Potter M, Walker MM, Talley NJ. **Non-coeliac gluten or wheat sensitivity: emerging disease or misdiagnosis?** Med J Aust. 2017 Aug 4;207(5):211-215.

Non-coeliac gluten or wheat sensitivity (NCG/WS) is a condition characterised by adverse gastrointestinal and/or extra-intestinal symptoms associated with the ingestion of gluten- or wheat-containing foods, in the absence of coeliac disease or wheat allergy. Up to one in 100 people in Australia may have coeliac disease but many more report adverse gastrointestinal and/or extra-intestinal symptoms after eating wheat products. In the absence of validated biomarkers, a diagnosis of NCG/WS can only be made by a double-blind, placebo-controlled, dietary crossover challenge with gluten, which is difficult to apply in clinical practice. Of people self-reporting gluten or wheat sensitivity, only a small proportion (16%) will have reproducible symptoms after a blinded gluten challenge of gluten versus placebo in a crossover dietary trial and fulfil the current consensus criteria for a diagnosis of NCG/WS. A wide range of symptoms are associated with NCG/WS, including gastrointestinal, neurological, psychiatric, rheumatological and dermatological complaints. The pathogenesis of NCG/WS is not well understood, but the innate immune system has been implicated, and there is overlap with coeliac disease and the functional gastrointestinal disorders (irritable bowel syndrome and functional dyspepsia). Identification of NCG/WS is important as gluten-free diets carry risks, are socially restricting and are costlier than regular diets.

Watkins RD, Zawahir S. **Celiac Disease and Nonceliac Gluten Sensitivity**. Pediatr Clin North Am. 2017 Jun;64(3):563-576.

Gluten-related disorders include celiac disease (CD), wheat allergy, and nonceliac gluten sensitivity. CD is an autoimmune enteropathy caused by damage to small intestinal mucosa when gluten is ingested in genetically susceptible individuals. Currently, the only available treatment of CD is gluten-free diet. Several potential treatments are being researched. Wheat allergy is a hypersensitivity reaction caused by IgE-mediated and/or non-IgE-mediated immune response, and can involve the gastrointestinal tract, skin, or respiratory tract. Nonceliac gluten sensitivity is one of a variety of immunologic, morphologic, or symptomatic manifestations precipitated by ingestion of gluten in individuals in whom CD and wheat allergy are excluded.

Burkhardt JG, Chapa-Rodriguez A, **Bahna SL. Gluten sensitivities and the allergist: Threshing the grain from the husks.** Allergy. 2017 Nov 13.

'"Gluten sensitivity" has become commonplace among the public. Wheat allergy (WA) and celiac disease (CD) are well-defined entities, but are becoming a fraction of individuals following a gluten-free diet. WA has a prevalence of <0.5%. Wheat, specifically its omega-5 gliadin fraction, is the most common allergen implicated in food-dependent, exercise-induced anaphylaxis. CD is a non-IgE hypersensitivity to certain cereal proteins: gluten in wheat, secalin in rye, hordein in barley, and to a lesser extent avenin in oat. It is a rare disease, with an estimated prevalence that varied widely geographically, being higher in Northern Europe and the African Saharawi region than in Southeast Asia. In addition to suggestive symptoms, serologic testing has high diagnostic reliability and biopsy is a confirmatory procedure. CD patients have extra-intestinal autoimmune comorbid conditions more frequently than expected. A third entity is non-celiac gluten sensitivity, which has been created because of the increasing number of subjects who claim a better quality of life or improvement of their variety of symptoms on switching to a gluten-free diet. The phenomenon is being fueled by the media and exploited by the industry. The lack of a specific objective test has been raising substantial controversy about this entity. Allergists and gastroenterologists need to pay attention to the multitudes of individuals who elect to follow a gluten-free diet. Many such subjects might have WA, CD, or another illness. Providing them with appropriate evaluation and specific management would be of great advantages, medically and economically.

Casella G, Pozzi R, Cigognetti M, Bachetti F, Torti G, Cadei M, Villanacci V, Baldini V, Bassotti G. **Mood disorders and non-celiac gluten sensitivity**. Minerva Gastroenterol Dietol. 2017 Mar;63(1):32-37.

