

NKDA: No Known Drug Allergies?
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Objectives

- ▶ Differentiate between types of hypersensitivity reactions
- ▶ Understand the difference between true drug allergy, pseudoallergy, and expected drug side-effect
- ▶ Become familiar with questions used to assess for drug allergies
- ▶ Identify & review the most commonly reported drug allergies
- ▶ Based on a patient's drug allergy history, become comfortable determining whether a particular medication can or cannot be safely administered

Background

- ▶ Over 200,000 patients are treated in ED annually for drug allergies
- ▶ Allergies to opioids, penicillins, sulfa, and aspirin are the most commonly reported
- ▶ Penicillin is the most common drug allergy
- ▶ Parenteral medications more likely to cause allergic reactions than oral medications

Classification of Allergic Drug Reactions

- ▶ Type I Hypersensitivity Reaction/Anaphylactic: IgE-mediated
 - ▶ AKA Antibody-mediated anaphylactic reactions
 - ▶ Responsible for urticaria, laryngeal edema, bronchospasm, wheezing, and/or hypotension
 - ▶ Immediate hypersensitivity reactions
 - ▶ Onset: minutes to 2 hrs after drug exposure
 - ▶ Life-threatening
 - ▶ Accelerated reactions
 - ▶ Onset: 1-72 hrs after drug administration
 - ▶ Rarely life-threatening

Classification of Allergic Drug Reactions

- ▶ Type II Hypersensitivity Reaction/Cytotoxic
 - ▶ Possesses cytolytic and cytotoxic activity
 - ▶ IgG & IgM – mediated
 - ▶ Occurs 7-21 days after drug initiation
 - ▶ Result in hemolytic anemia, thrombocytopenia, neutropenia

Classification of Allergic Drug Reactions

- ▶ Type III Hypersensitivity Reaction/Immune Complex Reaction
 - ▶ IgG & IgM-mediated
 - ▶ Antibody-antigen complexes cause damage to entire organs
 - ▶ Symptoms: fever, rash, lymphadenopathy, arthralgias
 - ▶ Skin, joints, & kidneys are most commonly affected
 - ▶ Occur in 5-21 days after drug initiation
 - ▶ Results in vasculitis, maculopapular rash, glomerulonephritis, or erythema multiformae

Classification of Allergic Drug Reactions

- ▶ Type IV Hypersensitivity Reaction/Delayed
 - ▶ AKA cell-mediated hypersensitivity
 - ▶ Mediated by cytokines released by sensitized T-cells
 - ▶ Result in activation of immune cascade leading to tissue damage
 - ▶ Occur 48 - 72 hrs after exposure
 - ▶ Examples: contact dermatitis, Stevens-Johnson syndrome (SJS)

Patients' Perspective on Drug Allergies

- ▶ "Allergy" to:
 - ▶ Sulfa: family history; has not tried per MD
 - ▶ Epinephrine: "It makes my heart race."
 - ▶ Meperidine: "It makes me die."
 - ▶ Morphine: "It gives me a bad trip."
 - ▶ Hydrocodone: "It makes me hear voices."
 - ▶ Codeine: "It causes vomiting."
 - ▶ Prednisone: "Upsets my stomach"

Classification of Drug Reactions

- ▶ Non-allergic Reactions
 - ▶ Examples: nausea, vomiting, diarrhea, HA, dizziness
 - ▶ Unpleasant but not mediated by the immune response
 - ▶ **Not:**
 - ▶ True allergic reactions
 - ▶ Life-threatening
 - ▶ A contraindication to re-treatment with the offending agent
 - ▶ N/V: try oral medications with food or snack

Classification of Drug Reactions

- ▶ Pseudoallergic Reactions
 - ▶ Direct stimulation of mast cells resulting in release of histamine
 - ▶ Example: opiates, vancomycin
 - ▶ Non-immunologic activation of the complement cascade
 - ▶ Example: radiocontrast media
 - ▶ Change in metabolism or production of inflammatory mediators
 - ▶ Example: ACE inhibitors, aspirin, NSAIDs
 - ▶ Photosensitivity reaction to sulfa medications

