

Managing CF patients with antibiotic hypersensitivity

Oded Breuer, MD

**Pediatric Pulmonology and CF center
Hadassah Hebrew University Medical Center**

Drug Hypersensitivity

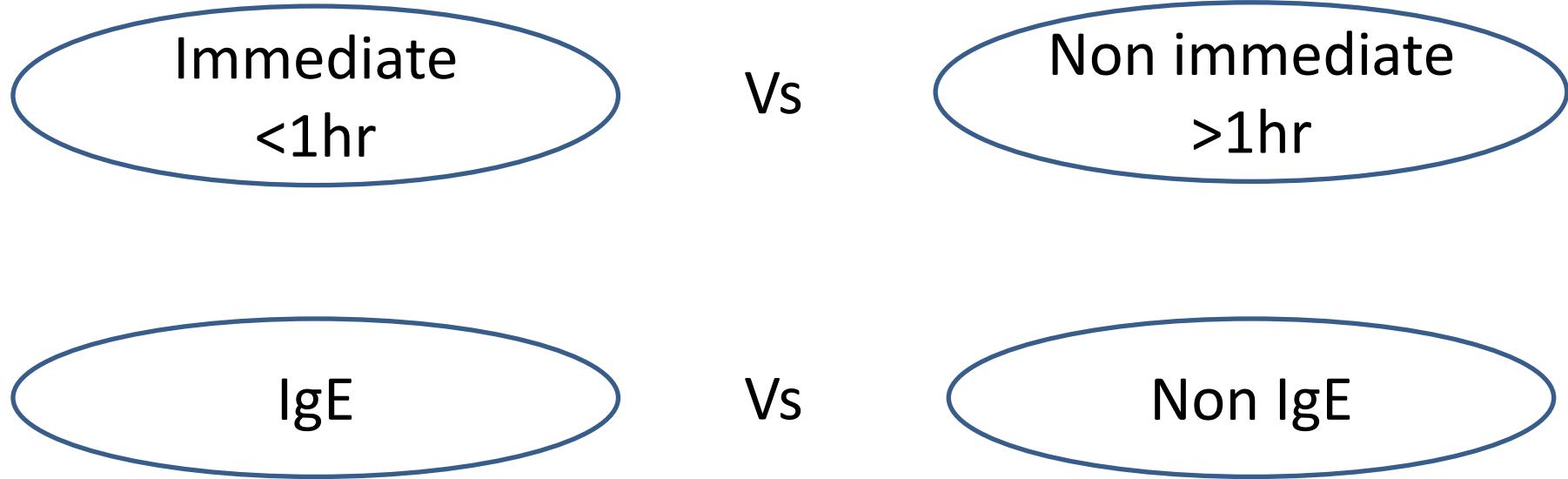
ADRs are known (or presumed) to be mediated by an immunologic mechanism

Gell and Coombs classification scheme for allergic reactions

Reaction		Type	Mechanism	Drug	Result
I			IgE antibodies leading to mast-cell/basophil degranulation	Penicillin	Anaphylaxis
II			IgG/IgM-mediated cytotoxic reaction against cell surface	Quinidine	Hemolytic anemia
III			Immune complex reaction	Cephalexin	Serum sickness
IV			Delayed T lymphocyte-mediated reaction	Neomycin	Contact dermatitis

Solenski R. Med Clin N Am 90 (2006) 233–260

Drug Hypersensitivity



Serious adverse drug reactions occur in 6.7% of hospitalized patients.

and are one of the leading cause of death in these patients

Beta-lactam allergy in adults with cystic fibrosis

Judith A. Burrows ^{a,b}, Lisa M. Nissen ^b, Carl M.J. Kirkpatrick ^b, Scott C. Bell ^{a,c,*}

- prevalence of allergic reactions to antibiotics is high in adults with CF (up to 36%)
- Risk factors:
 - Increasing age
 - cumulative courses
 - decreasing FEV1

What is desensitization?

