Objectives

- Diagnose cutaneous adverse drug events in pediatric and adolescent patients
- Develop management plans for pediatric drug reactions

Case

4-year-old boy with Acute Lymphocytoid Leukemia (ALL) in remission, admitted for concern of possible Stevens Johnson Syndrome

- Crusting of lips
- Mild injection of conjunctiva
- 2-month history of redness and edema of backs of hands
- 2-3 weeks of dry, cracked lips
- 1 week of dry patch on right cheek

Medications:
- Voriconazole daily (liver abscesses), 6-mercaptopurine, methotrexate weekly, Vitamin D, ondansetron PRN
- TMP/SMX prophylaxis (Sat/Sun) - discontinued about 3 weeks prior due to concern of drug reaction

What are you most concerned about?

1. Serum-sickness like reaction
2. Drug-induced hypersensitivity syndrome
3. Phototoxicity reaction
4. Photo-allergic contact dermatitis
5. Stevens-Johnson syndrome (SJS)
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Voriconazole

- Antifungal medication
- Used prophylactically for cancer, transplant, and other immunocompromised patients
- Phototoxic reactions from voriconazole develop in:
  - ~10-20% of treated adults
  - ~20-47% of treated children
- Longer durations of therapy and higher doses appear to increase risk of phototoxicity
- Described phototoxicity reactions:
  - Phototoxicity with erythema and blistering
  - Pseudoporphyria
  - Photo-onycholysis
  - Lentigines
  - Solar elastosis

Bolognia, et al. Dermatology, 3rd edition

Voriconazole: cutaneous malignancy

- Increased risk of squamous cell carcinoma of skin (SCC)
  - 73% increased risk for cutaneous squamous cell carcinoma (SCC) occurring in lung transplant patients taking voriconazole
  - Often aggressive or multifocal SCC
- Increased risk of melanoma
  - Case reports of melanomas and melanomas in situ reported in context of accelerated photo-aging
- Risk factors for voriconazole-associated cutaneous malignancies
  - Fitzpatrick skin types I and II
  - Significant UV light exposure
  - Prolonged and/or intense immunosuppression especially T-cell directed therapy
  - Tropical sunlight
  - Long-term voriconazole use

Williams and Arron. JAMA Dermatol. 2016 Jun 1;152(6):719-20

16-year-old boy with history of cystic fibrosis, 1 year after lung transplant

- Rapidly growing nodule in conchal bowl
- Moderately-differentiated Squamous Cell Carcinoma (SCC)

Medications:
- Prednisone
- Mycophenolate
- Tacrolimus
- Voriconazole

Voriconazole: summary

- Voriconazole
  - Systemic azole antifungal agent
  - Frequently used as prophylaxis in patients with cancer, transplant and other immunocompromised patients
- Associated with:
  - Phototoxic reactions
  - Accelerated photo-damage
  - Increased risk of cutaneous malignancies
- Excellent photo-protection and frequent skin screening is recommended for patients taking voriconazole regularly
Case

16 year-old girl with history of ALL and refractory seizure disorder

- Skin eruption x 2 days
- Fever 38.4 °C (101 °F)
- Non-productive cough

- Cervical lymphadenopathy
- Facial and hand edema

Medication History

- Divalproex sodium (depakote)
  - 5 weeks before rash
- Added lamotrigine (lamictal)
  - 4 weeks before rash

Labs

- Eosinophils 12%
- AST 118
- ALT 74
- Free T4 0.68 (0.8 - 1.8 ng/L), TSH within normal limits
- Cr within normal limits
- UA within normal limits

Which additional laboratory finding may help with diagnosis?

1. Atypical lymphocytosis
2. Thrombocytosis
3. Elevated divalproex sodium serum level
4. Serum PCR positive for HHV 5
5. Positive EBV IgM titers

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Drug-Induced Hypersensitivity Syndrome (DIHS)

- Manifests 2 to 6 weeks after the initiation of offending drug
- 10% Mortality rate
- Fever
- Skin eruption
- Most often morbiliform
- Lymphadenopathy
- Edema of face and hands
- Eosinophilia
- Atypical lymphocytosis
- Hepatitis/Transaminitis up to 50%
- Pulmonary infiltrates
- Nephritis
- Myocarditis
This 15-year-old girl taking lamotrigine x 4 weeks for bipolar disorder has fever to 101°F, morbiliform eruption, the lip findings shown, and a 1 cm superficial erosion on the vulvar mucosa.

Labs: ALT 68, AST 80
8.5% eosinophils

Which condition are you most concerned about?

1. Stevens-Johnson Syndrome
2. Toxic Epidermal Necrolysis
3. Erythema Multiforme
4. DRESS/drug-induced hypersensitivity syndrome

Mucosal involvement in DRESS

- Estimated to occur in 50% of DRESS cases
- Milder than TEN/SJS spectrum
  - Conjunctival injection
  - Mild mucosal ulcerations


DRESS Stevens-Johnson syndrome

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Evaluation
- CBC/diff
- Liver function tests
- Creatinine
- Urinalysis
- Baseline thyroid function studies

Treatment
- Discontinue offending medication
- Oral corticosteroids with 3-6 week taper if reaction severe
- Monitoring
  - Thyroid function tests- 2 to 3 months after

<table>
<thead>
<tr>
<th>Aromatic Anticonvulsants</th>
<th>Antibiotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Sulfonamides</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Minocycline</td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Lamotrigine</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>Allopurinol</td>
</tr>
</tbody>
</table>
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Cross reactivity between anticonvulsant medications may be as high as 75%
- If DRESS occurs with aromatic anticonvulsant, avoid the other aromatic anticonvulsants

