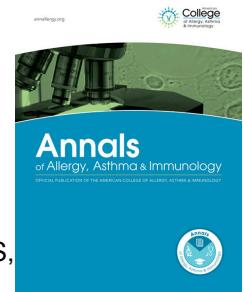


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Letter to the Editor

Challenges and safety of beta lactam desensitization during extracorporeal membrane oxygenation

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Abbreviations/acronyms: rapid drug desensitization (RDD); extracorporeal membrane oxygenation (ECMO); pharmacokinetics (PK); V-V (veno-venous); cystic fibrosis (CF)

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Extracorporeal membrane oxygenation (ECMO) is an advanced life support therapy used in patients with refractory cardiac and/or respiratory failure. The growth of ECMO use internationally over the past decade has been exponential¹ paralleling an increase in lung transplant volume⁴. Trends at our institution, an urban, tertiary academic medical center reflects this growth, approximately doubling in volume each year and paralleling the increase of transplants in CF patients. ECMO has been used as a temporizing measure for progressive respiratory failure in patients with cystic fibrosis (CF) as a bridge to lung transplant². Notably CF patients have higher rates of drug allergy than the general population and are at high risk of respiratory failure requiring ECMO³. Therefore, the use of rapid drug desensitization (RDD) in the ECMO setting is important and timely. To our knowledge, there have been no prior published reports of RDD during ECMO. Here we describe the pharmacologic challenges for RDD posed by the ECMO setting. We then present three cases of beta-lactam desensitization successfully performed in CF patients receiving ECMO. We propose that pharmacokinetic (PK) changes must be a primary consideration for Allergists considering RDD in this setting.

Patients receiving ECMO pose several challenges with regards to medication administration due to altered pharmacokinetics (PK) beyond that of critical illness and co-morbid diseases. Patients exhibit an increased volume of distribution and altered drug clearance, which may result in inappropriate drug serum concentrations. ECMO-specific factors include the systemic inflammatory response induced by the ECMO circuit and drug sequestration within the circuit, hemodilution, and fluid shifts. Drug-specific factors, such as lipophilicity and protein-binding also greatly impact PK⁵⁴. In CF patients, drug PK is further altered due to increased clearance and volume of distribution for highly hydrophilic drugs such as aminoglycosides, and for many beta-lactam agents due to differences in body mass compared with the non-CF population⁶⁵. RDD has previously been shown to be safe and effective in the CF population outside the ECMO setting⁶⁷.

The consequences of altered PK in the ECMO setting are especially concerning for antimicrobials because of the risk for treatment failure. ~~Optimizing drug plasma concentration is important for bactericidal effect.~~ Based on *ex vivo* and *in vivo* data of ECMO circuits, there may be sequestration of beta-lactam agents within the ECMO circuit lowering plasma drug concentrations. Recent data ~~limited data~~ suggests there may be higher loss of meropenem, ampicillin, cefazolin, and cefotaxime within the circuit than with meropenem, ceftazidime, cefepime, piperacillin, oxacillin and amoxicillin^{5,97}. Therefore, each drug needs to be assessed independently for the impact of PK changes on dosing management. However, as beta-lactams differ in their chemical properties, extrapolating this data to other agents in the same class may be inappropriate. Variable PK that results from critical illness and ECMO also may warrant more aggressive dosing for more resistant microorganisms, like *Pseudomonas aeruginosa*.

The unpredictable PK of patients receiving ECMO poses a unique consideration ~~unique challenge to~~ for desensitization protocols, which classically depend on precise dosing. This is particularly relevant to the cystic fibrosis (CF) population who have high rates of drug allergy and are at high risk of respiratory failure requiring ECMO. RDD is used for the treatment of drug hypersensitivity reactions to induce a state of unresponsiveness to a certain antigen or drug by serial dosage and rate increases⁹⁸. The challenges of RDD in increasing the threshold concentration of a reaction is further complicated by the high-risk ECMO setting.

Key patient and desensitization characteristics are presented in ~~Figure~~ Table 1. All three patients had CF and were admitted to our institution with acute on chronic hypoxemic and hypercarbic respiratory failure. ~~They~~ Patients were initiated on veno-venous (V-V) ECMO as a bridge to bilateral lung transplant. Complete circuit and CardioHelp machines from Marquet (Wayne, NJ), Sorin pump (LivaNova: Arvada,

CO) and Sorin circuit (part number #050300700) were used in all cases. Antibiotics were selected in consultation with the hospital's Infectious Disease Transplant service based on available microbiology sensitivities and patients' individual resistance patterns.

