Review Article

Current Concepts

CELIAC SPRUE

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CELIAC sprue, also known as celiac disease and gluten-sensitive enteropathy, is characterized by malabsorption resulting from inflammatory injury to the mucosa of the small intestine after the ingestion of wheat gluten or related rye and barley proteins. There is clinical and histologic improvement on a strict gluten-free diet, and relapse when dietary gluten is reintroduced.[1] Accounts of celiac sprue date back to the first century A.D.[2] It was not until the 1940s, however, that the link to gluten ingestion was established; Dicke, a Dutch pediatrician, observed that the condition of children with celiac sprue improved during the food shortages of World War II, only to relapse after cereal supplies were restored.[3] Until fairly recently, celiac sprue was considered uncommon in the United States, with an estimated prevalence of 1 per 3000 population.[4] However, greater awareness of its presentations and the availability of new, accurate serologic tests have led to the realization that celiac sprue is relatively common, affecting 1 of every 120 to 300 persons in both Europe[5-7] and North America.[8]

EPIDEMIOLOGY AND PATHOGENESIS

The true prevalence of celiac sprue is difficult to ascertain, because many patients have atypical symptoms or none at all. A large, multicenter Italian study identified seven new cases of celiac sprue in children for each patient with established disease.[7] The highest reported prevalence is in western Europe and in places where Europeans emigrated, notably North America and Australia.[5-8] Celiac sprue is also found in parts of northwest India, and it may be underdiagnosed in South America, North Africa, and Asia.[9] It is rare among people from a purely African-Caribbean, Chinese, or Japanese background. In most series there is a slight female preponderance.

Celiac sprue results from an inappropriate T-cell–mediated immune response against ingested gluten in genetically predisposed people.[10] The importance of genetic factors is supported by the approximately 10 percent prevalence of the disease among first-degree relatives.[11] Over 95 percent of patients with celiac sprue express the HLA-DQ(α1*501,β1*02) heterodimer (HLA-DQ2), which preferentially presents gluten-derived gliadin peptides on its antigen-presenting groove to stimulate intestinal mucosal T cells (Fig. 1).[12,13] The enzyme tissue transglutaminase is one of the targets of the autoimmune response in celiac sprue.[14] The modification of gliadin by host tissue transglutaminase has a key role in enhancing the gliadin-specific T-cell response,[15] and a single tissue transglutaminase–modified peptide is the dominant α-gliadin T-cell epitope[16] and may be a target for antigen-specific peptide therapy.

CLINICAL MANIFESTATIONS

Celiac sprue has a wide spectrum of gastrointestinal and extraintestinal manifestations (Table 1).

Celiac Sprue in Children

Classically, infants with celiac sprue present between the ages of 4 and 24 months with impaired growth, diarrhea, and abdominal distention.[17] Vomiting is common in young infants, as are pallor and edema. The onset of symptoms is gradual and follows the introduction of cereals into the diet. The velocity of weight gain slowly decreases before weight loss ensues. Some children present with constipation, although diarrhea is more typical. Patients with severe, untreated celiac sprue may present with short stature, pubertal delay, iron and folate deficiency with anemia, and rickets. Atypical celiac sprue is usually seen in older children or adolescents, who often have no overt features of malabsorption. In addition to recurrent abdominal pain, hypertransaminasemia, recurrent aphthous stomatitis, arthralgia, and defects in dental enamel, children may have behavioral disturbances such as depression, may be irritable, and may perform poorly in school.

Celiac Sprue in Adults

The diagnosis of celiac sprue is increasingly being made in adults. About 20 percent of cases occur in patients who are older than 60 years of age.[18] Some patients are short or have symptoms dating back to childhood. However, many have no history of symptoms, suggesting that celiac sprue can develop in adulthood.[19] Celiac sprue may present during pregnancy or

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post partum, and the diagnosis should be considered in pregnant women in whom severe anemia develops.

Many adults present with episodic or nocturnal diarrhea, flatulence, and weight loss. Enteropathy often results in symptomatic lactose intolerance. Steatorrhea is associated with severe, extensive enteropathy, but it is often absent in patients whose disease is limited to the more proximal portion of the small intestine. Abdominal discomfort and bloating are common and often lead to a mistaken diagnosis of irritable bowel syndrome. Malaise and lassitude are also common even when anemia is absent. Recurrent aphthous stomatitis may be the sole symptom at presentation.

