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Rashes and other hypersensitivity reactions associated with antiepileptic drugs: A review of current literature

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ABSTRACT

This article provides an overview of the pathogenesis and risk factors associated with antiepileptic drug (AED) hypersensitivity reactions, provides prescribing guidelines that may minimize the risk of antiepileptic induced rashes, and discusses treatment options for rashes. Articles indexed in PubMed, Science Citation, and Google Scholar (January 1946–March 2019) were systematic searched using the following key terms: hypersensitivity, rash, antiepileptic, epilepsy, cross-sensitivity, desensitization, patch testing and supplemented with our clinical experiences. Additional references were identified from a review of literature citations. AEDs are associated with cutaneous adverse reactions. Aromatic AEDs and higher titration rates are associated with increased risk of hypersensitivity reaction. Patient characteristics, underlying health conditions, and genetic variations may increase the likelihood of a hypersensitivity reaction. Once a hypersensitivity reaction occurs, the likelihood of cross sensitivity to another AED increases, especially among other aromatic AEDs. Withdrawal of the causal agent and initiation of a lower risk agent usually leads to resolution of symptoms. Desensitization protocols may be an option for patients whose seizures only respond to the AED causing the rash.

1. Introduction

Antiepileptic drugs (AEDs) are associated with rashes and other hypersensitivity reactions. The incidence varies depending on the type of rash, the AED used, and the previous history of rash with quoted incidences ranging from 1.7 to 8.8%. Drugs with the greatest risk include phenytoin, carbamazepine, oxcarbazepine, and lamotrigine, while several other AEDs have a risk $<1\%$ [1,2]. AEDs are commonly used in adult and pediatric patients with epilepsy (PWE), pain, and behavioral health problems [3]. It is important to understand the rash risk of various AEDs and be able to recognize the difference between mild and more serious rashes that need immediate attention and discontinuation of therapy. In the last decade, genetic tests have been introduced to identify patients with increased risk for hypersensitivity reactions to specific seizure drugs. In this review we provide an overview of the clinical presentation, pathogenesis, risk factors, treatment for rash, management of seizures, and guidance on a desensitization protocol.

2. Methods

PubMed, Science Citation, and Google Scholar literature were systematically searched for articles ranging from January 1946 – March 2019. The following key terms were searched: hypersensitivity, rash, antiepileptic, epilepsy, cross-sensitivity, desensitization, and patch testing. Additional references were identified from a review of literature citations. Emphasis was given to treatment guidelines and review articles of the most clinically relevant studies, and the content was supplemented with our clinical experiences.

3. Presentation of hypersensitivity reactions to AEDs

The presentation can be immediate or delayed. The symptoms, diagnosis, and management depend on the type of rash (Table 1). A small study compared the incidence of different types of rashes in people taking antimicrobial agents, anti-inflammatory analgesics,

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Table 1
Immune-mediated adverse cutaneous reactions and treatment.

Cutaneous Rash	General AED-Induced Incidence	Timeline	Presentation	Hypersensitivity Reaction Type[a]	Diagnostics	Management
MILD-MODERATE						
Morbilliform exanthematous eruptions	50–95% [4]	5 days–8 weeks after starting medication and resolves in 1 week [5,6]	Small (2-100 mm), pink, pruritic macules and papules. Trunk, and pressure bearing areas and spreading to other areas of the body [5]	Type IVb/c	No labs or biopsy required.	Rarely requires systemic treatment. Mid-potency topical corticosteroids and oral antihistamines if significant pruritis [7,8]
Fixed drug Eruption	0% [9,10]*	Within hours after exposure. Typically reoccurs at the same site [7,8].	One or a few dusky red to violaceous patches, recur in same area with future exposure to the offending medication [5,7].	Type IV	No labs or biopsy required but can be confirmatory.	Symptomatic treatment usually sufficient. Moderate to high potency topical corticosteroids, and oral antihistamines as needed [7,8].
Lichenoid eruption	66.67% [10]*	Latent months to years, resolves in 2–4 months and recurs with re-challenge [11].	Eruption resembling lichen planus, with symmetric presentation of purple, polygonal flat-topped papules. Presents primarily on the extremities and trunk [11].	Type IV	No labs or biopsy required but can be confirmatory.	Symptomatic treatment usually sufficient. Moderate to high potency topical corticosteroids, and oral antihistamines as needed [7,8].
Erythema multiforme	25% [10]*	24–48 h [5]	Classically round, targetoid lesions, with well-defined pink to red patches or plaques in a concentric ring pattern. May vary in shape and have an atypical appearance when progressing to SJS/TEN [7,8].	Type IVb/c	Associated with HSV and *Mycoplasma pneumoniae* infection. Skin biopsy not necessary when clinical picture clear. Drug induced EM is rarer.	Oral antihistamines and topical steroids are options for symptomatic relief. Oral acyclovir or prednisone may be used but is controversial [7,8].
MODERATE-SEVERE						
Acute generalized exanthematous pustulosis (AGEP)	5% [12]	1–2 days, up to 1–2 weeks later [5].	Diffuse erythema especially in body folds, superficial involvement, spiking fevers and leukocytosis [5].	Type IVd	Histology characteristic biopsies to confirm diagnosis. Neutrophils and necrotic keratinocytes in upper part of epidermis. Patch testing causes a localized pustular reaction [5].	Supportive care. If severe corticosteroids. If erythrodermic, will likely require inpatient management [7,8].
Drug reaction with eosinophilia and systemic symptoms (DRESS)	78% [10]*	1–12 weeks after initiation. [4] and resolves in 1–6 months [13]	Malaise, fever, resembles morbilliform drug eruption until hemorrhagic, bullous lesions, central facial edema, and conjunctivitis appear [5,7] Lymphadenopathy and eosinophilia may present [5,14]	Type IVb	Test liver and thyroid function. Monitor for late onset autoimmune thyroiditis, diabetes, and myocarditis.	Oral or intravenous prednisone 1-2 mg/kg/day for severe cases [7,8].
Stevens-Johnson syndrome (SJS)	7.4% [15]	5–28 days [5].	Detachment below 10% of the BSA plus widespread macules or flat atypical targets [5]	Type IVc	Frozen skin section biopsy.	Immediate discontinuation of drug and supportive care. Systemic glucocorticoid therapy may be useful but, they are associated with increased mortality. Lack of data to support the use of IVIG and etanercept. Cyclosporine speeds healing and decreases mortality in small cohort studies [7,8].
Toxic epidermal necrolysis (TEN)	7.4% [15]	5–28 days [5].	Spots, with or without blisters, Detachment above 30% of the BSA plus widespread macules or flat atypical targets [5]	Type IVc	Frozen skin section biopsy.	
Immediate Reactions [5,7]						
Urticaria	5-22% [4]	Acute onset within minutes to hours after exposure. Urticaria resolves within 24 h and angioedema resolves in 72 h.	Itchy wheals with or without redness, not commonly painful [5].	Type I	No labs or biopsy required.	Oral non-sedating H_1-recetpor blockers. If severe, intramuscular epinephrine, secure airway, vasopressors, and intravenous corticosteroids [7,8].
Angioedema			Deeper, sometimes painful swelling of mucus membranes and feet			
Anaphylaxis			Hoarseness, dyspnea, wheezing, abdominal pain, dizziness, hypotension.			

