

eMedicine Specialties > Dermatology > Bullous Diseases

Epidermolysis Bullosa Acquisita

Lawrence Chan, MD, Department Head and Director of Skin Immunology Research, Professor, Departments of Dermatology and Microbiology/Immunology, University of Illinois College of Medicine
David Woodley, MD, Co-Chair, Professor, Department of Medicine, Division of Dermatology, University of Southern California

Updated: Oct 22, 2008

Introduction

Background

Epidermolysis bullosa acquisita (EBA) is a chronic autoimmune subepidermal blistering disease of the skin and mucus membranes. Epidermolysis bullosa acquisita is characterized clinically by blisters, scars, and milia primarily at the trauma-prone areas. However, a subset of patients has a generalized inflammatory skin blister phenotype. Immunologically, epidermolysis bullosa acquisita is characterized by the presence of immunoglobulin G (IgG) autoantibodies (in most patients) targeting the noncollagenous (NC1) domain of type VII collagen, the major component of anchoring fibrils that connect the basement membrane to dermal structures. A small group of patients demonstrated IgG autoantibodies to the central triple-helical (collagenous) domain of type VII collagen. However, a small subset of patients exhibited immunoglobulin A (IgA), rather than IgG, class autoantibodies that target the type VII collagen.

Epidermolysis bullosa acquisita is rare in humans. In animals, epidermolysis bullosa acquisita has been reported in dogs only. In canine epidermolysis bullosa acquisita, the IgG autoantibodies also target the type VII collagen noncollagenous (NC1) domain, which shares greater than 80% homology in amino acid sequence with the human NC1 domain.^{1,2}

Pathophysiology

Epidermolysis bullosa acquisita primarily involves the skin, but it also can affect mucus membranes. The trauma-prone areas of the skin, such as the extensor surfaces of elbows, knees, ankles, and buttocks, most commonly are affected.

IgG autoantibodies specific for anchoring fibrils (type VII collagen) of the skin basement membrane have a heterogeneous subclass and light chain composition, and their complement-activating capacities do not correlate with the inflammatory phenotype. It is hypothesized that autoantibodies and trauma are contributing factors to the disease process.^{3,4}

Passive transfer of antibodies raised in rabbits against mouse type VII collagen induced blister formation in mice, thus confirming the potential role of antitype VII collagen antibody in the pathogenesis of the disease. The failure to

induce blisters in C5-deficient mice by these rabbit antimouse type VII collagen antibodies supports a role for complement activation in the disease pathogenesis.

Induction of an active model of autoimmunity against type VII collagen in a hairless mouse strain (SKH1) revealed that regulatory T cells, which have been identified for their ability to inhibit the development of autoimmune diseases, do not inhibit the development of autoantibodies against the self-protein mouse-type VII collagen.

Frequency

United States

Epidermolysis bullosa acquisita is a rare disease; its frequency of occurrence is not known.

International

Epidermolysis bullosa acquisita has been reported in Europe and Asia. Since it is a rare disease, the frequency of occurrence in other countries is not known.

Mortality/Morbidity

Epidermolysis bullosa acquisita is a chronic inflammatory disease with periods of partial remissions and exacerbations. Mortality as a direct consequence of the disease is rare; however, epidermolysis bullosa acquisita is relatively unresponsive to treatment and can cause significant morbidity. Adverse effects associated with the medications used to treat epidermolysis bullosa acquisita also are associated with significant morbidity.

- The chronic inflammation and scar formation on patients' extensor surfaces can severely hinder the daily activities of patients.
 - Oropharyngeal involvement can lead to dysphagia and weight loss.
- Subject: Epidermolysis Bullosa Acquisita: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:36:04 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="-----=_NextPart_000_00A6_01CA2CF7.AF8B80E0" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. -----=_NextPart_000_00A6_01CA2CF7.AF8B80E0 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: <http://emedicine.medscape.com/article/1063083-print>



emedicine.medscape.com

**eMedicine Specialties > Dermatology >
Bullous Diseases**

Epidermolysis Bullosa Acquisita

Lawrence Chan, MD, Department Head and Director of Skin Immunology Research, Professor, Departments of Dermatology and Microbiology/Immunology, University of Illinois College of Medicine

David Woodley, MD, Co-Chair, Professor, Department of Medicine, Division of Dermatology, University of Southern California

Updated: Oct 22, 2008

Introduction

Background

Epidermolysis bullosa acquisita (EBA) is a chronic autoimmune subepidermal blistering disease of the skin and mucus membranes. Epidermolysis bullosa acquisita is characterized clinically by blisters, scars, and milia primarily at the trauma-prone areas. However, a subset of patients has a generalized inflammatory skin blister phenotype. Immunologically, epidermolysis bullosa acquisita is characterized by the presence of immunoglobulin G (IgG) autoantibodies (in most patients) targeting the noncollagenous (NC1) domain of type VII collagen, the major component of anchoring fibrils that connect the basement membrane to dermal structures. A small group of patients demonstrated IgG autoantibodies to the central triple-helical (collagenous) domain of type VII collagen. However, a small subset of patients exhibited immunoglobulin A (IgA), rather than IgG, class autoantibodies that target the type VII collagen.

Epidermolysis bullosa acquisita is rare in humans. In animals, epidermolysis bullosa acquisita has been reported in dogs only. In canine epidermolysis bullosa acquisita, the IgG autoantibodies also target the type VII collagen noncollagenous (NC1) domain, which shares greater than 80% homology in amino acid sequence with the human NC1 domain.^{1,2}

Pathophysiology

Epidermolysis bullosa acquisita primarily involves the skin, but it also can affect mucus membranes. The trauma-prone areas of the skin, such as the extensor surfaces of elbows, knees, ankles, and buttocks, most commonly are affected.

IgG autoantibodies specific for anchoring fibrils (type VII collagen) of the skin basement membrane have a heterogeneous subclass and light chain composition, and their complement-activating capacities do not correlate with the inflammatory phenotype. It is hypothesized that autoantibodies and trauma are contributing factors to the disease process.^{3,4}

Passive transfer of antibodies raised in rabbits against mouse type VII collagen induced blister formation in mice, thus confirming the potential role of antitype VII collagen antibody in the pathogenesis of the disease. The failure to induce blisters in C5-deficient mice by these rabbit antimouse type VII collagen antibodies supports a role for complement activation in the disease pathogenesis.