Classification of Drug Reactions

- ▶ True Allergic Reactions
 - ▶ Mediated by immune response
 - ▶ Involve IgE, or IgM and/or IgG antibodies or T-cells
 - ▶ Lead to mast cell degranulation and histamine release
 - ▶ Potential presentation:
 - ▶ Hives, severe itching, angioedema, laryngeal edema, dyspnea, wheezing, anaphylaxis, severe hypotension
 - ▶ May recur within or across drug classes
 - ▶ Medications with similar structural components may elicit similar antigenic responses
 - ▶ Contraindications to re-treatment with the offending agent and/or treatment with other similar drugs

Classification of Drug Reactions

- ▶ Severe Idiopathic Reaction
 - ▶ May or may not be mediated by body's immune response
 - ▶ Life-threatening or severe enough to contraindicate further use
 - ▶ Examples: SJS, toxic epidermal necrolysis, agranulocytosis

Severe Idiopathic Reactions



Classification Based on Severity

- | | |
|---|--|
| <ul style="list-style-type: none">▶ Mild allergic reaction▶ Response mediated by body's immune system▶ Not life-threatening▶ Contraindication to re-treatment with the offending agent▶ May not prohibit treatment with other similar drugs▶ Examples: rash, mild itching, sneezing | <ul style="list-style-type: none">▶ Severe allergic reaction▶ Response mediated by body's immune system▶ May be life-threatening▶ Contraindication to re-treatment with the offending agent▶ Prohibits use of certain other similar drugs▶ Examples: laryngeal edema, wheezing, angioedema, severe itching, bronchospasm, severe drop in BP, anaphylaxis |
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"Sulfa" Allergy - Background

- ▶ Words used to describe sulfa allergy
 - ▶ Sulfa
 - ▶ Sulfur
 - ▶ Sulfite
 - ▶ Sulfate
- ▶ Presentation
 - ▶ Most commonly as maculopapular rash 7-14 days after therapy initiation
 - ▶ Rarely: anaphylaxis, SJS, toxic epidermal necrolysis
 - ▶ Allergic reactions may be in response to oral, topical, vaginal, systemic, & ophthalmic routes

What are Sulfonamides, Sulfites, & Sulfates?

- ▶ Sulfur (S)
 - ▶ Sulfur-containing medications
 - ▶ Examples: amoxicillin, captopril, omeprazole, ranitidine, spironolactone, sulindac
 - ▶ Not sulfonamides
 - ▶ Do not cross-react
- ▶ Sulfates (SO₄)
 - ▶ Examples: zinc sulfate, morphine sulfate, ferrous sulfate
 - ▶ Chemically unrelated to sulfonamides
 - ▶ No risk of cross-reactivity
 - ▶ Report as sulfate allergy

Sulfites (SO₃)

- ▶ Examples
 - ▶ Sulfur dioxide
 - ▶ Sodium sulfite
 - ▶ Sodium bisulfite
 - ▶ Potassium bisulfite
 - ▶ Sodium metabisulfite
 - ▶ Potassium metabisulfite
- ▶ Chemically unrelated to sulfonamides
- ▶ Common food and drug additives
- ▶ Used as antioxidants
 - ▶ Epipen, Pred Forte
- ▶ No risk of cross-sensitivity
- ▶ Report as sulfite allergy
- ▶ May cause own reactions in patients with asthma
 - ▶ Dyspnea, wheezing

Sulfates (SO₄)

- ▶ Examples:
 - ▶ Zinc sulfate
 - ▶ Morphine sulfate
 - ▶ Ferrous sulfate
- ▶ Chemically unrelated to sulfonamides
- ▶ No risk of cross-reactivity
- ▶ Report as sulfate allergy

Saccharin

- ▶ Sulfonamide derivative
- ▶ Artificial sweetener
 - ▶ Ingredient in many liquids and tablets
 - ▶ Not required to appear in drug labeling
- ▶ Reports of dermatologic reactions & cross-reactivity with sulfonamide antibiotics
- ▶ American Academy of Pediatrics recommends against use in children with sulfonamide allergy

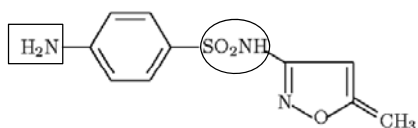
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Sulfonamides

