

The use of standardized drug desensitization protocols at a pediatric institution



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Clinical Implications

- Standardized antibiotic desensitization protocols specific to a pediatric population have been developed at our tertiary care center. These protocols result in ease of dose calculation, and use higher concentrations of the base solutions, which minimizes the volume reaching the patient.

TO THE EDITOR:

For patients with a history of a mast cell–mediated hypersensitivity reaction with a drug, a safe method of drug administration is available.^{1–8} Through this process known as rapid drug desensitization (RDD), temporary tolerance to the drug is induced in the hypersensitive individual. The temporary tolerance remains effective as long as the drug is continued.⁹ RDD is indicated only if the historical reaction is consistent with an IgE-mediated mechanism, although it can be considered in some non–IgE-mediated reactions (type I hypersensitivity reactions only).^{1,9} The risk during a desensitization ranges from mild reactions including flushing, itching, erythema, and urticaria to more severe reactions including anaphylaxis.¹ RDDs should be performed only in the absence of a reasonable alternative drug.

Desensitization protocols involve the stepwise administration of the drug in controlled incremental dosing without eliciting serious reactions.^{2,4,5,9} Although the development of protocols by the Brigham and Women's Hospital Rapid Desensitization Program^{1,2} has largely resolved the obstacles in dose calculations, challenges with the dispensation of small doses for pediatric patients remained. The use of standard volume (250 mL) bags in these protocols necessitated the use of small concentrations for small doses, resulting in large volumes.

To overcome these issues, we decided to standardize desensitization protocols for 12 commonly used antibiotics at the Children's Hospital of Philadelphia. Pharmacists created calculation sheets that use the pharmacy's standard concentration for each individual antibiotic as the most concentrated solution (concentration 3). This solution is then further diluted 10-fold and 100-fold to make concentrations 2 and 1, respectively. The minimum rate that can be run through the pump is 0.1 mL/h. The concentrations are chosen such that the rate does not go below 0.1 mL/h. Therefore, for some drugs, the solution may be diluted 100-fold or 1000-fold for concentrations 2 and 1, respectively.

The steps of administration are based on the principles established by the Brigham and Women's Hospital Rapid Desensitization Program.^{1,2} Each protocol is administered via

12 steps with increasing rates every 15 minutes such that the administered dose increases in fixed increments. The doses administered in the first 11 steps of the procedure are the equivalent of 1/50,000th, 1/25,000th, 1/10,000th, 1/5,000th, 1/2,000th, 1/1,000th, 1/500th, 1/250th, 1/100th, 1/50th, and 1/25th of the final dose. The dose remaining after the 11th step is administered via step 12 over 174 minutes. To achieve these dose increments, our protocol calculates the rate depending on the predetermined fixed concentration for the specific antibiotic.

Pharmacy prepares the various drug doses in either 4 syringes or 3 syringes and 1 bag on the basis of the volume of drug left for step 12. The first syringe contains the solution with concentration 1 (lowest concentration of the drug). The second syringe contains the solution with concentration 2 (intermediate concentration). Both syringes 3 and 4 (or bag 4) contain the solution with concentration 3 (highest concentration).

For enhanced safety awareness and to further minimize medical error, the colors on the Desensitization Calculation Sheet correlate to a specific concentration (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Concentration 3 is assigned 2 different colors to differentiate between steps 9 to 11 and step 12. In addition to the calculation sheets, standardized orders have also been created in our Computerized Physician Order Entry (CPOE) system. Each desensitization requires the prescriber to enter 4 orders that match the corresponding color code on the desensitization sheet.

To analyze the success of these protocols, we performed a retrospective analysis of desensitizations performed at Children's Hospital of Philadelphia on children in the age group of 2 to 21 years from November 2014 to July 2015, and analyzed their outcomes.

A total of 5 antibiotic RDDs were carried out in the given period. The drugs desensitized were ertapenem (Figure 1), ceftriaxone (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org), linezolid (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org), ceftazidime (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org), and oxacillin (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org).

Two of the 5 patients (40%) were male. The average age of patients at the time of desensitization was 12 years (3–19 years). Two of our patients required treatment for a cystic fibrosis respiratory exacerbation, 2 others required treatment for endocarditis, and 1 patient required treatment for pyelonephritis (Table I). Three of the 5 patients had a history of very recent reactions (2 during the same hospitalization, and one 6 months earlier). One patient had a reaction 6 years earlier, and 1 patient had a distant reaction history (>15 years earlier).

Three of the 5 patients had underlying asthma. The severity of reaction history varied, with 3 patients having a history of cutaneous reactions (hives only). The history of 1 patient was vague and consisted of cyanosis of legs immediately after the use of ceftazidime 6 years earlier. One patient had anaphylaxis during the same hospitalization with another carbapenem (imipenem). His desensitization was carried out with a different drug in the same drug family (ertapenem) because his risk was thought to be high.

