DRUG REACTIONS FOR THE CLINICAL RESEARCHER

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DISCLAIMER

- Many!!! But None related to this lecture
- Most of the slides are provided by the AAD medical curriculum

OBJECTIVES

- Describe the morphology of some common and rarer, severe drug eruptions
- Describe how to create a drug timeline
- Locate resources for identifying causes of drug eruptions
- Describe initial steps in the management for drug eruptions
- Recognize when to refer a patient with a drug eruption to a dermatologist

CTCAE AE DEFINITION

- An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

GRADES

- Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

General Principles

- It is always prudent to consider drugs as the cause of a rash
- Most cutaneous drug reactions are inflammatory, generalized, and symmetric
- Diagnosis is established by their clinical features, including morphology and timing
- Histology (skin biopsy) can be helpful

Types of Drug Reactions

This module will focus on the most common and most severe drug reactions

- Exanthematous drug eruption
- Fixed drug eruption
- Drug-induced hypersensitivity syndrome (DIHS), also called Drug-related eosinophilia with systemic symptoms (DRESS)
- Epidermal necrolysis: Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)

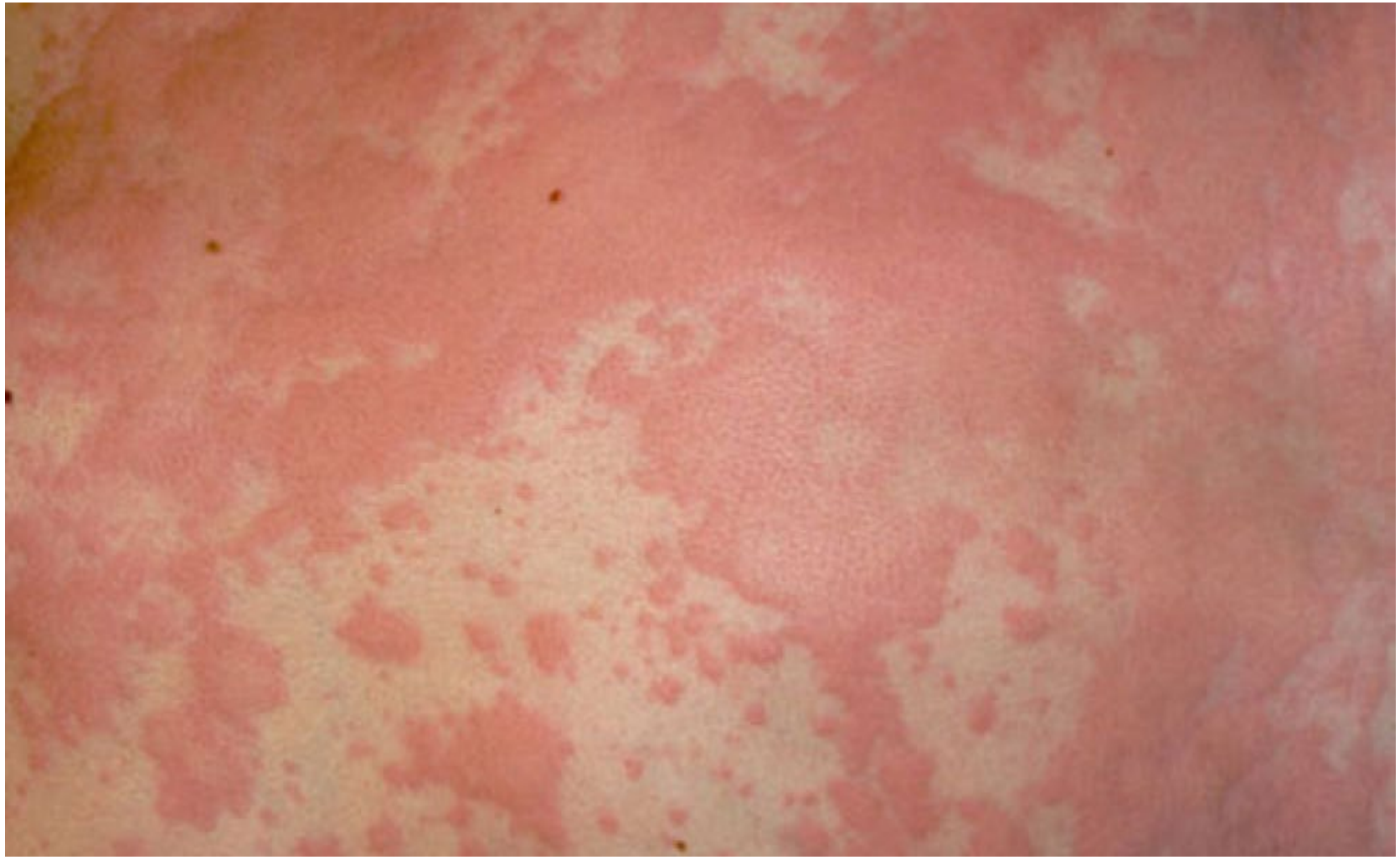
Immediate vs. Delayed Reactions

Drug-induced skin reactions can be classified according to timing:

- Immediate reactions: occur less than 1 hour of the last administered dose
  - Urticaria, angioedema, anaphylaxis*
- Delayed reactions: occurring after one hour, but usually more than 6 hrs and occasionally weeks to months after the start of administration
  - Exanthematous eruptions
  - Fixed drug eruption
  - Systemic reactions (DIHS, SJS, TEN)
  - Vasculitis (may also be systemic)*

Case

- HPI: 56 y/o female with 3 day history of widely pruritic erythematous wheals that come and go. She switched her detergent 3 weeks ago.
- PMH: knee replacement 6 weeks ago
- Allergies: none
- Medications: oxycodone for pain and aspirin



Acute urticaria

- Days to weeks evanescent wheals
- Lasts less than 12 hours
- Complete resolution in less than 6 weeks
- Children: URI, viral infections Adults: drugs and foods
- F>M

Chronic urticarias

- Defined as daily episodes of wheals and/or angioedema that lasts more than 6 weeks
- F>M
- 50% unknown etiology. Up to 35% may be physical

Case 1: History

- **HPI:** Mr. Sutton is a 35-year-old man who presented to his primary care provider with a sore throat and fatigue. He was diagnosed with acute pharyngitis and started on ampicillin for empiric treatment. His symptoms improved. Within a few days of his treatment he presented to urgent care with a new, itchy rash that began on his trunk and has spread to his extremities. He has no new fever and he is feeling generally well.

Case 1: Question 1

What else would you like to know about Mr. Sutton's medical history?

