup> Although there is some evidence of the effects of gluten in animal models or cancer cell lines,<sup>7–9</sup> little else is known about this entity. For example, mechanisms have not been identified and dose dependence has not been demonstrated.

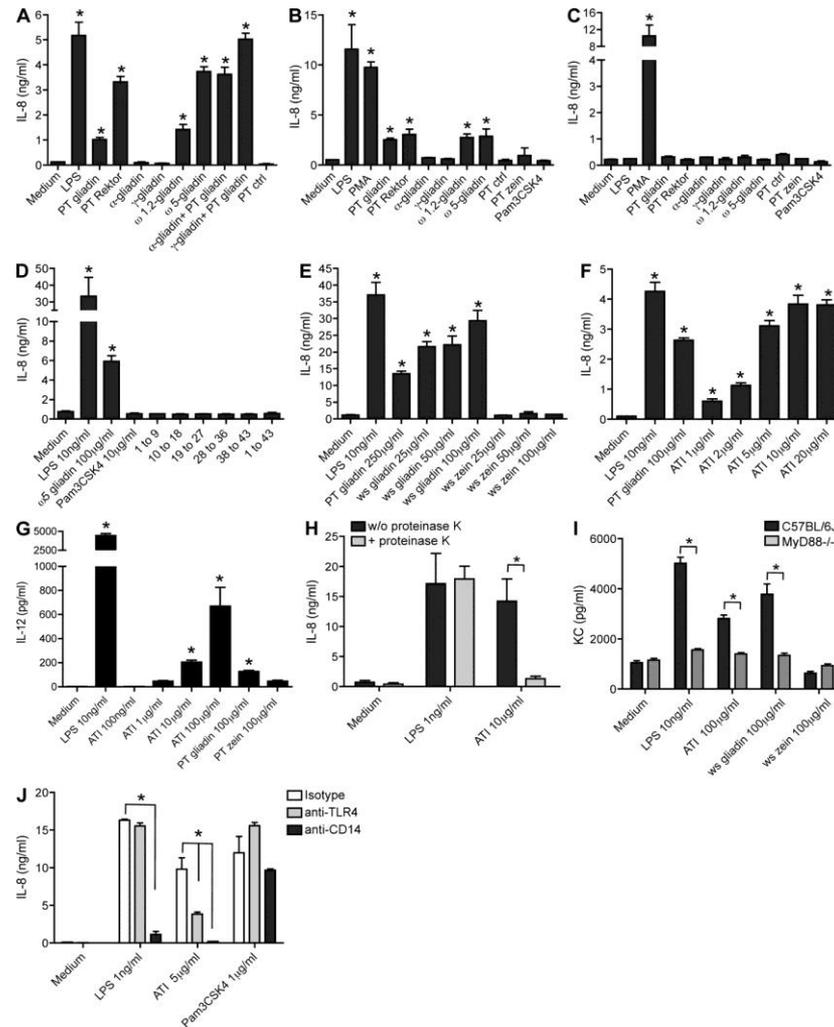
To further evaluate this concept of NCGS, the current study aimed to examine the hypotheses that, in subjects who report to have NCGS, gluten induces dose-dependent, reproducible gastrointestinal and systemic symptoms. To do this, a randomized, double-blind, cross-over controlled feeding trial of 3 diets differing in gluten content was conducted in patients with IBS fulfilling the definition of NCGS, followed by a rechallenge trial in the same patient cohort. In order to control other potential triggers of gut symptoms, all diets had reduced content of fermentable, poorly absorbed short-chain carbohydrates (ie, fermentable, oligo-, di-, monosaccharides, and polyols [FODMAPs])<sup>10</sup> and, in the second, dairy products and food chemicals were additionally controlled.

### Patients and Methods

#### Patients

Patients were recruited between January 2010 and January 2011 via advertisements in e-newsletters and community newspapers in metropolitan Melbourne, Australia and by referrals from private dietetics practice or gastroenterology clinics. The inclusion