THE NEW ENGLAND JOURNAL OF MEDICINE

**PENICILLIN ALLERGY AND DESENSITIZATION IN SERIOUS INFECTIONS
DURING PREGNANCY**

GEORGE D. WENDEL, JR., M.D., BARBARA J. STARK, M.D., RICHARD B. JAMISON, M.D.,
RICHARD D. MOLINA, M.D., AND TIMOTHY J. SULLIVAN, M.D.

First series of penicillin desensitizations

Escalating oral doses

15 pregnant syphilis- infected women

General considerations on rapid desensitization for drug hypersensitivity – a consensus statement

J. R. Cernadas^{1*†}, K. Brockow^{2*†}, A. Romano^{3*†}, W. Aberer^{4†}, M. J. Torres^{5†}, A. Bircher^{6†}, P. Campi^{7†}, M. L. Sanz^{8†}, M. Castells⁹, P. Demoly^{10†} & W. J. Pichler^{11†}, for the European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity[†]

Table 2 Successful protocols for drug desensitizations described in the literature

Type of drug	Drugs	References
Antibiotics	Penicillins	(18, 23, 49, 50, 56, 57, 59, 64, 74)
	Aminoglycosides	(53)
	Cephalosporins	(49, 52)
	Vancomycin	(54, 62)
	Anti-tuberculous agents	(80, 81)
	Sulfonamides	(42, 51, 82–87)
	Pentamidine	(87)
Other agents	Aspirin, Lysine-acetylsalicylate (LAS), NSAIDS	(26–28, 75, 95–97)
	Chemotherapeutics	(29, 41, 48, 55, 70, 71, 73, 77, 78, 88, 89, 98)
	Deferoxamine	(90)
	Tetanus toxoid	(91, 92)
	D-penicillamine	(93)
	Heparin	(94)
	Insulin	(60, 61)
	Monoclonal antibodies	(41, 55, 63, 99)

