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Evaluation of Pharmacy-Developed Antibiotic Desensitization Protocols

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Abstract

Background: Parameters within reconstitution, storage, stability, and administration may be optimized according to the unique pharmacokinetics of each antibiotic to ensure a successful desensitization. **Objective:** The study aims to evaluate the successfulness and safety of antibiotic desensitization protocols developed by the pharmacy department at our institution. **Methods:** A retrospective study was conducted at an 800-bed, urban, tertiary care, academic medical center. A total of 36 patients 18 years of age or older, admitted to our intensive care units between March 2013 and July 2017, who underwent antibiotic desensitization utilizing our pharmacy developed protocols were included. **Results:** In 36 patients, 61 desensitization cases were identified and included; 17 (47%) were male, 27 (75%) were Caucasian, and the median age was 55 years (range 19-94). In all, 15 different antibiotics were administered for desensitization, with meropenem (n = 12, 20%), ampicillin (n = 7, 11%), piperacillin/tazobactam (n = 7, 11%), and penicillin (n = 7, 11%) being the most common; 59 (97%) of 61 desensitizations were completed successfully with or without experiencing reactions, and 53 (89%) of the successful desensitization cases were completed without reactions. Two cases were categorized as anaphylaxis, which was severe enough to terminate the desensitization process. Of the 59 cases successfully completed, the 6 (10%) cases that experienced reactions were managed successfully during desensitization with completion of the process. **Conclusion and Relevance:** The findings suggest that our pharmacy-developed antibiotic desensitization protocols are successful and safe and may be adapted by other institutions.

Keywords

desensitization, antibiotics, allergy, infectious diseases, clinical pharmacy, pharmacokinetics

Drug hypersensitivity reactions are immunological responses to medications, classified based on pathogenesis and the temporal pattern relative to the antigen exposure. Type 1 or IgE-mediated hypersensitivity reactions are of greatest clinical concern because they occur immediately and can be severe and life-threatening.[1] The drug antigen interacts with IgE bound to receptors on mast cells, leading to cross-linkage and triggering the degranulation and the release of inflammatory mediators and cytokines.[2] As a result, patients can experience flushing, pruritus, urticaria, angioedema, dyspnea, wheezing, and hemodynamic instability.[3]

Although these reactions may be provoked by various medication classes, β-lactam antibiotics are the most common drug class with reported allergy among individuals receiving health care in the United States.[4] Specifically, penicillin is the most common β-lactam allergy, which when present, creates a challenging therapeutic phenomenon.[4] The antibodies against penicillin are directed at the β-lactam ring, a common chemical moiety within the structure of agents belonging to this drug class.[3] Rising antibiotic resistance along with slow antimicrobial drug development has, consequently, limited the pharmacotherapy options available for patients with these documented allergies.[5]

For patients who experience IgE-mediated reactions to antibiotics, desensitization may be utilized to facilitate antimicrobial stewardship and allow a patient to receive an optimal agent for treatment.[1,6] The principle behind desensitization is to induce drug tolerance by delivering increasing doses of an antigen to blunt the response of

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triggering doses of the desensitizing antigen.[6] Traditional desensitization protocols begin with the introduction of drug in very small amounts as a bolus, which are then successively increased or doubled manually at a fixed interval over several hours until a target dose is reached.[7] According to a review conducted by Liu et al,[6] desensitization success rates with current protocols range from 58% to 100%. A frequent limitation observed in previous studies is the presence of ambiguity regarding reconstitution, storage, stability, and administration of the administered agent in the desensitization process, which may pose significant risks.[8-10] These risks can include medication errors caused by incorrect reconstituted concentrations or inappropriate product administration as a result of unfamiliarity with dosing strategies or administration techniques, possibly leading to the exacerbation of an allergic reaction. Parameters within these crucial steps may be optimized by providing granular reconstitution and administration instructions from a multidisciplinary approach to ensure a successful desensitization. More important, recommendations for the management of acute allergic reactions as an attempt to salvage the desensitization have not been thoroughly described in the current literature.[8] When specific instructions related to the fundamentals of desensitization are absent and considering the high risks associated with this process, there may be tremendous difficulty for clinicians to interpret the clinical usefulness of these protocols.

Beginning in 2008, our department of pharmacy piloted our antibiotic desensitization protocols. We utilize a continuous infusion method, as compared to an intermittent intravenous bolus method, to provide antigen continuously. Although the cellular basis for desensitization is not fully understood, increasing amounts of antigen may induce a state of mast cell hyporesponsiveness or refractoriness.[1,11] Our hypothesis is that by providing a stepwise increase of an antigenic substance via continuous infusion administration, there would be constant antigen–mast cell interaction without gaps in plasma concentration (particularly important for short half-life medications [ie, β-lactam antibiotics]). This study aims to determine the successfulness and safety of the antibiotic desensitization protocols developed by pharmacy at our institution.