Approximately 50 percent of adult patients do not have clinically significant diarrhea. Iron-deficiency anemia is now the most common clinical presentation in adults with celiac sprue. Other laboratory abnormalities include macrocytic anemia due to folate (or, rarely, vitamin B_{12}) deficiency, coagulopathy resulting from vitamin K deficiency, or vitamin D deficiency leading to hypocalcemia and an elevated alkaline phosphatase level.[20] Other increasingly recognized extraintestinal manifestations include bone fractures,[21] infertility,[22] psychiatric syndromes,[23] and various neurologic conditions, including peripheral neuropathy, ataxia, and seizures.[24]

Associated Conditions

Many conditions occur in association with celiac sprue[25] (Table 1). Dermatitis herpetiformis is characterized by intensely pruritic papulovesicular lesions that occur symmetrically over the extensor surfaces of the arms and legs as well as the buttocks, trunk, neck, and scalp. The diagnosis requires the demonstration by immunofluorescence studies of granular deposits of IgA in an area of normal-appearing skin.[26] A small-bowel biopsy in patients with dermatitis herpetiformis demonstrates a mild and patchy gluten-sensitive enteropathy. The skin lesions respond to the withdrawal of gluten from the diet or to treatment with dapsone.

Autoimmune diseases occur more commonly in patients with celiac sprue, especially type 1 diabetes mellitus[27,28] and autoimmune thyroiditis.[29] The prevalence of celiac sprue in patients with type 1 diabetes is approximately 3 to 8 percent.[27,28] Unexpected episodes of hypoglycemia or diarrhea should alert clinicians to the possibility of coexisting celiac sprue in patients with type 1 diabetes. The duration of gluten exposure is associated with the prevalence of associated autoimmune diseases, which is additional rationale for early diagnosis and treatment of celiac sprue.[30]

DIAGNOSIS

Serologic Tests

The availability of highly sensitive and specific serologic markers greatly facilitates the diagnosis of celiac sprue (Table 2). These serologic tests are used to evaluate patients with suspected disease, monitor adherence and response to a gluten-free diet, and screen patients with atypical, extraintestinal manifestations.[9] IgA antiendomysial antibodies are usually detected by indirect immunofluorescence with the use of sections of human umbilical cord or, less commonly, monkey esophageal smooth muscle.[34] The reported sensitivity and specificity of antiendomysial antibodies are 85 to 98 percent and 97 to 100 percent, respectively.[9,34-36] Tissue transglutaminase is the autoantigen recognized by antiendomysial antibody.[14] An IgA enzyme-linked immunosorbent assay that uses guinea pig tissue transglutaminase is now widely available and is cheaper, easier to perform, and more sensitive but less specific than the antiendomysial antibody assay.[31,32] A simple dot blot test that uses human recombinant tissue transglutaminase may be more specific than the assay that uses guinea pig tissue transglutaminase.[33] Although false positive results are rare, false negative antiendomysial and tissue transglutaminase antibody results can occur in mild enteropathy, in children under two years of age, and especially in patients with IgA deficiency.

Tests for IgA and IgG antigliadin antibodies have moderate sensitivity but are far less specific than tests for IgA antiendomysial antibodies.[9,37,38] Many normal persons as well as patients with gastrointestinal inflammation from other causes test positive for antigliadin antibodies.[38] Consequently, the positive predictive value of antigliadin antibody tests in a general population is poor. However, IgA antigliadin antibody is the most useful serologic marker in symptomatic children younger than two years of age. A test for IgG antigliadin antibody is useful in the 2 to 10 percent of patients with celiac sprue who have coexisting IgA deficiency. Levels of IgA antigliadin, IgA antiendomysial, and IgA tissue transglutaminase antibody all become undetectable in patients who are on a strict gluten-free diet. Tests for IgA antigliadin antibody are useful to monitor dietary compliance, since levels of this antibody are the easiest to quantify.[39] Levels of IgA antigliadin antibody gradually become undetectable within three to six months after gluten is withdrawn from the diet.

