



Letters

Desensitization for inhaled vancomycin

Treatment of pulmonary infections in cystic fibrosis (CF) can be challenging because of organisms unique to CF and antibiotic resistance.¹ Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are prevalent in patients with CF and have been associated with poor clinical outcomes. The increasing prevalence of MRSA infections in CF has led to the advent of newer modalities of receiving antibiotics, such as inhaled therapies.² Inhaled vancomycin is often used in the CF population to treat refractory MRSA infections and has been reported to improve clinical outcomes.^{2,3} In addition, intravenous vancomycin is associated with complications such as nephrotoxicity, unlike inhaled vancomycin, in which adverse effects are more localized. Vancomycin hypersensitivity has been previously reported in the literature. Adverse drug reactions to vancomycin can include both red man syndrome (RMS) and immunologically-mediated immediate hypersensitivity reactions.⁴ Notably, RMS is considered a pseudoallergic reaction thought to occur by direct mast cell degranulation through the mast cell-specific G-protein coupled receptor (MRGPRX2).⁵ Symptoms of RMS include dermal flushing, pruritus, and erythema, often of the facial and the cervical region. In addition, RMS is thought to be an infusion rate–related reaction that can be managed by pretreatment with antihistamines and decreasing the infusion rate.⁶ Immunologically-mediated immediate hypersensitivity reactions do not respond to those measures, and 1 option for management is drug desensitization. Immunologic immediate hypersensitivity to vancomycin is thought to be mediated by antigen-specific immunoglobulin E–mediated reactions and can present clinically as urticaria, angioedema, vomiting, hypotension, and anaphylaxis. It can often be difficult to distinguish RMS from vancomycin immunologic immediate hypersensitivity. The purpose of drug desensitization is to induce rapid and temporary tolerance to a drug. This has been well described for many intravenous and oral drugs, but there are no known protocols for desensitization to vancomycin using only the inhaled route.

This case presents a 23-year-old man at a tertiary care center with CF who was diagnosed as having MRSA pneumonia through radiography and sputum cultures. The patient had multiple CF-related complications including renal disease, bronchiectasis, pneumothorax, and distal intestinal obstruction syndrome. In addition, he had a history of multiple life-threatening reactions to intravenous vancomycin, including episodes of anaphylaxis with symptoms such as angioedema, dyspnea, and oxygen desaturations. The reactions were refractory to the adjustments to the rate of intravenous vancomycin delivery and to the pretreatment of the infusions with diphenhydramine. No tryptase levels were checked during the previous reactions or at baseline. His CF specialists and infectious disease physicians deemed it necessary to use inhaled

vancomycin after multiple other failed treatments to treat his MRSA. He has never received inhaled vancomycin before, given his reactions to intravenous vancomycin. He was deemed high risk to receive this medication given his reaction history. The options for management were discussed by his allergists. Percutaneous skin testing to vancomycin was not considered a feasible option for multiple reasons. First, immediate hypersensitivity skin testing has not been validated for vancomycin, and the positive and negative predictive values for such testing to this drug is unknown.⁷ Second, skin testing relies on histamine release from mast cells, but the patient was on a first-generation antihistamine and cyproheptadine that could not be stopped. A drug challenge was thought to be inappropriate in this case given the patient's life-threatening reaction history and predicted low forced expiratory volume in 1 second of 52%. There was no vancomycin immunoglobulin E in vitro testing available. Drug desensitization was thought to be the best option for management; however, on literature review, it was found that no protocols for inhaled vancomycin desensitization have been published. This led to the creation of a novel desensitization protocol (Table 1). This is the first desensitization protocol to utilize only an inhaled route of administration. With 500-mg powder vials, 4 separate solutions were created by means of serial dilutions of vancomycin. The cumulative desired dose was 250 mg, and this protocol has a cumulative dose of 260.075 mg. One concern regarding the administration of the medication doses in the protocol was the actual received dose of the medication, given the variability of the pharmacokinetics of inhaled vancomycin. Studies have reported measuring vancomycin levels in the sputum, but this is not a widely clinically used practice.⁸ An AeroEclipse II (Monaghan, New York, New York) breath-actuated nebulizer was utilized for this patient to ensure maximal delivery of this medication to the patient. Informed consent was obtained. The patient had a respiratory therapist at the bedside administering the medication every 15 minutes under close observation. The patient was also on telemetry throughout the desensitization and had dedicated one-to-one nursing. Vital signs were checked before each dose, including blood pressure, heart rate, oxygen saturation, and respiratory rate. There were no changes in his vital signs throughout the procedure. He was observed for 6 hours after the last dose. The patient tolerated the procedure with no reactions and continues to be given a dose of 250 mg inhaled vancomycin twice daily.

Management of antibiotic allergies can be challenging, and desensitization is a useful management tool to allow patients to receive optimal inhaled therapies needed to treat infections. A previously published approach demonstrated performing intravenous desensitization followed by an inhaled drug challenge.⁹ In this case, successful desensitization to vancomycin by only the inhaled route was achieved without any adverse drug reactions. According

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Table 1
Inhaled Vancomycin Desensitization Protocol

Drug source (mg/mL)	Step	Dose (mg)	Volume (mL)	Cumulative dose (mg)	
Dilution A	0.05	1	0.025	0.5	0.025
Dilution A	0.05	2	0.05	1	0.075
Dilution A	0.05	3	0.1	2	0.175
Dilution A	0.05	4	0.2	4	0.375
Dilution A	0.05	5	0.4	8	0.775
Dilution B	0.5	6	0.8	1.6	1.575
Dilution B	0.5	7	1.5	3	3.075
Dilution B	0.5	8	3	6	6.075
Dilution C	5	9	5	1	11.075
Dilution C	5	10	10	2	21.075
Dilution C	5	11	20	4	41.075
Dilution D	50	12	40	0.8	81.075
Dilution D	50	13	60	1.2	140.075
Dilution D	50	14	120	2.4	260.075

NOTE: Vancomycin in 500-mg powder vials was diluted with saline for nebulization.

to his specialists, remaining on inhaled vancomycin has resulted in decreased length of stay during hospitalizations and has prevented the need for frequent inpatient hospitalizations.

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