Appendix 4: Drug Allergy

INTRODUCTION

TABLE A4-1

Classification of Allergic Drug Reactions

Type	Descriptor	Characteristics	Typical Onset	Drug Causes
I	Immediate (IgE mediated)	Allergen binds to IgE on basophils or mast cells, resulting in release of inflammatory mediators	Within 1 hour (may be within 1–6 hours)	Penicillin anaphylaxis, angioedema Blood products Polypeptide hormones Vaccines Dextran
II	Delayed; cytotoxic	Cell destruction occurs because of cell-associated antigen that initiates cytolysis by antigen-specific antibody (IgG) and complement. Most often involves blood elements	Typically >72 hours to weeks	Penicillin, quinidine, quinine, heparin, thiouracils, sulfonamides, methyldopa
III	Delayed; immune complex	Antigen–antibody (IgG or IgM) complexes form and deposit on blood vessel walls and activate complement. Result is a serum sickness-like syndrome or vasculitis	>72 hours to weeks	Penicillins, sulfonamides, minocycline, hydantoins
IV	Delayed; T cell–mediated	Antigens cause activation of T lymphocytes, which release cytokines and recruit effector cells	>72 hours	
	IVa	Th1 cells, interferon-γ, monocytes, and eosinophils respond to the antigen	1–21 days	Tuberculin reaction, contact dermatitis
	IVb	Th2 cells, interleukin-4, and interleukin-5 respond to the antigen	1–6 weeks	Maculopapular rashes with eosinophilia
	IVc	Cytotoxic T cells, perforin, granzyme B, FasL respond to the antigen	4–28 days	Bullous exanthems; fixed drug eruptions
	IVd	T cells and interleukin-8 respond to the antigen	>72 hours	Acute generalized exanthematous pustulosis

TABLE A4-2

Top 10 Drugs and Agents Reported to Cause Skin Reactions

Drug Name	Reactions per 1000 Recipients
Amoxicillin	51.4
Trimethoprim–sulfamethoxazole	33.8
Ampicillin	33.2
Iopodate	27.8
Blood	21.6
Cephalosporins	21.1
Erythromycin	20.4
Penicillin G	18.5
Cyanocobalamin	17.9

Source: Data from Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272–1285.

TABLE A4-3

Treatment of Anaphylaxis

1. Remove the inciting allergen, if possible.
2. Assess airway, breathing, circulation, and orientation. Support the airway.
3. Cardiopulmonary resuscitation: Start chest compressions (100/min) if cardiovascular arrest occurs at any time.
4. Administer epinephrine 1:1000 (adults: 0.3–0.5 mg; children: 0.01 mg/kg) IM in the lateral aspect of the thigh.
5. Place the patient in a recumbent position.
6. Administer oxygen 8–10 L/min through facemask or up to 100% oxygen as needed; monitor by pulse oximetry, if available.
7. Repeat IM epinephrine every 5–15 minutes for up to 3 injections if the patient is not responding.
8. Establish IV line for venous access. Keep line open with 0.9% saline solution. For hypotension or failure to respond to epinephrine, administer 1–2 L at a rate of 5–10 mL/kg in the first 5–10 minutes. Children should receive up to 30 mL/kg in the first hour.
9. Consider nebulized albuterol 2.5–5 mg in 3 mL of saline for lower airway obstruction; repeat as necessary.
10. In cases of refractory bronchospasm or hypotension not responding to epinephrine because a β-adrenergic blocker is complicating management, glucagon 1d5 mg IV (20–30 mcg/kg; maximum, 1 mg in children) should be given IV over 5 minutes.
11. Give epinephrine by continuous IV infusion for patients with inadequate response to IM epinephrine and IV saline. Add 1 mg (1 mL of 1:1000) of epinephrine to 1000 mL of 0.9% saline solution; start infusion at 2 mcg/min and increase up to 10 mcg/min based on blood pressure, heart rate, and cardiac function.
12. Consider intraosseous access for either adults or children if attempts at IV access are unsuccessful.
13. Consider the antihistamine diphenhydramine (adults 25–50 mg; children 1 mg/kg, up to 50 mg) IM or by slow IV infusion.
14. Consider ranitidine 50 mg in adults and 12.5–50 mg (1 mg/kg) in children. The dose may be diluted in 5% dextrose in water to a volume of 20 mL and injected over 5 minutes.
15. Consider methylprednisolone 1–2 mg/kg/dose up to 125 mg (or an equivalent steroid) to reduce the risk of recurring or protracted anaphylaxis. Prednisone 20 mg orally can be given in mild cases. These doses can be repeated every 6 hours as required.

IM, intramuscular.

Source: Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis: A practice parameter update 2015. Ann Allergy Asthma Immunol. 2015;115:341–384.