Hematologic and Biochemical Tests

Deficiencies of iron, folate, calcium, and vitamin D may be found in patients with untreated celiac sprue. Combined iron and folate deficiency is a characteristic consequence of enteropathy of the proximal portion of the small bowel but is less frequent than iron-deficiency anemia. A vitamin B_{12} deficiency is uncommon, since the enteropathy seldom extends to the ileum, where there is little or no exposure to gluten. Features of hyposplenism (Howell–Jolly bodies and

thrombocytosis) are frequently seen in older patients with untreated sprue.[40] A prolonged prothrombin time due to vitamin K deficiency is uncommon but should be corrected before a small-bowel biopsy is performed. Celiac sprue should also be considered in patients with persistent hypertransaminasemia.[41]

Tests of Intestinal Absorption

Only patients with extensive and severe enteropathy will have evidence of steatorrhea on a microscopical evaluation of the stool or a three-day measurement of fecal fat.[42] Similarly, although the results of an oral D-xylose–absorption test may be abnormal in patients with untreated celiac sprue, the test will not provide a specific diagnosis and is normal in many patients with mild-to-moderate enteropathy.[43] Consequently, with the advent of highly sensitive serologic tests, measurement of fecal fat and D-xylose–absorption testing are no longer important tools in cases of suspected celiac sprue.[44]

Biopsy of the Small Intestine

Histologic examination of a biopsy specimen of the small intestine remains the diagnostic gold standard for celiac sprue. In current practice, most biopsies in children and adults are performed during upper endoscopy. Endoscopy is more reliable than previous capsule-biopsy techniques, because it allows multiple specimens to be obtained, thus reducing sampling error, and because, in many cases, examination of the upper gastrointestinal tract may in itself be indicated (e.g., in iron-deficiency anemia).[45] Specimens should be obtained from the distal duodenum (second or third part) to avoid the architectural distortion produced by Brunner's glands or peptic duodenitis. Absent, flattened, or scalloped duodenal folds are not specific for celiac sprue.[46]

The classic lesion in patients with untreated celiac sprue (Fig. 2) is characterized histologically by striking mucosal architectural changes, with absent villi and hyperplastic crypts.[47] There are increased numbers of intraepithelial lymphocytes and of plasma cells and lymphocytes in the lamina propria. The severity and extent of the histologic abnormalities in celiac sprue vary widely. Patients who have mild, focal abnormalities confined to the proximal small intestine are likely to have fewer symptoms and less malabsorption than patients with severe, extensive enteropathy.

Imaging

Small-bowel barium studies are usually unnecessary. However, the threshold for obtaining a small-bowel x-ray film, an abdominal or pelvic computed tomographic (CT) scan, or both should be low in patients with refractory sprue or in cases in which a complication such as lymphoma, carcinoma, or ulcerative jejunoileitis is suspected. Radiographic studies should be considered in patients who do not have the expected response to a strict gluten-free diet or in patients with dramatic weight loss, abdominal pain, an abdominal mass, hypoalbuminemia, and intestinal bleeding or obstruction. Typical radiologic features include dilatation of the small intestine with thickening or obliteration of the mucosal folds, straightening of the valvulae conniventes, and diffuse bone demineralization on plain films. Abdominal CT or magnetic resonance imaging may suggest a diagnosis of celiac sprue by revealing hyposplenism, ascites, or lymphadenopathy, including cavitating mesenteric lymph nodes, whereas thickening of the small bowel may suggest the presence of lymphoma.[48]

Approach to Diagnostic Evaluation

An approach to the diagnosis of celiac sprue is outlined in Figure 3. When the clinical index of suspicion is low (as it would be in the case of a patient with diarrhea but no other features of celiac sprue), a negative test for antiendomysial antibodies or tissue transglutaminase has a high negative predictive value, obviating the need for small-bowel biopsy. Because the specificities of tests for antiendomysial antibodies and tissue transglutaminase approach 100 percent, their positive predictive values are high even in low-risk populations.[31-33,36] When the index of suspicion is moderate to high (as it would be in the case of a patient with gastrointestinal symptoms and a family history of celiac sprue), we recommend that both tests for antiendomysial antibodies (or tissue transglutaminase) and a small-bowel biopsy be performed.

Figure 1 (facing page). Pathogenesis of Celiac Sprue.