Induction of an active model of autoimmunity against type VII collagen in a hairless mouse strain (SKH1) revealed that regulatory T cells, which have been identified for their ability to inhibit the development of autoimmune diseases, do not inhibit the development of autoantibodies against the self-protein mouse-type VII collagen.

Frequency

United States

Epidermolysis bullosa acquisita is a rare disease; its frequency of occurrence is not known.

International

Epidermolysis bullosa acquisita has been reported in Europe and Asia. Since it is a rare disease, the frequency of occurrence in other countries is not known.

Mortality/Morbidity

Epidermolysis bullosa acquisita is a chronic inflammatory disease with periods of partial remissions and exacerbations. Mortality as a direct consequence of the disease is rare; however, epidermolysis bullosa acquisita is relatively unresponsive to treatment and can cause significant morbidity. Adverse effects associated with the medications used to treat epidermolysis bullosa acquisita also are associated with significant morbidity.

- The chronic inflammation and scar formation on patients' extensor surfaces can severely hinder the daily activities of patients.
- Oropharyngeal mucus membrane involvement can lead to periodontal disease, oral mucosal erosions, and esophageal strictures, which limit oral intake, and supraglottic stenosis with airway compromise. Ocular involvement can lead to obstruction of nasolacrimal ducts, conjunctival scarring, and blindness.
- The scarring nature of epidermolysis bullosa acquisita can lead to nail destruction and hair loss.

Race

The race distribution of epidermolysis bullosa acquisita is not known. In one of the largest patient groups (24 patients) followed by the authors, 19 were white and 5 were black. This distribution is roughly proportional to the general population of whites and blacks in the United States; thus, there appears to be no significant racial predilection.

Sex

The sex distribution of epidermolysis bullosa acquisita is not known. In the 24 patients followed by the authors, the male-to-female ratio is 1:1.4.

Age

Epidermolysis bullosa acquisita can occur at any age. Epidermolysis bullosa acquisita more frequently affects elderly persons; however, children with epidermolysis bullosa acquisita have been reported including one child with the onset of epidermolysis bullosa acquisita at age 3 months. Internationally, about 25 cases of childhood onset epidermolysis bullosa acquisita have been reported in the literature. In the 24 patients followed by the authors, the average age of onset was 53 years.

Clinical

History

Most patients with epidermolysis bullosa acquisita (EBA) experience a slow onset and chronic disease that affects the trauma-prone extensor skin surfaces. The nature of the disease usually leads to skin fragility, and the secondary scarring often causes restriction of mobility in the extensor skin surfaces.

- In a subset of patients with generalized disease, the onset of disease is somewhat rapid, more wide spread, and inflammatory. In this group of patients, blisters occur in both trauma-prone and non-trauma-prone areas. Clinically, this phenotype resembles bullous pemphigoid or linear IgA bullous dermatosis.
- In a subset of patients with predominant mucus membrane involvement, the disease manifests with blisters and scar formation in the oral, ocular, vaginal, and other mucous membranes, leading to significant dysfunction, such as visual function loss, dysphagia, malnutrition, or even mortality.

- The clinical phenotype of this subset of patients is indistinguishable from that of mucous membrane pemphigoid.
 - In a published international consensus statement on mucous membrane pemphigoid, 26 international experts of mucous membrane pemphigoid had decided to include this group of patients (previously designated as epidermolysis bullosa acquisita based in part on their autoantibodies to type VII collagen) in the category of mucous membrane pemphigoid.
 - The rationale for such inclusion is that this subset of patients has the clinical phenotype of mucous membrane pemphigoid and that the autoantibodies of patients with mucous membrane pemphigoid (as a group) target not single, but multiple skin basement membrane components, such as bullous pemphigoid antigen 2 (BP180), integrin beta-4 subunit, laminin-5, and laminin-6. Because this subset of patients cannot be distinguished from mucous membrane pemphigoid by clinical phenotype and autoantigen identity alone cannot be used to include or exclude a diagnosis of mucous membrane pemphigoid, it seems reasonable to include this subset of patients under the general category of mucous membrane pemphigoid.
- Epidermolysis bullosa acquisita has been reported to develop in a 73-year-old patient after a 2-week treatment of antibiotics.

Physical

The skin and mucus membrane manifestations of epidermolysis bullosa acquisita (EBA) take several forms, as follows: a noninflammatory or mildly inflammatory disease affecting trauma-prone extensor skin surfaces, a generalized inflammatory disease, and a predominant mucus membrane disease.

- A noninflammatory or mildly inflammatory form is the most common form of epidermolysis bullosa acquisita, manifested as tense vesicles and bullae, and erosions primarily on the extensor surfaces of hands, knuckles, elbows, knees, and ankles. The blisters may be hemorrhagic. Blisters on mucus membranes rupture easily; the most common manifestation is erosion.
 - This form of epidermolysis bullosa acquisita usually heals with significant scar and milia formation. Nail dystrophy and scarring alopecia also have been observed in some patients.
 - This form clinically resembles porphyria cutanea tarda in elderly patients, and it resembles the dominantly inherited form of epidermolysis bullosa dystrophica in children.
- The generalized inflammatory form presents with widespread, tense vesicles and bullae (some hemorrhagic), and is not localized to trauma-prone sites. Generalized erythema, urticarial plaques, and generalized pruritus may occur in some patients.
 - This form of epidermolysis bullosa acquisita clinically resembles bullous pemphigoid or linear IgA bullous dermatosis.⁵
 - The generalized inflammatory form usually heals with minimal scarring and milia formation.
- A third variant of epidermolysis bullosa acquisita predominantly involves mucus membranes.
 - This form of epidermolysis bullosa acquisita can affect mucous membranes of buccal, conjunctival, gingival, palatal, nasopharyngeal, rectal, genital, and esophageal mucosae.
 - This variant clinically resembles mucous membrane pemphigoid and can result in significant mucosal scarring and dysfunction. A recent international consensus statement published in *Archives of Dermatology* (March 2002) has reassigned this group of patients to the category of mucous membrane pemphigoid.⁶
- Some patients with epidermolysis bullosa acquisita present with marked head and neck involvement, scarring, and minimal mucosal disease, which resembles the Brunsting-Perry variant of cicatricial pemphigoid.
- An inflammatory variant with autoantibodies to central collagenous domain
 - Three young patients with Japanese ethnic background were reported to have a generalized inflammatory blistering disease.
 - These patients were readily responsive to systemic corticosteroids treatment, and the disease healed without scarring.

