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Principles and Strategies for Monitoring Individuals with Celiac Disease

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1. Introduction

Gluten-free diet is an effective therapy for celiac disease. There are few diseases in medicine where a nutritional intervention alone can produce such rapid, gratifying results. One may therefore question the need for following these patients long-term. In the past, a rather simplistic approach was taken towards treatment and follow-up of patients with celiac disease. "Go home, don't eat anything with gluten and you'll be fine", patients were told. But as more individuals were diagnosed with celiac disease and our understanding of this disorder improved, several important issues emerged. Firstly, it was recognized that gluten-free diet is complex, costly and socially restrictive, and that cross contamination of the diet with gluten was very common. For a gluten-free diet to be fully effective, adherence to the diet must be strict and life-long, thereby adding further challenges. Gluten-free diet should be viewed as a "prescribed therapy" rather than a mere change in life style. Furthermore, celiac disease is not simply a malabsorptive gastrointestinal disorder. It is a multisystem, auto-immune disease that carries a significant health burden and risk of complications (Freeman et al. 2011). These factors necessitate ongoing, careful monitoring of patients with celiac disease. The following six key elements of management of celiac disease include long-term follow-up (NIH, 2004):

Consultation with a skilled dietitian
Education about the disease
Lifelong adherence to a gluten-free diet
Identification and treatment of nutritional deficiencies
Access to an advocacy group
Continuous long-term follow-up by a multidisciplinary team

This chapter highlights the important issues in long-term follow-up of patients with celiac disease and offers guidelines for practicing physicians and allied health professionals involved in their management. Issues around the diagnosis of celiac disease and details of the gluten-free diet will not be covered. Because this is a rapidly evolving field, recommendations for follow-up may get modified over time.

2. Importance of follow-up

Because most patients with celiac disease recover symptomatically with therapy they may not perceive the need for follow-up. This view may be shared by some of their health care

providers. Hence, not all patients with celiac disease receive regular follow-up care. In a study of 126 adults with celiac disease in United Kingdom, only 62% were receiving formal follow-up care (Bebb et al., 2006). Of these, 92% were being followed at a hospital clinic and 8% by their general practitioner.

Follow-up is essential not only to assess symptomatic recovery and to monitor complications but also to assist the patient in adhering to the diet (Pietzak, 2005). Follow-up care is the key to dietary compliance. There is good objective evidence that proactive follow-up measures can reinforce adherence to the gluten-free diet, both in children and adults (Bardella et al. 1994, Hogberg et al. 2003, Ljugman & Myrdal, 1993, Lamontagne et al, 2001). Follow-up visits also provide an opportunity to give patients updated information on new developments in the field.

3. Who should provide follow-up?

Gastroenterologists are often the ones who establish or confirm the diagnosis of celiac disease. But who should provide their long term follow-up care… the patient's family physician, internist/paediatrician or the gastroenterologist? A survey of Canadian gastroenterologists revealed that 76% routinely provided long-term follow-up care to patients with celiac disease (Silvester & Rashid, 2010). Significantly more paediatric gastroenterologists provided long-term follow-up, as compared with adult gastroenterologists. Also, the elements of follow-up varied, including the frequency of laboratory testing and of repeat duodenal biopsies. The most commonly cited reason (86%) for not providing long-term follow-up was that the patient`s primary care physician was providing this care. Other reasons included, a) not having an organized system to recall patients; b) lack of time and c) the belief that follow-up was not required once the patient was on a gluten-free diet. In some cases, the patients themselves did not want follow-up.

Who eventually provides long-term care to patients with celiac disease may depend on the availability of resources, both personnel and funding, the severity of the patient's illness and the complexity of the disease course. It is probably prudent that all patients be followed by their gastroenterologists for at least the first year after diagnosis. Thereafter, the family physician or internist can follow the patient and request gastroenterologist's input as needed. All children with celiac disease should be followed by either their pediatricians or gastroenterologist.

There is less controversy about the role of the dietitian in follow-up of these patients. Treatment of celiac disease is primarily nutritional and the dietitian's role is therefore of paramount importance. In one survey, the preferred method of follow-up by most patients was to see a dietitian with a doctor being available (Bebb et al. 2006).