# Glutadin-induced innate immune responses are elicited by wheat ATI, a protein copurifying with $\omega$ -glutadins.



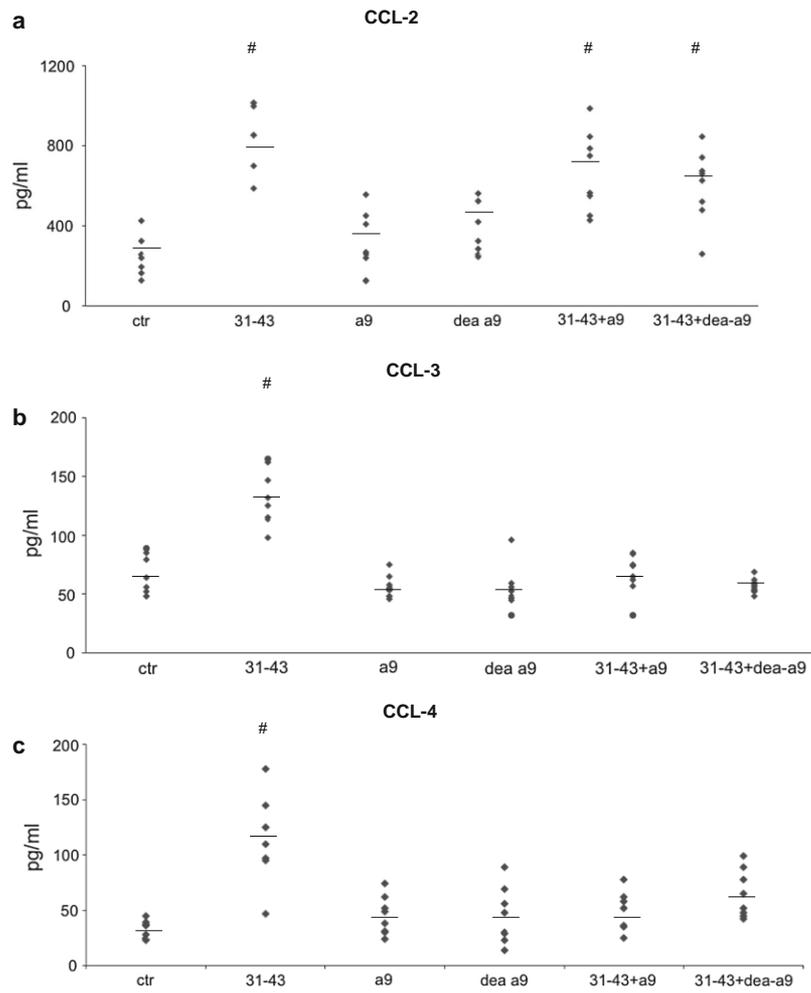
Yvonne Junker et al. J Exp Med 2012;209:2395-2408

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## Differential Mucosal IL-17 Expression in Two Gliadin-Induced Disorders: Gluten Sensitivity and the Autoimmune Enteropathy Celiac Disease

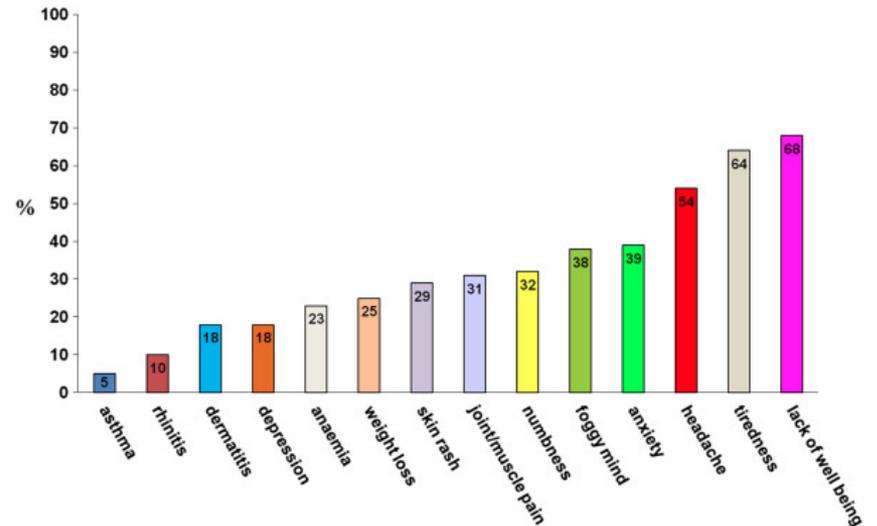
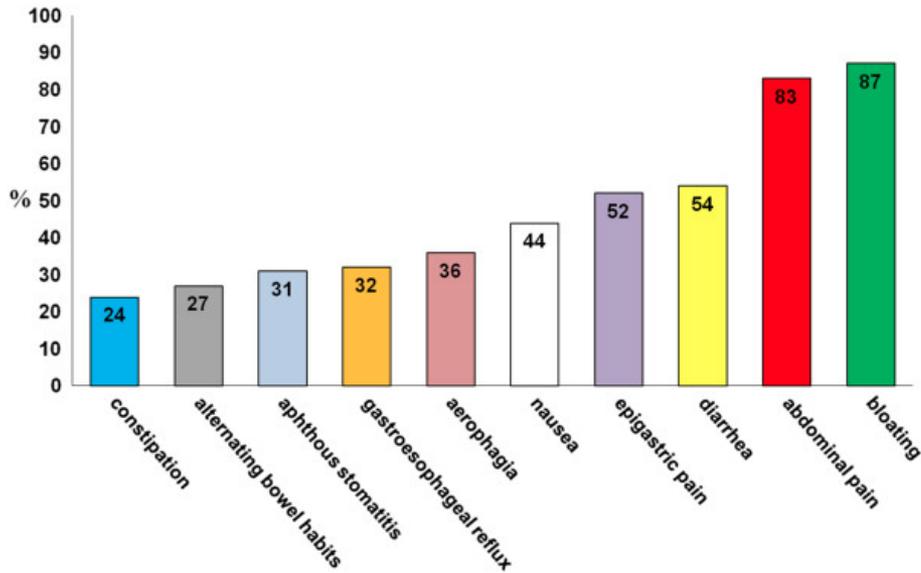
Anna Sapone<sup>a,b</sup> Karen M. Lammers<sup>b</sup> Giuseppe Mazzearella<sup>d</sup> Irina Mikhailenko<sup>c</sup>  
Maria Carteni<sup>a</sup> Vincenzo Casolaro<sup>b,e</sup> Alessio Fasano<sup>b</sup>

