Which Guideline for Celiac Disease Is Best?

The Guidelines

Guidelines for the care of patients with suspected or known celiac disease are changing rapidly as new research leads to new understanding of the pathophysiology, assessment, and management of this increasingly common condition. Medscape spoke with Joseph A. Murray, MD, a member of several guideline panels and current President of the North American Society for the Study of Celiac Disease, about the current evidence underlying standards for care.

About the Interviewee

Dr. Murray is Professor of Medicine and Consultant in the Division of Gastroenterology and Hepatology and the Department of Immunology and Director of the Celiac Disease Program at the Mayo Clinic in Rochester, Minnesota.

Dr. Murray’s research interests focus on celiac disease and esophageal disorders. A research program, sponsored by the National Institutes of Health and the Centers for Disease Control and Prevention, focuses on clinical epidemiology of celiac disease, the role of genetics in predicting disease, clinical trials, the development of animal models for the disease and its associated dermatologic condition, and dermatitis herpetiformis. These studies encompass complications of celiac disease including small bowel cancer and intersect with programs in the Mayo Comprehensive Clinical Cancer Center and the Clinical Research Unit and complement the celiac disease clinic activity.

Background to the Interview

Celiac disease is recognized to be an inflammatory disorder of the small intestine with an autoimmune component and strong heritability. Once viewed primarily as a disease of childhood, occurring mainly in white persons, it is now understood to occur in people of any age and in populations outside Europe and North America. Previously considered a rare disease, the prevalence of celiac disease is currently estimated at 1 in 100-300 in most parts of the world, and the incidence and prevalence have been increasing markedly over the past few decades.

It has also become clear that celiac disease is associated with many other nongastrointestinal signs and symptoms and strongly associated with autoimmune diseases such as type 1 diabetes.

As a result of advances in the understanding and diagnosis of celiac disease, major guidelines have been updated recently, including those issued by the American College of Gastroenterology (ACG), European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), the British Society of Pediatric Gastroenterology, Hepatology, and Nutrition/Coeliac UK, and the World Gastroenterology Organisation. The US and European guidelines differ in their emphasis on the relative importance of serologic, genetic, and histologic testing in diagnosis, but all of the recommendations aim at achieving high diagnostic accuracy and improving rates of diagnosis.

The detection and management of celiac disease increasingly involve general practice. At the same time, diagnostic algorithms are becoming more complicated, requiring specialized knowledge apart from procedures and biopsies.

To further assist primary care providers (PCPs), Dr. Murray spoke to Medscape about the guidance provided by the latest guidelines for diagnostic strategies in the primary care setting for patients with suspected celiac disease. Management after diagnosis, with particular attention to strategies used in primary care, was also discussed. Dr. Murray is coauthor of the latest guidelines on diagnosis and management of celiac disease issued by the ACG and previously the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. He is also senior author of international guidelines on the use of video capsule endoscopy in celiac disease as well as many
The Interview -- Diagnosis

Medscape: With the increasing prevalence of celiac disease in Western countries, have you noticed increases in any particular subgroup, such as the young or elderly, or it is occurring in the broad population?

Dr. Murray: New-onset celiac disease is occurring at all ages, although the most dramatic increases are in older people, by which I mean those in their 40s and 50s and beyond. It is remarkable that those are people who have eaten gluten their entire lives without getting celiac disease. A Finnish study in subjects over the age of 50 years showed that there was substantial occurrence of celiac disease in people who previously tested negative, suggesting that you can get celiac disease at any age, even a relatively advanced age, despite a lifetime's exposure to gluten. I think that observation and another study from Maryland, almost more than anything else, have to change our approach to celiac disease in general. That is why there is the current profusion of guidelines and an effort to make PCPs understand that celiac disease is a condition they really have to be aware of now. Twenty years ago, it was usual to regard celiac as a rare condition, and we could wait until someone demonstrated severe malabsorptive disease in childhood before considering the possibility of celiac disease. Now we can no longer ignore it; it is becoming much more common. If you were a PCP with a panel of 1000 patients, most of them white, you could have 7 or 8 patients in your practice with celiac disease -- not an inconsiderable number, though most remain undetected.

Medscape: Despite the increased prevalence, celiac disease continues to be underdiagnosed, as you and others have shown. Why is this, and how can PCPs become more aware of celiac disease?

