



# Drug Allergy/ Hypersensitivity Management: an Examination of Drug Allergies likely to be Encountered by the Practicing Allergist

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# Disclosures

- Speaker, Advisory Board Member;  
Honorarium
  - Takeda Pharmaceuticals
  - GSK
  - Astra-Zeneca



# objectives

- Recognize types of clinical reactions to fluoroquinolone antibiotics and distinguish allergic from non-allergic reactions
- Identify the key features of Symmetrical Drug-related Intertriginous and Flexural Exanthem (SDRIFE)
- Management of the patient with multiple drug “allergies”: multiple drug hypersensitivity syndrome (MDHS) and multiple drug intolerance syndrome (MDIS)



# Adverse Drug Reactions

- Type A: predictable
  - Overdose
  - Side effect
  - Secondary effects
  - Drug-Drug interactions

## Type B:

- Drug intolerance (tinnitus with ASA)
- Drug idiosyncrasy (hemolysis in pt with G6PD def with primaquine)
- Pseudoallergic reactions (vancomycin and RED man syndrome)
- Immune Mediated reactions (drug allergy)



# Modern approach to ADR Classification

- 1. Primary on-target pharmacological effects
- 2. Off target effects at distant receptors
  
- Drug Hypersensitivity Reactions comprise 6%-10% of all adverse drug reactions.



# Off-Target Reactions

- Hypersensitivity reactions to abacavir and carbamazepine, allopurinol and dapsone. Due to HLA phenotypes leading to drug induced hypersensitivity syndrome (DRESS)
- **CARMBAMAZEPINE:**
  - Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) caused by carbamazepine in Han Chinese shows a strong association with HLA-B\*15:02
  - In Caucasians: HLA-A\*31:01 DiHS/DRESS
- **Abacavir:** HLA-B\*57:01 in Caucasians
- **Allopurinol/oxypurinol** binds to the HLA-B\*58:01
- **Dapsone** hypersensitivity syndrome disproportionately affects Chinese patients with HLA-B\*13:01



# Drug Allergy Definition

- Immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person
  - Requires sensitization so should not be on first exposure
  - Type I: immediate reactions mediated by drug specific IgE abs leading to urticaria, angioedema, bronchospasm, anaphylaxis
  - Type II: IgM or IgG mediated
  - Type III: Immune complex mediated
  - Type IV: cell mediated (most common)



## Exceptions to prior exposure for type B reactions:

- Neuromuscular blocking agents (succinylcholine, rocuronium etc)
  - 2 possible mechanisms: IgE and non-IGE (MRGPRX2)
- Cetuximab

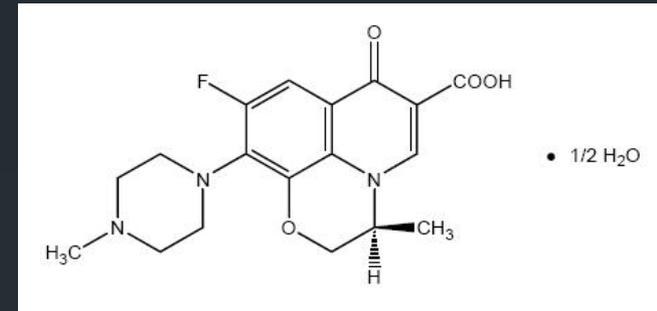
# Case: 54 yo woman with Type I DM presenting with drug rash

- 3 d history of fevers and chills but no localizing symptoms. PCP concerned about risk of infection in setting of Type I DM prescribed ciprofloxacin 500 mg bid x 3 days
- 1 day after completion broke out in a bumpy rash. Initially on arms but soon spread to involve to lower extremities
- No mucosal involvement
- No desquamation
- Not pruritic
- Given methylprednisolone dose pack: no major impact
- Rash resolved over 10 days.