- The IgG autoantibodies from these 3 patients did not recognize the NC1 domain, but it did recognize the central triple-helical collagenous domain of type VII collagen.

Causes

Epidermolysis bullosa acquisita (EBA) is an autoimmune disease, manifested by IgG autoantibodies that target a major skin basement membrane component, collagen VII. Collagen VII is the major protein of anchoring fibrils and connects the epithelial basement membrane to the dermis. Autoantibodies specific for collagen VII alter the dermal-epidermal junctional adhesion and lead to dermal-epidermal separation. The initiating event that leads to autoantibody production is unknown. Recently, a subset of epidermolysis bullosa acquisita, which is milder clinically, has been identified to be mediated by IgA, rather than IgG autoantibodies. A small group of patients had autoantibodies to the collagenous domain, rather than the NC1 domain of collagen VII.⁷

- Immunogenetic studies revealed that most black patients from the southeastern part of the United States had an association with human leukocyte antigen DR2 (HLA-DR2). Subsequent studies on a larger population of white patients failed to reveal any statistically significant HLA allele associations with epidermolysis bullosa acquisita.
- Rarely, patients with systemic lupus erythematosus (SLE), a systemic autoimmune disease, develop a generalized blistering skin disease with clinical and immunopathologic features of epidermolysis bullosa acquisita.
 - These patients have a subepidermal blistering skin disease characterized by IgG, IgA, and C3 deposition at the skin basement membrane zone. Sera from these patients recognize the NC1 domain of type VII collagen, the same target antigen recognized by patients with epidermolysis bullosa acquisita.
 - The fact that epidermolysis bullosa acquisita, an organ-specific autoimmune disease, can develop in patients who already have a systemic autoimmune disease suggests that systemic autoimmunity can provoke an organ-specific autoimmune disease. Alternatively, the nonspecific inflammatory process present in systemic lupus may induce the release and exposure of basement membrane antigens to autoreactive lymphocytes by a process termed epitope spreading, subsequently leading to autoimmunity against the epidermolysis bullosa acquisita antigen.⁸
- Epidermolysis bullosa acquisita also is associated with Crohn disease, an inflammatory bowel disease characterized by T-cell infiltration in the small intestine. Type VII collagen is expressed in intestinal epithelial basement membranes. The association of epidermolysis bullosa acquisita and inflammatory bowel disease may have an immunologic basis. It has been observed that a significant number of patients with Crohn disease have circulating IgG autoantibodies that recognize the NC1 domain as demonstrated by enzyme-linked immunosorbent assay (ELISA), although they do not have epidermolysis bullosa acquisita clinically. The presence of these autoantibodies may represent a preclinical epidermolysis bullosa acquisita phenomenon, induced by the release and exposure of intestinal type VII collagen to autoreactive lymphocytes because of epitope spreading caused by the inflammatory reaction in their gut.
- An initial experiment of passively transferring IgG autoantibodies from human patients with epidermolysis bullosa acquisita to mice does not induce clinical disease in mouse skin. The failure of passive transfer experiments to induce disease may be due to several possible reasons. Subsequently, however, rabbit antibodies raised against human recombinant protein type VII collagen were able to induce blisters in mice, as did rabbit antibodies raised against mouse type VII collagen.^{9,10} Lately, affinity-purified antitype VII collagen autoantibodies from epidermolysis bullosa acquisita patients have been shown to induce blisters in an adult hairless mouse strain (SKH1), further supporting a pathogenic role of these autoantibodies.¹¹
 - The binding of pathogenic IgG to type VII collagen may be a necessary but insufficient step for blister formation. Additional steps required for blister formation, such as recruitment and release of inflammatory mediators, may not occur in this model.
 - The binding of human anti-type VII collagen autoantibodies may not recognize critical sites on mouse type VII collagen, thus rendering these autoantibodies incapable of inducing blister formation.
 - The turnover of existing anchoring fibrils may be very slow such that epidermolysis bullosa acquisita develops only after autoantibodies inhibit new anchoring fibril formation over a prolonged period of time. This would not be similar to short-term neonatal mouse studies.
- In some patients with epidermolysis bullosa acquisita and bullous systemic lupus erythematosus, circulating autoantibodies against other skin basement membrane components, such as bullous pemphigoid antigens, laminin-5,

and laminin-6, in addition to type VII collagen, have been reported. These observations further support the role of epitope spreading.^{6,12,13}

- An active experimental animal model of epidermolysis bullosa acquisita would facilitate the understanding of the disease pathogenesis; however, it is currently unavailable.
- New findings were recently reported that autoantibodies from patients affected with epidermolysis bullosa acquisita recognized not only the NC1 domain but also the NC2 domain of type VII collagen. Furthermore, the NC2 domain mediates antiparallel dimer formation in experimental conditions. Therefore, the targeting of the NC2 domain by epidermolysis bullosa acquisita autoantibodies may destabilize anchoring fibrils by interfering with antiparallel dimer formation, leading to dermal-epidermal disadherence.
- Rabbit antimouse type VII collagen antibodies induced subepidermal blisters in mice, identically as occurs in human patients with epidermolysis bullosa acquisita, supporting the role of antitype VII collagen autoantibodies in the pathogenesis of epidermolysis bullosa acquisita. Rabbit antimouse type VII collagen antibodies were not able to induce blisters in C5-deficient mice, pointing to a role for complement activation in the pathogenesis of epidermolysis bullosa acquisita.

Differential Diagnoses

Bullous Pemphigoid

Cicatricial Pemphigoid

Linear IgA Dermatitis

Lupus Erythematosus, Bullous

Porphyria Cutanea Tarda

Other Problems to Be Considered

Bullous eruption of systemic lupus erythematosus

Dominantly inherited epidermolysis bullosa dystrophica

Workup

Laboratory Studies

- To establish a diagnosis for EBA, the following tests should be performed: histopathology from the edge of a new blister, direct immunofluorescence on normal-appearing perilesional skin, and indirect immunofluorescence with the patient's serum on salt-split normal human skin substrate.
- Histopathology
 - Histopathology documents the presence of a subepidermal blister, ie, a separation has occurred between the epidermis and the dermis.
 - In addition, histology also reveals a mixed inflammatory cell dermal infiltrate.
- Direct immunofluorescence (see Media File 1)
 - Direct immunofluorescence documents the immune-mediated disease process.
 - Usually, it detects a thick band of IgG, and to a lesser extent C3, deposited linearly at the basement membrane zone. Other immunoreactants such as immunoglobulin M (IgM) or IgA may be seen.
 - A *U*-serrated pattern is typical of EBA, whereas an *n*-serrated pattern is typical of pemphigoid.
- Indirect immunofluorescence (see Media File 2)
 - Indirect immunofluorescence demonstrates the presence of IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component, type VII collagen.
 - Usually, it detects IgG circulating autoantibodies in patient's serum that bind to the dermal floor (lower part) on salt-split normal human skin substrate. This test differentiates EBA from bullous pemphigoid because

IgG autoantibodies from patients with bullous pemphigoid bind to the epidermal roof (upper part) of salt-split skin.

