

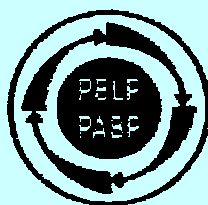
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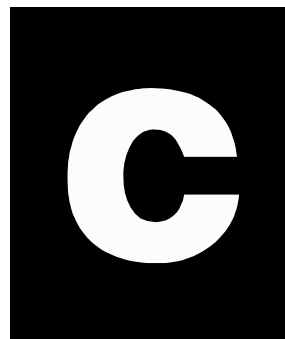
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CELIAC DISEASE

Celiac disease is now considered one of the most common inherited diseases in the world. Its high prevalence has been well established in western Europe (up to 1 in every 100) and recent studies have shown similar rates in North America. Despite this, celiac disease continues to be underdiagnosed—due, in large part, to its diverse, often extraintestinal, presentation. Yet early diagnosis and treatment can reduce or prevent serious, sometimes life-threatening, complications associated with the disease.

This module aims to clarify:

- prevalence, pathophysiology and clinical presentation of celiac disease among adults and children
- screening and prompt diagnosis of the disease
- treatment and ongoing monitoring

CASES

Case 1: Lois A., age 43, female

Part One

Lois comes to the office expressing concerns about her bowels. For many years she has had diarrhea associated with abdominal cramps and bloating. Her previous family doctor diagnosed irritable bowel syndrome (IBS). Lately, her symptoms have been getting worse. Nothing else worrisome is found on history or exam. She has no family history of inflammatory bowel disease or celiac disease. A recent CBC and ESR were normal.

What investigations would you do at this point?

Part Two

The serologic test for celiac disease (IgA tTG) was positive (elevated above 100).

What would you do now?

How would your approach differ if the IgA tTG was negative?

EDUCATIONAL MODULE

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Case 2: Mrs. Elma P., age 70, female**INFORMATION SECTION****Part One**

Elma, married with two grown children, presents today with an itchy, “burning” rash on both elbows that looks like chicken pox—the classic appearance of dermatitis herpetiformis. On specific questioning, she indicates that she has been experiencing fatigue, and mild abdominal bloating and discomfort for over 10 years. She also has osteopenia (T-score of -2.0) but no fractures.

Her physical exam reveals that she is somewhat overweight (BMI 28). Heart sounds are normal. There is no adenopathy. Her chest is clear. An abdominal exam reveals no areas of tenderness.

What investigations would you order?

Part Two

Elma is subsequently found to have iron deficiency anemia and celiac disease (positive blood work, confirmed with small bowel biopsy). No other abnormalities are detected.

How would you proceed with management?

Case 3: Fiona M., age 26, female

Fiona is here today for an introductory visit. She mentions that her mother was diagnosed with celiac disease five years ago. Fiona says that she has never had any symptoms that her mother has—marked fatigue and significant bowel-related symptoms.

Would you screen Fiona for celiac disease?

What would you do if Fiona opted for screening and her IgA tTG was elevated?

What if her IgA tTG was normal?

BACKGROUND**Prevalence**

1. “Evidence is mounting that celiac disease is one of the most prevalent genetically based diseases throughout the world.”¹
 - a. Epidemiologic studies in European populations have found that celiac disease occurs at a prevalence ranging from 1 in every 300 to 1 in every 70 people.²⁻⁵
 - b. A recent large multi-centre study (n=13,145) found a similar prevalence in the U.S.—1:133 in the general population (recruited from blood donors, schoolchildren and outpatients having routine checkups). In this group, celiac disease was far more common in adults (1:105) than in children (1:320).¹
 - c. Although prevalence less than 1:1000 has been reported in patients of other ethnic origins, recent epidemiologic studies suggest that, in other parts of the world (e.g., South America,⁶ North Africa⁷ and Asia), celiac disease is more common than previously thought.⁸⁻¹⁰
2. Significantly higher prevalence rates of celiac disease are evident among “at risk” groups:^{1,11,12}
 - about 10% in first-degree relatives (reported range from 4-20%)
 - about 7% (4-12%) for key conditions such as type 1 diabetes, autoimmune thyroid disease, Down syndrome (Table 2)
 - 2.5% in second-degree relatives
 - 1-3% in patients with specific symptoms associated with celiac disease (Table 1 and Table 2)

Note: It is estimated that about 20% of patients who are diagnosed with celiac disease have a positive family history.⁵ However, the prevalence of celiac disease appears to be as high in first- and second-degree relatives *without* symptoms, as it is in those *with* symptoms.¹
3. A female-to-male ratio of 2:1 has generally been accepted.¹³ However, recent data suggest that celiac disease may affect men and women equally.^{1,12}