# Fluoroquinolones: Delayed Maculopapular Eruption

- 2-3 % of patients treated with fluoroquinolones
- T-cell mediated (1)
- Self-limited, no urticaria or angioedema
- Treatment: stopping the drug
  
- Evaluation: patch testing not useful
- 101 pts with fluoroquinolone allergy: 37 had delayed reactions. Underwent patch testing: no positive results 28 had graded challenge with culprit drug: 2 reacted (2)
- Rechallenge: 66 pts: only 3 reacted (3)



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# Fluoroquinolones: Delayed Maculopapular Eruption



- Management:
- Careful history
- Graded challenge with alternative fluoroquinolone (1/10<sup>th</sup> dose followed in 1 h by full-dose) observe for 1 h
- May still have delayed reaction
- May miss a reaction that would occur with prolonged use

Case revisited: inadvertently rechallenged with culprit drug and developed similar rash. Subsequently, challenged with levofloxacin and tolerated drug  
\*provocative challenge with 3 day dosing.



# Immediate Reactions to Fluoroquinolones

- Occur within 1 h of exposure: urticaria, flushing, angioedema, pruritus, wheezing, anaphylaxis etc.
- Incidence: between 1 and 5 per 100,000 prescriptions (insurance database looking for anaphylaxis code) Comparable to PCN (2 of 100,000)
- Mechanism: mast cell and basophil activation. Can be IgE vs non-IgE mediated. Limited data that IgE is common
- -MRGPRX2 receptor mast cell
- Dilemma:
  - Pts with past immediate reactions to one fluoroquinolone may react to others (no clear patterns of cross-reactivity)
  - Many pts with past reactions will tolerate the culprit drug

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# Approach to the patient with immediate reactions to fluoroquinolones



- Consider the future need for this class of drugs: if likely to need it is worth pursuing further evaluation
- Determine when the last reaction occurred: if > 5 years it can be considered as remote. If with recent anaphylaxis, testing may be inconclusive and risk for bad outcome with challenge is high.
- No validated skin tests. The drugs may cause nonspecific mast cell degranulation

<b>Fluoroquinolone</b>	<b>Non-Irritating Concentration</b>
Levofloxacin	0.025mg (1:1000 dilution of 25 mg/ml IV dose)
Moxifloxacin	0.016 mg/mL (1:100 dilution IV 1.6 mg/mL)
Ciprofloxacin	A nonirritating concentration has not be identified!



Skin test at a presumed non-irritating concentration of levofloxacin is negative in a patient with a remote history of possible reaction to levofloxacin. What do you do now?

- A. Tell the patient they do not have an allergy to levofloxacin and they may take the medication.
- B. Do a challenge dose of levofloxacin and observe for 1 hour
- C. Do a challenge with a different fluoroquinolone, eg moxifloxacin and observe the patient.
- D. Skip the skin testing and challenge with alternative fluoroquinolone

# Fluoroquinolones: immediate reactions what to do with skin test results

- Positive skin test may be indicative of allergy (positive predictive value = 50%)
- If drug is needed: desensitization, otherwise avoid all fluoroquinolones
- Negative skin test: perform graded challenge (in case series about 7% will be positive)
- Graded Challenge:
  - Alternative fluoroquinolone (x-reactivity ~50%)
  - 1/100<sup>th</sup> of full dose with 2-4 steps to reach full dose 1h apart

## ■ Case presentation:

- 68 yo woman referred for : “Running out of options for antibiotics”
- Recent history: prescribed levafloxacin for a bronchitis. Developed wheezing and SOB 2h post second dose. Took diphenhydramine on way to UCC. Given steroids in UCC and switched to azithromycin
  - Similar symptoms with cefdinir
  - First reaction was many years ago to amoxicillin. More recently had been skin tested for penicillin with an Allergist. After negative ST underwent open oral graded challenge . After first dose developed tingling of her lips. 10 mins post remaining dose: developed subjective symptoms of shortness of breath with wheezing. No wheezing heard on exam. No change in PFTs. Has avoided PCN since that time
- PAST MEDICAL HISTORY:
  - 1. Multinodular goiter in 2012 status post thyroidectomy, now on supplementation.
  - 2. Vitamin D deficiency.
  - 3. Anxiety and insomnia.
  - 4. Obstructive sleep apnea, on CPAP.
  - 5. Status post total abdominal hysterectomy, left ovary intact.
  - 6. Dyslipidemia.
  - List of allergies: amoxicillin, cefdinir, doxycycline, erythromycin, levaquin, clindamycin