A. A detailed medication history

B. Family history of drug reactions

C. If the primary care provider ordered a test for mononucleosis

D. Past medical history

E. All of the above

A complete drug history includes the following:

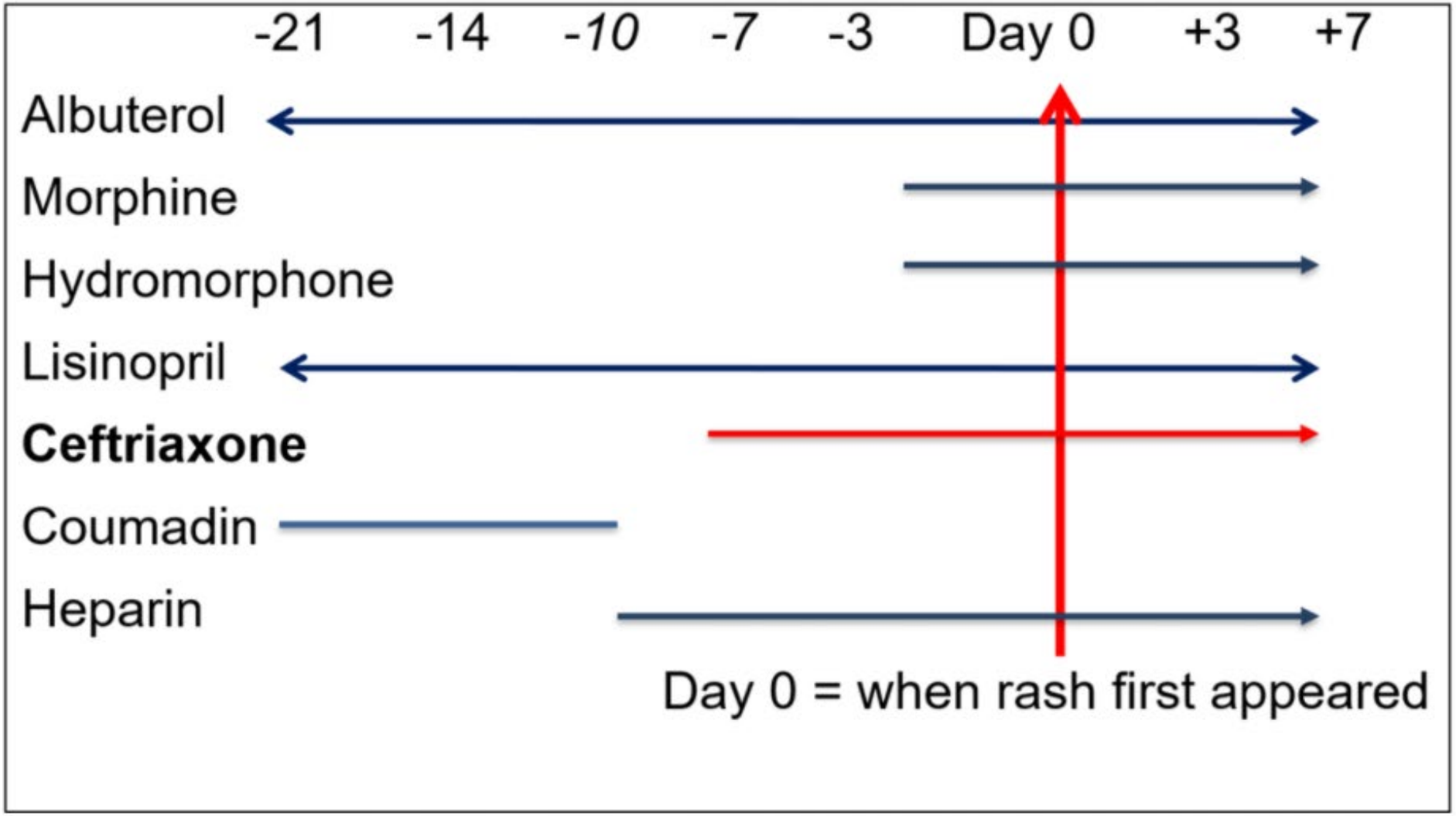
Remember the seven "I's":

- Instilled (eye drops, ear drops)
- Inhaled (steroids, beta adrenergic)
- Ingested (capsules, tablets, syrup)
- Inserted (suppositories)
- Injected (IM, IV)
- Incognito (herbs, non- traditional medicine, homeopathic, vitamins, over-the-counter)
- Intermittent (patients may not reveal medications they take on an intermittent basis unless specifically asked)

Drug Timeline

- When assessing possible drug causation of a rash, consider the timing of drug initiation with relation to rash onset
- Preparing a drug timeline can be helpful in this process
- Start with the onset of the rash as Day 0, and work backwards and forwards
- For exanthematous drug eruptions, the initiation of the medication is often **7-10 days before** first onset and shorter (24 to 48 hours) for repeat exposures

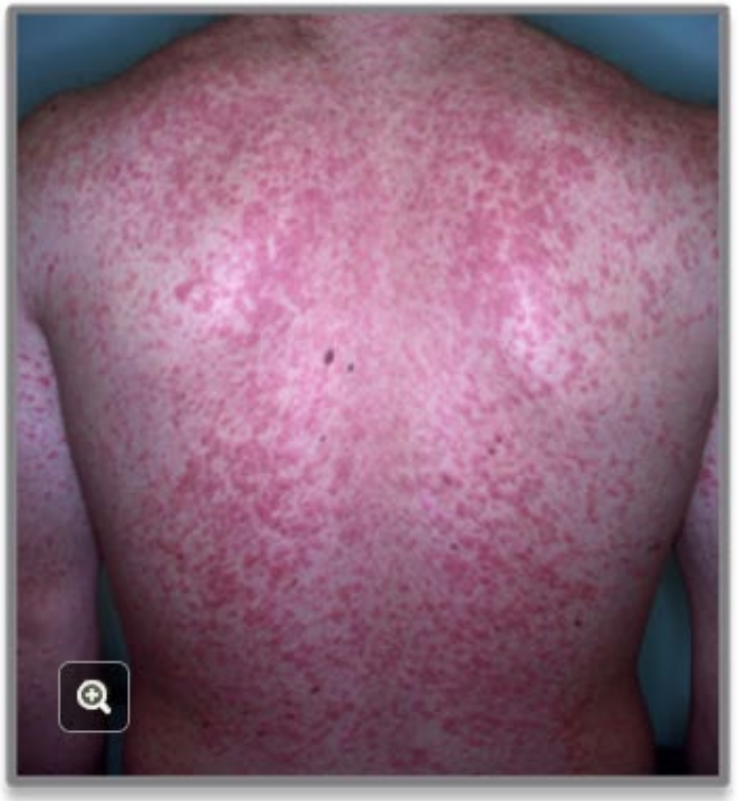
Example of a Drug Timeline



Case 1: Skin Exam

Widespread, symmetric, confluent erythematous macules and papules on the trunk and extremities; a “morbilliform” (measles-like) eruption