Methods

Setting

This retrospective study was conducted in an 800-bed, urban, tertiary care academic medical center. Desensitization protocols for multiple antibiotics have been developed by our pharmacy, which include amikacin, ampicillin, ampicillin/sulbactam, cefepime, ceftaroline, ceftazidime, ceftolozane/tazobactam, ceftriaxone, imipenem, levofloxacin, meropenem, nafcillin, oxacillin, penicillin, and piperacillin/tazobactam. Every protocol has been used on at least 1 patient. For each protocol, specific instructions regarding reconstitution, administration, time to target dose, monitoring, reaction, management, storage, and stability were included. Specifically, for the management of reactions during desensitization, instructions to modify the protocol and continue were available, rather than immediately terminating the desensitization process. Premedication was not standard for any of our protocols. However, standard medications such as epinephrine 0.3 mg/0.3 mL auto-injector for intramuscular injection, diphenhydramine 50-mg vial, hydrocortisone 50-mg vial or methylprednisolone 125-mg vial, and famotidine 20-mg vial were available at the bedside for intravenous administration if reactions were to occur. Antibiotic desensitizations were conducted in an intensive care unit (ICU) at our institution through a well-established multidisciplinary collaborative approach, including a clinical pharmacotherapy specialist, infectious diseases attending physician, critical care attending physician, and a 1:2 nurse-to-patient ratio. Consent was obtained from each patient prior to desensitization. The New York University Institutional Review Board approved the study with a waiver of informed consent.

Study Design

Patients were screened for inclusion using a list of all intravenous antibiotics administered in the ICU during the study period generated from the electronic health record. Patients were included if they were at least 18 years of age or older, admitted to the ICU between March 2013 and July 2017, and underwent antibiotic desensitization utilizing our pharmacy-developed protocols. For each desensitization case, data on patient demographics, self-reported or clinically documented allergies (including IgE or non-IgE mediated reactions), concomitant medications, clinical characteristics, microbiology, desensitization antibiotic and reaction, and course of treatment were collected retrospectively through the electronic health record. Type I or IgE-mediated hypersensitivity reactions were defined as cutaneous (urticaria, pruritus, flushing, angioedema), cardiovascular (tachycardia, syncope, hypotension, dysrhythmia), respiratory (dyspnea, wheezing, throat tightness, oxygen desaturation), gastrointestinal (vomiting and abdominal pain), or neuromuscular (anxiety, disorientation, numbness/weakness) signs and symptoms that occurred during or immediately after a past antibiotic administration.[9,12] These reactions most frequently occur within 1 hour of antibiotic exposure and most commonly include urticaria, angioedema, hypotension, wheezing, or anaphylaxis.[3] Our institution's general approach to self-reported penicillin or aminopenicillin allergies is to investigate further in regard to the reaction through patient/family member interviews, which may have limitations. In these clinical scenarios, the

patient's clinical status, infection severity, and available antimicrobial susceptibilities are assessed by a multidisciplinary group (infectious disease, critical care, and clinical pharmacotherapy specialist) to determine the optimal agent for treatment. When antibiotic agents with any risk of cross-reactivity to their reported allergy are absolutely necessary and an IgE-mediated reaction is suspected, the patient would be transferred to the ICU for desensitization.[13] Each desensitization to 1 antibiotic was regarded as an individual event; therefore, patients were allowed to be included more than once in this study.

The primary outcome was the successfulness of our pharmacy-developed antibiotic desensitization protocols, defined as successful completion of the protocol with or without a reaction. Secondary outcomes include safety, characterized by the incidence of any observed reactions.

Statistical Analysis

Categorical data are presented as proportions, and continuous variables are presented as medians and ranges.

Results

Between March 2013 and July 2017, a total of 61 desensitization cases in 36 patients, ranging from 1 to 10 cases per patient (median 1), were identified and included as described in Tables 1 and 2. In all, 17 (47%) patients were male, 27 (75%) were Caucasian, and the median age was 55 years (range 19-94). Four (11%) patients had cystic fibrosis, and 6 (17%) and 5 (14%) were receiving corticosteroids and antihistamines prior to admission, respectively. Among the 36 patients, 56 antibiotic allergies were identified, and 46 (82%) were self-reported; 35 (97%) patients had a β-lactam allergy reported, 9 (25%) had a fluoroquinolone allergy, and 4 (11%) had an aminoglycoside allergy. Based on the type of allergic reaction, 20 (56%) patients reported rash/pruritus only, 16 (44%) reported urticaria/hives, 14 (39%) reported anaphylaxis, 8 (22%) reported angioedema, and 6 (17%) reported bronchospasm. In all, 10 (28%) patients reported a total of 3 or more medication and/or nonmedication allergies.