Rashes may occur earlier in patients who have been exposed to the drug previously [1,13,16].
Diagnosis of AGEP, DIHS, SJS, and TEN are difficult as symptoms overlap, and treatment should be geared towards the dominant clinical features [7,8]. * The incidence of this type of rash was calculated by dividing the number of rashes due to AEDs by the total number of that particular rash due to all drugs evaluated.

[a] Hypersensitivity reactions may be categorized by type according to Gell-Coombs classification by immune component involvement. Type I-III reactions are antibody-mediated reactions while Type IV is a cell-mediated reaction that may be subdivided into further groups based on the effector cell. Type I reactions are IgE-mediated reactions incited by mast cell activation by a soluble antigen. Type II reactions are IgG-mediated reactions incited by phagocytes or NK cells by a cell or antigen. Type III reactions are IgG-mediation reactions associated with immune complex formation incited by phagocytes, NK cells, or complement leading by a soluble antigen. Type IV reactions are associated with inflammatory cytokines as a result of antigen presentation which leads to either macrophage (Type IVa), eosinophil (Type IVb), T-cell (Type IVc), or neutrophil (Type IVd) activation [6,17].

antiepileptics, antineoplastics, radiocontrast agents, or antihypertensive agents. Out of 106 rashes evaluated, 43 were due to antimicrobial agents, 33 due to anti-inflammatory analgesics, and 12 due to antiepileptics [10].

Mild rashes include morbilliform exanthematous eruption, fixed drug eruption, lichenoid eruption, and acute generalized exanthematous pustulosis. Morbilliform dermatitis is the most common AED hypersensitivity reaction. It typically occurs between five days and eight weeks after the start of therapy in adults and presents with limited involvement of the face and no associated facial or neck edema [5,6,18]. Symptoms typically resolve quickly after discontinuation of the medication [5].

Less common but more serious adverse reactions to AEDs include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). DRESS usually develops one to twelve weeks after therapy initiation, and symptoms can persist for weeks to months [4]. The syndrome has both cutaneous and systemic symptoms and usually begins with a fever $>38\,^{\circ}C$ or a maculopapular/morbilliform rash. The rash most commonly begins on the face and upper trunk and may spread diffusely. Periorbital and facial edema and severe exfoliative dermatitis may occur. Other symptoms include tender lymphadenopathy, dry mouth, hepatomegaly, myalgias and arthralgias. Systemic organ involvement, such as hepatitis, pneumonitis, myocarditis, pericarditis, nephritis and colitis, is the major cause of morbidity and mortality with mortality rates up to 10%. DRESS is more frequently associated with aromatic AEDs such as phenytoin or carbamazepine [19]. However, there is a case report of DRESS in a patient receiving levetiracetam (non-aromatic) [20].

Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) lie on a spectrum with EM having the mildest presentation [8]. Symptoms begin within 24–48 h for EM and 5–28 days for SJS and TEN [5]. The skin may initially show changes consistent with EM but the symptoms can progress along the SJS/TEN spectrum. It is difficult to predict the outcome based on initial cutaneous presentation. EM presents with erythematous to purple annular plaques called target lesions, often on the palms and soles in addition to other areas of the skin. SJS and TEN have full epidermal thickness bullous lesions which may present anywhere on the body [6]. The amount of skin detachment is typically $<10\%$ with EM and SJS, 10–30% with SJS-TEN overlap syndrome and $>30\%$ for TEN [8].

Some AED-induced hypersensitivity syndromes also variably cause systemic effects involving the gastrointestinal and respiratory tracts [6]. There is often a prodrome of flu-like symptoms such as malaise, fever and headache prior to the eruption of blistering exanthema targetoid lesions [6]. Mucosal involvement is common, involving ulcerations and blistering in the eyes, nose, oropharynx and/or genitalia. Severe ocular involvement may occur, posing a significant risk of infection [21]. Mortality rate is positively correlated to the degree of cutaneous involvement [8], with rates of 9% of SJS patients and 50% of TEN patients [6,19,21,22].

4. Pathogenesis of AED-induced drug rash

The underlying pathogenesis of AED-induced hypersensitivity is hypothesized to result from toxic AED-metabolites which either directly cause cell death or act as prohaptens to evoke an immune response by binding to T cells [23]. T cell activation is thought to be involved in most drug hypersensitivity reactions. In skin lesions of morbilliform drug-induced rashes, CD4 + T cells are the major cell type found [24]. SJS/TEN is a drug-specific CD8+ T-cell-mediated cytotoxic response while DRESS results in massive nonspecific T cell activity and immune-inflammatory responses [4]. Four hypotheses have been suggested to explain the mechanism by which drugs activate T cells: the hapten hypothesis, the direct metabolite MHC binding concept, the pharmacological interaction (PI) concept, and the drug-dependent altered human leukocyte antigen (HLA) peptide repertoire concept [6]. The hapten hypothesis proposes that small molecules, such as drug metabolites, must bind to a carrier protein, be processed by antigen-presenting cells, and then react with MHC molecules to generate an immune reaction. The direct metabolite MHC binding hypothesis states that chemically reactive metabolites activate T cells through direct binding to HLA peptides [25]. The PI concept asserts that the drug binds to HLA peptides in the absence of drug metabolism [26]. In addition, the altered self-concept suggests that the drug metabolite binds to MHC and alters MHC-binding surface peptides on APCs. These altered peptides activate T cells [27,28]. Finally, IgE-mediated reactions to antiepileptics are rare, but have been demonstrated with aromatic AEDs [29].

Reactive intermediates may also play a role in hypersensitivity reactions to carbamazepine, phenytoin, phenobarbital, valproic acid, and lamotrigine [4,6]. Carbamazepine and lamotrigine and their reactive metabolites have been shown to directly activate T cells. [6,30].

5. Risk factors for developing AED-induced rashes

History of a previous AED-related skin reaction is the most significant predictor of a future rash. After a rash to one AED, the risk of developing a rash to another AED increases from 1.7% to 8.8% (ranging from $<1\%$ to 25% depending on the AED) [1,31]. In patients who had a previous rash or other adverse reaction to a non-AED medication, AED-rash rates are significantly higher for carbamazepine, lamotrigine and phenytoin [16].

Other risk factors include gender, age, ethnicity, nutritional status, and co-morbidities. Skin reactions from AEDs occur more than twice as often in female patients compared to male patients, but these differences do not persist in patients greater than 50 years old [1,2]. This may due to estrogenic sex hormones increasing the production of T-cells, antibodies, and proinflammatory mediators [2]. However, increasing advanced age in adults may be an additional risk factor for AED rashes, as elderly patients have higher rates of drug-induced skin reactions [18,27,32]. The increased reports of carbamazepine, phenytoin, and oxcarbazepine-related rash in elderly men may be due to decreased testosterone concentrations [2]. Conversely, a prospective multivariate logistic regression analysis of aromatic AED use in 570 children found the greatest risk factors for developing rash to be: less than 12 years of age, aromatic AEDs, and polytherapy [33]. The authors suggested that children may have a higher risk of rash than adults due to increased drug metabolism resulting in higher concentrations of reactive metabolites [16,33]. Genetic factors that delay clearance and increase accumulation of phenytoin metabolites may increase the risk of phenytoin-induced rashes [34]. Concomitant use of medications that decrease AED clearance may also increase hypersensitivity risk. For example, the risk of lamotrigine-induced rash is increased when it is administered with valproic acid which inhibits lamotrigine metabolism [2].