Nutritional adequacy of a gluten-free diet is also a concern because it may be deficient in certain vitamins, iron, calcium and fiber (Kupper, 2005). These micronutrient deficiencies require monitoring which is best provided by a dietitian. However, a gluten-free diet is complex and not all dietitians are well-versed in this area. Therefore, ongoing nutritional counseling should be provided by a dietitian skilled in the use of a gluten-free diet (Case, 2005).

4. What constitutes appropriate follow-up?

Evaluation of current practice guidelines issued by various professional organizations has revealed significant differences in recommendations for long-term follow-up of patients with celiac disease (Silvester & Rashid, 2007). As information accumulates, broad guidelines for long-term management are beginning to emerge (Haines et al, 2008, AGA, 2006, Hill et al, 2005). While there is consensus on some aspects, others remain controversial.

Celiac disease has a wide clinical spectrum. In order to individualize the type of follow-up needed, it is important to stratify patients according to their risk of developing complications. Genetic factors strongly influence the development of celiac disease; specifically, the major histocompatibility complex class II antigens. About 90% of patients with celiac disease carry the HLA-DQ2 heterodimer encoded by alleles DQA1*05 and DQB1*02. The remainder have either HLA DQA1*05 or HLA DQB1*02, or express HLA-DQ8 encoded by alleles DQA1*03 and DQB1*0302. The HLA-DQ2 and DQ8 are within haplotypes also associated with other autoimmune disorders such as type-1diabetes and autoimmune thyroid disease. Patients with celiac disease who are homozygous for HLA-DQ2 tend to have more severe complications, including refractory celiac disease and enteropathy-associated T cell lymphoma (Al-Toma et al. 2006). The phenotype of patients who are homozygous for DQB1*02 tends to be associated with more severe symptoms, marked villous atrophy at diagnosis and slower recovery after instituting a gluten-free diet (Karinen et al. 2006, Jores et al. 2007). As our understanding of the genetics of celiac disease improves and HLA testing becomes more routinely available, it may be possible to identify patients who require more intensive follow-up.

Follow-up of patients with celiac disease should focus on three key areas; nutritional deficiencies, adherence to gluten-free diet and monitoring of complications. A proposed follow-up plan is listed in Table 1.

The physician's assessment at each visit should include a complete history, especially noting symptoms of abdominal pain, diarrhoea, weight loss, anorexia and fatigue. Physical examination should include measurement of weight, height and body mass index (BMI). Children should be serially evaluated with a growth chart to detect alterations in growth velocity. A complete, systemic examination should be performed in all patients.

The utility of serological testing and the usefulness of a repeat intestinal biopsy will be discussed later.

Yearly monitoring of thyroid function is recommended as thyroid disease develops commonly in celiac disease (Elstrom et al. 2008, Meloni et al. 2009). Hypothyroidism can be easily identified by laboratory tests (thyroid stimulating hormone, free thyroxine) and treated with hormone replacement therapy. Thyroid antibody testing may not be cost effective as it does not necessarily predict the development of clinical thyroid dysfunction. Also, currently there are no means of preventing the development of thyroiditis or other auto-immune disorders such as type-1 diabetes. There is controversy whether a gluten-free diet prevents autoimmune thyroiditis that is established or is in evolution (Meloni et al. 2009, Cassio et al, 2010).

The follow-up plan listed in Table 1 is the minimum recommended for an average, uncomplicated patient with celiac disease. If the patient remains ill, additional investigations

