
Dermatitis herpetiformis

Part II. Diagnosis, management, and prognosis

Diana Bolotin, MD, PhD, and Vesna Petronic-Rosic, MD, MSc
Chicago, Illinois

The prompt recognition of the clinical features of dermatitis herpetiformis (DH) is important, but securing a definitive diagnosis requires further work-up. Recent advances in understanding of the immunologic basis for DH have led to the development and wider availability of serologic testing, which is rapidly becoming an essential part of the diagnosis and management of DH. Part II of this series will detail the diagnosis, treatment, and follow-up for patients with DH, and will particularly focus on recent advances in the field. (J Am Acad Dermatol 2011;64:1027-33.)

Key words: autoimmune bullous disease; celiac disease; dapsone; dermatitis herpetiformis; enzyme-linked immunosorbent assay; gliadin; gluten-free diet; gluten-sensitive enteropathy; human leukocyte antigen-DQ2; human leukocyte antigen-DQ8; immunofluorescence; immunoglobulin A; sulfapyridine.

DIAGNOSIS**Key points**

- **Physical examination and routine histopathology are often suggestive of dermatitis herpetiformis, while direct immunofluorescence findings in perilesional skin are pathognomonic**
- **Serologic testing is a useful adjunct for diagnosis and may be used to monitor dietary adherence**
- **Genetic testing for human leukocyte antigens DQ2 and DQ8 is useful in ruling out dermatitis herpetiformis**

The diagnosis of dermatitis herpetiformis (DH) is based on a constellation of findings on physical examination, routine histopathology, immunofluorescence studies, and serologic testing (Fig 1). Physical examination alone may be suggestive; however, given the varied morphologic presentation of DH, additional testing is usually required.¹ Biopsy specimens for routine histopathology should ideally contain an intact vesicle.² The classic histopathologic features of DH seen on light microscopy include a subepidermal cleft with neutrophils and a few eosinophils at the tips of dermal papillae (Fig 2, A).^{1,2} These findings are often accompanied by a perivascular mixed inflammatory infiltrate (Fig 2, A).^{1,2}

While routine histopathology may be highly suggestive of DH, other conditions, such as linear immunoglobulin A bullous dermatosis (LABD) and bullous lupus erythematosus, can present nearly identical histologic findings. Therefore, immunofluorescence studies are critical for definitive diagnosis. Granular deposits of IgA at the tips of dermal papillae are pathognomonic for DH (in contrast to the linear pattern of IgA deposition seen in LABD; Fig 2, B).¹⁻⁴ The IgA deposits in DH are thought to be polyclonal but are mainly composed of IgA1.⁵ Occasionally,

granular deposits along the basement membrane zone occur in DH, which can lead to misdiagnosis as LABD.¹

Interestingly, these deposits are not altered by pharmacologic therapy for DH, but do slowly resolve on a gluten-free diet (GFD).^{2,3} The site of biopsy for direct immunofluorescence is of vital importance.

Although IgA deposition occurs in both lesional and nonlesional areas, a study comparing lesional, perilesional, and nonlesional skin in DH showed significantly greater IgA deposition in normal appearing perilesional skin.³ In fact, biopsy specimens of lesional skin often yield false-negative results on direct immunofluorescence.^{3,6}

Serologic testing is a useful adjunct to tissue-based studies. A number of serologic markers are shared between DH and CD, as might be expected given their close relationship. Circulating IgA antibodies to endomysium, the fine connective tissue

sheath surrounding a muscle fiber, are detected in both conditions.⁵ Testing for antiendomysial antibody is based on indirect immunofluorescence using monkey esophagus as substrate; despite some operator-dependent variability, it is a highly specific and moderately sensitive test for the diagnosis of DH.^{1,5} IgA antitissue transglutaminase (tTG) testing is performed by a widely available enzyme-linked immunosorbent assay (ELISA)—based test and has a specificity range of 97.6% to 100% and sensitivity of 48.8% to 89.1%.^{5,7,8} This test may be useful in differentiating DH from LABD and reflects the degree of mucosal changes on small bowel biopsy specimens in these patients.⁷

