Clinical Approach to Diffuse Blisters

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KEYWORDS

• Blisters • Vesicles • Diffuse blisters • Vesiculobullous
• Autoimmune bullous disorders • Bullous drug eruptions

KEY POINTS

- A thorough history is essential because it may provide clues for both internal and external triggers of certain vesiculobullous eruptions. Medications are an important cause of bullous eruptions, which have the potential to be life threatening (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis).
- Immunocompromised patients often have more severe and atypical manifestations of infectious vesiculobullous disease (eg, herpetic infections) and require more aggressive therapy.
- Specialized tests such as direct immunofluorescence and serologies are helpful in diagnosing certain autoimmune blistering diseases.
- Appropriate further testing should be considered because specific bullous eruptions are strongly associated with systemic diseases (eg, myeloproliferative disorders, connective tissue diseases, systemic vasculitides, inflammatory bowel disease, and certain infections).

At some point during their careers, it is likely that most physicians will encounter a patient who presents with blisters. The clinical presentation of vesicles and bullae suggests a broad differential and confusion often arises in how to approach such patients, especially if a dermatology service is not readily accessible. In most circumstances, these tend to be acute presentations. Although some blistering eruptions may be self-limited, others are life threatening, and prompt diagnosis and management are critical. This article (1) provides a systematic diagnostic approach to such patients, including history, physical examination, and relevant work-up (**Fig. 1**); and (2) introduces some common blistering diseases that may be encountered by primary care physicians and subspecialists.

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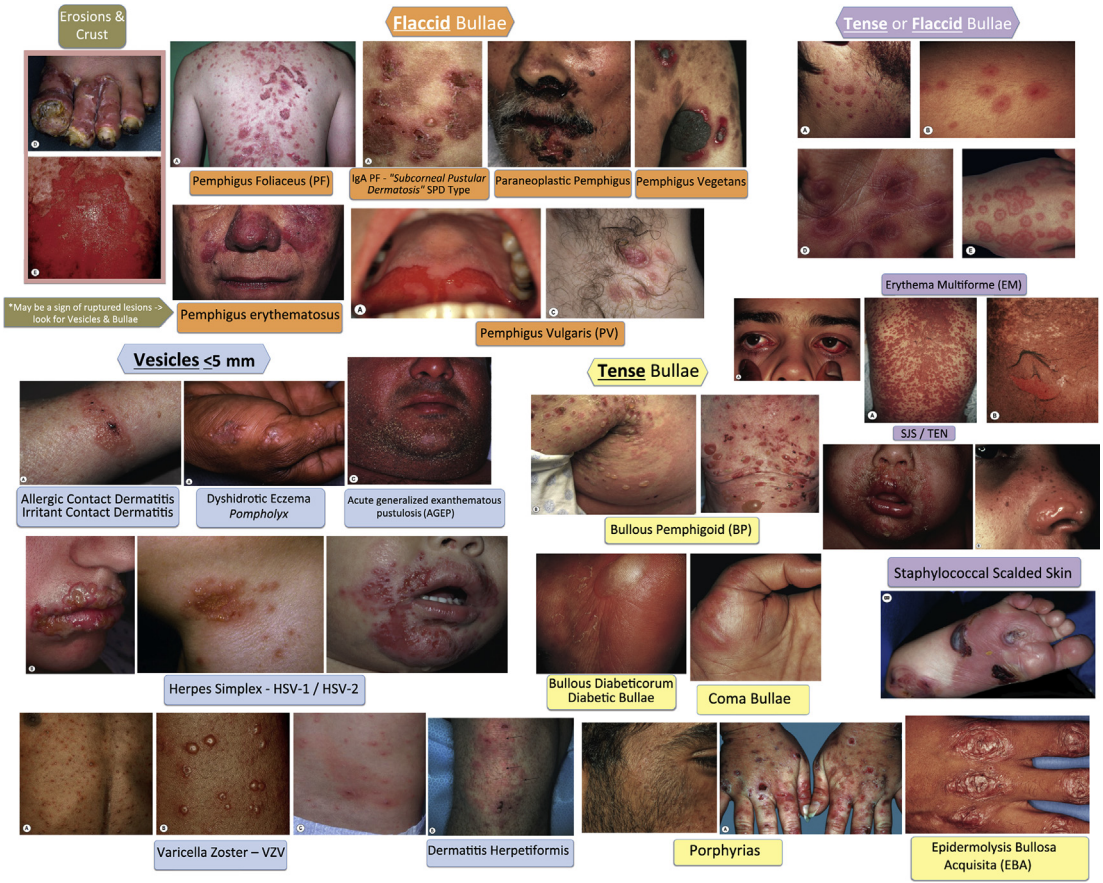

Fig. 1. Diagnostic approach for common vesiculobullous eruptions. Assoc., associated; IgA, immunoglobulin A; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

PATIENT HISTORY

During the initial encounter, a thorough history can play a vital role in determining the cause of a bullous eruption. There are many pertinent points in a history that help exclude possibilities, especially if the blistering eruption is atypical. Many of these variables are discussed here.

The age of onset can be crucial because certain bullous diseases are more common in specific age groups. Inherited blistering disorders such as epidermolysis bullosa begin in childhood, and may continue into adulthood.[1] Acquired processes such as autoimmune bullous disorders (ABDs) and bullous diseases secondary to systemic disease or external triggers can present in all age groups, but presentation may vary between children and adults.[2] For example, herpes zoster frequently presents in adults, whereas primary varicella presents more often in children.[3,4] Another example, staphylococcal scalded skin syndrome (SSSS), is more common in young children.

The timing of a rash can help identify acute causes, and tends to be related to particular triggers. Vesicles and bullae in the setting of external triggers, such as new medications, contact with chemicals/allergens, and infections, are acute in onset and tend to resolve after removal of the trigger. However, some ABDs and eruptions secondary to systemic disease are usually subacute to chronic with intermittent exacerbations and remissions.[2] As with any presenting illness, it is important to inquire about modifying factors that the patient may have observed in exacerbated and possibly accelerated progression of blisters. For example, photoaggravation of disease is seen in bullous lupus,[5] porphyria cutanea tarda,[6] and phytophotodermatitis,[7] whereas cold, wet environments worsen chilblains.[8]

A comprehensive review of systems is important because some diseases have particular prodromal symptoms that tend to continue as the blisters present and progress. Although diabetic bullae are asymptomatic,[9] bullous pemphigoid and contact dermatitis can be preceded by intense pruritus.[2,10] Necrotizing fasciitis and sepsis are frequent complications of bullous cellulitis associated with organisms like *Vibrio vulnificus*.[11] Immunosuppressed patients occasionally have atypical presentations, such as disseminated zoster.[3]

