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Bullosis Diabeticorum and other Bullous Disorders of the Lower Extremity

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Abstract: Bullous disorders of the lower extremity can present as a diagnostic challenge to the foot and ankle physician due to the wide range of differentials and clinically similar presentations. Bullosis diabeticorum is likely to be encountered due to the large demographic population of diabetics in podiatry clinics. It is important, when diagnosing bullosis diabeticorum, to rule out differentials as there may be high morbidity and mortality associated with delayed or incorrect diagnosis. This article presents two cases of bullosis diabeticorum and reviews the complex list of skin conditions that manifest on the lower extremity and are associated with the development of bullae. The differentials for bullosis diabeticorum comprise bacterial and fungal infections, metabolic and autoimmune disorders, mechanical injuries, variants of dermatitis and papulosquamous rashes.

Key words: Bullae, blister, vesicle, lower extremity, podiatry, dermatology

Bullous disorders of the lower extremity comprise a wide range of disorders, both common and rare, acquired or congenital and can be both with or without significant morbidity and mortality. Sorting through this complex list of differentials can present as a daunting task, but with detailed history taking, clinical analysis and focused laboratory testing, diagnosis is made easier. This article presents two cases of bullosis diabeticorum and additionally reviews the differential diagnosis for bullous disorders that can present in the lower extremity.

Blistering disorders are defined by cleavage of either the epidermis or dermis and can be clinically difficult to distinguish. The severity, prognosis and treatment algorithms vary widely across the spectrum of bullous disorders. When patients initially present, whether as an outpatient or in an emergency department, history taking is a key element to diagnosis. An accurate history can quickly eliminate many of the differentials, sometimes narrowing the options to simply one or two bullous conditions. Some can appear in a quite dramatic fashion; significantly reducing the ability to don shoe gear and limiting function and independent ambulation. Bullous disorders can be inherited conditions while others are acquired via various disease states or lifestyles. Of the congenitally acquired blistering conditions, not all present in childhood. Some manifest later in life and may initially present to a podiatric foot and ankle specialist seeking guidance and treatment on their new onset symptoms. Familiarity with the following entities can help guide treatment, increase pertinent consultation to other specialist providers and overall improve outcomes for patients without delaying therapy. The goal of this article is to review both common and uncommon dermatologic bullae that present on the lower extremity including clinical pearls for accurate identification and treatment.

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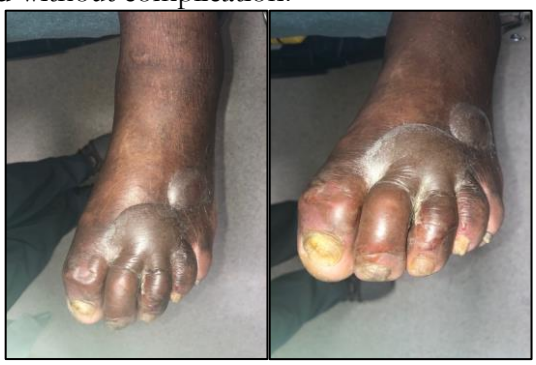
Case One:

Sixty-one-year-old male presents to the Emergency Department (ED) after concerns for new onset blisters and edema to the left forefoot. Volumetric changes noted to the affected foot beginning the day prior to presentation with rapid progression, initiating medical attention. He denied any antecedent trauma, novel drugs, or changes in shoe gear. The patient has a past medical history significant for type 2 diabetes mellitus, chronic kidney disease (CKD) stage three, hypertension, hyperthyroidism, gout with ankle involvement, congestive heart failure and non-ischemic cardiomyopathy.

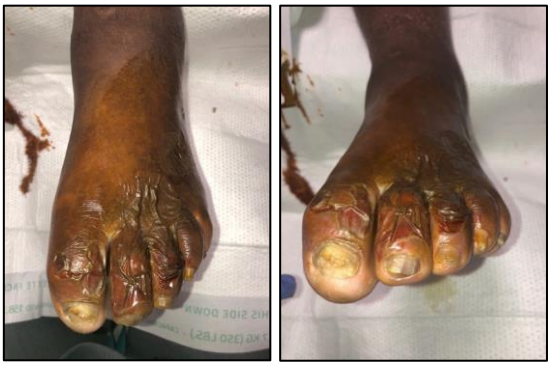
Laboratory values significant for elevated hemoglobin A1c to 11.2% with point of care hyperglycemia to 349 mg/dL. No leukocytosis or elevations in c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) appreciated. Imaging of the left foot revealed only focal soft tissue swelling over the dorsum of the forefoot up to 4.9 cm in length with no acute osseous abnormalities visualized.

Physical examination revealed non-palpable pedal pulses and decreased protective sensation. Tense bulla formation was noted to the dorsal left foot. One large bulla encompassing the dorsal 2nd, 3rd, and 4th digits with extension proximally to the level of the metatarsal heads. A second smaller bulla noted laterally over the lateral 4th and 5th metatarsals. The third, and smallest, bulla was located to the lateral aspect of the dorsal hallux. Negative Nikolsky sign and Asboe-Hanson sign.

The patient underwent blister evacuation with a #11 blade, under sterile conditions, with the roof remaining intact. Local wound care with betadine, non-adherent layer and a dry sterile dressing was performed. At the request of the ED physician, a short course of prophylactic antibiotics was dispensed. The patient followed up in the outpatient setting and the lesions healed without complication.