With the discovery that epidermal transglutaminase (eTG) is the key autoantigen in DH, serologic testing for autoantibodies against this protein has attracted increasing interest. Recent studies report a high sensitivity (60-80.8%) and specificity (92.8-100%) of serologic testing for DH with a commercially available ELISA-based assay to detect IgA anti-eTG antibodies.^{8,9} Serologic testing offers the advantages of entailing a generally lower cost and being less invasive than a skin biopsy; pending more validation, it may become a useful initial screening method in patients in whom DH is suspected clinically. Levels of anti-tTG and anti-eTG IgA correlate with the extent of

CAPSULE SUMMARY

- Direct immunofluorescence testing of perilesional skin shows pathognomonic findings
- Tissue and epidermal transglutaminases are serologic tests that may confirm the diagnosis of dermatitis herpetiformis and be used to monitor disease activity
- A gluten-free diet is the cornerstone of therapy, while dapsone provides the most rapid relief of skin signs and symptoms
- Extensive counseling and a multidisciplinary approach to care improve the outcomes of patients with dermatitis herpetiformis

From the Section of Dermatology, The University of Chicago.

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Reprint requests: Vesna Petronic-Rosic, MD, MSc, Section of Dermatology, The University of Chicago, 5841 S Maryland Ave, MC5067, Chicago, IL 60637. E-mail: vrosic@medicine.bsd.uchicago.edu.

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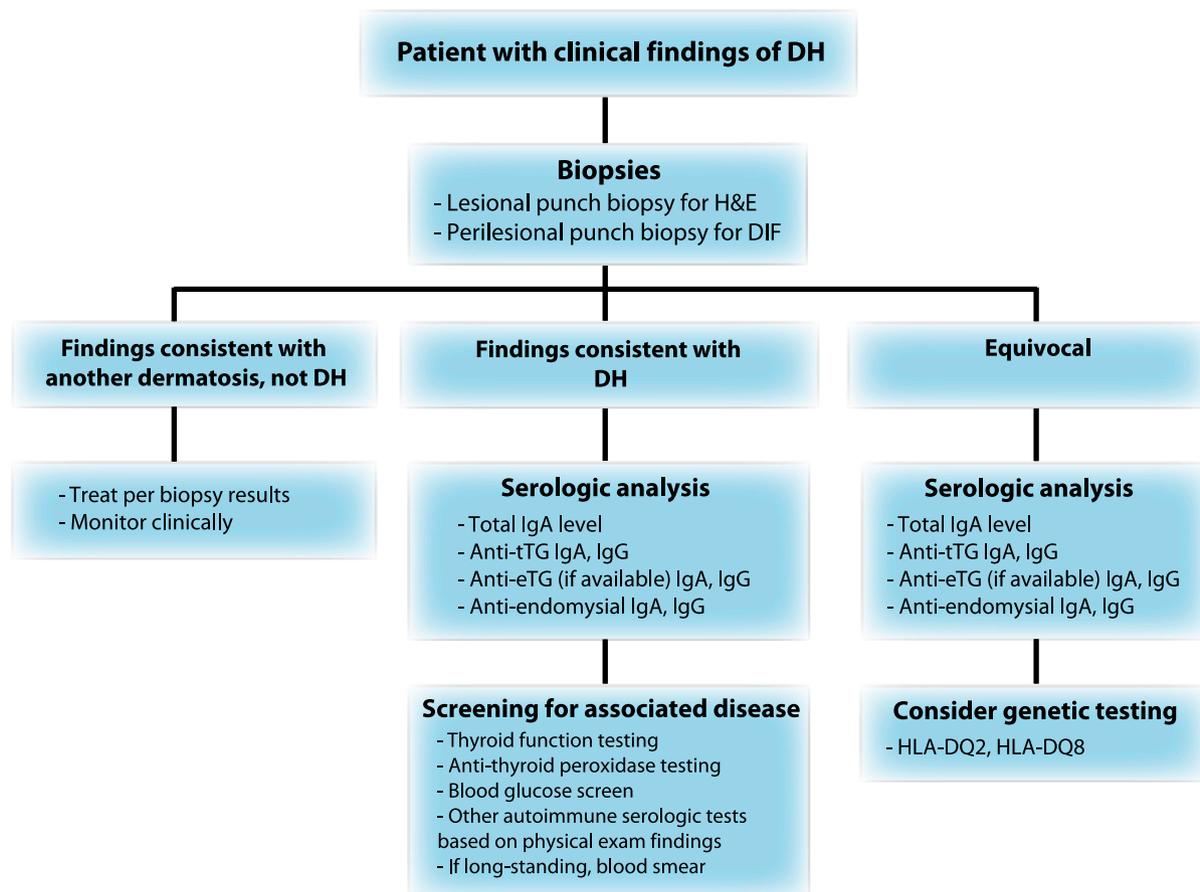