PHYSICAL EXAMINATION

Vesicles are elevated, fluid-filled, well-circumscribed clefts in the skin less than 1 cm in diameter, whereas bullae are greater than or equal to 1 cm in diameter (see **Fig. 1**). Although vesicles and bullae are the primary lesions, secondary changes such as crusting and erosions are concomitant in most blistering disorders. Herpes simplex and zoster, dyshidrotic eczema, and dermatitis herpetiformis present with a predominantly vesicular eruption, although in the dermatitis herpetiformis the eruption is often intensely itchy such that vesicles are excoriated before being recognized as blistering. Tense bullae (subepidermal split) are frequently seen in bullous pemphigoid, and flaccid bullae (intraepidermal split) in pemphigus vulgaris. Occasionally, only large erosions are present in cases of pemphigus foliaceous because the superficial bullae rupture before presentation. Nikolsky sign (shearing of epidermis with lateral pressure) is often seen with toxic epidermal necrolysis (TEN), SSSS, and pemphigus. Other commonly associated findings, such as erythematous urticarial plaques (eg, bullous pemphigoid), palpable purpura (eg, small vessel vasculitis), or targetoid macules (eg, erythema multiforme), can help facilitate a diagnosis.[12]

The configuration and pattern of blisters in a particular area can often provide clues to the diagnosis. Grouped vesicles are strongly suggestive of herpetic infections.[3] Geometric shapes and/or linear patterns are usually seen in the setting of

phytophotodermatitis and contact dermatitis.[7,10] Annular configurations of bullae can suggest linear immunoglobulin (Ig) A bullous disease,[13] which is often described as resembling a string of pearls.

The area of distribution has important diagnostic implications, and includes the observation of key features such as the body areas involved (eg, acral/perioral/perineal), localized versus diffuse, photoexposed surfaces, and mucosal or conjunctival involvement. Localized distributions are seen in herpes zoster (dermatomal),[3] porphyria cutanea tarda (hands),[6] phototoxic drug eruptions (face, neck, and dorsal arms),[14] and diabetic bullae (areas of trauma, typically shins).[9,14] Mucosal involvement is seen in pemphigus and some variants of pemphigoid.[15,16]

DIAGNOSTIC TESTING

Initial diagnostic testing is ordered based on history and physical examination. In acute settings, diagnosis often relies on a bedside clinical assessment. If there are multiple possibilities, a skin (punch) biopsy of a new vesicle or the edge of an intact blister is recommended. Direct immunofluorescence (DIF) testing of a biopsy from perilesional skin along with serologic testing for relevant antibodies is helpful in differentiating various autoimmune bullous diseases. Special stains for infections can also be performed on biopsies. However, swabbing the skin for cultures and viral polymerase chain reaction (PCR) is easier, faster, and may provide more information. Additional pertinent blood tests can be performed based on the initial results to help identify any systemic causes.[12]

BLISTERING CONDITIONS CAUSED BY EXTERNAL TRIGGERS

Allergic Contact Dermatitis

Background

Allergic contact dermatitis (ACD) is the result of a type IV, delayed type, hypersensitivity response to specific allergens in the setting of prior sensitization. Subsequent reexposure to an allergen at low concentrations is often sufficient to elicit a response.[10,17,18]

History

Patients with ACD present with significant pruritus accompanying a rash, which usually develops within days of exposure to a specific allergen. It is important to inquire about changes to a patient's daily routine, including new hobbies or occupations, or the recent use of new products. Location of the rash may help determine the cause. For example, a rash around the neck and earlobes may indicate an allergy to nickel, which is present in some jewelry. A detailed history can help identify the cause of less common presentations such as eyelid dermatitis, which may be caused by a new nail polish.[10,17,18]

Physical examination

ACD typically presents as a well-demarcated pruritic eruption. Blisters and vesicles are often seen in an acute setting, whereas eczematous erythematous patches and plaques are more typical in the chronic setting. Geometric configurations, such as linear streaks caused by poison ivy dermatitis, are a key examination clue to ACD. Diffuse patchy eruptions well away from the primary contact reaction may be associated with autosensitization (the so-called id reaction). Occasionally, ACD and systemic autosensitization may result in erythroderma.[10,17,18]

Differential diagnosis

Irritant contact dermatitis (discussed later), dyshidrotic eczema, and bullous tinea pedis. Erythroderma that is caused by mycosis fungoides, medications, or other causes.

Diagnostic study/biopsy

ACD is generally diagnosed by history and physical examination. In some cases, a biopsy may help exclude other diagnoses. The histology usually shows spongiotic dermatitis with a mixed inflammatory infiltrate including eosinophils. Patch testing is the gold standard to identify an allergen. The top 10 common allergens are presented in **Table 1**.[10,17,18]

Treatment

The primary treatment is avoidance of the allergen, and provision of information regarding products containing identified allergens. It may take several weeks for the eruption to resolve despite allergen avoidance. Medium-potency to high-potency topical steroids may be used in localized cases. A systemic corticosteroid taper over 2 to 3 weeks may be indicated in severe cases. This treatment is typically reserved for contact dermatitis involving involvement of body surface areas of greater than 20%.[10,18]

Irritant Contact Dermatitis

Background

Irritant contact dermatitis (ICD) results from a local caustic reaction to chemicals. Chronic repetitive exposure to various mild irritants, such as soaps and cleansers, leads to breakdown of the skin barrier, and can present with various morphologies ranging from erythema and scaling to vesicles and bullae.[19,20]

History

Onset often is not abrupt, and the condition is usually chronic with intermittent flares. Affected areas tend to be painful rather than pruritic. Patients usually have a history of repetitive chronic exposure to low-grade irritants such as soaps and solvents. Bullae are more likely with exposure to strong irritants such as alkali or acids.[20]

Physical examination

Patients usually present with well-defined vesicular, bullous, or scaly erythematous patches corresponding with sites of contact. For example, ICD of the hands frequently presents with vesicles and scaly erythematous patches on the lateral aspects of

Table 1
Top 10 allergens as identified by the North American Contact Dermatitis Group

Test Substance	Allergic Reactions (%)	Relevant Reactions: Definite, Probable, Possible Combined (%)
Nickel sulfate	19	57
Myroxylon pereirae (balsam of Peru)	12	87
Fragrance mix 1	11.5	86
Quaternium-15	10	89
Neomycin sulfate	10	28
Bacitracin	9	39
Formaldehyde	9	91
Cobalt chloride	8.5	48
Methyldibromoglutaronitrile/ phenoxyethanol	6	75
p-Phenylenediamine	5	56

From Mowad CM, Marks JG. Allergic contact dermatitis. In: Bolognia JL, Jorizzo JL, Schaeffer JV, editors. Dermatology. London: Saunders; 2012; with permission.

fingers in the setting of chronic exposure to soaps and cleansers. Prolonged contact with irritants may eventually cause thickening of skin and fissuring. Involved areas can be painful and thus limit activity.[20] ACD to leather gloves can have similar appearance with localized lesions at sites of contact.[14]

Differential diagnosis

Excluding ACD can be difficult without patch testing. Also consider tinea manuum or pustular psoriasis with localized lesions on the hands. Dyshidrotic eczema (pompholyx) is a chronic and recurrent palmoplantar dermatosis with a similar clinical appearance, and is a result of atopic dermatitis with a component of ICD and/or ACD.[7,20] However, this entity is a diagnosis of exclusion and external triggers must be addressed.

