

Beta-lactam Desensitizations



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Drug Desensitization Terminology



Drug Desensitization

- *Definition of Drug desensitization*
 - is one form of induction of immune drug tolerance by which effector cells are rendered less reactive or non-reactive to IgE-mediated immune responses by rapid administration of incremental doses of an allergenic substance



Drug Provocation vs. Drug Desensitization

	Drug provocation test	Drug Desensitization
Hypersensitivity	Unproven	proven
Purpose	Confirm or disprove hypersensitivity	Produce temporary tolerance
Effect on immune system	None	Tolerance
Risk of allergic reactions	Present	Present
Initial dose	1/100-1/10 th therapeutic dose	1/10,000 th therapeutic dose
Number of steps	2-5	>10
Time interval between doses	According to reaction	15 minutes

Cernades JR et al. Allergy 2010;65:1357-66.



Drug Desensitization

- Key Features

- IgE mediated drug allergy
- Reduce or eliminate drug sensitization (e.g. IgE)
- Rapid protocols
- Incremental dosing



Induction of Drug Tolerance Procedures

Type of tolerance	Time/ Duration	Initial Dose	Possible outcomes	Example
Immunologic IgE (drug desensitization)	Hours	mcg	antigen-specific mediator depletion, down-regulation of receptors	penicillin
Immunologic non-IgE	Hours to Days	mcg-mg	Unknown	TMP/SMX
Pharmacologic	Hours to Days	mg	metabolic shift, internalization of receptors	aspirin
Nonimmunologic mast cell activation	Hours	mcg	Unknown	paclitaxel
Undefined	Days to Weeks	mcg-mg	Unknown	allopurinol



Induction of Drug Tolerance

- **Induction of drug tolerance is a temporary phenomenon**
- State of drug tolerance exists only while on drug
- Discontinuation of drug will revert patient back to allergic state



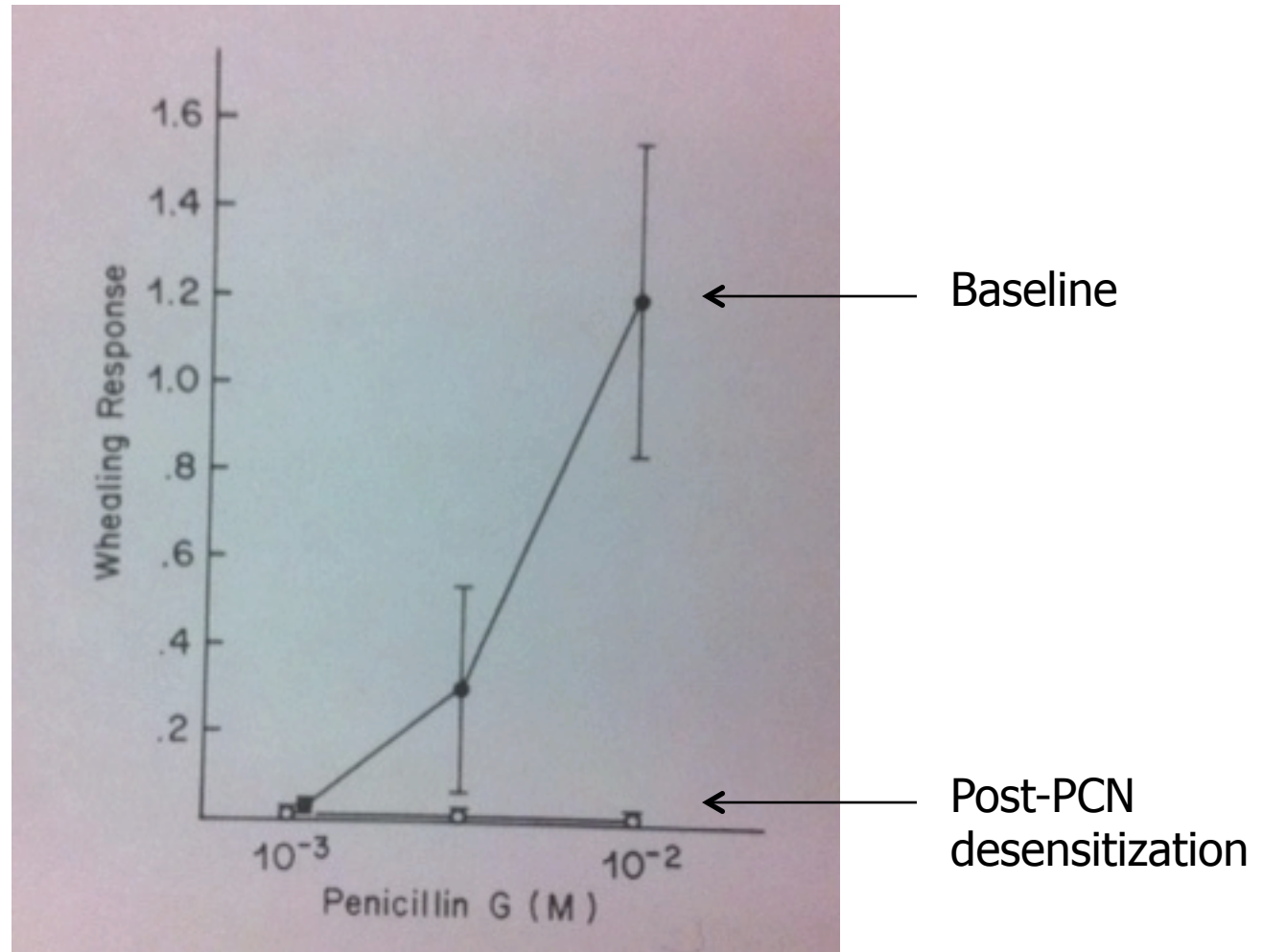
Mechanisms of Induction of Drug Tolerance Procedures



