Drug Hypersensitivity Reaction (HSR): DRESS Syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)

Farzaneh Dastan
Assistant Professor of Clinical Pharmacy
Shahid Behehshti University of Medical Sciences
Cutaneous Drug Reactions

- With an underlying immune mechanism: hypersensitivity reaction.
- With a non-immunological cause: are more common and include cumulative toxicity, overdose, photosensitivity, drug interactions, and metabolic alterations.
Adverse Drug Reactions

- Type A reactions are pharmacological effects that are predictable and dose-dependent and consist of side effects and drug interactions.

- Type B reactions are HSR that are unpredictable and not dose-dependent, usually occurring at normally tolerated doses. Comprise about 10%–15% of all ADRs.
The term hypersensitivity is applied when the immune response to an agent (immunogen) results in an increased or exaggerated response.
Different types of immune effect or mechanism can produce diverse clinical patterns of HSR, for example, penicillins, as the classic drugs acting as haptens, are reported to cause type 1 IgE mediated (immediate-type) HSRs as well as non-IgE mediated reactions.
Certain patient groups

- There is a high incidence of HSR in patients with altered immune status, for example due to viral infections (Epstein–Barr virus or HIV).
- Example is the increased risk of co-trimoxazole hypersensitivity in HIV patients.
### Medications Involved in HSR

- Abacavir
- Dapsone
- Nevirapine
- Allopurinol
- Diltiazem
- Oxicam
- NSAIDs
- Atenolol
- Gold salts
- Phenobarbitone
- Azathioprine
- Isoniazid
- Phenytoin
- Captopril
- Lamotrigine
- Sulfasalazaine
- Carbamazepine
- Mexiletine
- Sulfonamides
- Clomipramine
- Minocycline
- Trimethoprim
Drugs rarely causing cutaneous eruptions
(rates estimated to be 3 cases per 1000)

<table>
<thead>
<tr>
<th>Antacids</th>
<th>Muscle relaxants</th>
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<tr>
<td>Antihistamines (oral)</td>
<td>Nitrates</td>
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<td>Atropine</td>
<td>Nystatin</td>
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<td>Benzodiazepines</td>
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<td>Corticosteroids</td>
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<td>Digoxin</td>
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<td>Ferrous sulphate</td>
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<td>Insulin</td>
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<td>Laxatives</td>
<td>Vitamins</td>
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<td>Local anaesthetics (other than topical)</td>
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The timing of skin reactions

- New drugs taken within the previous month are the most likely cause.
- Rechallenge and skin prick are not recommended.
- Onset occurs within a few weeks of the introduction.

Exceptions
- Penicillins, Gold, Practolol
Future Prevention

- Cross-hypersensitivity reactions are common and can occur between the three main aromatic anticonvulsants (i.e. phenytoin, carbamazepine and phenobarbitone) as well as NSAIDs.

- As genetics are suspected in HSR, first-degree relatives may be at increased risk of developing hypersensitivity reactions to similar medicines.
Review of Skin Reactions
Drug Eruptions

- DRESS Syndrome
- Urticaria
- Angioedema/anaphylaxis
- Drug-induced exanthems
- Hypersensitivity vasculitis
- Exfoliative dermatitis/Erythroderma
- SJS/TEN
- Fixed drug eruption
- Photosensitivity
DRESS Syndrome

- Drug Rash with Eosinophilia and Systemic Symptoms
- Formerly called Hypersensitivity Syndrome (HSS)
- Typically presents with rash and fever (87%), classically erythematous follicular papules and pustules, but may also include bullae or purpura.
- Other severe systemic manifestations such as hepatitis (51%), arthralgias, lymphadenopathy (75%), interstitial nephritis (11%), or hematologic abnormalities (30%).
- Can affect any organ system (lungs, CNS, GI, etc.)
- Usually occurs 2-6 weeks after initiation of the medication, which is later than most drug eruptions.
DRESS Syndrome

- Common causes: aromatic anticonvulsants (oxcarbazepine, carbamazepine, phenytoin, phenobarbital, etc.) and sulfonamides.
- Other drugs implicated:
  - lamotrigine
  - allopurinol
  - NSAIDs
  - captopril
  - CCBs
  - mexiletine
  - fluoxetine
  - dapsone
  - metronidazole
  - minocycline
  - antiretrovirals.
Urticaria

- Time to onset: immediate, accelerated (hours), or delayed (days).
- Type I hypersensitivity reactions: antibiotics (especially PCN, cephalosporins, and sulfonamides), local anesthetics, radiocontrast media, blood products, and gamma globulin.
- Non-immune urticaria: radiocontrast media and long-acting ACE-inhibitors (due to changes in vascular response to bradykinin).
- Mast cell degranulation by non-IgE mechanisms: opiate analgesics, anesthetic muscle relaxants, and Vancomycin (Red Man Syndrome, which can be worsened by concomitant opiate use).
Angioedema/Anaphylaxis