- The dermal floor pattern of indirect immunofluorescence on salt-split skin substrate also is found in sera of patients with bullous SLE, antiepiligrin cicatricial pemphigoid (with autoantibodies to laminin-5 and laminin-6), and anti-p105 pemphigoid (with autoantibodies to a 105-kd lower lamina lucida protein).¹⁴

Other Tests

- Other investigative studies available in investigative laboratories that further document the diagnosis of epidermolysis bullosa acquisita (EBA) include direct and indirect immunoelectron microscopy, immunoblotting, ELISA, and immunoprecipitation.
- Direct and indirect immunoelectron microscopy
 - Direct and indirect immunoelectron microscopy document the ultrastructural localization of in vivo-bound IgG autoantibodies (by direct method) or the binding site of circulating IgG autoantibodies (by indirect method) at the basement membrane.
 - This technique detects IgG autoantibodies at the lamina densa and sublamina densa areas of skin basement membrane. In contrast, bullous pemphigoid IgG autoantibodies are localized to the hemidesmosome and upper lamina lucida.¹⁵
- Immunoblotting
 - Immunoblotting documents the specific skin basement membrane antigen recognized by the patient's IgG autoantibodies.
 - This test detects a denatured 290-kd skin basement membrane protein extracted from the dermis that corresponds to a single alpha chain of the type VII collagen homotrimer molecule.
- Enzyme-linked immunosorbent assay¹⁶
 - ELISA documents the specific basement membrane antigen recognized by the patient's IgG circulating autoantibodies.
 - ELISA is preferred over immunoblotting because the ELISA method uses nondenatured type VII collagen, usually in a recombinant form. It is a more sensitive and specific method than immunoblotting.
- Immunoprecipitation
 - Immunoprecipitation demonstrates the specific basement membrane antigen in its native form recognized by the patient's IgG circulating autoantibodies.
 - This method detects a 290-kd protein either from cultured keratinocytes or from fibroblasts. It is a more difficult method to use than immunoblotting.

Treatment

Medical Care

Patients with epidermolysis bullosa acquisita (EBA) may require therapy with oral corticosteroids and immunosuppressants.

- For patients who are on long-term systemic corticosteroid treatment, daily calcium and vitamin D supplements are essential for reducing steroid-induced osteoporosis.
- In addition, patients who are on long-term systemic corticosteroid treatment should take bisphosphonate, a class of specific inhibitor of osteoclast-mediated bone resorption (eg, alendronate [Fosamax]).
- For patients who do not respond to oral corticosteroids and immunosuppressives, physicians could also consider using some other newer, but not-yet-proven therapeutic options, including intravenous immunoglobulin and intravenous infusion of anti-CD20 antibodies (rituximab).^{17,18,19,20,21}

Consultations

Consultation and coordination of the patient's care with the patient's primary care provider are important for monitoring side effects of therapy and the overall management of the patients.

- Because there is a strong association of epidermolysis bullosa acquisita with inflammatory bowel disease, patients with epidermolysis bullosa acquisita should be asked about symptoms related to their GI tract. If there are any symptoms suggestive of inflammatory bowel disease, patients with epidermolysis bullosa acquisita should be referred to gastroenterologist for consultation.
- In patients with oral involvement, coordination of care with the patient's dentist also is recommended. These patients may have difficulty with regular dental care and prophylaxis may induce exacerbations of oral blistering.
- In patients with ocular involvement, consultation with an ophthalmologist is recommended.

Diet

In patients with oral involvement, hard or brittle foods and foods with high acid content (eg, tomatoes, orange juice) should be avoided. Ingestion of these foods may traumatize mucosa and precipitate new lesions.

Activity

- Since epidermolysis bullosa acquisita is a disease that primarily affects trauma-prone skin surfaces, patients are instructed to avoid direct physical trauma to their skin surfaces. When physical activities are planned, patients are instructed to use protective pads to cover their extensor skin surfaces.
- Gentle but thorough daily oral hygiene should be encouraged.

Medication

In epidermolysis bullosa acquisita(EBA), as in other autoimmune diseases, treatment is directed at decreasing the development of new blisters, promoting healing, and preventing scarring and the sequelae of scarring.

For an autoimmune disease, such as epidermolysis bullosa acquisita, the logical approach for treatment is to modify or reduce the autoimmune responses, and to decrease the production of autoantibodies.

A target-specific immunomodulatory treatment that blocks the autoimmune response would be the treatment of choice and remains the holy grail of investigators in the field.

To date, only non–target-specific immunosuppressive and anti-inflammatory agents²² are available.

Mycophenolate mofetil, a drug with a similar mechanism of action to azathioprine, is being used with increasing frequency to treat autoimmune diseases. It may prove to be a viable alternative to azathioprine, although more data are needed.

Anti-inflammatory agents

In the inflammatory form of EBA, there may be an inflammatory cell infiltration near the basement membrane zone. Theoretically, anti-inflammatory agents would block the inflammatory process and improve the disease.

In the author's experience, systemic steroids have not proved to be very beneficial in treating EBA.

Prednisone (Deltasone)

Used as sole agent or in conjunction with other medications (eg, immunosuppressives) to treat EBA.

May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and also suppresses lymphocytes and antibody production.

Dosing

Adult

1-1.5 mg/kg/d PO; taper as condition improves; single morning dose is safer for long-term use but divided doses have more anti-inflammatory effect

Pediatric

Administer as in adults

Interactions

Coadministration with estrogens may decrease prednisone clearance; when used with digoxin, digitalis toxicity secondary to hypokalemia may increase; phenobarbital, phenytoin, and rifampin may increase the metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics

Contraindications

Documented hypersensitivity; viral infection; peptic ulcer disease; hepatic dysfunction; connective tissue infections; fungal or tubercular skin infections; GI disease

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in diabetes, hypertension, history of tuberculosis, osteoporosis, peptic ulcer disease, and psychologic problems; abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use; may cause aseptic necrosis

Dapsone (Avlosulfon)

Bactericidal and bacteriostatic against mycobacteria; mechanism of action is similar to that of sulfonamides where competitive antagonists of PABA prevent formation of folic acid, inhibiting bacterial growth. Used in conjunction with other anti-inflammatory medications and immunosuppressives.