Dr. Murray: I think there are several reasons for the underdiagnosis of celiac disease. One reason is that the symptoms can be subtle; they are not specific to celiac disease. Celiac disease can present with many symptoms, including typical gastrointestinal symptoms (eg, diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain) and nongastrointestinal abnormalities like abnormal liver function tests, iron deficiency anemia, bone disease, and skin disorders. There are so many other conditions that could explain those symptoms. For example, a syndrome like iron deficiency anemia in a menstruating woman in her 30s could be due to celiac disease. The symptoms of celiac disease often overlap with the symptoms of irritable bowel syndrome, which is much more common than celiac disease, with worldwide prevalence rates ranging from 9% to 23% and US rates generally in the area of 10%-15%.

The second reason for underdiagnosis is that there may be a long period before symptoms occur. People who develop celiac disease may have no symptoms at all for years. So a portion of people with celiac disease at any one time will be truly asymptomatic. The third reason, which is mostly patient-related, is that the symptoms may be so subtle or come on so gradually that a person doesn't recognize them as abnormal. In patients I have diagnosed with celiac disease, it is common that they have been having 5 or 6 bowel motions a day that were steatorrheic, and they never realized that that was abnormal. So the symptoms can be so gradual in onset and so insidious that patients do not think to complain about them. There may be other patient factors. Some patients may have the symptoms, they may know that there is something wrong, but they don't complain about it. That may be a gender issue, as men tend to be less likely to report these symptoms than women.

Another physician-related issue is that there may be low suspicion for celiac disease, and if there is low suspicion, physicians will not test for it. If they are not going to test for it, they are not going to find it. A problem is that we don't routinely ask, "Do you have a family history of celiac disease?" If patients don't volunteer that information, we are probably not going to ask for it. I recommend that when we see patients, any family history of celiac disease should be part of what we ask about at the same time we ask about a family history of high blood pressure, heart disease, colon cancer, etc., because this is one of the more common chronic diseases for which family history has a significant impact on risk.

I also think there may be fewer diagnoses made because there is more empiric treatment without diagnostic testing. There is also the high popularity of a gluten-free diet preceding testing for celiac disease. People will go on a gluten-free diet either of their own accord or perhaps because an "alternative" practitioner, such as a naturopath, chiropractor, or even a certain type of nutritionist, has told them to go on a gluten-free diet without first testing for celiac disease.
Medscape: What should PCPs do if they suspect celiac disease before the patient is referred to a specialist? There may be some clinicians who are unfamiliar with the appropriate testing for celiac disease, which nowadays is antibody testing as the primary detection method. What do you advise for families in which someone has been diagnosed with celiac disease?

Dr. Murray: First, the PCP should discover something about the context or the family of the patient. If a first-degree relative has celiac disease, there is a very good rationale for testing the entire family or testing a child when they reach the age of 3 or 4 years and have been exposed to gluten for at least a couple of years. I emphasize a proactive approach.

Medscape: Would you test family members if they are asymptomatic?

Dr. Murray: Yes, even if they are asymptomatic, because the likelihood of being affected is high. Serologic testing is straightforward, and a PCP can order it.

Medscape: Would you routinely test children with type 1 diabetes for celiac disease? I understand that this is a controversial topic.

Dr. Murray: Many of the pediatric endocrinologists or pediatricians who look after children with type 1 diabetes are now testing more routinely. However, some adult patients we see aren’t getting tested by endocrinologists, so that is in flux. There is broad agreement that a patient with type 1 diabetes who has any gastrointestinal symptoms should be checked for celiac disease. There isn’t broad agreement on whether everybody with type 1 diabetes should be tested for celiac disease, although there has been a shift toward testing rather than not.

Medscape: What about children without a family history of celiac disease or associated conditions? Many with celiac disease may have no symptoms at all. A recent study has suggested that screening all children might be the only way to identify all children with celiac disease.[16,17]

Dr. Murray: I agree that the only way to detect all individuals with celiac disease is to test everyone who could have it; however, there is a significant societal burden of undertaking such a broad screening process. While my research would suggest that celiac disease is far more common than we detect clinically, I think we do have to figure out how and when and indeed if all of these people with hidden celiac disease need to be discovered. While in general I don’t think of having celiac disease as a good thing, some patients may actually derive some benefit from having undiagnosed celiac disease, particularly as it may mitigate some of the impact of excess caloric intake and obesity. Currently, the best advice is to think about celiac disease in patients with very nonspecific symptoms, test far more often than before, seek a family history, and test family members.

The 2 most important pieces of advice I would give to PCPs are: First, please test much more often than you are probably doing now. Test more patients with subtle but chronic symptoms.

