

Refractory Sprue

Andrea N. Culliford, MD and Peter H.R. Green, MB, BS, MD

Address

Division of Digestive and Liver Diseases, Columbia University College of Physicians and Surgeons, 161 Fort Washington Avenue, Suite 645, New York, NY 10032, USA.
E-mail: pg11@columbia.edu

Current Gastroenterology Reports 2003, 5:373–378

Current Science Inc. ISSN 1522-8037

Copyright © 2003 by Current Science Inc.

Celiac disease is a T cell-mediated disorder that results from intolerance to gluten. The major cause of failure to respond to a gluten-free diet is continuing gluten ingestion. In poorly responsive patients diagnosis of refractory sprue can be established after exclusion of a limited number of conditions. Refractory sprue may occur after an initial response to the diet or without evidence of preexisting celiac disease. The detection of aberrant, clonally expanded, intraepithelial lymphocytes has led to better definition and classification of patients with refractory sprue. Only a few series of patients with well-characterized refractory sprue have been reported in the literature. The prognosis is poor, though some patients respond to corticosteroids and immunosuppressive agents. The presence of an aberrant clonal intraepithelial T-cell population has led to the designation of refractory sprue as a cryptic intestinal T-cell lymphoma.

Introduction

Celiac disease is a genetically determined chronic inflammatory intestinal disorder caused by T cell-mediated immune response to gluten in the diet [1]. "Gluten" is the term for the storage proteins of wheat. Similar proteins occur in rye and barley and are also toxic to individuals with celiac disease. The disease has a wide range of clinical presentation from a classic diarrhea-predominant malabsorption syndrome to a silent or asymptomatic form [2]. Diagnosis of celiac disease requires a small intestinal biopsy that shows characteristic changes of intraepithelial lymphocytosis, crypt hyperplasia, and varying degrees of villous atrophy, together with either clinical or histologic improvement on a gluten-free diet [3,4]. Positive celiac serologic tests are supportive of the diagnosis, though not essential [4].

Response to the Gluten-free Diet

Most patients respond clinically to a gluten-free diet within weeks or months; however, a subset of patients are poorly

responsive to the diet [5,6]. Some of these patients are slow responders who eventually do respond. Others who do not respond can be classified into several groups. The major cause of a poor response to the diet is continuing gluten ingestion. The sources of gluten may be obvious, such as intentional or regular ingestion of gluten, as in the classic example of regularly ingested communion wafers. They may also be subtle, as in ingestion of prescription or over-the-counter medications that contain gluten.

An important step in the management of poorly responsive patients is consultation with a dietician who is familiar with the intricacies of a gluten-free diet. Another important step is to review the initial biopsy material to ensure that the patient does in fact have celiac disease. Inadequate biopsy material and misinterpretation of poorly oriented biopsies may lead to overinterpretation of villous atrophy by pathologists who are unfamiliar with the interpretation of duodenal biopsies [7].

A repeat small intestinal biopsy should be performed after a period on a gluten-free diet to demonstrate histologic improvement, although this is not necessary for diagnosis. A follow-up biopsy as early as 3 to 4 months after starting the diet has been advocated [1], but an early biopsy in a patient doing well on the diet does not serve a useful role. Whereas return to normal is common in children, many adults do not normalize their histology even after long periods on the diet [8,9].

Celiac serologies normalize on a gluten-free diet. Normalization usually occurs after 6 to 12 months; however, it may take up to 30 months, depending on the height of the original titer of antibodies [10]. Serologic tests become negative prior to normalization of the histologic appearance of duodenal biopsies [11]. In addition, the antibodies are not sensitive markers of minor dietary indiscretion [12]. Persistence of the antibodies suggests ongoing gluten ingestion.

Patients in whom the diagnosis is confirmed are on a strict gluten-free diet and have persistent symptoms that fall into two categories. Either another disease process is present in addition to celiac disease or they have refractory sprue.