Pathophysiology

4. Celiac disease is an immune disorder triggered by the ingestion of gluten in genetically predisposed individuals (HLA-DQ2 and HLA-DQ8 genotypes).^{5,12,14,15}
 - a. Gluten is an insoluble protein found in wheat, barley, rye and other grains. Rice, corn,

sorghum and millet are from a different subgroup of grains and do not cause celiac disease.¹²

- b. The ingestion of gluten results in a T-cell mediated inflammatory response in the small bowel that damages the mucosa, leading to malabsorption of iron, folic acid, fat-soluble vitamins and calcium. As long as the patient continues to ingest gluten, this inflammatory response will continue unabated.^{12,14,16}

CLINICAL PRESENTATION

- 5. Celiac disease can present at any age.¹⁶ The natural history of celiac disease is marked by “intermittent exacerbations and relative remissions.”¹⁴
- 6. Clinical manifestations of celiac disease differ from person to person, ranging from classic features (e.g., diarrhea, weight loss) to clinically silent genetic susceptibility. In addition, many of the symptoms are not specific to celiac disease, resembling those of other disorders that involve malabsorption or poor nutrition.¹⁴

Children

- 7. Classically, children with celiac disease have been described as presenting between the ages of 4–24 months (after introduction of grain into the diet) with impaired growth, chronic diarrhea and abdominal distension.^{15,17} However, for reasons unknown, this classic presentation has become rare. Other GI symptoms (Table 1) are now more common. As well, more subtle, extraintestinal symptoms (e.g., recurrent dental caries, short stature, delayed puberty) may be present.^{5,12,15}
 - a. In children and adolescents, silent celiac disease (characterized by positive serology and villous atrophy, on small bowel biopsy with no or mild symptoms) is about 7–15 times more common than symptomatic celiac disease.¹⁸
 - b. The peak period of diagnosis in children has shifted upwards to 1–5 years of age.¹⁹
- 8. Celiac disease is a life-long condition. However, clinical remission may occur during the second decade of life. This “remission” may be permanent or symptoms may recur decades later.¹⁴ Occasionally, other diseases may mimic celiac disease, so diagnostic confirmation is essential.

Adults

- 9. The diagnosis of celiac disease in adults is increasing—about 20% of diagnoses occur in people over 60 years of age.²⁰ While some adults

exhibit signs (e.g., short stature) or report symptoms dating back to childhood, many others do not have a long-standing history of symptoms, suggesting that celiac disease may develop in adulthood.¹⁷

- 10. In adults, the nature and intensity of symptoms of celiac disease vary widely. The classic features of diarrhea and weight loss may be present, but, increasingly, adults present with milder symptoms (e.g., abdominal discomfort, altered bowel habits).^{12,14,18} About 50% of adults with celiac disease do not have significant diarrhea.¹⁷
- 11. Many adults present with symptoms suggesting IBS, and can be misdiagnosed. Primary care studies have shown an increased prevalence of celiac disease in patients “diagnosed” with IBS (3–5% in IBS vs 0.25–1% in the general population).²¹⁻²³ [Level 3–4 Evidence] This association highlights the importance of considering celiac disease in patients with non-specific GI symptoms or in those diagnosed with IBS, particularly if other extraintestinal features (Table 1) are present.¹²
- 12. Iron-deficiency anemia—especially when not explained by another condition and unresponsive to oral iron therapy—is now the most common clinical presentation of celiac disease in adults. Other laboratory abnormalities include:^{12,17}
 - macrocytic anemia due to folate (or, rarely) vitamin B₁₂ deficiency
 - coagulopathy caused by vitamin K deficiency
 - hypocalcemia caused by vitamin D deficiency
 - elevated alkaline phosphatase

Table 1. Key Clinical Features of Celiac Disease

Common GI Symptoms	Extraintestinal
<p>Children</p> <ul style="list-style-type: none"> • nausea and vomiting • steatorrhea or watery diarrhea • abdominal distension/pain <p>Adults</p> <ul style="list-style-type: none"> • bloating • diarrhea • weight loss • aphthous stomatitis • abdominal pain 	<p>Hematologic</p> <ul style="list-style-type: none"> • anemia (commonly iron and folate deficiency) <p>Musculoskeletal</p> <ul style="list-style-type: none"> • osteoporosis, osteopenia • dental enamel hypoplasia <p>Metabolic or Laboratory Abnormalities</p> <ul style="list-style-type: none"> • vitamin D deficiency • calcium deficiency • increased transaminases