Specific ethnic populations may also have an increased risk of rash from AEDs due to specific HLA alleles. The prevalence of these alleles varies per ethnicity, and the hypersensitivity risks vary based on the specific AED and the specific reaction type. Each year, new data with new HLA alleles for specific AEDs, magnitude of risks, reactions types and ethnicities are published. Thus, the risk estimates and yield for using this allele testing will depend on some understanding of patient ethnicity and AED being considered. We have provided examples of the most common HLA alleles tested commercially in specific ethnic populations in Section 8. Low vitamin concentrations may be associated with increased risk of developing AED-induced rashes, but there is a need for additional prospective studies. A retrospective case series of 24 patients determined that a majority of patients presenting with drug-induced hypersensitivity reactions had low vitamin D concentrations [35]. Of the 18 patients who had their Vitamin D concentration measured, nine had concentrations <10 ng/mL and five had concentrations

less than 10–20 ng/mL. Another retrospective study noted that 44 out of 45 patients with DRESS syndrome had low serum concentrations of vitamin D3 with 21 patients having a D3 concentration < 10 ng/mL, and 23 patients having a D3 concentration of 10–30 ng/mL [36].

Other risk factors include immunological status and certain comorbidities. A chart review of 1890 patients found patients with juvenile absence epilepsy, systemic lupus erythematosus, any immunologic disorder, atrial fibrillation, and coronary artery disease have an increased risk of developing an AED-induced rash [1].

Aromatic AEDs are associated with the greatest occurrence of rash and cutaneous adverse reactions [1,2,6,13,16]. A literature review identified 172 cases of DRESS over twelve years, with aromatic AEDS accounting for 46% of the cases [37]. An analysis of an FDA adverse event database showed AEDs were the most reported medication class associated with SJS/TEN. The highest risk estimates were for aromatics with carbamazepine, lamotrigine, phenytoin, and zonisamide accounting for more than 75% of the AED cases [38].

Finally, the risk of AED rash is increased with higher starting doses and faster titration rates. A relationship between rash and dose titration has been noted for carbamazepine, phenytoin, and lamotrigine. In addition, the risk of rash is increased when valproic acid is administered with lamotrigine because it slows the elimination of lamotrigine and increases the plasma concentration of lamotrigine [1,6,18]. A review indicated that 85% of 75 patients who developed a rash were able to restart lamotrigine after slower dose titration [39].

Cross-sensitivity among aromatic AEDs is estimated to occur clinically in 40–58% of patients, while in-vitro assays show rates as high as 80% [16,37,40]. However, cross-sensitivity is not a predictor of the development of a more serious or complicated hypersensitivity reaction [41]. There is no evidence of cross-reactivity with AEDs in patients with allergies to other aromatic structures such as sulfonamide medications. However, these patients may be more prone to allergic reactions in general. Zonisamide contains a sulfonamide group and has an FDA contraindication in patients with a hypersensitivity reaction to sulfonamides. We are aware of one published single patient case report of severe TENS hypersensitivity [42] and another report of a single patient with rash [1] after receiving zonisamide while having a prior history of sulfa drug allergy. However, sulfa allergy is far from an absolute contraindication to using zonisamide, as one study showed that one of six patients with prior sulfa allergy and initiated on zonisamide had rash [1]. Another study noted that no rash or allergic/hypersensitivity reaction occurred in any of the eight patients with documented allergies to sulfonamide antibiotics given zonisamide for at least three months [43].

6. Diagnostics and monitoring

The diagnostic criteria of mild rashes are nebulous. Many early drug reactions look like simple dermatitis or morbilliform eruptions. Others may be targetoid in morphology, suggesting erythema multiforme-like reactions. Diagnosis is based on clinical judgment and if unclear, a dermatology and/or allergy evaluation is essential. It is impossible to know whether an eruption will stay as a minor dermatitis or progress along the SJS/TEN spectrum. Therefore, close follow up and clinical examination of the patient is key to appropriate management.

Drug-induced hypersensitivity is diagnosed by history, physical exam and sometimes skin biopsy. Specialized skin tests (percutaneous or intradermal) may be available for hypersensitivity reactions [5]. Patch testing is reliable for diagnosis of contact dermatitis resulting from topically applied medications [21] and may confirm the culprit drug in DRESS induced by antiepileptic drugs [44,45]. Skin prick tests and intradermal tests are performed to demonstrate an IgE-dependent mechanism. However, nonirritating concentrations for skin testing have not been evaluated for AEDs [17,46].

A systematic review of patch testing for diagnosing anticonvulsant hypersensitivity syndrome concluded that the positive predictive value (PPV) of the test is higher than its negative predictive value (NPV) and therefore a negative patch test necessitates a drug re-challenge to confirm the diagnosis. The highest PPV has been obtained with carbamazepine and the lowest with phenobarbital with values ranging from 20% to 80%. Thus, patch testing 2 to 6 months after the reaction is of maximal benefit for certain drugs, such as carbamazepine and phenytoin, and for strong immune reactions [44,45]. The use of routine patch testing for AED hypersensitivity is limited due to the risk of re-activation or recurrence of the skin reaction [44]. Commercially available allergens for patch testing are not readily available in the United States, and the US Food & Drug Administration has not evaluated those that are available for sale from other countries. [44,45].

While the diagnosis of SJS and TEN is often made by clinical presentation, a skin biopsy should be done for confirmation [24]. For rapid diagnosis, a “jelly-roll” frozen section biopsy can be performed. Detached skin from the edge of an active, fresh blister/ulceration is removed to confirm full thickness involvement and the diagnosis of SJS/TEN [47]. If the jelly-roll biopsy is not available, a large punch biopsy (4–6 mm) from the active edge, including both blister and attached skin of a fresh lesion, can be sent for histopathological evaluation. The benefit of a punch biopsy is that other potential diagnoses can be evaluated, whereas a frozen section is primarily useful for evaluating the level of skin blistering.