The most common reasons for desensitization included treatment for bacteremia (n = 22, 36%), cystic fibrosis exacerbation (n = 19, 31%), endocarditis (n = 13, 21%), and neurosyphilis (n = 6, 10%). The most common causative pathogens included *Enterococcus* spp (n = 12, 20%), *Pseudomonas aeruginosa* (n = 11, 18%), *Enterobacteriaceae* spp (n = 11, 18%), *Achromobacter* spp (n = 10, 16%), and *Staphylococcus aureus* (n = 8, 13%). A total of 27 (44%) cases were complicated by multidrug resistance; 15 different antibiotics were administered for desensitization, with meropenem (n = 12, 20%), ampicillin (n = 7, 11%), piperacillin/tazobactam (n = 7, 11%), and penicillin (n = 7, 11%) being the most common.

In all, 59 (97%) of 61 desensitizations were completed successfully with or without experiencing reactions; 53 (89%) of the successful desensitization cases were completed without reactions and are shown in Table 1. As described in Table 2, there were 8 cases with reactions. Two cases manifested as urticaria, angioedema, oxygen desaturation, bronchospasm, and/or hypotension, which were categorized as anaphylaxis, requiring diphenhydramine, methylprednisolone, and/or epinephrine. The desensitization process was prematurely aborted with resolution of symptoms in both these patients. The remaining 6 (75%) cases that experienced reactions were managed successfully during desensitization without terminating the desensitization process. Three of the 6 reactions were managed by administering diphenhydramine, repeating prior steps in the protocol, and/or decreasing the rate of infusion. After previously failing, 1 patient (patient 35 in Table 2) was rechallenged successfully in 24 hours after premedicating with acetaminophen, diphenhydramine, and hydrocortisone along with extending the infusion duration. Gastrointestinal and neuromuscular symptoms were not reported by any patient during the desensitization process. Of our 61 patients, 58 (95%) successfully tolerated the desensitization and subsequent full-dose treatment course during their hospital stay. One of the 59 patients who successfully tolerated the desensitization process developed symptoms 48 hours later. The patient (patient 34 in Table 2) initially tolerated desensitization with only mild bronchospasm but developed a subsequent reaction 2 days later with worsened respiratory symptoms and diffuse pruritus and erythema of the extremities. Respiratory symptoms were successfully managed with albuterol inhalation, diphenhydramine, and famotidine. However, erythema persisted for 4 days and became bothersome for the patient, which prompted the switch to an alternative antibiotic.

Discussion

In this retrospective evaluation of antibiotic desensitization, a high success rate was observed to support the successfulness and safety of our pharmacy-developed protocols. The protocols used in this study are shown in Appendixes 1 to 15.

This is the largest study to report successful desensitization to 15 different antibiotics, including ceftolozane/tazobactam, an antibiotic recently approved by the Food and Drug Administration. The success rate in our study was similar to that in Legere et al,[9] a retrospective study of 52 antibiotic desensitizations that reported a 13.4% reaction rate, with a successful completion rate of 100%.[9] Comparable to our study, Legere et al[9] had their protocols amendable for re-desensitization in the setting of reactions by adjusting the concentration of the last bag to match the concentration of the antibiotic at the therapeutic dose.

Table 1. Desensitization Without Reaction Details (n = 53).