13. Increasingly, other extraintestinal manifestations of celiac disease are being recognized:^{17,24}

- short stature
- delayed puberty
- infertility, recurrent abortions
- depression, anxiety
- neurologic conditions (e.g., peripheral neuropathy, ataxia, seizures)
- features of hyposplenism (Howell-Jolly bodies and thrombocytosis)

Associated Conditions (Table 2)

14. Celiac disease is associated with many other disorders, particularly:^{11,12,25}

- dermatitis herpetiformis—nearly all patients with dermatitis herpetiformis have celiac disease, so it is sometimes called "celiac disease of the skin"; however, only 10–20% of patients with celiac disease have this skin disorder^{26,27}
- type 1 diabetes—up to 8% of patients with type 1 diabetes have celiac disease, and the percentage is much higher if there is diarrhea or other GI symptoms

Table 2. Conditions Associated with Celiac Disease^{11,12,25,28-33}

Condition	Reported Prevalence of Celiac Disease in Patients with this Condition* Note: Prevalence of celiac disease in the general population is 0.25-1%.	Estimated Prevalence in General Population
Dermatitis herpetiformis	>85%	rare (about 10 per 100,000)
Type 1 Diabetes	3-8%	about 1% (wide range in different ethnic groups)
Irritable Bowel Syndrome	3-4%	10-15%
Iron-Deficiency Anemia, unexplained	3-15%	3-5% (higher in women)
Selective IgA Deficiency	2-7%	~0.2%
Autoimmune Thyroid Disease/Thyroiditis	0.6-4-5%	2-7% (highest in older women)
Down Syndrome	4-12%	0.1%
Turner Syndrome	4-8%	0.02%
Addison Disease	7-12%	rare (4-12 per 100,000)
Ulcerative Colitis, Including Microscopic Colitis	uncertain (1-20%)	0.1%
Sjögren Syndrome	uncertain (0-15%)	0.5%

*Based primarily on retrospective cohort or case-control studies in specialty clinics [Level of evidence 3-4]

15. Associations with other conditions have been reported but the link is uncertain.^{12,25,28}
- inflammatory bowel disease
 - rheumatoid arthritis
 - autoimmune hepatitis
 - primary biliary cirrhosis
 - polymyositis
 - vasculitis
 - sarcoidosis

Complications

Malabsorption

16. Osteopenia and osteoporosis are more common in patients with untreated celiac disease than in the general population. Once thought to be caused solely by chronic malabsorption of calcium and vitamin D, recent evidence suggests additional problems with bone metabolism.¹⁵
- a. Up to 70% of patients with untreated celiac disease have osteopenia or osteoporosis—the prevalence increases with age at diagnosis.¹⁸ Studies suggest a rate of osteoporosis at about 35%. When compared to age-matched controls, men were more severely affected than women.³⁴
 - b. The consequences of osteopenia and osteoporosis are unclear. One study (165 patients with celiac disease; 165 controls) found an increased risk of fractures in patients with celiac disease compared to control subjects (25% vs 8%).³⁵ However, a more recent study (244 patients with celiac disease; 161 controls) found no increased risk.³⁶ [both studies Level 2b Evidence]

Malignancies

17. Extensive evidence has established an association between celiac disease and various malignancies (e.g., non-Hodgkin's lymphoma, adenocarcinoma of the small intestine, squamous cell carcinoma of the oropharynx and esophagus). These malignancies are the leading causes of death in celiac patients.^{37,38} [Level 2b Evidence]
18. The most common malignancy associated with celiac disease is T-cell non-Hodgkin's lymphoma. While previous studies have estimated a 30-70-fold increase in risk compared to the general population, a more recent retrospective study (n=11,000 hospitalized celiac patients) found only a 6-fold increase³⁸—"likely a more accurate estimate."¹² [Level 2b Evidence]
19. A population-based cohort study in primary care (n=4,732) found that most of the increased risk of malignancy and mortality occurs in the first year after diagnosis of celiac disease—suggesting that some of the overall excess risk is likely due to

malignancies being detected during investigations for celiac disease.³⁹ [Level 2b Evidence]

Asymptomatic Celiac Disease

Silent

20. This form of celiac disease is characterized by histologic changes (on small bowel biopsy) that are present in individuals who are apparently asymptomatic. On closer scrutiny, many of these people are affected by "low-intensity illness". Common findings in these patients include:²⁵
- iron deficiency (with or without anemia)
 - depression, irritability
 - fatigue
 - reduced bone mineral density
21. Expert opinion is divided over the implications of silent celiac disease.⁵ Some experts believe that people with silent celiac disease are at risk of developing the same long-term complications as those people with typical symptoms of celiac disease.²⁵ Others assert that the risk of complications remains unclear in this population.⁴⁰