In children, physicians should consult the patient's pediatrician before prescribing this medication.

Dosing

Adult

50-300 mg PO qd

Pediatric

25-50 mg/d PO

Interactions

May inhibit anti-inflammatory effects of clofazimine; hematologic reactions may increase with folic acid antagonists, eg, pyrimethamine (monitor for agranulocytosis during the second and third months of therapy); probenecid increases dapsone toxicity; trimethoprim with dapsone may increase toxicity of both drugs; because of increased in renal clearance, dapsone levels may significantly decrease when administered concurrently with rifampin

Contraindications

Documented hypersensitivity; known G-6-PD deficiency

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Adverse effects include anemia, agranulocytosis, methemoglobinemia, hepatitis, neuropathy, headache; perform weekly blood counts (first mo); then perform WBC counts monthly (6 mo); then semiannually; discontinue if a significant reduction in platelets, leukocytes, or hematopoiesis is seen; caution in methemoglobin reductase deficiency, G-6-PD deficiency, or hemoglobin M because of high risk for hemolysis and Heinz body formation; caution in patients exposed to other agents or conditions (eg, infection, diabetic ketosis) capable of producing hemolysis; peripheral neuropathy can occur (rare); phototoxicity may occur when exposed to UV light

Immunosuppressive agents

EBA is an autoimmune disease, targeting the skin basement membrane component type VII collagen. Immunosuppressives are used in patients with severe disease. Immunomodulatory medications or therapies, if used properly, may be able to correct this alteration.

Azathioprine (Imuran)

Antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. May decrease proliferation of immune cells, which results in lower autoimmune activity.

Dosing

Adult

1-2 mg/kg/d PO is suggested dose; adjust dose based on blood level of thiopurine methyltransferase (enzyme responsible for drug metabolism)

Pediatric

Not established

Interactions

Toxicity increases with allopurinol; concurrent use with ACE inhibitors may induce severe leukopenia; may increase levels of methotrexate metabolites and decrease effects of anticoagulants, neuromuscular blockers, and cyclosporine

Contraindications

Documented hypersensitivity; allergy; pregnancy; combined treatment with other immunosuppressives; low thiopurine methyltransferase activity (TPMT)

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Closely monitor bone marrow suppression; may cause hepatitis and central nausea; increases risk of neoplasia; caution with liver disease and renal impairment; hematologic toxicities may occur

Photophoresis agents

Is a therapeutic method that uses UV-sensitizing medication (psoralen) and extracorporeal ultraviolet A irradiation of the sensitized WBCs. The photoinactivated cells are reinfused into the patient.

Methoxsalen (8-MOP, Oxsoralen)

Inhibits mitosis by binding covalently to pyrimidine bases in DNA when photoactivated by UV-A.

Dosing

Adult

0.57 mg/kg 1.5-2 h before exposure to UV light, at least 48 h apart

Pediatric

Not established

Interactions

Toxicity increases with phenothiazines, griseofulvin, nalidixic acid, tetracyclines, thiazides, and sulfanilamides

Contraindications

Documented hypersensitivity; squamous cell cancer; cataract; light sensitive diseases (eg, lupus, porphyria); ingestion of photosensitizing drugs; hepatic disease; arsenic therapy

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Severe burns may occur from sunlight or UV-A if dose or treatment frequency exceeded; use only if response to other forms of therapy is inadequate; long-term use may increase risk of skin cancer; fluid overload, hypovolemia, or sepsis may occur

Biological Response Modulator

Rituximab (Rituxan)

Rituximab is a monoclonal antibody (mostly human origin, partly mouse protein) that is specifically targeting a immune cell surface marker termed CD20, which is primarily expressed by B lymphocytes (B cells). The antibody is an IgG class immunoglobulin with kappa light chain.

Dosing

Adult

375 mg/m² body surface area IV qwk for 4 consecutive weeks; the 4 weekly infusions may be followed by a monthly infusion schedule for 4 more consecutive months

Pediatric

Not established

Interactions

Coadministration with cisplatin is known to cause severe renal toxicity including acute renal failure; may interfere with immune response to live virus vaccine (MMR) and reduce efficacy (do not administer within 3 months of vaccine)

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Use with caution in patients with dormant infections such as hepatitis B, hepatitis C, or CMV due to risk of reactivation; hypotension, bronchospasm, and angioedema may occur, premedication with acetaminophen and diphenhydramine may decrease incidence; discontinue treatment if life-threatening cardiac arrhythmias occur; must administer by slow IV infusion, do not administer IV push or bolus

Follow-up

Further Outpatient Care

- Patients with epidermolysis bullosa acquisita (EBA) should be monitored regularly by physicians with experience in treating autoimmune skin disease. During the active disease stage, patients should be monitored by their physicians on a monthly basis. When in remission, patients should be monitored by their physicians annually.

Deterrence/Prevention

- For patients who are treated with systemic corticosteroid for longer than 1 month, a combined supplement of calcium and vitamin D should be instituted to prevent osteoporosis. The guideline for this combined supplement is stated in the recommendations established by the American College of Rheumatology Task Force in 1996.²⁹

Complications

- Infection is a possible consequence of open erosions and wounds in the setting of immunosuppression.
- Malignancies may occur, secondary to chronic inflammation and immunosuppressive treatments.
- Bone marrow suppression is possible, secondary to medication.
- Growth retardation may occur, secondary to medications used during childhood.
- Complications secondary to prednisone treatment include adrenal insufficiency and osteoporosis.

Prognosis

- Patients with epidermolysis bullosa acquisita, if treated and cared for properly, should expect to live a normal life span.
- Patients with scarring secondary to epidermolysis bullosa acquisita may develop dysfunction.

Patient Education

- Since both trauma and autoantibodies contribute to blister formation in epidermolysis bullosa acquisita, patients require education about the disease. They also require significant education about the medications and the associated adverse effects and drug interactions of these medicines.
- The first aspect of patient education is trauma avoidance. Patients with epidermolysis bullosa acquisita should be instructed to avoid contact sports whenever possible and to use protective padding on their extensor skin surfaces on a

regular basis. Those with oral involvement need instruction on oral hygiene and diet. They should avoid foods that induce significant mucosal injury such as pretzels, nuts, chips, and other hard foods.