- ▶ Sulfonamides
 - ▶ Any compounds containing (SO_2NH_2) moiety
 - ▶ Divided into three different groups based on chemical structure
 - ▶ Sulfonylarylamines
 - ▶ Sulfonamide moiety directly attached to benzene ring and unsubstituted amine ($-NH_2$) moiety at N4 position
 - ▶ Sulfonamide-type antibiotics: silver sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfacetamide, sulfanilamide
 - ▶ Two protease inhibitors: amprenavir (Agenerase[®]), fosamprenavir (Lexiva[®])

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Sulfonylarylamines: Sulfamethoxazole



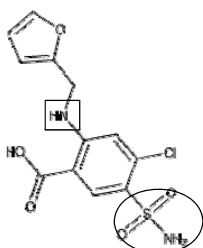
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NonSulfonylarylamines

- ▶ Sulfonamide moiety attached to a benzene ring or other cyclic structure & no amine group (-NH₂) at N4 position
- ▶ Carbonic anhydrase inhibitors
 - ▶ Acetazolamide (Diamox), brinzolamide (Azopt), dorzolamide (Trusopt)
- ▶ Loop & thiazide diuretics
 - ▶ Bumetanide (Bumex), furosemide (Lasix), torsemide (Demadex)
 - ▶ Chlorothiazide (Diuril), chlorthalidone, HCTZ, metolazone (Zaroxolyn)
- ▶ Sulfonylureas
 - ▶ Glyburide (Diabeta), glipizide (Glucotrol), glimepiride (Amaryl)
- ▶ Other agents
 - ▶ Probenecid (Benemid), sulfasalazine (Azulfidine), tamsulosin (Flomax), tipranavir (Aptivus), celecoxib (Celebrex)

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NonSulfonylarylamines: Furosemide

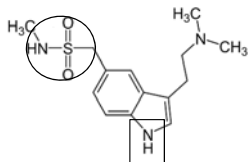


Chemical Formula: C₁₂H₁₄ClN₂O₅S

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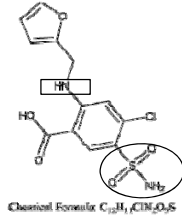
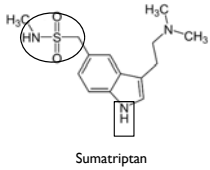
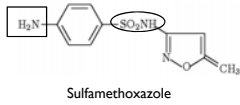
Sulfonamide-Moiety Containing Drugs

- ▶ Sulfonamide group is not directly connected to a benzene ring
- ▶ Examples
 - ▶ 5-HT antagonists: naratriptan (Amerge), sumatriptan (Imitrex)
 - ▶ Other: ibutilide (Corvert), sotalol (Betapace), topiramate (Topamax), zonisamide (Zonegran)



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Chemical Structures of Sulfonamides



FDA Product Labeling for Sulfonamide Nonantibiotics

Contraindicated	Use with Caution	Safe to Administer	No Specific Rules
Acetazolamide	Furosemide	Sulfonylureas	Topiramate
Thiazides	Thiazides	Probenecid	Sotalol
Bumetanide	Tamsulosin	Sumatriptan	Ibutilide
Torsemide	Tipranavir	Naratriptan	
Celecoxib			
Sulfasalazine			
Zonisamide			

Scientific Evidence

- ▶ **REFERENCE:** Strom BL, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; 349 (17): 1628-35.
- ▶ Retrospective cohort study utilizing a large UK medical practice database
 - ▶ About 8 million patients over 12-year period
- ▶ Adjusted odds ratio = 2.8 for association between risk of an allergic reaction after receiving a non-antibiotic sulfonamide and a history of allergy to sulfonamide antibiotics, compared to no such history.
- ▶ Adjusted OR = 3.9 for association between penicillin hypersensitivity and a history of allergy to sulfonamide antibiotics, compared to no such history.

Scientific Evidence

- ▶ Among those with an allergic reaction after receipt of a sulfonamide antibiotic, the risk for an allergic reaction to a subsequent sulfonamide non-antibiotic was lower than the risk following subsequent receipt of penicillin (adjusted OR, 0.7).
- ▶ The risk of an allergic reaction following receipt of a sulfonamide non-antibiotic was lower among patients with a history of sulfonamide antibiotic hypersensitivity than among patients with a history of penicillin allergy (adjusted OR = 0.6).