Latent

22. There is good evidence [Level 1b–2b] that in children and young adults belonging to certain at-risk groups (e.g., patients with type 1 diabetes, first-degree relative with celiac), serological tests may initially yield negative results. Repeat testing of higher-risk patients over a period of some years or if any symptoms develop, can identify those patients who develop celiac disease later in life.⁴¹

DIAGNOSIS

The Tools

Serological Tests

23. The advent of serologic antibody markers has facilitated the diagnosis of celiac disease.
- a. The older antigliadin antibody (AGA) markers—immunoglobulin A (IgA AGA) and immunoglobulin G (IgG AGA)—have significant false-positive rates and are no longer recommended in adults or older children.¹²
 - b. The IgA AGA is still considered the most sensitive marker for detecting celiac disease in children less than 2 years of age.⁴⁰
24. The more accurate tissue transglutaminase antibody (IgA tTG) and endomysial antibody (IgA EMA) have supplanted the older AGA markers.¹² See Table 3.
- a. The IgA tTG is the recommended initial test, due to relatively low cost, ease of test performance and reliability. The IgA EMA is thought to be

- more subject to human error.⁵
 - b. In high-risk patients (Appendix 1), it may be prudent to use *both* IgA tTG and IgA EMA tests, as reliance on either as a single test “underestimates the prevalence of celiac disease by 20%.”^{5,24}
 - c. There is controversy about whether total IgA should be ordered *routinely* along with IgA tTG and/or IgA EMA.⁵ As there is a 2% prevalence of IgA deficiency in celiac disease,^{41,42} there is an increased risk of a false negative IgA ETG or IgA EMA. A normal IgA indicates that a patient has sufficient IgA, but this strategy is not warranted when screening asymptomatic or low-risk patients in the general population.^{5,41}
25. It is important to note that the accuracy of serologic tests in the clinical setting may not be as high as that reported in the research setting.⁴¹
- a. “Despite the high sensitivity, the positive predictive value of these tests decreases when used in the general population rather than in groups at risk for celiac disease.²⁵ In symptomatic patients, the positive predictive value of tTG and EMA assays for finding biopsy evidence of CD approaches 100%. However, in screening-identified individuals, IgA AGA+IgA EMA, IgA EMA alone and IgA tTG alone have positive predictive values for biopsy evidence of CD ranging from 60–100%.⁴¹
 - b. In children, the sensitivity and specificity of tests (as well as appropriate cut-off values) vary according to age.⁴⁰ For example, the EMA test may be less accurate in children less than 2 years of age.

27. In patients presenting only with non-specific symptoms (e.g., episodic diarrhea or fatigue), negative results may essentially rule out the disease, due to the high negative predictive values of IgA tTG and IgA EMA (93-98%; 80–95% respectively).¹⁷

Small Bowel Biopsy

28. Small bowel biopsy (performed during upper GI endoscopy) remains the gold standard for diagnosis.
- a. If clinical suspicion for celiac disease is high, small bowel biopsy is recommended, regardless of the results of serological testing.^{17,25} See Appendix 1.
The compelling reasons to perform a small bowel biopsy are:
 - 1) Celiac is defined by an enteropathy, not by the presence of a serum autoantibody.
 - 2) False positive and false negative serologic tests do occur, and the emotional and financial costs of a false diagnosis of celiac disease are enormous!
 - 3) It may guide therapy, as it is not yet clear that a gluten-free diet in a patient with a positive antibody screen but negative histology is beneficial.
 - b. **Note:** Some experts state that a small bowel biopsy *may not* be needed in a patient with biopsy proven dermatitis herpetiformis and positive celiac antibody test.¹¹
 - c. The improved accuracy of the IgA EMA and IgA tTG tests, at least in the research setting, has raised the question whether intestinal biopsy is always necessary for diagnosing celiac disease in high-risk patients. A recent study of 181 celiac patients referred to tertiary care suggests that, in high-probability adult patients (e.g., patients presenting with the classic signs and symptoms of the disease or with its associated disorders), positive IgA EMA *and* IgA tTG titres *might* preclude the need for small bowel biopsy to establish the diagnosis of celiac disease.⁴³ However, further study is needed.

