Drug eruptions can mimic a wide range of dermatoses

Is a common cause of dermatological consultation.

The morphologies are myriad (countless) and include morbilliform: maculopapular (most common 75-95%), urticarial 5-6%, papulosquamous, pustular, and bullous.

A drug-induced reaction should be considered in any patient who is taking medications and suddenly develops a symmetric cutaneous eruption.

Medications can cause pruritus or dysesthesia (painful sensation) without an obvious eruption.

Medications that are causing cutaneous reactions include: antimicrobial agents, nonsteroidal anti-inflammatory drugs (NSAIDs), cytokines, chemotherapeutic agents, anticonvulsants, and psychotropic agents.

**Pathophysiology of Drug eruptions**

immunologically and nonimmunologically reactions:

A. **Immunologically mediated reactions**: are 4 types

*Type I* is immunoglobulin E (IgE)–dependent reactions: result in urticaria, angioedema, and anaphylaxis. Insulin and other proteins are associated with type I reactions.

*Type II* is cytotoxic reactions: result in hemolysis and purpura. Penicillin, cephalosporins, sulfonamides, and rifampin

*Type III* is immune complex reactions: result in vasculitis, serum sickness, and urticaria. Quinine, salicylates, chlorpromazine, and sulfonamides.

*Type IV* is delayed-type (cell-mediated hypersensitivity):

- Results in Allergic Contact Dermatitis (neomycin), exanthematous reactions, and photoallergic reactions.
- The cells playing role are Langerhan’s cells.
- Most drug eruptions are type IV hypersensitivity reactions, only a minority are IgE-dependent (type I).
- Not dose dependent,
- Usually begin 7-20 days after the medication is started
- May involve blood or tissue eosinophilia
- May recur if the drugs are readministered.

B. **Nonimmunologically mediated reactions**: Due to:

1. Accumulation: *argyria* (blue-gray discoloration of skin and nails) observed with use of silver nitrate nasal sprays.
2. adverse effects:
3. direct release of mast cell mediators:
4. idiosyncratic reactions:
5. Imbalance of endogenous flora: may occur when antimicrobial agents suppress the growth of one species of microbe
6. Intolerance:
   - Herxheimer phenomenon is a reaction due to bacterial endotoxins and microbial antigens that are liberated by the destruction of microorganisms.
   - fever, tender lymphadenopathy, arthralgias, transient macular or urticarial eruptions, and exacerbation of preexisting cutaneous lesions.
   - The reaction is not an indication to stop treatment because symptoms resolve with continued therapy.
   - seen with penicillin therapy for syphilis griseofulvin or ketoconazole therapy for dermatophyte infections.
   - Overdosage
   - Phototoxic dermatitis

**Epidemiology of Drug eruptions**
- Occur in 2-3% of inpatients.
- More prevalent in women and Elderly patients
- Mortality/Morbidity:
  - Most drug eruptions are mild, self-limited, and usually resolve after the offending agent has been discontinued.
  - Severe and potentially life-threatening eruptions occur in 1 in 1000 hospital patients.
- Mortality rates for
  - Erythema multiforme (EM) major are significantly higher.
  - Stevens-Johnson syndrome (SJS) has a mortality rate of less than 5%.
  - TEN approaches 20-30%; most patients die from sepsis.

**History in drug reactions:**
- Review the patient's complete medication list
- History of previous adverse reactions to drugs or foods.
- Consider alternative etiologies, especially viral exanthems and bacterial infections.
  - Morbilliform or exanthematous (maculopapular):
    - in children are due to a viral infection
    - in adults are due to medications.
- any concurrent infections: (eg, due to HIV infection, cancer, chemotherapy) because these increase the risk of drug eruptions.