TABLE A4-4

Procedure for Performing Penicillin Skin Testing

Step 1: Prick Test

This will be performed first on the patient, before proceeding to intradermal testing.

a. Clean the volar surface of either forearm with an alcohol swab.
b. Using an ink pen, draw 3 vertical lines approximately 1 in. (2.5 cm) apart on the designated testing site of the arm.
c. Draw up 0.1 mL of the 4 solutions (Pre-pen, diluted Penicillin G, histamine positive control, and saline negative control) in 4 separate allergy syringes.
d. Apply a small drop of each solution to the separate pre-marked sites on the testing arm.
e. The histamine test site should be the most distal site from the elbow, followed up the arm by saline, Pre-Pen, and Pen G.
f. Puncture the epidermis using a twisting motion with a sterile 22–28 gauge needle at each drop site. Do not draw blood. Very little pressure is required.
g. Read the test in 15–20 minutes: (document test results below)
    1. Test is negative: change in diameter of the wheal is **less than** 3 mm than that observed with the negative control. Proceed to intradermal test.
    2. Test is positive: change in diameter of the wheal is **greater than** 3 mm than that observed with the negative control. As soon as a positive response is observed, the solution should be wiped off the skin. Do not proceed to intradermal test.
    3. The positive control (histamine skin test) should be positive to ensure the results are not falsely negative.
    4. The negative control (saline skin test) should be negative. If a wheal >2–3 mm develops after 20 minutes, repeat prick skin test. Upon retesting, if control still creates a wheal >2–3 mm after 20 minutes, discontinue test and notify the ID Physician and/or the ID Stewardship Pharmacist.

Step 2: Intradermal Test

Only conduct this test if the patient produced a negative result with the prick test in step 1.

a. Select 5 sites on the volar surface on the forearm. These sites should be on the opposite arm from the prick test if possible.
b. Using a 26–30 gauge, short bevel needle, intradermally inject 0.02 mL of Pre-Pen solution **twice** (separate at least 2 cm apart). Mark the margins of the initial blebs with an ink pen.
c. Using separate needles and syringes, intradermally inject diluted Pen G (0.02 mL = 200 units of penicillin) **twice** (separate at least 2 cm apart) and 0.02 mL of saline (separate at least 5 cm apart from other sites).
d. Read in 20 minutes: (document test results below)
    1. Test is negative: there is no increase in the original bleb and no greater reaction than the negative control site.
    2. Test is positive: bleb or wheal increases >2 mm from its original size or is >2 mm larger than the negative control. Patient is NOT to receive penicillin.

Step 3: (Optional) Oral Penicillin Challenge

a. If deemed necessary by ordering physician
    1. Oral penicillin (eg, amoxicillin 250 mg) challenge or graded challenge of target drug in a monitored setting for 30–45 minutes.

Source: Data from Jones BM, Bland CM. Penicillin skin testing as an antimicrobial stewardship initiative. Am J Health Syst Pharm. 2017;74:232–237.

TABLE A4-5

Characteristics of Drug Tolerance Protocols

Underlying Mechanism	Initial Dose	Duration of Protocol	Potential Outcome of Process	Duration of Induced Tolerance	Example
Immunologic IgE (desensitization)	Micrograms	Hours	Desensitization; render mast cells less responsive to degranulation	Temporary	β-Lactam antibiotics; taxanes
Immunologic non-IgE	Milligrams	Hours to days (eg, 6 hours–10 days)	Not known	Temporary	Delayed cutaneous reactions to trimethoprim–sulfamethoxazole in HIV-infected individuals
Pharmacologic	Milligrams	Hours to days (eg, 2 hours–5 days)	Cautious induction of a reaction followed by a shift in a metabolic process	Temporary	Aspirin
Undefined	Micrograms to milligrams	Prolonged; days to weeks	Not known	Temporary	Isolated cutaneous reactions to allopurinol

Source: Solensky R, Khan DA. Drug allergy: An updated practice parameter. Ann Allergy Clin Immunol. 2010;105:259–273.

TABLE A4-6

Induction of Drug Tolerance Protocol for IV Cephalosporin[a]

Preparation of Solutions			
	Volume of Diluents (eg, 0.9% NSS)	**Total to be Injected in Each Bottle**	**Final Concentration (mg/mL)**
Solution 1	250 mL	10 mg	0.04
Solution 2	250 mL	100 mg	0.4
Solution 3	250 mL	1000 mg	4

Induction of Drug Tolerance Protocol					
Step	**Solution**	**Rate (mL/hr)**	**Time (min)**	**Administered Dose (mg)**	**Cumulative Dose (mg)**
1	1	2	15	0.02	0.02
2	1	5	15	0.05	0.07
3	1	10	15	0.1	0.17
4	1	20	15	0.2	0.37
5	2	5	15	0.5	0.87
6	2	10	15	1	1.87
7	2	20	15	2	3.87
8	2	40	15	4	7.87
9	3	10	15	10	17.87
10	3	20	15	20	37.87
11	3	40	15	40	77.87
12	3	75	184.4	922.13	1000

[a]Full dose equals 1000 mg. Total time was 349.4 minutes.

NSS, normal saline solution.

Source: Solensky R, Khan DA. Drug allergy: An updated practice parameter. Ann Allergy Clin Immunol. 2010;105:259–273.

(*See e/Chapter 104, Drug Allergy, authored by Christopher M. Bland and Bruce M. Jones, for a more detailed discussion of this topic.*)