

Navigating the World of Adverse Drug Reactions

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Adverse Drug Reactions

Upon completion of this activity, the participant should be able to:

- Understand how to categorize various adverse medication effects.
- Demonstrate the ability to take a thorough history of a medication intolerance episode.
- Summarize the management of medication intolerance, based on a thorough history.

Definition

- Adverse Drug Reactions:

– “Any noxious, unintended and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment.”

– World Health Organization

Overview: Adverse Drug Reactions (ADRs)

- Case illustrating history-taking skills
- Breaking down ADRs
- Skin manifestations
- Common ADRs in Clinical Practice
- Summary

Essential History Taking

- Medication name?
- How long ago did reaction occur?
- Which organ systems were involved?
- When during the course did the reaction occur?
- Why was the medication prescribed?
- What other meds were being taken?

Essential History Taking

- What was the therapeutic management taken secondary to the reaction?
- Has the patient experienced similar reactions in the absence of drug therapy?
- Has the patient experienced a similar reaction to the same or similar medication?
- Does the patient have an underlying condition that predisposes to the reaction?

Case

- Mr. Hyper Tension is a 50 year old man who was found to have serial high BP recordings, usually around 150/90. He was started on lisinopril 10 mg daily. One week later his blood pressure was 110/70 and he (and his potassium) were tolerating the lisinopril well.
- Two months later, he calls back complaining of a dry cough for the past month. He denies fever or cold symptoms. He stopped the lisinopril 3 days ago, because he thought it had triggered the cough.
- Other medications include aspirin, simvastatin and MVI.

Essential History Taking

- Medication name? Lisinopril
- How long ago did reaction occur? 1 month
- Which organ systems were involved? Respiratory
- When during the course did the reaction occur? One month after starting
- Why was the medication prescribed? High BP
- What other meds were being taken? Aspirin, simvastatin, MVI.

Essential History Taking

- What was the therapeutic management taken secondary to the reaction? Patient stopped taking
- Has the patient experienced similar reactions in the absence of drug therapy? No
- Has the patient experienced a similar reaction to the same or similar medication? No
- Does the patient have an underlying condition that predisposes to the reaction? Don't know

Predictable ADRs

- 80% of all ADRs
- Healthy subjects
- Dose-dependent, Pharmacologic
- Examples:
 - Overdose (acetaminophen and hepatic failure)
 - Side effects (tremulousness with albuterol)
 - Secondary effects (bacterial overgrowth after antibiotics)
 - Drug interaction (one drug affecting another drug's metabolism)

Khan and Solensky 2010

Unpredictable ADRs

- 20% of all ADRs
- Susceptible subjects
- Dose-independent, non-pharmacologic
- Examples:
 - Drug intolerance (tinnitus after taking one aspirin)
 - Drug idiosyncrasy (G6PD deficiency: anemia after taking hydroxychloroquine)
 - Drug allergy (Anaphylaxis after penicillin)
 - Pseudoallergic reactions (Hives after taking morphine)

Khan and Solensky 2010

TABLE I. Heterogeneity of drug-induced allergic reactions

Organ-specific reactions	Clinical features	Examples of causative agents
Cutaneous		
Exanthems	Diffuse fine macules and papules Evolves over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Often IgE mediated	IgE mediated: β -lactam antibiotics Bradykinin mediated: ACE-I
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, NSAIDs, and carbamazepine
Postules	Acneiform Acute generalized eczematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SIS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxycam NSAIDs, and allopurinol
TEN	Similar features as SIS but >30% epidermal detachment Mortality as high as 50%	Same as SIS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium-channel blockers, ACE-Is

Khan and Solensky 2010

Table 1. Heterogeneity of drug-induced allergic reactions (continued)

Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
Multiorgan reactions		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non-IgE-dependent reactions	β -Lactam antibiotics, mAbs
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