Figures 1 & 2: Initial clinical presentation in the ED, left foot



Figures 3 & 4: Post drainage, left foot

Case Two:

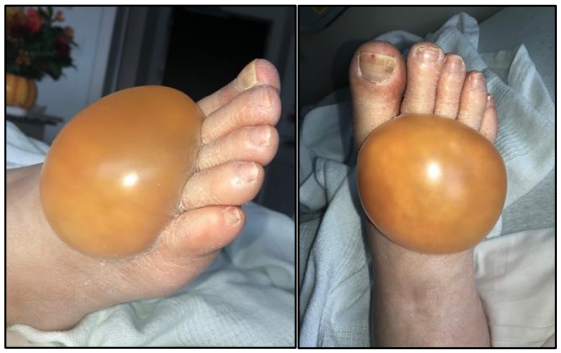
Sixty-seven-year-old female was admitted after transesophageal echocardiogram (TEE) which showed severe bioprosthetic mitral valve stenosis associated with a left atrial thrombus. During admission the patient suddenly developed significant volumetric swelling to the right dorsal foot with multiple foci of blister formation to the left dorsal foot. Unclear time interval from initial incidence to the presentation at evaluation. The patient's husband reported that the bulla was present for several days without any antecedent trauma. She denied any novel drugs and was minimally ambulating due to hospitalization. The patient had a past medical history significant for coronary artery disease (status post coronary artery bypass surgery), mitral valve regurgitation and infective endocarditis with group B-Strep (status post mitral valve replacement), CKD stage 4, hypertension, non-alcoholic steatohepatitis with hepatocellular carcinoma (status post orthotopic liver transplant), esophageal varices, and type 2 diabetes mellitus.

Laboratory examination was significant for a mild leukocytosis of 15.77 with mildly elevated CRP of 1.6. Her most recent hemoglobin A1c was 6.7%. Radiographic imaging of the right foot revealed a large ovoid soft tissue process overlying the dorsum of the foot at the level of the metatarsophalangeal joints (MPJ) without evidence of acute osseous process.

Physical examination revealed non-palpable pedal pulses with protective sensation intact to bilateral feet. Integumentary examination with large bullous lesion with serous fluid contents located to the dorsal right foot with multiple small bullous foci to the dorsal left foot. Negative Nikolsky sign and Asboe-Hanson sign.

Treatment consisted of bedside incision and drainage using a sterile 18-gauge needle with gradual evacuation of the large bullae. The roof was left intact.

Post-evacuation dressings included antibiotic ointment, non-adherent layer and dry sterile dressing. The patient was followed throughout her inpatient stay and the lesions healed without secondary infection or wound complications.



Figures 5 & 6: Clinical presentation, right foot

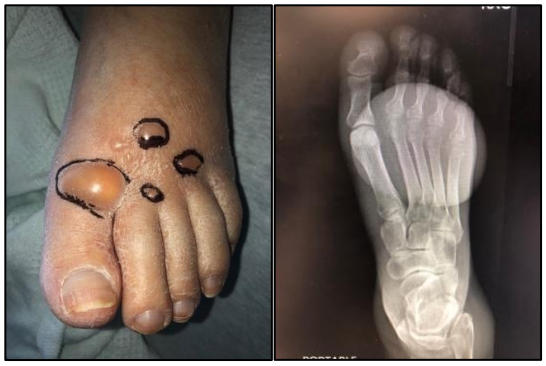


Figure 7: Initial presentation, left foot

Figure 8: Anterior posterior radiograph of right foot

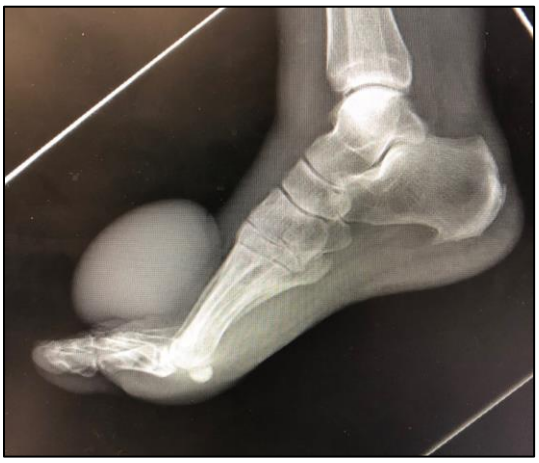


Figure 9: Lateral radiograph of right foot

Bullous Disorders of the Lower Extremity

Blisters of the skin occur when the epidermis or dermis is cleaved from its adjacent anatomical structures. Vesicles, bullae and pustules are the primary skin lesions that correspond to the various classifications of blisters. A vesicle is a well-circumscribed, fluid-filled epidermal elevation that measures less than 0.5 cm in diameter [6]. Vesicles on the plantar surface of the foot may not be raised or palpable as on other areas of the body [6]. A pustule is a vesicle that is filled with purulent fluid, as opposed to serous or hemorrhagic fluid [4]. Bullae are large vesicles, typically measuring greater than 0.5 cm in diameter [5]. Bullae and vesicles can be either tense or flaccid. Tense bullae are more often associated with scarring and are more likely to be subepidermal [17]. Whereas, flaccid bullae are more often intraepidermal in nature [17]. When vesicles or bullae occur on the hands and the feet, they are more likely to develop as tense blisters due to the thickened stratum corneum seen on palms and soles. The fluid within most blisters is either serous or hemorrhagic with hemorrhagic blisters, by definition, involving the subepidermal region of the skin due to the location of blood vessels in the dermis.