At Diagnosis (Physician and Dietitian)
- Education on celiac disease
- Gluten-free dietary counseling by a skilled dietitian
- Recommend family screening
- Recommend membership in a celiac support group
- Bone densitometry*
- Celiac serology (if not previously obtained)
- Other Routine Tests (complete blood count, iron studies, folate, thyroid function tests, liver enzymes, calcium, phosphate, vitamin D)
At 2 months (Physician and Dietitian)
- Assess symptoms and coping skills
- Dietary review
At 6 months (Physician and Dietitian)
- Assess symptoms
- Complete physical examination
- Dietary review
- Celiac serology
- Repeat Other Routine Tests (if previously abnormal)
At 12 months (Physician and Dietitian)
- Assess symptoms
- Complete physical examination
- Dietary review
- Celiac serology (if still positive)
- Repeat Other Routine Tests (if previously abnormal)
- Bone densitometry (if previously abnormal)
- Small intestinal biopsy*
Yearly (Physician and Dietitian)
- Assess symptoms
- Complete physical examination
- Dietary review
- Celiac serology
- Thyroid function tests
- Other Tests (as clinically indicated)

* Not recommended routinely for children. *See text*

Table 1. Proposed Routine Follow-up Plan for Patients with Celiac Disease

may be needed, as guided by the clinical findings. For example, micronutrients such as zinc should be measured in severe malnutrition. In patients with macrocytic anemia and normal folate, vitamin B12 status should be assessed by measuring serum cobalamin, homocystine and methylmalonic acid. Any abnormalities detected should be followed up with appropriate retesting after supplementation.

Celiac disease can be associated with other autoimmune disorders, such as type I diabetes mellitus or thyroiditis. If a patient suffers from one or more of these, follow-up should include relevant assessment and investigations.

Patients who remain symptomatic despite following a gluten-free diet may need to be seen more frequently, whereas those who were asymptomatic at diagnosis and remain so, may require less frequent visits.

5. Follow-up of paediatric patients

The general principles of management described above also apply to the paediatric population with a few notable differences. Growth sets children apart from adults. Celiac disease can adversely affect physical and neurodevelopmental growth, primarily due to nutritional deficiencies. Also, since very young children are unable to communicate their symptoms, a high index of suspicion should be maintained when inquiring about their health from the parents.

In children, all anthropometric measurements should be plotted as percentiles on growth charts. The BMI in children is not a fixed value but is age dependent and is expressed in percentiles. For children under three years of age, head circumference should also be measured. Poor growth implies a nutritional deficit. Normal growth is reassuring but does not rule out micronutrient deficiencies.

According to the revised guidelines of the European Society for Paediatric Gastroenterology and Nutrition, in children older than 2 years of age with symptoms suggestive of celiac disease, the characteristic histologic findings on small intestinal biopsy and unequivocal clinical resolution after institution of a gluten-free diet, the diagnosis can be considered definitive for lifelong celiac disease without need for further biopsies (Walker-Smith et al. 1990). A follow-up biopsy may be required only in selected patients in whom the diagnosis is in doubt, or if the child remains symptomatic despite being on a strict gluten-free diet.

In children with celiac disease, secondary nutritional problems such as iron deficiency, anemia and osteoporosis resolve completely after starting a gluten-free diet. Once corrected, routine follow-up laboratory testing for these conditions is not required.

6. Utility of serological testing in follow-up

Serological tests usually become negative within a year on a strict gluten-free diet and may be used to monitor compliance with the gluten-free diet. However, these tests are insufficiently sensitive to reflect occasional dietary transgressions (Kaukinen et al. 2002, 2007, Tursi et al. 2006). The degree and duration of gluten exposure will affect the results. Thus, these tests may be more useful in predicting non-adherence rather than strict adherence. Furthermore, normalization of the antibodies does not necessarily imply complete villous healing (Tursi et al. 2003). Some patients with normalized antibodies may have ongoing villous atrophy.

A persistently positive serological test after a patient has been on a gluten-free diet is highly indicative of ongoing gluten exposure and may indicate mucosal injury or development of refractory celiac disease. A negative test is reassuring only to a certain degree.

7. Role of routine repeat small intestinal biopsy

Small intestinal biopsy is the definitive way to document mucosal healing after starting a gluten-free diet. However, there is controversy as to whether all patients with celiac disease should undergo a follow-up biopsy to document intestinal healing. Some adult gastroenterologists routinely perform a follow-up biopsy in all patients after 12 months of starting a gluten-free diet. Others perform a biopsy only in selected cases.

