READING HEALTH SYSTEM
Advancing Health. Transforming Lives.

Bullous pemphigoid: a review of literature with principal focus on updates regarding medications that induce disease

Payvand Kamrani D.O., Kate Braunlich, D.O.

Objective

- To provide physicians a comprehensive up-to-date list of classes of medications that may induce bullous pemphigoid and should be avoided in patients with a history of bullous pemphigoid.

Introduction

- Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disorder.[1,2] It is an antibody-mediated disease belonging to the pemphigoid group, a family of diseases known to cause blistering of the skin and mucous membranes.
- BP is often considered a chronic disease with spontaneous exacerbations and remissions accompanied by significant morbidity.[3]
- Drug-induced bullous pemphigoid (DIBP) describes the development of bullous pemphigoid (BP) in association with the ingestion, or topical application of medication. Unlike classic BP, DIBP is often characterized by a younger age of onset, positive Nikolsky sign, target lesions on palms and soles and peripheral eosinophilia.
- Overall, DIBP can be a daunting subject, as many patients are on a multitude of medications at the time of disease onset. Polypharmacy creates a conundrum when trying to delineate the specific medication notable for the disease and what medications to avoid in patients with a prior history of BP.

Clinical Features

- The clinical presentation of BP can be polymorphic with a broad spectrum of presentations. Generally, there are two phases – the non-bullous and the bullous phase.[3,13]
- The non-bullous phase consists of non-specific signs and symptoms such as mild to severe pruritus with eczematous or urticarial plaques. Pruritus may even be the only presenting symptom of the disease.
- The bullous phase consists of the development of tense vesicles and bullae on urticarial or erythematous plaques. It is important to remember patients may not present with blisters due to rupture prior to evaluation

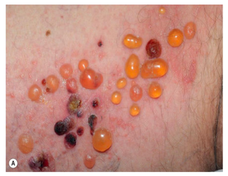

Figure 1. Bullous pemphigoid Bullous presentation

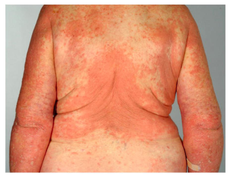

Figure 2. Bullous pemphigoid Urticarial presentation

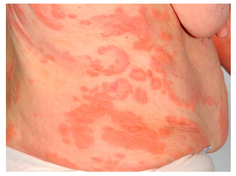

Figure 3. Bullous pemphigoid Eczematous presentation

Methods

Data for this review was defined by advanced searches of PubMed. We also reviewed the reference lists of articles identified by our search strategy and selected relevant manuscripts. Additionally, we have cited book chapters to provide readers with a full and inclusive list of references. The medications listed within this review had to meet the following criteria: available for prescription in the United States as of January 2020. Our approach is to first highlight the historic medications and then provide information regarding the more recently identified medications.

Results

Table 1: Emerging Medications Associated with DIBP [19,38-43, 44-50,52,54]

Category	Medications
DPP4 inhibitors	Sitagliptin, Linagliptin, Alogliptin, Saxagliptin
Anti-PD-1/PD-L1	Pembrolizumab, Nivolumab, Durvalumab, Atezolizumab
CTLA-4 inhibitors	Ipilimumab, Tremelimumab
TNF-alpha inhibitors	Adalimumab, Etanercept

Abbreviations: DPP4, dipeptidyl peptidase 4; Anti-PD-1/PD-L1, programed cell death 1 and programmed death ligand 1 inhibitors; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; TNF-a, Tumor necrosis factor alpha

Table 2: Historic Medications Associated with DIBP [3,5-7,13,19,33,37]

Category	Medications
Diuretics	Furosemide, Bumetanide, Hydrochlorothiazide, Spironolactone
Antibiotics	Amoxicillin, Ampicillin, Amoxicillin, Ampicillin, Cephalexin, Ceftriaxone, Cefepime, Ciprofloxacin, Levofloxacin, Clindamycin
Anti-hypertensives	Captopril, Enalapril, Lisinopril, Metoprolol, Losartan, Clonidine
Analgesics	Acetaminophen, Hydrocodone, Diclofenac, Ibuprofen, Aspirin
Vaccines	influenza, swine flu, tetanus toxoid and herpes-zoster-virus