Patient	Age/Sex/Number of Allergies	Allergy[a]/Reaction[b]	Indication[c]	Causative Pathogen[d]	Desensitization Antibiotic	Time to Target Dose Reflects Protocol	Successful
1	46/F/1	Penicillin/Rash	Bacteremia, endocarditis	*Enterococcus* spp	Ceftriaxone	No	Yes
2	52/M/1	Penicillin/Rash, angioedema	Neurosyphilis	Other	Penicillin	Yes	Yes
3	36/M/2	Penicillin/Anaphylaxis	Cystic fibrosis exacerbation	*Achromobacter* spp	Piperacillin/ Tazobactam	No	Yes
						No	Yes
						No	Yes[e]
					Ampicillin/ Sulbactam	Yes	Yes
					Meropenem	No	Yes
						Yes	Yes
						Yes	Yes
						No	Yes[f]
					Imipenem	No	Yes
4	46/M/2	Oxacillin/Rash, angioedema	Bacteremia	MSSA	Oxacillin	Yes	Yes
5	53/M/1	Penicillin/Anaphylaxis	Bacteremia, meningitis	*Streptococcus* spp	Ceftriaxone	Yes	Yes[f]
6	69/M/2	Penicillin/Anaphylaxis	Bacteremia	Other	Ceftaroline	No	Yes
			Pneumonia	*Enterobacteriaceae* spp	Meropenem	No	Yes
7	50/F/3	Levofloxacin/Rash, urticaria	Bacteremia, osteomyelitis	*Streptococcus* spp, other	Levofloxacin	No	Yes
8	75/F/2	Penicillin/Rash, pruritus	Neurosyphilis	Other	Penicillin	Yes	Yes
9	35/F/2	Moxifloxacin/Rash	Other	Other	Levofloxacin	No	Yes[f]
10	90/M/1	Penicillin/Anaphylaxis	Bacteremia, endocarditis	MRSA	Ceftaroline	No	Yes
11	94/F/3	Penicillin/Rash, urticaria	Bacteremia	Other	Ampicillin	No	Yes
12	52/F/1	Penicillin/Bronchospasm	Bacteremia	MSSA	Nafcillin	No	Yes
13	77/M/2	Penicillin/Rash	Bacteremia, endocarditis	*Enterococcus* spp	Ampicillin	No	Yes
14	32/F/6	Ceftazidime/Rash, urticaria	Cystic fibrosis exacerbation	*Pseudomonas aeruginosa*	Ceftolozane/ Tazobactam	No	Yes
15	56/M/1	Penicillin/Rash	Bacteremia	*Enterobacteriaceae* spp, other	Ampicillin/ Sulbactam	No	Yes
16	81/M/1	Penicillin/Anaphylaxis	Bacteremia, pneumonia	MSSA	Oxacillin	No	Yes
17	19/M/1	Penicillin/Rash	Bacteremia, endocarditis	MSSA	Nafcillin	No	Yes
18	75/F/2	Penicillin/Angioedema	Bacteremia, endocarditis	*Streptococcus* spp, *Enterococcus* spp, other	Ceftriaxone	No	Yes
					Ampicillin	No	Yes
			Pneumonia	*Enterobacteriaceae* spp	Meropenem	No	Yes
19	70/F/2	Penicillin/Anaphylaxis	Other	Other	Ceftriaxone	Yes	Yes

(continued)

Table 1. (continued)

Patient	Age/Sex/Number of Allergies	Allergy[a]/Reaction[b]	Indication[c]	Causative Pathogen[d]	Desensitization Antibiotic	Time to Target Dose Reflects Protocol	Successful
20	30/M/2	Cefepime, Ceftazidime/ Pruritus	Cystic fibrosis exacerbation	*P aeruginosa*	Ceftazidime	Yes	Yes
						No	Yes
					Piperacillin/ Tazobactam	No	Yes
						No	Yes
					Meropenem	No	Yes
					Ceftolozane/ Tazobactam	No	Yes
21	64/M/2	Penicillin/Anaphylaxis	Bacteremia, endocarditis	*Streptococcus* spp	Penicillin	No	Yes
22	50/M/3	Penicillin/Bronchospasm	Neurosyphilis	Other	Penicillin	No	Yes
23	80/F/1	Penicillin/Anaphylaxis	Bacteremia, endocarditis, SSTI	MSSA	Oxacillin	No	Yes
			Osteomyelitis	MSSA	Oxacillin	Yes	Yes
24	24/F/3	Penicillin/Rash, urticaria	Urinary tract infection	—	Cefepime	No	Yes
25	50/F/5	Ceftriaxone, Penicillin/Rash, urticaria	Other	*Enterobacteriaceae* spp, *P aeruginosa*	Meropenem	No	Yes
				Enterobacteriaceae spp, *P aeruginosa, Enterococcus* spp	Meropenem	No	Yes
26	37/F/1	Cefaclor/Urticaria	Bacteremia	MSSA	Oxacillin	No	Yes
27	68/F/2	Penicillin/Anaphylaxis	Pneumonia	—	Meropenem	No	Yes
28	69/F/1	Penicillin/Anaphylaxis	Other	*Enterococcus* spp	Ampicillin	Yes	Yes
29	29/F/5	Penicillin/Anaphylaxis	Urinary tract infection	*Enterobacteriaceae* spp	Meropenem	No	Yes
30	91/M/3	Penicillin/Bronchospasm, hypotension	Bacteremia, endocarditis	*Enterococcus* spp	Ampicillin	Yes	Yes
					Ceftriaxone	Yes	Yes
31	80/M/1	Penicillin/Rash, pruritus	Neurosyphilis	Other	Penicillin	Yes	Yes
32	46/M/2	Meropenem/Rash, bronchospasm, urticaria, angioedema	SSTI	*Enterococcus* spp, *Enterobacteriaceae* spp	Meropenem	No	Yes
33	59/F/3	Piperacillin/Tazobactam/ Rash, urticaria	Cystic fibrosis exacerbation	*P aeruginosa*	Piperacillin/ Tazobactam	Yes	Yes
					Ceftazidime	Yes	Yes

Abbreviations: F, female; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SSTI, skin and soft-tissue infection.
[a]Patients may have >1 allergy.
[b]Allergies may have >1 reaction type.
[c]Desensitization cases may involve >1 infection.
[d]Desensitization cases may involve >1 causative pathogen.
[e]Concomitant antihistamine therapy.
[f]Concomitant corticosteroid therapy.