7. Treatment of rash

Consultation with a dermatologist is useful to confirm the diagnosis because therapy depends on the type and severity of the cutaneous drug reaction (Table 1). Skin biopsies are routine procedures that are key in the early evaluation of suspected cutaneous AED reactions. Few dermatologists perform patch testing for adverse medication reactions and this type of testing should be postponed until the immediate skin reactions have subsided. An allergist can determine if a reaction is allergic or non-allergic and may perform skin testing or oral challenge to confirm the diagnosis. In general, initial management begins with stopping the AED and providing appropriate care for AED withdrawal symptoms such as seizures or worsening behavioral symptoms as well as symptomatic treatment of rash. Patients with mild rashes can be treated at home, while patients with severe rashes should be hospitalized.

EM that presents with cutaneous involvement and limited oral mucosal involvement can be managed in an outpatient setting. The treatment includes topical steroids and oral antihistamines as well as topical anesthetics, such as lidocaine and diphenhydramine [48]. Those with ocular involvement should be immediately evaluated by an ophthalmologist [49].

EM that presents with extensive oral mucosal involvement may require management in an inpatient setting. The treatment includes tapering doses of oral corticosteroids; however, the efficacy of this method has not been proven, and many patients with this form of EM are unable to take anything by mouth. Thus, hospitalization may be necessary for therapeutic management as well as for nutrition, pain control, and parental medication utilization [50,51].

Patients with EM should be carefully monitored for progression to SJS/TEN, since skin and mucous membrane lesions can progress over hours to days. While no blanket recommendation is possible, use clinical judgement for follow up intervals, erring on the side of shorter rather than longer durations between evaluations.

Supportive care in a burn intensive care unit is always first-line for the treatment of SJS/TEN [21]. Supportive care focuses on preventing fluid loss, preventing infections, and promoting skin healing with a variety of different biological dressings, conformant (nonadherent contact layer), lidocaine anesthetic gel, chlorhexidine mouth rinse, or dexamethasone eye drops. Appropriate consultation with dermatology, ophthalmology and, if necessary, obstetrics/gynecology is standard of care for SJS/TEN [21,52]. There is debate about the use of adjuvant systemic therapy [52]. The use of IVIG in addition to supportive care for

the treatment of SJS/TEN is currently under scrutiny. IVIG does not reduce mortality in adults though high dose IVIG therapy has been shown to lower mortality in children [52–54]. If IVIG is chosen, care must be taken in those patients with renal, thrombotic or cardiovascular disease.

There is no consensus on the use of adjunctive systemic treatments such as oral or intravenous corticosteroids, IVIG, cyclosporine A, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, and granulocyte colony-stimulating factors [55]. Evidence on the use of corticosteroids, IVIG, or a combination of these agents is conflicting. Hemoperfusion, plasmapheresis, cyclophosphamide, tumor necrosis factors, and granulocyte stimulating factors do not seem to decrease mortality [52, 55]. Thalidomide may not be effective and may increase mortality [52,55,56].

Oral cyclosporine use in severe SJS/TEN shows significant promise for slowing disease progression, promoting re-epithelialization and decreasing overall mortality [53,57,58]. Adding cyclosporine to supportive care may lead to quicker recovery and decreased mortality [52,53,59–61]. Thus, with severe disease, we recommend early and immediate addition of cyclosporine. Dosing is variable in the literature, but cyclosporine orally 3 mg/kg/day for one week, followed by 1 subsequent week of cyclosporine 1.5 mg/kg/day is recommended [52]. Doses should be divided for twice daily administration.

8. Prescribing an AED: considerations, recommendations and guidelines

When starting or restarting an AED, it is important to review the above-mentioned risk factors for rash. Consider if HLA genetic testing would be helpful. The FDA recommends genotyping all Asians for HLA-B*15:02 before starting carbamazepine although the risk of carrying HLA-B*15:02 is not homogeneous among all Asian subpopulations [62]. This recommendation originally was for those of Han Chinese ancestry, but other Southeast Asian-ancestries have been included (e.g. China, India, Hong Kong, Thailand, Malaysia, Vietnam, and Cambodia) because studies have demonstrated a 1–20% allele prevalence in these populations [63]. Since the HLA-B*15:02 allele is very rare (<1%) in patients with other ancestry (e.g. Japanese, Korean, Caucasian, African, Mid East, Hispanic), testing these groups is not routine [64]. Recent guidelines suggest avoiding carbamazepine, oxcarbazepine and phenytoin/fosphenytoin in HLA-B*15:02 positive patients and we assume this avoidance may also extend to eslicarbazepine acetate [64]. A recent meta-analysis also associated SJS and TENS in HLA-B*15:02 positive patients receiving lamotrigine [65]. They also suggest using caution when considering other aromatic AEDs in patients with this allele, although the level of association of SJS and TEN with other aromatic AEDs in patients with this allele is lower than with carbamazepine. Guidelines suggest assessing for the HLA-A*31:01 allele before starting carbamazepine in patients of European and Japanese ancestry because it is associated with SJS/TEN, DRESS, and maculopapular rash in these patients [64]. An economic modelling study reports this screening in European populations is cost-efficient [66]. Currently, the HLA-A*31:01 allele association with aromatic AEDs other than carbamazepine and SJS/TEN, DRESS and maculopapular rash has limited evidence.