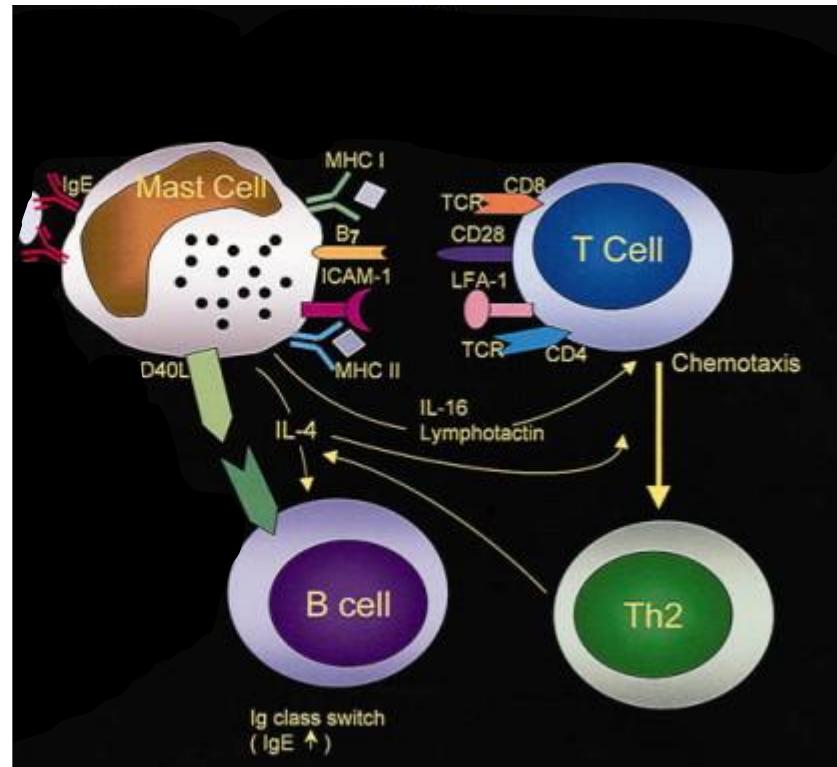
A typical protocol

Name of medication: <i>Ceftazidime</i>				Total mg per bag	Amount of bag infused (ml)	
Solution 1 250 ml of 0.080 mg/ml				20.00	9.25	
Solution 2 250 ml of 0.800 mg/ml				200.00	18.75	
Solution 3 250 ml of 7.937 mg/ml				1984.26	250.00	
Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.040	0.040
2	1	5.0	15	1.25	0.100	0.140
3	1	10.0	15	2.50	0.200	0.340
4	1	20.0	15	5.00	0.400	0.740
5	2	5.0	15	1.25	1.000	1.740
6	2	10.0	15	2.50	2.000	3.740
7	2	20.0	15	5.00	4.000	7.740
8	2	40.0	15	10.00	8.000	15.740
9	3	10.0	15	2.50	19.843	35.583
10	3	20.0	15	5.00	39.685	75.268
11	3	40.0	15	10.00	79.370	154.638
12	3	80.0	174.375	232.50	1845.362	2000.000
<i>Total time = 339.37 minutes (5h 39m)</i>						

