Winnipeg Regional Health Authority | Office régional de la santé de Winnipeg
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Non-Celiac Gluten Sensitivity
PRACTICE ISSUE EVIDENCE SUMMARY

Best Practice Issue (state as a question, PICO):

Does incorporating gluten free eating strategies have a positive effect on the management of gastrointestinal (GI) symptoms for those individuals without celiac disease but have celiac-like GI symptoms?

Members:	**Site:**
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Date Completed: September 10, 2015	To be Reviewed:
Date of Final Approval:	

Purpose: (goals, scope, intended users, settings, and patient/client groups)

Goal: To provide consistent guidance and messaging around the nutritional management of possible non-celiac gluten sensitivity in order to assist individuals self-manage their GI symptoms.

Settings: All

Users: Registered Dietitians (RDs), Primary Care practitioners

Patients/clients: All

Definitions:

Celiac disease (CD): A medical condition in which ingestion of gluten causes damage to the absorptive surface of the small intestine which causes malabsorption of nutrients. Diagnosis includes a blood screening test followed by a definitive diagnosis that can only be made by biopsy of the small intestine (Canadian Celiac Association, 2011).

Gluten: A structural protein found in wheat, rye and barley and foods processed with wheat (Canadian Celiac Association, 2011).

Wheat allergy (WA): An allergic reaction to foods containing wheat (Health Canada, 2012).

Gluten-free diet (GFD): Elimination of all forms of gluten and foods that may be contaminated with gluten (e.g. contaminated oats (National Foundation for Celiac Awareness, 2014).

Human Leukocyte Antigen DQ2 & DQ8 (HLA-DQ2/HLA-DQ8): Two gene molecules present in 95% of individuals with CD (Sapone et al., 2012).

Non-celiac gluten sensitivity (NCGS): A condition being referred to when individuals report sensitivity to gluten and share symptoms similar to those seen in CD, but yet lack the same elevation in antibodies, increased mucosal permeability and intestinal/mucosal damage as seen in CD (Sapone et al., 2011).

Irritable bowel syndrome (IBS): Condition which affects the large intestine and produces **gastrointestinal (GI)** symptoms such as cramping, abdominal pain, gas, bloating, diarrhea and constipation (Mayo Clinic, 2011).

Extra-intestinal symptoms: Symptoms outside of the intestinal tract including "foggy mind", headache, fatigue, joint and muscle pain, leg/arm numbness, eczema, rash, depression/anxiety and anemia (Caio et al., 2014).

FODMAPs: Acronym for fermentable, oligo-, di-, and monosaccharides and polyols. FODMAPs are poorly absorbed, short chain carbohydrates that are rapidly fermented by bacteria in the large intestine causing an increase in water and gas production, GI tract distension and motility changes. For some individuals, ingestion of foods higher in FODMAPs may result in IBS-like symptoms (Gibson & Shepherd, 2010).

Recommendations:

There is currently insufficient evidence to clearly diagnose or direct the management for those who experience CD-like GI symptoms. However, based on the evidence summary below, the following recommendations are made:

1. Individuals who are experiencing GI symptoms in response to ingestion of foods containing wheat, rye, and barley should NOT avoid gluten. They should be tested for CD and WA while on a gluten containing diet for at least 4-6 weeks. For those who have already removed gluten from their diet, re-introducing gluten before the test is advisable and imperative for accuracy in ruling out CD and WA.
2. If tests for both CD and WA are negative, trial of gluten elimination from the diet (the GFD diet) is warranted with continued monitoring of GI symptoms. Nutritional adequacy of the GFD needs to be considered or evaluated.
3. If GI symptoms improve and are under good control, introduction of gluten into the diet through a gluten challenge should be initiated with monitoring of symptoms. A gluten challenge should be designed and monitored by a trained health care provider. If symptoms return, NCGS can be suggested but no definite diagnosis can be made. Since it is unclear at this time if those with NCGS must strictly avoid gluten for life like those with CD, it is reasonable to recommend gluten-free eating. GFD counselling and education by a trained professional is necessary to ensure nutritional adequacy of the diet. Gluten threshold should be evaluated on an individual basis. Re-challenging with gluten after 1-2 years of following a GFD should be considered.
4. If GI symptoms are not improved on the trial of gluten elimination, individuals should re-introduce gluten and explore other diagnosis (e.g. IBS).

