Personalized Medical Care: Recognition, Management, and Maybe Prevention of Cutaneous Hypersensitivity Reactions

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Learning Objectives

• Survival dermatology: Primer on systematic approach
  *Clues: gestsalt, distribution, pattern recognition, anatomic depth, distribution, setting, other clues
• Pattern recognition: viral exanthem models
• Pattern recognition: specific drug reactions
• Management
• Risk factors and prevention
Drug Reactions: Epidemiology

• Cutaneous reactions cause 3% of disabling “injuries” during hospitalization
• 0.1-0.3% associated with mortality
• Risk factors: female, increasing age, number of drugs, immunosuppression
• Eg. HIV 10-15X risk with sulfonamides
• Resources: Boston Collaborative Drug Surveillance Program
Drug Reactions: Pathogenesis

- **Hypersensitivity reactions/immunologic?**
  - IgE dependent (type I)
  - Cytotoxic (type II)
  - Immune complex (type III)
  - Cell mediated (IV)

- **Non-immunologic**
  - Overdose, pharmacologic side effects, cumulative/delayed toxicity, drug-drug interaction, alteration in metabolism, exacerbation of disease

- **Idiosyncratic (possible immunologic)**
  - DRESS, TEN/SJS, in HIV setting, Drug-induced lupus

- **Importance of Immunologic parameters and genetic predisposition (stay tuned)**
Systematic Evaluation: History

• How long, chronology?
• Does it itch, hurt?
• Self treatment?
• Other drugs?
• Myths?
Systematic Evaluation: Exam

- Good light
- Good skin exposure
- Good eye
- Good book
"If it doesn’t itch, don’t worry about it."
Systematic Evaluation: General Considerations

- General health, chronology
- Distribution
- PATTERN
- Organization
- Morphology
- Anatomic depth
- Tumor v inflammatory
Sun Exposed Sites

- Phototoxic reactions (sun burn, eg. valproic acid)
- Photoallergic reactions (eg. drug)
- Psoriasis (isomorphic phenomenon)
- Polymorphous light eruption
- Porphyria
- Lupus erythematosus
a. Flexural rashes
- Atopic dermatitis (childhood)
- Infantile seborrheic dermatitis
- Intertrigo
- Candidiasis
- Tinea cruris
- Epidermolytic hyperkeratosis (ichthyosis)
- Inverse psoriasis

b. Sun-exposed sites
- Phototoxic reaction (sunburn)
- Photodermatitis
- Polymorphous light eruption
- Viral exanthem
- Porphyria
- Xeroderma pigmentosum

c. Acrodermatitis
- Papular acrodermatitis (viral exanthem)
- Acrodermatitis enteropathica
- Atopic dermatitis (infantile)
- Tinea pedis with "id" reaction
- Dyshidrotic eczema
- Poststrepococcal desquamation

d. Pityriasis roseaform
- Pityriasis rosea
- Secondary syphilis
- Drug reaction (e.g., gold salts)
- Fungal psoriasis
- Atopic dermatitis

e. Clothing-covered sites
- Contact dermatitis
- Miliaria
- Psoriasis (summer)

f. Acneiform rashes
- Acne vulgaris
- Drug-induced acne (e.g., prednisone, lithium, isotretinoin)
- Cushing syndrome (endogenous steroids)
- Chloracne
Anatomic Depth

Superficial vs Deep Processes

Epi

Derm

SG
Anatomical Depth

- Capillary
- Sebaceous gland
- Pilar smooth muscle
- Hair shaft/follicle
- Eccrine sweat gland
...and the age of the patient

- Variable morphology of the rash
- Variable course
- Variable exposure/susceptibility
- Variable incidence of disease
Scabies in an adolescent
Immunologic Parameters

- Hereditary immunodeficiency
- Acquired immunodeficiency
- Drug induced immunosuppression
- Cutaneous disease in transplantation
Inside v Outside Job

• How did the eruption get there?
• Localized?
  Contact reaction
  Primary cutaneous innoculation
  Local reactivation
• Disseminated?
  Reactive process
    (viral, drug, immunologically mediated)
  Embolic
  Toxin mediated
Measles = morbilliform
Although morbilliform = exanthematous = maculopapular