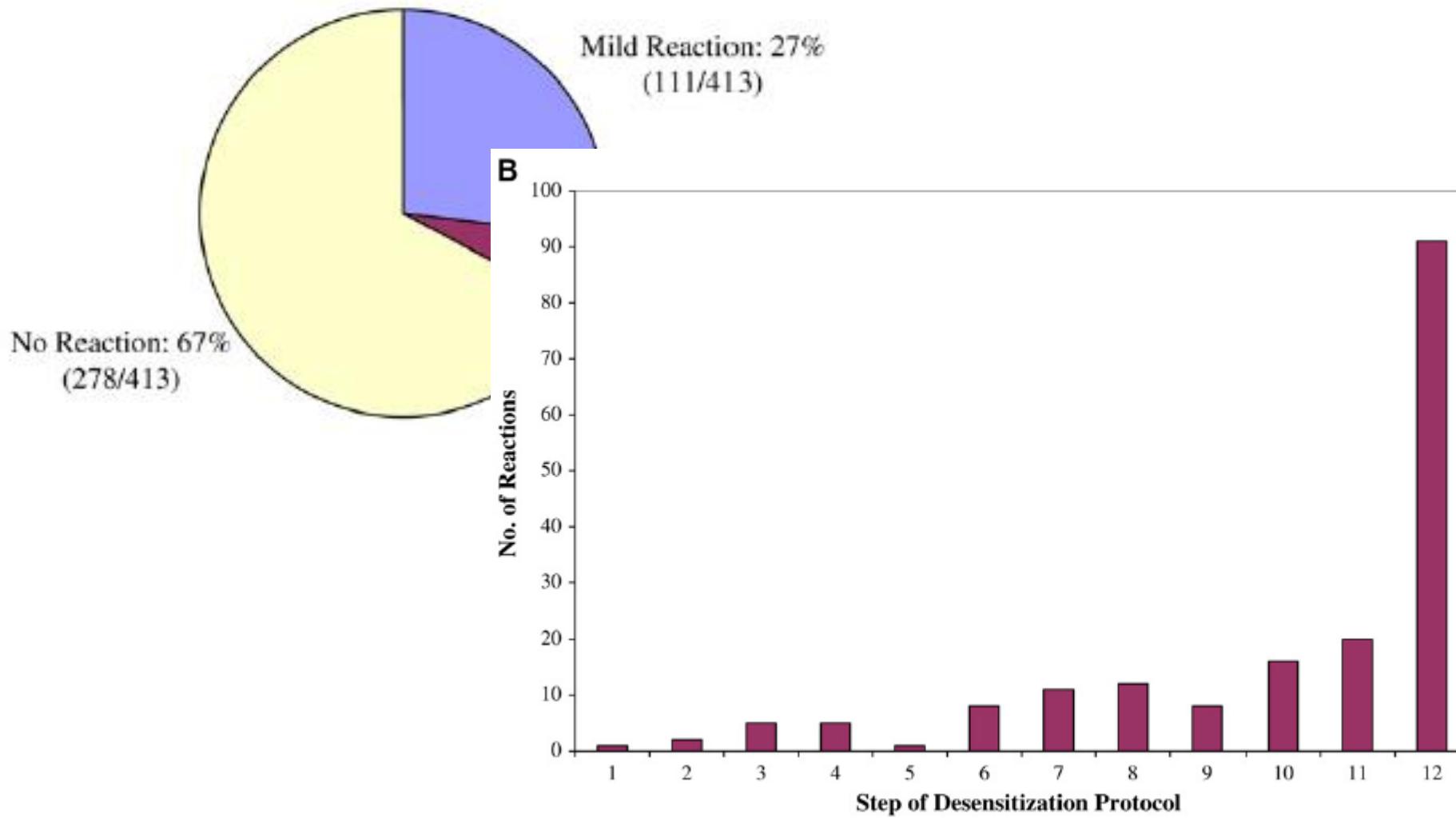
Mechanism

“Despite its clinical success, little is known about the mechanisms and molecular targets of drug desensitization”

Cernadas JR, et al. Allergy 2010; 65: 1357–1366.



Adverse Events



Adverse Events

Table 1 Patient, allergy and desensitisation description

Patient No.	Age ^a	Gender ^b	Current status ^c	Atopy ^d	Previous allergic rxn ^e	Time from first allergy		No. desens. (to no. drugs) ^g	No. desens. successful ^h	Desens. to drug ^e	Reaction during (or after) desensitization	When rxn occurred ⁱ
						to first desens (mo) ^f	No. desens.					
1	22	F	D	N	2a, 3a	>48	1 (1)	0	2a	Urticarial rash (2a)*	D10	
2	31	M	A	N	1a, 1c, 2a, 2c, 3b, 4	8	2 (1)	1	2a	Urticarial rash (2a) [†]	D2	
3	18	M	D	Y	1d, 3a, 4, 5	16	12 (2)	10	3a, 3b	Morbilliform rash (3a) [#] , urticarial rash (3b)	D1, D1	
4	24	M	D	Y	1b, 2a, 4, 7	0.25	2 (2)	0	2a, 4	Urticarial rash (2a)*, bronchospasm (4)*	D21, D1	
5	24	F	D	N	1a, 2a, 8	26	2 (2)	0	1c, 2a	Morbilliform rash (2a)* urticarial rash (1c)*	D1, D1	
6	34	F	D	Y	1a, 1b, 2a, 9	>48	3 (2)	0	1b, 2a	Urticarial rash (1b)* fixed drug rxn (2a)*	D7, D2	
7	26	F	A, T	ND	2a, 3b	3	4 (1)	4	2a	Nil (2a)	Nil	
8	27	F	D	ND	1b, 2a, 3a, 5	>48	5 (3)	5	1b, 3a, 3b	Nil (1b, 3a, 3b)	Nil	
9	23	F	D	N	1b, 2a, 2b, 3b, 5	2	3 (2)	3	2a, 5	Nil (2a, 5)	Nil	
10	23	M	A	N	1b, 2a, 4, 5	35	2 (1)	2	2a	Angioedema (2a) [†]	D1	
11	24	F	A	Y	2a, 3a, 3b, 4	8	3 (2)	1	2a, 4	? Angioedema (2a) [†] , bronchospasm (4)*	D1, D2	
12	28	M	A	N	1a, 1b, 2a, 3b, 4, 5	46	6 (3)	3	2a, 2b, 4	Angioedema (2a, 2b)**, bronchospasm (4)	D18, D4, D	
13	38	F	A	N	1a, 1b, 2a	>48	2 (1)	2	1b	Nil (1b)	Nil	
14	27	F	A	N	2a	>48	3 (2)	2	2a, 2b	Urticarial rash (2a)*, nil (2b)	D1	
15	30	F	A	ND	2a	5	4 (1)	4	2a	Facial flushing (2a)*	D1	
16	39	F	A, T	N	3b	10	1 (1)	1	3b	Nil (3b)	Nil	
17	56	F	A	N	6	>48	1 (1)	0	6	Urticarial rash (6)*	D4	
18	16	F	A, T	N	1b, 2a, 3b, 4	>48	13 (2)	13	2a, 3a	Nil (2a, 3a)	Nil	
19	29	M	A	N	1a, 1b, 2a	14	3 (1)	3	2a	Nil (2a)	Nil	