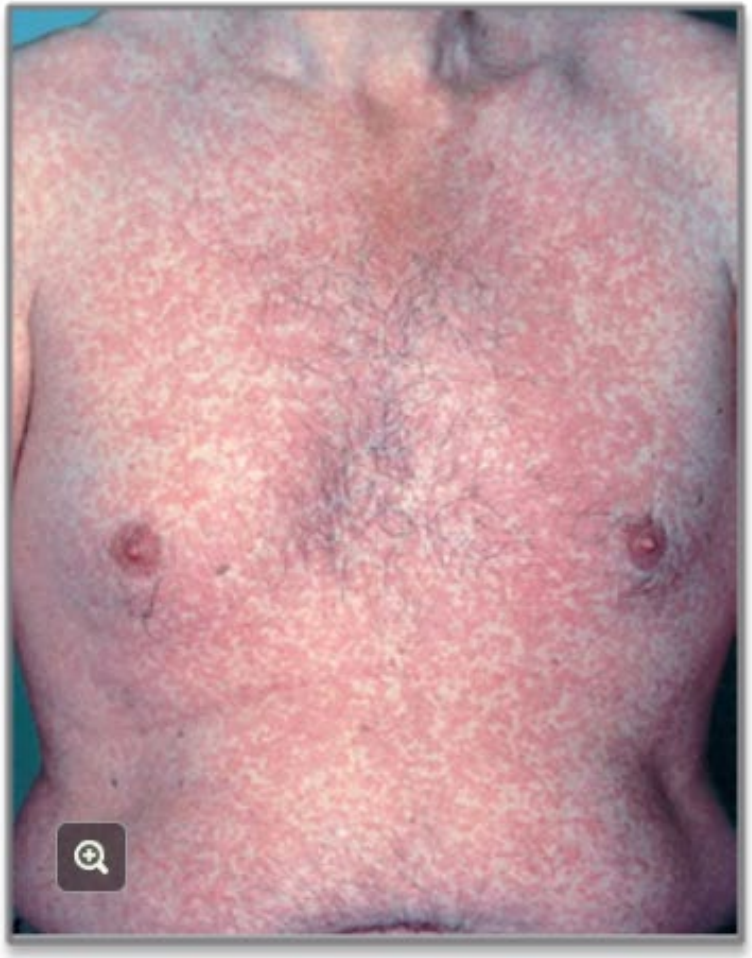
“Maculopapular” is sometimes used in this context, but is imprecise and best avoided

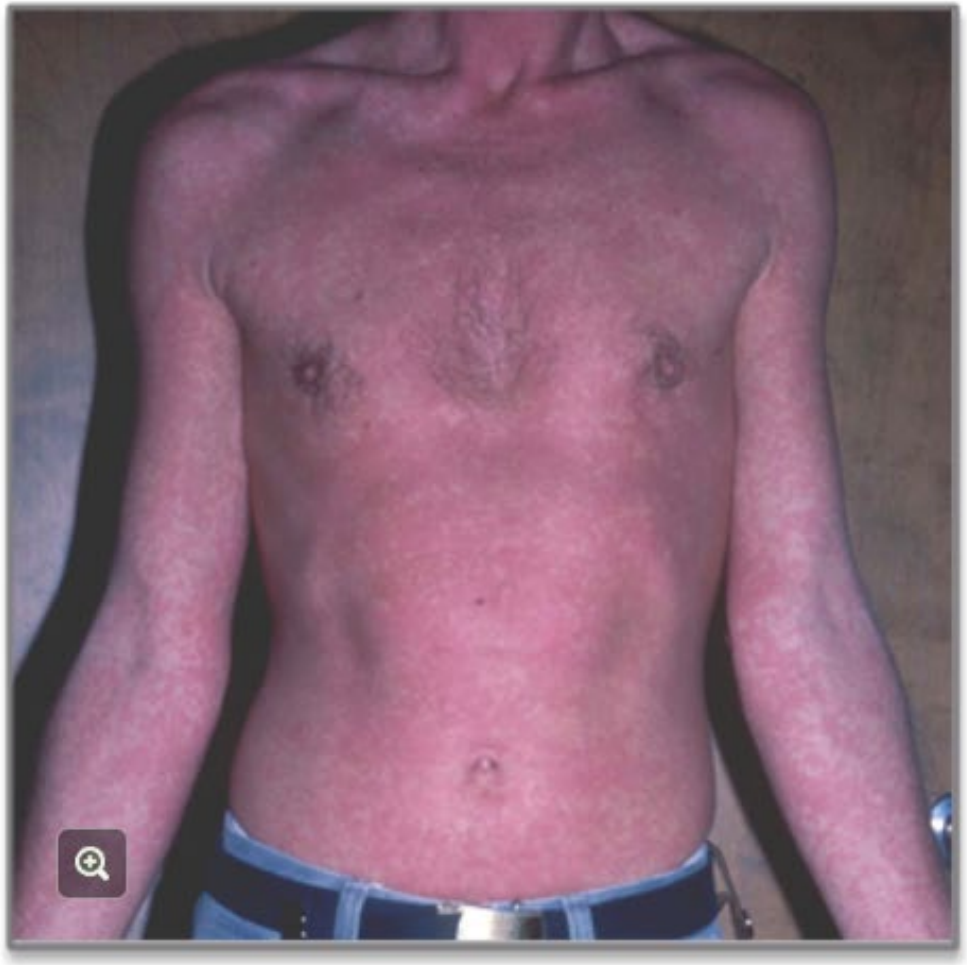


Exanthematous Drug Eruptions

- Exanthematous eruptions are the most common of all cutaneous drug eruptions (~90%)
- Limited to the skin
- Erythematous macules and papules appear on the trunk and spread centrifugally to the extremities in a symmetric fashion
- Pruritus and mild fever may be present
- Rash appears 7 to 10 days after drug initiation if it is the first episode, or 24 to 48 hours after repeat drug initiation