Table 2. Desensitization Reaction Details (n = 8).

Patient	Age/Sex/ Number of Allergies	Allergy/Reaction	Indication	Causative Pathogen	Desensitization Antibiotic	Time to Target Dose Reflects Protocol	Signs and Symptoms	Time to Reaction (hours)	Management	Successful
1	46/F/1	Penicillin/Rash	Bacteremia, endocarditis	*Enterococcus* spp	Ampicillin	—	Rash, urticaria	1	Rescue medications,[a] decreased rate of infusion and repeated prior steps	Yes
2	52/M/1	Penicillin/Rash, angioedema	Neurosyphilis	Other	Penicillin	Yes	Rash	8	Rescue medications,[a] repeated last step	Yes
3	36/M/2	Penicillin/ Anaphylaxis	Cystic fibrosis exacerbation	*Achromobacter* spp	Piperacillin/ Tazobactam	No	Rash, urticaria, pruritus	54	None, continued	Yes
34	76/F/2	Ampicillin, Penicillin/ Rash	Bacteremia, endocarditis	*Enterococcus* spp	Ceftriaxone	Yes	Bronchospasm, oxygen desaturation, other	4	Rescue medications,[b] ceftriaxone discontinued	No
34	76/F/2	Ampicillin, Penicillin/ Rash	Bacteremia, endocarditis	*Enterococcus* spp	Ampicillin	No	Bronchospasm	4	None, continued	Yes
35	49/F/6	Amikacin/Rash	Urinary tract infection	*Enterobacteriaceae* spp	Amikacin	—	Urticaria, angioedema, hypotension	2	Rescue medications,[a] amikacin discontinued	No
35[c]	49/F/6	Amikacin/Rash	Urinary tract infection	*Enterobacteriaceae* spp	Amikacin	—	Angioedema, pruritus	5	Rescue medications,[d] extended infusion duration	Yes
36	61/M/1	Penicillin/Urticaria	Neurosyphilis	Other	Penicillin	Yes	Rash, hypotension	11	Rescue medications,[a] continued	Yes[e]

Abbreviations: F, female; M, male.
[a]Diphenhydramine.
[b]Diphenhydramine, methylprednisolone, and epinephrine.
[c]Patient premedicated with acetaminophen, diphenhydramine, and corticosteroids.
[d]Diphenhydramine and methylprednisolone.
[e]Concomitant corticosteroid therapy.

However, our final step would not only mirror the concentration, but also the infusion rate of the actual therapeutic dose. Adapting the final step to mimic the concentration and infusion rate of the actual therapeutic dose provides the assurance of tolerability prior to concluding the desensitization process. Another contrast to previous published studies is our avoidance of standard premedications.[6,9,14] The rationale to discourage the routine use of premedications is to allow accurate and prompt detection of any early signs of reaction. A concern associated with premedicating practice is the expected low rate of mast cell degranulation with the desensitizing antibiotic that may be altered, leading to reduced suppression of IgE receptors.[1,11] There was one patient in our study who at the discretion of the attending physician received premedication after the first failed attempt. Additionally, there were a small number of patients who were receiving corticosteroids and antihistamines for other medical indications prior to admission and during the desensitization process. Although any such use would be considered noncompliant according to our protocols, these patients technically did not receive these medications as premedication and, thus, were still included in our observational study because this may be reflective of real-life circumstances.

The success of the desensitization rate in our study may be explained by embedding the elements of drug-specific pharmacokinetics such as half-life elimination and excretion into each protocol. When establishing the appropriate time to initiate the actual final therapeutic dose of the desensitized antibiotic, consideration of the agent's half-life may be critical. At the conclusion of the last step of each protocol, a significant portion of the antibiotic from the previous steps probably has been metabolized and/or eliminated. Consequently, the total dose of the antibiotic administered for desensitization cannot be regarded as a therapeutic dose. The intent is to avoid a decline in serum concentration of the desensitized antibiotic, which has the potential to provoke breakthrough reactions, requiring termination of the planned treatment. Furthermore, immediately administering a therapeutic dose after the desensitization process may be premature, with the potential to induce drug toxicity, especially in patients with renal insufficiency. Therefore, each of our protocols specifies the start time of the planned therapeutic dose after the successful desensitization, taking into consideration the half-life of each antibiotic.