- The second aspect of education is their medication. Patients with epidermolysis bullosa acquisita should be educated about the potential adverse effects of their medication, such as infection, malignancies, osteoporosis, aseptic necrosis, peptic ulcer disease, and adrenal insufficiency. Patients should be familiar with the symptoms and signs of these adverse effects and should report any changes in their health status to their physicians.

Miscellaneous

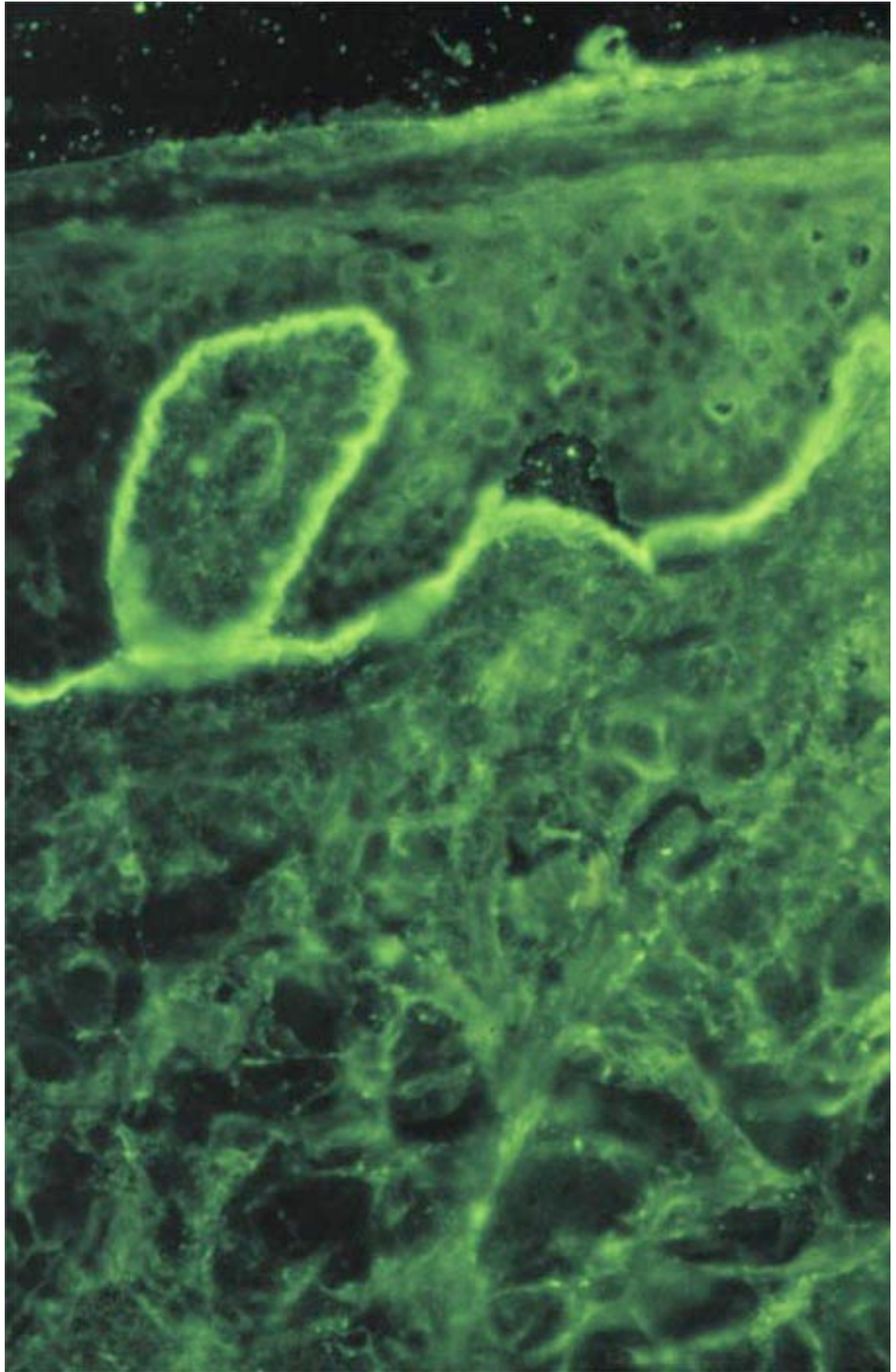
Medicolegal Pitfalls

- It is important that an accurate diagnosis be obtained before treatment is begun since patients affected with epidermolysis bullosa acquisita require treatments with long-term medications, which carry potentially severe adverse effects. Furthermore, monitoring and preventing these potential adverse effects of corticosteroids and immunosuppressives are also essential. Failure to make an accurate diagnosis or failure to monitor and to prevent severe adverse effects of medications may result in detrimental sequelae.
- The Medscape Medical Malpractice and Legal Issues Resource Center may be of interest.