Gliadin is absorbed into the lamina propria and presented in conjunction with HLA-DQ2 or DQ8 cell-surface antigens by antigen-presenting cells, probably dendritic cells, to sensitized T cells expressing the α/β T-cell receptor. Tissue transglutaminase deamidates gliadin peptides, generating acidic, negatively charged residues of glutamic acid from neutral glutamines (inset). Because negatively charged residues are preferred in positions 4, 6, and 7 of the antigen-binding groove of HLA-DQ2, deamidated gliadin elicits a stronger T-cell response. These lymphocytes then activate other lymphocytes to generate cytokines, such as interferon-γ, interleukin-4, and tumor necrosis factor α (TNF-α), which damage the villi, resulting in enteritis. Induction of aberrant HLA class II cell-surface antigens on the enterocytes may permit these cells to present additional antigens to the sensitized lymphocytes.

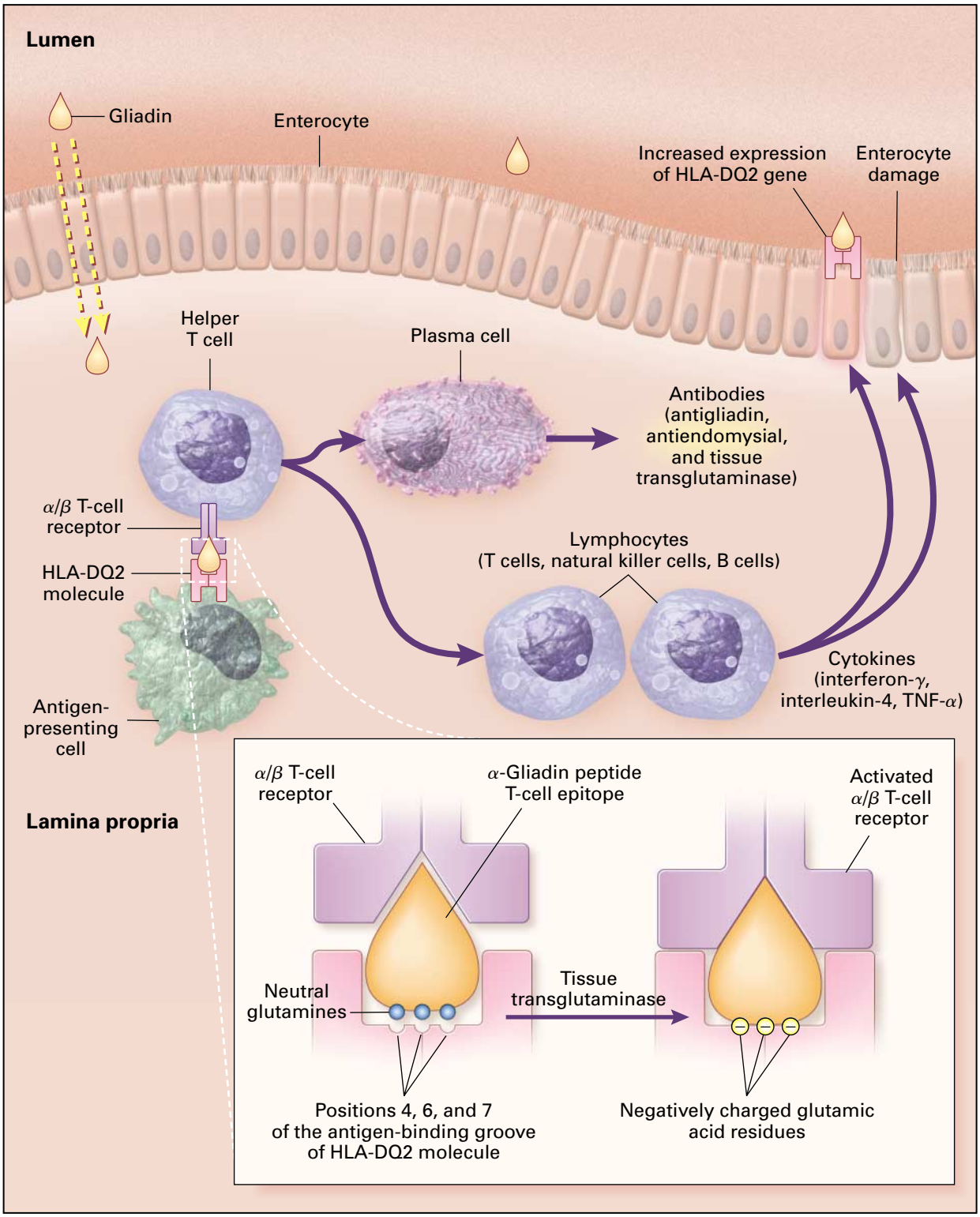

TABLE 1. THE SPECTRUM OF CLINICAL PRESENTATIONS OF CELIAC SPRUE.