Fig 1. Approach to the patient with suspected dermatitis herpetiformis.

small bowel pathology.¹⁰ Finally, levels of antiendomysial, anti-tTG, and anti-eTG antibodies are low or undetectable in patients following strict GFD and, therefore, these may be useful quantitative markers of adherence to this dietary regimen. Although promising, the anti-eTG assay has not yet been approved in the United States for in vitro use to diagnose DH.⁸

Selective IgA deficiency is about 10 to 15 times more prevalent in patients with celiac disease (CD) compared with the general population.^{11,12} The presence of selective IgA deficiency often leads to a delay in diagnosis of CD because of the lower detection rates of IgA autoantibodies through serologic testing. No cases of selective IgA deficiency in DH have been reported, emphasizing the critical role of IgA autoantibodies in the pathogenesis of skin lesions in DH. However, partial IgA deficiency has been reported in DH and needs to be considered during the serologic work-up.¹² In patients with IgA deficiency, IgG antibodies to endomysium and transglutaminases may be useful to monitor disease.

Genetic testing to determine a patient's HLA haplotype is useful in cases where DH cannot be

excluded. The absence of human leukocyte antigens (HLAs)-DQ2 or -DQ8 has a high negative predictive value, such that patients lacking these alleles are very unlikely to have DH.^{1,13} However, because the prevalence of these alleles in the general population is rather high, a positive test is not sufficient to diagnose DH. Therefore, genetic testing is not recommended as part of the routine work-up of DH.

A biopsy specimen of the small bowel is usually not necessary in DH work-up. Because of the high sensitivity and specificity of serologic testing and the clinical definition of DH (representing a skin manifestation of CD), the addition of this invasive test will not change the diagnosis or treatment in most DH patients.^{1,14} However, should clinical signs of gastrointestinal disease or malignancy be evident on physical examination, further imaging and work-up may be indicated.

Because a significant number of DH patients do develop other immune-mediated conditions, screening for such disorders is generally indicated. In particular, patients should be screened for thyroid disease by checking both thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase antibody titers. The

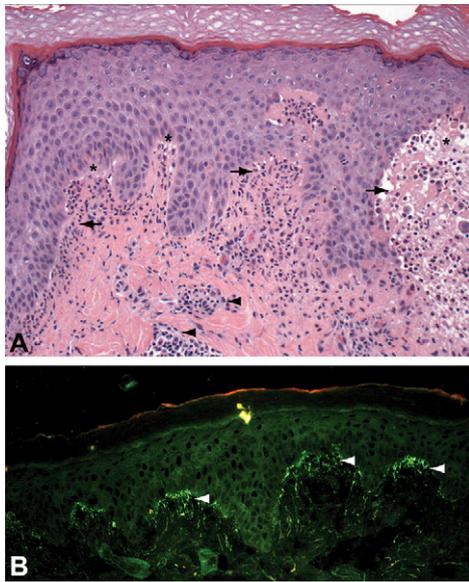


Fig 2. **A**, Light microscopy shows collections of neutrophils at the tips of dermal papillae (*black arrows*) and subepidermal clefting (*asterisks*) and a mixed perivascular inflammatory infiltrate (*black arrowheads*). **B**, Direct immunofluorescence of perilesional skin shows granular deposits of immunoglobulin A at the tips of dermal papillae (*white arrowheads*). (**A**, Hematoxylin–eosin stain.)

detection of elevated anti–thyroid peroxidase antibodies in the setting of a normal TSH level is useful to identify patients with a predisposition to develop thyroid disease in the future.^{1,15} Measuring the blood glucose level to assess for diabetes is also recommended. Finally, screening for autoimmune connective tissue diseases should be considered, especially in patients with suspicious symptoms, such as joint pains, sicca syndrome, or photosensitivity.

Patients with long standing, untreated CD with or without DH are at a higher risk for developing splenic atrophy.^{16,17} A blood smear should be checked in DH patients with symptomatic CD to evaluate for presence of Howell–Jolly bodies (basophilic debris within erythrocytes), which may signify splenic dysfunction. That finding would mandate further evaluation of splenic function and the appropriate immunizations against encapsulated organisms (eg, pneumococcal vaccine).