The association between gluten related disorders and psychiatric diseases has been firmly demonstrated. Non-celiac gluten sensitivity (NCGS) is a syndrome diagnosed in patients responsive to gluten-free diet after ruling out celiac disease and wheat allergy. The pathogenesis of neuro-psychiatric disorders in NCGS is unclear. An association between gluten and schizophrenia was described for the first time in 1950 by Bender et al. In the 1950's, Dicke noted that gluten-free diet improved mood in celiac patients. In 1970, Goldberg et al., in a study of 80 celiac patients, found that 34% of them showed minor affective disorders. Bipolar disorder patients show an increase of blood anti gliadin deamidated antibodies (IgG). The effect of diet and nutrition on autistic spectrum disorders has been investigated in the last two decades, particularly focusing on the symptoms of hyperactivity and attention. *Toxoplasma gondii* and other neurotropic pathogens as *Influenzavirus* and *Coronavirus* may be associated with mood disorders, probably secondary to an increased

intestinal permeability. Abnormalities of host-microbiota interactions or of gut-microbiota composition have been associated with central nervous system disorders, such as autism, anxiety, depression and the integrity of intestinal microbiota may be considered a potential therapeutic goal to treat these conditions.

Skodje GI, Henriksen C, Salte T, Drivenes T, Toleikyte I, Lovik AM, Veierød MB, Lundin KE. **Wheat challenge in self-reported gluten sensitivity: a comparison of scoring methods.** Scand J Gastroenterol. 2017 Feb;52(2):185-192.

BACKGROUND:

The condition non-coeliac gluten sensitivity (NCGS) is clinically similar to coeliac disease, but lack objective diagnostic criteria. Symptom relief on gluten-free diet followed by gluten containing food challenge may confirm the condition in clinical settings.

AIM:

To describe the results of an open bread challenge in patients with suspected NCGS, and to compare the results with recently suggested cut-offs for symptom change.

MATERIAL AND METHODS:

Fifty-six patients (12 males) self-instituted on gluten-free diet with negative coeliac disease diagnostics were examined for NCGS by an open bread challenge. Symptoms were reported by Gastrointestinal Symptom Rating Scale, IBS-version (GSRS-IBS) and visual analogue scale (VAS). Results were retrospectively compared to the Salerno and Monash cut-offs for symptom change.

RESULTS:

Forty-seven patients were diagnosed with NCGS. Total GSRS-IBS score and overall symptoms by VAS increased significantly in NCGS ($p < .001$), but not in non-NCGS patients ($p < .12$ and $p = .08$, respectively). Total GSRS-IBS challenge score and overall symptoms by VAS were significantly higher in NCGS than in non-NCGS patients (53 vs. 37, $p = .004$ and 76 vs. 39 mm, $p = .02$, respectively). Applying the Salerno and Monash cut-offs, 63 and 75% would be classified with NCGS, respectively. According to total GSRS-IBS absolute agreement was lowest between clinician's diagnosis and Salerno cut-off (63%) and highest between Salerno and Monash cut-offs (88%).

CONCLUSION:

Clinician diagnosed 85% with NCGS. The proportion of NCGS was lower according to the Salerno and Monash cut-offs. The Salerno cut-off should be the starting point for a common definition of symptom change.

Igbinedion SO, Ansari J, Vasikaran A, Gavins FN, Jordan P, Boktor M, Alexander JS. **Non-celiac gluten sensitivity: All wheat attack is not celiac**. World J Gastroenterol. 2017 Oct 28;23(40):7201-7210.

Currently, 1% of the United States population holds a diagnosis for celiac disease (CD), however, a more recently recognized and possibly related condition, "non-celiac gluten sensitivity" (NCGS) has been suggested to affect up to 6% of the United States public. While reliable clinical tests for CD exist, diagnosing individuals affected by NCGS is still complicated by the lack of reliable biomarkers and reliance upon a broad set of intestinal and extra intestinal symptoms possibly provoked by gluten. NCGS has been proposed to exhibit an innate immune response activated by gluten and several other wheat proteins. At present, an enormous food industry has developed to supply gluten-free products (GFP) with GFP sales in 2014 approaching $1 billion, with estimations projecting sales to reach $2 billion in the year 2020. The enormous demand for GFP also reflects a popular misconception among consumers that gluten avoidance is part of a healthy lifestyle choice. Features of NCGS and other gluten related disorders (*e.g.*, irritable bowel syndrome) call for a review of current distinctive diagnostic criteria that distinguish each, and identification of biomarkers selective or specific for NCGS. The aim of this paper is to review our current understanding of NCGS, highlighting the remaining challenges and questions which may improve its diagnosis and treatment.