<sup>a</sup>Sezione Biotecnologia e Biologia Molecolare, Dipartimento di Medicina Sperimentale, Seconda Università degli Studi di Napoli, Naples, Italy; <sup>b</sup>Mucosal Biology Research Center and <sup>c</sup>Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, Md., USA; <sup>d</sup>Istituto Scienze Alimentari, CNR, Avellino, Italy; <sup>e</sup>Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, Md., USA



## Gliadin-dependent cytokine production in a bidimensional cellular model of celiac intestinal mucosa

Olimpia Vincentini · Francesca Maialetti ·  
 Elena Gonnelli · Marco Silano



Volta et al. *BMC Medicine* 2014, **12**:85  
<http://www.biomedcentral.com/1741-7015/12/85>

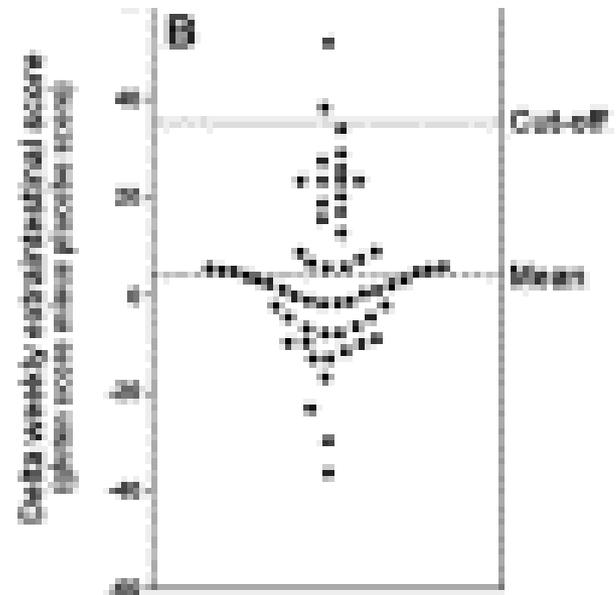
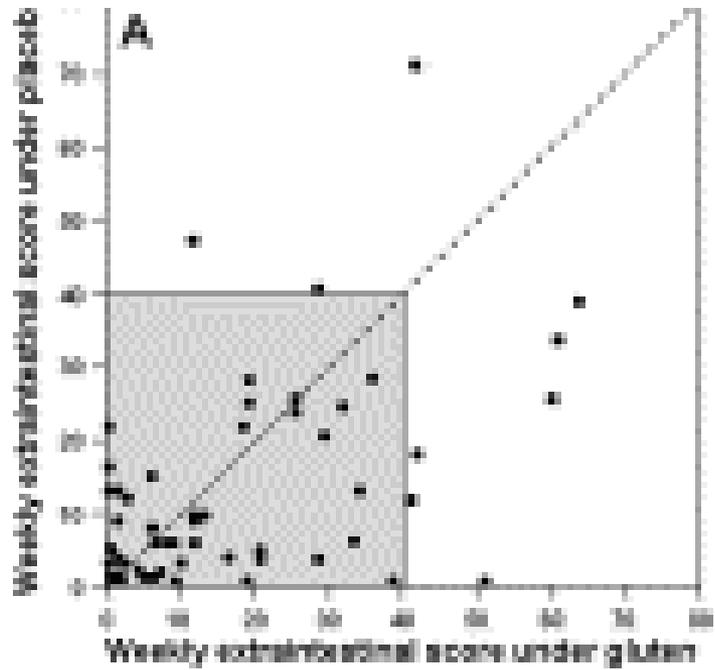