Mechanisms of Induction of Drug Tolerance

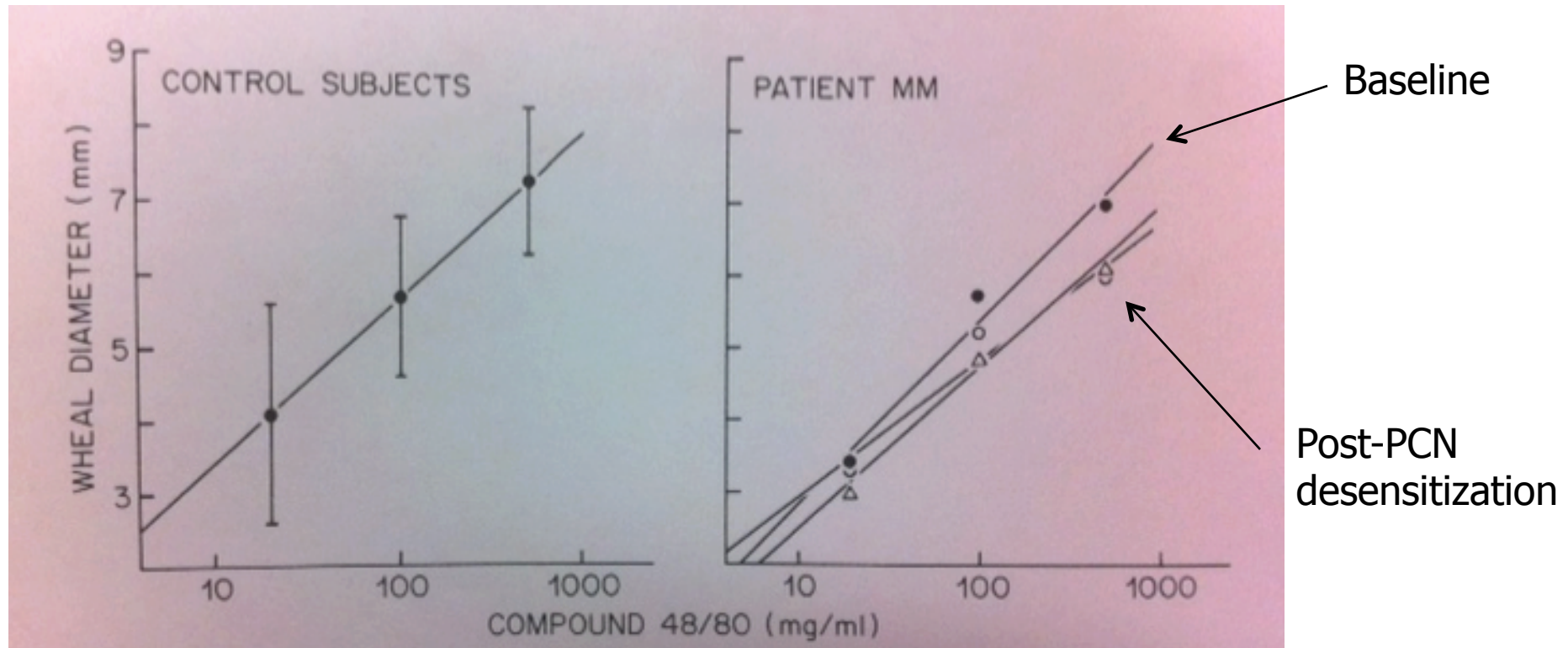
- Immunologic IgE IDT (rapid drug desensitization)
 - Theories
 - Depletion of mediators
 - Blocking IgG antibodies
 - Consumption of IgE in immune complexes
 - Hapten inhibition
 - Mast cell desensitization
 - Internalization of Fc ϵ RI
 - Depletion of signal transduction molecules

