DRUG REACTIONS
FROM THE CASES SEEN

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Objectives

• Recognize the common mild to severe drug reactions
• Know the different tests useful to incriminate the right medication
• Could we do pretests BEFORE giving medications?
Case one

• Called in emergencies for Hand Cellulitis
• Patient receiving IV antibiotics ceftriaxone
• Rash was on one hand, now affects both hands and has been worse since beginning of the therapy
• It all happened after a cut on one finger a few days prior.
Bilateral hand “cellulitis”

- Blisters, vesicles, crusts
- Edema
- All fingers and dorsum of hands
Questions to ask?
Questions to ask?

• Every cellulitis, ask:
  - Is it painful?
  - Is it Itchy?

• A cellulitis is NOT itchy, it is painful!
• If itchy, it is NOT A CELLULITIS
Second question

• What are you applying on your hands?
• Patient had a wound, was applying **polysporin**, then she had a rash, was applying polysporin
• then got worse, was on oral antibiotics
• then got worse, was on IV antibiotics
• Was still applying polysporin.
Contact dermatitis

• Needs 48 to 72 hours for the cellular reaction
• Not immediate, not the same day
• Patch tests are read at 3rd day.
Polysporin allergy

• Polymyxine B and **Bacitracine**
• Same: **Bioderm**
• Cortisporin ( plus **Neomycin**)

More often allergy to **aminoside** ( Bacitracine Neomycin ), than to Polymyxine B
Polysporin (Bacitracin) allergy

Hand (cellulitis) acute dermatitis  Square pattern under band aid
Treatment

• Stop Polysporin
• Topical steroid, Betaderm ointment 0.1% BID until heals
Test possible?

• Yes patch test possible
• Send to a contact dermatitis specialist
• Or do it yourself
• One of my patient forgot about the rash and used polysporin for a soccer knee laceration, He was treated for “Knee cellulitis” until he decided to come and see me for “wound care”
Questions?
Case 2

- Called for localized leg rash and blister, CELLULITIS?
- 80 years old female
2 red plaques with a large central blister
Questions to ask:

- 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)

(American Academy modules)
Two lesions, one on each calf

• Long list of medications, no auto-medications
• Newly given were
  – Amlodipine
  – Acetaminophen
  – Ibuprofen
• “But I had the same rash last time I was admitted”
Exact same rash last admission

• Look at the meds to find the same culprit:
  – One different calcium channel inhibitor, Nifedipine
  – Acetaminophen
  – Maybe ibuprofen?
Fixed drug eruption (FDE)

In this 3-year analysis, the most common drug was paracetamol, followed by the non-steroidal anti-inflammatory drugs.


Calcium channel blockers, very rarely described
Drugs commonly associated with FDE

- Acetaminophen
- Acetylsalicylic acid
- Allopurinol
- Chloral hydrate
- Dapsone
- Dextromethorphan
- Diflunisal
- Erythromycin
- Metamizole
- Metronidazole
- Nystatin
- Penicillin
- Phenolphthalein
- Piroxicam
- Pseudoephedrine
- Sulfadiazine
- Sulfamethoxazole--trimethoprim
- Tetracyclines
- Tetrahydrazoline
What to do?

- Stop Acetaminophen
- Stop Ibuprofen
- Wound care
- Send to Sunnybrook drug safety for testing

- Testing are patch test on the area of the rash.
Fixed drug eruption: pathogenesis and diagnostic tests.

- **Shiohara T.**
- **Author information**
- **Abstract**
- **PURPOSE OF REVIEW:**
  - Fixed drug eruption is a simplified disease model for elucidating the mechanism(s) of how skin inflammation is induced by skin-resident T cells. In this review, we focus on how the presence of intraepidermal CD8+T cells resident in the fixed drug eruption lesions can provide exciting new clues to our understanding of pathomechanisms of inflammatory skin diseases.
- **RECENT FINDINGS:**
  - Intraepidermal CD8+T cells with an effector-memory phenotype resident in fixed drug eruption lesions have a major contributing role in the development of localized tissue damage. Activation of these CD8+T cells is sufficient for triggering the lesion, however, but not sufficient to cause extensive tissue damage observed in the fully evolved lesions; additional recruitment of CD4+ and CD8+T cells to a specific tissue site would also contribute to the late stage of lesion development. The influx of regulatory T cells into the epidermis observed in fully evolved lesions would serve to limit harmful immune reactions. Consistent with this, positive patch test reactions are only observed at the site of previous lesions harboring significant numbers of intraepidermal CD8+T cells.
- **SUMMARY:**
  - Intraepidermal CD8+T cells may represent double-edged swords of the skin immune system with protective and destructive capacity.