Diagnostic study/biopsy

Diagnosis is based on clinical history. Biopsy can be helpful but is not definitive, and usually shows a spongiotic dermatitis with occasional necrotic keratinocytes and a lymphocytic infiltrate.[19]

Treatment/further work-up

The focus of treatment is the restoration of the skin barrier and removal of the trigger. In general, topical steroids, barrier creams, and avoidance of irritants are critical in management. Treatments in the setting of exposure to alkali or acid products are agent dependent.[19]

Phototoxic Bullous Eruption (Phytophotodermatitis)

Background

Phototoxic bullous eruptions are caused by contact with agents containing furocoumarins. Furocoumarins are toxic to skin on conversion by ultraviolet (UV) light. Phytophotodermatitis is a result of UV exposure to plant sources of furocoumarins.[7,21]

History and physical examination

The eruption begins 30 minutes to 2 hours after UV exposure and progresses to burning, erythema, vesicles, and blisters over the following 2 to 3 days. The clinical appearance is distinctive, with vesicles in a linear or geometric pattern, and bulla with concomitant erythema. The rash usually resolves with hyperpigmentation that can persist for several months. Of note, some cases show recurrence in the identical site on exposure to UV several months after the initial presentation. Patients may present at any stage, and diagnosis may be difficult when asymptomatic or with only residual hyperpigmentation. It is important to obtain a history regarding exposures within 2 to 3 days before initial presentation to plants (ie, celery, lime, or rue), medications (application of insect repellants or consumption of psoralens), and fragrances containing bergamot compounds.[7,21]

Differential diagnosis

Photoallergic contact dermatitis, bullous lupus, porphyria cutanea tarda, photoallergic drug-induced photosensitivity, and pseudoporphyria.

Diagnostic study/biopsy

A biopsy can be helpful when the diagnosis is unclear, and usually shows epidermal hyperkeratosis, spongiosis with necrotic keratinocytes, and occasionally intraepidermal and subepidermal blistering. The inflammatory infiltrate can vary with neutrophils and a perivascular lymphohistiocytic infiltrate with occasional eosinophils (in the acute setting). Later stages may show melanophages with pigment incontinence, increased melanin, melanocytic hyperplasia with variable acanthosis, hyperkeratosis, and hypergranulosis.[7,21]

Treatment/further work-up

Treatment in the acute setting depends on the severity of involvement. Topical steroids with antihistamines can be considered initially. Oral corticosteroids may be required for severe involvement. Strict, long-term sun avoidance is also necessary to avoid flares.[7,21]

Bullous Arthropod Bite Reactions

Background

An exaggerated bite response to mosquitoes, fleas, scabies, and bed bugs can sometimes be seen in children or in individuals with myeloproliferative disorders such as chronic lymphocytic leukemia.[14,22]

History

Patients present with an acute onset of blisters associated with intense pruritus localized to the affected site. Patients may not always recall a history of bug bites, but they have usually been outdoors.[14,22]

Physical examination

Bites usually present as grouped pink papules, but in some cases progress to vesicles or blisters. In cases associated with hematological malignancies, large bullae and necrosis can be seen (**Fig. 2**).[14,22]

Differential diagnosis

Bullous impetigo, bullous erythema multiforme, bullous Sweet syndrome, and localized ABDs such as bullous pemphigoid.

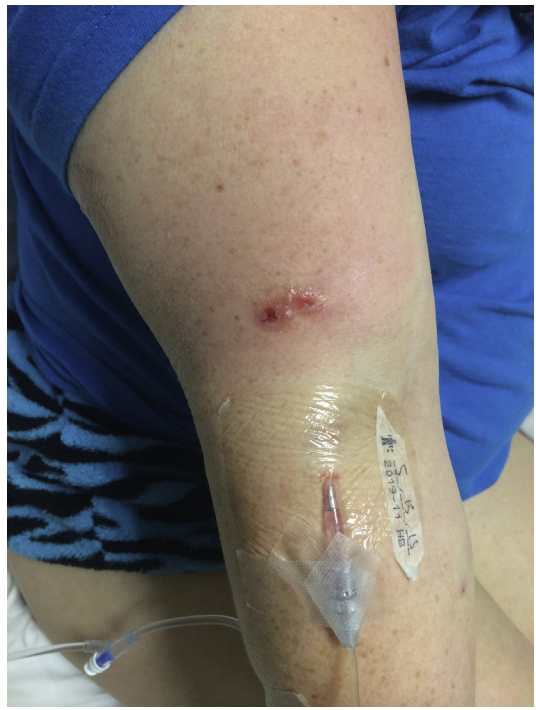

Fig. 2. Bullous arthropod bite eruption in a patient with myeloproliferative disorder.

Diagnostic study/biopsy
Biopsy shows a superficial and deep perivascular infiltrate with eosinophils along with possible epidermal necrosis at the bite site. Eosinophilic spongiosis is seen in the early phase, and may progress to subepidermal blisters.[14,22]

Treatment
Supportive care with antihistamines and topical corticosteroids for symptomatic control. Consider systemic corticosteroids if previous treatments are not sufficient. Counsel on insect avoidance and the use of insect repellants and protective clothing.[14,22]

AUTOIMMUNE BULLOUS DISORDERS

ABDs are a group of diseases with autoantibody formation to various components of the epidermis and basement membrane.[5] For example, autoantibodies targeting desmosomes in the epidermis result in an intraepidermal split presenting as flaccid bullae and erosions (mucosal and skin), as seen in pemphigus (see **Fig. 1**). Autoantibodies against hemidesmosomes and other components of the basement membrane zone result in a subepidermal split leading to disorders including pemphigoid, as detailed in **Table 2**.[1,2,12,15,16,23–25] Diagnosis requires a combination of clinical, histopathologic, immunofluorescence, and serologic findings. In performing a skin biopsy, a well-developed new vesicle or the edge of an intact blister should be sampled. The level of split, along with concomitant histologic findings, is essential to the diagnosis. DIF evaluation of perilesional skin is helpful in differentiating an ABD from a non-ABD and between various ABDs. In some cases, such as dermatitis herpetiformis, sampling of normal skin directly adjacent to vesicles and bullae is necessary in order to detect sufficient antibodies to make the diagnosis. Special stains can also be used to detect organisms. Various serologic tests are also commercially available to confirm the diagnosis of various ABDs (see **Table 2**). Appropriate early treatment and management are critical given the significant disease morbidity and mortality.[12]

BULLOUS ERUPTIONS ASSOCIATED WITH INTERNAL DISEASES

Bullous Diabeticorum

Background
Diabetic patients can develop bullae on distal extremities, most commonly at sites of trauma. Although the cause is unclear, these bullae are exacerbated by concomitant microangiopathy.[9,14]

History
Blisters are sudden in onset and generally asymptomatic, but patients may experience a prodrome of burning in the affected area before onset. Patients tend to have other diabetic complications, such as diabetic neuropathy and systemic organ involvement (ie, nephropathy, retinopathy).[9,14]

Physical examination
Tense bullae are typically distributed on the distal extremities (most commonly feet and legs), and usually have no surrounding inflammation or erythema. The fluid within the bullae is usually clear and viscous in consistency.[9,14]

Differential diagnosis
Friction blisters, pseudoporphyria, bullous pemphigoid, and edema bullae.