Penicillin G Skin Test Reactivity is Absent Post PCN Desensitization



Sullivan TJ. J Allergy Clin Immunol 1982;69:500-8.

Compound 48/80 Skin Test Response is Intact Pre and Post PCN Desensitization

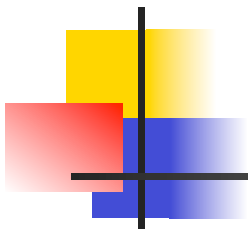


Sullivan TJ. J Allergy Clin Immunol 1982;69:500-8.



Evidence Against Mediator Depletion Theory

- Skin test reactivity after penicillin desensitization was not diminished to other aeroallergens or histamine
- This data is strong evidence against tachyphylaxis to mediators, mast cell mediator depletion or unresponsiveness to IgE signaling
- “The decrease in responsiveness appears to be at the level of the IgE antipenicillin signal to the mast cell...”



Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting Fc ϵ RI internalization

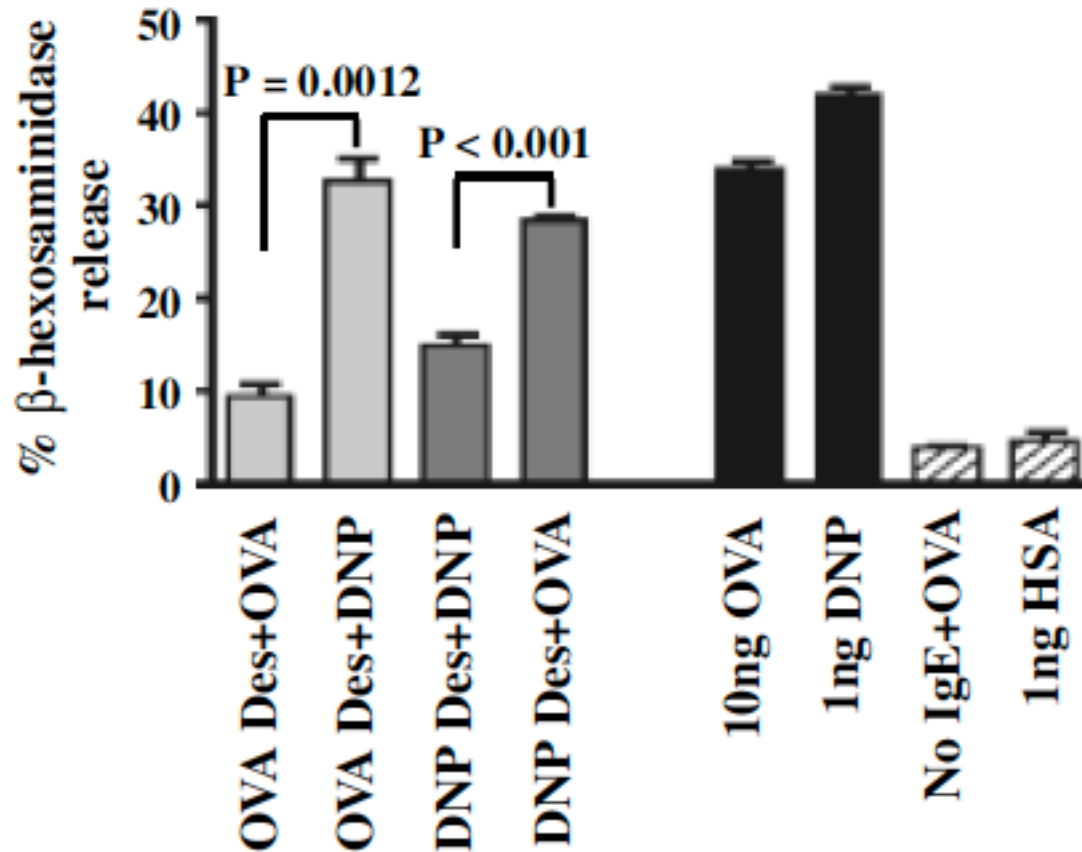
Maria del Carmen Sancho-Serra¹, Maria Simarro² and Mariana Castells¹

in vitro model of rapid IgE desensitization
for mouse BM-derived mast cells

Table 1. Rapid desensitization protocol^{a)}

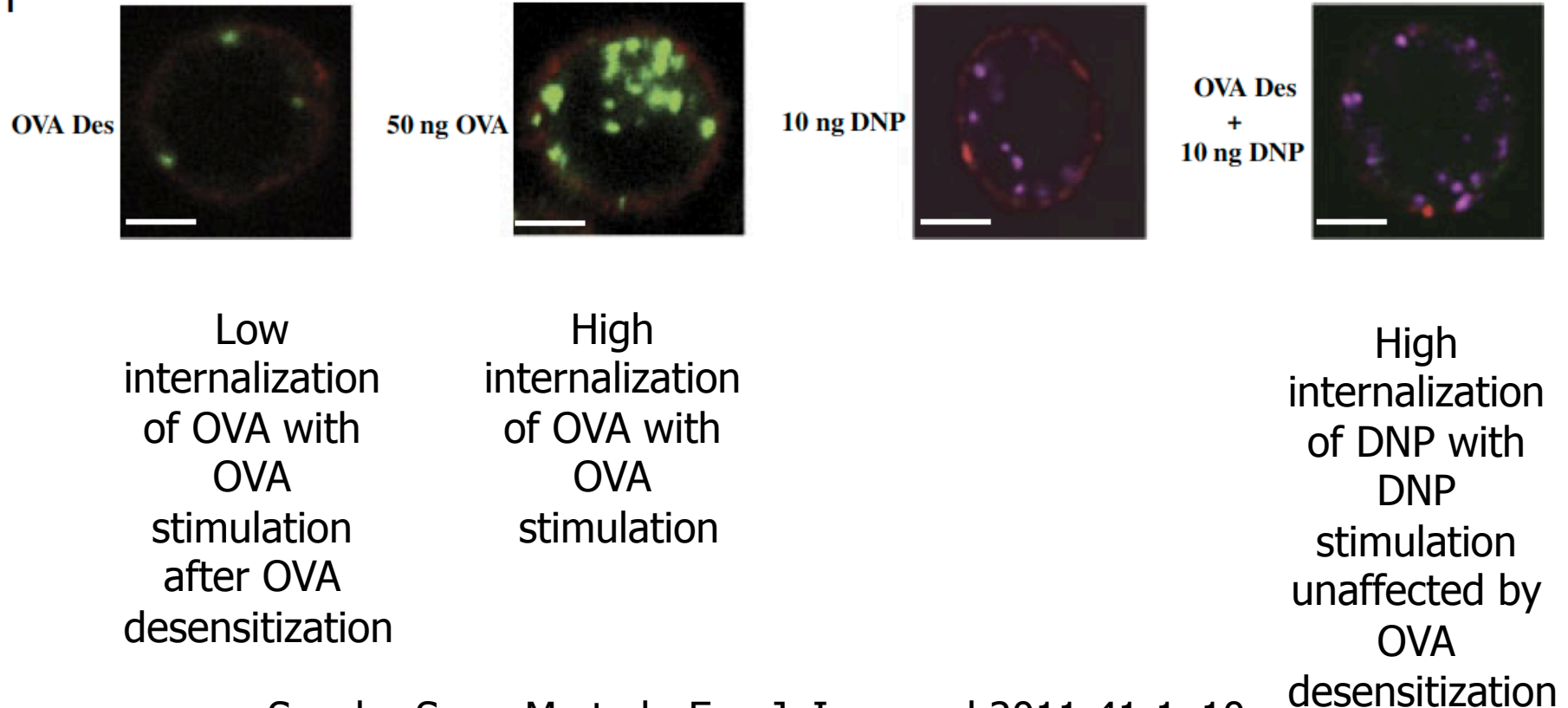
Steps	Time (min)	Volume (μL)	Concentration ($\text{pg}/\mu\text{L}$)		Dose (pg)	
		DNP-HSA/OVA	DNP-HSA	OVA	DNP-HSA	OVA
1	0	1	1	10	1	10
2	10	1	5	50	5	50
3	20	1	5	50	5	50
4	30	1	10	100	10	100
5	40	1	10	100	10	100
6	50	2	10	100	20	200
7	60	2	20	200	40	400
8	70	4	20	200	80	800
9	80	8	20	200	160	1600
10	90	16	20	200	320	3200
11	100	17.5	20	200	350	3500
11 Steps	100min	54.5 $\mu\text{L}^{\text{b)}$			1 ng	10 ng