Rates of mucosal healing are highly variable. In some studies, up to 40% of patients had persisting villous atrophy after two years (Tursi et al, 2006) and about 10% after five years on a gluten-free diet (Wahab et al. 2002). This raises the question of whether symptoms alone constitute a reliable guide to mucosal healing (Kaukinen et al. 2007). Ongoing villous atrophy can lead to nutritional problems such as osteoporosis and may increase the risk of developing complications such as lymphoma. Clinical symptoms, celiac serology and laboratory markers of inflammation are not robust enough measures to confirm mucosal healing. Until better non-invasive tests of mucosal healing can be developed, a repeat intestinal biopsy after a year of gluten-free diet is recommended.

Mucosal healing tends to be more rapid and more complete in children. Also, since endoscopy requires a general anesthetic in most cases, a repeat follow-up biopsy is not recommended in children with celiac disease who recover clinically and normalize their celiac antibody tests.

8. Non-responsive celiac disease

Most patients with celiac disease will improve and their symptoms will resolve after starting a gluten-free diet. However, some do not … a phenomenon referred to as non-responsive celiac disease. Non-responsive celiac disease is defined as failure to respond to at least six months of treatment with a gluten-free diet (*primary*) or re-emergence of symptoms or laboratory abnormalities typical of celiac disease while continuing on treatment with a gluten-free diet (*secondary*). The six months of treatment duration with gluten-free diet is used an arbitrary cut off point since patients should have significant improvement by this time.

Non-responsive celiac disease is common. Among 603 patients followed at one health care facility over five years, 113 (19%) had non-responsive celiac disease (Leffler et al. 2007).

The causes of non-responsive celiac disease are listed in Table 2. Before embarking on any investigations, one must ensure that the diagnosis of celiac disease was correct in the first place. Of 55 patients referred to a tertiary care medical institution with a presumed diagnosis of non-responsive celiac disease, 6 (9.2%) did not have celiac disease (Abdulkarim et al. 2002). Some patients may self-diagnose and never undergo an intestinal biopsy. In others who do undergo intestinal biopsy, the specimen may get interpreted incorrectly. Furthermore, villous atrophy is not unique to celiac disease. Similar lesions can be seen in infectious, allergic or autoimmune enteropathy and in other disorders such as Crohn's disease and collagenous sprue.

-	Gluten exposure
-	Irritable bowel syndrome
-	Refractory celiac disease
-	Lactose intolerance
-	Pancreatic insufficiency
-	Microscopic colitis
-	Small intestinal bacterial overgrowth
-	Ulcerative jejunitis
-	Other co-existing conditions (gastroesophageal reflux disease, peptic ulcer, food allergy, eating disorder, inflammatory bowel disease, immunodeficiency)

Table 2. Causes of Non-Responsive Celiac Disease

Ongoing exposure to gluten in the diet is the most common cause of non-responsive celiac disease, occurring in 36% to 51% of patients (Leffler et al. 2007, Abdulkarim et al. 2002). The gluten exposure may be accidental or intentional. The recently proposed international definition of the gluten-free diet states that the gluten content should be less than 20 parts per million (ppm) i.e. less than 20 mg gluten in 1 kg of dry weight food product (Codex Alimentarius Commission, Standard 118-1979, July 2008). Although individuals may have varying degrees of gluten tolerance, ingestion of 50 mg of gluten daily over three months can be sufficient to cause injury to the small intestinal mucosa (Catassi et al. 2007). For example, an average slice of bread contains approximately 3.0-3.5 gm of gluten. Hence, an amount as little as 1/70th of a slice of bread consumed on a regular basis may lead to villous damage. Avoiding gluten contamination in diet is very difficult for many patients because there are many hidden sources of gluten in the diet. In some cases, the patient may be knowingly consuming gluten-containing foods and, for whatever reason, does not tell the physician. (Some patients feel guilty or embarrassed in admitting dietary transgressions!). Furthermore, patients may believe that occasional consumption of small quantities of gluten-containing foods is safe. A dietitian with expertise in gluten-free diet can help evaluate gluten ingestion in such cases.