Another reason for the success rate observed in this study may be the appreciation for the precision of the desensitization process. A total of 15 mL of solution per bag is expected to be discarded within the intravenous tubing at the end of the infusion of each bag. Any remaining solution of a prior bag may impede the timing of the proceeding step of the new bag concentration. As a solution to this concern, our intravenous tubing is exchanged and primed with the new concentration of the subsequent bag prior to the start of each new respective bag concentration. An additional aspect that contributes to the uniqueness of our protocols is utilizing a medication pump for continuous infusions. The pump alarm would sound every 15 minutes, on completion of the infusion rate, reminding the nurse to either increase the rate or switch the bag to a different concentration. This ensures that there are no interruptions in the desensitization process and serves as a guide for the nurse to follow the protocol in a stepwise approach.

The process of desensitization is a resource-intensive intervention that often necessitates the use of an ICU bed and monitoring by physicians, nurses, and pharmacists.[14] Our protocols are constructed with a completion time between 2 and 4 hours. Of note, all 61 cases in our study were desensitized within the time frame noted in the respective protocols. This time frame may provide an advantage to traditional protocols, which could facilitate a shorter ICU and hospital length of stay. A notable feature to highlight in our study is that the utilized desensitization protocols were developed by the department of pharmacy and piloted under the guidance and direction of critical care and infectious diseases attending physicians, in the absence of a formal inpatient immunology service or dedicated immunologist/allergist. Our protocols could potentially be utilized by other hospitals or institutions that might not have an inpatient immunology service. Another important observation was that the safety of 1:2 nurse-to-patient ratio proved to be sufficient with the use of our protocols.

When interpreting the results of this study, there are limitations that should be considered. The eligibility for antibiotic desensitization was guided by clinical history rather than allergy testing. Additionally, details of allergy history were solely dependent on documentation within the electronic health record or patient/family recollection. The majority of allergies were self-reported, with considerable reactions reported as only rash/pruritus. However, the decision for desensitization was based on a thorough assessment of the patient's allergy history and clinical need for antibiotics, between the infectious diseases and critical care attending physicians. There was a possibility that there were patients without a true IgE-mediated allergy who successfully completed our desensitization process. Given the difficulty associated with identifying true Ig-E mediated hypersensitivity reactions and their severe consequences, many physicians are often reluctant to challenge patients with antibiotic agents with any risk of cross-reactivity to their reported allergy, which is most commonly penicillin. Acknowledgment should be given to the possibility that there were more patients desensitized than truly necessary, and the results of our successfulness may be inflated; however, our study is reflective of real-life clinical scenarios. Although penicillin skin testing would have been ideal to test patients with a reported history of Ig-E mediated hypersensitivity reactions, there are several limitations, including availability and applicability. The commercially available PRE-PEN test was not implemented at our institution until

2017 for logistical reasons, and its utility may not be applicable to other antibiotics such as fluoroquinolones and aminoglycosides. Of the 8 desensitization cases with reactions, there were only 2 cases (patient number 34 in Table 2) with a documented allergy to ampicillin, which was reported as a rash. Importantly, the only 2 unsuccessful cases that reacted to the desensitization with anaphylaxis initially reported their respective allergies as only rashes. Our time to the therapeutic or target dose of the desensitized antibiotic reflected the respective protocol in only 19 cases (16 cases in Table 1 and 3 cases in Table 2), which suggests that there are barriers to the initiation of the therapeutic dose at a certain time. This may be explained by the lack of standard computerized physician order entry (CPOE) pathways for our desensitization protocols, including the initiation of the therapeutic dose. However, this limitation did not appear to affect the success and the overall utility of our desensitization protocols. A future direction from our study is to develop individualized CPOE pathways for our desensitization protocols to standardize the process of our order entry. Furthermore, caution is advised when considering the adoption of the desensitization protocol for amikacin, which was designed for a specific patient (patient number 5 in Table 2). Of note, this protocol was only used in one patient, leading to an unsuccessful initial attempt and requiring premedication and extension of the infusion duration for a successful repeat desensitization. Compared to β-lactam antibiotics, amikacin has concentration-dependent pharmacokinetic properties and is dosed according to patient body weight. When considering the use of the amikacin desensitization protocol, modification of the protocol with consideration of the patient weight is strongly advised. In regard to the study design, its retrospective nature poses residual confounding and bias.

Conclusion and Relevance

In this retrospective study of patients desensitized to antibiotics, there was a high rate of success using the continuous infusion protocols developed by our department of pharmacy. Antibiotic-specific properties are incorporated into our protocols to ensure safe and successful desensitization. Additional benefits to these protocols include their comprehensiveness and practicality. Our findings suggest that these antibiotic desensitization protocols are successful and safe. Future studies in patients with positive penicillin skin testing may help validate our findings.

Appendix 1

Amikacin Desensitization Protocol

This is a patient-specific protocol which is not intended for the general population; target dose: 550 mg q12h (7.5 mg/kg q12h).