Bottom Line on “Sulfa” Allergy

- ▶ Data suggest that the risk of cross-reactivity between sulfonamide antibiotics and non-antibiotic sulfonamides reflects a general heightened risk of allergic reactions in the former group, rather than a specific cross-reactivity with drugs containing a sulfa moiety.
- ▶ Patients with a history of sulfonamide antibiotic allergy need not necessarily avoid all sulfonamide compounds.
- ▶ Inconsistency between product labeling and scientific evidence places clinicians in a difficult position
 - ▶ Risk of liability vs. unnecessary compromise of patient care
- ▶ Decisions should be made on a case by case basis

Recommendations

- ▶ Investigate any reports of sulfa allergy
 - ▶ Identify as sulfonamide, sulfate, or sulfite allergy
- ▶ Carefully review medication orders in patients with true sulfonamide allergy
 - ▶ Assess medications for presence of sulfonamide group
- ▶ Consider patient-specific factors
 - ▶ Do not use sulfonamide nonantibiotics in patients with serious reactions to sulfonamide antibiotics
 - ▶ Do not use sulfonamide nonantibiotics in patients with multiple drug allergies
 - ▶ Special caution in patients with HIV

Beta-lactam Antibiotics & Penicillin Allergy

- ▶ Beta-lactams
 - ▶ Penicillins
 - ▶ Cephalosporins
 - ▶ Carbapenems: Imipenem, ertapenem, meropenem, doripenem
 - ▶ Monobactams: Aztreonam
- ▶ About 10% of the population report PCN allergy
 - ▶ True PCN allergy (IgE-mediated) exists in 2-3% of US population
- ▶ Second-line therapy may adversely affect patient care
 - ▶ Less effective
 - ▶ More adverse effects
 - ▶ More expensive
 - ▶ Broader spectrum of activity leading to increased resistance

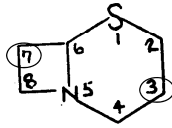
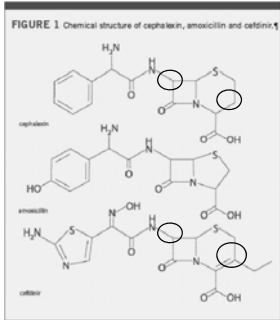
Penicillins & Cephalosporins

- ▶ Studies of 1960s & 1970s report the cross-reactivity rate as high as 50%
 - ▶ Cephalothin & cephaloridine share similar side chain with benzyl PCN
 - ▶ Cephalosporins contaminated with trace amounts of penicillin
- ▶ Current rate of cross-reactivity is about 1%
- ▶ Rate of cross-reactivity is highest with 1st generation cephalosporins

Penicillins & Cephalosporins

- ▶ Patients with PCN allergy are 3x more likely to have an adverse reaction to other antibiotics including sulfa
- ▶ Likelihood of a PCN-allergic patient experiencing cross-reaction is due to degree of similarity of cephalosporin's side-chains
 - ▶ Similarity is in side chains and NOT the beta-lactam ring structure

Amoxicillin vs. Cephalosporins



Beta-Lactams & 7-Position Side Chain

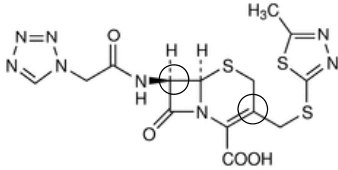
Similar Side Chains at 7-Position of the Beta-Lactam Ring		
Group 1	Group 2	Group 3
Penicillin G	Amoxicillin	Cefotaxime (Claforan)
Cefoxitin (Mefoxin)	Ampicillin	Ceftizoxime (Cefizox)
	Cefaclor (Ceclor)	Ceftriaxone (Rocephin)
	Cephalexin (Keflex)	Cefpodoxime (Vantin)
	Cephadrine (Velosef)	Cefepime (Maxipime)
	Cefprozil (Cefzil)	
	Cefadroxil (Duricef)	

Beta-Lactams & 3-Position Side Chain

Similar Side Chains at 3-Position of Beta-Lactam Ring					
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Cefdinir (Omincef)	Cephadrine (Velosef)	Cefoperazone (Cefobid)	Cephapirin (Cefadyl)	Cefuroxime (Zinacef)	Ceftibuten (Cedax)
Cefixime (Suprax)	Cefadroxil (Duricef)	Cefotetan (Cefotan)	Cefotaxime (Claforan)	Cefoxitin (Mefoxin)	Ceftizoxime (Cefizox)
	Cephalexin (Keflex)				

What's Special About Cefazolin?