Protocol for ertapenem ≥ 100 mg				
Update total mg/DOSE		Full Dose:	220	mg
Concentration 1	0.02	mg/ml		
Concentration 2	2	mg/ml		
Concentration 3	20	mg/ml		
Step	Concentration	Rate (mL/h)	Time (min)	Administered dose (mg)
Ertapenem Desensitization (Step 1- 4)				
1	1	0.88	15	0.0044
2	1	1.76	15	0.0088
3	1	4.4	15	0.022
4	1	8.8	15	0.044
Ertapenem Desensitization (Step 5 - 8)				
5	2	0.22	15	0.11
6	2	0.44	15	0.22
7	2	0.88	15	0.44
8	2	1.76	15	0.88
Ertapenem Desensitization (Step 9 -11)				
9	3	0.44	15	2.2
10	3	0.88	15	4.4
11	3	1.76	15	8.8
Ertapenem Desensitization (Step 12)				
12	3	3.5	174	202.8708
CPOE Order		Ordering Dose (mg) Per CPOE Order		Total Volume (mL) Administered Per CPOE Order
Ertapenem Desensitization (Step 1 - 4)		0.079		3.960
Ertapenem Desensitization (Step 5 - 8)		1.65		0.825
Ertapenem Desensitization (Step 9 - 11)		15.4		0.770
Ertapenem Desensitization (Step 12)		202.871		10.14354

FIGURE 1. A 12-step ertapenem desensitization performed on patient P1. CPOE, Computerized physician order entry.

All 5 of our patients completed initial desensitization and the subsequent therapeutic treatment course. Therefore, 100% of our desensitizations were considered successful. One of the patients (P2) developed facial erythema a week after the desensitization procedure and completed the remaining course with the use of an antihistamine as a premedication. The other patient (P3) had a history of “chronic idiopathic urticaria.” He had urticaria at the time of start of desensitization. He was also the only patient premedicated for the desensitization. There was no escalation in urticaria during the desensitization procedure. He continued to have urticaria through the course of drug administration and completed the dosing with the use of antihistamines and steroids.

The development of standardized protocols at our institution has simplified all steps of the medication use process (ordering, verification, preparation, dispensing, administration, and quality improvement). The higher concentrations of the base solutions

have also resulted in lower volume requirements in pediatric patients.

Although the number of RDDs reported here is small, we believe that our experience provides evidence that the use of standardized drug-specific desensitization protocols in a pediatric population may be able to minimize the errors, and volumes associated with the administration of smaller pediatric dosing.

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TABLE I. Demographic characteristics of patients challenged, drug allergy history, and indication and outcome of desensitization

Patient no.	Age (y)	Sex	Comorbidities	Asthma	Timing of initial reaction	History of initial reaction	WAO grading	Drug used for desensitization	Premedications	Outcome
P1	3	F	VUR, pyelonephritis	No	Recent (same hospitalization)	Inspiratory stridor, SOB, lip and facial swelling after the second dose of imipenem	3	Ertapenem	None	Successful
P2	16	F	Endocarditis, atopy	Yes	Recent (same hospitalization)	Hives with the second infusion of ceftriaxone	1	Ceftriaxone	None	Successful*
P3	15	M	CF, epilepsy, tracheomalacia, atopy, CIU	Yes	6 mo prior	Hives about 2 h after 11th day of PO linezolid and with each dose of linezolid	1	Linezolid	Diphenhydramine, acetaminophen, methylprednisolone	Successful*
P4	7	F	CF, atopy	Yes	Infancy	Cyanosis with ceftazidime	1	Ceftazidime	None	Successful
P5	19	M	CHD, s/p repair, endocarditis	No	As a toddler	Hives after a few doses of amoxicillin as a toddler	1	Oxacillin	None	Successful

CF, Cystic fibrosis; CHD, congenital heart disease; CIU, chronic idiopathic urticaria; F, female; M, male; PO, *per os* (by mouth); SOB, shortness of breath; s/p, status post; VUR, vesicoureteral reflux; WAO, World Allergy Organization. WAO subcutaneous immunotherapy systemic reaction grading¹⁰: Grade 1: Symptoms/signs of single organ system involvement, Grade 2: Symptoms/signs of more than 1 organ system or Lower respiratory (<40% peak expiratory flow [PEF] or FEV₁, drop responding to an inhaled bronchodilator) or Gastrointestinal or Other, Grade 3: Lower respiratory (40% PEF or FEV₁ drop not responding to an inhaled bronchodilator) or Upper respiratory (laryngeal, uvula, or tongue edema ± stridor), Grade 4: Lower or upper respiratory or Cardiovascular, Grade 5: Death.

