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Letter

Continuous intravenous β -lactam antibiotics in cystic fibrosis patients with severe drug hypersensitivity

Intravenous antibiotics are widely used in the treatment of pulmonary exacerbation in patients with cystic fibrosis (CF). High rates of allergic reactions to antibiotics, especially β lactams, have been reported in patients with CF.¹ These reactions often complicate patient management. Several parenteral antibiotic rapid drug desensitization (RDD) protocols have been described for allergic patients with CF.^{2–5} In these protocols, the allergenic antibiotic is delivered initially at a highly diluted concentration with a gradual increase in dose and concentration until the desired therapeutic dose is reached. Desensitization is considered successful when the patient tolerates the RDD and the repeated antibiotic administration until the full therapeutic course is completed. Most reported adverse reactions to an RDD protocol occur in the final steps of desensitization and are mild to moderate,⁶ but severe breakthrough reactions occurring during the full-dose treatment and requiring termination of treatment also have been reported.^{2,3,5} We report our experience with successful treatment using RDD followed by a continuous intravenous β -lactam antibiotic in a subset of patients with CF who could not complete the regular RDD procedure because of severe life-threatening allergic reactions.

After obtaining institutional review board approval, the medical records of all patients with CF who underwent antibiotic desensitization procedures at our CF center from 2005 through 2013 were reviewed. Information on the nature of the hypersensitivity reaction to individual drugs, the success of the desensitization procedures, and adverse reactions during the RDD protocol and intravenous treatment course were recorded. Adverse reactions were defined as mild or severe according to criteria described by Castells et al.⁶ The rapid desensitization protocol performed at our institution from 2005 to 2013 adhered to an 8-step procedure adapted from the 7-step procedure described by Borish et al.⁷ Premedication consisting of an antihistamine was given to patients who had allergic reactions during prior desensitizations. After desensitization, the selected antibiotic was administered in standard therapeutic doses at regular intervals for the full treatment period, usually for 2 weeks. In patients whose desensitization procedure of a β -lactam antibiotic failed during the full treatment course, a second desensitization was attempted, followed by treatment by a continuous infusion of the selected β -lactam antibiotic (23.5-hour infusion of 9 g/d of ceftazidime or 12 g/d of piperacillin, using a portable pump, for the entire treatment course).

Patient characteristics and information regarding the desensitizations are listed in Table 1. In total, 27 desensitization procedures involving 6 different antibiotics were performed in 8 patients. In 3 of these patients (patients 1, 4, and 5), there was

evidence of a prior severe allergic reaction. Of the 27 desensitizations, 17 were performed according to the 8-step protocol followed by a regular-dose treatment course; of these 17 procedures, 12 were completed successfully (70.5%).

Ten desensitizations in 3 patients were performed subsequent to severe allergic reactions using our new approach, ie, the same 8-step protocol followed by a continuous infusion of the β -lactam antibiotic for the full treatment course. All 10 procedures were completed successfully without any adverse events. In patients 1 and 4, the new protocol was used after the standard desensitization procedure failed owing to a severe allergic reaction. In patient 5, a standard desensitization procedure was not attempted, because this patient had previously experienced acute respiratory compromise from allergic angioedema during intravenous antibiotic treatment. Therefore, it was decided in advance to provide continuous antibiotic treatment after RDD protocol that was considered safer in our center.

Hence, similar to other reports of RDD protocols, most of the reported adverse events were mild and occurred on the first day of treatment, mainly during the RDD protocol (Table 1). However, some patients experienced severe events after successfully completing the RDD protocol and during the course of the full-dose antibiotic treatment. This led us to search for an alternative method to deliver the required antibiotic.

The β -lactam antibiotics exhibit minimal concentration-dependent killing.⁸ Thus, maximal β -lactam activity is thought to be achieved by optimizing the duration of exposure and not by achieving peak serum drug levels. Comparative studies have shown that continuous administration of ceftazidime is as effective as 3 times daily and has favorable pharmacokinetic properties with a lower total therapeutic dose.^{9,10} A continuous 24-hour infusion of a specific total daily dose allows for the delivery of a low concentration of the selected drug with effective serum levels throughout the entire treatment course. Thus, because continuous infusion of β -lactam antibiotics has a pharmacokinetic advantage, we speculated that the constant serum drug levels would serve as a prolongation of the desensitization process and help ensure ongoing tolerance to the selected drug after RDD and lower the rate of serious allergic reactions.