After gluten ingestion, irritable bowel syndrome (IBS) is the second most common cause of non-responsive celiac disease. This is sometimes referred to as post-inflammatory IBS. A variety of symptoms including abdominal pain, diarrhoea and constipation can occur. The diagnosis is clinical and requires exclusion of other causes. The management is symptomatic and may include cognitive behavior therapy.

The villous atrophy present at the time of diagnosis of celiac disease may lead to secondary lactose intolerance, causing symptoms such as abdominal pain, gas, bloating and diarrhoea. A breath hydrogen test may provide objective evidence of lactase deficiency. A trial of a lactose-free diet or lactase enzyme supplements may help alleviate the symptoms. Patients require calcium and vitamin D supplements while on a lactose-free diet.

Microscopic colitis is an autoimmune inflammatory condition. There are two types, namely lymphocytic colitis and collagenous colitis. The main symptom is watery diarrhoea. A colonoscopy and biopsies are needed to make this diagnosis. Treatment includes a strict gluten-free diet and, in some cases drugs including 5-aminoslicylates, budesonide and azathioprine.

Pancreatic insufficiency may occur in some patients with celiac disease. The exact cause is unknown. Villous atrophy causing impaired secretion and action of enteric hormones such as enterokinase, cholecystokinin and secretin may play a role. Steatorrhoea and weight loss can occur. Tests for exocrine pancreatic insufficiency will be abnormal. Pancreatic enzyme replacement therapy and fat-soluble vitamin supplements should be prescribed. The problem is usually transient and pancreatic function recovers.

A damaged small intestinal mucosa provides a nidus for bacterial growth. Bacterial overgrowth in the small bowel can lead to diarrhoea and weight loss from steatorrhoea. Iron and vitamin B12 deficiency can occur. While the diagnosis is confirmed by a small bowel aspirate for bacterial colony counts, a course of empiric antibiotic therapy may be recommended. Bacterial overgrowth can be successfully treated with oral antibiotics.

Patients with celiac disease are at risk for developing other autoimmune disorders, most commonly autoimmune thyroid disease. Hypothyroidism can lead to a variety of symptoms that may mimic those of celiac disease, such as chronic fatigue and constipation. If celiac serology and intestinal biopsy are normal in a symptomatic patient who has good adherence to gluten-free diet, development of another autoimmune disorder should be considered.

An approach to the assessment of patients with non-responsive celiac disease is described in Table 3. If lymphoma is suspected, upper and lower gastrointestinal endoscopy, abdominal CT scan, capsule endoscopy, and possibly double-balloon enteroscopy should be considered.

-	Review of original diagnosis of celiac diagnosis
-	Careful review of gluten-free adherence by a skilled dietitian
-	Obtain IgA-tissue transglutaminase antibody (TTG)
-	If TTG abnormal, reinforce dietary adherence and reassess
-	If TTG normal (or remains abnormal on reassessment despite a strict gluten-free diet), obtain small intestinal biopsy to rule our refractory celiac disease
-	If biopsy normal, investigate for alternative diagnoses (Table 2)

Table 3. An Approach to Assessment of Non-Responsive Celiac Disease

9. Refractory celiac disease

Refractory celiac disease (RCD) or refractory sprue refers to initial or subsequent failure of a strict gluten-free diet to restore normal intestinal architecture and function in patients who have celiac-like enteropathy and have no evidence of other pathology including intestinal lymphoma.

Weight loss and diarrhoea are the most consistent symptoms of RCD. The diagnosis requires a small intestinal biopsy. Based on the histological appearance of the small intestinal mucosa, RCD is divided into two types. In RCD type-1 there is apparently a normal intraepithelial lymphocyte phenotype whereas in RCD type-2 there is monoclonal or polyclonal expansion of an aberrant intraepithelial lymphocyte population as shown by histochemical staining (Freeman, 2008). This latter type carries a high risk of overt enteropathy associated T cell lymphoma (EATL) and is associated with a greater mortality at two years (41%) compared to RCD type-I (14%).