Table 3. Performance of Serologic Markers for Celiac Disease^{12,41} [Level 2b–3b Evidence]

Assay	Sensitivity (%)	Specificity (%)
IgA tTG	children & adults: 92–100%	children & adults: 91–100%
IgA EMA	children: 88–100% adults: 85–89%	children: 91–100% adults: 97-100%
IgA AGA	children: 52–100% adults: 75–100%	children: 92–97% adults: 82–97%

***Note:** Costs of the serological tests can vary considerably (from \$20 to over \$110 each) in different laboratories *and* may *not* be covered by health insurance plans. Some labs offer a combination of tests (a “celiac antibody profile”).

26. In symptomatic high-risk patients, where there is a strong clinical suspicion for celiac disease but IgA tTG and/or IgA EMA are negative, consider referral for endoscopy and possible biopsy. Measurement of total serum IgA should be done in these individuals to check for IgA deficiency.⁴¹

29. The pathological interpretation of small bowel biopsies can be problematic. Most experts recommend that during endoscopy multiple biopsies be taken because “the disease is patchy” and not all biopsy specimens will allow appropriate interpretation.²⁴ However, there are no detailed studies on the optimal number of biopsies required to detect changes consistent with celiac disease.⁴⁰

30. Biopsies generally need to be repeated only in patients who have an “equivocal or inadequate response to a gluten-free diet.”¹⁶

Who and How To Test

31. Assessing the pretest probability of celiac disease can guide the diagnostic process.¹² See Appendix 1 for an algorithm that illustrates this approach.

Asymptomatic Individuals

32. The screening of asymptomatic people for celiac disease is controversial.²⁵
- Some experts favour mass screening because they conclude that this disease fulfills the WHO criteria for generalized screening (see box below).^{16,25}
 - Others argue against mass screening because:
 - the positive predictive value of serologic tests is decreased in the general population
 - the appropriate age to screen, and whether to re-screen to rule out latent disease, are unknown²⁵
 - treating patients with apparently silent celiac disease can be problematic, since a lifelong, gluten-free diet is complex, expensive, socially disruptive,^{25,44} **and** has not yet been shown to protect these patients from the development of complications.

WHO Criteria for Generalized Screening

- The disease should be an important health problem for the individual and/or the community (in terms of death, suffering, economic or social costs).
- The natural course of the disease should be well-known, and the disease should go through an initial latent stage or be identified by risk factors.
- Appropriate tests (highly sensitive and specific for the disease) are available and are acceptable to the person screened.
- Adequate treatments or other intervention possibilities are available. Adequacy is determined both by proven medical effect and ethical and legal acceptability.
- Screening followed by diagnosis and intervention in an early stage of the disease should provide a better prognosis than intervention after spontaneously sought treatment.
- The cost, including diagnosis and subsequent treatment, should be economically balanced in relation to expenditure on medical care as a whole.

Adapted from: Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. *Bol Oficina Sanit Panam* 1968;65(4):281-393. PM:4234760

TREATMENT

Gluten-Free Diet

33. Gluten-free diets are **not** recommended until after the diagnosis of celiac disease is firmly established because the response is often equivocal, and abnormal serology and biopsy results may revert to normal, making diagnosis difficult.^{17,24}
34. The cornerstone of treatment is a lifelong gluten-free diet, avoiding all products containing wheat, rye and barley.^{14,17}
- A recent randomized trial (following 92 adult patients with celiac disease over 5 years) found that moderate amounts of oats (up to 2oz) can be safely included in a gluten-free diet.⁴⁵ However, caution is advised given the risk of cross-contamination with wheat.¹⁷ [Level 2b Evidence]
 - Constant surveillance is needed, as many processed foods and medications contain gluten.
See Patient Information Sheet for an overview of a gluten-free diet.
35. Education for both the patient and family is vital. Referral to an experienced clinical dietitian is important, and support groups can be an invaluable source of information.^{14,17} The online resources provided on the Patient Information Sheet provide information on local support groups/meetings.

The cost of gluten-free foods is a concern to many patients with confirmed celiac disease.⁴⁶ The incremental costs of purchasing gluten-free food (i.e., the increased cost compared to the cost of a similar non-gluten-free item) often can be claimed as medical expenses for tax purposes. The following link provides further information: www.cra-arc.gc.ca/tax/individuals/topics/celiac-e.html

Prognosis

36. The prognosis is excellent for patients who adhere to a gluten-free diet.¹⁷
- Two weeks after starting a gluten-free diet, about 70% of patients experience an improvement in symptoms.¹⁷
 - In general, the degree of histologic improvement lags behind the clinical response and may only be evident on repeat biopsy 2–3 months later.⁴⁷ Half of adults experience partial resolution in biopsy; children generally have complete resolution.¹⁷ [Level 4 Evidence]
- Note:** If a patient has no response to a gluten-free diet, incomplete adherence is often the culprit. Persistent symptoms may also be

caused by co-existing conditions (e.g., IBS, lactose intolerance, pancreatic insufficiency, microscopic colitis). Once these conditions have been ruled out, refractory celiac disease may be considered. Referral to a gastroenterologist for further investigations is indicated.^{12,17}