This study has some limitations. First, skin tests to confirm IgE-mediated responses were not performed in any of these patients and patients were included in the study based on their clinical history as recorded in their files, which did not always have a clear temporal description of the allergic reaction. Second, given the small sample, it is possible that with further experience continuous antibiotic infusion after RDD might be associated with breakthrough reactions. The use of a control group and a blinded assessment protocol also might be envisaged. Third, these patients could possibly be administered the target antibiotic using an alternative RDD protocol, ie, the highly successful RDD protocol for

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Table 1
Desensitization description—outcomes of RDD protocols (a standard RDD protocol and an RDD protocol followed by a full treatment course of continuous β -lactam antibiotic; see text)

Patient	Age ^a	Sex	Previous allergic reactions ^b	Desensitization				
				Protocol	Antibiotic	Reaction/step ^c	Treatment	Completed successfully
1	38	F	ceftazidime—severe piperacillin—severe meropenem—mild	RDD	ceftazidime	no	—	yes
				RDD		anaphylaxis/D2	in ICU	no
				RDD + cont β lactam		no	—	yes
				RDD + cont β lactam		no	—	yes
				RDD	meropenem	no	—	yes
				RDD		no	—	yes
2	19	M	ceftazidime—mild cefepime—mild piperacillin—mild aztreonam—mild	RDD	aztreonam	pruritus	—	no
				RDD	piperacillin/tazobactam	urticaria/D1	AH	yes
				RDD	cefepime	urticaria/D1	AH	yes
				RDD	ceftazidime	urticaria/D1	AH	yes
3	26	M	ceftazidime—mild piperacillin—mild	RDD	ceftazidime	rash/D6	—	yes
4	37	F	ceftazidime—severe piperacillin—severe	RDD	ceftazidime	fever and dyspnea/D2	no data	no
				RDD		hypotension/D1	fluids	no
				RDD + cont β lactam		no	—	yes
				RDD + cont β lactam		no	—	yes
				RDD + cont β lactam	piperacillin/tazobactam	no	—	yes
				RDD + cont β lactam		no	—	yes
5	42	F	ceftazidime—severe piperacillin—severe	RDD + cont β lactam	ceftazidime	no	—	yes
				RDD + cont β lactam		no	—	yes
6	25	M	piperacillin—mild	RDD	piperacillin	pruritus/D1	AH	yes
				RDD	piperacillin/tazobactam	pruritus/D1	AH	yes
7	14	M	piperacillin—mild	RDD	piperacillin	no	—	yes
				RDD	piperacillin	no	—	yes
8	21	F	ceftazidime—mild piperacillin—mild	RDD	ceftazidime	urticaria/D2	—	no

Abbreviations: AH, antihistamine; cont, continuous; D1, day 1 (includes desensitization procedure); D2, day 2; D6, day 6; F, female; ICU, intensive care unit; M, male; RDD, rapid drug desensitization.

^aAge at first desensitization.

^bAllergic reactions experienced previously, during a regular course of antibiotic treatment.

^cThe day of treatment protocol when the allergic reaction occurred.

patients with CF described by Legere et al.² Nevertheless, alternative protocols were not attempted, initially because of the pharmacokinetic advantage and supposed therapeutic benefit of continuous antibiotic treatment and later because of the success of this protocol.

In conclusion, we have described a new approach to treating patients with CF who cannot tolerate intravenous β -lactam antibiotic therapy owing to severe allergic reactions despite a full RDD procedure. This approach is likely to be safer than RDD followed by a regular intermittent-dose treatment course and thus may be used in all patients at high risk of developing severe life-threatening allergic reactions to β -lactam antibiotics.

Oded Breuer, MD
Malena Cohen-Cymberknoh, MD
Shoshana Armoni, RN
Eitan Kerem, MD
David Shoseyov, MD
Department of Pediatrics, Pediatric Pulmonology
Cystic Fibrosis Center
Hadassah-Hebrew University Medical Center
Mount Scopus, Jerusalem, Israel
odedbr@hadassah.org.il

References

- [1] Roehmel JF, Schwarz C, Mehl A, Stock P, Staab D. Hypersensitivity to antibiotics in patients with cystic fibrosis. *J Cyst Fibros*. 2014;13:205–211.
- [2] 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;8:418–424.
- [3] Turvey SE, Cronin B, Arnold AD, Dioun AF. Antibiotic desensitization for the allergic patient: 5 years of experience and practice. *Ann Allergy Asthma Immunol*. 2004;92:426–432.
- [4] Whitaker P, Shaw N, Gooi J, Etherington C, Conway S, Peckham D. Rapid desensitization for non-immediate reactions in patients with cystic fibrosis. *J Cyst Fibros*. 2011;10:282–285.
- [5] Burrows JA, Toon M, Bell SC. Antibiotic desensitization in adults with cystic fibrosis. *Respirology*. 2003;8:359–364.
- [6] Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122:574–580.
- [7] Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol*. 1987;80:314–319.
- [8] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1–10. quiz 1–2.
- [9] Riethmueller J, Junge S, Schroeter TW, et al. Continuous vs thrice-daily ceftazidime for elective intravenous antipseudomonal therapy in cystic fibrosis. *Infection*. 2009;37:418–423.
- [10] Hubert D, Le Roux E, Lavrut T, et al. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother*. 2009;53:3650–3656.