Burrows et al. Antibiotic desensitization in adults with cystic fibrosis *Respirology* (2003)
8, 359–364

Our experience

Our patients

Patient	Age	Sex	FEV1	Sputum Culture	Prior allergic reactions
1	38	F	38-42	B. cepacia	Ceftazidime – severe Piperacillin - Severe Meropenem – Mild
2	19	M	20-25	PA	Ceftazidime, Cefepime, Piperacillin Tazobactam, Aztreonam - Mild
3	26	M	<30	PA	Ceftazidime, piperacillin –mild
4	37	F	44-57	PA	Ceftazidime – Severe Piperacillin - Severe
5	21	M	39	PA	Ceftazidime – Mild Piperacillin - Mild
6	25	M	30-45	PA	Piperacillin - Mild
7	14	F	>80	PA, MSSA	Piperacillin - Mild
8	42	F	64-77	Achromo. xyl. PA	Piperacillin and Ceftazidime – severe

Our protocol

Ceftazidime 2gr

Step	Concentration of Stock solution (mg/ml)	Concentration of infused solution – in 50 ml NS (mg/ml)	Total cumulative dose (mg)
syringe n 1	0.00002	0.000004	0.0002
syringe n 2	0.0002	0.000036	0.002
syringe n 3	0.002	0.00036	0.02
syringe n 4	0.02	0.0036	0.2
syringe n 5	0.2	0.036	2
syringe n 6	2	0.36	20
syringe n 7	20	3.6	200
syringe n 8	200	36	2000

Infused over 30 min

Patient	antibiotic	Reaction/step	Treatment	Completed successfully
1	Ceftazidime	No	-	Yes
		Anaphylaxis/D2	In ICU	No
	Meropenem	No	-	Yes
		No Pruritus	-	Yes No
2	Aztreonam	Urticaria/D1	AH	Yes
	Piperacillin/tazobactam	Urticaria/D1	AH	Yes
	Cefepime	Urticaria/D1	AH	Yes
	Ceftazidime	Urticaria/D1	AH	Yes
3	Ceftazidime	Rash/D6	-	Yes
4	Ceftazidime	Fever and dyspnea/D2	No data	No
		Hypotension/D1	Fluids	No
5	Ceftazidime	Urticaria/D2	-	No
6	Piperacillin	Pruritus/D1	AH	Yes
	Piperacillin/tazobactam	Pruritus/D1	AH	Yes
7	Piperacillin	No	-	Yes
		No	-	Yes