Table 3: Differential for Autoimmune Tense Bullae [3,7,13]

Disease	Clinical Features	Diagnostic clues
BP/DIBP	Elderly (>70), pruritic disease characterized by tense, fluid-filled vesicles/bullae on an urticarial base. Oral involvement 10-30%, peripheral eosinophilia 50%	H&E: subepidermal blister with eosinophils DIF: linear BMZ C3 (95%) and IgG (80%) IIF (ideal substrate: salt split normal human skin, not patients): stains to the roof/epidermal
Epidermolysis bullosa acquisita [EBA]	Noninflammatory, trauma-induced bullae. + skin fragility. Heal with scarring and milia.	H&E: non-inflammatory subepidermal split DIF: linear IgG at BMZ IIF (ideal substrate: salt split normal human skin, not patients): stains to the base/dermal side
Linear IgA (LABD)	Often recent history of vancomycin. Can present with urticaria or oral lesions but, frequently the vesicles/bullae are annular, “crown of jewels” favoring intertriginous sites	H&E: subepidermal blister with neutrophils DIF: linear IgA at the BM 100% IIF (ideal substrate: salt split normal human skin, not patients): stains to the epidermal side
Chronic Bullous Disease of Childhood (CBDC)	Child with “crown of jewels” annular vesicles/bullae typically on the groin/lower extremities	H&E: subepidermal blister with neutrophils +/- eos DIF: linear IgA IIF: circulating IgA in ~50%

Abbreviations: BP/DIBP, bullous pemphigoid/drug induced bullous pemiphigoid; H&E, hematoxylin & eosin; BMZ, basement membrane; DIF, direct immunofluorescence; IIF, indirect immunofluorescence

Emerging medications associated with DIBP

– **Dipeptidyl peptidase 4 (DPP4) inhibitors,** anti-hyperglycemic agents, are used to treat type 2 diabetes mellitus. DPP4 inhibitors can enhance eosinophil recruitment into the dermis and alter the antigenic properties of the basement membrane.[19] Keratinocytes also express DPP4.[6] These factors may explain the causative role of in the development of DIBP.

– **Programed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors** serve as check-point inhibitors by blocking the PD-1/PD-L1 pathway. PD-1/PD-L1 inhibitors induce an antitumor response by reversing T-cell suppression and thus, provide a clinical benefit in the treatment of advanced malignancy.[44,45] A consequence to these promising immunotherapies is non-specific activation of the immune system which can result in therapy-induced cutaneous toxicity.

– **Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors**, checkpoint inhibitors, induce sustained immune-mediated antitumor activity by removing inhibition of the immune system.[50] cutaneous toxicities appear to be one of the most prevalent adverse reactions associated with CTLA-4 inhibitors.

– **Tumor necrosis factor alpha (TNF-alpha) inhibitors** are commonly used by dermatologists. With increasing use comes increasing responsibility to be knowledgeable of the emerging side effects. The question remains whether the observation of anti-TNF-alpha therapy induced BP is coincidental, the result of immunologic activation or a different cause entirely. [19,52,54]

Conclusion

•The diagnosis of DIBP is crucial for early management and improvement in patient’s quality of life.

•DIBP can be easily overlooked which carries significant implications including prolonged treatment with the causative medication.

•We recommend a multidisciplinary approach with the support of primary care physicians, oncology and the associated prescribing specialist with identification of the culprit medication.

•In time, we hope more studies on this subject will be performed to help patients and physicians further delineate the most likely causative agents of DIBP.

References

Please scan this code with your smart phone to get a full list of all references used for this review.

Payvand Kamrani and Kate Braulich have no financial disclosures.

Contact Info:
Payvand Kamrani, D.O.
PGY-1, Reading Hospital
payvand.kamrani@towerhealth.org