Causes of Persistent Diarrhea in Celiac Disease

Other disease processes that occur in patients with celiac disease and account for failure to respond to a gluten-free diet include lactose intolerance [13], pancreatic insufficiency [14], bacterial overgrowth [15], and microscopic or collagenous colitis [13]. Less commonly, this failure may be caused by intolerance of another food, such as fructose,

or a sensitivity to other foods, though this is rare. Patients may be intolerant of other types of food, including soy, milk, fish, and chicken. Other causes of persistent symptoms include anal sphincter dysfunction, resulting in fecal incontinence and irritable bowel syndrome [6•, 13]; inflammatory bowel disease; enteropathy-associated T-cell lymphoma; ulcerative jejunitis; and autoimmune enteropathy. Patients with autoimmune enteropathy have anti-enterocyte antibodies, negative endomysial antibodies, enteropathy without a triggering dietary protein, continued diarrhea with fasting, and the presence of other organ-specific autoimmune disease. However, autoimmune disease is rare [16].

Evaluation of Poorly Responsive Patients

Patients who are poorly responsive to the gluten-free diet may benefit from a trial of pancreatic enzyme supplements because a relative pancreatic insufficiency is common. Breath tests to exclude lactose or fructose intolerance and bacterial overgrowth are appropriate. A trial of an antibiotic to treat bacterial overgrowth or of bismuth subsalicylate for microscopic colitis is also appropriate. In poorly responsive patients we have found that pancreatic supplements (gluten-free) and bismuth subsalicylate frequently bring resolution of diarrhea. Colonoscopy with biopsy to exclude microscopic colitis, or less commonly to identify the presence of inflammatory bowel disease, is an important step in evaluation of these patients. Radiologic imaging studies are helpful to exclude lymphoma and chronic pancreatitis. The role of video capsule endoscopy has not been evaluated. Antienterocyte antibodies, mentioned in the previous section, are available in several centers. Laparotomy may be required in patients with a high index of suspicion for intra-abdominal lymphoma. A systematic approach to the evaluation of poorly responsive celiac disease allows the greatest opportunity to identify potentially reversible processes in this population (Fig. 1) [6•].

Refractory Sprue

Refractory sprue was originally described by Trier *et al.* [17] in 1978. The term was coined to encompass patients with villous atrophy and persistent diarrhea who were refractory to the gluten-free diet administered for at least 6 months. Some patients with refractory sprue definitely have celiac disease. Despite an initial response to the diet they develop tolerance to it and recurrence of symptoms. Relapse after an initial response to a gluten-free diet is called secondary refractory sprue or refractory celiac disease. Patients whose clinical or pathologic picture is similar to that of celiac disease but who have no history of response to a gluten-free diet lack a crucial component in the diagnosis of celiac disease: response to the diet. These patients are considered to have primary refractory sprue [5, 18]. Other evidence, such as family history of celiac disease, presence of an appropri-

ate HLA type, splenic atrophy, and presence of an endomysial antibody have been used to determine whether patients with refractory sprue have celiac disease [3•, 19••].

Frequency of refractory sprue

Refractory sprue is uncommon. The literature consists mainly of case reports. Cellier *et al.* [19••] identified 21 patients diagnosed between 1974 and 1998 from 56 French gastroenterology referral centers, and Maurino *et al.* [20•] reported recently from Argentina on seven patients from a gastroenterology referral center. What is the frequency of diagnosis of refractory sprue in the United States? Refractory sprue was identified in nine patients among 55 with poorly responsive celiac disease at the Mayo Clinic. Robert *et al.* [21] from the University of California at Los Angeles reported on 10 patients who were seen over an unspecified time period, some of whom had undergone suction capsule biopsy previously. At our institution we have identified 18 patients with refractory celiac disease/sprue among 580 patients with celiac disease. Approximately 20% of these patients were initially assessed because of a poor response to a gluten-free diet; the greatest number had persistent gluten ingestion. From this experience it can be discerned that refractory sprue is uncommon, with only a few centers gaining experience in the management of this challenging condition.

Refractory sprue has been associated in case reports with ulcerative jejunitis, mesenteric lymph node cavitation [22], collagenous sprue, lymphoma and enteropathy-associated T-cell lymphoma (EATL), and progressive neurologic disorders. Pathologically, small intestinal biopsies in refractory sprue and active celiac disease are similar. However, Robert *et al.* [21] noted prominent subcryptal chronic inflammation, marked mucosal thinning, and collagenous sprue in a group of refractory patients. Hypoplasia of crypts is considered a very late irreversible finding [3•].