For β Lactam Ab

Time which drug concentration
remains above the MIC

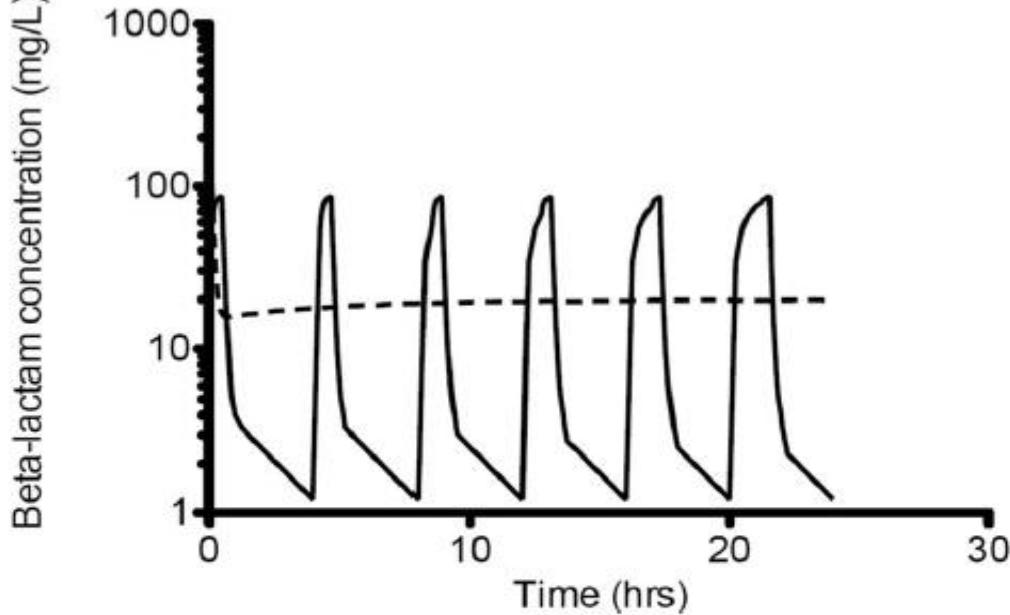


$$\int T_{>MIC}$$

Bacterial Killing
Characteristics

Continuous beta-lactam infusion in critically ill patients: the clinical evidence

Mohd H Abdul-Aziz¹, Joel M Dulhunty^{1,2*}, Rinaldo Bellomo³, Jeffrey Lipman^{1,2} and Jason A Roberts^{1,2,4}



$$f^T > \text{MIC}$$

Figure 2 The simulated concentration-time profile of a beta-lactam antibiotic when administered by intermittent bolus dosing or continuous infusion ($V_d = 0.22 \text{ L/kg}$; $T_{1/2} = 2.45 \text{ hr}$). Intermittent bolus dosing (solid lines); continuous infusion (dotted lines).

Continuous vs Thrice-Daily Ceftazidime for Elective Intravenous Antipseudomonal Therapy in Cystic Fibrosis

J. Riethmueller, S. Junge, T.W. Schroeter, K. Kuemmerer, P. Franke, M. Ballmann, A. Claass, S. Broemme, R. Jeschke, A. Hebestreit, D. Staab, K. Koetz, G. Doering, M. Stern

Isabelle Rappaz · Laurent A. Decosterd · Jacques Bille
Marianne Pilet · Nicole Bélaz · Michel Roulet

Continuous infusion of ceftazidime with a portable pump is as effective as thrice-a-day bolus in cystic fibrosis children

**200 mg/kg per day ceftazidime in three doses as a
30-min intravenous infusion**

“equally effective regimens for antipseudomonal therapy in clinically stable patients with CF.”

Vs

“Continuous infusion of ceftazidime was no different from that achieved with the conventional bolus infusion regimen”