Evidence Review: (Please list type and grade of evidence reviewed)

1) **Emergence of celiac disease and wheat allergy**

According to the Canadian Celiac Association, CD was first described in the second century and is now highly prevalent in Canada with an estimated 1 in 133 Canadians living with the disease (Canadian Celiac Association, 2011). Similar diagnostic rates of CD have been shown in individuals worldwide (Leonard & Vasagar, 2014). CD is characterized by symptoms such as diarrhea, weight loss, anemia, irritability, bloating and cramping, and in some cases, dermatitis herpetiformis (severe skin rash) (Canadian Celiac Association, 2011). Celiac disease may be diagnosed at any age and some individuals may present with no symptoms (National Foundation for Celiac Awareness, 2014).

Although both CD and WA are immune system mediated, these are two different conditions. An allergy to wheat produces an abnormal immune reaction to proteins found in wheat with acute symptoms common in other allergic reactions. With CD, gluten causes damage to the lining of the small intestine which is not seen in WA (Health Canada, 2012).

2) **Non-celiac gluten sensitivity**

Since the 1980s, individuals who do not have CD or WA have been reporting GI symptoms similar to those seen in CD when consuming foods containing gluten. Improvement or elimination of those symptoms is reported while following a GFD (Cooper et al., 1980). Studies have shown that it may be possible to have sensitivity to gluten and not have CD (Case, 2010). This condition is being referred to as NCGS and is thought to affect 6% of the American population compared to 1% for CD (National Foundation for Celiac Awareness, 2014). Recently, the term NCGS is expanding and is being used to help define CD-like extra-intestinal symptoms such as headache, "brain fog," tingling and/or numbness in hands and feet, fatigue, and musculoskeletal pain in those people without CD. However, other symptoms such as rash and more severe neurologic and psychiatric conditions including schizophrenia and cerebellar ataxia have also been reported to be associated with NCGS (Lundin & Alaedini, 2012).

The pathophysiology of NCGS is not yet understood but early research suggests this condition does not cause long-standing adverse complications (National Foundation for Celiac Awareness, 2014; Lundin & Alaedini, 2012). Currently, no research has been done to evaluate risk factors or prevention of NCGS (Leonard & Vasagar, 2014). It is suggested that NCGS is an innate immune response and not an adaptive immune response (i.e. autoimmune reaction) as seen with CD or allergic reactions (National Foundation for Celiac Awareness, 2014). One mechanism proposes differences in

gut permeability and intestinal mucosal response to gluten when comparing CD and gluten sensitivity, the latter not being associated with intestinal damage or an autoimmune response (Sapone et al., 2011). Increased intestinal permeability seen in NCGS is often referred to as the "leaky gut syndrome" (Catassi et al., 2015).

NCGS has become widely prevalent and is being accepted as a "true" condition. However, emerging research is disputing if this condition even exists (Biesiekierski et al., 2013). Recent studies are suggesting that there may be other components of wheat, other than gluten, that may be responsible for the symptoms seen in NCGS (Catassi et al., 2013). Biesiekierski et al. (2013) conducted a follow-up study where NCGS and IBS subjects were placed on a GFD low in FODMAPs. For all participants, reduction of FODMAPs in their diets improved GI symptoms and no specific or dose-dependent effects of gluten were found. A large nocebo response was shown (i.e.) participants expected to experience symptoms regardless of which diet they were on and consequently did experience symptoms. Therefore, the authors suggest that FODMAPs can cause GI symptoms similar to those experienced in individuals with self-reported NCGS and IBS. (Biesiekierski et al., 2013). The low FODMAPs diet is emerging as a highly accepted method of treatment for IBS (Gibson & Shepherd, 2010).

3) **Diagnosis**

Unlike CD which can be definitively diagnosed by blood test and intestinal biopsy, there is no indicative test to diagnose someone with NCGS and there are no known specific serologic markers. Sapone and colleagues (2012) reported that 95% of individuals with CD carry the gene encoding HLA-DQ2 or HLA-DQ8 molecules. Consequently, negative results for both these gene encodings can exclude a diagnosis of CD in 95% of cases. In individuals thought to have NCGS, half of them may carry the same DQ2 or DQ8 genotype, compared to one third for the general population (Sapone, 2012). Very recently, some nutrigenomic companies started offering genetic testing for NCGS. However, genetic profiling is still in its early days, and experts disagree on whether the current level of knowledge is sufficient for recommending dietary changes (Practice-based Evidence in Nutrition, 2007). Other methods of testing include saliva, blood or stool samples but these have not been validated and cannot be used to diagnose an individual with NCGS (National Foundation for Celiac Awareness, 2014). Therefore, NCGS is not a condition that is diagnosed; rather, it can only be suggested by process of exclusion and challenge.