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction: 50 mg of amikacin in 250 mL of 0.9% sodium chloride (NS)/dextrose 5% in water (D5W). Dilute 500 mg/vial with 10 mL of sterile water for injection (SWFI), mix, and then withdraw 1 mL = 50 mg to dilute with 249 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Amikacin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg
Step 5	60 Minutes	160 mL/h for 15 minutes	8 mg (Total 40 mL)	15.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction: 500 mg of amikacin in 250 mL of D5W/NS. Dilute 500 mg/vial with 10 mL of SWFI, mix, and then dilute with 240 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Amikacin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	25.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	45.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	85.5 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	80 mg (Total 40 mL)	165.5 mg
Step 10	135 Minutes	320 mL/h for 15 minutes	160 mg (Total 80 mL)	325.5 mg
Step 11	150 Minutes	380 mL/h for 15 minutes	190 mg (Total 95 mL)	515.5 mg

- If step number 11 is tolerated, then start therapeutic dose of amikacin 500 mg/250 mL given over 1 hour at 12 hours after completion of the desensitization process.
  - If any steps between steps 1 and 11 get interrupted or missed, then return to 2 steps prior and restart.
- Stability of amikacin is for 24 hours at room temperature (25°C or 77°F).
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 2.75 hours.

Monitoring and management of reactions (standard for all protocols)

- Monitor and document blood pressure and heart rate every 15 minutes starting at 0 minutes.
- Observe for new signs of rash, flushing, wheezing, respiratory distress, angioedema, or anaphylaxis.
- If new rash appears, administer diphenhydramine 50 mg via intravenous piggyback and return to 2 steps prior and restart.
- If respiratory distress or systolic blood pressure falls >20 mm Hg or to < 95 mm Hg, then stop the infusion and notify the physician.
- Keep Epi-Pen 1:1000 (3 mL), hydrocortisone 100 mg, famotidine 20 mg, and diphenhydramine 50 mg vial by bedside.

Appendix 2

Ampicillin Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction for ampicillin (Bag A): 20 mg of ampicillin in 100 mL of NS. Dilute a 1000 mg/vial with 10 mL SWFI, mix well, withdraw 1 mL = 100 mg, dilute with 9 mL of SWFI, and then withdraw 2 mL = 20 mg to dilute with a 98 mL NS bag.

Infusion Instruction: (Prime Tubing With Ampicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction for ampicillin (Bag B): 200 mg of ampicillin in 100 mL of NS. Dilute a 1000 mg/vial with 10 mL SWFI, mix well, and then withdraw 2 mL = 200 mg to dilute with a 98-mL NS bag.

Infusion Instruction: (Prime Tubing With Ampicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	5 mg (Total 2.5 mL)	12.5 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	22.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	42.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	82.5 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	80 mg (Total 40 mL)	162.5 mg

III. Start Infusion of Bag C at Concentration of 20 mg/mL

Reconstitution instruction for ampicillin (Bag C): 2000 mg of ampicillin in 100 mL of NS. Dilute 2 vials of 1000 mg/vial with 20 mL SWFI, mix well, and then dilute with an 80-mL NS bag.

Infusion Instruction: (Prime Tubing With Ampicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	25 mL/h for 15 minutes	125 mg (Total 6.25 mL)	287.5 mg
Step 11	150 Minutes	50 mL/h for 15 minutes	250 mg (Total 12.5 mL)	537.5 mg
Step 12	165 Minutes	100 mL/h for 15 minutes	500 mg (Total 25 mL)	1037.5 mg
Step 13	180 Minutes	200 mL/h for 15 minutes	1000 mg (Total of 50 mL)	2037.5 mg

- If step number 13 is tolerated, then start therapeutic dose in 2 hours given over 30 minutes.
  - If any steps between steps 1 and 13 get interrupted or missed, then return to 2 steps prior and restart.
- Stability of parenteral admixture in NS at room temperature (25°C or 77°F) is 8 hours.
- For desensitization, only use NS as the admixture.
  - If dextrose-containing solutions are used, the resultant solution will only be stable for 2 hours.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3.25 hours

Appendix 3

Ampicillin/Sulbactam Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.03 mg/mL

Reconstitution instruction for ampicillin/sulbactam (Bag A): 1.5 mg of ampicillin/sulbactam in 50 mL of NS. Dilute 1.5 g ampicillin/sulbactam vial with 10 mL of SWFI, mix well, withdraw 1 mL = 150 mg, dilute with 9 mL of SWFI, withdraw 1 mL = 15 mg, dilute with 9 mL of SWFI, and then withdraw 1 mL = 1.5 mg to dilute with 49 mL NS.