Second, test before treatment; don’t let patients go on a gluten-free diet until you have tested them. One of the most common challenges nowadays is patients who are already on a gluten-free diet when they come to the office. It is a very big problem. In ideal circumstances, patients are on a normal gluten-containing diet before they get tested.

The Interview -- Diagnostic Confirmation

Medscape: How should the PCP usually proceed to confirm a diagnosis?

Dr. Murray: Detection is only the first stage in diagnosis. A single immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody test is probably the single most accurate detection test. When you get a positive result for a test, how you respond is very important because that single positive does not mean that your patient has the disease. It means that the patient has a much higher probability of having the disease; a single serologic test result does not constitute a diagnosis. You have done the first step, and that may be all you need to do as a PCP. Next, refer the patient to a specialist who can confirm the diagnosis. In the United States, you usually refer to a gastroenterologist. In the United Kingdom, it may be referral to a local celiac clinic, depending on available resources.
An important issue for every practitioner who uses these types of blood tests is not to be a slave to a threshold. We have cut-offs. Let us say the cut-off is 10; if the result is 10.1, we call that positive; and if it is 9.9, we call that negative. But in truth, when you compare them in the laboratory, they are indistinguishable. So I think we have to be cognizant that somebody whose test result is quite close to the negative threshold is less likely to have the disease, but somebody who is at the very top end of the negative threshold but not quite positive, in the right circumstances, might actually have the disease. There are some intercontinental differences in how testing is used. There is a different philosophy about how blood tests are expected to perform outside the United States. In Ireland, where I have worked, blood tests have generally been used with the goal of maximizing sensitivity, not wanting to miss people with the disease. When you increase the sensitivity, you accept some loss of specificity because you know you can send the patient for confirmation, and the patients do not usually pay out of pocket for their confirmation tests. In the United States, on the other hand, there is an expectation of higher specificity, maybe even at the expense of some sensitivity. You want to emphasize specificity because you know that doctors and patients are going to place more reliance on positive tests, and patients may not go on to get further testing because of the personal financial cost.

Medscape: In the United States, the specialist would follow ACG recommendations to confirm the diagnosis by doing an endoscopy with a biopsy. I believe the European and US guidelines on this differ slightly. Don't the European guidelines regard serologic testing and HLA determination as equally important to histologic testing and indicate that a diagnosis can be confirmed without doing endoscopy?

Dr. Murray: The difference between the guidelines is actually a lot more subtle than many people think. The ESPGHAN guidelines, which, it should be remembered, are for children, emphasize that there may be a circumstance in which a biopsy may be avoided, and they provide very specific criteria for that.[7] The problem that I have seen is that people have heard that they don't need to do the biopsy after a positive serologic test. But they haven't actually read the guidelines, which say that in children and adolescents with signs or symptoms suggestive of celiac disease and high TTG IgA levels >10 times the upper limit of normal, the pediatric gastroenterologist can consider the option of performing further endomysium antibody (EMA) and HLA testing, in a different blood sample, to make the diagnosis without biopsies. If the EMA test is positive and the disease-associated HLA type is identified from the same blood sample, then you don't need a biopsy to confirm the disease. In practice, those confirmatory tests don't get done.

Medscape: The ACG and ESPGHAN guidelines specify that HLA genotyping should not be used routinely in the initial diagnosis of celiac disease, only to rule out the disease in selected clinical situations. In practice, is it done very often?

Dr. Murray: It can be done readily, and it is even offered in the United States as direct-to-patient testing. I do it fairly often but in very specific circumstances. Patients can also write away and send in a cheek swab and get it done; that is a service that they have to pay for themselves. It is widely done in the United States, and it is often done by nonclinicians. The issues that I have with doing HLA genotyping are: First, it is a genetic test, and whenever you do a genetic test, you have to think of all the connotations of genetic tests for individuals, and that would imply that you need to do genetic counseling. The second challenge is how to interpret a positive genetic test in a patient who has had a seronegative test or no serologic testing at all. Does that mean the patient could get it or might get it? It means it is possible that they could get it. The problem is, the patients don't know this, and most PCPs do not know how to interpret it or how to instruct the patients on how to deal with it. Far too often, I see people who have been on a gluten-free diet just because they have found out they carry the gene for celiac disease. It is a classic error or problem with genetic testing. Patients conflate the notion of having the gene and having the disease; that is "genetic counseling 101."