Measles

• Measles virus, genus Morbillivirus, family Paramyxoviridae
• Respiratory droplet spread
• 7-10 day incubation $\rightarrow$ 2-4 day prodrome cough, coryza, conjunctivitis, Koplik spots
• 10 day skin eruption
• DEFINES MOST COMMON DRUG REACTION PATTERN
Amoxicillin induced morbilliform eruption
Enteroviral exanthem... morbilliform eruption
Morbilliform (Exanthematous)
Drug Reactions

- Most common cause cutaneous reactions
- Type IV?, drug or metabolite binds? MHC II-peptide complexes, cytotoxicity results in keratinocyte necrosis
- May be potentiated by viral infections (HHV6, HIV, adenovirus, EBV, CMV, Parvovirus B19)
- 7-14 days after initiation of med
- 1% of most drugs, but increased with aminopenecillins, sulfonamides, cephalosporins, ANTICONVULSANTS
- Usually resolve, occasionally marker for more severe reaction
Urticaria...
urticaria
Urticaria, Angioedema, Anaphylaxis

- IgE mediated type I reaction
- Edematous papules, expanding plaques, angioedema with deeper lesions
- Transient <24 hours, migratory
- Urticarial vasculitis >24 hours
- Acute < 6 wks v chronic
- Drugs: aminopenecillins, cephalosporins, sulfonamides, erythromycycin, tetracycline
- Skin testing for PCN only
Graft v host disease...sort of morbilliform too
Scarlet Fever-2nd Disease

- Pyrogenic exotoxin producing group A beta-hemolytic streptococcal infection
- Early 20\textsuperscript{th} century-toxin A
- 1950’ s-toxin types C and B
- Risk of Rheumatic fever/serious complications declined before introduction of antibiotics
- DEFINES <5% OF DRUG REACTION PATTERNS
Enanthem - strawberry tongue
What else can give you a scarlatiniform eruption and a strawberry tongue?

• Staphylococcal infection (Staph/strep TSS)
• Viral exantheme
• Drug reaction
• Kawasaki syndrome
Leukocytoclastic Vasculitis
Vasculitis-Clinical pattern that you must know!

- Palpable purpura—destruction of small vessels
- Infectious (and non-infectious)
- Infections=fever, sick patient (usually)
- May be life-threatening
- Early recognition and treatment life-saving
- DEFINES <5% OF DRUG REACTION PATTERNS, BUT IMPORTANT TO MAKE DX, RECOGNIZE SYSTEMIC SX’S
Leukocytoclastic vasculitis....
Leukocytoclastic Vasculitis

- 7-21 days after initiation of med
- 3-5 days on rechallenge
- Penecillins, NSAID’s, sulfonamides, cephalosporins, PTU, thiazide diuretics, allopurinol, PHENYTOIN, biologic agents, hydralazine, minocycline
- Often restricted to skin but may be systemic
Recurrent itchy rash on the ankle of a 40-year-old man...
Fixed Drug Eruption

- Recurrent itchy violaceous plaques/target lesions with admin of same drug
- NSAID’s, sulfonamides, BARBITURATES, tetracyclines, CARBAMAZEPINE
- Red acutely, PIH following D/C of drug
- Lips, trunk, legs, arms, genitals
- Systemic reactions unusual
- More common in adults
- Cause unclear but “memory” T-cell resides in dermis
- Tx: stop the drug
Staphylococcal scalded skin syndrome...exfoliative toxin → superficial epidermal cleavage, **mucous membranes spared**
v. Stevens-Johnson syndrome (or TEN)... drug-induced injury with skin cleavage at basement membrane zone, severe mucous membrane involvement
SJS/TEN

- Spectrum of ds or distinctive?
- SJS: at least 2 mucous membranes, <10-30% BSA
- SJS 1.2-6/million people/yr
- TEN 0.4-1.9/million people/yr
- HIV 1/thousand people/yr (antiretroviral use)
- 80-95% assoc with drugs
- 1-8 weeks after initiation of drug, within hours on reexposure
- Morbilliform, atypical targetoid lesions
- Widespread flaccid bullae, erosions, ulceration of skin, inflammation and ulceration of mouth/mmm
SJS/TEN Systemic Disease

