Drug Hypersensitivity

Rashes to know about

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May 17th 2024

- No Disclosures

About Me

- Medical Dermatologist at Ochsner Jefferson Highway with special interest in inpatient dermatology, transplant dermatology and oncodermatology
- Staff our inpatient consultation service for acute dermatologic events and drug-related rashes
- Site Director for LSU and Tulane dermatology residents

Adverse Drug Reactions

- Type A reactions
  - Linked to drug pharmacology - i.e. bleeding due to warfarin
- Type B reactions
  - Idiosyncratic, immune mediated - difficult to predict
  - Immediate (IgE) vs delayed
    - Majority of those discussed are *T-cell mediated delayed type IV hypersensitivity reactions*

Urticaria

Immediate Hypersensitivity

- Itchy pink puffy wheals that can occur anywhere on the body
- Occurs minutes to hours after exposure
- Each lesion resolves within 24 hours

Urticaria

Immediate Hypersensitivity

- Treatment is antihistamines

Angioedema

Immediate Hypersensitivity

- Risk of airway compromise +/- anaphylaxis
- Emergency
- Steroids, antihistamines, epinephrine

Morbilliform Drug Eruption

Delayed Hypersensitivity

- Small, pink macule and papule
- Tends to start on trunk and spread distally
- Starts 5 days to 8 weeks after starting medication

Morbilliform Drug Eruption

Delayed Hypersensitivity

- Typically resolves within 1-2 weeks
- Symptomatic treatment with topical steroids and oral antihistamines

Morbilliform Drug Eruption

also known as“MPE”
Maculopapular exanthema

Fixed Drug Eruption

- One or multiple annular dusky red to violaceous patches
- Often affects mucosal surfaces
- Occurs within hours after exposure/ingestion of medication

Fixed Drug Eruption

- Tends to recur at the same site (s) with subsequent exposure to medication
- Self resolves
- Can treat with topical steroids

Lichenoid Drug Eruption

- Erythematous to violaceous polygonal flat papule on trunk and extremities
- Can start months to years after initiation of medication

Lichenoid Drug Eruption

- Can have overlapping features with typical lichen planus
- Treat with topical steroids, antihistamines, NBUVB light therapy

Erythema Multiforme

EM

- Targeted lesions on palms, soles, mucosae
- Starts within 24-48 hours of medication ingestion

Erythema Multiforme

- Resolves in weeks
- Treatment with topical steroids
- Must monitor for progression to SJS
- Consider treating with acyclovir given HSV association

AGEP

Acute Generalized Exanthematous Pustulosis

- Diffuse erythema of trunk, face, extremities, body folds; studded by tiny superficial pustules
- Often accompanied by fever and leukocytosis
- Starts within 1-2 days and last for 1-2 weeks

AGEP

Acute Generalized Exanthematous Pustulosis

- Supportive management
- Topical and oral steroids
- Characteristic diffuse sloughing is a hallmark of AGEP resolution

The SCARs - Severe Cutaneous Adverse Reactions

- DRESS - Drug Reaction with Eosinophilia and Systemic Symptoms
  - *Mortality approaches 10%*
- SJS/TEN - Stevens Johnsons Syndrome/Toxic Epidermal Necrolysis
  - *Mortality up to 30%*

DRESS

Drug Reaction with Eosinophilia and Systemic Symptoms

- Presents with:
  - Morbilliform eruption
  - Prominent facial edema
  - Lymphadenopathy
  - Fever
  - Systemic symptoms/malaise
  - Eosinophilia
  - Liver or hematologic abnormalities

DRESS

Drug Reaction with Eosinophilia and Systemic Symptoms

- Starts within 2 weeks to up to 2 months after offending medication
- Treatment involves hospitalization, high dose systemic steroids with slow taper, close monitoring for immune-mediated organ damage
  - Myocarditis - high mortality rate