Corticosteroid therapy may improve clinical symptoms in some patients with RCD but the response is not consistent. Patients with RCD type-1 often require immunosuppressive therapy. The treatment of RCD type-2 is unsatisfactory and the disease carries a high mortality with most patients dying within two years of diagnosis (Rubio-Tapia et al. 2009, Malamut et al. 2009). A variety of therapies have been tried including azathioprine, anti-tumor necrosis factor-alpha, cladribine, anti-CD-52, IL-15 antagonists and stem cell transplantation to replace the abnormal lymphocyte population. Because of the complex nature of therapy, RCD type-2 is best managed by centers with expertise in this condition.

10. Monitoring of complications

The two major complications of celiac disease that require careful monitoring include development of other autoimmune disorders and malignancy.

There is controversy whether a gluten-free diet prevents the development of other autoimmnune diseases (Ventura et al. 1999, Viljamaa et al. 2005, Sategna Guidetti et al. 2001). Molecular mimicry, one of the proposed mechanisms for autoimmunity, does implicate ongoing gluten exposure. Continued gluten ingestion may also contribute to systemic symptoms and development of other disorders like osteoporosis from production and circulation of pro-inflammatory cytokines (Fornari et al. 1998, Romaldini et al. 2002).

While a gluten-free diet may not completely eliminate risk of developing other autoimmune disorders, continued ingestion of gluten definitely increases the risk. This information may also help motivate patients to stay strictly gluten-free.

Patients with untreated celiac disease have a higher risk of developing malignancy compared to the general population. Such malignancies include lymphoma and oropharyngeal, esophageal and small intestinal cancer. A careful history, physical examination and appropriate investigations should be conducted in patients who are either non-adherent to the diet or who remain symptomatic despite following a strict gluten-free diet.

There is good evidence that a gluten-free diet is protective against the development of malignancy. Patients on a strict gluten-free diet for >5 years have the same overall risk for cancer as the general population (Cooper et al, 1982, Holmes et al. 1989). This information should be shared with patients to provide them with reassurance and encouragement for strict adherence to the diet.

11. Ongoing emotional and psychological support

The diagnosis of celiac disease can be overwhelming and coping with it challenging. Patients may feel depressed to learn that they can never eat wheat products again. Feelings of anxiety, anger, deprivation and frustration may develop. Eating in social situations can be especially problematic (Rashid et al. 2005, Zarkadas et al. 2006). Pressures from the extra time and cost involved in buying/preparing foods, along with competing priorities like family, job, etc. may further impair coping abilities and act as barriers to compliance. Dietary transgressions often occur in adolescents and young adults because of the need to conform to peers in social situations.

Long-term follow-up of patients with celiac disease will help monitor both their physical and psychological well being and maintain trust in the physician and dietitian. Normal physical examination and test results will provide patients on a strict gluten-free diet reassurance and encouragement. Abnormal test results can be a powerful motivator especially for those who do not get symptoms when they eat gluten-containing foods. Ongoing psychological support counseling improves compliance with gluten-free diet especially in patients with anxiety and depression (Addolorato et al. 2004).

A referral to a professional psychologist may be required in select cases to help improve the patient's coping skills.

12. Role of patient advocacy groups

Patient and family support and advocacy groups can help support patients with celiac disease who are starting a gluten-free diet. Models such as the Expert Patients Program in the United Kingdom in which individuals learn from each other how to cope with the challenges of a chronic condition can be used (Donaldson et al. 2003). Volunteer celiac support organizations in several countries provide excellent resources to their members and keep them updated on new developments. Physicians and patients have identified such organization as important sources of information (Zarkadas et al. 2006). Physicians should recommend their patients with celiac disease to become members of such support groups.

13. Conclusions

Celiac disease is not a trivial disorder. While most patients do well on a gluten-free diet, some do not. Complications including nutritional deficiencies, risk of developing other autoimmune disorders, refractory celiac disease and malignancy are important considerations. Symptoms alone do not provide a reliable guide to the presence of complications. In future, better stratification of risk factors for developing complications may allow for individualized follow-up plans for specific patients. All patients with celiac disease should have regular, systematic follow-up by a health care team that includes a physician and a dietitian.