# ARS: What is your working diagnosis based on the initial history?

- A. Multiple drug hypersensitivity syndrome
- B. Anxiety
- C. Multiple Drug Intolerance Syndrome
- D. Bad luck



## Multiple Drug Hypersensitivity Syndrome (aka Multiple Drug Allergy Syndrome)

- History of adverse reactions to 2 or more structurally unrelated drugs that appear to have an underlying immune-mediated mechanism
- Uncommon
- When does occur, typically due to a T-cell mediated immune response

# Drug Intolerance

- Hypersensitivity reaction that includes any undesirable and non-immune mediated effect of a drug
- (AKA type B reactions)
- GI symptoms, headaches
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# MDIS

- Intolerance to 3 or more chemically unrelated drugs
- Not immune mediated
- Almost all our pts can fall into this category
- Prevalence: 2-6% vs MDHS 1%

# History

1. Route of administration
2. Why was it prescribed
3. Alternative drug available
2. # of prior exposures to culprit drug or similar drugs?
2. Other drugs given at same time? (NSAIDs, opiates, ACE etc)
3. Time between last dose of drug and onset of symptoms?
4. Signs and symptoms of rxn?
5. Did symptoms resolve when drug d/c'd?
6. Duration since rxn occurred?
1. Cutaneous rxns more common with parentally administered vs oral meds
2. Concomitant viral/bacterial infections (EBV HIV, mycoplasma)
3. If no alternatives, need more aggressive work-up
4. IgE med. More likely > exposures
5. May exacerbate rxn or be the cause
6. IgE with in 2-4 h
7. Objective and subjective sx: O2 desat, tachycardia, hypotension, wheezing, etc)
8. If persistent, consider other cause
9. If remote, may be forgotten

# Immunologic Drug Reactions

- **IgE, mast cell & basophil mediated, Type 1 Gell and Coombs Common (allergic symptoms to anaphylaxis)** Occurs quickly with drug exposure. **Common drugs: B-lactams, muscle relaxants, foreign proteins, carboplatins/CTX.** Testing available: tryptase at time of reaction. Skin testing
- **Antibody-mediated IgG/IgM cell destruction (type II Gell Coombs)** Uncommon. Hemolytic anemia, thrombocytopenia etc, Delayed onset: can be weeks after starting a therapy. **B-lactams, NSAIDs, quinidine, ticlodipine.** Dx: direct coombs test for anti-platelet/anti-neutrophil antibodies.
- **Immune Complex Mediated (type 3 reaction):** Uncommon. serum sickness, vasculitis drug fever, acute GN. Onset is delayed weeks to months after starting Tx. (faster onset with reexposure): **B-lactams, sulfonamides, tacrolimus.** No testing
- T-cell mediated (+/-) eos, pmns. Common. Presents with morbilliform rashes, DRESS/DHS, AGEP, exfoliative dermatitis. Delayed onset @ least 24-48h. **B lactams, sulfonamides, sulfasalazine, minocycline, phenytoin, carbamazepine, lamotrigine, allopurinol, abacavir.** Testing is possible for some drugs (not standardized)





# Skin Testing

- Epicutaneous followed by ID if negative
- A positive skin test to a non-irritating concentration in a pt with a history of immediate-type allergic drug reaction is helpful
- A negative skin test does not indicate low risk because of the poor negative predictive value of skin testing for most reagents except penicillin

Class	Drug	Full-strength concentration (mg/ml)	NIC (as dilution of full-strength concentration)
PCNs	Ticarcillin	200	10 <sup>-1</sup>
	Nafcillin	250	10 <sup>-4</sup>
Cephalosporins	Cefotaxime	100	10 <sup>-1</sup>
	Cefuroxime	100	10 <sup>-1</sup>
	Cefazolin	330	10 <sup>-1</sup>
	Ceftazadime	10	10 <sup>-1</sup>
	Ceftriaxone	100	10 <sup>-1</sup>
Fluoroquinolones	Levofloxacin	25	10 <sup>-3</sup>
	Moxifloxacin	4	10 <sup>-3</sup>
Sulfonamides	Cltrimoxazole	80	10 <sup>-2</sup>
Aminoglycosides	Tobramycin	40	10 <sup>-1</sup>
	Gentamycin	40	10 <sup>-1</sup>
Macrolide	Erythromycin	40	10 <sup>-3</sup>
	Azithromycin	100	10 <sup>-4</sup>
	Clarithromycin	50	1mg/ml