There are both internal and external factors that play a role in the development of vesicles and bullae. Some external factors include mechanical trauma from friction or pressure, thermal injuries or chemical reactions. Internal conditions vary from reactions to therapeutic medications, metabolic derangements or congenital pathologies.

Nikolsky's sign is a clinical characteristic unique to very few dermatologic conditions and is defined denudation of the skin with only slight tangential pressure [17]. This sign implies suprabasilar splitting or full thickness epidermal necrosis. Similarly, the Asboe-Hanson sign describes the condition of blister extension as pressure is applied over the top aspect of the blister. This is similar to, but clinically more benign, and is therefore termed the "pseudo-Nikolsky sign".

Bullosis Diabeticorum

Bullosis diabeticorum was first recognized in the early 1900's but has remained an underdiagnosed condition seen in patients with diabetes. The etiology of bullosis diabeticorum is not well understood, but theories consist of enhanced vulnerability to trauma secondary to either neuropathic and/or microangiopathic complications of the disease. Although often documented in association with severe hyperglycemia, current literature has not shown a direct link to patient's glycemic control and incidence of disease [19]. Diabetic bullae are prevalent in approximately 0.5% of the diabetic population, 2x more common in men than in women [19].

Clinically, symptoms of bullosis diabeticorum include spontaneous eruption of large blisters, typically on acral surfaces of the extremities in areas with otherwise normal-appearing skin. Blisters often range in size from a few centimeters to very large bullae. Symptoms are often relapsing and remitting with resolution sometimes as quickly as onset. Classically, the lesions heal without scarring, but risk of secondary infection after rupture can complicate the course.

Diagnosis can be made clinically, but microscopy and histologic evaluation are often used to rule out other, more sinister differentials. Treatment generally consists of supportive care, as bullae usually heal even without intervention in 2-6 weeks. Topical therapy is not required, but topical antibiotics such as mupirocin and bacitracin may be useful prophylactic agents. If blister formation and tissue loss are more extensive with evidence of necrosis, debridement and grafting can be considered. Some providers advocate more aggressive interventions, given the risk of secondary infection in a diabetic patient, however most bullae will spontaneously resolve without complications.

Differentials for bullosis diabeticorum include, but are not limited to bullous erysipelas, Steven Johnson syndrome & toxic epidermal necrolysis, dyshidrotic eczema (pompholyx), bullous lichen planus, fracture & friction blisters, bullous pemphigoid, pemphigus vulgaris, porphyria cutanea tarda, pseudoporphyria and epidermolysis bullosis acquisita.

Bacterial & Fungal Infections

Bullous Erysipelas

Erysipelas, aka St. Anthony's Fire, is a superficial form cellulitis caused by beta hemolytic streptococci, most commonly *Strep. pyogenes*. Classically, erysipelas is seen on the legs, as well as the face, with induration, erythema and edema, often associated with fevers, chills and ascending lymphangitis. This series of symptoms make erysipelas very difficult to distinguish from cellulitis. Approximately 5% of cases are complicated by bullous involvement with flaccid intraepidermal blisters that are more frequently seen in patients with liver or renal disease and with a higher prevalence in women [7]. Additionally, bullous erysipelas shows increased rates of superinfection with methicillin sensitive *Staph. aureus* (MSSA) or methicillin resistant *Staph. aureus* (MRSA).

Diagnosis is often a process of elimination, excluding pathologies such as cellulitis, allergic contact dermatitis, bullous pemphigoid and necrotizing fasciitis [7]. Fluid culture is often performed, but with statistically low yield. Treatment of erysipelas is frequently a combination of antibiotic therapy with superficial debridement, compression therapy and draining of bullae. However, bullous erysipelas represents a more aggressive form of the infection and typically is more resistant to therapy. High recurrence rates, upwards of 30% within 3 years, are often attributed to lymphatic obstruction [7].

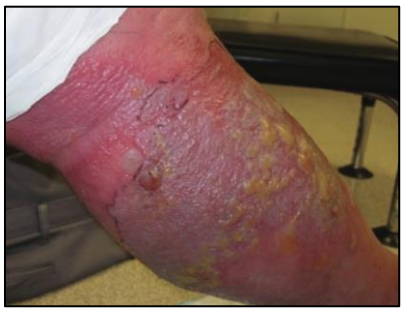


Figure 10: Bullous Erysipelas [7]

Drug-Induced

Steven Johnson Syndrome / Toxic Epidermal Necrolysis

Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) exist on the same pathologic spectrum of a severe drug-induced rash with associated vesicles and bullae. The condition is seen with mucosal and cutaneous lesions that result in an acute macular, erythematous rash with scattered 2-ring-target-like lesions [16]. The cutaneous manifestations are seen in sun-exposed areas beginning on the trunk and spreading to the neck. The limbs are often spared; however, the palms and soles are frequently affected. Both SJS and TEN exhibit Nikolsky's sign where gentle tangential pressure to the skin causes sloughing and bullae formation with total epidermal loss within 24 hours [16]. SJS is classified as cutaneous involvement of less than 10% total body surface area with TEN involving greater than 30% total body surface area and an overlap of SJS and TEN between 10-30% total body surface area.