*These patients had symptoms during the course of treatment but completed the full therapeutic course (described in text).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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REFERENCES

- Liu A, Fanning L, Chong H, Fernandez J, Sloane D, Sancho-Serra M, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy* 2011;41:1679-89.
- Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 2006;6:476-81.
- Castells MC. A new era for drug desensitizations. *J Allergy Clin Immunol Pract* 2015;3:639-40.
- Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
- Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005;99:393-9.
- Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* 2004;95:370-6.
- Burrows JA, Toon M, Bell SC. Antibiotic desensitization in adults with cystic fibrosis. *Respirology* 2003;8:359-64.
- Legere HJ III, Palis RI, Rodriguez Bouza T, Uluer AZ, Castells MC. A safe protocol for rapid desensitization in patients with cystic fibrosis and antibiotic hypersensitivity. *J Cyst Fibros* 2009;8:418-24.
- Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259-73.
- Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. *J Allergy Clin Immunol* 2010;125:569.

METHODS

We conducted a retrospective chart review of the outcome of all RDD procedures carried out at the Children's Hospital of Philadelphia, a pediatric tertiary care center, between November 2014 and July 2015. The electronic health record was queried for demographic information, drug allergy information, drug desensitization protocol used, and outcome of the protocol. Relevant clinical information was abstracted from the allergy consult and progress notes. This included patient characteristics that could be associated with higher risk of reactions specifically age, sex, the presence of asthma, and severity of previous reactions. Other factors that could affect the outcome of the desensitization procedure such as the use of premedications, comorbidities, and indication for drug use were also assessed.

The study was approved by our institutional review board and was conducted in full accordance with all applicable institutional Research Policies and Procedures and all applicable federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Waiver of consent for this retrospective chart review was approved by the institutional review board.

Desensitization protocols. Desensitization is considered for patients when the primary physician/medical team in conjunction with the Infectious Disease service determines that the antibiotic is necessary for treatment and no comparable

alternative is available. The allergy consultant further evaluates the patient to determine whether the history of reaction and patient's clinical status are appropriate for proceeding with drug desensitization. The use of premedications is dependent on physician discretion based on the history of reaction and patient status. When possible, desensitization is performed during weekday/daylight hours to ensure adequate staffing. Nursing support should be 1:1 for the patient undergoing desensitization. Medications required for treatment of any symptoms or anaphylaxis are requested to be available at the patient's bedside and given as needed. These include antihistamines, steroids, albuterol, and epinephrine. Oxygen and bag and mask are requested to be present at the bedside. We use 2 different pumps for these protocols. These include the Medfusion 4000 Syringe Pump by Smiths Medical (St. Paul, Minn) and the Alaris Large Volume Pump by Becton Dickinson (formerly Carefusion) (Franklin Lakes, NJ).

Outcome. The primary objective of the study was to review the use of standardized desensitization protocols in a pediatric population. A specific desensitization was considered "successful" if the drug was tolerated by the patient and continued for the desired therapeutic duration. If the patient experienced adverse effects during the desensitization process that led to the cessation of drug administration, it was considered "unsuccessful."

Protocol for ceftriaxone doses ≥ 500 mg				
Update total mg/DOSE		Full Dose:	2000 mg	
Concentration 1	0.4 mg/ml			
Concentration 2	4 mg/ml			
Concentration 3	40 mg/ml			
Step	Concentration	Rate (mL/h)	Time (min)	Administered dose (mg)
Ceftriaxone Desensitization (Step 1- 4)				
1	1	0.4	15	0.04
2	1	0.8	15	0.08
3	1	2.	15	0.2
4	1	4.	15	0.4
Ceftriaxone Desensitization (Step 5 - 8)				
5	2	1.	15	1
6	2	2.	15	2
7	2	4.	15	4
8	2	8.	15	8
Ceftriaxone Desensitization (Step 9 -11)				
9	3	2.	15	20
10	3	4.	15	40
11	3	8.	15	80
Ceftriaxone Desensitization (Step 12)				
12	3	15.9	174	1844.28
CPOE Order		Ordering Dose (mg) Per CPOE Order		Total Volume (mL) Administered Per CPOE Order
Ceftriaxone Desensitization (Step 1 - 4)		0.72		1.8
Ceftriaxone Desensitization (Step 5 - 8)		15.		3.75
Ceftriaxone Desensitization (Step 9 - 11)		140.		3.5
Ceftriaxone Desensitization (Step 12)		1844.28		46.107

FIGURE E1. Ceftriaxone desensitization performed on patient P2. CPOE, Computerized physician order entry.