Antigen Specific Desensitization



Internalization of Antigen/Fc ϵ RI is Impaired with Antigen Specific Desensitization

F



Low internalization of OVA with OVA stimulation after OVA desensitization

High internalization of OVA with OVA stimulation

High internalization of DNP with DNP stimulation unaffected by OVA desensitization



How Does Drug Desensitization Work?

- Theories

- ~~Depletion of mediators~~
- ~~Blocking IgG antibodies~~
- Consumption of IgE in immune complexes
- Hapten inhibition
- ~~Mast cell desensitization~~
- **Internalization of Fc ϵ RI**
- ~~Depletion of signal transduction molecules~~



Indications and Contraindications



Indications for Drug Desensitization

- No alternative drug exists
- Drug is more effective than alternatives
- Moderate-high likelihood that drug allergy exists or evidence of drug allergy (e.g. + skin test)



Contraindications for Beta-lactam Drug Desensitization

- Absolute contraindication
 - Severe cutaneous adverse reactions (SJS/TEN, DRESS)
 - Immunocytotoxic reactions, vasculitis, other non-IgE mediated drug reactions
- Relative contraindication
 - Poorly controlled asthma
 - Unstable cardiac disease
 - Patients on beta-blockers
- Individual risk-benefit evaluation needed in all patients



Protocols for Beta-lactam Desensitization



Beta-lactam Drug Desensitization

- Typical starting dose is $1/10,000^{\text{th}}$ of target therapeutic dose
- Can also use calculated dose from skin test as starting point
- Further dosage increases are typically twice the previous dose
- Administered at 15-20 minute intervals until therapeutic dosage achieved



Rapid Drug Desensitization

- Rapid drug desensitizations should be performed in an appropriate setting, supervised by physicians familiar with the procedure, with continual monitoring of the patient and readiness to treat reactions including anaphylaxis
- Do not need to be performed in intensive care setting
 - Advantage of intensive care setting is typically closer nursing supervision
- Many experienced centers may perform desensitizations in outpatient setting



Oral Penicillin Desensitization

Step	PCN V (units/ml)	Dose (ml)	Dose (units)	Cumulative Dose
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,000
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Administer PCN V orally every 15 minutes per step

Total time: 3 hours 45 minutes; Total dose 1.3 million units; Total volume 36.1 ml

Wendel GD et al. New Engl J Med 1985;312:1229-32.