Special Concerns

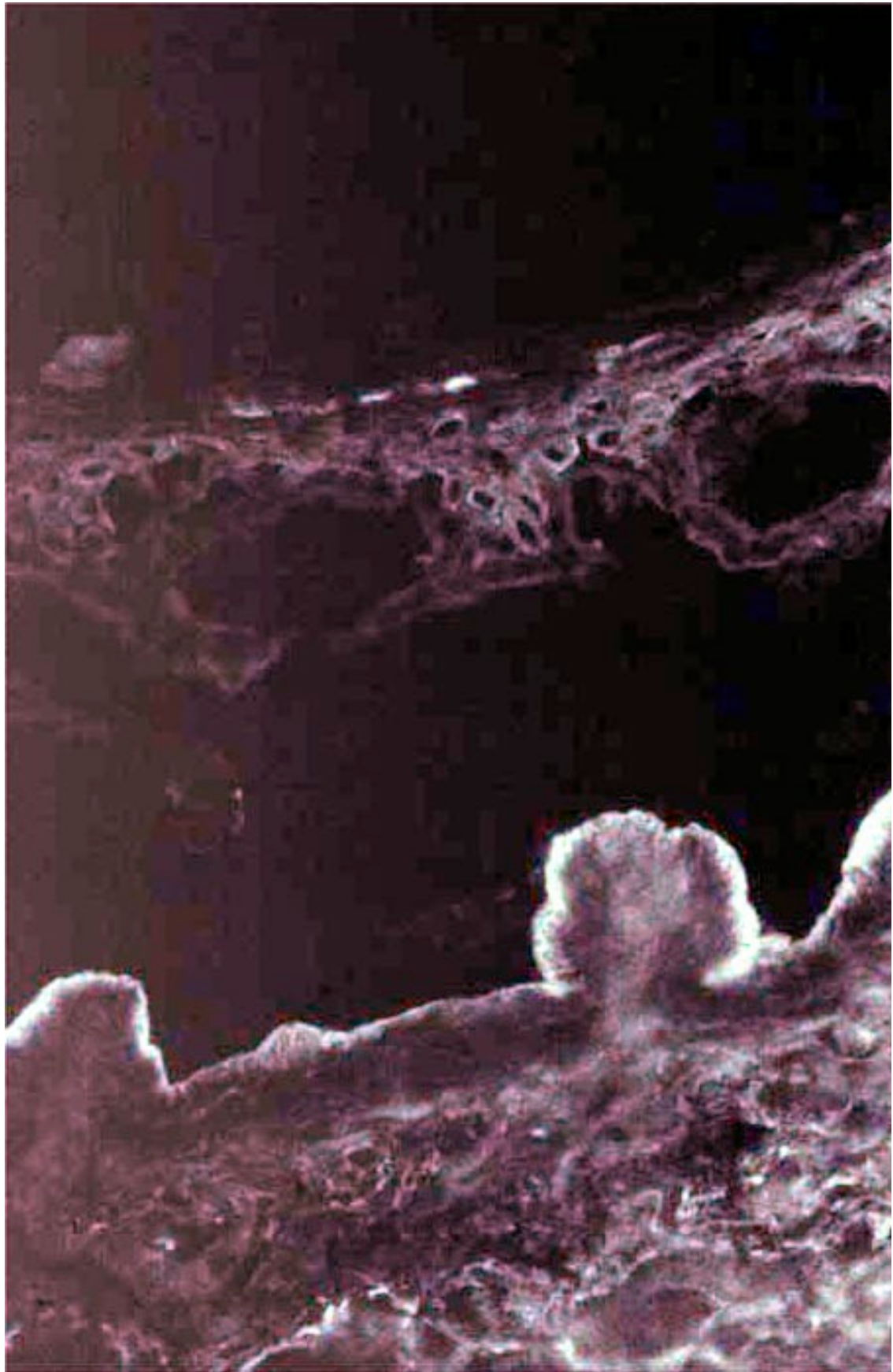
- When epidermolysis bullosa acquisita occurs in early childhood, its resemblance to the heritable forms of blistering skin disease epidermolysis bullosa dystrophica may lead to a misdiagnosis. Therefore, a direct immunofluorescence study is recommended for childhood-onset blistering diseases.
- Because the association between epidermolysis bullosa acquisita and inflammatory bowel diseases is rather strong, GI symptoms occurring in a patient with epidermolysis bullosa acquisita should alert the physician for a possible GI disorder such as Crohn disease or ulcerative colitis.
- Epidermolysis bullosa acquisita has also been associated with internal malignancies.

Multimedia



Media file 1: Direct immunofluorescence performed on perilesional skin biopsy specimen from a patient with

epidermolysis bullosa acquisita detects a linear band of immunoglobulin G deposit along the dermoepidermal junction.



Media file 2: Indirect immunofluorescence performed on salt-split normal human skin substrate using serum from a patient affected with epidermolysis bullosa acquisita detects immunoglobulin G class circulating autoantibodies that bind to the dermal (base) side of the basement membrane.

References

54. Olivry T, Fine J, Dunston SM, et al. Canine epidermolysis bullosa acquisita: Circulating autoantibodies target the aminoterminal noncollagenous (NC1) domain of collagen VII in anchoring fibrils. *Vet Dermatol*. 1998;9:19-32.
55. Xu L, Chen M, Peng J, O'Toole EA, Woodley DT, Chan LS. Molecular cloning and characterization of a cDNA encoding canine type VII collagen non-collagenous (NC1) domain, the target antigen of autoimmune disease epidermolysis bullosa acquisita (EBA). *Biochim Biophys Acta*. Oct 22 1998;1408(1):25-34. [\[Medline\]](#).
56. Bernard P, Prost C, Aucouturier P, Durepaire N, Denis F, Bonnetblanc JM. The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. *J Invest Dermatol*. Aug 1991;97(2):259-63. [\[Medline\]](#).
57. Gandhi K, Chen M, Aasi S, Lapierre JC, Woodley DT, Chan LS. Autoantibodies to type VII collagen have heterogeneous subclass and light chain compositions and their complement-activating capacities do not correlate with the inflammatory clinical phenotype. *J Clin Immunol*. Nov 2000;20(6):416-23. [\[Medline\]](#).
58. Hashimoto T, Ishiko A, Shimizu H, Tanaka T, Dodd HJ, Bhogal BS, et al. A case of linear IgA bullous dermatosis with IgA anti-type VII collagen autoantibodies. *Br J Dermatol*. Feb 1996;134(2):336-9. [\[Medline\]](#).
59. Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol*. Mar 2002;138(3):370-9. [\[Medline\]](#).
60. Vodegel RM, de Jong MC, Pas HH, Jonkman MF. IgA-mediated epidermolysis bullosa acquisita: two cases and review of the literature. *J Am Acad Dermatol*. Dec 2002;47(6):919-25. [\[Medline\]](#).
61. Chan LS, Vanderlugt CJ, Hashimoto T, Nishikawa T, Zone JJ, Black MM, et al. Epitope spreading: lessons from autoimmune skin diseases. *J Invest Dermatol*. Feb 1998;110(2):103-9. [\[Medline\]](#).
62. Sitaru C, Mihai S, Otto C, Chiriac MT, Hausser I, Dotterweich B, et al. Induction of dermal-epidermal separation in mice by passive transfer of antibodies specific to type VII collagen. *J Clin Invest*. Apr 2005;115(4):870-8. [\[Medline\]](#).
63. Woodley DT, Ram R, Doostan A, Bandyopadhyay P, Huang Y, Remington J, et al. Induction of epidermolysis bullosa acquisita in mice by passive transfer of autoantibodies from patients. *J Invest Dermatol*. Jun 2006;126(6):1323-30. [\[Medline\]](#).
64. Chen L, Peterson JD, Zheng WY, Lin SX, Chan LS. Autoimmunity to type VII collagen in SKH1 mice is independent of regulatory T cells. *Clin Exp Immunol*. Aug 2006;145(2):322-31. [\[Medline\]](#).
65. Chen M, Marinkovich MP, Jones JC, O'Toole EA, Li YY, Woodley DT. NC1 domain of type VII collagen binds to the beta3 chain of laminin 5 via a unique subdomain within the fibronectin-like repeats. *J Invest Dermatol*. Feb 1999;112(2):177-83. [\[Medline\]](#).
66. Jonkman MF, Schuur J, Dijk F, Heeres K, de Jong MC, van der Meer JB, et al. Inflammatory variant of epidermolysis bullosa acquisita with IgG autoantibodies against type VII collagen and laminin alpha3. *Arch Dermatol*. Feb 2000;136(2):227-31. [\[Medline\]](#).
67. Chan LS, Fine JD, Briggaman RA, Woodley DT, Hammerberg C, Drugge RJ, et al. Identification and partial characterization of a novel 105-kDalton lower lamina lucida autoantigen associated with a novel immune-mediated subepidermal blistering disease. *J Invest Dermatol*. Sep 1993;101(3):262-7. [\[Medline\]](#).
68. Gammon WR, Briggaman RA, Inman AO 3rd, Queen LL, Wheeler CE. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. *J Invest Dermatol*. Feb 1984;82(2):139-44. [\[Medline\]](#).
69. Chen M, Chan LS, Cai X, O'Toole EA, Sample JC, Woodley DT. Development of an ELISA for rapid detection of anti-type VII collagen autoantibodies in epidermolysis bullosa acquisita. *J Invest Dermatol*. Jan 1997;108(1):68-72. [\[Medline\]](#).