**Note and detail the following:**

All prescription and over-the-counter drugs, including topical agents, vitamins, and herbal and homeopathic remedies

The interval between the introduction of a drug and onset of the eruption
Route, dose, duration, and frequency of drug administration

Use of parenterally administered drugs, which are more likely than oral agents to cause anaphylaxis

Use of topically applied drugs, which are more likely than other drugs to induce delayed-type hypersensitivity reactions

Use of multiple courses of therapy and prolonged administration of a drug, which can cause allergic sensitization

Any improvement after drug withdrawal and any reaction with readministration

**Physical Examinations in drug reactions:**

Most drug eruptions are Morbilliform or exanthematous (maculopapular)

The following are features of severe, potentially life-threatening drug reaction, (TEN or hypersensitivity syndrome:

- Mucous membrane erosions = (Enanthems)
- Blisters (Blisters herald a severe drug eruption.)
- Nikolsky sign (epidermis sloughs with lateral pressure; indicates serious eruption that may constitute a medical emergency)
- Confluent erythema
- Angioedema and tongue swelling
- Palpable purpura
- Skin necrosis
- Lymphadenopathy
- High fever, dyspnea, or hypotension

*The morphology and features of drug eruptions can help the clinician determine the causative medication and the most appropriate treatment.*

*Exanthem: is skin eruption*

*Enanthem: eruption on a mucous membrane (as the inside of the mouth)*

**Morbilliform or exanthematous (maculopapular) drug eruption**

Is the most common pattern of drug eruptions

Is the quintessential (the most perfect) drug rash.

Exanthem: typically symmetric, with confluent erythematous macules and papules that spare the palms and soles.

It typically develops within 2 weeks after the onset of therapy.

Drugs: ACE inhibitors, allopurinol, amoxicillin, ampicillin, anticonvulsants, barbiturates, carbamazepine, isoniazid, NSAIDs, phenothiazine, phenytoin, sulfonamides, thiazides.........
Acneiform eruption: (steroid acne)

- Inflammatory papules or pustules that have a follicular pattern.
- localized primarily on the upper body
- In contrast to acne vulgaris, comedones are absent in acneiform eruptions.
- Drugs: corticosteroids, halogens, haloperidol, hormones, isoniazid, lithium, phenytoin

Acral erythema

- is a relatively common reaction to chemotherapy, e.g.: Methotrexate-Induced Acral Erythema with Bullous Reaction
- symmetric tenderness, edema, and erythema of the palms and soles.
- Often resolves 2-4 weeks after chemotherapy is discontinued.

Acute generalized exanthematous pustulosis (AGEP)

- occurs with many small, sterile, nonfollicular pustules.
- is similar to pustular psoriasis, but AGEP has more marked hyperleukocytosis with neutrophilia and eosinophilia.
- Causes:
  - Drugs (primarily antibiotics) (Most cases), often in the first few days of administration.
  - Viral infections, mercury exposure, or UV radiation (few cases)
- Resolves spontaneously and rapidly, with fever and pustules lasting 7-10 days then desquamation over a few days.
- Drugs: Most commonly beta-lactam antibiotics, macrolides, and mercury

Dermatomyositis like

- Gottron papules but no muscle involvement
- Drugs: BCG vaccine, hydroxyurea (most common), lovastatin and simvastatin, omeprazole and penicillamine

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

- Triad of fever, skin eruption, and internal organ involvement
- Most commonly, aromatic anticonvulsants (phenytoin, phenobarbitone, carbamazepine, sulfonamides, minocycline, and doxycycline

Erythema Multiformis: (EM minor, EM major)

- EM minor is a mild disease; patients are healthy.
- It is characterized by target lesions on the extremities.
- Mucous membrane involvement may occur but is not severe.
- Patients recover fully, but relapses are common.
- Most cases are due to infection with herpes simplex virus, and treatment and prophylaxis with acyclovir is helpful.
- Drugs: Busulfan, chlorambucil, cyclophosphamide, diethylstilbestrol (DES), hydroxyurea, MTX
**SJ S and TEN are categorized as EM major:**

**A. SJS: Stevens-Johnson syndrome:**
- Widespread skin involvement, large and atypical targetoid lesions, significant mucous membrane involvement, constitutional symptoms, and sloughing of 10% of the skin.
- caused by drugs and infections
- Drugs: Allopurinol, anticonvulsants, aspirin/NSAIDS, barbiturates, carbamazepine, cimetidine, ciprofloxacin........