COMMON FEATURES	LESS COMMON FEATURES	ASSOCIATED CONDITIONS	COMPLICATIONS
Adults	General features	Definite associations	Refractory sprue
Iron-deficiency anemia	Short stature	Dermatitis herpetiformis	Enteropathy-associated T-cell lymphoma
Diarrhea	Delayed puberty	IgA deficiency	Carcinoma of the oropharynx, esophagus, and small bowel
Children	Gastrointestinal features	Type 1 diabetes	Ulcerative jejunoileitis
Diarrhea	Recurrent aphthous stomatitis	Autoimmune thyroid disease	Collagenous sprue
Failure to thrive	Recurrent abdominal pain	Sjögren's syndrome	
Abdominal distention	Steatorrhea	Microscopic colitis	
	Extraintestinal features	Rheumatoid arthritis	
	Folate-deficiency anemia	Down's syndrome	
	Osteopenia or osteoporosis	IgA nephropathy	
	Dental-enamel hypoplasia	Possible associations	
	Vitamin K deficiency	Congenital heart disease	
	Hypertransaminasemia	Recurrent pericarditis	
	Thrombocytosis (hyposplenism)	Sarcoidosis	
	Arthralgia or arthropathy	Cystic fibrosis	
	Polyneuropathy	Fibrosing alveolitis	
	Ataxia	Lung cavities	
	Epilepsy (with or without cerebral calcification)	Pulmonary hemosiderosis	
		Inflammatory bowel disease	
	Infertility	Autoimmune hepatitis	
	Recurrent abortions	Primary biliary cirrhosis	
	Anxiety and depression	Addison's disease	
	Follicular keratosis	Systemic lupus erythematosus	
	Alopecia	Vasculitis	
		Polymyositis	
		Myasthenia gravis	
		Schizophrenia	

TABLE 2. SENSITIVITY AND SPECIFICITY AND POSITIVE AND NEGATIVE PREDICTIVE VALUES OF SEROLOGIC TESTS FOR UNTREATED CELIAC SPRUE.

SEROLOGIC TEST	SENSITIVITY*	SPECIFICITY*	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
		percent		
Test for IgA antiendomysial antibody				
Indirect immunofluorescence assay	85–98	97–100	98–100	80–95
ELISA that uses guinea pig tissue transglutaminase†	95–98	94–95	91–95	96–98
Dot blot test that uses human tissue transglutaminase	93	99	99	93
Test for IgA antigliadin antibodies	75–90	82–95	28–100	65–100
Test for IgG antigliadin antibodies	69–85	73–90	20–95	41–88

*There are wide variations in the sensitivity and specificity of these tests among different laboratories. The data on tissue transglutaminase antibodies are based on three recent large studies.[31-33]

†ELISA denotes enzyme-linked immunosorbent assay.

Repeated Biopsy and Gluten Challenge

Although a small-bowel biopsy is recommended to establish the diagnosis, the availability of accurate serologic tests has reduced the need for a second biopsy. A second biopsy can now be reserved for selected patients who have an unsatisfactory or equivocal clinical response to a strict gluten-free diet. In current practice, gluten challenge is reserved for the few patients in whom the diagnosis remains in doubt after a period of gluten restriction (e.g., patients who began to follow a gluten-free diet empirically without documentation of a characteristic intestinal lesion or