37. Strict adherence to a gluten-free diet also leads to:
- complete recovery and maintenance of bone mineral density in children;⁴⁸ [Level 3b Evidence] in adults, bone mineral density is stabilized, although levels often do not return to normal³⁴ [Level 3b Evidence]
 - reduced risk of associated cancers⁴⁹ [Level 4 Evidence], perhaps with the exception of T-cell lymphoma⁵⁰ [Level 3b Evidence]
 - improved survival rates—among patients who strictly adhere to a gluten-free diet, the mortality rate can be reduced to that of the general population (from the two-fold increase in mortality rates found in celiac disease when compared to age-matched controls).^{51,52} [Level 3b Evidence]

Other Treatment Issues

38. Initial management also includes:¹⁷
- screening for iron and folate deficiency, osteoporosis
 - multivitamin and other supplements (as required)
- Patients with features of hyposplenism should receive prophylactic antibiotics before invasive procedures and may benefit from pneumococcal vaccination.¹⁷

Monitoring

39. Once a gluten-free diet has been initiated and improvement is evident, yearly follow-up and reassessment has been suggested.^{12,13} [Level 5 evidence] However, no evidence-based approach to repeating serology to measure response to diet or to screening for complications has been established.¹¹ In addition to reinforcing the need for the gluten-free diet, these visits do provide an opportunity to repeat investigations (CBC, folate, etc.) when indicated.^{11,12} Consider bone density to monitor stabilization of bone density in adults at risk.⁵³

THE BOTTOM LINE

- Celiac disease is common.
- Assessing pretest probability can facilitate the diagnostic process.
- Prompt diagnosis and adherence to a gluten-free diet, though challenging, can reduce morbidity and mortality.

CASE COMMENTARIES

Case 1: Lois A., age 43, female

Part One

What investigations would you do at this point?

Due to the absence of a family history, Lois would fall into the intermediate pretest probability category (Appendix 1) for celiac disease. Celiac disease would be considered because she was previously diagnosed with IBS (Info point 11). Therefore, an IgA tTG (or IgA EMA) would be recommended (Info points 24, 25, Table 3)

Part Two

What would you do now?

Referral for a small bowel biopsy would be indicated to confirm diagnosis (Info point 28, Appendix 1). An empiric gluten-free diet would *not* be recommended until biopsy was taken and the diagnosis confirmed (Info point 33). Assessment for other abnormalities associated with malabsorption is also recommended—folate, ferritin, INR, calcium, alkaline phosphatase (Info point 12).

How would your approach differ if the IgA tTG was negative?

The high negative predictive value of the IgA tTG would effectively rule out celiac disease and obviate the need for further investigations for celiac disease, including biopsy (Info point 27).

Case 2: Mrs. Elma P., age 70, female

Part One

What investigations would you order?

Elma's dermatitis herpetiformis should be confirmed by skin biopsy, and investigations for celiac disease are indicated (Info points 14 and 28, Appendix 1). These would include a CBC, an IgA tTG and/or IgA EMA (Info points 24, 25, Table 3) and a total IgA (Info point 24c). Her age and symptoms would also raise concern about

a possible GI malignancy, so colonoscopy would be recommended and a search for other malignancies considered (Info points 17-19).

Part Two

How would you proceed with management?

Elma would be encouraged to commit to a lifelong gluten-free diet (Info point 34)—to treat both her skin condition and her GI symptoms. This dramatic dietary change may be daunting, particularly for an elderly person. Referral to a dietitian experienced in celiac disease and information on support groups (see Appendix 3) is helpful. Elma would also require:

- an iron supplement to treat her anemia
- dapsone (usually 50-100 mg/day) for her dermatitis herpetiformis rash
- reassessment of osteoporosis risk (Info points 38, 39) and appropriate treatment

Yearly follow-up would be appropriate (Info point 39).

Case 3. Fiona M., age 26, female

Would you screen Fiona for celiac disease?

Because the prevalence of celiac disease among first-degree relatives is high (Info point 2), screening Fiona for celiac disease may be warranted. However, since Fiona is asymptomatic, the benefits of screening are unclear and serological tests are less reliable (Info point 32). It may be appropriate to share this uncertainty with Fiona and provide sufficient information to let her decide.

What would you do if Fiona opted for screening and her IgA tTG was elevated?