Further examples of Exanthematous Drug Eruptions





Clinical Course and Treatment

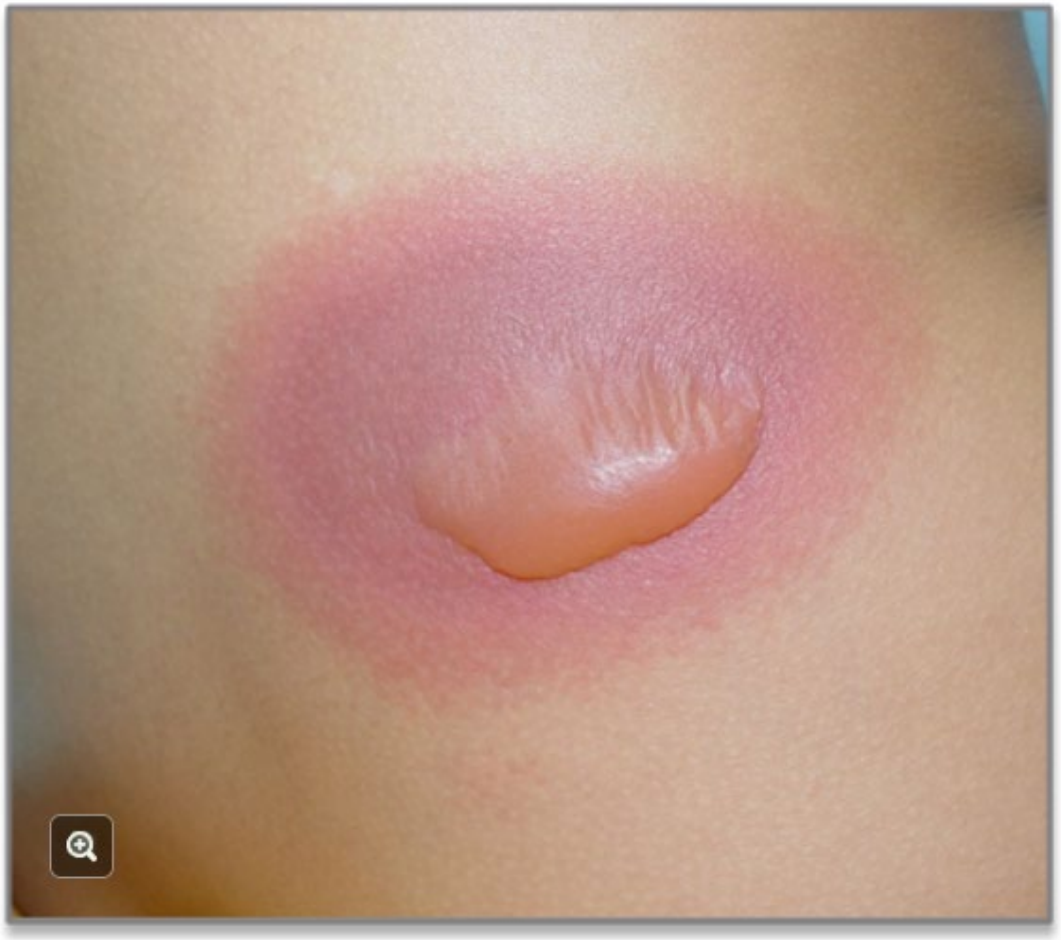
- Resolves in a few days to a week after the medication is stopped
- May continue the medication safely if the eruption is not too severe and the medication cannot be substituted
- Resolves without sequelae (though extensive scaling/desquamation can occur)
- Treatment consists of topical steroids, oral antihistamines, and reassurance

Case 2: History

- **HPI:** Ms. Hernandez is a 26-year-old woman who was recently diagnosed with bacterial vaginosis and prescribed oral metronidazole for treatment. She returned to her primary care provider the following day because she developed a “spot” on her thigh. She recalls having a similar lesion in the same location after her last episode of treated bacterial vaginosis.
- **PMH:** no major illnesses or hospitalizations
- **Medications:** metronidazole 500 mg PO BID x 7 days (on day 2)
- **Allergies:** no known drug allergies
- **Family history:** mother with history of BCC
- **Social history:** recently married, works as a realtor
- **Health-related behaviors:** no tobacco, alcohol, or drug use
- **ROS:** no fevers, sweats, chills

Case 2: Skin Exam

Oval erythematous plaque with a central bulla



Fixed Drug Eruption

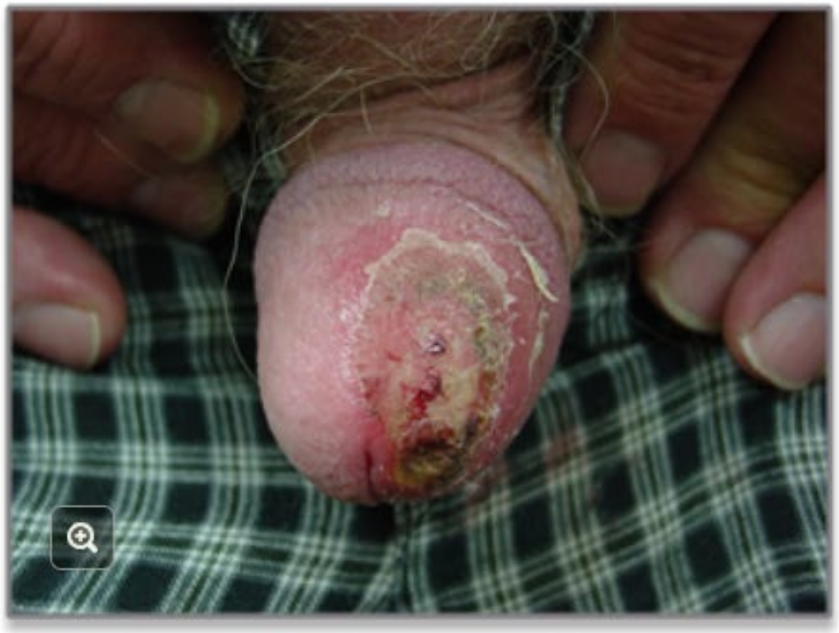
- Fixed drug eruption (FDE) is characterized by the formation of one or more round or oval patches or plaques that will recur at the same site with re-exposure to the drug
  - This distinguishing feature is why it's called "fixed"
- Common drug culprits include:
  - phenolphthalein (laxatives)
  - tetracyclines
  - metronidazole
  - sulfonamides
  - barbiturates
  - NSAIDs
  - salicylates
  - food coloring (yellow)

More on FDE

- Often affects the mouth, genitalia, face, and acral areas, but can occur anywhere
- In previously sensitized individual, lesions may occur from 30 minutes to 8 hours after ingesting the drug
- Early lesions are sharply demarcated erythematous macules
- Lesions become raised, forming plaques, which may evolve to become bullae and then erosions
- In the healing phase, a violet hue may be seen followed by post-inflammatory hyperpigmentation
- Commonly solitary and can be large; may be multiple with random distribution