The pathologic mechanism of action is characterized by a delayed hypersensitivity reaction with cell mediated cytotoxicity and increased expression of tumor necrosis factor – alpha (TNF-$\propto$) and interferon – gamma (IFN-γ). A prodromal phase of symptoms mimicking an upper respiratory tract infection is followed by epidermal detachment, bullae and erosions approximately 1-3 weeks after the introduction of a drug.

Common inciting medications include antibiotics such as trimethoprim-sulfamethoxazole, ciprofloxacin, the penicillins, and vancomycin; NSAID's such as meloxicam; the antiepileptic drug carbamazepine; and allopurinol [1]. It is believed that there is a strong genetic predisposition to either SJS or TEN via the human leukocyte antigen (HLA) system. Rates of frequency vary with the medication in combination with ethnic background and genetic viability.

Histologic analysis of SJS/TEN shows necrosis of keratinocytes allowing for vacuolization and formation of subepidermal bullae. There are currently no specific tests to link a particular drug to the clinical manifestations of SJS/TEN especially given extended prodromal period and polypharmacy commonly seen in the majority of patients.

Both SJS and TEN have high rates of morbidity and mortality. Nearly 50% of all cases lead to acute respiratory failure requiring intubation and mechanical ventilation with upwards of 60% complicated by secondary infection [1]. The mortality for SJS is around 5%, where TEN has a mortality rate closer to 15-30% [1]. Long term sequela includes ocular complications, oral complications such as sicca syndrome, and cutaneous complications including hyperpigmentation, hypopigmentation, keloid scaring, nail dystrophy, chronic pruritus, photosensitivity, hyperhidrosis and heterotopic ossification [1, 16].

Treatment for SJS/TEN is immediate discontinuation of the inciting medication along with supportive care. Typically, these patients are treated in a burn unit rather than intensive care or the regular nursing floor. Some medications that have been used with conflicting results include corticosteroids, plasmapheresis, TNF-$\propto$ inhibitors and IVIG therapy. Wound care is critical in these patients, as cutaneous complications can be severe. Blister evacuation, topical wound care and regular dressing changes can improve outcomes.

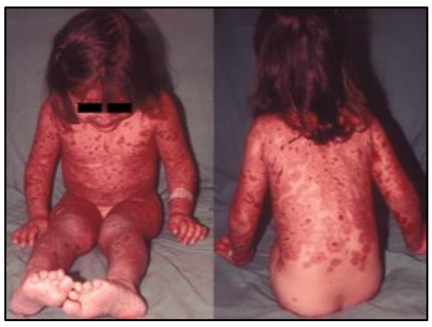


Figure 11: Steven Johnson Syndrome [1]

Dermatitis

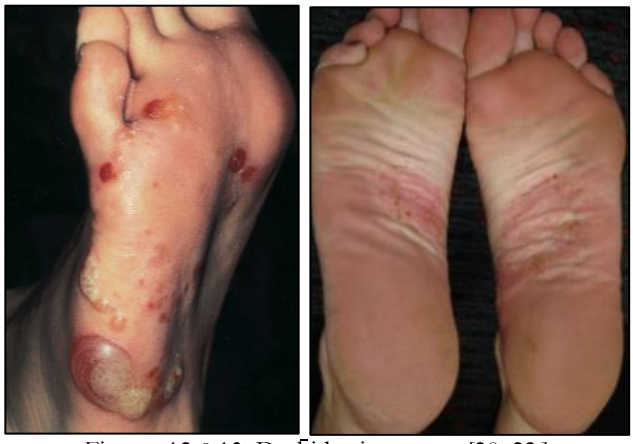
Dyshydrotic Eczema (Pomphylox)

Dyshydrotic eczema also known as pompholyx is an idiopathic skin condition that symmetrically affects the hands and feet. It is characterized by pruritic red/pink lesions that are round and flat but can often progress to bullous lesions [20]. It generally begins with mild itching and increased sweat to the affected extremity. In severe cases vesicles can coalesce to large bullae that are fragile and prone to drainage. The bullae can be quite large and dramatic, forming acutely and lasting approximately 7-10 days.

Pompholyx is often seen in adults and teenagers and is more common in the summer months or in individuals who work in hot, humid conditions [9]. Women are more commonly affected than men and an increase in incidence is seen in patients under significant stress. Additionally, 50% of patients have underlying history of atopy [20]. Other risk factors or aggravating factors include skin irritants, some drugs and contact allergens such as metallic products made of nickel, Rhus toxicodendron (poison ivy), or rubber in shoe gear. For this reason, along with the clinical characteristics, pompholyx may be confused with irritant contact dermatitis. In such cases, patch testing can be performed to clarify the diagnosis [25].

Pompholyx can also be difficult to differentiate from the bullous variant of tinea pedis. [20]. The usual fungal culprit for bullae formation in tinea pedis is *Trichophyton mentagrophytes*. When trying to differentiate between bullous tinea and pomphylox, potassium hydroxide (KOH) scrapings and visualization under a microscope can aid in diagnosis.

Treatment of pompholyx requires targeting the underling pathogenic process as well as a combination of systemic and topical therapies. The goal of treatment should include decreasing bullous eruptions, relieving any remaining pruritis and burning sensations, prevent secondary infection and decrease sweating. Topical steroids, that are moderately potent are the mainstay of treatment and are used to penetrate the thick epidermis of the feet [20]. In severe or refractory cases, immunosuppressants may be initiated. Other treatments include the avoidance of irritants or allergens and solutions to decrease sweating including cotton socks and alternating shoe gear.