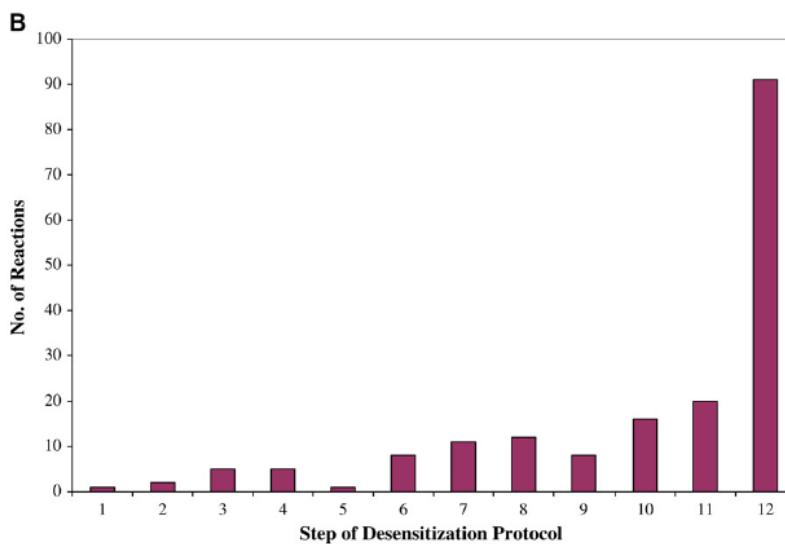
continuous **23.5-h** infusion of **100 mg/kg** per day ceftazidime

Bolus Vs. Continuous

Bolus - 6 gr per day q8h
2 gr over 30 min

Continuous - 6 gr per day
2 gr over 8 hr

X 16 reduction in administered dose per time



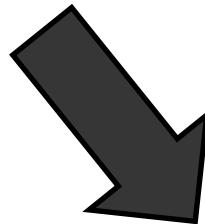
Ceftazidime 2gr			
Step	Concentration of Stock solution (mg/ml)	Concentration of infused solution – in 50 ml NS (mg/ml)	Total cumulative dose (mg)
syringe n 1	0.00002	0.000004	0.0002
syringe n 2	0.0002	0.000036	0.002
syringe n 3	0.002	0.00036	0.02
syringe n 4	0.02	0.0036	0.2
syringe n 5	0.2	0.036	2
syringe n 6	2	0.36	20
syringe n 7	20	3.6	200
syringe n 8	200	36	2000

Infused over 30 min

Our new protocol

In high risk patients for severe allergic reaction

Standard 8 step RDD



Continuous infusion of a β lactam Ab

Patient	Age	Sex	FEV1	Sputum Culture	allergic reactions
1	38	F	38-42	B. cepacia	Ceftazidime – severe Piperacillim - Severe Meropenem – Mild
2	19	M	20-25	PA	Ceftazidime, Cefepime, Piperacillin Tazobactam, Aztreonam - Mild
3	26	M	<30	PA	Ceftazidime, piperacillin – Moderate
4	37	F	44-57	PA	Ceftazidime – Severe Piperacillin - Severe
5	21	M	39	PA	Ceftazidime – Mild Piperacillin - Mild
6	25	M	30-45	PA	Piperacillin - Mild
7	14	F	>80	PA, MSSA	Piperacillin - Mild
8	42	F	64-77	Achromo. xyl. PA	Piperacillin and Ceftazidime – severe

Novel protocol for patient 1,4 and 8

The new protocol - Results

Patient	antibiotic	Reaction /step	Continuous IV	reaction	Tx	Completed successfully
1	Ceftazidime	No	Yes	No	-	Yes
		No	Yes	No	-	Yes
4	Ceftazidime	No	Yes	No	-	Yes
		No	Yes	No	-	Yes
	Piperacillin/tazobac tam	No	Yes	No	-	Yes
		No	Yes	No	-	Yes
		No	Yes	No	-	Yes
		No	Yes	No	-	Yes
		No	Yes	No	-	Yes
8	Ceftazidime	No	Yes	No	-	Yes
		No	Yes	No	-	Yes

Conclusions

1. RDD protocols have allowed providing allergic CF patients with first-line therapy
2. Still, some CF patients cannot complete a full treatment course due to severe allergic reactions
3. Our novel protocol allows these patients to complete the desired treatment course and receive effective first line therapy

Thank you



Acknowledgments

Hadassah Hebrew University Medical Center

- The Pediatric Pulmonology and CF Center:
 - Eitan Kerem, MD
 - David Shoeeyov, MD
 - Malena Cohen-Cymberknob, MD
 - Shoshana Armoni, RN