RegiSCAR to assess DRESS likelihood

- RegiSCAR
  - 0-1 not DRESS
  - 2-3 possible
  - 4-5 probable
  - >6 likely

MDCalc.com has easy-to-use calculator for this

RegiSCAR group study criteria	No	Yes	Unknown
Fever ≥ 38.5°C	-1	0	1
Enlarged lymph nodes (≥2 sites, >1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700-1,499 or 10%-19.9%		1	
≥1,500 or ≥20%		2	
Skin rash	0		0
Extent >50%	0	1	0
At least 2 of: edema, infiltration, purpura, scaling	-1	1	0
Biopsy suggestive of DRESS	-1	0	0
Internal organ involved	0		0
1		1	
≥2		2	
Resolution in >15 days	-1	0	1
≥3 negative biological investigations to exclude alternative diagnosis	0	1	0

SJS/TEN

Stevens Johnsons syndrome/Toxic Epidermal Necrolysis

- Presents with widespread dusky skin rash with:
  - Blistering of skin
  - Skin detachment
  - Involvement of 2 or more mucosal surfaces (eyes, mouth, genital)

SJS/TEN

Stevens Johnsons Syndrome/Toxic Epidermal Necrolysis

- Starts within 5-28 days of medication exposure
- SJS is defined as 10% body surface area involvement
- SJS/TEN overlap is between 10-30% body surface involvement
- TEN is >30% body surface involvement

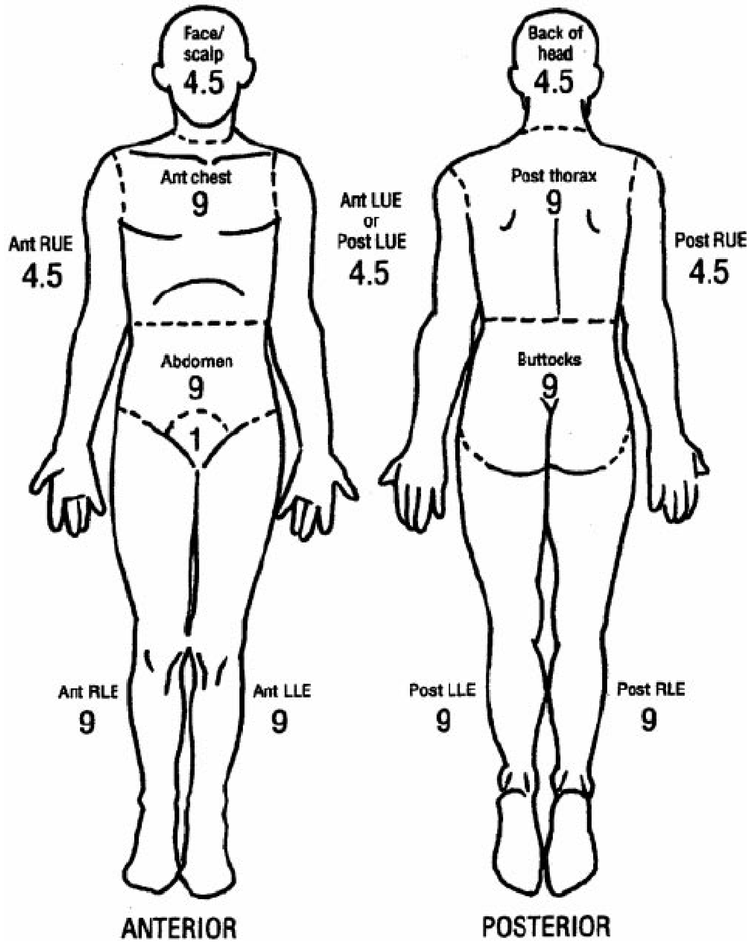
SJS/TEN

Stevens Johnsons syndrome/Toxic Epidermal Necrolysis

- Critical to withdraw offending drug as soon as possible
- Severe cases must be managed supportively in burn unit given fluid losses and infection/sepsis risk
- Systemic adjunctive therapies - not standardized:
  - High dose steroids +/- IVIG
  - Cyclosporine
  - Enbrel
- Significant morbidity and mortality