Leccioli V, Oliveri M, Romeo M, Berretta M, Rossi P. **A New Proposal for the Pathogenic Mechanism of Non-Coeliac/Non-Allergic Gluten/Wheat Sensitivity: Piecing Together the Puzzle of Recent Scientific Evidence.** Nutrients. 2017 Nov 2;9(11). Täisartikkel on vabalt saadaval: *http://www.mdpi.com/2072-6643/9/11/1203*

Non-coeliac/non-allergic gluten/wheat sensitivity (NCG/WS) is a gluten-related disorder, the pathogenesis of which remains unclear. Recently, the involvement of an increased intestinal permeability has been recognized in the onset of this clinical condition. However, mechanisms through which it takes place are still unclear. In this review, we attempt to uncover these mechanisms by providing, for the first time, an integrated vision of recent scientific literature, resulting in a new hypothesis about the pathogenic mechanisms involved in NCG/WS. According to this, the root cause of NCG/WS is a particular dysbiotic profile characterized by decreased butyrate-producing-*Firmicutes* and/or *Bifidobacteria*, leading to low levels of intestinal butyrate. Beyond a critical threshold of the latter, a chain reaction of events and vicious circles occurs, involving other protagonists such as microbial lipopolysaccharide (LPS), intestinal alkaline phosphatase (IAP) and

wheat α-amylase trypsin inhibitors (ATIs). NCG/WS is likely to be a multi-factor-onset disorder, probably transient and preventable, related to quality and balance of the diet, and not to the presence of gluten in itself. If future studies confirm our proposal, this would have important implications both for the definition of the disease, as well as for the prevention and therapeutic-nutritional management of individuals with NCG/WS.