Examples of FDE

This patient had a FDE to acetaminophen



This patient had a FDE to doxycycline

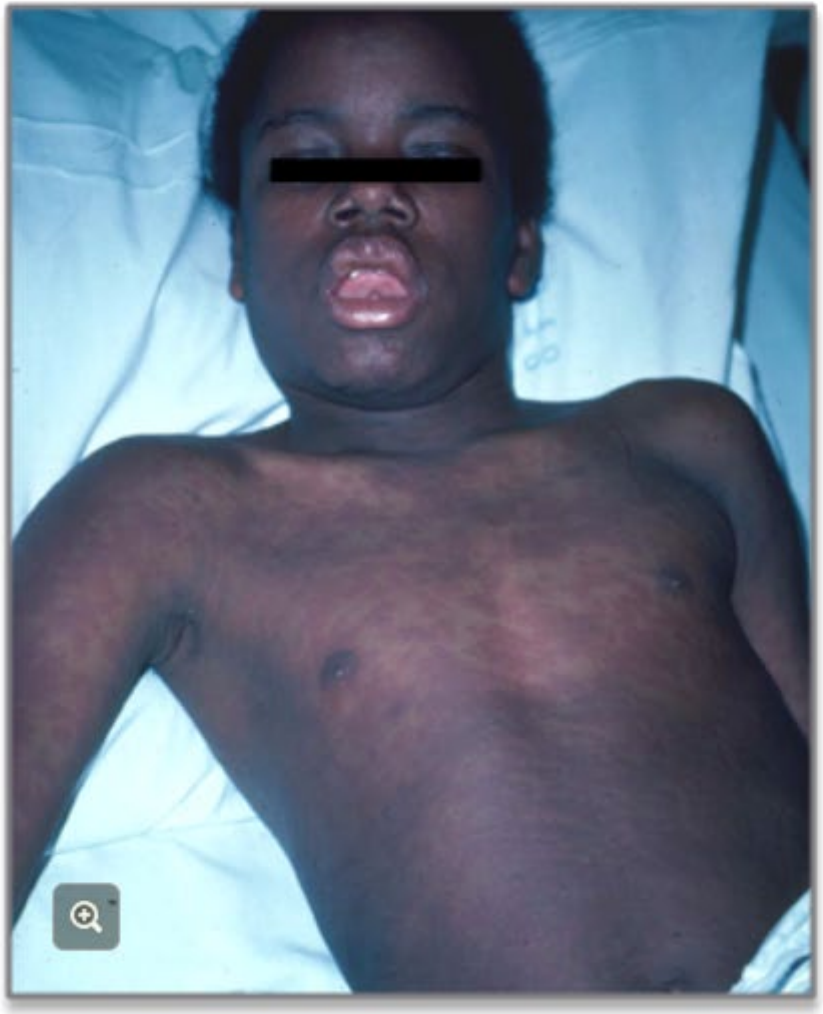
FDE Treatment

- Lesions resolve days to weeks after the drug is discontinued
- Post-inflammatory hyperpigmentation may persist beyond this time frame
- Non-eroded FDE can be treated with a potent topical corticosteroid ointment
- Eroded cutaneous FDE can be treated with a protective or antimicrobial ointment and a dressing until the site has reepithelialized
- Address pain, especially for mucosal lesions
- If widespread or generalized, refer the patient to dermatology

Case 3: History

- **HPI:** Erik is a 12-year-old boy with a seizure disorder who was recently started on phenytoin. Three weeks after starting therapy, he began to feel unwell with fever and malaise. He was brought to the emergency room by his mother when a generalized rash appeared.
- **PMH:** appendectomy at age 5
- **Medications:** phenytoin 300mg PO daily
- **Allergies:** no known drug allergies
- **Family history:** father with hypertension
- **Social history:** lives at home with his parents and younger brother, attends junior high
- **Health-related behaviors:** no tobacco, alcohol or drug use
- **ROS:** as above

Case 3: Skin Exam



Vital signs: T 101.4, HR 100, BP 100/60, RR 16, 0_2 sat 97% on RA

Gen: ill-appearing male in NAD

Skin: facial edema, diffuse erythematous macules and plaques on the trunk and extremities

Clinical Pearl

When a patient presents with the combination of rash and facial edema, it is important to suspect a drug reaction with eosinophilia and systemic symptoms (DRESS). So it is recommended that patients with this presentation have a complete blood count with differential (to evaluate for eosinophilia) as well as liver function and renal function tests (to evaluate for systemic inflammation and end-organ damage).

Laboratory Data

Patient Laboratory Data

- Hematocrit – 38
  (normal range = 36-48%)
- Platelets – 300 x 10^9/L
  (normal range = 150-450 000/ml)
- Wbc – 14 x 10^9/L
  (normal range = 4.5 to 11.0 x 109/L)
- Eosinophils – 16%
  (normal range = 0-6%)
- Atypical lymphocytes – 12%
  (normal range = 0)
- AST – 200 u/l
  (normal range = 10-40 U/L)
- Creatinine – 0.8
  (normal range = 0.6 to 1.2 mg/dL)

Drug-Induced Hypersensitivity Syndrome (DIHS)

- Also known as Drug Reaction with Eosinophilia and Systemic Symptoms - DRESS
- Skin eruption with systemic symptoms and internal organ involvement (e.g. liver, kidney, heart)
- Typical signs and symptoms: exanthem, erythematous centrofacial swelling, fever, malaise, lymphadenopathy, and involvement of other organs (liver, kidneys)
- >70% of patients have an eosinophilia
- Liver function test abnormalities and/or hepatosplenomegaly are helpful diagnostic clues

DIHS: Clinical Course

- Signs and symptoms typically begin in the 3rd week (range 1 to 12 weeks) after start of the medication or after increasing the dose
    - This helps to distinguishes DIHS from exanthematous drug eruption, which appears in up to 10 days
- Signs and symptoms may persist and recur for many weeks even after cessation of drug treatment
- Fatality rate may be up to 10%

Medications implicated in DIHS:

- Allopurinol
- Antibiotics
  - Sulfonamide
  - Penicillin
  - Minocycline
  - Metronidazole
- Anti-TB Drugs
  - Isoniazid
- Anticonvulsants
  - Phenytoin
  - Carbamazepine
  - Lamotrigine
- NSAIDs
  - Sulindac
  - Diclofenac
  - Meloxicam
- Anti-HIV Drugs
  - Abacavir

DIHS Treatment

- Stop suspect medication(s)
- Consult dermatology and other specialists depending on clinical presentation
- If not severe, can use topical steroids and systemic antihistamines, and continue to follow laboratory values
- If severe, start systemic steroids (prednisone 1mg/kg/day) and taper very gradually over weeks to months as syndrome can recur as the dose reduces
- Severely ill patients may need to be hospitalized and monitored in an Intensive Care Unit setting

