Drug Rashes

Basic Dermatology Curriculum

Last updated January 2015
Goals and Objectives

By completing this module, the learner will be able to:

• Describe the morphology of common drug eruptions
• Describe how to create a drug timeline
• Locate resources for differentiating causes of drug eruptions
• Describe initial steps in management for drug eruptions
• Recognize when to refer a patient with a drug eruption to a dermatologist
General Principles

- It is always prudent to consider drugs as the cause of a skin reaction.
- 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.
- Be sure to document the drug reaction in the patient’s chart with the medication and description of the reaction.
Types of Drug Reactions

This module will focus on the most common and important types of adverse drug reactions

- Exanthematous
- 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)*

* Refer to the modules on urticaria and vasculitis for more information regarding these skin reactions
Allergy testing is of limited value in evaluating adverse cutaneous reactions to medications

Penicillin is the exception to this rule

• “Penicillin” skin testing is the preferred method of evaluation of possible type I, IgE-mediated penicillin allergy (urticaria due to penicillin)

• Ideally, this testing also includes the major and minor determinant mixes (metabolites of penicillin)
Case One

Mr. Carl Sutton
Case One: 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. Within a few days of his treatment he presented to urgent care with a new rash that began on his trunk and has spread to his extremities.
Case One, Question 1

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

a. A detailed medication history
b. Family history, including history of drug reactions
c. If the primary care provider ordered a test for mononucleosis
d. Past medical history
e. All of the above
Case One, Question 1

Answer: e
What else would you like to know about Mr. Sutton’s medical history?

a. A detailed medication history (Yes! See the following slide for more information)

b. Family history of drug reactions (Certain HLA types are associated with adverse drug reactions)

c. If the primary care provider ordered a test for mononucleosis (Ampicillin in the setting of acute mononucleosis often causes a characteristic rash)

d. Past medical history (Risk factors for adverse drug reactions include certain disease states and previous history of drug eruptions)

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

- The most important data in determining if a rash is medication-related is its timing.
- By preparing a drug timeline, you can help find likely medication causes.
- 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 the rash.
  - For repeat exposures, it may be much shorter.
## Example of a Drug Timeline

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<th>-14</th>
<th>-10</th>
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Day 0 = when rash first appeared
Risk Factors for Drug Reactions

- Female
- Prior history of drug reaction
- Recurrent drug exposure
  - Repeated courses of therapy with the same drugs or related drugs are associated with higher rates of adverse drug reactions
- HLA type
  - HLA-B*1502: carbamazepine and SJS/TEN in Han Chinese, SE Asians
  - HLA-B*5701: abacavir and DRESS in whites, hispanics
  - HLA-B*5801: allopurinol and SJS/TEN in Han Chinese, Taiwanese, Thai
- Certain disease states
  - Reactions to aminopenicillins occur more commonly in patients with Epstein Barr virus (EBV) infection
  - HIV-positive patients have high rates of dermatologic reactions to sulfonamides and other drugs
Case One: Skin Exam

Widespread, symmetric, 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
Case One, Question 2

What type of drug reaction is this?

a. Drug-Induced Hypersensitivity Reaction
b. Exanthematous
c. Fixed Drug Eruption
d. Stevens-Johnson Syndrome
e. Vasculitis
Case One, Question 2

Answer: b

What type of drug reaction is this?

a. Drug-Induced Hypersensitivity Reaction
b. Exanthematous

c. Fixed Drug Eruption
d. Stevens-Johnson Syndrome
e. Vasculitis
Exanthematous Drug Eruption

- Exanthematous eruptions are the most common of all cutaneous drug eruptions (~90%)
- Limited to the skin
- Lesions initially appear on the trunk and spread centrifugally to the extremities in a symmetric fashion
- Erythematous macules and infiltrated papules
- Pruritus and mild fever may be present
- Skin lesions usually appear more than 2 days after the drug has been started, mainly around day 8-11, and occasionally persists several days after having stopped the drug
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 Two

Ms. Amanda Hernandez
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 last year.

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 Two: Skin Exam

Erythematous patch with central bulla
Case Two, Question 1

What’s the likely diagnosis?

a. Bullous pemphigoid
b. Erythema migrans
c. Fixed drug eruption
d. Spider bite
e. Vasculitis
Answer: c

What’s the likely diagnosis?

a. Bullous pemphigoid (tends to present as multiple bullae)
b. Erythema migrans (presents as an erythematous macule, which expands to produce an annular lesion with central clearing causing a target-like appearance)
c. Fixed drug eruption
d. Spider bite (generally more necrotic and painful, though these can be difficult to exclude and are frequently misdiagnosed)
e. Vasculitis (presents as multiple non-blanching macules or papules)
Fixed Drug Eruption

- Fixed Drug Eruption is an adverse drug reaction characterized by the formation of a solitary erythematous patch or plaque that will recur at the same site with re-exposure to the drug.
  - This distinguishing feature is why it’s called “fixed”

- Commonly involved drugs include:
  - phenolphthalein (laxatives)
  - tetracyclines
  - metronidazole
  - sulfonamides
  - barbiturates
  - NSAIDs
  - salicylates
  - food coloring (yellow)
FDE Morphology

- Often affects the mouth, genitalia, face, and acral areas
- 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 edematous, forming a plaque, which may evolve to become a bulla and then an erosion
- Healed lesions are dark brown with violet hue
- Commonly solitary and can become 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
- Non-eroded lesions can be treated with a potent topical corticosteroid ointment
- Eroded cutaneous lesions 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 Three