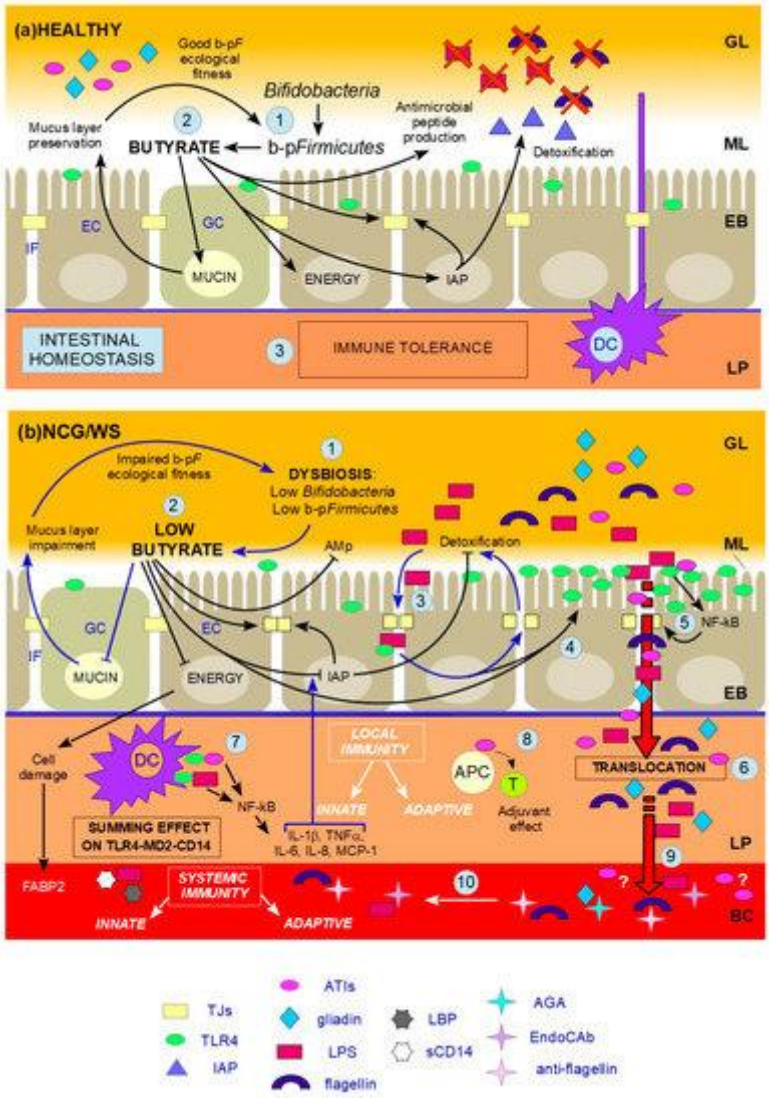

Figure 1

Schematic drawing that shows what happens in a healthy gut versus a non-coeliac gluten/wheat sensitivity gut according to our hypothesis. NCG/WS = non-coeliac gluten/wheat sensitivity; EC = enterocyte; GC = goblet cell; IF = interstitial fluid; GL = gut lumen; ML = mucus layer; EB = epithelial barrier; LP = lamina propria; BC = blood circulation; numbers in light blue balloons indicate the various steps in the chain reaction; → indicates stimulation; ⊣ indicates inhibition.

(a) HEALTHY:

1. Butyrate-producing Firmicutes (b-pF) provide adequate levels of butyrate in the ML and Bifidobacteria support the production of butyrate thanks to cross-feeding interactions with b-pF;

2. Butyrate in the ML, close to ECs, plays different trophic and protective functions: it stimulates GCs in the production of mucins, resulting in the preservation of the ML, and thus in a good b-pF ecological fitness. Butyrate constitutes the major energy supply for ECs; it favours the preservation of tight junctions (TJs) integrity by stimulating the expression and membrane co-localization of tight junction proteins (TJPs). Butyrate stimulates the production of antimicrobial peptides (AMp), and the expression and activity of intestinal alkaline phosphatase (IAP), thereby favouring the detoxification of microbial components;

3. All these functions together prevent that the content of the GL directly contacts and/or translocates across the EB, and, together with dendritic cells (DCs) which probe the GL for the presence of antigens, allow gut homeostasis and immune tolerance.

b) NCG/WS:

(1) A dysbiosis characterized by low levels of b-pF and/or Bifidobacteria results in not sufficient levels of butyrate in the ML;

(2) As a consequence, a chain reaction of events and vicious circles occur: the production of mucins is no longer stimulated, resulting in impairment of the ML. The consequent lowering of b-pF ecological fitness further promotes low levels of butyrate. ECs, without adequate energy source, run into inefficiency and cell damage, resulting in high serum levels of fatty acids binding protein 2 (FABP2). Moreover, TJs integrity is compromised, and the production of AMp is decreased. Low levels of butyrate also cause a decrease in the expression levels and activity of IAP; as a consequence, TJs integrity is further impaired, and the detoxification of microbial components is not sufficient;

(3) The failed detoxification enables microbial lipopolysaccharide (LPS) to penetrate in the IF, where it increases paracellular permeability, with a consequent vicious cycle;

(4) Furthermore, both LPS in the IF and low levels of butyrate upregulate toll-like receptors 4 (TLR4);

(5) Because of the compromised ML, the lumenal content can reach EC surface. LPS and wheat amylase trypsin inhibitors (ATIs) can stimulate overexpressed TLR4, resulting in the production of NF-kB, and then later, inflammatory cytokines, which further damage TJs integrity;

(6) Food-borne antigens and microbial components can cross the leaky EB;

(7) In the LP, both translocated LPS and ATIs stimulate, at the same time, the TLR4-MD2-CD14 complex on myeloid cells, such as DCs, resulting in a local innate immune response with the production of inflammatory cyokines and chemokines. Among the latter, IL-1β and TNFα further inhibit the activity of IAP, thus maintaining this condition;

(8) Moreover, ATIs have an adjuvant effect on possible pre-existing antigenic exposition of antigen-presenting cells (APC) to T-cells (T), triggering an adaptive immune response;

(9) Microbial and food-borne antigens translocate in the BC (10), and trigger a systemic innate and adaptive immune response, respectively resulting in high serum levels of lipopolysaccharide-binding protein (LBP) and soluble CD14 (sCD14), and EndoCAb, anti-flagellin and anti-gliadin (AGA) antibodies.