If her IgA tTG was elevated, a biopsy would be required to confirm the diagnosis (Info point 28).

The treatment of asymptomatic, “silent” celiac disease is controversial. It may be helpful to discuss (with both the GI specialist and Fiona) the uncertainty regarding the benefits of a gluten-free diet in asymptomatic people versus the possibility of developing complications if her celiac disease is left untreated (Info points 21, 32).

What if her IgA tTG was normal?

The most likely possibility is that she does not have celiac disease. It also is possible that she may have a false negative test, either because of IgA deficiency (Info point 24) or limited sensitivity of the test (Table 3). Since she is in the high-probability group (Appendix 1), the total IgA would have been done. If it is normal, this rules out the possibility of IgA deficiency (Info point 24).

Since the serologic tests may miss celiac disease 20% of the time (Info point 24b), it may be worth repeating this at some point in the future—and definitely repeating if she develops any suggestive symptoms (Info point 32, Appendix 1).

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LEVELS OF EVIDENCE

Level of Evidence	Therapy/Prevention	Prognosis	Diagnosis
1a	Systematic review (with homogeneity) or meta-analysis of well-designed randomized trials	Systematic review (with homogeneity) of inception cohort studies or a CDR (clinical decision rule or guide) validated in different populations	Systematic review (with homogeneity) of Level 1 diagnostic studies; or a clinical decision rule validated in different clinical centres
1b	Large individual randomized trial with clear-cut results (narrow confidence intervals and low risk of error)	Individual inception cohort study with ≥80% follow-up	Study with independent blind comparison of an appropriate spectrum of consecutive patients
1c	<i>All or none</i> case-series	<i>All or none</i> case-series	<i>Absolute</i> positive specificity (rules in diagnosis) <u>or</u> negative sensitivity (rules out)
2a	Systematic review of well-designed cohort studies with homogeneity	Systematic review (with homogeneity) of retrospective cohort studies or untreated control groups in RCTs	Systematic review (with homogeneity) of diagnostic studies at 2b level
2b	Small RCT (or subgroup analysis within larger RCT) with moderate to high risk of error [low power]: a. Trial with high false-positive (α) error—interesting positive trend that is <i>not</i> statistically significant. b. Trial with high false-negative (β) error—a ‘negative’ trial that could not exclude the real possibility of a clinically important benefit or difference because of small numbers. Individual well-designed cohort study	Retrospective cohort study or follow-up of untreated control patients in an RCT or CPG not validated in a test set	Any of: • Independent blind or objective comparison; • Study performed in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard; • A diagnostic CDR not validated in a test set
2c	“Outcomes” Research; Ecological studies	Audit or “Outcomes” Research	
3a	Systematic review of case-control studies with homogeneity		Systematic review with homogeneity of 3b studies
3b	Individual well-designed case-control study		Study in which the reference standards not applied consistently to all study patients; Non-consecutive study
4	Case-series; Low-quality cohort and case-control studies (lack defined comparison groups and/or did not measure interventions & outcomes in appropriate ways)	Poor quality prognostic cohort studies (sampling was biased or measurement of outcomes achieved in <80% of study patients); Case series	Case-control study with poor or non-independent reference standard
5	Expert opinion (individual or committee) without explicit critical appraisal or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