Khan and Solensky 2010

Skin Manifestations

Exanthem

Morbilloform = "Measles-like"
Maculopapular
Eg. Amoxicillin, sulfonamides



Urticaria



Fixed Drug Eruptions

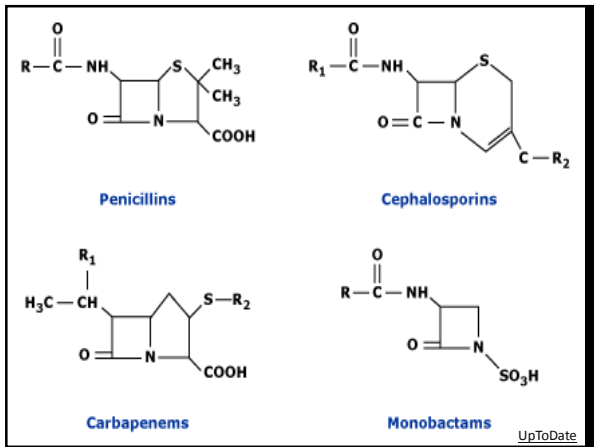


Stephen Johnson Syndrome



Common Drug Allergy Concerns in Clinical Practice

- ### Beta Lactam Antibiotic Allergy
- Penicillin is still the drug of choice for:
 - Group A -hemolytic streptococcal pharyngitis
 - Certain subtypes of endocarditis
 - Tertiary syphilis in pregnancy
 - Carbapenems (doripenem, imipenem, ertapenem, meropenem) share B-lactam ring, but >99% of PCN skin test POSITIVE patients... can be given a carbapenem without a reaction.
 - The monobactam aztreonam can be given to penicillin-allergic patient without testing.



Cephalosporins and penicillins with common side chains

Amoxicillin	Ampicillin
Cefadroxil	Cefaclor
Cefprozil	Cephalexin
Cefatrizine	Cephadrine
	Cephaloglycin
	Loracarbef (carbacephem)

List of cephalosporins that share identical R₁-group side chains with R-group side chain of amoxicillin and ampicillin.

Results of cephalosporin challenges in patients with histories of penicillin allergy

Reference	Cephalosporin reaction rate		Cephalosporins administered
	History of pen allergy (percent)	No history of pen allergy (percent)	
Dash CH	25/324 (7.7)	140/17,216 (0.8)	Cephalexin and cephaloridine
Petz LD	57/701 (8.1)	285/15,007 (1.9)	Cephalexin, cephaloridine, cephalothin, cefazolin and cefamandole
Goodman EJ	1/300 (0.3)	1/2431 (0.04)	Cefazolin (in all but one patient)
Dault SB	1/606 (0.17)	15/22,664 (0.07)	1st generation (42 percent) 2nd generation (21 percent) 3rd/4th generations (37 percent)
Fonacier L	7/83 (8.4)	Not reported	1st generation (59 percent) 2nd generation (8.4 percent) 3rd generation (25 percent) 4th generation (7 percent)

Summary of studies of cephalosporin challenges in patients with a history of penicillin (pcn) allergy without preceding penicillin allergy testing.

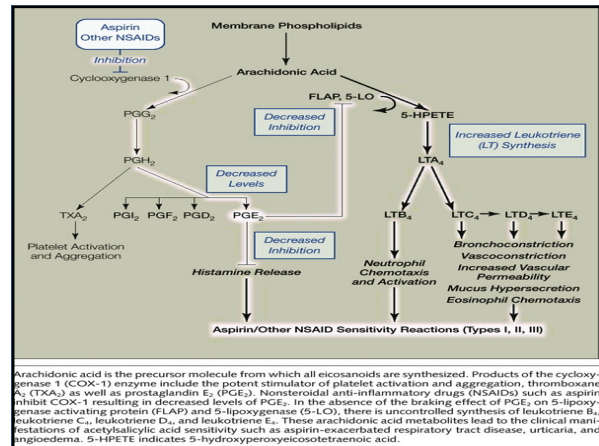
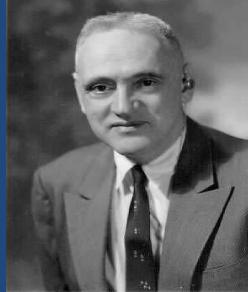
Retrospective data:

- From 0.17% to 8.4 % Of patients with history Of PCN allergy will react To Cephalosporins
- From 0.04% to 1.9% of Patients without history Of PCN allergy will react To cephalosporins

- ### Beta Lactam Antibiotic Allergy
- Of all patients reporting a history of PCN allergy, 85-90% will tolerate PCN
 - Allergy has been lost
 - Misdiagnosis (“my grandmother was allergic, so I was told I was allergic”)
 - Among PCN skin test positive patients, approximately 2% will react to a cephalosporin
 - Penicillin is the only antibiotic for which there is standardized skin testing available
 - Penicillin can participate in all 4 of the classic Gel & Coombs reactions!