In addition to the FDA warnings related HLA-B*15:02 for Asian patients receiving carbamazepine or oxcarbazepine, at least 5 additional alleles have been identified as potential risk factors (HLA-B*15:01, HLA-B*15:11, HLA-A*02:01,and HLA-DRB1*01:01, HLA-A*24:02) [67]. These additional alleles are the subject of an ongoing study screening Han Chinese patients for HLA genes prior to initiating an aromatic AEDs and measuring the reduction in the incidence of AEDs-induced cutaneous adverse drug reactions (https://clinicaltrials.gov/ct2/show/NCT03184597) [67]. Additionally, HLA-A*02:07 may be a biomarker for susceptibility to zonisamide-induced SJS/TEN in Japanese patients [68]. Genotyping in medicine is an evolving field, and further guidance can be found at https://cpicpgx.org/guidelines/, which is periodically updated [69].

For patients with a high risk for rash, it is generally advised to avoid aromatic AEDs, including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, zonisamide, and lamotrigine as they have higher rates of hypersensitivity reactions [1]. In addition, cross-reactivity appears to be greater between aromatic AEDS; thus, other aromatic AEDs should be avoided [4,16,41,70]. We also suggest avoiding eslicarbazepine acetate and perampanel because they are aromatic, and rash and DRESS have been reported. Felbamate and primidone are also aromatic AEDs, but they have not been reported with high rates of hypersensitivity reactions [1,4,40,71]. The number of hypersensitivity reports with felbamate and primidone may be greater if they were more commonly used in the U.S. Clobazam, an aromatic AED, has been associated with rash, angioedema, SJS and TEN, but its rash rate is not as high compared to other aromatic AEDs, and there is a lower risk of cross-sensitivity [1,16,41,72]. Strong and moderate inhibitors of CYP2C19 (e.g. fluconazole, fluvoxamine, omeprazole) may result in increased exposure of the active metabolite N-desmothylcobazam [3].

The use of cannabidiol (CBD, EPIDIOLEX©), FDA-approved as a purified pharmaceutical-grade prescription drug for epilepsy in 2018 [73] should be evaluated in patients with previous rash history. The drug is aromatic, and it is delivered in a vehicle containing sesame oil. It should be avoided in patients with sesame oil hypersensitivity. Controlled trials have reported morbilliform dermatitis and angioedema with a dose-dependent incidence. Consider using lower starting doses and slower titrations of CBD in patients on moderate-strong inhibitors of CYP3A4 or CYP2C19 due its metabolism by those isoenzymes. Despite no reported SJS-TEN cases for CBD, providers should report potential CBD-hypersensitivity reactions given its limited use in controlled studies thus far [74,75].

Aromatic AEDS should be used with caution in pediatric patients and they should be carefully monitored for rash risk within the first few weeks of AED initiation. If an aromatic AED is administered, titrate the dose slowly, minimize the use as polytherapy, particularly with valproic acid, and monitor children less than 12 years old more aggressively [33].

Prescribers should also be aware that the FDA recently updated the warning label for lamotrigine because there were eight cases of hemophagocytic lymphohistiocytosis. It is a potentially life-threatening immune reaction that may be confused with other serious immune-related adverse reactions such as DRESS [76].

For patients with major risk factors for rash consider using valproate, gabapentin, topiramate, levetiracetam, pregabalin, felbamate, primidone, vigabatrin, or lacosamide as they are associated with a low risk of rash [1,10] (Table 2). Brivaracetam (FDA-approved in 2016) also likely has a low rate of rash as it is structurally related to levetiracetam. Providers and pharmacists should inform patients to observe for rash, especially in the first two months, and alert their provider as soon as possible if it occurs. Patients should be advised to seek immediate medical attention if: the rash is progressing and/or severe (i.e. disabling, diffuse, desquamating, or blistering); involves the face; or if fever, mucositis or symptoms of another organ dysfunction are present. Especially when prescribing an aromatic AED, providers should document in the patient's medical record an alternative AED that can be used if an adverse event occurs. If a patient experiences a disabling rash, the medication should be discontinued and an alternative agent with low chance of cross-reactivity should be initiated. Consideration should be given to dose modification in inhibitory drug pharmacokinetic interactions that would increase the concentration of the newly started AED and increase risk of hypersensitivity reaction (e.g. lamotrigine dose reduction when starting lamotrigine in patient taking valproate).

9. Managing seizures in patients with rash

Hospital admission may be necessary to evaluate more severe

Table 2
Incidence of Rash.