- **Macrolides:** IgE reactions anecdotal reports
  - Maculopapular exanthems most common
  - Azithromycin 1% rate of skin eruption in pediatrics
  - Can skin test with azithromycin (0.01 mg/ml highest NIC)
  - Challenge with azithromycin: 25 mg 1 h later 250 mg
- **Aminoglycosides:** rare except for ACD, rare cases of anaphylaxis
  - Significant cross-reactivity
  - Gentamycin 0.4 mg/ml Tobi: 4 mg/ml, streptomycin 0.1 mg/ml NIC
- **Tetracyclines:**
  - Minocycline severe non IgE mediated rxns (DRESS, serum sickness, SJS, eosinophilic pneumonia, drug-induced lupus) DIL: 2 y before onset
- **Clindamycin:** C diff colitis, GI ses, Maculopapular eruptions. No reported IgE reactions. No utility in skin testing or patch testing
- **Metronidazole:** fixed drug eruption, SJS, generalized exanthams, serum sickness, and 1 case anaphylaxis
- Significant cross reactivity with other imidazoles (clotrimazole, ketoconazole, miconazole and abendazole)

# Multiple Drug Intolerance Syndrome (MDIS)

- Adverse drug reactions to at least 3 drugs, chemically, pharmacologically and immunogenetically unrelated, manifested upon 3 different occasions, with negative allergy testing.
- -symptoms are typically subjective
- The patients believe themselves to be allergic to all drugs, GPs tend to agree and they avoid drug therapy even if necessary.
- Schaviano et al. published some of the earliest data on this phenomenon and coined the term ALEXITHYMIA
- When multiple unrelated drugs trigger similar symptoms: need to consider role of a conditioned response

# Alexithymia

- Reduced ability to identify and differentiate emotional aspects of social interaction.
- Difficulty in decoding the meaning of affective signals
- An impaired linguistic affect symbolization
- A cognitive style preferentially oriented towards external facts
- A poor fantasy life
- A disturbed emotional exchange with close relationships
- Complex phenomenon caused by genetic, neuropsychologic, psychological and social factors
- Associated with enhanced risk for psychological impairment (somatoform disorders, depression eating disorders etc).
- Seems to represent a vulnerability factor that promotes the appearance of psychological or psychosomatic symptoms



# MDIS

- Need multidisciplinary clinical approach



# Approach to management of patients with proven MDAS

- Find at least 2 classes of antibiotics that are safe for use
- Penicillin testing and challenge is low hanging fruit
- Beyond antibiotics: consider evaluation based on need for the specific drug



# Drug Challenges

- Should be considered when after a full evaluation, pt is deemed to be at low risk for being allergic to a drug
- Contraindications: autoimmune disease (drug-induced lupus), SCARs (SJS/TENS, DRESS), Vasculitis, hepatitis, nephritis, or pneumonitis, and serum sickness.
- Starting dose:  $1/100^{\text{th}}$  or  $1/10^{\text{th}}$  of therapeutic dose
  - Full dose 60 minutes later
  - For delayed reactions: dose every several days
  - Placebos are your friend!