The other common issue is that, if you do genetic testing in someone with a positive family history, the test is not very discriminatory. Most children of a parent with celiac disease or siblings of a celiac disease patient carry the genes anyway, but most of them won't get the disease. If I have celiac disease, the chance that a child of mine carries the gene for celiac disease is 67%, but there is only a 10% chance of their getting celiac disease.[18]

The other potential problem is the so-called "unexpected paternity" result, which can happen and which raises many other issues.

I use genotyping in very specific circumstances, as we describe in the ACG guidelines. Even with the ESPGHAN.
recommendations for children, the expectations are that the majority of children will still get biopsied.

Medscape: The ACG guidelines recommend multiple biopsies of the duodenum for confirmation of the diagnosis. Presumably there's no reason to avoid endoscopy in adults?

Dr. Murray: Our assessment is that endoscopy and biopsies in adults are proportionately much less invasive than they are in children. You are making a lifetime diagnosis with a life-changing treatment, and one should not make a diagnosis on less than robust grounds. There are other issues with adults. For example, a higher proportion of adults (vs children) don't experience intestinal healing. And if they don't heal, there are consequences to that. If you don't have a prior or baseline biopsy, it is hard to know at follow-up whether any healing has gone on at all. So that may be a bigger issue with adults than in children. All of us as practitioners would like to minimize the invasiveness and the costs of any testing that we do, but we have to offset that against the certainty of diagnosis, and we certainly don't want to have people being put on a gluten-free diet for life without robust evidence for that.

Medscape: What about people who are already on a gluten-free diet and need a confirmation of celiac disease?

Dr. Murray: This is one of the most common challenges and a very large problem, which we tried to address in the ACG guidelines. If you do the blood tests and their serology is positive, then you could submit them to a biopsy right away. If they are negative, then we do HLA genotyping; and if this is positive, we proceed to a gluten challenge -- not a super-high gluten challenge but a moderate gluten challenge for 2 weeks. Then, if they are able to continue it, we do it for another 6 weeks, for a total of 8 weeks. Then we test the serology, and if it has turned positive, we biopsy them. If it stays negative, then we follow them for another 6 weeks, and then if it turns positive, they potentially have celiac disease. When we put patients back on a gluten challenge, it is important to tell them that they must eat gluten daily when we want them on a challenge.

The Interview -- Management

Medscape: Life-long adherence to a gluten-free diet is the only option for patients with confirmed celiac disease, but what about follow-up after they have started on the diet? You and your colleagues have reported a study in which the quality of follow-up of celiac patients was found to be poor.[19]

Dr. Murray: There was poor follow-up, at least in that particular community (Olmsted County, Minnesota), but I don't think that is anything unusual. That is a community with one of the highest concentrations of doctors in the world, but we are not doing a very good job of following up with patients with celiac disease.

Medscape: The ACG guideline makes the point that a dietitian is effective in follow-up. In the United Kingdom, patients have been reported as preferring to consult a dietitian, only seeing a physician when necessary.[20] What do you think the role of a dietitian should be in follow-up?

Dr. Murray: Dietitians have a role beyond simply enabling and verifying adherence to a gluten-free diet. An important point for management that I think we now need in 2014 is to emphasize that just because something is gluten-free doesn't mean it is healthy. If it is full of fat and sugar, whether it is gluten-free or not, it is still unhealthy. So part of the dietitian's role is to help patients maintain a healthy weight and avoid other pitfalls of their diet, like eating far too much fat. Gaining weight is a common problem in patients with celiac disease. As their malabsorption corrects, they start to get into difficulty with absorbing too many calories. So another follow-up issue is maintaining a healthy weight after diagnosis of celiac disease.

There are differences between dietitian services in the United States and elsewhere, however. For example, dietitians in the United Kingdom typically have had a lot more experience with celiac disease, and often they work in concert with the gastroenterology clinic in a hospital environment. In the United States, more and more dietitians are becoming expert in advising on a gluten-free diet, but they don't necessarily have the skill set of managing celiac disease, like antibody testing, etc. And, as far as I know, they cannot order tests in the United States. For that reason, follow-up is still physician-based. Also, getting reimbursement for dietitian services for celiac disease in the United States can be difficult. In countries where they are regarded as an essential part of the care team, dietitians are readily available to
patients. In the United States, however, insurance companies often don’t even pay for the initial dietary consultation about a gluten-free diet. So these are very different situations.