70. Crichlow SM, Mortimer NJ, Harman KE. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol*. Jan 2007;156(1):194-6. [\[Medline\]](#).
71. Niedermeier A, Eming R, Pfütze M, Neumann CR, Happel C, Reich K, et al. Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). *Arch Dermatol*. Feb 2007;143(2):192-8. [\[Medline\]](#).
72. Sadler E, Schaffleitner B, Lanschuetzer C, Laimer M, Pohla-Gubo G, Hametner R, et al. Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol*. Aug 2007;157(2):417-9. [\[Medline\]](#).
73. Schmidt E, Benoit S, Bröcker EB, Zillikens D, Goebeler M. Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. *Arch Dermatol*. Feb 2006;142(2):147-50. [\[Medline\]](#).
74. Wallet-Faber N, Franck N, Batteux F, Mateus C, Gilbert D, Carlotti A, et al. Epidermolysis bullosa acquisita following bullous pemphigoid, successfully treated with the anti-CD20 monoclonal antibody rituximab. *Dermatology*. 2007;215(3):252-5. [\[Medline\]](#).
75. Hall RP, Lawley TJ, Smith HR, Katz SI. Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. *Ann Intern Med*. Aug 1982;97(2):165-70. [\[Medline\]](#).
76. American College of Rheumatology. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines. *Arthritis Rheum*. Nov 1996;39(11):1791-801. [\[Medline\]](#).
77. Chan LS. Epidermolysis Bullosa Acquisita. In: Lebowitz MG, Heymann WR, Berth-Jones J, Coulson I, eds. *Treatment of Skin Disease: Comprehensive Therapeutic Strategies*. 2nd ed. St. Louis, Mo: Mosby; 2005:191-3.
78. Chan LS, Chen M, Woodley DT. Epidermolysis bullosa acquisita in the elderly: Clinical manifestations, diagnosis and therapy. *J Geriatr Dermatol*. 1996;4:47-52.
79. Chan LS, Lapierre JC, Chen M, Traczyk T, Mancini AJ, Paller AS, et al. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. *Arch Dermatol*. May 1999;135(5):569-73. [\[Medline\]](#).
80. Chen M, Keene DR, Costa FK, Tahk SH, Woodley DT. The carboxyl terminus of type VII collagen mediates antiparallel dimer formation and constitutes a new antigenic epitope for epidermolysis Bullosa acquisita autoantibodies. *J Biol Chem*. Jun 15 2001;276(24):21649-55. [\[Medline\]](#).
81. Chen M, Marinkovich MP, Veis A, Cai X, Rao CN, O'Toole EA, et al. Interactions of the amino-terminal noncollagenous (NC1) domain of type VII collagen with extracellular matrix components. A potential role in epidermal-dermal adherence in human skin. *J Biol Chem*. Jun 6 1997;272(23):14516-22. [\[Medline\]](#).
82. Chen M, Woodley DT. The cartilage matrix protein NC1 submodule of type VII collagen binds to fibronectin and constitutes a major new antigenic epitope for EBA autoantibodies. *J Invest Dermatol*. 1999;112:536.
83. Delbaldo C, Chen M, Friedli A, Prins C, Desmeules J, Saurat JH, et al. Drug-induced epidermolysis bullosa acquisita with antibodies to type VII collagen. *J Am Acad Dermatol*. May 2002;46(5 Suppl):S161-4. [\[Medline\]](#).
84. Domloge-Hultsch N, Gammon WR, Briggaman RA, Gil SG, Carter WG, Yancey KB. Epiligrin, the major human keratinocyte integrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. *J Clin Invest*. Oct 1992;90(4):1628-33. [\[Medline\]](#).
85. Gammon WR, Woodley DT, Dole KC, Briggaman RA. Evidence that anti-basement membrane zone antibodies in bullous eruption of systemic lupus erythematosus recognize epidermolysis bullosa acquisita autoantigen. *J Invest Dermatol*. Jun 1985;84(6):472-6. [\[Medline\]](#).
86. Jones DA, Hunt SW 3rd, Prisanh PS, Briggaman RA, Gammon WR. Immunodominant autoepitopes of type VII collagen are short, paired peptide sequences within the fibronectin type III homology region of the noncollagenous (NC1) domain. *J Invest Dermatol*. Feb 1995;104(2):231-5. [\[Medline\]](#).
87. Keene DR, Sakai LY, Lunstrum GP, Morris NP, Burgeson RE. Type VII collagen forms an extended network of anchoring fibrils. *J Cell Biol*. Mar 1987;104(3):611-21. [\[Medline\]](#).
88. Kirtschig G, Murrell D, Wojnarowska F, Khumalo N. Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol*. Mar 2002;138(3):380-4. [\[Medline\]](#).
89. Lapierre JC, Chan LS, Woodley DT. Epidermolysis bullo