Preparing Penicillin Solutions

Preparation of PCN-V Solutions

Use penicillin V elixir 250 mg/ml=80,000 units/ml (1 mg = 1600 units)

Add 2 ml of 80,000 unit/ml PCN to 14 ml normal saline to make 10,000 unit/ml PCN V

Add 2 ml of 10,000 unit/ml PCN V to 18 ml normal saline to make 1,000 unit/ml PCN V

Quantity of PCN-V Solutions

# syringes	Syringe volume	PCN-V Solution
1	1 cc	1000 U/ml
2	10 cc	1000 U/ml
1	10 cc	10,000 U/ml
1	20 cc	80,000 U/ml



Cephalosporin Desensitization

TABLE II. Rapid intravenous cephalosporin desensitization protocol: Goal dose, 1 g and 2 g intravenously

Dose	Goal dose, 1 g IV		Goal dose, 2 g IV	Time
	mg	mg, rounded	mg, rounded	
1	0.1	0.1	0.1	15 min
2	0.2	0.2	0.4	15 min
3	0.7	1.0	1.0	15 min
4	2.2	2.0	4.0	15 min
5	6.9	10.0	10.0	15 min
6	21.8	20.0	40.0	15 min
7	69.0	70.0	140.0	15 min
8	218.1	200.0	400.0	15 min
9	689.7	700.0	1400.0	15 min
Cumulative	1008.6	1003.3	1995.5	2 h, 15 min

Protocol for intravenous desensitization to all cephalosporins with a goal dose of 1 g and 2 g (Barnes-Jewish Hospital).

IV, Intravenous.



Cephalosporin Desensitization Protocol

Table 1 Rapid intravenous desensitization to 1 g of ceftazidime in a cystic fibrosis patient

Full dose	1000.0 mg	Total to be injected in each bottle (mg)			
Solution 1	250 ml of 0.040 mg/ml	10.000			
Solution 2	250 ml of 0.400 mg/ml	100.000			
Solution 3	250 ml of 3.969 mg/ml	992.130			

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.0200	0.0200
2	1	5	15	0.0500	0.0700
3	1	10	15	0.1000	0.1700
4	1	20	15	0.2000	0.3700
5	2	5	15	0.5000	0.8700
6	2	10	15	1.0000	1.8700
7	2	20	15	2.0000	3.8700
8	2	40	15	4.0000	7.8700
9	3	10	15	9.9213	17.7913
10	3	20	15	19.8426	37.6339
11	3	40	15	39.6852	77.3191
12	3	75	186	922.6809	1000.0000
			Total time = 351 min		

Castells MC. Curr Opin Allergy Clin Immunol 2006;6:476–481.



Outcomes and Safety



Outcomes and Safety of Penicillin Desensitizations

- Most all patients can be desensitized
- ~1/3 patients have mild cutaneous reactions during desensitization
- Severe reactions extremely rare
- Delayed reactions (cutaneous, serum sickness, nephritis) <10%
- Long-acting benzathine penicillin may be administered after desensitization safely at intervals of 1-3 weeks*

*Wendel GD et al. New Engl J Med 1985;312:1229-32.



Reactions During Desensitization

- No consensus approach
- Options
 - 1) Treat through reaction and continue
 - 2) Treat symptoms, reduce by 1-2 doses and continue protocol
 - 3) Treat symptoms, modify protocol (adding steps) and resuming



Conclusions

- Penicillin desensitization protocols have been studied the most
- Similar desensitization principles can be used for other beta-lactams
- Drug desensitization protocols for beta-lactam antibiotics appear to be very effective and generally safe