Aspirin Exacerbated Respiratory Disease

- Max Samter, MD
 - U of I, Chicago
 - ENT
- Samter's Triad
 - Asthma
 - Aspirin sensitivity
 - Nasal polyposis



Aspirin Sensitive Asthma

- ASA sensitive most common, ages 20-40
- Females with slightly greater incidence in Scripps series (58% vs. 42%, N=300)¹.
- Giraldo² noted 5% incidence of a past history of ASA-induced respiratory reactions in hospitalized, adult asthmatics
- 1972 Scripps study¹, oral challenge in adult asthmatic patients
 - Found 9% to be ASA sensitive
 - 30-40% prevalence if also carried history of rhinitis OR nasal polyps

¹McDonald et al 1972;²Giraldo et al 1969

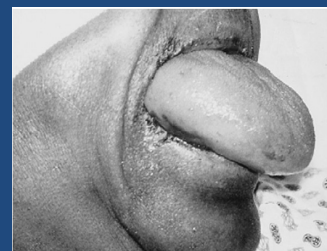
Angiotensin Converting Enzyme Inhibitors - Cough

- Incidence 5-20%
- Onset - one week to six months
- Mechanism – Bradykinin or Substance P (both normally metabolized by ACE) increase, inducing prostaglandin E₂ accumulation and vagal stimulation.
- Angiotensin II receptor blockers do not cause cough
- 4 weeks off of ACE inhibitor is sufficient to make the diagnosis

Angiotensin Converting Enzyme Inhibitors - Angioedema

- African Americans, smokers at higher risk
- Face, lips and tongue, classically
- 0.1-0.7% incidence
 - Highest incidence during 1st month of treatment
 - 27% may occur greater than 6 months after starting therapy
- Inhibiting ACE leads to unopposed bradykinin formation, causing angioedema

Angiotensin Converting Enzyme Inhibitors - Angioedema



Intensive Care Med 1997;23(7):795

Vaccines: Points to Consider

- Mild local reactions and/or constitutional symptoms following vaccine administration are not contraindications for future use
- Anaphylaxis to vaccines is rare (1 in a million, out of 235 million vaccines per year)
- Report adverse events (Vaccine Adverse Events Reporting System, VAERS)
- Fatalities exceedingly rare

WWW.CDC.GOV

Vaccines

- Td toxoid
 - Local reactions common
- MMR
 - Gelatin allergy is an issue, not egg (do not need to test for egg – chick fibroblast culture)
- Rabies vaccine – chick fibroblast culture
- Influenza
 - Egg allergy is listed as contraindication for flu shot
 - But, the vast majority of patients with egg allergy can safely receive flu shot
 - Guillain Barre Syndrome, rarely
- Yellow fever
 - Contains egg and gelatin
- Japanese encephalitis
 - Gelatin (anaphylaxis has been reported)

Patterson 2002

Multiple Drug Allergy Syndrome

- Familial tendency for immunologic drug reactions
 - Having just one parent with an antibiotic allergy makes one 15 times more likely to carry a drug sensitivity, by history
- Penicillin reactors have higher incidence of other drug allergies
- Vast array of clinical reactions are possible
- Mechanism is likely that of enhanced immunogenicity to drugs that are more apt to haptenate
 - Can be IgE or non-IgE in origin

Middleton 2003

Anaphylactoid Reactions

- No IgE Involvement (no testing available)
- Involve same final common pathway as type I, IgE-mediated reaction
- Three examples:
 - Contrast dye used in computed tomography
 - Premedication regimen available
 - Opiate-induced urticaria
 - Aspirin-induced asthma (AERD)

Middleton 2003

Dentist's Office

- True, IgE-mediated anaphylaxis to local anesthetics is extraordinarily rare!
- Adverse effects of anesthetics/vasoconstrictor combinations include:
 - Vasovagal syncope
 - Paresthesias, lightheadedness (“caines”)
 - Palpitations, anxiety (epinephrine)
- General anxiety/panic

Reporting Adverse Reactions to MedWatch

- Internet
 - www.fda.gov/medwatch
- Phone
 - 1 800 FDA 1088 (general line)
 - 1 800 FDA 0178 (to fax report)
 - 1 800 FDA 7967 (for Vaccine Adverse Event Reporting System (VAERS))

Summary

- Adverse drug reactions are a component in a substantial numbers of patients utilizing any type of pharmacotherapy
- A complete history is the most useful tool to assess whether certain symptoms are due to ADRs
- Standardized skin testing for Type 1 hypersensitivity is only available for penicillin at this time