- Caused by degranulation of mast cells in the deeper dermis and subcutaneous tissues.
- May occur along with urticaria (50% of cases)
- Can be life-threatening if it causes laryngeal edema or tongue swelling.
- Can be non-mast cell mediated, as in the case of ACE-inhibitors.
Drug-induced Exanthems

- Account for close to 75% of all drug eruptions.
- Morbilliform, maculopapular eruptions.
- Most commonly prescribed medications (antibiotics, sulfa).
- Often associated with pruritis, low-grade fever, eosinophilia.
Drug-induced Exanthems

- May be the early stage of more severe reactions such as TEN, DRESS, or SSLR
- Onset within 2 weeks of starting a new drug, or within days of re-exposure.
- More common in patients with altered immunity, such as those with HIV or mononucleosis ("ampicillin rash").
- Treatment is discontinuation of the drug. Antihistamines, topical steroids, and topical antipruritics may also help.
**Morbilliform eruption** Drug-induced exanthems, such as this morbilliform eruption, often begin in dependent areas and generalize. A morbilliform eruption can be the presenting sign of a more serious reaction such as toxic epidermal necrolysis, hypersensitivity syndrome, or serum sickness. Courtesy of Andrew Samel, MD.
Morbilliform Drug Eruption
Erythema Multiforme Major
Stevens-Johnson Syndrome

- Widely distributed purpuric macules and blisters and prominent involvement of the trunk and face are likely to have SJS, which is usually drug-induced.

- Generalized eruption of lesions that initially had a target-like appearance but then became confluent, brightly erythematous, and bullous.
Stevens-Johnson Syndrome and toxic epidermal necrolysis are likely two manifestations on the same spectrum. The disease is best termed SJS when epidermal detachment involves less than 10% of the body surface area, whereas TEN involves greater than 30%.

SJS and TEN usually occur 1-3 weeks after exposure, but can occur more rapidly with re-exposure, which suggests an immunologic mechanism.

Mucosal involvement is seen in 90% of cases, including painful crusts and erosions on the oral mucosa, conjunctivae, and genital mucosa.

Corticosteroids are not recommended.

Patients are best managed as burn victims.
Stevens-Johnson Syndrome
Vancomycin 10 days (on 20th day of life)
Hypersensitivity vasculitis

- American College of Rheumatology proposed the following five criteria. The presence of three or more had a sensitivity of 71% and a specificity of 84% for the diagnosis.
  - Age > 16
  - Use of possible offending drug in temporal relation to symptoms
  - Palpable purpura
  - Maculopapular rash
  - Biopsy of a skin lesion showing neutrophils around an arteriole or venule.
- Most likely due to drugs that can act as haptens to stimulate the immune response: PCN, cephalosporins, sulfonamides, phenytoin, and allopurinol.
- Additional findings: fever, urticaria, arthralgias, low complement levels, and elevated ESR.
Hypersensitivity Vasculitis
Fixed Drug Eruptions

- Drug eruption that occurs at the same location every time a particular medication is used.
- Begins as an erythematous, edematous plaque with a grayish center or frank bullae, then progresses to dark, post-inflammatory pigmentation.
- Sites include the mouth, genitalia, face, and extremities.
- Causes include phenolphthalein, tetracyclines, barbituates, sulfonamides, NSAIDs, and salicylates.
Fixed drug eruption  An acute fixed drug eruption in this patient who took Donnatal® is characterized an edematous plaque with a bullous center. Courtesy of Andrew Samel, MD.
Two types include phototoxic eruptions and photoallergic eruptions.

Phototoxic eruptions are due to absorption of UV light (usually UVA) by the drug, which causes a release of energy and damage to cells. Looks like a bad sunburn, which may blister.

Photoallergic eruptions are a lymphocyte-mediated reaction caused by exposure to UVA, which converts the drug to an immunologically active compound that activates lymphocytes, causing an eczematous reaction in a photodistribution.

- Usually due to topical agents including fragrances and biocides in soaps.

Both types can be caused by phenothiazines, chlorpromazine, sulfa, and NSAIDS, although phototoxic reactions are more common with these agents.
Warfarin-induced Skin Necrosis

- A rare and devastating effect of warfarin therapy is skin necrosis, a consequence of occlusive thrombi in vessels of the skin and subcutaneous tissue, and typically begins three to five days after therapy is initiated.

- Red, painful plaques evolve to necrosis with hemorrhagic blisters or necrotic scars, frequently in areas with large quantities of adipose tissue, including the breasts, hips, and buttocks.
Warfarin-induced Skin Necrosis
References


• UpToDate Online