MANAGEMENT

Key points

- A gluten-free diet is an essential component of any dermatitis herpetiformis treatment plan
- The skin lesions and pruritus of dermatitis herpetiformis respond slowly to a gluten-free diet but are rapidly responsive to oral dapsone

Table I. Therapeutic options for patients with dermatitis herpetiformis

Treatments for dermatitis herpetiformis	Level of evidence*
Gluten-free diet	IIA
Dapsone [†]	III
Sulfapyridine [†]	III
Sulfasalazine	III
Sulfamethoxypyridine	III
Systemic corticosteroids	IV
Topical corticosteroids	IV
Antihistamines	IV

IA, Metaanalysis of randomized controlled trials (RCTs); IB, at least one RCT; IIA, at least one controlled study without randomization; IIB, any experimental study; III, descriptive studies; IV, expert committee reports, opinions, or experience of respected authorities. *Highest level of evidence is cited.

[†]These treatments for dermatitis herpetiformis are approved by the US Food and Drug Administration.

• Regular clinical follow-up and laboratory monitoring are essential in patients receiving oral dapsone

The cornerstone of DH management is the GFD (Table I); strict adherence to a GFD leads to the resolution of skin disease and an improvement in bowel pathology.^{1,18–24} Even with a rigorous GFD, however, IgA deposits at the dermoepidermal junction of patients with DH usually disappear slowly and may take up to several years to completely resolve.¹ Gluten challenge in such patients leads to a swift resurgence of IgA deposits in the skin and a flare of the cutaneous symptoms of DH. The rare patients with DH who do not respond adequately to a strict GFD may have alternative antigens involved in the pathogenesis of their disease (J. Zone, personal communication, May 2009).

Consultation with a dietician is recommended, because the maintenance of a GFD can be difficult and requires a great deal of commitment on the part of the patient. Gluten-containing products are made from cereals, including wheat, barley, and rye.^{1,14,18} In addition, a number of food additives found in vitamin supplements or otherwise gluten-free foods may contain derivatives of gluten-containing grains and would, therefore, have to be eliminated from a strict GFD.²⁵ Some authors recommend the avoidance of oats because a number of oat-based products are contaminated with gluten-containing cereals.²⁶ However, multiple studies have now demonstrated that patients with DH can consume pure, unadulterated oats without risking a flare of their symptoms.^{27–30} The advantages of a GFD in DH are numerous. In addition to relieving the clinical symptoms of gluten sensitivity, GFD

decreases the malabsorption associated with gluten intolerance, often leads to a general sense of well-being, and may nullify the increased risk of lymphoma promoted by chronic antigen stimulation in patients with DH.^{1,18,19,31} Whether adherence to a GFD affects the development of associated autoimmune disease in DH remains to be investigated.

Gastrointestinal symptoms tend to respond faster to a GFD than the skin disease, which can take months to years to resolve on a GFD alone; the addition of medication may be necessary to achieve more rapid control. Sulfones, such as dapsone and sulfapyridine, may rapidly suppress the skin manifestations of DH and are approved by the US Food and Drug Administration to treat this condition (Table I).^{18,32-34} Dapsone has both antiinflammatory and antibacterial properties and inhibits neutrophil recruitment and local neutrophil- and eosinophil-mediated tissue injury.³⁴⁻³⁹ Accordingly, the skin manifestations and symptoms of DH usually resolve within days of starting dapsone therapy.^{1,18,35} Dosages of 25 mg to 100 mg daily usually suffice to control symptoms.³⁴ Unfortunately, dapsone therapy alone does not suppress gastrointestinal involvement caused by gluten sensitivity, nor does it decrease the risk of DH-associated conditions. Accordingly, pharmacologic therapy should be considered an adjunct to GFD in patients with DH. A combination regimen of a GFD and dapsone is usually recommended at the time of diagnosis. Patients who adhere to a strict GFD are often able to be weaned off dapsone within several months, and may subsequently restart for brief periods as needed to control flares.