Generalized fixed drug eruptions

Picture from Article below

Figure 6: Generalized bullous fixed drug eruption.
Reference for severe drug eruptions

Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy

Maja Mockenhaupt

Center for Documentation of Severe Skin Reactions, Department of Dermatology, University Medical Center, Freiburg, Germany

J Dtsch Dermatol Ges. 2009 Feb;7(2):142-60;
Questions?
Case 3

- Male 38 years admitted for fever and a rash
- Sore throat 5 days ago was given Amoxicillin
- Amoxicillin -allergy suspected
- No past history of allergy
- Only Past history: Migraines
- Father dermatitis
Look for risk factors

- Female no
- Prior history of drug reaction no
- Recurrent drug exposure no
  - Repeated courses of therapy with the same drugs or related drugs are associated with higher rates of adverse drug reactions
- HLA type ?
  - SJS/TEN caused by allopurinol shows a strong association with HLA-B 5801 in Han Chinese
- Certain disease states
  - Reactions to aminopenicillins occur more commonly in patients with Epstein Barr virus (EBV) infection neg
  - HIV-positive patients have high rates of dermatologic reactions to sulfonamides and other drugs neg
Drug timeline

- 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.
- Drug hypersensitivity and Stevens Johnson TEN. It may be longer 3 to 6 weeks.
Carbamazepine

Amoxicillin

Sore-throat
On examination

- Fever chills,
- Edema of face and eyes
- Crusted lips
- Buccal sores
- Purple generalized rash with some small areas of sloughing.
- Papules on palms
BLOODWORK

At admission
CBC, Eosinophils ,
liver kidney
All was normal.
Carbamazepine treatment for Migraines

• Very happy with the treatment, first efficient treatment of a long series.

• Was reluctant to stop
Diagnosis Stevens Johnson Syndrome: SJS

- The sore throat and fever was the beginning of the SJS

- If was more than 30% of body surface sloughing, it would be called Toxic Epidermal Necrosis: TEN
SJS

AAD picture Septra

Patient seen in emergencies on Septra for a wound
Mucosal erosions in SJS and TEN
TEN
Treatment

1- **Remove the causal medication**
   - Stop the carbamazepine

2 –Admit and send to a burns unit (if not ICU) for acute skin failure:
   - Monitoring of the fluid – electrolyte balance,
   - Provision of **enteral** or parenteral nutrition,
     - ASAP nasogastric tube.
   - Wound care
   - Treatment of sepsis.

3- **Multidisciplinary approach**,  
   - Eye involvement may need emergent Ophthalmological care
   - Endocrine failure (TSH)
• Patient Admitted, IV fluid, was able to swallow food.
• Topical steroids on the skin, as not too much sloughing
• Cyclosporin 3mg/kg 10 days then taper,
• Favorable outcome, no sequellae
Questions?
Neurology consulted for migraine

\[\text{TEST FOR HLA}\]

- HLA-B*1502
- HLA-A*3101
- Patient is from Indian origin but he states that his family comes from “Persia”,
- Which is more the middle East or South East Europe.
What HLA for What medicine?

- Allopurinol HLA *B 58 01
- Carbamazepine HLA *B 15 02 HLA * A 31 01
- Abacavir HLA *B 57 01
Genotyping for severe drug hypersensitivity.

- Karlin E¹, Phillips E.
- Author information
- Abstract
- Over the past decade, there have been significant advances in our understanding of the immunopathogenesis and pharmacogenomics of severe immunologically-mediated adverse drug reactions. Such T-cell-mediated adverse drug reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug-induced liver disease (DILI) and other drug hypersensitivity syndromes have more recently been shown to be mediated through interactions with various class I and II HLA alleles. Key examples have included the associations of
  - **HLA-B*15:02 and carbamazepine induced SJS/TEN in Southeast Asian populations and**
    - **HLA-B*57:01 and abacavir hypersensitivity.**
  - HLA-B*57:01 screening to prevent abacavir hypersensitivity exemplifies a successful translational roadmap from pharmacogenomic discovery through to widespread clinical implementation. Ultimately, our increased understanding of the interaction between drugs and the MHC could be used to inform drug design and drive pre-clinical toxicity programs to improve drug safety.
- PMID: 24429903 [PubMed - indexed for MEDLINE]
Genetics and the potential for predictive tests in adverse drug reactions.