Protocol for linezolid doses ≥ 25 mg				
Update total mg/DOSE		Full Dose:	600	mg
Concentration 1	0.02	mg/ml		
Concentration 2	0.2	mg/ml		
Concentration 3	2	mg/ml		
Step	Concentration	Rate (mL/h)	Time (min)	Administered dose (mg)
Linezolid Desensitization (Step 1- 4)				
1	1	2.4	15	0.012
2	1	4.8	15	0.024
3	1	12.	15	0.06
4	1	24.	15	0.12
Linezolid Desensitization (Step 5 - 8)				
5	2	6.	15	0.3
6	2	12.	15	0.6
7	2	24.	15	1.2
8	2	48.	15	2.4
Linezolid Desensitization (Step 9 -11)				
9	3	12.	15	6
10	3	24.	15	12
11	3	48.	15	24
Linezolid Desensitization (Step 12)				
12	3	95.39	174	553.284
CPOE Order	Ordering Dose (mg) Per CPOE Order		Total Volume (mL) Administered Per CPOE Order	
Linezolid Desensitization (Step 1 - 4)	0.216		10.8	
Linezolid Desensitization (Step 5 - 8)	4.5		22.5	
Linezolid Desensitization (Step 9 - 11)	42.		21	
Linezolid Desensitization (Step 12)	553.284		276.642	

FIGURE E2. Linezolid desensitization performed on patient P3. CPOE, Computerized physician order entry.

Protocol for ceftazidime doses ≥ 250 mg				
Update total mg/DOSE		Full Dose:	1635	mg
Concentration 1	0.1	mg/ml		
Concentration 2	1	mg/ml		
Concentration 3	100	mg/ml		
Step	Concentration	Rate (mL/h)	Time (min)	Administered dose (mg)
Ceftazidime Desensitization (Step 1- 4)				
1	1	1.31	15	0.0327
2	1	2.62	15	0.0654
3	1	6.54	15	0.1635
4	1	13.08	15	0.327
Ceftazidime Desensitization (Step 5 - 8)				
5	2	3.27	15	0.8175
6	2	6.54	15	1.635
7	2	13.08	15	3.27
8	2	26.16	15	6.54
Ceftazidime Desensitization (Step 9 -11)				
9	3	0.65	15	16.35
10	3	1.31	15	32.7
11	3	2.62	15	65.4
Ceftazidime Desensitization (Step 12)				
12	3	5.2	174	1507.6989
CPOE Order		Ordering Dose (mg) Per CPOE Order	Total Volume (mL) Administered Per CPOE Order	
Ceftazidime Desensitization (Step 1 - 4)		0.589	5.886	
Ceftazidime Desensitization (Step 5 - 8)		12.263	12.2625	
Ceftazidime Desensitization (Step 9 - 11)		114.45	1.1445	
Ceftazidime Desensitization (Step 12)		1507.699	15.076989	

FIGURE E3. Ceftazidime desensitization performed on patient P4. CPOE, Computerized physician order entry.

Protocol for oxacillin doses ≥ 250 mg				
Update total mg/DOSE		Full Dose:	2000	mg
Concentration 1	0.05	mg/ml		
Concentration 2	5	mg/ml		
Concentration 3	50	mg/ml		
Step	Concentration	Rate (mL/h)	Time (min)	Administered dose (mg)
Oxacillin Desensitization (Step 1- 4)				
1	1	3.2	15	0.04
2	1	6.4	15	0.08
3	1	16.	15	0.2
4	1	32.	15	0.4
Oxacillin Desensitization (Step 5 - 8)				
5	2	0.8	15	1
6	2	1.6	15	2
7	2	3.2	15	4
8	2	6.4	15	8
Oxacillin Desensitization (Step 9 -11)				
9	3	1.6	15	20
10	3	3.2	15	40
11	3	6.4	15	80
Oxacillin Desensitization (Step 12)				
12	3	12.72	174	1844.28
CPOE Order		Ordering Dose (mg) Per CPOE Order		Total Volume (mL) Administered Per CPOE Order
Oxacillin Desensitization (Step 1 - 4)		0.72		14.4
Oxacillin Desensitization (Step 5 - 8)		15.		3
Oxacillin Desensitization (Step 9 - 11)		140.		2.8
Oxacillin Desensitization (Step 12)		1844.28		36.8856

FIGURE E4. Oxacillin desensitization performed on patient P5. CPOE, Computerized physician order entry.

TABLE E1. Color coding on the desensitization calculation sheets

CPOE order no.	Color	Drug administration steps	Concentration of the solution
1	Blue	Steps 1-4	Concentration 1 (1/100th or 1/1000th of SC)
2	Green	Steps 5-8	Concentration 2 (1/10th or 1/100th of SC)
3	Purple	Steps 9-11	Concentration 3 (SC)
4	Orange	Step 12	Concentration 3 (SC)

CPOE, Computerized Physician Order Entry; SC, standard concentration.

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