14. References

Abdulkarim AS, Burgart LJ, See J et al. 2002. Etiology of Nonresponsive Celiac Disease: Results of a Systematic Approach. *Am J Gastroenterol*,97(8):2016-21.

Addolorato G, De Lorenzi G, Abenavoli L et al. 2004, Psychological support councelling improves gluten-free diet compliance in celiac disease. *Aliment Pharmacol Ther*, 20(7):777-782.

AGA-American Gastroenterological Association Institute medical position statement on the diagnosis and management of celiac disease. 2006. *Gastroenterology*, 131(6):1977-80.

Al-Toma A, Goerres MS, Meijer JW et al. 2006. Human leukocyte antigen-DQ2 homozygosity and the development of refractory celiac disease and enteropathy-associated T-cell lymphoma. *Clin Gastroenterol Hepatol*, 4:315-9.

Bardella MT, Molteni N, Prampolini L, et al. 1994. Need for follow up in coeliac disease. *Arch Dis Child*, 70:211-3.

Bebb JR, Lawson A, Knight T et al. 2006. Long-term follow-up of coeliac disease–what do coeliac patients want? *Aliment Pharmacol Ther*, 23:827-31.

Case S. 2005. The gluten-free diet: how to provide effective education and resources. *Gastroenterology*, 128(suppl 1):S128-S134.

Cassio A, Ricci G, Baronio F et al. 2010. Long-term clinical significance of thyroid autoimmunity in children with celiac disease. *J Pediatr*,156(2):292-5

Catassi C, Fabiani E, Iacono G, et al. 2007. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *Am J Clin Nutr*, 85:160-166.

Cooper BT, Holmes GK, Cooke WT. 1982. Lymphoma risk in coeliac disease of later life. *Digestion*, 23:89-92.

Donaldson L. 2003. Expert patients usher in a new era of opportunity for the NHS. *BMJ*, 14;326(7402):1279-80.

Elfstrom P, Montgomery SM, Kampe A et al. 2008. Risk of thyroid disease in individuals with celiac disease. *J Clinic Endocrinol Metab*, 93(10):3915-21.

Fornari MC, Pedreira S, Niveloni S, et al. 1998. Pre- and post-treatment serum levels of cytokines IL-1beta, IL-6, and IL-1 receptor antagonist in celiac disease. Are they related to the associated osteopenia? *Am J Gastroenterol*, 93:413-8.

Freeman HJ, Chopra A, Clandinin MT et al 2011. Recent advances in celiac disease. *World J Gastroenterol,* 17(18):2259-2272.

Freeman HJ. Refractory celiac disease and sprue-like intestinal disease. 2008. *World J Gastroenterol,* 14(6):828-830.

Haines ML, Anderson RP, Gibson RP. 2008. Systematic review:the evidence base for long-term management of celiac disease. *Aliment Pharmacol Ther*, 28:1042-1066.

Hill ID, Dirks MH, Liptak GS, et al. 2005. Guideline for the diagnosis and treatment of celiac disease in children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*, 40(1):1-19.

Hogberg L, Grodzinsky E, Stenhammar L 2003. Better dietary compliance in patients with coeliac disease diagnosed in early childhood. *Scand J Gastroenterol*, 38:751-4.

Holmes GK, Prior P, Lane MR et al. 1989. Malignancy in coeliac disease– effect of a gluten free diet. *Gut*, 30:333-8.

Jores RD, Frau F, Cucca F et al. 2007. HLADQB1*0201 homozygosis predisposes to severe intestinal damage in celiac disease. *Scand J Gastroenterol*, 42:48–53.

Karinen H, Karkkainen P, Pihlajamaki J et al. 2006. Gene dose effect of the DQB1*0201 allele contributes to severity of celiac disease. *Scand J Gastroenterol*, 41:191-9.

Kaukinen K, Sulkanen S, Maki M, et al. 2002. IgA-class transglutaminase antibodies in evaluating the efficacy of gluten-free diet in coeliac disease. *Eur J Gastroenterol Hepatol*, 14:311-5.