The first step upon suspicion of NCGS is to eliminate the likelihood of CD and WA. This can be done by serologic testing, including testing for IgA and IgG antibodies for CD, and IgE antibodies to wheat proteins for WA (Lundin & Alaedini, 2012). It is important that individuals not start a GFD before serologic testing has been completed to avoid false negative results and further complicate the diagnostic process (National Foundation for Celiac Awareness, 2014). For those who have already removed gluten from their diet, re-introducing gluten before the test is advisable. Research is limited on how long it takes for antibodies to develop once gluten is added back to the diet. There is no consensus on length of time needed to be on a gluten containing diet prior to serologic testing. Patient or client tolerance to gluten is often taken into consideration. The Canadian Celiac Association recommends the equivalent of 4 slices of bread/day for at least 12 weeks prior to the small intestine biopsy but has no recommendations for the amount of gluten that should be consumed prior to serologic testing.

If both CD and WA have been excluded, a gluten-free elimination diet is recommended (National Foundation for Celiac Awareness, 2014) and should be supervised and monitored by a trained health care provider. If there is improvement of GI symptoms following a GFD, NCGS can be suspected (Lundin & Alaedini, 2012). Upon improvement of symptoms, a gluten challenge needs to be conducted in order to confirm specific sensitivity to gluten. Currently there is a lack of well-designed studies or consensus as to the length of time an individual should remain on a GFD before re-challenging with gluten. Some studies suggest anywhere from two to four weeks (Carroccio et al. 2012; Catassi et al. 2013; Biesiekierski et al., 2013), other studies suggest between two to twenty-one months (Volta et al., 2012; Brottveit et al., 2012; Campanella,et al., 2008).

Studies also varied greatly in their design and approach to the gluten challenge. Brottveit et al. (2012) compared the response following a gluten challenge between NCGS and CD patients after consuming a 4 slice white bread gluten re-challenge for three days. Biesiekieski et al. (2011) re-challenged with two slices of bread and one muffin for six weeks, while Carroccio et al. (2012) utilized capsules containing wheat for two-weeks. Since some challenges may not be blinded, a placebo effect could be possible (Lundin & Alaedini, 2012). Severity of symptoms may dictate length of the challenge and should be discussed with client and practitioner.

Please see Appendix A for a proposed algorithm for suspected NCGS, adapted from Nijeboer et al. (2013).

4) **Evaluation and Treatment**

NCGS is currently a subjective condition based on individual symptom management, and there is no clear consensus on how to evaluate GI symptoms after a gluten challenge (Lundin & Alaedini, 2012). It is also not clear if this is a chronic condition or whether some may outgrow it over time (Canadian Celiac Association, 2011). Re-challenging with gluten after 1-2 years of being on a gluten-free diet has been suggested (Volta & De Giorgio, 2012).

Dietitians of Canada and Practice-based Evidenced in Nutrition (PEN) were accessed for this evidence review and revealed no nutrition practice guidelines for NCGS. According to leading international nutrition expert on CD and the GFD, Registered Dietitian and member of the Professional Advisory Board of the Canadian Celiac Association, Shelly Case, NCGS does not lead to nutritional deficiencies or the development of other complications (Case, 2010). Data on long term complications of NCGS and individual degrees of gluten sensitivity or threshold is still very limited and emerging. Further studies are required to expand the research related to causes, gluten threshold, diagnosis, treatment and intervention guidelines for the management of NCGS (Sapone et al., 2012). More research is also needed to confirm whether or not NCGS is a "true" condition (Biesiekierski et al., 2013).

In view of the insufficient evidence to clearly diagnose or direct the management of possible NCGS, it is reasonable to present the above information to clients so they can make informed decisions about appropriate testing and food trials. The GFD is the only known treatment for NCGS at this time. One study has found that less than half of adult women following a GFD were consuming adequate amounts of fibre, iron and calcium (Thompson et al., 2005). Therefore, GFD counselling and education by a trained professional is necessary to ensure nutritional adequacy of the diet. If GI symptoms are improved and controlled, then a GFD should be supported. If GI symptoms have not improved on a GFD, individuals should re-introduce gluten and explore other food sensitivities such as FODMAPs.

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Practice Implications:

Communicate recommendations to other health care professionals.