Drug	Rash Incidence from Package insert (%) [77]	Rash Risk from Literature and Other Comments
Aromatic AEDs		
Ethosuximide (ETX)	Rash listed but not quantified	6/154 (3.9%) children on had moderate or severe rash on ETX monotherapy [78].
Phenytoin (PHT)	5-10%	19/486 patients (3.9%) risk higher than average [1]. 30-58% hypersensitivity reaction incidence in patients with prior carbamazepine hypersensitivity reactions [16,41].
Phenobarbital (PHB)	Rash listed but not quantified	Risk less than average [1]. 26-67% hypersensitivity reaction incidence in patients with prior carbamazepine hypersensitivity reactions [16].
Carbamazepine (CBZ)	7%	10/570 patients (1.8%) risk higher than average [1]. 13% (15/114) of children developed a rash. 5.2% (6/114) developed a severe cutaneous drug reaction from CBZ [13]. 5.2-13% in children [33].
Oxcarbazepine (OXC)	4 to 5.3% or greater	3/210 patients (1.4%) risk is lower than average [1]. 29-80% hypersensitivity reaction incidence in patients with prior phenytoin or carbamazepine hypersensitivity reactions [2,16].
Zonisamide (ZNS)	6.7%	6/170 patients (3.5%) risk higher than average [1]. Less cross reactivity [1,16].
Lamotrigine (LTG)	7-14%	32/912 patients (3.5%), risk is higher than average [1]. Less cross reactivity than CBZ, OXC and PHT [41].
Clobazam (CLB)	Rash listed but not quantified	Less cross-reactivity [1,16]. FDA issued warning for SJS/TEN risk. No rash reported in survey study of neurologists prescribing drug to 877 pediatric and adult PWE [79]. Rash 3.4% in RCT of 179 child and adult PWE followed for 15 weeks. (3.4% incidence also in placebo arm) [80]
Felbamate (FBM)	3.4% to 3.5%	Low risk [1,16,81].
Primidone	Rash listed but not quantified	Low risk [1,16].
Eslicarbazepine (ESL)	1% to 3%	2.6% [82]. Risk greater with higher doses, pooled results of phase 3 RCTs of 990 pts followed up to 18 weeks; 0.8% in placebo; 4 patients had DRESS [83].
Perampanel (PER)	4%	2.4% [84]. Risk greater with higher doses. From RCT of 707 PWE > 12 yo from Asia-Pacific countries and followed 19 weeks [84].
Cannabidiol (CBD)	7 to 13%	18% [74]. Non-life-threatening rashes reported in clinical trial [73].
Non-Aromatic AEDs		
Valproate (VPA)	>1% to <5%	Low risk [1,16].
Gabapentin (GBP)	>1%	Low risk [1,16].
Topiramate (TPM)	4%	Low risk [1,16].
Levetiracetam (LEV)	2%	Low risk [1,16].
Pregabalin (PGB) –	<1%	Low risk [1,16].
Vigabatrin (VGB)	4 to 11%	Low risk [1,16]. Rash incidence of 3.8% (n = 129 drug group) vs. 2.2% (n = 45 placebo group) in RCT of adults [85]
Lacosamide (LCM)	<1%	Rash reported in 1 patient receiving drug vs 3 patients on placebo in meta-analysis of 2264 patients receiving LCM in RCTs [86].
Brivaracetam (BRV)	Not available	No rash reported in meta-analysis of 2505 PWE receiving BRV up to 16 weeks [87]. The PI notes hypersensitivity (angioedema and bronchospasm) but no dermatologic reactions.

Arif- average risk of rash for those who did not have a rash to other AEDS was 1.7%.

hypersensitivity reactions or if seizure medications need to be managed in a controlled setting to minimize withdrawal seizures. In our experience, how quickly to discontinue the AED depends on multiple factors (e.g. reaction severity; dose and concentration of the AED; how recently the AED was started; type of AED; concurrent AED usage; and severity of epilepsy). Patients with mild rashes may be managed with AED dosage reduction (e.g. 50%) and observation. The risk of seizure exacerbation is relatively low when abruptly stopping a low dosage AED, when the AED was started in the past two weeks, and when the patient remains on concurrent other AEDs that have helped their seizures. In the absence of these factors, the situation is more complicated. Additionally, the time for the new AED to reach steady state allows for increased risk of seizure during this transition. If the seizures are disabling or frequent during the medication adjustment, consider acute treatment with a benzodiazepine such as short-term clonazepam two times daily until the new AED has reached steady state concentrations and seizures are controlled. Counseling should include seizure precautions (e.g. avoiding driving, swimming, cooking, or operating heavy machinery), how to use rescue medicine, and a response plan for worsening seizures or rash symptoms. The patient should carry rescue medicine (e.g. diazepam rectal suppository; lorazepam tablet) when a benzodiazepine or phenobarbital is discontinued.

Patients using moderate dosage daily benzodiazepine or phenobarbital for more than one week are at greater risk of withdrawal seizures and they are typically weaned off slower than other AEDs. In an ideal situation, we suggest tapering the moderately-dosed benzodiazepine or phenobarbital based on the duration of use. For example, taper over 1–2 weeks if used less than 3 weeks; 2 weeks if used for 3–4 weeks; 2–4 weeks or longer if used >4 weeks. If the rash is severe, a more rapid taper should be done in a hospital setting.