Figures 12 &13: Dyshidrotic eczema [20, 22.]

Papulosquamous Diseases

Bullous Lichen Planus

Lichen planus is a common inflammatory skin condition that is classically presents as pruritic, purple, polygonal papules and plaques. It often affects the skin, nails, hair and mucous membranes. Many variants of LP exist including, but not limited to, oral, linear, atrophic, hypertrophic, ulcerative, and bullous. Bullous lichen planus (BLP) is a rare variant generally seen as tense bullae surrounded by the typical violaceous LP lesions [31].

BLP is caused by autoimmune mediated lysis via activation of CD8+ cells targeting the basal cell layer resulting in vacuolization [15, 31]. The exact prevalence is unknown, but lichen planus is estimated to affect between 0.5-1% of people, with an increased incidence in adult females [31]. Most diagnoses of lichen planus are made in adulthood, but approximately 5-10% of cases present in children [31]. Generally, the disease is sporadic, but lichen planus can often be associated with comorbidities including hepatitis C, primary biliary cirrhosis and other chronic liver pathologies, viral and bacterial antigens as well as numerous autoimmune diseases [31]. Familial forms BLP have been described in literature. These inherited conditions are associated with prolonged course, increased morbidity and younger age of onset [15].

In terms of distribution, many areas of the body can be affected, but the flexural surface of the legs is the most common site [31]. Other common locations include the dorsal hands and feet, and the trunk. Familial BLP mainly targets the upper and lower extremities with frequent involvement of the nails. In addition to bullae formation, Whickham's striae can be seen as white streaks that form adjacent to dry, shiny surfaces.

Microscopic evaluation of lichen planus lesions shows hypergranulosis of the epidermis with hyperkeratosis and the classically described "sawtooth" acanthosis of rete ridges [15, 31]. Increased Langerhan's cells are seen near the dermo-epidermal junction and colloid bodies are found in the lower dermis [15]. These features are consistent in the bullous variant as well.

Treatment goals are significant for early resolution and reducing of symptoms specifically bullous formation and pruritis. There is currently no established guideline for treatment, but topical corticosteroids are often used first line with generally successful results. In refractory cases, or when corticosteroids are contraindicated, other options include retinoids, metronidazole, psoralen plus UVA (PUVA), mycophenolate mofetil, and iontophoresis [31].

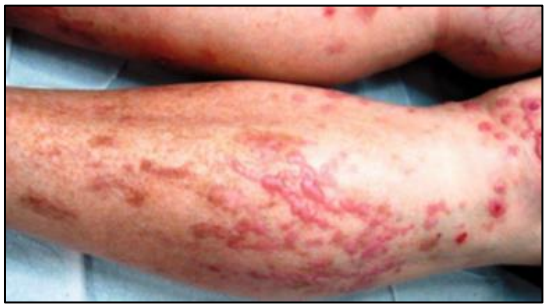


Figure 14: Bullous Lichen Planus [15]

Mechanical Injuries

Friction Blisters

Friction blisters are due to separation of the epidermis from the dermis and delamination of the stratum spinosum caused by pressure and shear force. Although often regarded as a minor injury, friction blisters can become a major irritation to active individuals. Friction blisters are common. Reported rates among hikers and backpacker ranges from 54-86%, military personnel report rates from 5-77% and marathon runners develop blisters approximately 26-76% of the time [32]. Risk factors include, but are not limited to moisture imbalance, temperature, duration of activity, features of shoe gear and external load [32].

Treatment of friction blisters includes reducing pain, encouraging healing and preventing infection [12]. Although treatment is an important part of blister care, significant effort is put into prevention of blisters. Prevent strategies include any combination of reduction of the coefficient of friction, pressure or

shear force. Some options include sock layers, tape barriers, antiperspirants, lubricants and orthotics [32]. Despite the many options available, no widespread consensus exists on either the prevention or treatment of friction blisters.

Fracture Blisters

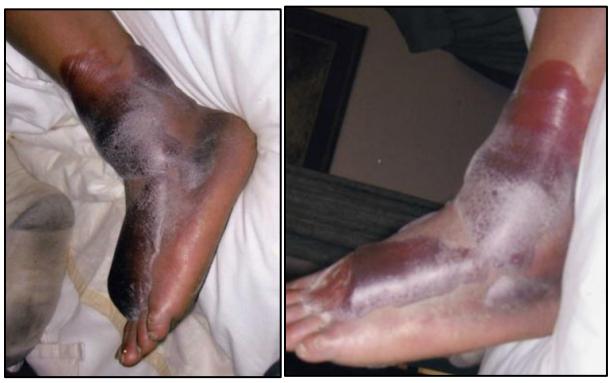
Fracture blisters form following traumatic events, especially when injuries occur in anatomic locations that lack a significant soft tissue envelope. Such locations most commonly include the ankle, wrist, elbow, foot and distal tibia. When a large strain is applied to the skin during high-energy injuries, localized tissue hypoxia and cellular cleavage result in the separation of the dermal-epidermal junction. This pattern of tissue injury results in the formation of either serous or hemorrhagic bullae. Additional forces from increased interstitial pressure and post-traumatic edema also contribute, facilitating fluid transport into the blister cavity. Although commonly associated with friction blisters, fracture blisters tend to more closely resemble second degree burns in their clinical and histologic presentation. The typical time frame for blister formation is 6 hours post injury but can develop up to 24-48 hours after the index event.