Table 2
Autoimmune bullous diseases: clinical characteristics, work-up, and management

Disease	Level of Split	Clinical Characteristics	DDX	Work-up	Treatment
Pemphigus: • PV • PF • Other subtypes (see Fig. 1)	Intraepidermal (suprabasal)	• Mean age of onset usually 50–60 y, but may affect all ages • Present with painful erosions and flaccid bullae, most commonly on torso • Tend to heal slowly with hyperpigmentation • Pruritus less common • PF: may have only erosions and crusts • PV: oral mucosa is most commonly affected and predominant finding is painful erosions • PV may involve other mucosal surfaces (conjunctiva, pharynx, larynx, esophagus, nasal, anal, genital) • Other symptoms: hoarseness and dysphagia • Clinical course: chronic with intermittent flares	• Acute herpetic flare, EM, SJS • Mucosal forms of pemphigoid may present with similar mucosal erosions and blisters • Consider paraneoplastic pemphigus in recalcitrant cases	• H&E: Intraepidermal acantholysis • DIF: perilesional skin with antibodies to keratinocyte cell surface • IIF and ELISA: IgG autoantibodies against DSG 1 and 3 correlate with disease activity • PF: autoantibodies to DSG1 (predominantly skin) • PV: autoantibodies to DSG3 (predominantly mucosal) ± DSG1 (skin)	• Prompt treatment is critical because it is potentially fatal • Initial treatment: systemic corticosteroids with slow transition to steroid-sparing agents to minimize adverse effects of corticosteroids • Supportive measures during flares: pain management, nonadherent dressings, topical steroids • Some commonly used steroid-sparing agents: azathioprine, MMF, cyclophosphamide, MTX, IVIg, rituximab, plasmapheresis

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Table 2
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Disease	Level of Split	Clinical Characteristics	DDX	Work-up	Treatment
BP	Supepidermal (hemides-mosome)	• Typically affects the elderly • Very pruritic • Rarely with pain in oral cavity, dysphagia, or dysuria secondary to mucosal involvement • Diverse skin manifestations: before progressing to bullae formation, may present with pruritus and no skin lesions, excoriations, erythematous eczematous plaques, and/or urticarial erythematous plaques • Some patients may present only with urticarial plaques with excoriations • Although mucosal involvement is rare, erosions and ulcers can involve the oral cavity and genitalia • Lesions distributed symmetrically predominantly on lower trunk and lower extremities • Clinical course: chronic with frequent exacerbations and remissions	• Nonbullous phase: urticaria, urticarial vasculitis • Bullous phase: EBA, bullous lupus, LABD, drug-induced, bullous EM, bullous bite reaction, edema bullae, bullous diabeticorum	• H&E: bullous phase, subepidermal blister with predominant eosinophils in a mixed inflammatory infiltrate • H&E: nonbullous phase, subepidermal cleft + epidermal spongiosis and/or dermal eosinophils • DIF: Perilesional skin shows antibodies against epidermal basement membrane (hemidesmosome components) • Salt-split skin[a]: IgG autoantibodies bind to epidermal side of blister • Commercial ELISA serologic tests are available to check for autoantibodies to BP antigens (180 and 230)	• Potent topical steroids: useful in mild and moderate nonprogressive disease • Systemic steroids: initial mainstay of treatment of severe progressive disease • Chronic systemic treatment can vary depending on severity of disease and comorbidities. These can include tetracyclines (± nicotinamide), dapsone, azathioprine, MTX, MMF, rituximab
Bullous lupus	Subepidermal (sub–lamina densa)	• Female predilection, affecting individuals aged 20–40 y • Acute onset and can be the first sign of SLE • Can be accompanied by other systemic manifestations of SLE	• Subepidermal ABDs (BP, inflammatory EBA) • Phototoxic drug reactions • PCT	• H&E: lesional skin from intact blister shows subepidermal blister with neutrophils • DIF: granular deposition of autoantibodies along the BMZ	• Dapsone along with other immunosuppressants • Rituximab has been used with some success in recalcitrant cases

		• Often presents in the spring and summer with more sun exposure • Vesicles and bullae develop within existing lupus lesions or de novo with predilection for sun-exposed areas such as face, trunk, and arms • Lesions tend to heal with no scarring or milia	• Can be mistaken for SJS/TEN if involvement is extensive and leading to desquamation	• Serologies: autoantibodies to type 7 collagen, ANA, anti-dsDNA, anti-Sm, anti-Ro/SS-A, anti-La/SS-B	
EBA	Subepidermal (sub–lamina densa)	• Rare chronic condition with slow onset affecting trauma-prone skin and mucous membranes • Can occur at any age • Has been associated with inflammatory bowel disease • Presents with tense bullae on trauma-prone sites (eg, knuckles, wrists, extensor surfaces, hands and feet) and tend to heal with milia, and scarring • Scarring alopecia may develop with scalp involvement • Inflammatory subtype of EBA tends to be more acute and generalized, and blisters may also involve flexural as well as intertriginous areas • Mucosal involvement: oral, nasal, conjunctival, laryngeal, pharyngeal, esophageal, urogenital, anal • Mucosal lesions can lead to irreversible scarring and dysfunction	• ABDs: BP, LABD, bullous lupus	• H&E: subepidermal blister with a mixed inflammatory infiltrate • DIF: autoantibody IgG along the BMZ in a U-serrated pattern • Salt-split skin[a]: autoantibody binding to the dermal side of the salt-split skin • ELISA: detect autoantibodies to type VII collagen • Age-specific cancer screening recommended	• Systemic corticosteroids, dapsone, colchicine, and other conventional immunosuppressants

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Table 2
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Disease	Level of Split	Clinical Characteristics	DDX	Work-up	Treatment
Pemphigoid gestationis	Subepidermal	• Rare pruritic blistering condition seen in late pregnancy or early postpartum • Present acutely with pruritic urticarial plaques progressing to grouped vesicles and tense bullae • May be present predominantly around the umbilicus/abdomen, and can progress to involve the entire body, especially around the time of delivery • Concurrent erythematous plaques and papules are also present • Occasionally, the neonate has vesicles and blisters caused by maternal transfer of antibodies (IgG) • Most cases resolve a few weeks after delivery, but may flare around menstruation, with use of oral contraceptives, or with recurrent pregnancies • Associated with an increased risk of Graves disease and antithyroid antibodies may be present on evaluation • Precautions should be taken because of a higher risk of prematurity and small-for-gestational-age size	• PEP/PUPPP • Urticaria	• H&E: subepidermal vesicle with eosinophils on lesional skin • DIF: most commonly shows C3 deposition along the BMZ • Monitor newborn for bullae	• Topical corticosteroids + antihistamines (category B) for minor disease • Oral corticosteroids for severe disease • Unusual for disease to persist after delivery • Provide counseling because the disease may flare with oral contraceptives and subsequent pregnancies