- **Pirmohamed M.**

  **Abstract**

  Drug hypersensitivity reactions are an immune-mediated reaction to otherwise innocuous antigens derived from drugs. These reactions can affect many different organs, with the skin being the commonest. Skin involvement can range in severity with hypersensitivity syndrome (or DRESS) and the blistering reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis), also termed serious cutaneous adverse drug reactions, being the most severe and most feared. There is increasing evidence for the role of the immune system in the pathogenesis of these reactions, with drug-specific T cells having been identified in many patients. Until recently, very little was known about the predisposition to these reactions. However, the availability of more accurate molecular typing methods, and the ability to analyse the whole genome in an unbiased fashion, has led to some remarkable findings of the role of the HLA genes as genomic biomarkers of predisposition. The 'revolution' started with abacavir where the predisposition to hypersensitivity was linked to HLA-B*57:01, which was confirmed in a clinical trial, and where its implementation has shown to reduce the incidence of hypersensitivity in a cost-effective manner. Since then, associations have also been shown for allopurinol (HLA-B*58:01)- and carbamazepine (HLA-B*1502 and HLA-A*3101)-induced serious cutaneous adverse drug reactions. The latter is interesting since the association with HLA-B*1502 is present in certain South-Eastern Asian populations, and the predisposition is phenotype specific (only for SJS/TEN). The utility of this biomarker has been shown in a prospective cohort study performed in Taiwan. By contrast, the association with HLA-A*3101 is seen in more diverse ethnic groups, and predisposes to mild as well more severe cutaneous reactions associated with carbamazepine. It is important to note that strong HLA associations have also been shown with a number of drugs that cause liver injury including flucloxacinil, lumiracoxib, lapatinib and ximelagatran, indicating that the immune system is also important in the pathogenesis of other forms of drug-induced organ toxicity. The crucial question as to whether these HLA alleles are truly causative or acting as surrogate markers of predisposition, however, is still unclear, and will require further investigations in larger patient cohorts, through the use of bioinformatic techniques, fine mapping using next generation sequencing technologies and functional studies.

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Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis.

- **Somkrua R**¹, Eckman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N.

**Abstract**

**BACKGROUND:** Despite some studies suggesting a possible association between human leukocyte antigen, HLA-B*5801 and allopurinol induced Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), the evidence of association and its magnitude remain inconclusive. This study aims to systematically review and meta-analyze the association between HLA-B*5801 allele and allopurinol-induced SJS/TEN.

**METHODS:**

A comprehensive search was performed in databases including MEDLINE, Pre-MEDLINE, Cochrane Library, EMBASE, International Pharmaceutical Abstracts (IPA), CINAHL, PsychInfo, the WHO International, Clinical Trial Registry, and ClinicalTrial.gov from their inceptions to June 2011. Only studies investigating association between HLA-B*5801 with allopurinol-induced SJS/TEN were included. All studies were extracted by two independent authors. The primary analysis was the carrier frequency of HLA-B*5801 comparison between allopurinol-induced SJS/TEN cases and each comparative group. The pooled odds ratios were calculated using a random effect model.

**RESULTS:**

A total of 4 studies with 55 SJS/TEN cases and 678 matched-controls (allopurinol-tolerant control) was identified, while 5 studies with 69 SJS/TEN cases and 3378 population-controls (general population) were found. SJS/TEN cases were found to be significantly associated with HLA-B*5801 allele in both groups of studies with matched-control (OR 96.60, 95%CI 24.49-381.00, p < 0.001) and population-control (OR 79.28, 95%CI 41.51-151.35, p < 0.001). Subgroup analysis for Asian and Non-Asian population yielded similar findings.

**CONCLUSION:**

We found a strong and significant association between HLA-B*5801 and allopurinol-induced SJS/TEN. Therefore, **HLA-B*5801 allele screening may be considered in patients who will be treated with allopurinol.**
Drugs commonly associated with SJS and TEN

- Allopurinol
- Amithiazone
- Amoxicillin Ampicillin
- Carbamazepine
- Chlormezanone
- Corticosteroids
- Felbamate
- Lamotrigine
- Phenobarbital
- Phenylbutazone
- Phenytoin
- Piroxicam
- Sulfadiazine
- Sulfadoxine
- Sulfamethoxazole--Trimethoprim
- Sulfasalazine
- Valproic acid
SHOULD WE SCREEN OUR PATIENTS?