T-cell studies in refractory sprue

Recent immunohistochemical studies have further defined patients with refractory sprue based on the presence of specific T-cell immunophenotypes. Much of the recent work on pathogenic mechanisms of celiac disease have concentrated on the role of HLA DQ2 and DQ8 restricted T cells in the lamina propria that react with gliadin peptides after deamination by tissue transglutaminase. These lamina propria intestinal CD4+ T cells recognize the peptides presented by DQ2 and DQ8. Subsequently, interferon- γ is released, causing villous atrophy and the inflammatory response [23••].

These studies have failed to invoke a pathogenic role for the intraepithelial lymphocytosis that occurs as an initial phenomenon in the pathology of gluten enteropathy [3•]. This failure can be attributed to the fact that no gliadin-restricted T-cell clones have been isolated from the epithelium. The importance of the intraepithelial lymphocyte (IEL) is underscored by its early appearance in celiac dis-

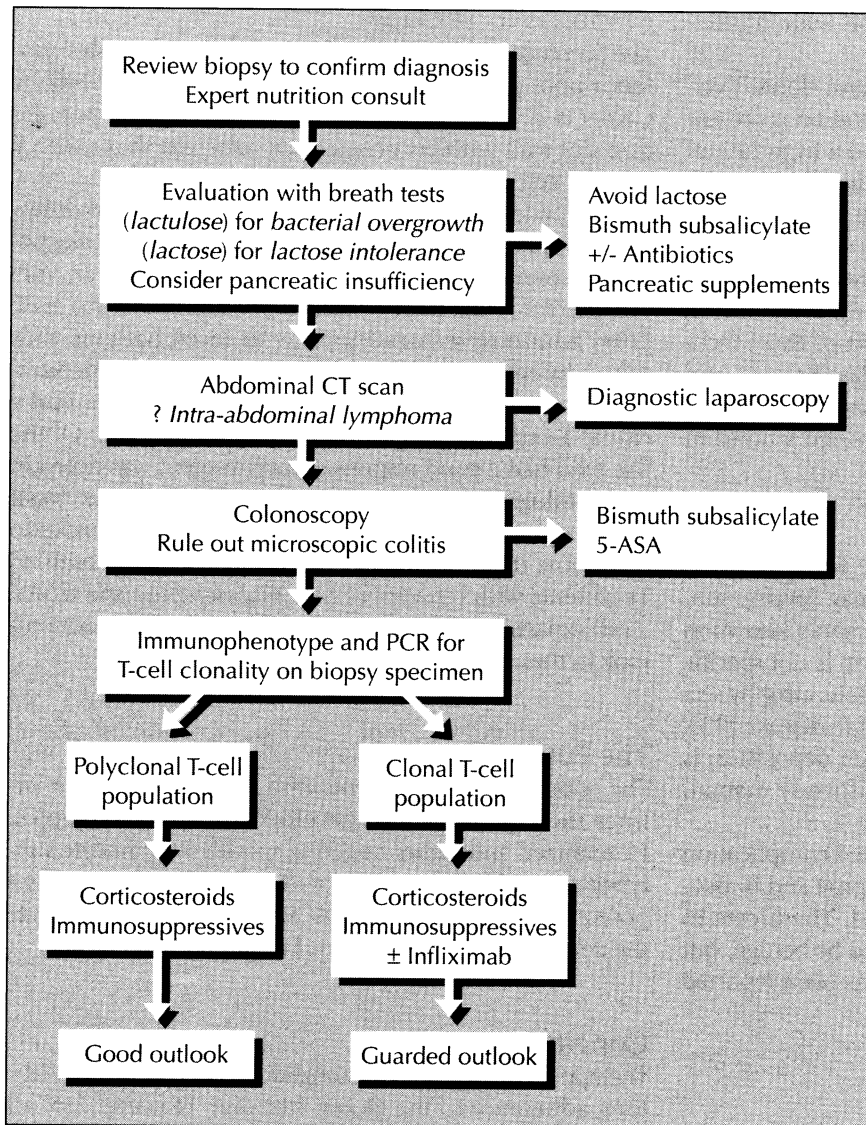


Figure 1. A systematic approach to evaluation of patients considered to have celiac disease who do not respond to a gluten-free diet. 5-ASA—5-aminosalicylic acid; PCR—polymerase chain reaction.

ease and by its role in two major diseases that complicate celiac disease: refractory sprue and EATL, also known as enteropathy-type intestinal T-cell lymphoma (EITCL) [19••,24].