Of all fractures that require hospitalization, fracture blisters occur at an incidence of 2.9% [26, 29]. In addition to anatomic location, other risk factors include comorbidities such as peripheral vascular disease, collagen vascular disease, hypertension, smoking, alcoholism, diabetes mellitus and lymphatic obstruction. High energy injuries are more prone to development of fracture blisters which include events such as motor vehicle collisions, falls averaging 18 feet or higher and Gustillo Anderson grade I and II open tibia fractures.

Serous fracture blisters represent only a partial separation of the dermal-epidermal junction with minimal injury to the dermis. Some of the epidermal cells remain attached allowing for faster healing and re-epithelialization typically within 12 days.

Hemorrhagic fracture blisters exhibit complete separation of the dermal-epidermal junction where the dermis is stripped of epidermal cells. These bullae are more severe than that of serous bullae and are associated with increased morbidity and extended healing times to around 16 days. [26, 29].

Fracture blisters can complicate the course of treatment for traumatic injuries due to soft tissue compromise. Incisions made through blister beds often lead to worse post-operative outcomes including wound dehiscence, surgical site infections and prolonged hospitalization. This is especially true for hemorrhagic bullae. Optimal treatment for fracture blisters can be controversial, but all options revolve around the mitigation of complications associated with skin integrity. In general, early surgical fixation of fracture sites to prevent blister formation is ideal, however if bullae are already present, most advocate for allowing resolution of the blisters prior to surgical intervention.



Figures 15 & 16: Fracture blisters [29]

Metabolic and Autoimmune Disorders

Bullosis Pemphigoid

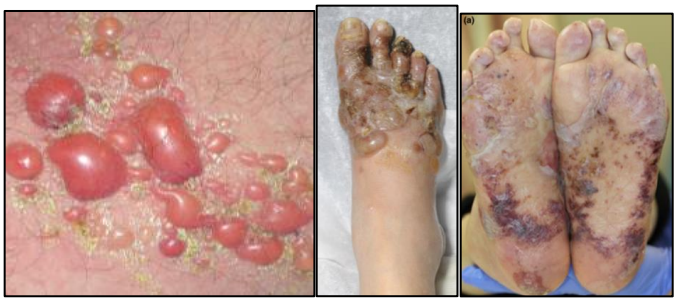
Bullous pemphigoid (BP) is part of the family of autoimmune blistering conditions and is defined by antibodies directed at a collagen component of the dermal basement membrane [13, 17]. Most cases of BP are idiopathic, but known triggers exist to exacerbate or incite the pathogenesis including trauma, burns, radiation (ultraviolet, ionizing or x-ray), underlying neurologic conditions and various medications. Reported cases have been associated even with the trauma of surgery with BP development seen at surgical sites, venous access sites and amputation stumps [24].

Bullous pemphigoid is an acquired condition which becomes more common with increasing age. The majority of patients present over the age of 80 and BP is rarely seen under the age of 50 [13, 18]. The estimated global incidence is 7-14 cases per one million people per year [24]. BP can be acute, but more frequently BP is seen as a chronic condition with relapsing and remitting episodes. Although BP is generally self-limited, mortality is double that of the general population which may be due to secondary complications, generalized older age and the long-term use of steroids as treatment [24].

Clinically, the early stages of BP include pruritus and urticaria with bullous formation that

develops over weeks to months. Flexural surfaces tend to be favored locations, especially confined to the lower extremity, but the abdomen, forearms or even widespread distribution can occur. Bullae formation consists of tense, intensely pruritic crops of lesions that are resistant to rupture and may heal with post-inflammatory hyperpigmentation. This is in contrast to that of pemphigus vulgaris, which exhibits fragile, flaccid bullae that rupture easily.

Diagnosis of BP is made via histologic examination with direct immunofluorescence showing antibodies congregating at the basement membrane. On pathology polymorphous inflammatory infiltrate is seen with a predominance of eosinophils lining up at the basement membrane [24]. The goal of treatment for BP is to promote healing of cutaneous lesions and suppress disease activity at the lowest effective dose [24]. The most common medical therapies include systemic corticosteroids, anti-inflammatory agents and immune suppressants. Currently the mainstay of treatment includes Prednisone, alone or in combination with a steroid sparing agent [18].



Figures 17, 18 & 19: Bullous Pemphigoid [18, 28, 11]

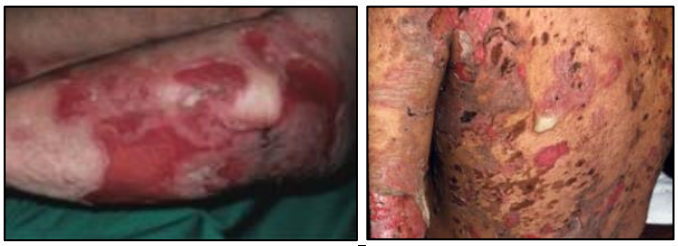
Pemphigus Vulgaris

Pemphigus Vulgaris (PV) a mucocutaneous autoimmune blistering disease that typically affects the mouth but can occasionally affect the non-mucous membranes including the lower extremities. Autoantibodies are directed against a portion of desmosomes called desmoglein 1 and 3. Dysfunction in these proteins results in the loss of cellular adhesion in the epidermis ultimately manifesting as intraepidermal blisters. Bullae in PV are typically flaccid in nature. Clinically, patients often present to a dentist or oral surgeon with complaints of sore throat, painful oral cavity or hoarseness.