Dermatitis herpetiformis	Subepidermal	• Seen in genetically predisposed individuals with gluten sensitivity and most patients have some form of gastrointestinal involvement (celiac disease) • Chronic, lifelong condition with intermittent flares and remissions correlating with gluten consumption. Spontaneous remission is rare • Significant pruritus • Diarrhea and abdominal pain may be present in patients with celiac disease • Symmetrically distributed grouped erythematous papules, vesicles, and plaques with surrounding erythema most commonly on extensor surfaces (dorsal forearms, elbows, knees), buttocks, and back • Secondary excoriations and hemorrhagic crusting also present in most cases caused by severe pruritus	• ABDs: LABD, EBA, BP • Infections (herpetic) • Drug-induced blisters • Folliculitis • Pityriasis lichenoides	• H&E: biopsy of a vesicle with a subepidermal blister and predominant neutrophils along the dermal papillae • DIF: uninvolved adjacent skin shows granular autoantibody IgA deposition along the dermal papillae • Serologies: positive for antiendomysial and antitransglutaminase (tissue and epidermal) autoantibodies • May be associated with other autoimmune diseases; consider monitoring of blood glucose and thyroid function • Referral to gastroenterology for celiac disease and surveillance for lymphoma	• Significant improvement can be seen with avoidance of gluten and use of dapsone

Abbreviations: ANA, antinuclear antibodies; anti-Sm, anti-Smith; Anti-SSA, Anti-Sjogren's Syndrome A; Anti-SSB, Anti-Sjogren's Syndrome B; BMZ, basement membrane zone; BP, bullous pemphigoid; C3, complement 3; DDX, differential diagnosis; DIF, direct immunofluorescence; dsDNA, double-stranded DNA; DSG, desmoglein; EBA, epidermolysis bullosa acquisita; ELISA, enzyme-linked immunosorbent assay; EM, erythema multiforme; H&E, hematoxylin and eosin; IVIg, intravenous immunoglobulin; La, Anti-SSB; LABD, linear IgA bullous disease (see text); IgA, immunoglobulin A; IgG, immunoglobulin G; IIF, ndirect Immunofluorescence; MMF, mycophenolate mofetil; MTX, methotrexate; PCT, porphyria cutanea tarda; PEP, polymorphic eruption of pregnancy; PF, pemphigus foliaceus; PUPPP, pruritic urticarial papules and plaques of pregnancy; PV, pemphigus vulgaris; Ro, Anti-SSA; SJS, Stevens-Johnson syndrome; SLE, systemic lupus erythematosus; TEN, toxic epidermal necrolysis.

[a] Specimens incubated in 5 mL of NaCl (1 mol/L) at 4°C for24 hours. Epidermis then separated from dermis and specimens processed in same manner and treated with IgG and C3 conjugates as in DIF. BP shows floor pattern and EBA shows roof pattern; correlates with autoantibodies against hemidesmosomal proteins versus collagen 7, respectively.

Diagnostic study/biopsy
Biopsy shows primarily subepidermal blisters in active lesions, and intraepidermal splits in older lesions. Friction blisters show a split below the stratum granulosum and are usually seen in the setting of repetitive trauma. DIF is negative.[9,14]

Treatment
Supportive care, treatment with an aluminum acetate solution, and prevention of infection.[9,14]

Chilblains

Background
Chilblains occur with exposure of acral surfaces (hands and feet) to cold, wet environments. It is an aberrant response in predisposed individuals, and has an unknown pathogenesis.[8,26]

History
Chilblains are commonly seen in women, children, and elderly living in cold climates with no central heating. It is a chronic condition affecting acral surfaces, and may involve the ears and nose. There is usually an associated burning pain and occasionally pruritus.[8,26]

Physical examination
The eruptions usually present as violaceous to erythematous macules, papules, or patches on volar surfaces of the distal toes and fingers, ears, and nose. Severe cases may progress to blistering and ulceration.[8,26]

Differential diagnosis
Cryoglobulinemia, myelomonocytic leukemia, hemolytic anemia, chilblain lupus erythematosus, Raynaud phenomenon, and several other cold-induced eruptions should be considered. Second-degree and third-degree frostbite also have a similar acral distribution with bullae.[8,26]

Diagnostic study/biopsy
Biopsy shows papillary dermal edema with a superficial and deep lymphocytic infiltrate, and can be helpful in distinguishing from other entities, such as chilblain lupus. Laboratory evaluation is necessary to rule out systemic causes.[8,26]

Treatment
Calcium channel blockers (amlodipine and nifedipine), cold weather clothing, and avoidance of cold and wet environments are recommended. Hydroxychloroquine can be considered if associated with systemic lupus erythematosus.[8,26]

Coma Bullae

Background
Coma bullae were previously referred to as barbiturate bullae. Although the exact cause is unknown, they are frequently seen with prolonged immobilization caused by loss of consciousness (ie, neurologic and endocrine disorders, medications, illicit drug use),[14,27] thus pressure-induced injury may play a role in pathogenesis.

History
Blisters generally develop acutely at sites of greatest pressure within 48 to 72 hours of loss of consciousness, and tend to be asymptomatic.[14,27]

Physical examination
Tense blisters develop over bony prominences and areas of greatest pressure, and eventually result in erosions.[14,27]

Differential diagnosis
Bullous diabeticorum and friction blisters.

Diagnostic study/biopsy
Biopsy shows a subepidermal split along with eccrine sweat gland necrosis, which helps to distinguish coma bullae from other blistering entities. Additional findings of rhabdomyolysis and compression neuropathy may be seen in some patients.[14,27]

Treatment
Avoidance of pressure to sites with bullae to prevent further progression, supportive wound care, toxicology evaluation, and review of medications.[14,27]

Edema Bullae

Background
Edema bullae develop because of sudden acute swelling in patients with underlying comorbidities such as congestive heart failure, renal disease, liver disease, or thrombosis leading to lower extremity edema and/or anasarca.[12,14]

History
Bullae usually develop acutely and are asymptomatic. In patients with conditions leading to chronic fluid overload, acute exacerbations can cause increased edema of the lower extremities that may be painful.[14,27]

Physical examination
Tense bullae with clear to serosanguineous fluid and minimal surrounding inflammation as well as concomitant edema are usually seen. This condition predominantly occurs in acutely ill hospitalized patients receiving excessive intravenous fluids, or in the setting of anasarca. Bullae may be localized to the distal lower extremities (dorsal foot and ankle) in patients with heart or kidney disease who acutely develop increased swelling from baseline.[14,27]

Differential diagnosis
Bullous diabeticorum, bullous pemphigoid, and medication-induced bullous eruptions, including drug-induced ABDs (discussed later).

Diagnostic study/biopsy
Biopsy usually shows a very edematous dermis with splayed collagen bundles, significant epidermal spongiosis, and occasionally subepidermal bullae.[14,27]

Treatment
Usually resolves with resolution of edema and, generally, no additional treatment is necessary.[14,27]

Porphyria Cutanea Tarda

Background
Porphyrias are a group of disorders resulting from acquired or inherited defects in the enzymes responsible for heme synthesis. Porphyria cutanea tarda results from decreased activity of uroporphyrinogen decarboxylase[6,10] and is the most common porphyria presenting in an adult population. Iron overload plays an integral part in its pathogenesis.