In normal subjects and patients with uncomplicated celiac disease, IELs express surface CD3 and CD8 (CD3+, CD8+) and the $\alpha\beta$ or $\gamma\delta$ T-cell receptor (TCR). They do not express surface CD4 (CD4-) [25,26]. In refractory sprue, IELs, while cytologically normal, have lost surface expression of CD3, CD8, and the TCR. The IELs express intracytoplasmic CD3 [25]. Because immunohistochemical studies do not distinguish between intracellular and surface CD3 expression, the immunohistochemical phenotype of these IELs is CD3+, CD8- [26,27]. In addition, these IELs were found to have an oligoclonal TCR γ gene rearrangement [19••,24,25]. However, other phenotypes are found even in patients with celiac disease-related refractory sprue. We identified a patient with refractory sprue in whom oligoclonal IELs were CD4+, CD56+ (Green and Jabri, Unpublished results).

Whereas lymphocytic gastritis and colitis occur in both celiac disease and refractory sprue, the aberrant monoclonal population of T cells found in the small intestine of patients with refractory sprue may also be identified in the stomach, colon, and blood [28]. This dissemination of the clonal T-cell population to the entire gastrointestinal tract suggests that refractory sprue is a diffuse gastrointestinal process. In addition, duodenal biopsy is adequate for the diagnosis of refractory sprue because clonally restricted T cells identified in jejunal biopsies were also found in duodenal biopsies [28]. Although enteroscopy may detect jejunal ulceration in up to 50% of patients with refractory sprue [29], the diagnosis can be based on duodenal biopsy.

As a result of the presence of IELs with clonal proliferations, refractory sprue has been regarded as a cryptic T-cell lymphoma [30]. Refractory sprue may in fact progress to overt lymphoma of the EATL type. However, not all EATL is considered to arise from refractory sprue. The major form of EATL, with an immunohistologic phenotype of CD3+CD8-CD4-, is compatible with an origin from refrac-

tory sprue, in which the IELs are CD8-CD4- with intracellular CD3+ [31].

Not all patients with refractory sprue have clonal T-cell proliferation. However, when T-cell proliferation is present there is a poor response to treatment and a high rate of progression to EATL with an associated dismal prognosis [19••]. Immunohistologic phenotyping and TCR gene rearrangement studies can be performed using formalin fixed tissue sections in nonspecialized pathology laboratories and are therefore widely available [26]. Frozen fresh biopsies are not required. The application of these techniques in refractory patients will allow classification and gathering of data with regard to the frequency of this rare condition and, one hopes, lead to controlled studies of innovative therapies.

Collagenous Sprue and Ulcerative Jejunitis

A subset of patients with refractory sprue may develop subepithelial collagen deposition, more commonly known as collagenous sprue [32]. Collagen deposition is not specific to refractory sprue. It has been noted in villous atrophy secondary to tropical sprue as well as in celiac disease [33]. When present in refractory sprue, collagen deposition is associated with a poor, though not uniformly dismal, prognosis [21].

Ulcerative jejunitis is a well-documented complication of celiac disease that occurs in refractory sprue and is associated with a poor prognosis [29,34,35]. The ulcers in ulcerative jejunitis and EATL may appear to be benign, but a high rate of clonal T-cell populations has been reported in biopsies from these ulcers [36].