- Conjunctivae, trachea, bronchi, gut, kidney
- Acute renal failure, ATN
- 25% pulmonary dysfunction, adult RDS, fibrosis
- Anemia, keukopenia, hepatitis
- Abdominal pain, diarrhea
- Encephalopathy, myocarditis
SJS/TEN: Pathogenesis

- T-cell mediated process
- CD8+ trigger keratinocyte necrosis
- Drug noncovalently bind to MHC and TCR vs metabolites of drugs binding covalently to cellular peptides that stimulate immune sys
- Apoptosis causes cell death with upregulation of CD8+ cells and granzyme B/perforin, soluble Fas ligant, NO, TNFalpha
Highest Risk Drugs

- Nevirapine
- Lamotrigine
- Carmazepine
- Phenytoin
- Antibiotic sulfonamides
- Allopurinol
- Oxicam NSAID’s
- Also Aminopenecillins, cephalo, quinolones

(European SCAR, Roujeau et al, Mockenhaupt et al)
SJS/TEN Prevention!

• Relationship to MHC allotype
• For aromatic seizure meds (carbamazepine, phenytoin, oxcarbazapine, lamotrigine and HLA-B*1502 and allopurinol and HLA-B*5801 in Han Chinese
• HLA-B*1502 and carbamazepine in Thai, Malaysian, South Indians
• HLA-B*5801 and allopurinol in W Europeans
• HLA-B*5701 and abacavir
• HLA-A*3101 and carbamazepine in Europeans
SJS/TEN: Management

- Systemic steroids, IVIG, cyclosporine, etc not proven better than supportive measures
- No repeat exposures
- Genetic HLA testing for East Asians before starting aromatic meds or abacavir
- Immediate cessation of med
- Burn unit management
19-year-old girl with 2 week history of high fever, increasing white count, eosinophilia, hepatitis.....

- Drug reaction with eosinophilia and systemic symptoms
- DRESS
- Old phenytoin reaction/anticonvulsant hypersensitivity reaction
- Dramatic elevation of HHV6
DRESS

- Drug eruption: generalized edema, morbilliform rash, tense bullae, lip erosions
- No epidermal sloughing
- Fever, multiorgan involvement
- Pharyngitis, cervical adenopathy
- Atypical lymphocytosis, eosinophilia
- Hepatitis, interstitial nephritis, pneumonitis, encephalitis and (thyroiditis, carditis, pancreatitis, epididymitis, myositis, etc)
**DRESS: Epidemiology**

- On first exposure to med
- 1-6 weeks post exposure
- 1:3,000 exposures
- Aromatic anticonvulsants, lamotrigine, sulfonamide antibiotics, dapsone, minocycline allopurinol, mevaripine
DRESS: Management

• Family history (possibly AD inheritance)
• Stop drug asap, supportive care
• Role of systemic steroids?
• Symptoms may persist or recur for months
• Complications (renal, hepatic, pulmonary)
Acute Generalized Exanthematous Pustulosis (AGEP)

• Acute onset of nonfollicular pustules on edematous red base, fever, facial edema, target lesions, purpura, vasculitis, blisters,
• Mucosal erosions in 50%
• Short period of sensitization, topical or systemic
• Clinical findings and course overlap with DRESS, TEN
AGEP and Anticonvulsants


- Tx: stop med
- Systemic steroids?
- HLA-B5, -DR11, -DRQ
- Release of neutrophil-activating cytokines?
- Beta-lactam antibiotics, calcium channel blockers, hydroxychloroquine, CARBAMAZEPINE, PHENYTOIN, other antimicrobials
Take home!

• Know your drug eruptions especially markers for severe reactions
• Know your skin exam: full skin exam including mucous membranes, palms and soles, genitals
• Know your patients: risk factors, HLA markers, personal or family history of reactions
• When in doubt stop the drug, sooner the better
• Know when to call your friendly neighborhood dermatologist
Bibliography: General


• **SJS/TEN**


  SJS and TEN: what do we know? Tartarone A, Lerose R. Ther Drug Monit 2010;32:669-72
Bibliography

• DRESS


• AGEP