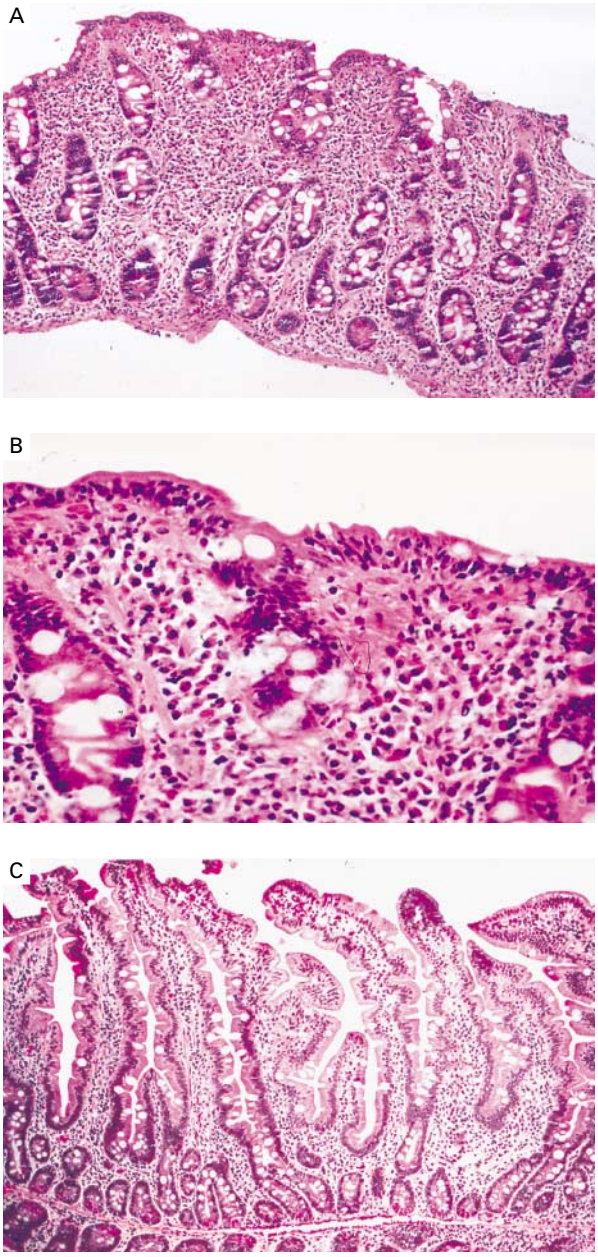

Figure 2. Mucosal Histopathological Findings in Celiac Sprue.

In Panel A, a duodenal-biopsy specimen from a patient with untreated celiac sprue shows a flat mucosal surface, severe enteritis, crypt hyperplasia, disarray of enterocytes, and extensive inflammatory infiltration of the lamina propria and epithelial-cell layer (hematoxylin and eosin, ×100). In Panel B, the epithelial cells in a patient with untreated celiac sprue are cuboidal and vacuolated and are infiltrated by numerous intraepithelial lymphocytes and plasma cells (hematoxylin and eosin, ×200). In Panel C, a duodenal-biopsy specimen from a normal person shows tall villi, shallow crypts, and sparse infiltration of the lamina propria and epithelial-cell layer with lymphocytes and plasma cells (hematoxylin and eosin, ×100). (Courtesy of Dr. Donald Antonioli and Dr. Jeremy Ditelberg, Department of Pathology, Beth Israel Deaconess Medical Center, Boston.)

the presence of antiendomysial or tissue transglutaminase antibodies). Gluten challenge should also be considered if a diagnosis of celiac sprue was made during childhood on the basis of a small-intestine biopsy without a positive test for antiendomysial antibodies, since a number of transient childhood enteropathies can mimic celiac sprue histologically. Gluten challenge should be initiated in consultation with a specialist and with caution, because patients are occasionally exquisitely sensitive to gluten.[49,50]

TREATMENT

Because a gluten-free diet represents a lifetime commitment, is more expensive than a normal diet, and may limit patients socially, especially children and teenagers, it should never be recommended unless the diagnosis of celiac sprue is firmly established. There is no role for an empirical therapeutic trial of gluten withdrawal because a patient's response is often equivocal and because the abnormal findings on both the serologic tests and small-bowel biopsy may revert to normal, making subsequent definitive diagnosis difficult.

The principles of initiating a gluten-free diet are outlined in Table 3.[51] Products that contain wheat gluten or are produced from barley or rye must be avoided. In reality, complete elimination of gluten is very difficult to achieve and maintain. Gluten is present in many processed foods because wheat flour is widely used as a thickener in many commercial products and convenience foods. Lists of gluten-free foods are only applicable in the country in which they were compiled. Even well-known brand names may be gluten-free in one region and not in others. The institution of an effective gluten-free diet requires extensive, repeated counseling and instruction of the patient by the physician and dietitian. It also requires a motivated, label-reading patient with a high index of suspicion. A gluten-free symbol is used widely by food manufacturers in Europe but, unfortunately, less so in the United States.