History
The initial symptoms include photosensitivity along with skin breakdown, and are usually precipitated by a variety of risk factors, such as alcohol consumption, increased estrogen levels, increased iron levels (as seen in hemochromatosis), hepatitis C, and human immunodeficiency virus (HIV).[6,10] Lesions are typically very slow to heal.

Physical examination
Minimal trauma leads to blistering and erosions with overlying crust symmetrically distributed on photoexposed skin (especially the face and dorsal hands). These areas heal with postinflammatory pigmentary alterations. Milia and waxy, yellow, plaquelike scarring may develop. In rare cases, contractures of the digits may occur. Patients may also have a unique finding of increased hair on the bitemporal and malar cheeks. In some cases, permanent loss of scalp hair and fingernails can be seen. Urine is usually slightly brown or discolored.[6,10]

Differential diagnosis
Drug-induced bullae, pseudoporphyria (**Table 3**), and ABDs (BP, epidermolysis bullosa acquisita, bullous lupus) (see **Table 2**).

Diagnostic study/biopsy
Diagnosis is confirmed with laboratory abnormalities showing increased serum and urine uroporphyrin, urine coproporphyrin, and fecal isocoproporphyrin. Further evaluation should include tests for hepatitis C, HIV, hemochromatosis, hemoglobin/hematocrit, liver function, and iron studies (particularly ferritin). Biopsy is not always necessary because the condition is fairly recognizable based on clinical appearance and laboratory testing.[6,10]

Treatment/further work-up
Initially consider serial phlebotomies every 2–4 weeks with monitoring of hemoglobin, hematocrit, and iron levels with the goal to reach a hemoglobin level of 10 to 11 g/dL and the lower limits of normal range of serum ferritin concentration without induction of iron deficiency anemia. Low-dose antimalarials (ie, hydroxychloroquine 100 mg twice weekly) have also been successful. Erythropoietin has been reported to be helpful in patients with renal failure. Photoprotection, avoidance of triggers such as alcohol, and treatment of associated conditions are also recommended. It is important to monitor for the development of hepatocellular carcinoma given the increased long-term risk in these patients.[6,10]

Bullous Neutrophilic Dermatoses

Background
Bullous neutrophilic dermatoses are inflammatory dermatoses with 2 major subtypes: bullous Sweet syndrome (BSS) and bullous pyoderma gangrenosum (BPG). There has been a suggestion that BSS and BPG are variants of the same disease process.[28]

History
BPG presents with painful blisters that are acute in onset and rapidly progressive. BPG has been seen in association with systemic diseases, including hematologic malignancies and inflammatory bowel disease.[28] Sweet syndrome usually presents with fever, an increased neutrophil count, and joint involvement, and may be associated with myelogenous leukemia, medications, autoimmune disorders, and infections.[29]

Physical examination
BPG presents as flaccid hemorrhagic bullae sometimes overlying an erythematous plaque, and progresses to superficial ulcerations most commonly on the face and

Table 3
Bullous drug eruptions

Disease	Examination Findings	Time Interval	Notes	Notable Responsible Drugs	Treatment
Fixed drug eruption	• Sharply circumscribed erythematous to dusky violaceous patches • Central blisters or erosions may appear • Often resolves with postinflammatory hyperpigmentation • Recurrence at same locations following drug reexposure • Can involve mucosa and genitalia	• First exposure, 1–2 wk • Reexposure, <48 h, usually within 24 h	• May have mucosal, acral, and genital involvement	Sulfonamides, TMP-SMX, NSAIDs, aspirin, acetaminophen (paracetamol), barbiturates, phenolphthalein, tetracyclines, metronidazole, pseudoephedrine	—
SJS TEN	• Prodromal symptoms: fever and painful skin • Dusky macules with or without epidermal detachment • Macular atypical targets • Flaccid bullous lesions, confluence, wide erosions + Nikolsky sign • Involves mucosa, face, trunk • Systemic symptoms: fever, lymphadenopathy, hepatitis, and cytopenias	7–21 d	• Mucosal, acral, and genital involvement • Percentage detachment of BSA ○ SJS <10% ○ SJS-TEN overlap 10%–30% ○ TEN >30%	Sulfonamides, TMP-SMX, allopurinol, β-lactam Abx, NSAIDs, piroxicam, anticonvulsants (aromatic), lamotrigine, phenytoin, barbiturates	• Critical = early withdrawal of responsible drug • No definitive therapy • Supportive care with burn team • Corticosteroids controversial • IVIg, cyclosporine, cyclophosphamide, plasmapheresis, *N*-acetylcysteine, TNF-α antagonists

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Table 3
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Disease	Examination Findings	Time Interval	Notes	Notable Responsible Drugs	Treatment
EM	• Rarely drug induced, ~90% from infections (HSV-1/2, *Mycoplasma pneumoniae*, VZV, EBV, CMV, *Histoplasma capsulatum*, dermatophytes, and so forth) • Targetoid lesions on extremities/face • EM minor: target lesions, papular atypical targets, possible mucosal involvement. No systemic symptoms • EM major: as above + severe mucosal involvement, systemic symptoms, may have bullous lesions	—	• Rarely drug induced • Mostly from infections • No progression to TEN	NSAIDs, sulfonamides, anticonvulsants, aminopenicillins, allopurinol	• Consider prophylaxis for recurrent disease (acyclovir/valacyclovir/famciclovir) • Early systemic corticosteroids or pulse methylprednisolone may help • Refractory disease: azathioprine, thalidomide, dapsone, cyclosporine, mycophenolate mofetil, PUVA
AGEP	• Acute onset with high fever • Usually occurs within 2 d of drug exposure • Areas of erythema studded with pustules and occasionally vesicles • Lesions begin on face or intertriginous areas	<4 d	• High fever • Malaise, leukocytosis • >90% of cases drug induced	β-Lactams, macrolides, pristinamycin, terbinafine, hydroxychloroquine, calcium channel blockers (diltiazem), carbamazepine, acetaminophen, metronidazole	• Withdrawal of responsible drug • Topical corticosteroids • Antipyretics
Phototoxic drug eruption	• Limited to sun-exposed areas • Resembles exaggerated sunburn	—	—	Tetracyclines (especially doxycycline), quinolones, psoralens, NSAIDs, diuretics	—