Erik Seavey
Case Three: 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 Three: Exam

Vital signs: T 101.4, HR 100, BP 100/60, RR 16, 02 sat 97% on RA

Gen: ill-appearing male in NAD

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

- Hematocrit – 38
- Platelets – 300 x 10^9/L
- Wbc – 14 x 10^9/L
- Eosinophils – 16%
- Atypical lymphocytes – 12%
- AST – 200 u/l
- Creatinine – 0.8

When a patient presents with the combination of rash and facial edema, order CBC and LFTs.
Based on the history and clinical findings, which of the following drug reactions do you suspect?

a. Drug-Induced Hypersensitivity Syndrome
b. Fixed Drug Eruption
c. Stevens-Johnson Syndrome
d. Toxic epidermal necrolysis
e. Vasculitis
Case Three, Question 1

Answer: a

Based on the history and clinical findings, which of the following drug reactions do you suspect?

a. Drug-Induced Hypersensitivity Syndrome
b. Fixed Drug Eruption
c. Stevens-Johnson Syndrome
d. Toxic epidermal necrolysis
e. Vasculitis
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 distinguishes DIHS from exanthematous drug eruption, which appears in 7-10 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
Which drug caused it?

• Litt’s Drug Eruptions and Reactions Manual
  – Print 19th Edition
  – On-line database requires subscription
  – www.drugeruptiondata.com

• VisualDX
  – Also requires subscription
  – App for iPhone or Android
Approach to the Patient with Suspected DIHS

How severe is the reaction? What organ systems are involved?
  • Thorough skin exam
  • Order CBC, LFTs, BUN, creatinine (bone marrow, liver and kidney are common targets)

Which drug is responsible?
  • Review clinical history
  • Examine the medical records for temporal relationship between the symptoms and administration of specific drugs
  • For each suspect drug, consider the likelihood of it causing the type of reaction in question
Stop (or substitute) all suspect medications and discontinue non-essential medications
DIHS Treatment

- Consult dermatology
- Stop suspect medication(s)
- If not severe, can use topical steroids and systemic antihistamines
- If severe, start systemic steroids (prednisone 1mg/kg/day) and very gradually taper
  - Steroids are indicated for nephritis and impending organ failure
Case Four

Ms. Michelle Holloway
Ms. 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 known 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 warm
Case Four: Skin Exam

Erythematous erosions, mainly localized on the face, upper trunk and hands

Lesions began as flaccid blisters
Case Four: Skin Exam

Erythematous erosions

Erythematous macules
Case Four, Question 1

What is the next best step in management?

a. Consult dermatology
b. Discontinue all non-life-sustaining medications
c. Request a tissue biopsy to confirm suspected diagnosis
d. Consider transfer to burn unit
e. All of the above
Case Four, Question 1

Answer: d

What is the next best step in management?

a. Consult dermatology (when there is concern for severe skin involvement dermatology should be consulted)

b. Discontinue all non-life-sustaining medications

c. Request a tissue biopsy to confirm suspected diagnosis

d. Consider transfer to burn unit

e. All of the above

Click here to watch an instructional video on punch biopsy
Michelle Holloway was diagnosed with a severe drug reaction of 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 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
Over 100 different drugs have been associated with SJS/TEN, the most high risk thought to be:

- Sulfa antibiotics, sulfasalazine
- Allopurinol
- Tetracyclines
- Anticonvulsants (carbamazepine, lamotrigine, phenobarbital, phenytoin)
- NSAIDS
- Nevirapine
- Thiacetazone

SATAN is a mnemonic that may help you remember these medications
Clinical Findings

- Typically begins within 8 weeks after the onset of drug exposure
- 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 more prominent symptom than itch in skin lesions SJS/TEN compared with morbilliform eruptions
  - Rash 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
- Dark center of atypical target lesions may blister
Clinical Findings

- 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

Atypical target lesion
Stevens-Johnson syndrome

Dusky appearance

Mucous membrane involvement
Toxic epidermal necrolysis

Tender/painful skin

Extensive sloughing
Toxic epidermal necrolysis
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 problems
- Nutrition problems
- 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 >25-30% BSA involvement
- Multidisciplinary approach is necessary; immediately consult ophthalmology if there is ocular involvement
Prevention of SJS / TEN / DIHS

• FDA recommends:
  – HLA-B*1502 genetic screening for all southeast Asian patients starting carbamazepine
  – HLA-B*5701 genetic screening for all patients starting abacavir

• Associated, but not an FDA recommendation:
  – HLA-B*5801 genetic screening for some southeast Asian, Japanese, European patients starting allopurinol
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
- Fixed drug eruptions will recur at the same with re-exposure to the drug
Take Home Points

- Drug-induced hypersensitivity syndrome is a cutaneous drug eruptions with systemic symptoms. Affected organs often include the liver and kidneys.
  - Check LFTs, CBC, Cr/BUN in morbilliform rash with fever, edema
- Signs and symptoms of DIHS may persist and recur for many weeks even after cessation of the offending medication
- SJS and TEN are acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal surfaces
- Consult dermatology at the earliest moment of concern for SJS/TEN
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References

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- Solensky R. Allergy to Penicillins. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2011.
To take the quiz, click on the following link:

https://www.aad.org/quiz/drug-eruptions-learners