There is a genetic component associated with PV more commonly seen in ethnic groups such as, Ashkanezi Jews and those of Mediterranean descent. Age of onset is generally between the ages of 40-60 years. PV is most often fatal without treatment, but with the introduction of corticosteroids, PV can vary in duration from a chronic course to complete remission.

As with other autoimmune blistering conditions, diagnosis is made via histopathology and direct immunofluorescence in addition to historical and clinical data. Classically PV exhibits suprabasilar acantholysis with "tombstone" keratinocytes on the basement membrane. Acantholysis is the pathologic term designated for the loss of cellular adhesions targeted by the active antigens in PV. On direct immunofluorescence, intracellular IgG in the epidermis has been described as a "chicken wire fence" and is considered the gold standard for diagnosis.

Treatment for PV is largely the same as for BP including topical and systemic steroids. Although due to side effects of long-term use, steroid-sparing agents have surged in popularity. Because PV has significant morbidity and mortality, a consolidation phase of treatment is followed by a maintenance period. The consolidation phase aims for the optimal medication dosing necessary until the lesions are healed, while the maintenance phase is used to down titrate to the lowest dose necessary to prevent outbreaks. Other options for treatment include antibiotics such as those in the tetracycline class, nicotinamide (active form of vitamin B3), immunosuppressants, Rituximab, and IV immunoglobulins. These other agents have mixed success in literature with limited conclusive recommendations and are typically combined with some form of steroid agent.



Figures 19 & 20: Pemphigus Vulgaris [13, 3]

The Porphyrias

The porphyrias are defined as an enzyme deficiency in the heme pathway resulting in the accumulation of porphyrin precursors in the bone marrow or liver. The various forms of porphyria are classified by the specific enzyme that is deficient in the heme pathway. There are many forms of porphyria including congenital and acquired presentations which can vary in inheritance patterns and clinical manifestations. Two forms of porphyria that classically

exhibit bullae formation are porphyria cutanea tarda (PCT) and pseudoporphyria.

Porphyria cutanea tarda is the most common of all the porphyrias and is classified as a deficiency in the enzyme uroporphyrinogen decarboxylase. Likely, PCT results from an autosomal dominant inherited gene, but can also be a byproduct of sporadic mutation or even acquired inhibition. There are many risk factors that can lead to acquired inhibition or can worsen clinical presentation of an already inherited defect. PCT has a strong association with hepatitis C and can be triggered by other viruses such as human immunodeficiency virus (HIV). Other comorbidities that increase risk include hereditary hemochromatosis and Sjogren's syndrome. Exogenous triggers can include alcohol use, chemotherapy agents, estrogens and others.

Although PCT is the most common of the porphyrias, the global prevalence is still relatively uncommon. Around 1 in every 10,000 people exhibit PCT with nearly equal sex ratio between men and women [10]. However, this prevalence is demographic dependent, more commonly occurring in regions such as Slovakia and the Czech Republic [10]. Clinically, PCT presents as subepidermal blisters and bullae in sun exposed areas including the dorsum of the hands, forearms, face, legs and feet. Rupture of the bullous manifestations often leads to atrophy and scarring. Other clinical characteristics include erosions, milia, scaring alopecia, hypertrichosis on the cheeks and temples of women and sclerodermoid changes with waxy yellow plaques.

PCT is diagnosed via histologic and immunofluorescent examination. On direct immunofluorescence IgG and C3 clump around the dermal epidermal junction and papillary dermal vessels creating "caterpillar bodies" otherwise termed "festooning of dermal papillae" [10, 17]. Gross examination of urine can also be carried out with the use of a Wood's lamp. The urine of patients with PCT will glow a pink-red fluorescence. First line diagnostics include spectrophotometric scanning of acidified urine [10]. Treatment for PCT includes phlebotomy and medical management with antimalarial medications. The goal of regular phlebotomy is to reduce hepatic iron stores. This is typically achieved by letting one unit of blood per two-week increment. This will gradually result in improved skin fragility and reduced blistering. Chloroquine or Hydroxychloroquine are options for medical management when phlebotomy is not an option.

Pseudophorphyria, also known as pseudoporphyria cutanea tarda is clinically and histologically identical to PCT but differs in pathologic origin. Whereas PCT is an enzymatic deficiency in porphyrin metabolism, pseudoporphyria is thought to be caused by free radical formation secondary to increasing UV light exposure. The free radicals produce cellular damage resulting in the clinical manifestations of photosensitivity, bullae, vesicles and skin fragility. Pseudoporphyria only rarely presents with the hypertrichosis, sclerodermoid changes and hyperpigmentation that are so commonly seen with PCT. Additionally, pseudophorphyria has often called the "drug induced PCT" because it is often exacerbated by various medical therapies. The drug-induced phenomenon is most often seen in patients with chronic kidney disease and is associated with non-steroidal anti-inflammatory drugs (NSAIDs), diuretics such as furosemide and antibiotics like the tetracyclines. Of note, a link between pseudoporphyria and "detoxifying" health supplements containing chlorophyll has also been suggested.