TEN

Toxic Epidermal Necrolysis

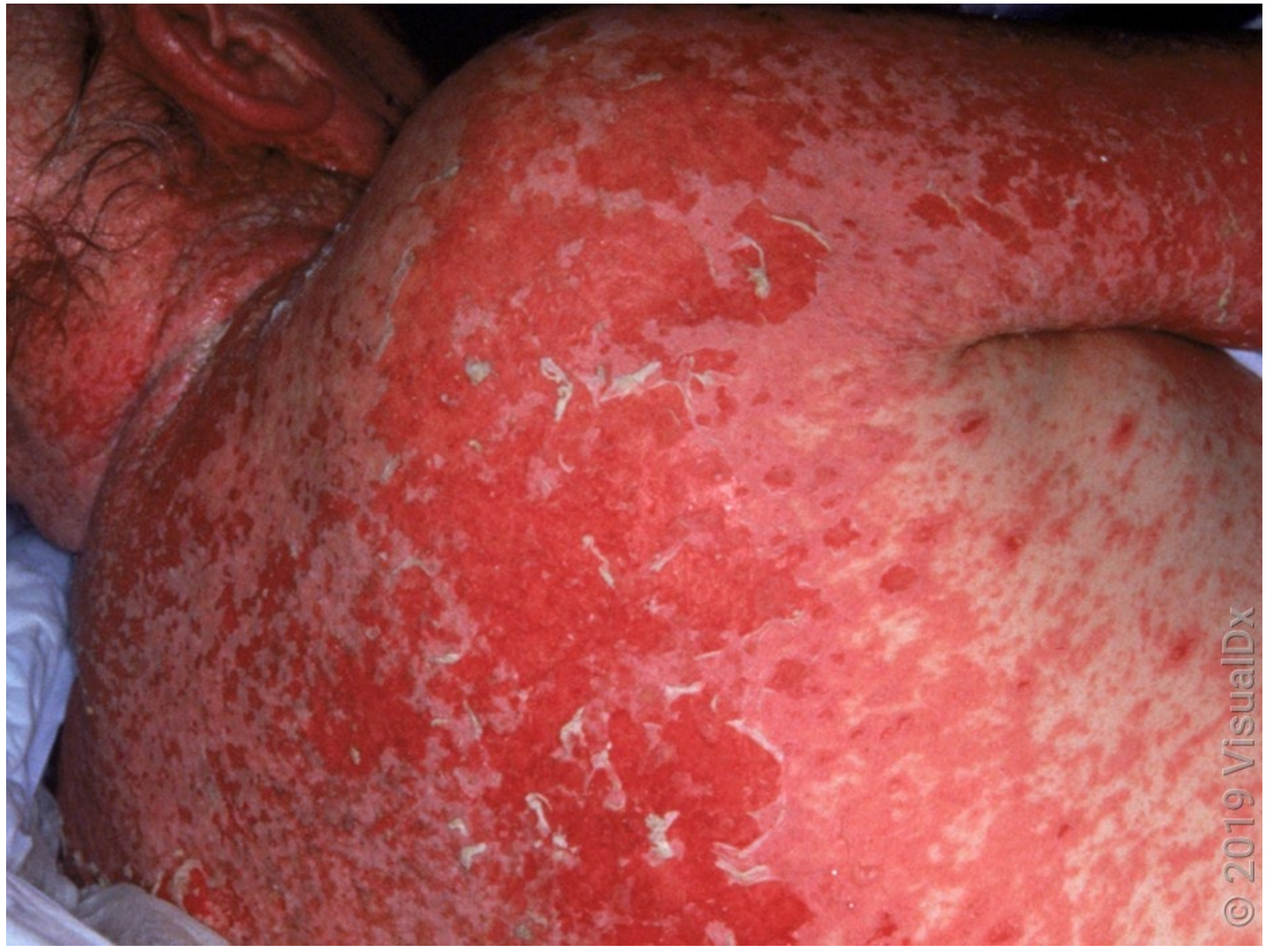


TEN

Toxic Epidermal Necrolysis

TEN

Toxic Epidermal Necrolysis



- SCORTEN score to predict mortality

Prognostic factors	Points
Age > 40 years	1
Tachycardia > 120 bpm	1
Neoplasia	1
Initial detachment > 10%	1
Serum urea > 10 mmol/L	1
Serum bicarbonate < 20mmol/L	1
Blood glucose > 14 mmol/L	1