Therapy for Refractory Sprue

Patients diagnosed with refractory sprue may require hospitalization and treatment with intravenous fluids, electrolyte and trace mineral repletion, hyperalimentation, and antidiarrheal agents. In addition to a gluten-free diet and nutritional support, most patients with refractory sprue have also received corticosteroids and immunosuppressive therapy. Cyclosporine [37-39], azathioprine [20•,38,40,41], and methotrexate [19••] have been used with variable benefit. Other innovative therapies have included infliximab [42], recombinant human interleukin (IL)-10 [43], and cladribine, a purine analogue that depletes T cells [44]. A small group of patients with refractory sprue do not improve until other protein-containing foods are removed from their diet. The foods identified include milk, egg, and soy protein [45,46], and in one patient eggs, chicken, and tuna [47]. One patient responded to an elemental diet [48]. However, in adults, non-gluten food protein-induced enteropathy is rare or has seldom been explored as a cause of refractory sprue.

Response to Therapy

The presence of a clonal T-cell population in biopsies confers a poor prognosis. Among the patients described by Cellier *et al.* [19••], those without a clonal T-cell population did well with corticosteroids, whereas those with a clonal T-cell population had a worse outcome.

The patients with refractory sprue reported by Abdulkarim *et al.* [6•] all did well. They received steroids, cyclosporine, bismuth subsalicylate, or infliximab; however, only one patient had a clonal T-cell expansion. Maurino *et al.* [20•] administered azathioprine to seven patients with refractory sprue after they failed to respond to corticosteroids. Five of six patients in whom it was sought had a clonal T-cell population. Only two patients died. Of the five who had a good response, improvement was noted in the histologic appearance of biopsies, although the clonal T-cell population persisted. Longer follow-up is needed to determine the outcome in this group. We have identified 11 patients with refractory celiac disease/sprue and clonal T-cell expansion; four (36%) died, indicating the poor outlook in these patients.

The Future

The poor outlook for patients with refractory sprue underlines the urgent need to develop innovative therapies. Humanized antibodies targeting specific lymphocyte subtypes or cytokines may have a therapeutic role. IL-15 is a potential target because it will activate IELs and promote the development of lymphoma [49,50].

Conclusions

Therapy for celiac disease is straightforward, consisting of lifelong adherence to the gluten-free diet. However, not all patients respond to this diet. In most patients a lack of response is due to persistent gluten ingestion, but in others a different disease process, such as lactose intolerance, pancreatic insufficiency, bacterial overgrowth, or microscopic colitis, may be found and treated with improvement in symptoms. A small subset of patients have refractory sprue, which is mainly a diagnosis of exclusion. This uncommon disorder develops in some patients during the course of celiac disease, but in others the cause is unclear. A number of patients have an aberrant intraepithelial T-cell population with specific immunophenotype and TCR γ gene rearrangements. This clonal expansion suggests that the disease process is a cryptic lymphoma. Many patients, in fact, progress to lymphoma. Refractory sprue and celiac disease can now be distinguished by intraepithelial lymphocyte phenotyping and the detection of TCR γ gene rearrangements. This capacity for precise phenotyping should become an important adjunct in classifying patients and designing innovative therapies, which are greatly needed because current therapies are inadequate.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Ciclitira PJ, King AL, Fraser JS: AGA technical review on celiac sprue. American Gastroenterological Association. *Gastroenterology* 2001, 120:1526-1540.
2. Lo W, Sano K, Lebowitz B, et al.: Changing presentation of adult celiac disease. *Dig Dis Sci* 2003, 48:395-398.
3. Marsh MN: Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* 1992, 102:330-354.

An important article classifying the pathologic findings in celiac disease.

4. Walker-Smith JA, Schmerling DM, Visakorpi JK: Revised criteria for diagnosis of coeliac disease: report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990, 65:909-911.
5. Ryan BM, Kelleher D: Refractory celiac disease. *Gastroenterology* 2000, 119:243-251.
6. Abdulkarim AS, Burgart LJ, See J, Murray JA: Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002, 97:2016-2021.

A good example of the range of causes for poorly responsive celiac disease.