**Medscape: Which type of provider should the patient see for follow-up: the PCP or a gastroenterologist?**

**Dr. Murray:** Once they are diagnosed, patients should go back to the PCP, as long as that clinician is reasonably familiar with celiac disease. In some circumstances, if a local hospital has an excellent celiac disease clinic with an expert dietitian and maybe a gastroenterologist, it may be worthwhile having them followed up there, especially for the more complex patients. The best person to manage follow-up is one who knows about celiac disease. PCPs have to be informed; they have to know at least the minimum about what the alarm symptoms are and what should send the patient back to the gastroenterologist for investigation. Most important are expertise and interest. We have found that a lot of PCPs or gastroenterologists aren’t interested in follow-up in these patients.

**Medscape: Why is that?**

**Dr. Murray:** It may be lack of familiarity. Another issue, especially in the United States for many years, is that the celiac community has felt medically orphaned. No one was really taking ownership of their care, so they were basically self-educating. Their advocacy groups would do a great job at collecting information and disseminating it, so often celiac patients felt they knew more than their providers. That doesn’t necessarily enhance trust and dependence.

**Medscape: How should the PCP approach follow-up in celiac disease patients?**

**Dr. Murray:** If I were a PCP, I would be seeing a patient with celiac disease a year after starting on a gluten-free diet. I would want to know how they were feeling, how well they were doing on their diet, and whether they were complying or adhering to the diet. Have they corrected any deficiencies that they had at the beginning? Are their symptoms better? You need to be aware that there are alarm symptoms (eg, rectal bleeding, unintended weight loss, fever, persistent diarrhea, or abdominal pain that wakes a patient at night); if they occur, that patient then gets referred on to the appropriate specialist. Of course, it is important to follow up, as it is in any chronic disease, on how well the patient is coping. For example, do they have they depression or anxiety? Those will have a substantial family and personal psychological impact. Some patients have a significant adjustment reaction to the diagnosis and going gluten-free, and those patients may need a lot more support. They need more extensive dietary counseling. The learning capacity of patients varies tremendously, and this diet is not simple. I get especially concerned about people who have severe anxiety relating to food that verges on paranoia. It is not very common, but it can have a substantial negative impact on an individual's quality of life. Studies examining burden of illness show that patients with celiac disease typically rate the burden of illness as relatively high. That may be because they are responsible for the treatment themselves; it is not as simple as taking a pill every day. So there is a substantial burden, and the burden is also economic. In many settings, the gluten-free diet is not cheap; it could cost many thousands of dollars a year in extra costs for food.

**Medscape: Does having celiac disease put a patient at increased risk for other diseases for which they should be monitored?**

**Dr. Murray:** Having celiac disease means that you are probably at risk for autoimmune diseases. Of note, all of the autoimmune diseases are more common in celiac patients, but often those diagnoses precede the diagnosis of celiac disease. So type 1 diabetes is much more commonly diagnosed before celiac disease than the other way around. Thyroid disease is probably the single most common association in adults. Up to 2%-7% of patients with celiac disease, depending on the study, have autoimmune thyroid disease. There are, of course, plenty of long-term risks for celiac disease, including bone disease and risk for fractures. We recommend checking bone densities either at diagnosis or sometime in the year after diagnosis. I do it at diagnosis, but other people say wait a year and just do it then because the patients are only getting better. I don't know that it matters a whole lot, just as long as you get it done. Of note, we have found that the risk for fractures doesn't necessarily go down after diagnosis. There is an elevated risk for fractures that may stay high. So I think bone health needs to be addressed in patients.

**Medscape: How often should patients be seen during follow-up?**

**Dr. Murray:** Here's what I typically do, and this is a broad recommendation. I want to make sure the patients have had
appropriate symptom response within 3 months. If they haven't, then we should readdress the diagnosis, what's going on, whether they are really adhering to a diet, whether they have had adequate instruction, to try to determine what is blocking their initial symptom response. Next, I want to see a response on their serology tests. By 6 months, it doesn't have to be negative, but the titers should be dropping. By 1 year, most of them should be negative. Then I typically re-biopsy all adults at 2 years. That is, again, not a universal practice; there are some who only re-biopsy if the patients are continuing to have or redevelop symptoms. I do it as a routine because failure to heal is, I believe, associated with some increased morbidity. There was a very interesting study from Sweden that I was part of that showed that healing of the biopsy does not predict survival, but having a follow-up biopsy increases your survival compared with those patients who do not have a follow-up biopsy.[22] It is interesting also that among the patients who had the biopsy, we found that whether they healed or not didn't seem to matter in terms of risk for lymphoma or malignancy.

Medscape: Do you ever re-biopsy patients after 2 years?

Dr. Murray: It depends on how they are doing. If their intestines have healed within 2 years, and they are doing well and they are staying on their gluten-free diet, I won't ever biopsy them again.

References


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