- ▶ Cefazolin (Ancef®, Kefzol®)
- ▶ Others: no longer available in USA



Cephalosporin-Allergic Patients

- ▶ Cephalosporins may cause allergic reactions in 1-3% of patients regardless of whether or not pt. has PCN allergy
- ▶ Likelihood of cross-reactivity relates to degree of similarity between side chains
- ▶ Pt. with a true allergy to a specific cephalosporin should not receive that cephalosporin again
- ▶ Risk of reaction with another cephalosporin is very low
 - ▶ Almost non-existent if side-chains are not similar

Penicillins & Carbapenems

- ▶ Carbapenems lead to allergic reactions in 1-3% of patients
- ▶ PCN and imipenem: likelihood of cross-reactivity is close to 1%
 - ▶ Skin-testing kits for imipenem are not available
 - ▶ Use concentration of 0.5 mg/ml if pt. needs to be tested
 - ▶ If skin test negative, use graded challenge to assess reaction:
- ▶ PCN & meropenem: cross-reactivity is estimated at 0.9%
 - ▶ For skin testing, use a concentration of 1 mg/ml
 - ▶ If skin test negative, use dose escalation to assess reaction
- ▶ No studies of ertapenem or doripenem cross-reactivity

Penicillins & Monobactams

- ▶ Estimated incidence of allergic reactions to aztreonam is < 1% regardless of previous drug allergies
- ▶ Estimate of cross-reactivity is close to none in general population
- ▶ As a general rule, monobactams can be safely used in beta-lactam allergic patients
- ▶ Aztreonam and ceftazidime (Fortaz®) have the same side chain
 - ▶ Potential for cross-reactivity exists in patients with specific allergy to ceftazidime
 - ▶ Do not give aztreonam to patients with type I hypersensitivity reaction to ceftazidime

General Guidelines

- ▶ Penicillins should be avoided in patients with a history of an immediate IgE-mediated reaction to any PCN
- ▶ Cephalosporins (2nd, 3rd, 4th) may be able to be administered to patients with type I reaction to PCN
 - ▶ Assess for side-chain similarity
- ▶ Patients with type I reaction to cephalosporins should not receive a cephalosporin with the same side chain
- ▶ Cephalosporins can be safely administered to patients with non-IgE-mediated PCN allergies

General Guidelines

- ▶ Imipenem & meropenem can be used in patients reporting type I reaction to PCN but only after skin testing and dose escalation
- ▶ Monobactams lack immune cross-reactivity with PCNs and can be safely used even in patients with true penicillin allergies

Understanding "Allergies" to Opioids

- ▶ Opioid allergy is a common patient complaint
- ▶ "Allergy" to opioids is often an expected side effect
- ▶ TRUE allergy to opioids is very rare
- ▶ The risk of cross-sensitivity between opioids is generally low
- ▶ Majority of allergic-type reactions to opioids involve codeine, morphine, or meperidine

Types of Reactions to Opioids

- ▶ Expected Adverse Effect
 - ▶ Nausea & vomiting
 - ▶ Not a true allergy; only a side-effect
 - ▶ Opioids can be safely administered
 - ▶ Recommend food or snack with oral medications

Types of Reactions to Opioids

- ▶ Pseudoallergy
 - ▶ Common presentation: itching, flushing, & sweating
 - ▶ Hives, tachycardia, & hypotension may be due to pseudoallergy or true drug allergy
 - ▶ Prior exposure to opioid or related opioid is not necessary
 - ▶ Caused by histamine-release from cutaneous mast cells
 - ▶ Codeine, morphine, meperidine, hydrocodone, hydromorphone and oxycodone are most potent histamine releasers
 - ▶ Opioids can be administered but educate patient to notify nurse at onset of these side effects
 - ▶ Although reactions range from mild to severe, these are NOT true drug allergies

Types of Reactions to Opioids

- ▶ True drug allergy
 - ▶ IgE - mediated
 - ▶ Allergic skin reactions include hives, maculopapular rash, erythema multiformae, pustular rash
 - ▶ Bronchospasm, wheezing, laryngeal edema represent true allergy
 - ▶ Elevated total IgE levels during the acute reaction suggest true allergy

True Allergy to Opioids: What Now?