Case 4: History

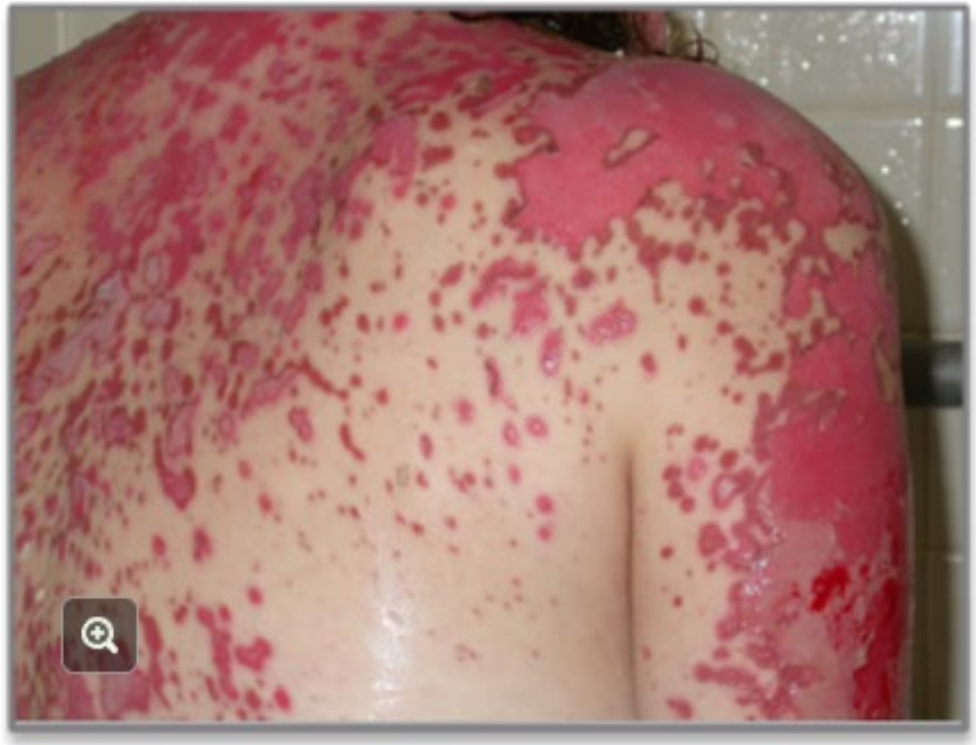
- Ms. Michelle Holloway is a 29-year-old woman who presented to the local emergency room with a painful, expanding, and "sloughing" rash.
- **PMH:** recent diagnosis of a urinary tract infection, on treatment with oral sulfamethoxazole and trimethoprim
- **Medications:** sulfamethoxazole and trimethoprim (1 double-strength q12hr), multivitamins
- **Allergies:** no know drug allergies
- **Family history:** no family history of drug allergies
- **Social history:** manages a book store
- **Health-related behaviors:** no tobacco, alcohol, or drug use
- **ROS:** feels unwell with sore throat, malaise

Case 4: Skin Exam

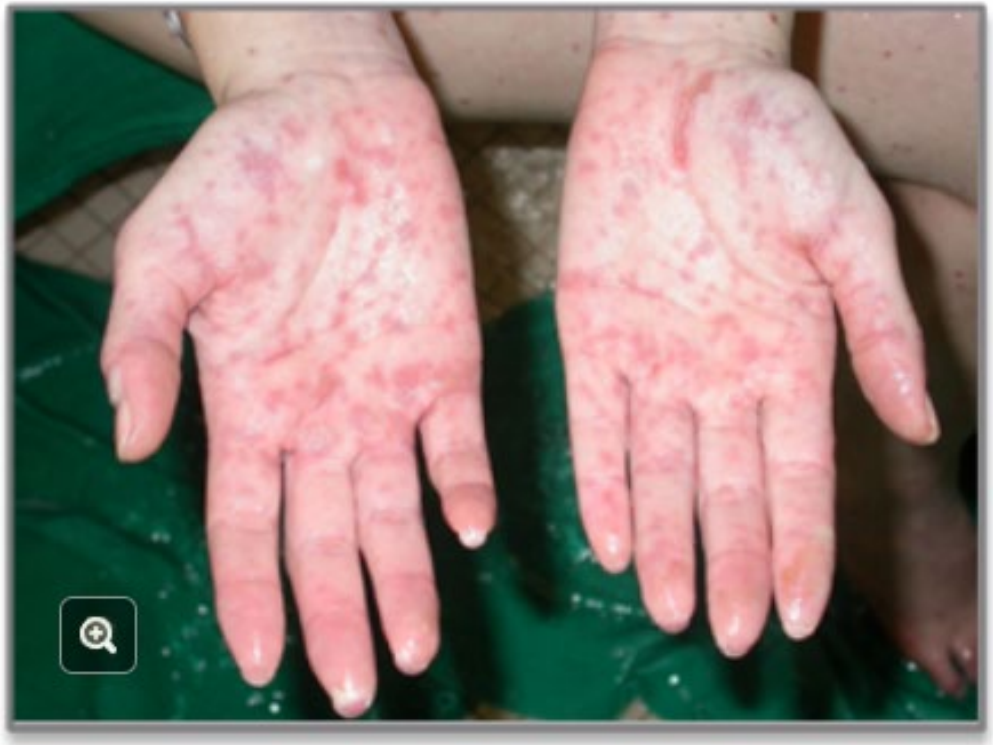
Widespread erosions, on the face, upper trunk and arms

Lesions began as painful flaccid blisters

Case 4: Skin Exam cont.



Erythematous erosions



Erythematous macules

Michelle Holloway was diagnosed with a severe drug reaction in the epidermal necrolysis spectrum

This spectrum includes Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS/TEN

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous reactions
- Characterized by extensive necrosis and detachment of the epidermis and mucosal surfaces
- These two conditions represent similar processes but differ in severity based on body surface area (BSA) that is involved

SJS/TEN cont.

- SJS/TEN is a dermatologic emergency
- Mortality rate varies from 5-12% for SJS and > 20% for TEN
- Increasing age, significant comorbid conditions, and greater extent of skin involvement correlate with poor prognosis

SJS/TEN cont.

Over 100 different drugs have been associated with SJS/TEN, the most high risk thought to be:

- **S**ulfa antibiotics, sulfasalazine
- **A**llopurinol
- **T**etracyclines, thiacetazone
- **A**nticonvulsants (carbamazepine, lamotrigine, phenobarbital, phenytoin)
- **N**SAIDS
- **N**evirapine

SATAN is a mnemonic that may help you remember these medications

Clinical Findings

- Typically begins within 8 weeks after drug initiation
- Fever, headache, rhinitis, and myalgias may precede the mucocutaneous lesions by 1-3 days
- Eruption is initially symmetric and distributed on the face, upper trunk, and proximal extremities
  - **Pain** is a prominent symptom in skin lesions of SJS/TEN and it signifies necrosis
  - Lesions can rapidly extend to the rest of the body
- Initial skin lesions are characterized by erythematous, irregularly shaped, dusky red to purpuric macules (atypical targets), which progressively coalesce

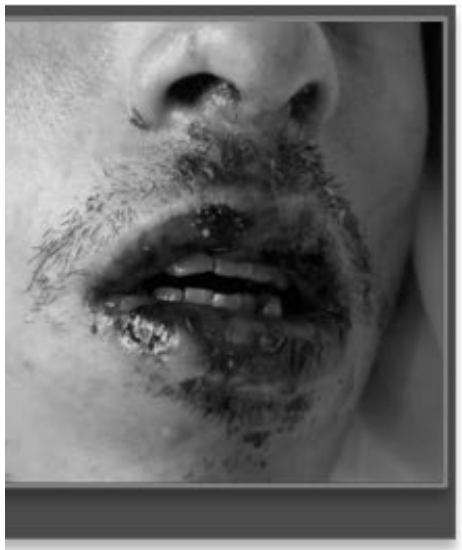
Clinical Findings cont.