**B. TEN: Toxic epidermal necrolysis:**
- is a severe skin reaction that involves a prodrome of painful skin (like sunburn) quickly followed by rapid, widespread, full-thickness skin sloughing, typically affects 30% the total body surface area.
- Drugs: Allopurinol, anticonvulsants, aspirin/NSAIDs, isoniazid, sulfonamides, and tetracyclines

**Erythema nodosum**
- Tender, red, subcutaneous nodules that typically appear on the anterior aspect of the legs.
- Lesions do not suppurate or become ulcerated.
- It is a reactive process often secondary to infection, but it may be due to medications, especially oral contraceptives and sulfonamides.

**Erythroderma**
- is widespread inflammation of the skin
- it may result from an underlying skin drug eruption, internal malignancy, or immunodeficiency syndrome.
- Lymphadenopathy is often noted, and hepatosplenomegaly, leukocytosis, eosinophilia, and anemia may be present.
- Drugs: Allopurinol, anticonvulsants, aspirin, barbiturates, captopril........

**Fixed drug eruptions**
- lesions recur in the same area when the offending drug is given.
- Circular, violaceous, edematous plaques that resolve with macular hyperpigmentation is characteristic.
- Lesions occur 30 minutes to 8 hours after drug administration.
- Perioral and periorbital lesions may occur, but the hands, feet, and genitalia are the most common
- Drugs: sulfonamides, tetracyclines, barbiturates, dapsone, Acetaminophen, ampicillin, anticonvulsants, aspirin/NSAID........

**Drug Hypersensitivity syndrome**
- is a potentially life-threatening complex of symptoms
- Patients have fever, sore throat, rash, lymphadenopathy, hepatitis, nephritis, and leukocytosis with eosinophilia.
• It usually begins within 1-3 weeks after a new drug is started, but it may develop 3 months or later into therapy.
• often caused by Aromatic anticonvulsant drugs cross-react (ie, phenytoin, phenobarbital, carbamazepine); valproic acid is a safe alternative.

**Leukocytoclastic vasculitis**

• is the most common severe drug eruption
• It is characterized by blanching erythematous macules quickly followed by palpable purpura.
• Fever, myalgias, arthritis, and abdominal pain may be present.
• It typically appears 7-21 days after the onset of drug therapy, and a laboratory evaluation to exclude internal involvement is mandatory.
• Drugs: Adalimumab, allopurinol, aspirin/NSAIDs, cimetidine......
• Vasculitic reaction on the legs (HSP):

**Lichenoid**

• Similar to lichen planus (LP) and may be severely pruritic.
• Drugs: Amlodipine, antimalarials, beta-blockers, captopril, diltiazem, enalapril, furosemide, gold, L-thyroxine, penicillamine, phenothiazine, pravastatin, proton pump inhibitors, sildenafil, tetracycline, and thiazides

**Drug-induced systemic lupus erythematosus (SLE)**

• Drug: most commonly associated with hydralazine, procainamide, and minocycline.
• Beta-blockers, chlorpromazine, cimetidine, estrogens, isoniazid, lovastatin, methyldopa, oral contraceptives, sulfonamides, tetracyclines, and tumor necrosis factor (TNF)-alpha inhibitors.

**Pseudoporphyria**

• While largely a drug-induced condition, it can also occur with use of tanning beds and hemodialysis.
• blistering and skin fragility identical to PCT: porphyria cutanea tarda, but
• hypertrichosis and sclerodermoid changes are absent and
• urine and serum porphyrin levels are normal.
• Treatment is sun protection and withdrawal of the medication.
• Drugs: Amiodarone, cyclosporine, dapsone, etretinate,
• 5-fluorouracil, flutamide, furosemide, hydrochlorothiazide isotretinoin, NSAIDs (including nalidixic acid and naproxen), oral contraceptive pills, and tetracycline

**Urticaria**

• usually occurs as transient small wheals that may coalesce or may have cyclical or gyrate forms.
• Lesions usually appear shortly after the start of drug therapy and resolve rapidly when the drug is withdrawn.
• Drugs: ACE inhibitors, aspirin/NSAIDs, blood products, cephalosporins, clopidogrel......
Serum sickness

- Serum sickness: type III hypersensitivity reactions mediated by the deposition of immune complexes (ICs) in small vessels, activation of complement, and recruitment of granulocytes.
- Begins with erythema on the sides of the fingers, hands, and toes and progress to (most often morbilliform or urticarial).
- Viscera may be involved, and fever, arthralgia, and arthritis are common.
- Drugs: Antithymocyte globulin for bone marrow failure, human rabies vaccine, penicillin, pneumococcal vaccine (in AIDS patients), and vaccines containing horse serum derivatives.