- ▶ Option 1: Substitute with a non-opioid analgesic (e.g. acetaminophen, NSAID)
- ▶ Option 2: Administer an opioid in a chemical class different from the one to which patient reacted
 - ▶ Requires close monitoring

Opioid Chemical Classes

Drug Class	Specific Agents	Brand Names
Phenylpiperidines	Meperidine Fentanyl Sufentanil Remifentanil	Demerol Duragesic, Sublimaze Sufenta Ultiva
Diphenylheptanes	Methadone Propoxyphene	Dolophine Darvon, Darvocet
Morphine group	Morphine Codeine Hydrocodone Oxycodone Oxymorphone Hydromorphone Nalbuphine Butorphanol Levorphanol Pentazocine	MS Contin Vicodin, Lortab, Norco Percocet, OxyContin Numorphan, Opana Dilaudid Nubain Stadol Levo-Dromoran Talwin

Opioid Intolerance Decision Algorithm

Generalized flushing, itching, hives, sweating
Mild hypotension
Itching, flushing, or hives at injection/application site

- ▶ May be due to pseudoallergy
- ▶ Try nonopioid analgesic
- ▶ Avoid codeine, morphine, and meperidine
- ▶ Use a more potent opioid less likely to release histamine
 - ▶ Meperidine (least potent) < codeine < morphine < hydrocodone < oxycodone < hydromorphone < levorphanol < fentanyl (most potent)
- ▶ If needed, administer with an antihistamine
 - ▶ H₁ blocker (e.g. diphenhydramine)
 - ▶ H₂ blocker (e.g. ranitidine)
- ▶ Start with a low dose
- ▶ If possible, avoid parenteral administration or slow down the rate



Opioid Intolerance Decision Algorithm

Severe hypotension
Skin reaction other than itching, flushing or hives (e.g. rash)
Breathing, speaking or swallowing difficulties
Swelling of face, lips, mouth, tongue, pharynx, or larynx

- ▶ May be signs and symptoms of true drug allergy
- ▶ Do not administer the offending agent
- ▶ Try nonopioid analgesic
- ▶ Try opioid from a different chemical class and monitor patient closely



Role of Health Care Professionals

- ▶ Investigate & determine type and severity of the reaction
 - ▶ Remember history is the most important diagnostic tool
 - ▶ Assess signs & symptoms of the reaction
 - ▶ If rash is described, ascertain its characteristics
 - ▶ Ask patients about foods and other medications ingested several hrs before the reaction
 - ▶ Inquire about the possibility of bites or stings
- ▶ Take steps to avoid labeling nonallergic patients allergic
 - ▶ Make sure to differentiate between ADR and allergic reaction



Role of Health Care Professionals

- ▶ Always weigh the benefits of a particular medication against the risk of a serious reaction
 - ▶ How severe was patient's reaction?
 - ▶ How badly does the patient need the drug?
- ▶ Make anaphylaxis treatment medications easily accessible
- ▶ Refer patients requiring a detailed workup to an allergist or immunologist

Medication Allergy Questionnaire

- ▶ Have you ever had a reaction of any kind after taking a medication?
 - ▶ If so what was the medication?
 - ▶ Nature of reaction (signs & symptoms)?
- ▶ How severe was the reaction? Describe the reaction in detail.
 - ▶ Was an antidote given?
 - ▶ Did it require a visit to ER?
 - ▶ Was there loss of consciousness?

Medication Allergy Questionnaire

- ▶ How did you take the medication (orally, intravenously, topically)?
- ▶ How long ago did this reaction occur? How old were you?
- ▶ Time of onset after drug administration (after 1st dose vs. several days)
- ▶ Any concurrent medications?

Medication Allergy Questionnaire

- ▶ Did you have a viral infection at the time of reaction?
- ▶ Did the reaction abate after drug was discontinued?
- ▶ If a reaction to penicillin, have you since taken other penicillins?
- ▶ Have you ever received a cephalosporin, carbapenem, or monobactam?
- ▶ What opioids have you tolerated in the past?
- ▶ If allergic to sulfa, have you ever taken a diuretic, Celebrex, sulfasalazine, etc.?

▶