# Suspected MDIS

- Set up your challenges with multiple placebos
- Can even consider doing it over several days so they don't know when they are getting the actual medication
- Document all symptoms.
- For patients with a conditioned response: often-times showing them the results will allow them to overcome the issue
  - You may need to have a psychologist for the more recalcitrant cases

# Case of mistaken identity

- 47 yo woman with history of inflammatory bowel disease referred for multiple drug allergies
- 5 or 6 years ago she was given **ciprofloxacin** for UTI. She developed some blotchiness of the skin. She spoke to her father who is a pharmacist. He recommended discontinuing Cipro. At that time there is no distinct hives. No difficulty breathing. No other symptoms.
- In February of this year she was given **Macrobid** for UTI. She states that with the first dose she began to sneeze. She developed a bumpy rash on her skin. It was intensely itchy. She took diphenhydramine. Symptoms resolved in about an hour. She was switched to Keflex. The infection did not clear with Keflex. She subsequently was given doxycycline
- On **doxycycline**, she states that with the first dose once again and within 20 minutes started sneezing. She broke out in a diffuse welt-like rash all over her body. She states it is the worst reaction that she had to a medication. She took several doses of Benadryl. She was getting ready to go to the emergency room but symptoms resolved.



## What would you do as the next step?

- A. Skin test for alternative fluoroquinolone, eg levofloxacin and do a challenge if negative.
- B. Skin test for nitrofurantoin and do a challenge if negative?
- C. Skin test for doxycycline and do a challenge if negative?
- D. Tell her to avoid all of the antibiotics to which she has had an issue.
- E. A,B, C.

# A case of mistaken identity cont.

- Skin tests to penicillin, nitrofurantoin, levofloxacin and doxycycline were negative.
- Patient came back to do an oral challenge. Before the first dose was given, she started to break out in urticaria and became flushed and tachycardic.
- She was given 10 mg cetirizine and watched.
- She forgot to tell us that she she took a metronidazole tablet prior to leaving the house for her appt. Due to her history of C. diff, she always takes metronidazole with antibiotics.
- Final impression: allergy to metronidazole

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- 76 yo gentleman with history of mild hyperlipidemia and hypertension presents with a 9 month history of recurrent rash primarily occurring on his buttocks and thighs. Prodrome of fatigue night before onset. He associated the development of the rash with use of azelastine and merlot
  - No history of allergic contact dermatitis
  - Biopsy: neutrophilic exocytosis with interstitial neutrophilic dermatosis with eosinophils



# What is your diagnosis?

- A. Atypical Sweet Syndrome
- B. Malignancy related dermatosis
- C. Recurrent cellulitis
- D. Contact dermatitis
- E. Baboon Syndrome





- Patch testing with North American Contact Dermatitis series 65, merlot wine, azelastine and ipratropium nasal spray were negative.
- Due to continued episodes with azelastine, pure azelastine was tested at various concentrations and was negative.
- Patch testing with EDTA triggered a stereotypical reaction. Ethylenediaminetetracetic acid is a common preservative



# SDRIFE: symmetrical-drug related intertriginous and flexural erythema

- **Baboon Syndrome:** systemic contact dermatitis secondary to topical sensitization (eg: nickel and mercury).
- SDRIFE is separate in that there is no preceding skin sensitization
  - Contact Allergen-induced baboon syndrome (excludes drugs)
  - Topical drug-induced baboon syndrome
  - Systemic-drug induced baboon syndrome (with preceding contact dermatitis)
- **Diagnosis:** exposure to systemically administered drug (2) sharply demarcated erythema of gluteal/perianal area; (3) involvement of at least one other intertriginous/flexural location; (4) symmetry (5) no systemic signs or symptoms



## Acral Reactions due to chemotherapy

- Acral Erythema (Hand-Foot Syndrome/ Palmar-plantar erthrodysesthesia) : cytosine arabinoside, doxorubicin, capecitabine, or docetaxel.
  - symmetric edema and erythema of the palms and soles, which may progress to blistering and necrosis
- Hand-Foot Syndrome caused by small molecule tyrosine kinase inhibitors:
  - well demarcated, bean to coin sized, hyperkeratotic, painful plaques with underlying erythema localized to the pressure areas of the soles
- Both conditions are preceded by dysesthesia of the involved areas

# Acral drug reactions





# Conclusions

- Role of the Allergist/Immunologist in the management of patients with drug allergy is critical particularly in era of the electronic medical record when the drug allergy list is not edited.
- Certain drugs are rare causes of immediate allergic reactions:
- It takes a certain amount of amount of diligence to work through the cases of patients with multiple drug allergy and multiple drug intolerance syndrome.

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