All patients had previously reacted to beta lactam drugs, including the target drugs under consideration for desensitization. However, only one patient had a prior history of positive skin testing to the target drug. All patients had evidence of atopy including other drug allergies (Figure 1). All patients had multiple drug allergies, and experienced anaphylaxis to at least one other beta lactam drug within the year prior to transplant. Patient A had no prior history of skin testing but anaphylaxis to a drug with cross-reactivity to the target drug⁹. Patient B had negative skin testing to a beta lactam but reacted on challenge within one year prior to transplant. Patient C had a positive challenge to the target drug within one year prior to transplant. Skin testing on the index admission was precluded by critical illness and transplant timing. Drug challenges were considered not feasible due to the acuity of ECMO cannulation and transplant status.

Key features of the desensitization protocols are described in Figure 1. Desensitization pre-medications used were included cetirizine 10mg orally (PO), famotidine 20mg intravenous (IV), and montelukast 10mg (PO). Desensitization was performed to a different target drug in each case: ceftazidime-avibactam (four bag-16 step), or meropenem (three bag-12 step), or cefepime (three bag-12 step). Choice of protocol was based on target drug and patient clinical history. Previously published protocols from the non-ECMO setting were used for meropenem and cefepime. At the time of desensitization there were no previously published protocols in any setting for ceftazidime-avibactam and a protocol was designed based on previously published ceftazidime protocols in the non-ECMO setting.

All patients tolerated desensitization to the target dose without any reactions. Patients subsequently successfully received lung transplants and were decannulated from ECMO. The remainder of the antibiotic courses were completed without any delayed reactions.

~~This case~~ In this real-world application of RDD in the acute hospital setting, our small series suggests that beta-lactam RDD can be safely completed during ECMO ~~despite complex pharmacokinetics~~. The three antimicrobials used in this series were potentially of lower risk for PK changes than other beta lactams, which supported their use in critically ill patients. This case series is limited by the lack of skin testing or challenge confirming that prior reactions represented true allergy to the target drug¹⁰. In our patients, critical illness and clinical acuity precluded testing on the transplant admission. As is often the case in acute settings, we relied on patient history to inform clinical decision-making in the absence of complete testing data.

This is the first report of the use of RDD techniques in the ECMO setting. As ECMO use continues to rise, Allergists will be called upon to manage high risk patients with complex drug hypersensitivity histories. We propose that the PK of each drug and sequestration risk must be a primary consideration prior to desensitization, in addition to routine considerations of reaction history and clinical context. This approach underscores RDD as a tool for personalized medicine and positions Allergists as leaders in this movement. Further cases will need to be reviewed to replicate these findings beyond the CF population and to ensure the safety of desensitization protocols for higher risk antimicrobials ~~other medications~~ during ECMO.

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Figure 1 Table 1. Key features of patient cases

Patient	Gender	Drug allergy (reaction)	Prior skin testing* / Challenge (reaction)	Atopy	Target drug	Target dose/ Protocol	Premedication	Outcome
A	Male	Cefepime (anaphylaxis with hypotension one year prior to transplant) Piperacillin-tazobactam (rash two years prior to transplant)	None	Allergic rhinitis	Ceftazidime-avibactam	2.5g / 4 bag 16 step	Cetirizine 10mg PO† Famotidine 20mg IV† Montelukast 10mg PO	Completed without reaction
B	Female	Penicillin (unknown) Meropenem (distant rash) Cefepime (distant delayed rash) Clindamycin (distant delayed rash)	Prepen ST- Penicillin G ST- Ceftazidime ST-/ challenge + (anaphylaxis with rash and chest tightness)	Allergic rhinitis	Meropenem	2g/ 3 bag 12 step	Cetirizine 10mg PO Famotidine 20mg IV Montelukast 10mg PO	Completed without reaction
C	Female	Cefepime (acute urticaria, mouth tingling two years prior to transplant while on double coverage with meropenem) Meropenem (acute urticaria, mouth tingling two years prior to transplant while on double coverage with meropenem)	Prepen ST- Penicillin G ST- Meropenem ST-/ challenge - Ceftazidime ST-/ challenge + (flushing, oral pruritis) Cefepime ST-/ challenge + (urticaria, mouth tingling)	Idiopathic urticaria [§] (single episode, one year prior to transplant)	Cefepime	2g/ 3 bag 12 step	Cetirizine 10mg PO Famotidine 20mg IV Montelukast 10mg PO	Completed without reaction

* Skin testing (ST) performed within one year prior to transplant

§ No prior or subsequent history of idiopathic urticaria or angioedema

† Orally (PO); Intravenous (IV)