Although the long-term safety of oats in adults or children with celiac sprue or dermatitis herpetiformis is unknown, consumption of moderate amounts of oats (50 to 70 g per day) for 6 to 12 months is nontoxic.[52-54] However, oat products may be contaminated with small amounts of wheat. Consequently, oats should be avoided in all patients with newly diagnosed celiac sprue until remission is achieved through the use of a gluten-free diet. Then, up to 2 oz of oats from a reliable source can be eaten every day and continued if the patient has no ill effects. Dairy products should be avoided initially because patients with untreated celiac sprue often have secondary lactase deficiency. After three to six months of treatment, dairy products can be reintroduced if the patient has no ill effects.

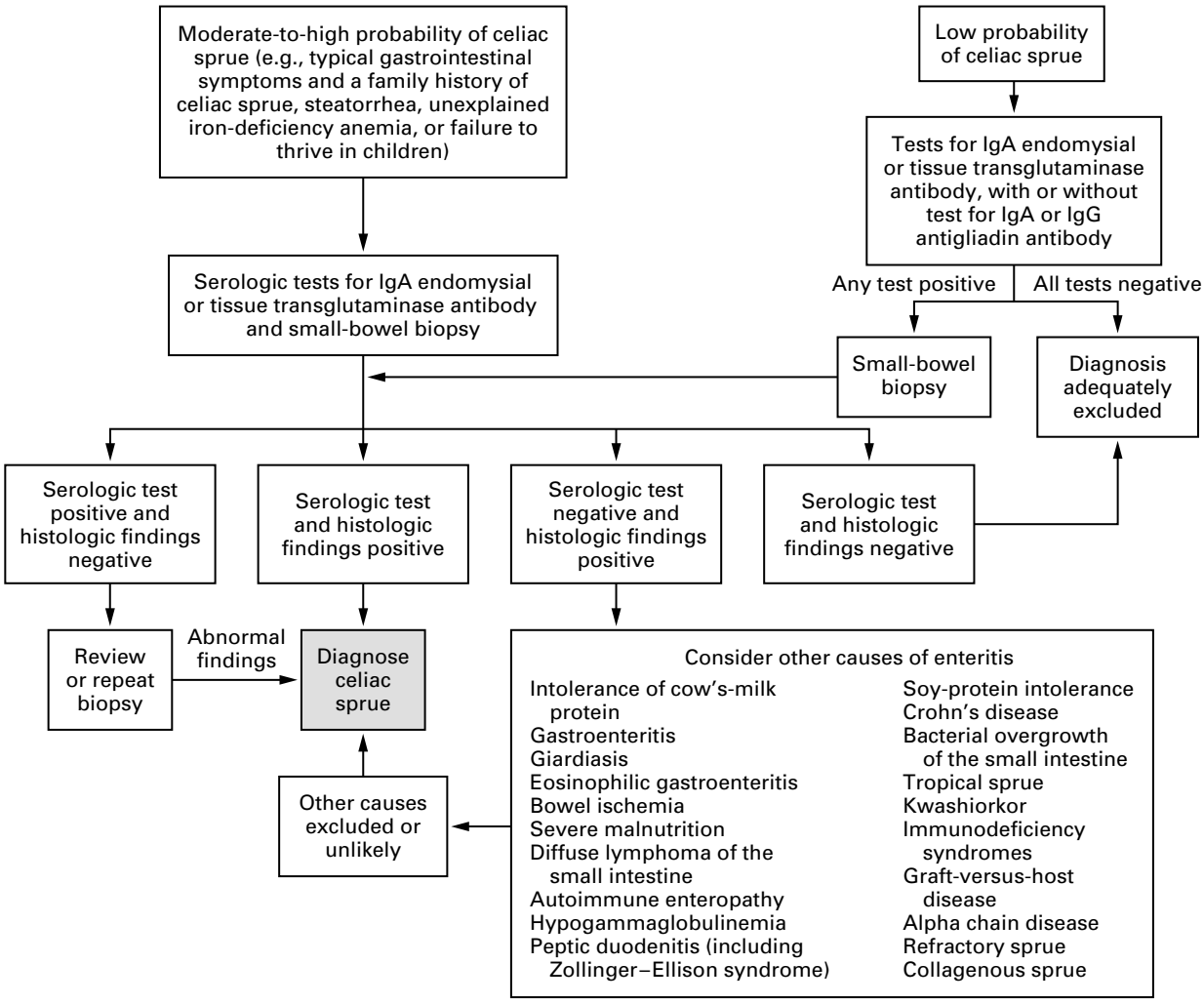

Figure 3. Approach to the Diagnosis of Celiac Sprue.

Approximately 70 percent of patients have symptomatic improvement within two weeks after starting a gluten-free diet.[55] The speed and eventual degree of histologic improvement are unpredictable[56] but invariably lag behind the clinical response and may not be evident on repeated biopsy for two to three months. Although a return to normal histologic findings is common in children, half of adults have only a partial resolution on biopsy. If a patient has no response to the diet, the most common cause is incomplete adherence. Persistent symptoms may be caused by coexisting disorders such as irritable bowel syndrome, lactose intolerance, microscopic colitis, or pancreatic insufficiency.

In a large Finnish study the five-year survival rate among patients who strictly adhered to a gluten-free diet was similar to that of the general population.[25] Growth and development in infants and children proceed normally with continued avoidance of gluten.

In addition to a gluten-free diet, all patients with newly diagnosed celiac sprue who have clinically evident malabsorption should initially receive a multivitamin preparation and appropriate supplements to correct any iron or folate deficiency. Patients with steatorrhea, hypocalcemia, or osteopenic bone disease should receive oral calcium and vitamin D supplementation. Patients with hyposplenism should receive prophylactic antibiotics before undergoing invasive manipulations and may benefit from pneumococcus vaccination. Occasionally, intravenous corticosteroid therapy is required for critically ill patients with acute celiac crisis, manifested by severe diarrhea, dehydra-