Sweet syndrome: (acute febrile neutrophilic dermatosis)

- Tender erythematous papules and plaques
- The surface of the lesions may become vesicular or pustular.
- Fever (most often), arthritis, arthralgias, conjunctivitis, episcleritis, and oral ulcers.
- Laboratory evaluation usually reveals an elevated ESR, neutrophilia, and leukocytosis.
- Drugs: retinoic acid, nitrofurantoin, oral contraceptives, tetracyclines, and trimethoprim-sulfamethoxazole.

Vesiculobullous reactions

- Resemble pemphigus, bullous pemphigoid, linear immunoglobulin A (IgA) dermatosis, dermatitis herpetiformis, herpes gestationis, or cicatricial pemphigoid.
- Drugs: ACE inhibitors, aspirin/NSAIDs, barbiturates, captopril, cephalosporins, entacapone, estrogen, furosemide, griseofulvin, influenza vaccine, penicillamine, penicillins, sertraline sulfonamides, and thiazides.

Pemphigus

- Thiols include captopril, D-penicillamine, gold sodium thiomolate, mercaptopropionylglycine, pyritinol, thiamazole, and thiopronine.
- Nonthiols include aminophenazone, aminopyrine, azapropazone, cephalosporins…
- Bullous pemphigoid: Ampicillin, D-penicillamine, captopril, chloroquine, ciprofloxacin, enalapril………
- Linear IgA dermatosis: Atorvastatin, captopril, carbamazepine, diclofenac, glibenclamide………

Alopecia: ACE inhibitors, allopurinol, anticoagulants, azathioprine, bromocriptine, beta-blockers, cyclophosphamide, hormones, NSAIDs, phenytoin, methotrexate (MTX), retinoids, and valproate

Photosensitivity: ACE inhibitors, amiodarone, amlodipine, chlorpromazine………

Psoriasis: ACE inhibitors, angiotensin receptor antagonists, antimalarials, beta-blockers, bupropion, calcium channel blockers, carbamazepine, interferon (IFN) alfa, lithium, metformin, NSAIDs, terbinafine, tetracyclines, valproate sodium, and venlafaxine

Psychotropic drugs may cause: Alopecia, EM, Morbilliform (exanthematous), Photosensitivity, Pigmentation, Urticaria, Vasculitis.
Chemotherapeutic agents may cause: Acneiform, Acral erythema, Alopecia, EM, Erythema nodosum, Fixed drug eruptions, Hyperpigmentation, Lichenoid, Lupus, Morbilliform (exanthematous), TEN, Vasculitis and Urticaria

Differential Diagnoses of drug reactions:
- Acute Febrile Neutrophilic Dermatosis
- Contact Dermatitis: Allergic and Irritant
- Erythema Multiforme (EM)
- Erythema Nodosum (EN)
- Erythroderma (Generalized Exfoliative Dermatitis)
- Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood)
- Graft Versus Host Disease
- Hypersensitivity Vasculitis (Leukocytoclastic Vasculitis)
- Lichen Planus
- Measles, Rubeola
- Pityriasis Rosea
- Porphyria Cutanea Tarda
- Psoriasis, Pustular
- Rubella
- 2ndary Syphilis
- Urticaria: Acute and Chronic

Prognosis of drug reactions
- Full recovery without any complications is expected for most drug eruptions.
- Even after the drug is discontinued, drug eruptions may clear slowly or worsen over the next few days.
- The time required for total clearing may be 1-2 weeks or longer.
- Patients with exanthematous eruptions should expect mild desquamation as the rash resolves.

Treatment:
1. Discontinue the offending medication if possible
2. Therapy for most drug eruptions is mainly supportive in nature.
   - Oral antihistamines
   - topical steroids
   - Prednisone tablets.
   - IV Ig is currently the most common agent used to treat TEN.
   - Cyclosporine may also have a role in the treatment of TEN.