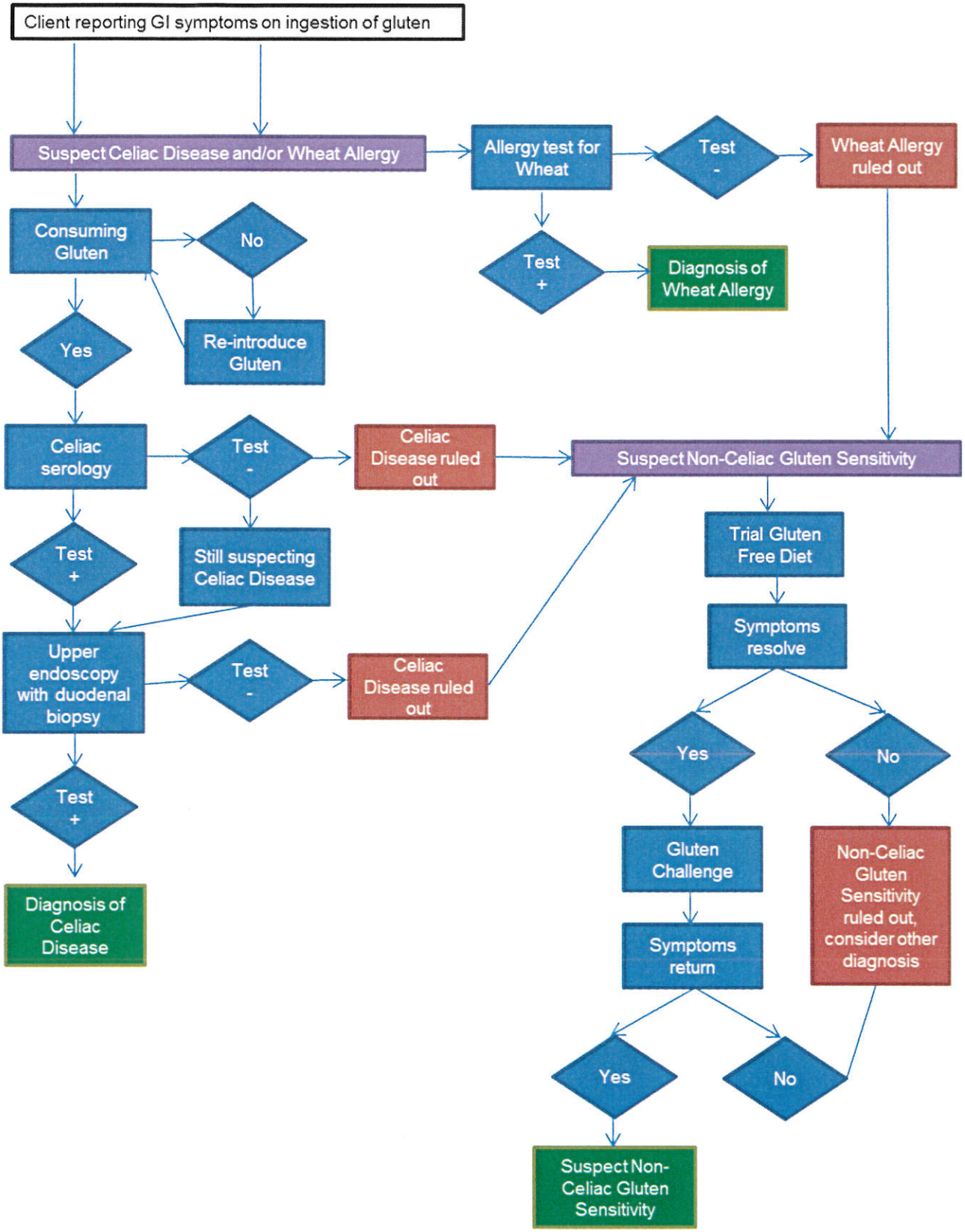
Recommendation for implementation:

These recommendations are being reviewed by:

Name and Credentials	Date Review Complete
Dr. Donald Duerksen, Medical Director WRHA NFS	January 2015

Appendix A

Proposed algorithm for suspected NCGS adapted from Nijeboer et al. (2013)


Client reporting GI symptoms on ingestion of gluten
Suspect Celiac Disease and/or Wheat Allergy
Allergy test for Wheat
Test -
Wheat Allergy ruled out
Consuming Gluten
No
Test +
Diagnosis of Wheat Allergy
Yes
Re-introduce Gluten
Celiac serology
Test -
Celiac Disease ruled out
Suspect Non-Celiac Gluten Sensitivity
Test +
Still suspecting Celiac Disease
Trial Gluten Free Diet
Upper endoscopy with duodenal biopsy
Test -
Celiac Disease ruled out
Symptoms resolve
Yes
No
Test +
Gluten Challenge
Non-Celiac Gluten Sensitivity ruled out, consider other diagnosis
Diagnosis of Celiac Disease
Symptoms return
Yes
No
Suspect Non-Celiac Gluten Sensitivity