RESEARCH ARTICLE

Open Access

## An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity

Umberto Volta<sup>1\*</sup>, Maria Teresa Bardella<sup>2</sup>, Antonino Calabrò<sup>3</sup>, Riccardo Troncone<sup>4</sup>, Gino Roberto Corazza<sup>5</sup> and The Study Group for Non-Celiac Gluten Sensitivity



# **NONCELIAC GLUTEN AND WHEAT SENSITIVITY**

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## **Nonceliac Gluten Sensitivity**



# Diagnosi

- esclusione MC e WA
  - eliminazione glutine dalla dieta per almeno 6 settimane con miglioramento del 30% dei sintomi
  - DB PB GC cross - over
- } *self administrated*  
} *questionnaire*

Nutrients 2015, 7, 4966-4977; doi:10.3390/nu7064966

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**nutrients**

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Article

## Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria

Carlo Catassi <sup>1\*</sup>, Luca Elli <sup>2</sup>, Bruno Bonaz <sup>3</sup>, Gerd Bouma <sup>4</sup>, Antonio Carruccio <sup>5</sup>, Gemma Castillejo <sup>6</sup>, Christophe Cellier <sup>7</sup>, Fernanda Cristofori <sup>8</sup>, Laura de Magistris <sup>9</sup>, Jernej Dolinsek <sup>10</sup>, Walburga Dieterich <sup>11</sup>, Ruggiero Francavilla <sup>8</sup>, Marios Hadjivassiliou <sup>12</sup>, Wolfgang Holtmeier <sup>13</sup>, Ute Körner <sup>14</sup>, Dan A. Leffler <sup>15</sup>, Knut E. A. Lundin <sup>16</sup>, Giuseppe Mazzarella <sup>17</sup>, Chris J. Mulder <sup>4</sup>, Nicoletta Pellegrini <sup>18</sup>, Kamran Rostami <sup>19</sup>, David Sanders <sup>20</sup>, Grylrene Skodje <sup>21</sup>, Detlef Schuppan <sup>22</sup>, Reiner Ullrich <sup>23</sup>, Umberto Volta <sup>24</sup>, Marianne Williams <sup>25</sup>, Victor F. Zevallos <sup>22</sup>, Yurdagül Zopf <sup>11</sup> and Alessio Fasano <sup>26</sup>

# Gluten sensitivity vs CD

- agente ambientale (gluten, wheat, ATIs) ??????
- predisposizione genetica NO
- marker serologico noto NO
- lesioni mucosali intestinali NO
- terapia ?????
- permanente NO
- sintomi SI

# Gluten sensitivity

## QUALCHE MITO, SENZA NESSUNA EVIDENZA SCIENTIFICA:

- ✓ 6 % della popolazione generale
- ✓ beneficio dai prodotti dietoterapici SG
- ✓ auto – diagnosi e auto-prescrizione della DSG

**Con il termine NCGS (Sensibilità al Glutine Diversa dalla Celiachia) si definisce una sindrome caratterizzata dalla presenza, in rapporto all'ingestione di alimenti contenenti glutine, di sintomi intestinali ed extra intestinali in pazienti in cui MC ed allergia alle proteine del frumento siano già state escluse. Pazienti con tali caratteristiche sono noti da anni ma è bene premettere che, nonostante un numero crescente di essi riferisca quadri di questo tipo, l'esistenza stessa della sindrome è ancora messa in dubbio da numerosi esperti. Più in particolare, il fatto che i disturbi (quasi tutti soggettivi!) migliorino all'esclusione del glutine e peggiorino alla sua reintroduzione viene considerato come legato al ben noto effetto placebo e nocebo delle diete da eliminazione e provocazione. D'altra parte studi «in cieco» sono resi difficili e scarsamente affidabili dalla riconoscibilità (mai adeguatamente testata «a priori») del glutine quando aggiunto o mescolato ad altri alimenti.**

**•Tutti, pertanto, concordano sul fatto che i risultati finora ottenuti si riferiscono a pazienti presunti, ma non sicuramente portatori di tale sindrome, e sulla necessità di studi ulteriori e più approfonditi.**

**•Sul piano clinico è fondamentale combattere l'autodiagnosi ed evitare che, il paziente abbia già escluso il glutine prima ancora di un consulto medico.**

***GRAZIE PER  
L'ATTENZIONE***