Drug-induced linear IgA bullous dermatosis	• Circumferential and linear vesicles and bullae • Annular and herpetiform vesicopustules and plaques	—	—	Vancomycin most common, β-lactam Abx, captopril, NSAIDs	• Topical steroids and withdrawal of drug usually lead to improvement • Systemic steroids and SSTs can be considered for patients with chronic disease
Drug-induced PV	• Most develop painful oral erosions • Flaccid blisters • Widespread cutaneous erosions • Associated pruritus uncommon (unlike bullous pemphigoid)	—	• Mucosal involvement • Paraneoplastic pemphigus has severe stomatitis/mucosal erosions	• 80% caused by drugs with a thiol group: penicillamine, ACE inhibitors (captopril), gold sodium thiomalate, pyritinol • Nonthiol drugs: antibiotics (especially β-lactams), pyrazolone derivatives, nifedipine, propranolol, piroxicam, and phenobarbital	• Mainstay = systemic corticosteroids • Topical = corticosteroids, antibiotics, immunomodulators (eg, tacrolimus) • If unresolved after medication withdrawal and corticosteroids, similar to pemphigus (see Table 2)
Drug-induced bullous pemphigoid	• Most common autoimmune subepidermal blistering disease • Associated with severe pruritus • Tense bullae on normal and erythematous skin • Concomitant erythematous or urticarial plaques	—	• May have mucosal, acral, and genital involvement • Predominantly elderly • May be preceded by a pruritic urticarial or exanthematous phase	Furosemide, penicillin and other β-lactams, sulfasalazine	• Mainstay = systemic corticosteroids • Topical = corticosteroids, antibiotics, immunomodulators (eg, tacrolimus) • If unresolved after medication withdrawal and corticosteroids, consider SSTs (see Table 2)
Drug-induced pseudoporphyria	• Resembles PCT • Porphyrins are within normal limits	—	• Sun-exposed surfaces	NSAIDs (naproxen), nalidixic acid, thiazides, furosemide, tetracyclines	Withdrawal of responsible drug

Abbreviations: Abx, antibiotics; ACE, angiotensin-converting enzyme; AGEP, acute generalized exanthematous pustulosis; BSA, body surface area; CMV, cytomegalovirus; d, days; EBV, Epstein-Barr virus; h, hours; EM, erythema multiforme; HSV, herpes simplex virus; IVIG, intravenous immunoglobulins; NSAID, nonsteroidal antiinflammatory drug; PCT, porphyria cutanea tarda; PUVA, psoralen (P) and ultraviolet A (UVA) therapy; PV, pemphigus vulgaris; SJS, stevens johnson syndrome; SSTs, steroid-sparing treatments; TEN, toxic epidermis necrolysis wk, week(s); TMP-SMX trimethoprim-sulfamethoxazole; TNF-α, tumor necrosis factor alpha; VZV, varicella zoster Virus.

Adapted from Bolognia JL, Jorizzo JL, Schaeffer JV, editors. Dermatology. London: Saunders; 2012.

upper extremities.[28] The typical lesions of Sweet syndrome are edematous, translucent, and erythematous papules and plaques that tend to localize to the head, neck, trunk, and upper extremities, but can also be widespread. Oral involvement may be seen in cases associated with hematologic malignancies. In BSS, vesicles containing viscous fluid can occasionally proceed to ulceration.[29]

Differential diagnosis
V vulnificus, leishmaniasis, and exaggerated bite reactions.

Diagnostic study/biopsy
Biopsies of both processes show a neutrophilic dermal infiltrate. Papillary dermal edema is prominent in BSS, and a subepidermal split is seen in BPG. A thorough history, review of medications, and evaluation for an underlying malignancy are important, and both diseases have shown a strong association with myelogenous leukemia. These diagnoses are of exclusion, and infectious causes of blisters and ulcerations should be excluded with a tissue culture.[28,29]

Treatment/further work-up
Systemic corticosteroids can be initiated when infection has been excluded. These disorders may require a longer course of therapy with corticosteroids or steroid-sparing agents such as dapsone, potassium iodide, and colchicine. Work-up to determine an underlying cause is critical.[28,29]

Small Vessel Vasculitis

Background
Small vessel vasculitis may occasionally present with blisters, and can have multiple causes, including medications and autoimmune, infections, paraneoplastic, and idiopathic causes.[14] Because the pathogenesis involves immune complex deposition on small vessel endothelium, the subsequent vascular destruction and erythrocyte extravasation lead to focal skin necrosis, with hemorrhagic blistering as a consequence.

History
Patients can present with a variety of symptoms based on cause. Pruritus can be associated with drug-induced vasculitis, and systemic symptoms can occur with connective tissue diseases, infections, and with paraneoplastic causes.[14]

Physical examination
Palpable purpura can precede hemorrhagic vesicles typically on the lower extremities. These lesions then progress to ulceration.[14]

Diagnostic study/biopsy
Biopsy shows small vessel leukocytoclastic vasculitis.[14] Further testing is based on suspicion for underlying causes.

Treatment
If the cause is idiopathic and removal of a possible underlying cause fails to resolve the vasculitis, systemic corticosteroids are the mainstay of treatment. Dapsone, colchicine, and immunosuppressive medications can be considered as steroid-sparing therapy.[14]

INFECTIOUS VESICULOBULLOUS DERMATOSES

Several bacterial, viral, and fungal infections can present with vesicles and bullae (**Table 4**).[3,11,12,30–32] Herpes infections usually present as localized or dermatomal

Table 4
Infectious bullous diseases

Form of Infection	Clinical Characteristics	Diagnosis and Management
HSV	• HSV-1 and HSV-2 (most prevalent serotypes) • Predominantly orolabial (vermillion border) and genital. Occasionally, also seen on buttocks, finger (herpetic whitlow), face, and other sites of contact (herpes gladiatorum) • Vesicles and erosions in a cluster preceded by burning and pain • Primary infection: occurs within a week after exposure. Usually accompanied by symptoms of fatigue, lymphadenopathy, and occasional fevers. Takes 2–6 wk to resolve • Recurrent HSV infections: spontaneous or secondary to stress, UV light, or immunosuppression. Usually takes 7–10 d to resolve and are mild compared with primary HSV • Immunocompromised: tend to have disseminated vesicles and are at risk for systemic involvement. Cutaneous findings: atypical with persistent enlarging ulcerations, as well as verrucous lesions oddly distributed in some cases on the tongue, esophagus, and gastrointestinal mucosa • Disseminated form: also seen in patients with extensive skin barrier breakdown such as eczema	• Diagnostic tests: Tzanck smear, DFA, viral culture, serology and VZV PCR. Biopsy shows viral cytopathologic changes • Recurrent genital herpes: oral acyclovir (800 mg PO bid $\times$ 5d), valacyclovir(1 g PO qd $\times$ 5 d), and famciclovir(1 g PO bid $\times$ 1 d) can be used in immunocompetent hosts. A protracted course is used in the setting of orolabial herpes flare • Immunocompromised: disseminated HSV requires IV acyclovir at 10 mg/kg every 8 h in most cases or 1 g PO bid valacyclovir until all cutaneous lesions have resolved. Foscarnet may be used in resistant cases • >6 episodes a year: chronic suppressive therapy with acyclovir (400–800 mg PO bid to tid), or valacyclovir (500 mg qd to 1 g qd PO bid), or famciclovir (250 mg PO bid) is recommended

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Table 4
(*continued*)