SCORTEN	Mortality (%)
0-1	3
2	12
3	35
4	58
≥ 5	90

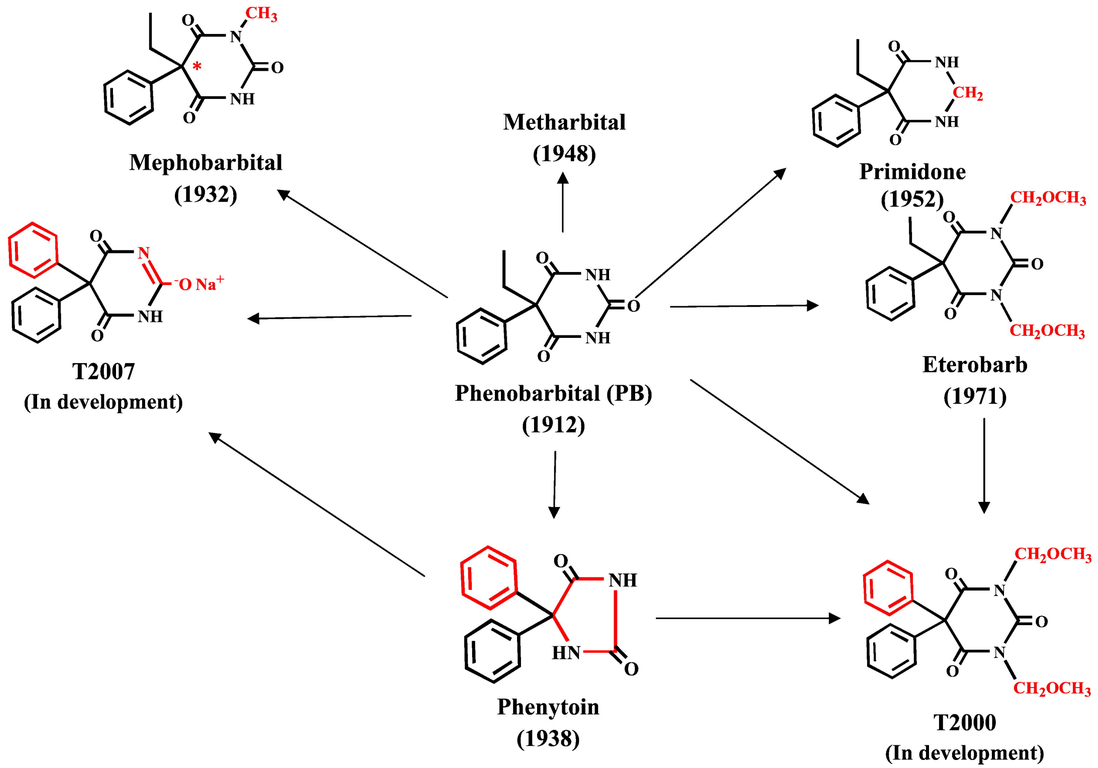
Risk Factors for Rash to Anti Epileptic Drugs

- Previous history of AED-related skin reaction is most significant predictor of future rash
- Higher starting doses and faster titration rates
- Occurs more than twice as often in female patients compared to males in age <50
- Specific ethnic populations may have increased risk due to presence of specific HLA alleles

Most Frequent Offenders

Aromatic AEDs

- Carbamazepine
- Oxcarbazepine
- Eslicarbazepine
- Phenytoin
- Lamotrigine
- Phenobarbital
- Zonisamide
- Ethosuximide
- Perampanel
- Cannabidiol