Patients with uncontrolled seizures are more likely to have worsening seizures (e.g. seizure frequency, a generalized convulsive seizure that was previously controlled, cluster seizures, and status epilepticus) and complications related to seizures (e.g. falls, other accidents and injuries, or postictal psychosis). Patients most at risk have long standing epilepsy with monthly or more frequent seizures and a history of status epilepticus or seizure clusters.

The risk of withdrawal seizures can be estimated from pooling the

data from several conversion to monotherapy trials [83,88–91]. In these trials, patients with uncontrolled epilepsy (e.g. two or more seizures/month) were tapered off their original 1–2 AEDs over 4–8 weeks and concurrently tapered up on a new AED. We conducted a pooled analysis of six conversion to monotherapy trials evaluating a total of 1258 patients. Of those patients, 39% had at least one seizure-related event concerning for insufficient efficacy of the new AED over 16 weeks follow-up. Approximately two thirds of patients had a doubling of seizure frequency over either multiple months or over a typical 2-day period, while one third had generalized convulsion, status epilepticus, or another more severe seizure manifestation not typical for their recent epilepsy history.

Further evidence regarding the risk of withdrawal seizures can be found in studies evaluating patients with uncontrolled epilepsy admitted to epilepsy monitoring units for pre-surgical evaluation. A study conducted at five US epilepsy monitoring units evaluated 169 patients for status epilepticus and cluster seizures and found that 10% had seizures that were more than 5 min in duration and 49% had seizure clusters [92]. Another study conducted at a single epilepsy monitoring unit in China evaluated 102 patients and found that 48.3% had seizure clusters [93]. Admitting patients to an inpatient EMU with continuous nursing support, video EEG monitor, IV access for rescue medication and protocols to deal with urgencies can reduce the percent of seizure clusters and status epilepticus [94]. Another reason for hospital admission is to minimize the risk of sudden unexpected death in epilepsy patients (SUDEP), as the MORTEMUS study found the risk of SUDEP or near-SUDEP from cardiopulmonary arrest to be approximately 1 per 100 patient-years [95].

10. Desensitization (induced drug tolerance)

Allergic reactions to AEDs usually require a change in therapy; however, some patients with refractory seizures may require reintroduction of a medication to which they have had a previous allergic reaction. An allergist may accomplish this using desensitization protocols. Drug desensitization, or temporary immunologic induction of drug tolerance, is defined as a state in which a patient with a drug allergy will tolerate that drug without an adverse reaction. This procedure may be effective for both IgE-mediated and some non-IgE mediated reactions. Desensitization is recommended if no acceptable alternative medication is available. It is contraindicated in patients who previously had cutaneous vasculitis, systemic vasculitis or severe rashes such as SJS, TEN or DRESS [17].

Desensitization is most often performed via the oral or intravenous route. Drug tolerance is induced by administration of incremental doses of the drug. The initial dose is approximately 1/10,000 of the full therapeutic dose. The very small starting doses are achieved by diluting medication powders with normal saline, water, or lactose. The dose is then increased over time until the full dose is reached. Patient specific factors to address when considering a desensitization protocol should include clinical manifestation of previous reactions, comorbidities, current clinical status, and hepatic and renal parameters [17].

It is difficult to predict the probability of successfully restarting a drug using a desensitization protocol because the number of publications are limited, the publications are single case reports, and failed desensitization procedures are likely to not be published due to publication bias.

Published protocols for AED desensitization are available for phenytoin, pentobarbital, lamotrigine, carbamazepine, oxcarbazepine, and valproic acid [96–103]. These protocols utilized small starting doses and most required weeks to months to achieve titration to the full dose. Achieving drug tolerance does not indicate that the patient will have a permanent state of tolerance [21,33]. Patients must be compliant with the dosing schedule as the state of “drug tolerance” is conditional on the regular continued administration of the drug. If the drug is stopped and restarted later, desensitization would need to be repeated [21,33].

11. Conclusion

Rashes cannot be prevented; however, the risk can be minimized by obtaining a comprehensive patient history, reviewing risk factors for rash, and documenting rashes when they occur. To minimize complications from rashes, patients should report their rash as soon as possible to their provider. Patients should be counseled on red flag signs and symptoms for hypersensitivity reactions necessitating stopping the drug and needing emergency evaluation to decrease morbidity and mortality.

When selecting AEDs, it is important to consider the patient’s complete clinical history. Patients who are taking other medications affecting drug clearance or have a previous history of rash to other AEDs can be at an increased risk for hypersensitivity to AEDs. The aromatic AEDs have a higher risk of rash and cross-reactivity. However, a specific AED with low cross reactivity may be an acceptable choice for patients with a history of allergic reactions to other aromatic AEDs.

If a patient develops a rash, consider the most recently added medication. Evaluate if the drug can be continued and the rash minimized with a slower dose titration or if the drug needs to be discontinued. Medications eliciting a hypersensitivity reaction should be well documented in the medical record, including a photograph of the rash, and the patient should be educated about the drugs they should avoid. Consider referral to a dermatologist or allergist for additional diagnostic evaluation or assistance with a desensitization procedure. If patients have a severe rash or a high-risk seizure complication, they should be admitted for observation and treatment.

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