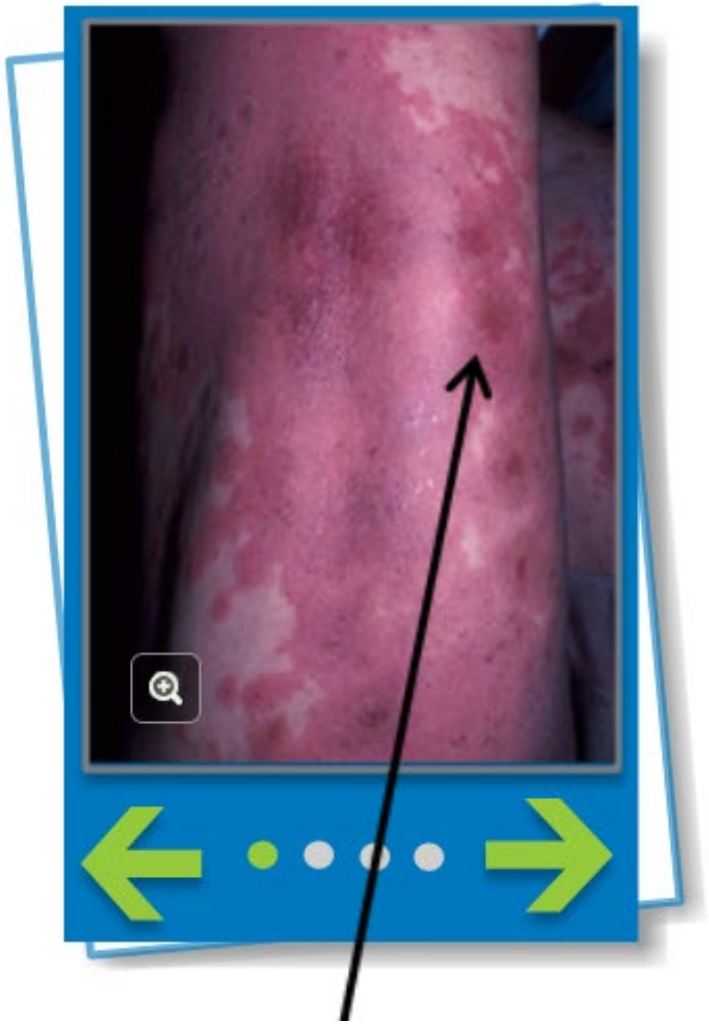
- Dark center of atypical target lesions may blister
- Lesions evolve to flaccid blisters, which spread with pressure and break easily
- Epidermis may dislodge with lateral pressure
- The necrotic epidermis is easily detached at pressure points or by frictional trauma, revealing large areas of exposed, red, sometimes oozing dermis
- Patients are classified into one of 3 groups according to total BSA in which the epidermis is detached or “detachable” (extent of skin loss)
    - SJS < 10%, SJS/TEN 10-30%, TEN > 30%

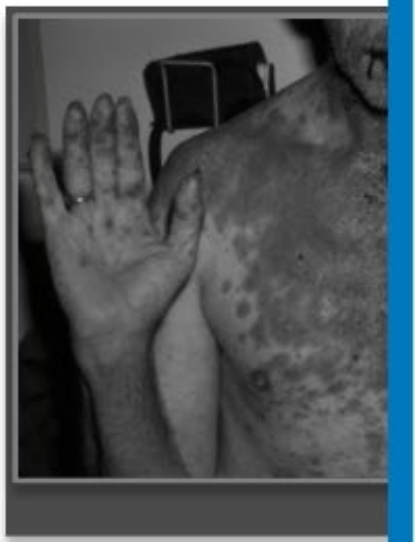
Mucous Membrane Involvement

- Mucous membrane involvement can precede skin eruption
- Begins with erythema followed by painful erosions of the buccal, ocular, and genital mucosa
- A significant percentage of patients with ocular involvement will suffer permanent ocular sequelae, even blindness