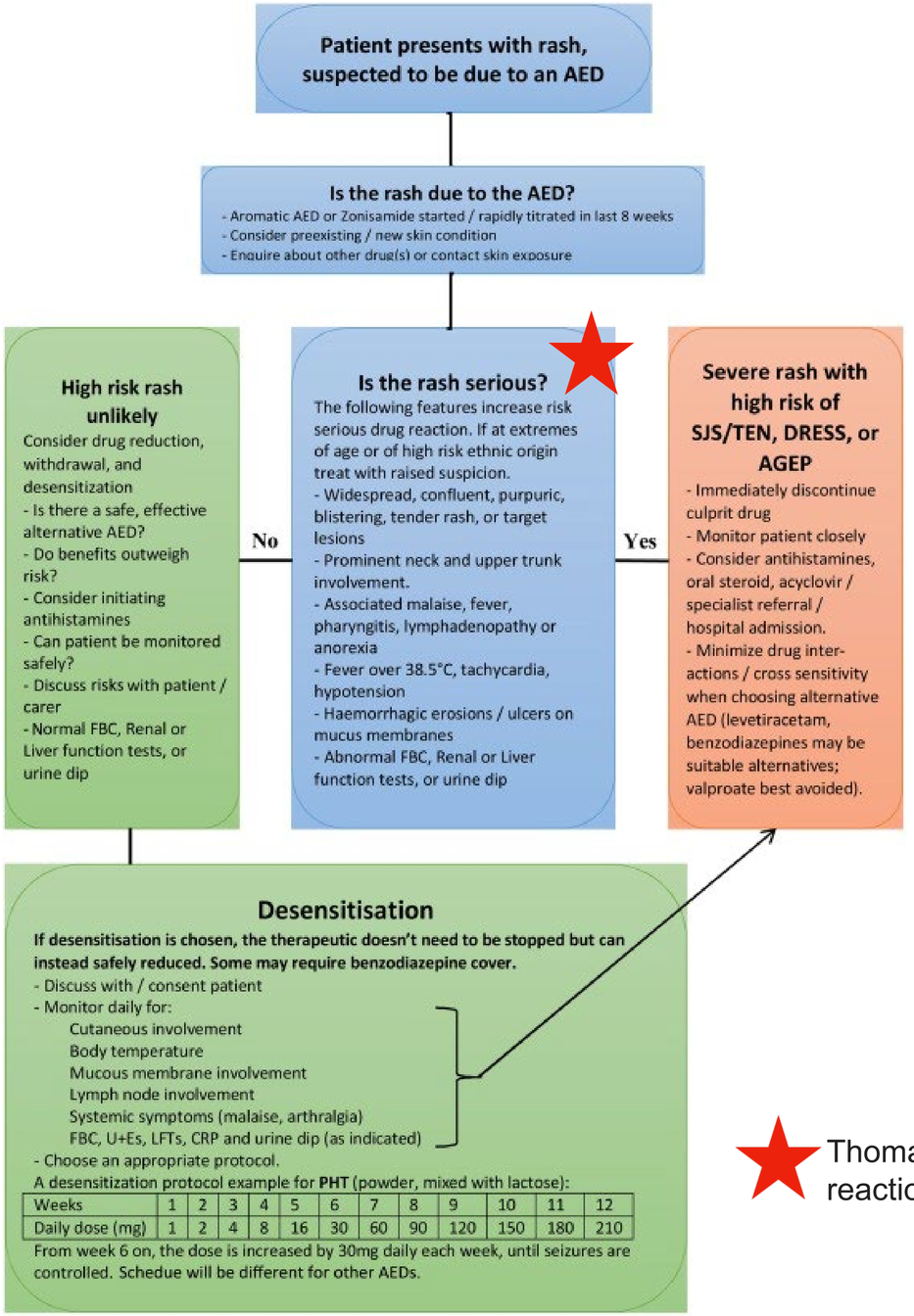
Meir Bialer, Chemical properties of antiepileptic drugs (AEDs)

- *Felbamate and primidone have lower reported rates of rash*

HLA typing

- HLA B*15:02 - Asian patients - strong association with SJS/TEN with CBZ
- HLA A*31:01- worldwide - CBZ association with SJS/TEN, DRESS
- Other high risk alleles for SJS/TEN:
  - HLA B*15:11
  - HLA B*15:08
  - HLA B*15:21

Food & Drug Administration 2018 -
*HLA-B*15:02 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry* ***taking other anti-epileptic drugs associated with SJS/TEN, including phenytoin.***



Is the rash serious?

Rashes cannot be prevented.

Minimize risk by reviewing patient history +/- genotyping.

Notify patients to report rash as soon as possible to provider.

Patients should be counseled on red flag signs for serious hypersensitivity reactions.

Stopping the medication is first step and seeking appropriate assistance depending on severity.

Thomas Fowler, et al. Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting. *Seizure*,Volume 72,2019, Pages 61-70

Hypersensitivity Pearls

- Cannabidiol (CBD) EPIDIOLEX - avoid in patients with sesame oil allergy
- Lamotrigine - risk of HLH (hemophagocystic lymphohistiocytosis) can have overlapping features with DRESS
- HLA genotyping guidelines - Clinical Pharmacogenetics Implementation Consortium: https://cpicpgx.org/guidelines

References

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Rash photographs courtesy of VisualDX