Dapsone is generally well tolerated. The most notable side effects are hematologic abnormalities, of which methemoglobinemia is the most common.^{1,18,34,39,40} Concurrent treatment with cimetidine or vitamin E has been reported to reduce the symptoms of mild methemoglobinemia.^{18,40} The hematologic adverse effects of dapsone are mediated via a product of its metabolism, hydroxylamine, which may induce hemolysis and, rarely, agranulocytosis.⁴⁰ Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are particularly prone to dapsone-mediated hemolysis and may need to be treated with lower doses and to receive more frequent follow-up.^{1,18,34,40} Agranulocytosis is a rare early complication of dapsone therapy; the mechanism of its development remains unclear. Another rare side effect of dapsone is a systemic drug hypersensitivity syndrome similar to that seen with certain antiepileptics.³⁴ This serious complication requires both withdrawal of the medication and systemic

Table II. Dapsone monitoring guidelines

Baseline evaluation	Follow-up evaluation
History and physical examination	History and physical examination
Complete blood cell count with differential	Peripheral motor neurologic examination
Liver function panel	Signs of methemoglobinemia
Renal function panel	Complete blood cell count with differential
Urinalysis	Weekly for 4 wks THEN
Glucose-6-phosphate dehydrogenase level	Every 2 wks for 8 wks THEN
	Every 3-4 months
	Stop therapy if WBC <4000/mm ³
	Liver function panel
	Every 3-4 months
	Renal function panel
	Every 3-4 months
	Reticulocyte count if clinically indicated
	Methemoglobin levels if clinically indicated

WBC, White blood cell.

Adapted with permission from Wolverton SE.³⁹

corticosteroid treatment.³⁴ Patients taking dapsone should have regular follow-up with frequent blood counts, especially in the first 3 months of therapy (Table II).^{34,39}

While dapsone is the mainstay of pharmacologic therapy for DH, several reports have described successful treatment with sulfasalazine and sulfamethoxyypyridazine.^{1,41-43} It is likely that these medications are effective because of their metabolism to sulfapyridine, and that the latter is therapeutic via a mechanism similar to that of dapsone.^{1,34,41} Because sulfasalazine is variably absorbed, clinical outcome may be less predictable; therefore, it is considered a second-line agent to treat DH.

Systemic corticosteroids are generally not effective in DH.¹ However, potent and superpotent topical steroids, such as clobetasol propionate, do have a role by locally decreasing the associated pruritus.¹ Topical steroids should not be used as monotherapy for DH but rather in conjunction with systemic treatments as discussed above, and only during the acute stage of the disease. In uncontrolled studies and case reports, cyclosporine, colchicine, heparin, tetracycline, and nicotinamide have all been claimed to be effective in patients with DH.⁴⁴⁻⁴⁹ Antihistamines may play a limited, adjunctive role to control DH-associated pruritus.¹

PROGNOSIS**Key points**

- **Patients with dermatitis herpetiformis require a multidisciplinary treatment plan**
- **The screening of family members should be discussed at the time of diagnosis**
- **Dermatitis herpetiformis is a treatable condition with a favorable prognosis**

The care of patients with DH should involve a team approach that includes a dermatologist, gastroenterologist, and nutritionist. Patients require regular follow-up to monitor long-term drug use and manage flares. Regular visits also allow for the screening and early detection of autoimmune or neoplastic conditions that may be associated with DH and for prompt referral for treatment. Laboratory testing (eg, a complete blood cell count to screen for nutritional depletion) may be indicated at regular intervals if patients are symptomatic and is mandatory for those undergoing systemic therapy (Table II). Counseling concerning family screening should take place at the time of diagnosis. Numerous resources are available for patients and their families, including educational workshops and free screening for CD. A unique preceptorship program for physicians—currently the only intense, hands-on medical/professional CD education in the country—takes place each December under the auspices of The University of Chicago Celiac Disease Center. More information can be found at <http://www.celiacdisease.net> or by calling (773) 702-7395. Given the increasing number of familial cases of DH, the close monitoring of first-degree relatives of patients with DH may be prudent.

The prognosis for patients who adhere to a strict GFD is favorable. One study has shown that only 15% of patients adhering to a GFD remained on a steady dose of dapsone, while the remainder were able to stop or reduce the daily dose by 50% or more.⁵⁰ Serum IgA antibodies against tTG and eTG may be useful in monitoring adherence. While some studies have suggested a possible protective effect of GFD against intestinal lymphoma, it is unclear whether it has any influence on development of associated autoimmune conditions. Overall, 10- and 15-year survival rates in patients with DH do not appear to differ from those of the general population.⁵⁰

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