Before Allopurinol?

Before Carbamazepine?
Review our case 3
Could it be DRESS?

- DRESS:
  
  Drug Reaction with Eosinophilia, and Systemic Symptoms
Common drugs associated with drug reaction with eosinophilia and systemic symptoms syndrome

- **Anticonvulsant**
  - Carbamazepine, lamotrigine, phenobarbital, phenytoin, valproic acid, and zonisamide
- **Antimicrobial**
  - Ampicillin, cefotaxime, dapsone, ethambutol, isoniazid, linezolid, metronidazole, minocycline, pyrazinamide, quinine, rifampin, sulfasalazine, streptomycin, trimethoprim-sulfamethoxazole, and vancomycin
- **Antiviral**
  - Abacavir, nevirapine, and zalcitabine
- **Antidepressant**
  - Bupropion and fluoxetine
- **Antihypertensive**
  - Amlodipine and captopril
- **Biologic**
  - Efalizumab and imatinib
- **NSAID (Nonsteroidal antiinflammatory drug)**
  - Celecoxib and ibuprofen
- **Miscellaneous**
  - Allopurinol, epoetin alfa, mexiletine, and ranitidine
DRESS Criteria J.SCAR

- Maculopapular Rash >3 weeks after starting offending drug
- Prolonged clinical symptoms after drug was discontinued
- Fever >38°C
- Liver abnormalities (ALT >100 U/L) or other organ involvement
- Leukocyte abnormalities (≥1)
  - Leukocytosis (>11 × 10⁹/L)
  - Atypical lymphocytes (>5%)
  - Eosinophilia (>1.5 × 10⁹/L)
- Lymphadenopathy
- HHV-6 reactivation
Let us review patient 3:

- Rash > 3 weeks after Carbamazepine
- Rash lasted 1 month after onset
- Liver anomalies? Yes, not at admission but 3 days later ALT was 4x N, AST 3 x N
- Late eosinophilia, normal at admission but at day 3 up to $0.980 \times 10^9$ L$^{-1}$ for a short period of time
- Leucocytes normal. Lymphocytes normal
- No Lymphadenopathy.
So the diagnosis at first sight was SJS
But the diagnosis is likely DRESS
Dress treatment?

• No real consensus. Steroids seem still first line as well as topical steroids but sparing agents advised, Cyclosporin described as very efficient in a case of DRESS with Vancomycin.

*DRESS syndrome: Part II. Management and therapeutics.*

One picture of a DRESS case in JAAD mucosal sloughing
Questions?
Acute Generalized Exanthematous Pustulosis (AGEP)
AGEP

• Very acute onset <10 days
• Erythematous plaques covered with confluent small pustules, specially in folds and flexural areas, non follicular
• Fever $\geq 38^\circ$C and elevated neutrophil counts ($7 \times 10^9$/L)
• Resolution in ( $\leq 5$ days)
AGEP differential

Generalized Pustular Psoriasis
Sneddon Wilkinson.
Two pustular non follicular rashles with flaccid pustules confluent.
HLA-DR-B1*07

• Has been detected in some AGEP patients and in some psoriasis patient

• CD4 CD8 T cells migrate in epidermis and express interleukine 8, attracting neutrophils.

• Same interaction T lymphocytes and neutrophils as in psoriasis.
What about exanthems?

• 1-Rule out the severe drug rashes, SJS DRESS AGEP, generalized FDE; check CBC eosinophils kidney, liver
• 2-remove the non vital drugs
• 3- differential with viral rashes, toxic rash in case of sepsis
• 4-If well tolerated and short course of possible causal medication, maybe finish the course?
Questions?
Thank you
Drug Induced Bullous Pemphigoides (BP)?

• About 1 case per month of Bullous Pemphigoides in the ward, or emergencies,
• All patients are elderly with many medications
• Should we suspect Drug induced BP?
Strong blisters on an urticarial background
Strong blisters – base fix urticaria
Drugs commonly associated with drug-induced bullous pemphigoid

- Ampicillin
- Captopril
- Chloroquine
- Enalapril
- Furosemide
- Penicillamine
- Penicillin
- Penicillin
- PUVA (Psoralen and UV light A)
- Salicylazo sulfapyridine
- Sulfasalazine
Most frequently used drugs

- Furosemide
- Other Sulfa:
  - Hydrochlorothiazide
  - Antidiabetic sulfamide drugs
- ACE inhibitors

- When possible it would be interesting to stop the medication? A case by case discussion.