TABLE 3. DIETARY GUIDELINES FOR PATIENTS WITH CELIAC SPRUE.*

Avoid all foods containing wheat, rye, and barley gluten.
Avoid all foods containing oats (at least initially).
Avoid foods containing lactose initially.
Use only rice, corn, maize, buckwheat, potato, soybean, or tapioca flours, meals, or starches.
Look for foods that have the gluten-free symbol.
Try foods containing wheat starch from which gluten has been removed after the diagnosis of celiac sprue is established.
Read all labels and study the ingredients of processed foods.
Beware of gluten in medications, food additives, emulsifiers, and stabilizers.
Avoid all beers, lagers, ales, and stouts.
Wine, liqueurs, most ciders, and other spirits, including whiskey and brandy, are allowed.
Give essential medications parenterally initially if malabsorption is severe.

*Modified from Trier[51] with the permission of the publisher.

tion, weight loss, acidosis, hypocalcemia, and hypoproteinemia,[57] or the rare condition of gliadin shock after a gluten challenge.[49]

REFRACTORY SPRUE AND ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA

Refractory sprue is a diagnosis of exclusion, defined as symptomatic severe enteritis that does not respond to at least six months of a strict gluten-free diet and is not accounted for by other causes of enteropathy or by overt intestinal lymphoma.[58] Patients with refractory sprue are at high risk for complications such as enteropathy-associated T-cell lymphoma, ulcerative jejunoileitis, and collagenous sprue. Almost 75 percent of such patients have an aberrant clonal intraepithelial T-cell population, a condition referred to as cryptic intestinal T-cell lymphoma.[59] These cells have destructive properties related to their cytotoxic phenotype,[60] which lead to mucosal ulceration, lymph-node cavitation, and frequently, cellular and clinical progression to lymphoma. Patients with refractory sprue may require treatment with corticosteroids and other immunosuppressants, including azathioprine or cyclosporine,[61,62] or even total parenteral nutrition. In one study strict adherence to a gluten-free diet reduced the risk of all disease-associated cancers including enteropathy-associated T-cell lymphoma.[63] Thus, it seems prudent to recommend lifelong strict adherence to a gluten-free diet in all patients with celiac sprue.

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