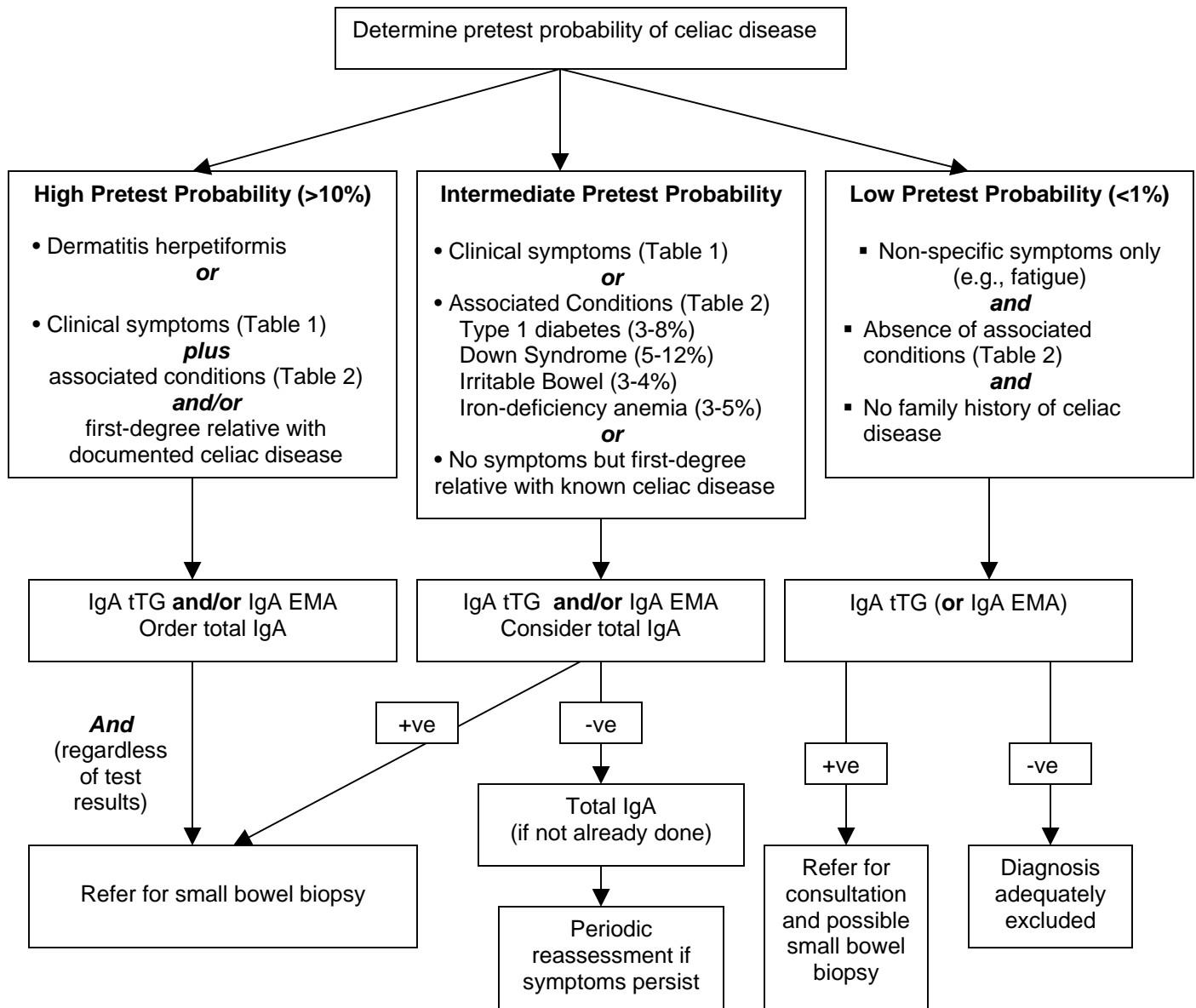
adapted from Centre for Evidence-Based Medicine, Institute of Health Sciences, Oxford 2001: http://www.cebm.net/levels_of_evidence.asp [accessed April 28, 2005]

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IgA-tTg = tissue transglutaminase antibody
IgA-EMA = endomysial antibody
Total IgA = serum level of all IgA antibodies

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GLUTEN-FREE DIET: DOs and DON'Ts

DOs	DON'Ts
<p>Gluten-free Grains and Starches</p> <ul style="list-style-type: none"> • amaranth • arrowroot • buckwheat • corn • flax • millet • montina • oats (cross-contamination with gluten-containing grains possible) • maize • potato • quinoa • rice • sorghum • tapioca • flours made from nuts, beans and seeds <p>Safe Ingredients</p> <ul style="list-style-type: none"> • cornstarch • maltodextrin (made from cornstarch, potato, starch or rice starch) • vinegar (not malt) <p>Alcohol</p> <ul style="list-style-type: none"> • distilled spirits (e.g., whiskey and brandy) • wine 	<p>Grains containing Gluten</p> <ul style="list-style-type: none"> • wheat • rye • barley <p>Foods Containing Lactose (initially)</p> <ul style="list-style-type: none"> • dairy products may be re-introduced after 3–6 months of treatment <p>Unsafe Ingredients</p> <ul style="list-style-type: none"> • maltodextrin made from gluten <p>Malt Products</p> <ul style="list-style-type: none"> • malt vinegar • beers, lagers, ales and stouts

Items to Consider (i.e., may contain gluten)
<ul style="list-style-type: none"> • lipstick/gloss/balms • mouthwash/toothpaste • play dough • stamp and envelope glues • vitamin, herbal and mineral preparations • prescription or OTC medications

Resources

The Canadian Celiac Association <http://www.celiac.ca>
 Celiac.com <http://www.celiac.com>
 The Gluten Intolerance Group <http://www.gluten.net>
 Celiac Disease Foundation <http://www.celiac.org>

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