7. Shidrawi RG, Przemioslo R, Davies DR, et al.: Pitfalls in diagnosing coeliac disease. *J Clin Pathol* 1994, 47:693-694.
8. Lee SK, Lo W, Memeo L, et al.: Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointest Endosc* 2003, 57:187-191.
9. Wahab PJ, Meijer JW, Mulder CJ: Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery. *Am J Clin Pathol* 2002, 118:459-463.
10. Sategna-Guidetti C, Pulitano R, Grosso S, Ferfaglia G: Serum IgA antiendomysium antibody titers as a marker of intestinal involvement and diet compliance in adult celiac sprue. *J Clin Gastroenterol* 1993, 17:123-127.
11. Dickey W, Hughes DF, McMillan SA: Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery. *Am J Gastroenterol* 2000, 95:712-714.
12. Troncone R, Mayer M, Spagnuolo F, et al.: Endomysial antibodies as unreliable markers for slight dietary transgressions in adolescents with celiac disease. *J Pediatr Gastroenterol Nutr* 1995, 21:69-72.
13. Fine KD, Meyer RL, Lee EL: The prevalence and causes of chronic diarrhea in patients with celiac sprue treated with a gluten-free diet. *Gastroenterology* 1997, 112:1830-1838.
14. Carroccio A, Iacono G, Montalto G, et al.: Pancreatic enzyme therapy in childhood celiac disease: a double-blind prospective randomized study. *Dig Dis Sci* 1995, 40:2555-2560.
15. Tursi A, Brandimarte G, Giorgetti G: High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. *Am J Gastroenterol* 2003, 98:839-843.
16. Corazza GR, Biagi F, Volta U, et al.: Autoimmune enteropathy and villous atrophy in adults. *Lancet* 1997, 350:106-109.
17. Trier JS, Falchuk ZM, Carey MC, Schreiber DS: Celiac sprue and refractory sprue. *Gastroenterology* 1978, 75:307-316.
18. Biagi F, Corazza GR: Defining gluten refractory enteropathy. *Eur J Gastroenterol Hepatol* 2001, 13:561-565.
19. Cellier C, Delabesse E, Helmer C, et al.: Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. *Lancet* 2000, 356:203-208.

A landmark paper describing the role of determining T-cell clonality in refractory patients.

20. Maurino E, Niveloni S, Chernavsky A, et al.: Azathioprine in refractory sprue: results from a prospective, open-label study. *Am J Gastroenterol* 2002, 97:2595-2602.

A good paper describing therapy for refractory sprue.