Form of Infection	Clinical Characteristics	Diagnosis and Management
VZV	• Primary varicella infection (chicken pox): prodromal systemic symptoms such as fevers and malaise with subsequent erythematous papulopustular eruption that then progress to vesicles on an erythematous base predominantly on the trunk with significant pruritus. Lesions at a given time can be at any stage of development. The lesions crust over within 10 d. Adults may have systemic complications such as pneumonia • Herpes zoster: prodromal burning pain or itching with subsequent development of clustered vesicles on an erythematous base in a dermatomal distribution usually on the trunk. They seldom cross the midline. Occasionally they can progress to bullae. Elderly or immunocompromised patients may develop postherpetic neuralgia with burning pain in the affected distribution. Pneumonitis and hepatitis occasionally develop • Immunocompromised: can have a more disseminated presentation with more than 20 vesicles outside of the dermatome along with occasional internal organ involvement	• Diagnostic tests: Tzanck smear, DFA, viral culture, serology, and VZV PCR • Biopsy shows viral cytopathologic changes • Varicella zoster immunoglobulin within 4 d of exposure can be considered in immunocompromised and pregnant women along with neonates without previous immunity • Primary varicella infection: acyclovir (20 mg/kg PO qid $\times$ $\times$5 d) or Valacyclovir (20 mg/kg PO tid $\times$ 5 d) is the treatment of choice • Reactivation: valacyclovir 1 g tid $\times$ 7 d with optimal results if treatment is initiated within 3 d of presentation. Oral acyclovir and famciclovir can also be used • Immunocompromised: IV acyclovir10 mg/kg every 8 h for 7-10 days or until lesions healed in some cases • In patients with postherpetic neuralgia, treatment with gabapentin or tricyclic antidepressants should be considered. Topical options include lidocaine creams, and 8% capsaicin patch • VZV live viral vaccine is effective in children • VZV vaccine is recommended for patients older than 60 y to prevent development of zoster and decrease the incidence of postherpetic neuralgia
Bullous impetigo	• Results from *Staphylococcus aureus*–derived local exfoliative toxin, which binds to a desmosomal protein leading to a blister formation. It is the same exfoliative toxin that mediates staphylococcal skin syndrome • It is usually seen in newborns and presents as small vesicles that progress to flaccid blisters that easily rupture leaving a collaret of scale predominantly on the trunk, axillae, face, buttock, and extremities • This is more localized, in contrast with staphylococcal scalded skin syndrome(also seen in children), which presents with diffuse erythema, flaccid bulla with positive Nikolsky sign, positive Asboe-Hansen sign, peeling, and erosions with accentuation in the intertriginous folds and perioral furrowing • Adult patients SSSS are typically more ill and complain of severe generalized skin tenderness. They have a prodrome of conjunctivitis, pharyngitis, and fever	• Culture: blister fluid usually grows *S aureus*. Biopsy shows acantholysis in the granular layer of the skin • Treatment: it usually resolves on its own by 6 wk. Topical antibiotic creams such as mupirocin, retapamulin, or fusidic acid can be used as first line and IV ceftriaxone can be used for complicated cases such as concomitant cellulitis or in patients with poor immunity • In adults, the mortality for SSSS is high and is seen most commonly in immunosuppressed individuals with HIV and renal failure. Isolation of exotoxin A and B may be difficult • Biopsy usually shows intraepidermal split. Blood cultures are positive in adults more often than in children • Toxic shock syndrome and TEN are on the differential • Pneumonia is the most frequent complication

Bullous cellulitis	• Severe cases of cellulitis can actually present with vesicles and bullae overlying the erythematous, swollen, very painful, and poorly defined areas of involvement (usually unilateral) • Systemic symptoms of fatigue and fever typically precede the skin presentation • Most common causes: *S aureus* and GAS • Immunocompromised: mixed flora • Long-term monitoring: renal function for acute glomerulonephritis in the setting of GAS cellulitis	• Mostly a clinical diagnosis • Differential diagnosis: deep venous thrombosis, superficial thrombophlebitis, and stasis dermatitis • Treatment: oral antibiotics in most cases. IV antibiotics (usually reserved for patients with complicated cellulitis) • Recurrent cellulitis: most common in patients with stasis dermatitis. These patients should also be evaluated for interdigital macerations and tinea pedis
V vulnificus	• Vibrio skin infection usually presents with violaceous purpuric macules that progress to hemorrhagic bullae and vesicles that can ulcerate • Severe complications: sepsis and necrotizing fasciitis • It is mostly seen in men more than 40 y of age with exposure of open wounds to warm coastal seawater and/or raw seafood (shellfish) • Risk factors: diabetes, hemochromatosis, cirrhosis, antacid use, renal disease, as well as immunosuppression	• Wound culture: confirms the diagnosis • Pseudomonas infection should be considered on the differential diagnosis • Treatment: combination of doxycycline and IV ceftriaxone. Other alternatives are cefotaxime or ciprofloxacin • Given high mortality from sepsis, prompt empiric treatment within 24 h is indicated • Surgical debridement and occasionally amputation may be needed in severe cases with rapidly expanding bullae
Bullous tinea	• Inflammatory variant of tinea pedis can present with vesicles and bullae, especially on the medial foot • Severe cases may present with a concomitant id reaction/dermatophytid response with poorly demarcated symmetric eczematous patches in distant sites such as the face and extremities	• Fungal culture: *Trichophyton mentagrophytes* (most common) • Treatment: topical antifungal such as econazole or terbinafine cream is usually sufficient. In severe cases especially with id reaction and/or onychomycosis, consider oral antifungals (fluconazole and terbinafine). We recommend avoidance of oral ketoconazole because of inherent greater hepatic risks

Abbreviations: bid, twice a day; d, days; DFA, direct fluorescent antibody; GAS, group A *Streptococcus*; h, hours; HSV, herpes simplex virus; IV, intravenous; Kg, kilogram; mg, milligram; PO, orally; qd, every day; qid; S aureus, staphylococcus aureus; SSSS, staphylococcal scalded skin syndrome; TEN, toxic epidermal necrolysis; 4 times a day; tid, 3 times a day; UV, ultraviolet; VZV, varicella zoster virus; wk, weeks; y, years.

vesicles, but are occasionally disseminated or form bullae in immunocompromised hosts.[3] Tinea pedis (especially zoophilic species such as *Trichophyton mentagrophytes*) can present as vesicles and bullae on the bilateral feet, which can often be confused with ACD from footwear.[32] *Staphylococcus aureus* produces exotoxins against desmoglein-1 that result in bullous impetigo when localized and SSSS when systemic.[31] *V vulnificus* presents acutely with hemorrhagic blisters and sepsis.[11] Treatment and management depend on the type of infection and extent of involvement. Immunocompromised hosts tend to have more extensive involvement and generally require more aggressive therapy.[3]

BULLOUS DRUG ERUPTIONS

This entity consists of different vesiculobullous eruptions seen in the setting of medications, as detailed in **Table 3**.[14,33] Note that although some drug-induced reactions result in cytotoxic or cytokine-induced necrosis of keratinocytes (eg, fixed drug eruption or Stevens-Johnson syndrome [SJS]/TEN), others can result in drug-induced autoantibody-mediated bullous diseases, such as vancomycin-induced linear IgA bullous dermatosis. Management includes discontinuation of the medication along with management of symptoms. Some acute severe reactions, such as SJS/TEN, require an urgent multidisciplinary approach along with ophthalmology and a burn team.[12]

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