Kaukinen K, Peraaho M, Lindfors K, et al. 2007. Persistent small bowel mucosal villous atrophy without symptoms in celiac disease. *Aliment Pharmacol Ther*, 25:1237-45.

Kupper C. 2005. Dietary guidelines and implementation for celiac disease. *Gastroenterology*, 128(suppl 1):S121-S127.

Lamontagne P, West GE, Galibois I. 2001. Quebecers with celiac disease: analysis of dietary problems. *Can J Diet Pract Res,* 62:175-81.

Leffler D, Dennis M, Hyett B et al. 2007. Etiologies and predictors of diagnosis in nonresponsive celiac disease. *Clin Gastroenterol Hepatol*,5(4):445-50.

Ljungman G, Myrdal U. 1993. Compliance in teenagers with coeliac disease–a Swedish follow-up study. *Acta Paediatr*, 82:235-8.

Malamut G, Afchain P, Verkarre V et al. 2009. Presentation and long-term followup of refractory celiac disease: comparison of type I with type II. *Gastroenterology,* 136(1):81-90.

Meloni A, Mandas C, Jores RD et al. 2009. Prevalence of autoimmune thyroiditis in children with celiac disease and effect of gluten withdrawal. *J Pediatr,* 155(1):51-5

NIH-National Institute of Health Consensus Development Conference Statement on Celiac Disease. June 28-30, 2004, 2005. *Gastroenterology*, 128:S1-S9.

Pietzak MM. 2005. Follow-up of patients with celiac disease: achieving compliance with treatment. *Gastroenterology*, 128:S135-41.

Rashid M, Cranney A, Zarkadas M et al. 2005. Celiac disease: Evaluation of the diagnosis and dietary compliance in Canadian children. *Pediatrics*, 116:e754-e759.

Romaldini CC, Barbieri D, Okay TS, et al. 2002. Serum soluble interleukin-2 receptor, interleukin-6, and tumor necrosis factor-alpha levels in children with celiac disease: response to treatment. *J Pediatr Gastroenterol Nutr*, 35:513-7.

Rubio-Tapia A, Kelly DG, Lahr BD et al. 2009. Clinical staging and survival in refractory celiac disease: a single center experience. *Gastroenterology*, 136(1):99-107.

Sategna Guidetti C, Solerio E, Scaglione N, et al. 2001. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. *Gut*, 49:502-5.

Silvester J, Rashid M 2010. Long-term management of patients with celiac disease: Current practices of gastroenterologists in Canada. *Can J Gastroenterol*, 24;(8):499-509.

Silvester J, Rashid M. 2007. Long-term follow-up of individuals with celiac disease: An evaluation of current practice guidelines. *Can J Gastroenterol*, 21(9):557-64.

Tursi A, Brandimarte G, Giorgetti GM. 2003. Lack of usefulness of anti-transglutaminase antibodies in assessing histologic recovery after gluten-free diet in celiac disease. *J Clin Gastroenterol,* 37:387-91.

Tursi A, Brandimarte G, Giorgetti GM et al. 2006. Endoscopic and histological findings in the duodenum of adults with celiac disease before and after changing to a gluten-free diet: a 2-year prospective study. *Endoscopy*, 38:702-7.

Ventura A, Magazzu G, Greco L. 1999. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. *Gastroenterology*,117:297-303.

Viljamaa M, Kaukinen K, Huhtala H, et al. 2005. Coeliac disease, autoimmune diseases and gluten exposure. *Scand J Gastroenterol*, 40:437-43.

Wahab PJ, Meijer JW, Mulder CJ. 2002. Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery. *Am J Clin Pathol*, 118:459-63.

Walker-Smith JA, Guandalini S, Schmitz J et al. 1990. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child*, 65:909-11.

Zarkadas M, Cranney A, Case S et al. 2006. The impact of a gluten-free diet on adults with coeliac disease: Results of a national survey. *J Hum Nutr Diet*, 19:41-49.

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