21. Robert ME, Ament ME, Weinstein WM: The histologic spectrum and clinical outcome of refractory and unclassified sprue. *Am J Surg Pathol* 2000, 24:676-687.
 22. Bardella MT, Trovato C, Quatrini M, Conte D: Mesenteric lymph node cavitation: a rare hallmark of celiac disease. *Scand J Gastroenterol* 1999, 34:1257-1259.
 23. Sollid LM: Coeliac disease: dissecting a complex inflammatory disorder. *Nat Rev Immunol* 2002, 2:647-655.
- An up-to-date review of the immunopathology of celiac disease.
24. Daum S, Weiss D, Hummel M, et al.: Frequency of clonal intraepithelial T lymphocyte proliferations in enteropathy-type intestinal T cell lymphoma, coeliac disease, and refractory sprue. *Gut* 2001, 49:804-812.
 25. Cellier C, Patey N, Mauvieux L, et al.: Abnormal intestinal intraepithelial lymphocytes in refractory sprue. *Gastroenterology* 1998, 114:471-481.
 26. Patey-Mariaud De Serre N, Cellier C, Jabri B, et al.: Distinction between coeliac disease and refractory sprue: a simple immunohistochemical method. *Histopathology* 2000, 37:70-77.
 27. Jabri B, Cellier C, Patey N, et al.: Intraepithelial lymphocytes in Coeliac disease. In *Proceedings of the Eighth International Symposium on Coeliac Disease*. Edited by Auricchio S, Greco L, Maiuri L. Naples, Italy: CNR, Istituto di Science dell'Alimentazione Avellino; 2000.
 28. Verkarre V, Asnafi V, Lecomte T, et al.: Refractory coeliac sprue is a diffuse gastrointestinal disease. *Gut* 2003, 52:205-211.
 29. Cellier C, Cuillerier E, Patey-Mariaud de Serre N, et al.: Push enteroscopy in celiac sprue and refractory sprue. *Gastrointest Endosc* 1999, 50:613-617.
 30. Carbonnel F, Grollet-Bioul L, Brouet JC, et al.: Are complicated forms of celiac disease cryptic T-cell lymphomas? *Blood* 1998, 92:3879-3886.
 31. Green PH, Jabri B: Celiac disease and other precursors to small-bowel malignancy. *Gastroenterol Clin North Am* 2002, 31:625-639.
 32. Weinstein WM, Saunders DR, Tytgat GN, Rubin CE: Collagenous sprue: an unrecognized type of malabsorption. *N Engl J Med* 1970, 283:1297-12301.
 33. Bossart R, Henry K, Doe WF, Booth CC: Collagenous basement membrane thickening in jejunal biopsies from patients with adult coeliac disease. *Gut* 1974, 15:338.
 34. Bayless TM, Kapelowitz RF, Shelley WM, et al.: Intestinal ulceration: a complication of celiac disease. *N Engl J Med* 1967, 276:996-1002.
 35. Baer AN, Bayless TM, Yardley JH: Intestinal ulceration and malabsorption syndromes. *Gastroenterology* 1980, 79:754-765.
 36. Ashton-Key M, Diss TC, Pan L, et al.: Molecular analysis of T-cell clonality in ulcerative jejunitis and enteropathy-associated T-cell lymphoma. *Am J Pathol* 1997, 151:493-498.
 37. Longstreth GF: Successful treatment of refractory sprue with cyclosporine. *Ann Intern Med* 1993, 119:1014-1016.
 38. Rolny P, Sigurjonsdottir HA, Remotti H, et al.: Role of immunosuppressive therapy in refractory sprue-like disease. *Am J Gastroenterol* 1999, 94:219-225.
 39. Wahab PJ, Crusius JB, Meijer JW, et al.: Cyclosporin in the treatment of adults with refractory coeliac disease: an open pilot study. *Aliment Pharmacol Ther* 2000, 14:767-774.
 40. Hamilton JD, Chambers RA, Wynn-Williams A: Role of gluten, prednisone, and azathioprine in non-responsive coeliac disease. *Lancet* 1976, 1:1213-1216.
 41. Vaidya A, Bolanos J, Berkelhammer C: Azathioprine in refractory sprue. *Am J Gastroenterol* 1999, 94:1967-1969.
 42. Gillett HR, Arnott ID, McIntyre M, et al.: Successful infliximab treatment for steroid-refractory celiac disease: a case report. *Gastroenterology* 2002, 122:800-805.
 43. Mulder CJ, Wahab PJ, Meijer JW, Metselaer E: A pilot study of recombinant human interleukin-10 in adults with refractory coeliac disease. *Eur J Gastroenterol Hepatol* 2001, 13:1183-1188.
 44. Goerres MS, Wahab P, Kerchhaert J, et al.: Cladribine treatment in refractory coeliac disease type II [abstract]. *Gastroenterology* 2003, 124(Suppl 1):131.

45. Walker-Smith JA: Cow milk-sensitive enteropathy: predisposing factors and treatment. *J Pediatr* 1992, 121(5 Pt 2): S111-5.
46. Ament ME, Rubin CE: Soy protein: another cause of the flat intestinal lesion. *Gastroenterology* 1972, 62:227-234.
47. Baker AL, Rosenberg IH: Refractory sprue: recovery after removal of nongluten dietary proteins. *Ann Intern Med* 1978, 89:505-508.
48. Mandal A, Mayberry J: Elemental diet in the treatment of refractory coeliac disease. *Eur J Gastroenterol Hepatol* 2001, 13:79-80.
49. Roberts AI, Lee L, Schwarz E, et al.: NKG2D receptors induced by IL-15 costimulate CD28-negative effector CTL in the tissue microenvironment. *J Immunol* 2001, 167:5527-5530.
50. Fehniger TA, Suzuki K, VanDeusen JB, et al.: Fatal leukemia in interleukin-15 transgenic mice. *Blood Cells Mol Dis* 2001, 27:223-230.