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Anticonvulsant hypersensitivity syndrome/DRESS
  - Among patients taking lamotrigine:
    - Rate of serious rashes = 0.1%
  - Of patients with anticonvulsant hypersensitivity (DRESS) syndrome to lamotrigine, 60% also taking valproic acid derivative
  - Co-administration of valproic acid triples the half-life of lamotrigine

- black box warning

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - Associated with reactivation of human herpesvirus (HHV)
    - HHV 6
    - HHV 7
    - HHV 6 positive DRESS is associated with a more severe course and longer hospital length of stay (LOS)
      - LOS (11.5 days vs. 5 days, P = 0.039)
      - Number of febrile days (12.5 days vs. 3 days, P = 0.032)

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Summary
  - Reported autoimmune sequelae
    - Autoimmune thyroiditis
    - Type 1 diabetes mellitus
    - Vaginitis
    - Alopecia areata
    - Systemic lupus erythematosus
  - In a study of 145 adult patients with DRESS/DIHS, the most common autoimmune sequelae were
    - Autoimmune thyroiditis (4.8%)
    - Type 1 diabetes mellitus (2.1%), minimal within 1-2 months

References:
Hara H, et al. Dermatology 2005; 211:159-161
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Summary

- In acute phase, may affect multiple organ systems
  - Liver
  - Lungs
  - Kidneys
  - Heart
- In subacute phase (~2-3 months after resolution), may affect
  - Thyroid

Cases: Drug-Induced Discoloration

Which acne medication likely resulted in this blue-grey acne scar discoloration?
1. Isotretinoin
2. Minocycline
3. Doxycycline
4. Tetracycline
5. Topical dapsone

What is your next best step?
1. Discontinue offending medication
2. Q-switched Neodymium: yttrium aluminum garnet (Nd:YAG) laser
3. Q-switched Alexandrite laser
4. Q-switched Ruby laser
Minocycline hyperpigmentation

- Develops in 2.4% to 14.8% of patients taking 100 mg or more daily for >3 months
  - More common in
    - Elderly patients
    - Patients with connective tissue disease
    - With higher daily dosing
- Type 1 (Most common)
  - Blue-black discoloration of scars/inflamed skin
- Type 2
  - Blue-grey discoloration of previously normal skin
  - Typically affects legs
- Type 3 (Least common)
  - Diffuse muddy brown dyspigmentation on sun-exposed skin

"Tincture of time"
- In most cases, abnormal pigmentation fades within several months after discontinuation of medication

Gradual fading 7 months after discontinuation of minocycline


Minocycline hyperpigmentation: Treatment

- Laser therapy
  - Q-switched lasers
    - Neodymium: YAG 1064 nm
    - Alexandrite 755 nm
    - Ruby 694 nm


Minocycline hyperpigmentation: Treatment

- Laser therapy
  - Fractional diode (1,550 nm) laser


Which medication do you suspect may be causing this hyperpigmentation?

1. Intravenous immunoglobulin (IVIG)
2. Hydroxychloroquine
3. Methotrexate
4. Hydrochlorothiazide

11-year-old Hispanic girl with systemic lupus erythematosus
- Grey discoloration on neck, chin
- No preceding erythema, scaling in affected areas
Which medication do you suspect may be causing this hyperpigmentation?

1. Intravenous immunoglobulin (IVIG)
2. Hydroxychloroquine
3. Methotrexate
4. Hydrochlorothiazide

Antimalarial-induced hyperpigmentation

• Antimalarial-induced hyperpigmentation is estimated to occur in ~25% of patients taking antimalarial medications (chloroquine, hydroxychloroquine, quinacrine, mefloquine)

• In a study of 209 patients treated with chloroquine or hydroxychloroquine, hyperpigmentation developed in:
  - 35% of patients taking chloroquine
  - 13% of patients taking hydroxychloroquine


Antimalarial-induced hyperpigmentation

• Case of hydroxychloroquine-induced hyperpigmentation generating concern for elder abuse


16-year-old girl with Dock8 Deficiency Syndrome, now 3-months after bone marrow transplant

Nail changes most likely reflect:
1. Onychomycosis
2. Busulfan-nail hyperpigmentation
3. Melanocyte activation
4. New manicure style

Chemotherapeutic agents associated with nail hyperpigmentation and/or generalized hyperpigmentation:

• Busulfan
• Cyclophosphamide
• Doxorubicin
• Hydroxyurea
• Bleomycin

16-year-old girl with Dock8 Deficiency Syndrome now 3-months after bone marrow transplant

Nail changes most likely reflect:
1. Onychomycosis
2. Busulfan-nail hyperpigmentation
3. Melanocyte activation
4. New manicure style
What chemotherapy agent may result in this hyperpigmentation pattern?

1. Busulfan
2. Bleomycin
3. Vincristine
4. 5-fluorouracil

Serpentine Hyperpigmentation

- Self-limited supravenous eruption associated with
  - Intravenous chemotherapy:
    - 5-fluorouracil
    - Vinorelbine
    - Fotemustine
    - Docetaxel
  - Avoid peripheral administration of these medications; administer via central lines

Flagellate Erythema/Hyperpigmentation

- Causative Agents
  - Bleomycin
    - Estimated to occur ~20% of patients treated with bleomycin
    - May develop within 1 day to months after treatment
    - Heat-induced recall can occur
  - Other causes
    - Peplomycin
    - Docetaxel
    - Shiitake mushroom dermatitis

Bleomycin-Induced Flagellate Hyperpigmentation

- Associated with
  - *intralesional* bleomycin
  - sclerotherapy for vascular malformations
  - Injection of recalcitrant warts


THANK YOU