Diagnosis of pseudoporphyria reveals normal levels of serum porphyrins and does not yield the same urine fluorescence as PCT. However, it appears identical to PCT on histology and can often be difficult to distinguish by pathology evaluation alone, making the clinical correlation important for diagnosis. Treatment of pseudoporphyria is treated similarly to PCT in addition to the elimination of the source or underlying trigger.

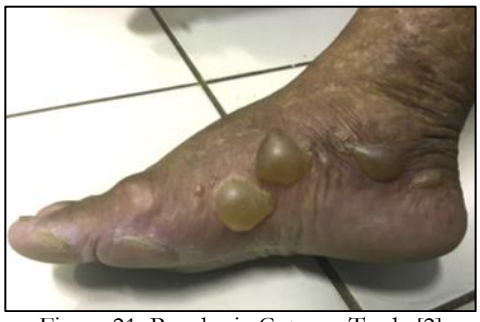


Figure 21: Porphyria Cutanea Tarda [2]

Epidermolysis Bullosis Acquisita

Epidermolysis bullosis acquisita (EBA) is another of the autoimmune blistering conditions that typically presents with vesicle and bullae formation more commonly on the skin, but, less commonly, can present as erosions on mucous membranes. There are three main subtypes of EBA, an inflammatory or non-mechanobullous type (55% of cases), classical or mechanobullous type (38% of cases), and a

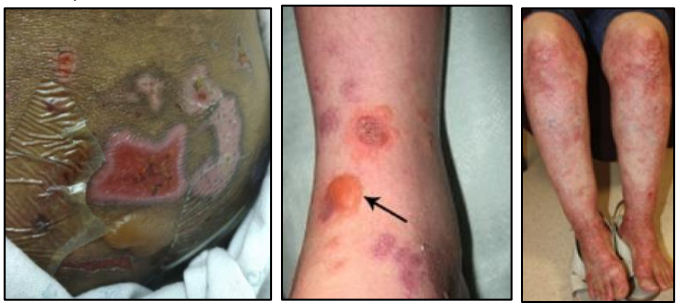
combination of the two (7% of cases) [14]. A genetic predisposition exists in association with the HLA system and includes autoantibodies directed at type VII collagen [14].

EBA is a rare condition with 0.08-0.5 new cases per one million people per year [14]. Males and females are equally affected, and the median age of incidence is 50 years with a bimodal peak around the first three decades and the seventh to eighth decades of life [14]. Due to the genetic component, these patients often have comorbid conditions such as inflammatory bowel disease, another autoimmune blistering condition, psoriasis or rheumatoid arthritis.

The mechanobullous type clinically presents with skin fragility and blisters seen on extensor surfaces and areas prone to trauma. Nail dystrophy, scarring and milia are common complications. Mild cases of the mechanobullous type appear very similar to PCT [14]. Whereas, the non-mechanobullous type manifests as vesicles and bullae on the trunk, flexural surfaces and intertriginous areas [14]. This subtype typically heals without scarring or milia and is more likely to present with urticarial skin and erythema. The non-mechanobullous type is known to mimic other conditions such as bullous pemphigoid.

Many diagnostic avenues exist for EBA given its ability to mimic other conditions, but the most common route is a combination of clinical presentation with histopathology and direct immunofluorescence. Autoantibodies are seen bound to the basement membrane zone and directed against type VII collagen on histological exam. Other diagnostic methods include ELISA, fluorescence overlay antigen mapping (FOAM), immunoelectron microscopy and immunoblot assays.

Treatment for EBA is challenging due to rarity of the condition in combination with lack of evidence-based medicine to back up treatment protocols. Common therapies include neutrophil targeting therapies such as colchicine, dapsone, and minocycline; immunosuppressives such as mycophenolate mofetil; IVIG; and rituximab.



Figures 22, 23 & 24: Epidermolysis Bullosa Acquisita [14, 8, 23]

Discussion and Conclusion

Dermatologic pathologies that involve vesicles and bullae encompass a diverse group of disorders. Physical exam findings alone can make diagnosis a daunting task as many of these skin conditions may mimic or even present identical to some of the others. This manuscript discusses a multitude of bullous disorders but is by no means the extent of all bullous and vesicular skin conditions. Variants and atypical presentations of traditionally non-bullous disorders secondarily broadens the pool of potential diagnoses. This can be an overwhelming task for even the experienced diagnostician.

Although bullosis diabeticorum is self-limited and benign, there are other bullous conditions of the lower extremity that may cause significant morbidity or potentially life-threatening consequences if not diagnosed in a timely manner. Using the lower extremity as a reference, a more manageable set of differentials can be achieved by ruling out those that present elsewhere on the body. Accurate history including timeline of events, pertinent past medical history, medication reconciliation and genetic profile are critical tools for additional consideration. When a patient presents to the podiatric physician with a new onset bullous condition, it is imperative to have a low threshold for consultation for collaborative therapeutic benefit and positive outcome for the patient. Some important references wound include specialties such as dermatology, rheumatology, and plastic surgery.

As podiatric physicians, treating diabetic patients has become a precedent. The growing prevalence of diabetic patients continues to inform our expertise in the area of diabetic extremity pathologies. The ability to identify bullosis diabeticorum and rule out other bullous disorders of the lower extremity is just another way to fine-tune our expertise on the diabetic foot.

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