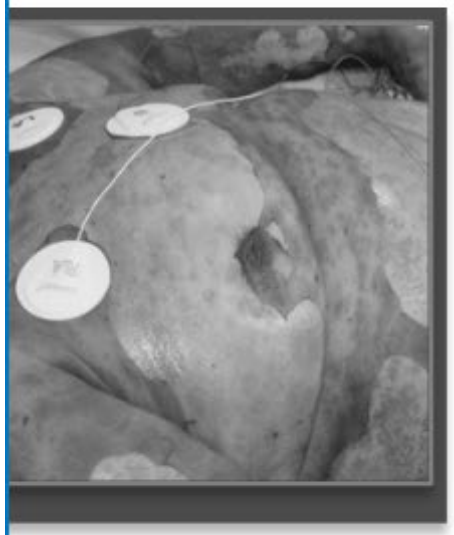
Stevens-Johnson Syndrome

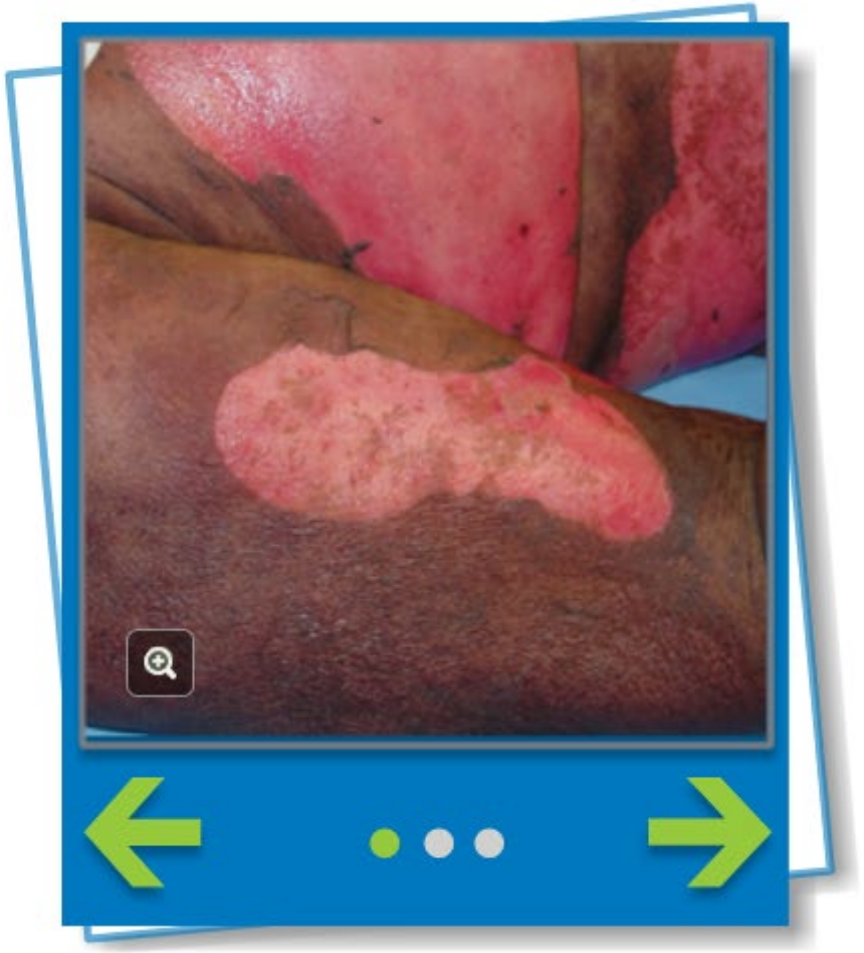






Toxic Epidermal Necrolysis





Extensive sloughing

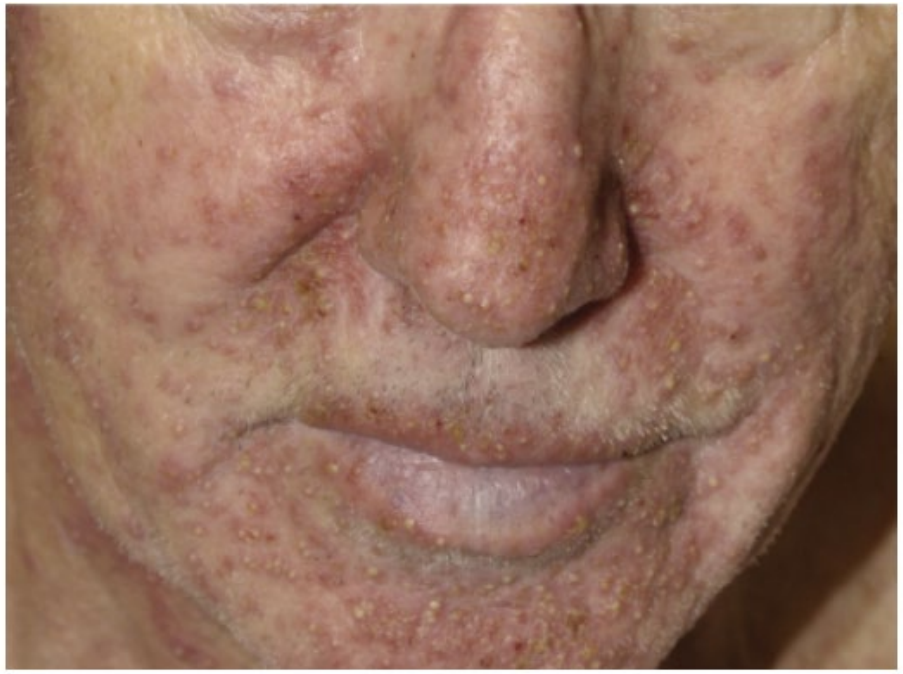
SJS/TEN Complications

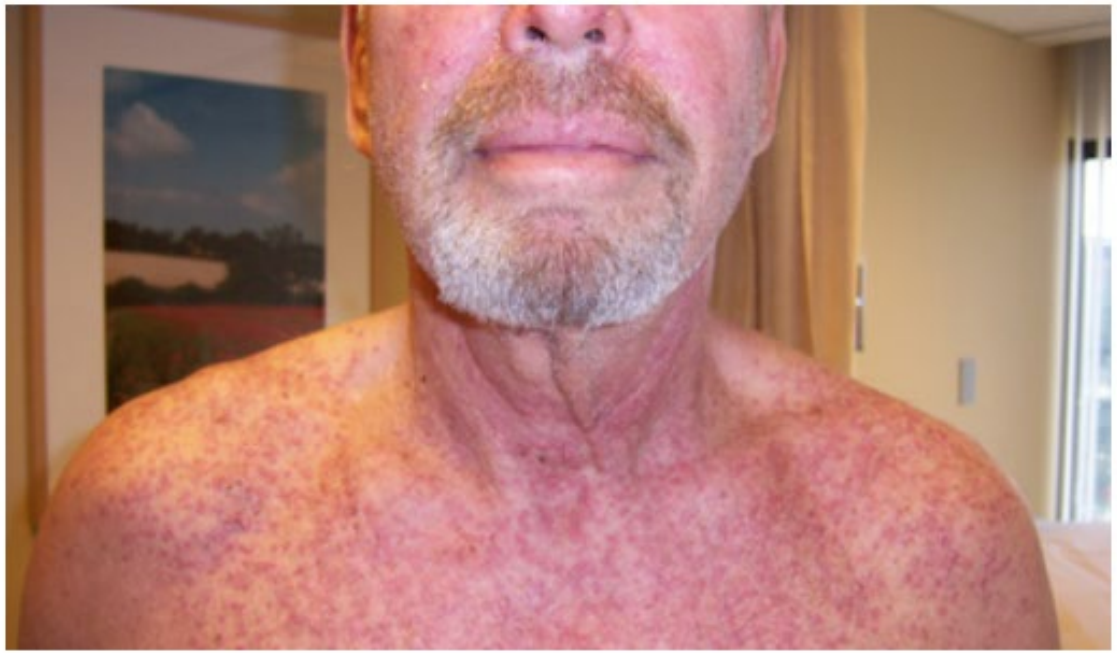
- Corneal damage (consult ophthalmologist)
- Oral cavity (Sicca syndrome, oral pain)
- GU damage (adhesions, urethral / introital erosions)
- Pulmonary damage (bronchitis, bronchiectasis)
- Fluid and electrolyte disturbances
- Nutrition requirements
- Secondary infection (bacteremia, sepsis)

Treatment

- Early recognition and withdrawal of the offending drug(s) and supportive care
- In case of doubt, all non-life-sustaining drugs should be stopped
- Consult dermatology at earliest moment of concern for SJS or TEN
- Care should proceed in a burn unit for patients with significant BSA involvement with detached or detachable skin, or any patient with an evolving clinical picture
- Multidisciplinary approach is necessary; immediately consult ophthalmology if there is ocular involvement
- Specific therapies, such as intravenous corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine or etanercept are employed variably at different centers for treatment.

EGFR inhibitors acneiform eruptions





CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death

Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center). **Navigational Note:** -					
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. **Navigational Note:** -					

Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death

Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.

Navigational Note: -

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Navigational Note: -					

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back. **Navigational Note:** -					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis. **Navigational Note:** -					

Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.					
Navigational Note: -					

Take Home Points

- A detailed medication history is essential in suspected drug reactions (remember the seven “I’s”)
- Be sure to document the drug reaction in the patient’s chart with the medication and description of the reaction
- Exanthematous eruptions are the most common of all cutaneous drug eruptions and tend to resolve without sequelae. Patients feel well. Rash may be itchy.
- Fixed drug eruptions will recur at the same with re-exposure to the drug

Take Home Points Continued

- Drug-induced hypersensitivity syndrome (DIHS) is a cutaneous drug eruptions with systemic symptoms. Patients may be febrile and feel unwell. Affected organs often include the liver and kidneys
  - Check LFTs, CBC, Cr/BUN in pt with an exanthematous rash with fever, facial edema
- Signs and symptoms of DIHS may persist and recur for many weeks even after cessation of the offending medication
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, life-threatening mucocutaenous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal surfaces
- Consult dermatology at the earliest moment of concern for SJS/TEN