Instruction: (Prime Tubing With Ampicillin/Sulbactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.075 mg (Total 2.5 mL)	0.075 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	0.15 mg (Total 5 mL)	0.225 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	0.3 mg (Total 10 mL)	0.525 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	0.6 mg (Total 20 mL)	1.125 mg

II. Start Infusion of Bag B at Concentration of 0.3 mg/mL

Reconstitution instruction for ampicillin/sulbactam (Bag B): 30 mg of ampicillin/sulbactam in 100 mL of NS. Dilute 3-g ampicillin/sulbactam vial with 10 mL of SWFI, mix well, withdraw 1 mL = 300 mg, dilute with 9 mL of SWFI, and then withdraw 1 mL = 30 mg to dilute with a 99 mL NS bag.

Infusion Instruction: (Prime Tubing With Ampicillin/Sulbactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	0.75 mg (Total 2.5 mL)	1.875 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	1.5 mg (Total 5 mL)	3.375 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	3 mg (Total 10 mL)	6.375 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	6 mg (Total 20 mL)	12.375 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	12 mg (Total 40 mL)	24.375 mg

III. Start Infusion of Bag C at Concentration of 3 mg/mL

Reconstitution instruction for ampicillin/sulbactam (Bag C): 300 mg of ampicillin/sulbactam in 100 mL of NS. Dilute 3 g ampicillin/sulbactam vial with 10 mL of SWFI, mix well, and then withdraw 1 mL = 300 mg to dilute with a 99-mL NS bag.

Infusion Instruction: (Prime Tubing With Ampicillin/Sulbactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	20 mL/h for 15 minutes	15 mg (Total 5 mL)	39.375 mg
Step 11	150 Minutes	40 mL/h for 15 minutes	30 mg (Total of 10 mL)	69.375 mg
Step 12	165 Minutes	80 mL/h for 15 minutes	60 mg (Total of 20 mL)	129.375 mg
Step 13	180 Minutes	160 mL/h for 15 minutes	120 mg (Total of 40 mL)	249.375 mg

IV. Start Infusion of Bag D at Concentration of 30 mg/mL

Reconstitution instruction for ampicillin/sulbactam (Bag D): 3000 mg of ampicillin/sulbactam in 100 mL of NS. Dilute 3 g ampicillin/sulbactam vial with 10 mL SWFI, mix well, and dilute with a 90-mL NS bag.

Infusion Instruction: (Prime Tubing With Ampicillin/Sulbactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 14	195 Minutes	10 mL/h for 15 minutes	75 mg (Total of 2.5 mL)	324.375 mg
Step 15	210 Minutes	20 mL/h for 15 minutes	150 mg (Total 5 mL)	474.375 mg
Step 16	225 Minutes	40 mL/h for 15 minutes	300 mg (Total 10 mL)	774.375 mg
Step 17	240 Minutes	80 mL/h for 15 minutes	600 mg (Total 20 mL)	1374.375 mg
Step 18	255 Minutes	160 mL/h for 15 minutes	1200 mg (Total 40 mL)	2574.375 mg

- If step number 18 is tolerated, then start therapeutic dose in 2 hours.
  - If any steps between steps 1 and 18 get interrupted or missed, then return to 2 steps prior and restart.
- After reconstitution, the solution is stable for 8 hours at room temperature (25°C or 77°F) in NS, 2 hours in D5W; recommend using NS for desensitization.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 4.5 hours.

Appendix 4

Cefepime Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction for cefepime (Bag A): 20 mg of cefepime in 100 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL of SWFI, mix well, withdraw 1 mL = 100 mg and dilute with 9 mL of SWFI, and then withdraw 2 mL = 20 mg to dilute with a 98-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Cefepime Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction for cefepime (Bag B): 200 mg of cefepime in 100 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL of SWFI, mix well, and then withdraw 2 mL = 200 mg to dilute with 98 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Cefepime Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	5 mg (Total 2.5 mL)	12.5 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	22.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	42.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	82.5 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	80 mg (Total 40 mL)	162.5 mg

III. Start Infusion of Bag C at Concentration of 20 mg/mL

Reconstitution instruction for cefepime (Bag C): 2000 mg of cefepime in 100 mL of D5W/NS. Dilute 2 vials of 1000 mg/vial of cefepime with 20 mL SWFI, mix well, and then dilute with an 80-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Cefepime Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	30 mL/h for 15 minutes	150 mg (Total 7.5 mL)	312.5 mg
Step 11	150 Minutes	60 mL/h for 15 minutes	300 mg (Total 15 mL)	612.5 mg
Step 12	165 Minutes	120 mL/h for 15 minutes	600 mg (Total 30 mL)	1212.5 mg

- If step number 12 is tolerated, then start therapeutic dose in 2 hours.
  - If any steps between steps 1 and 12 get interrupted or missed, then return to 2 steps prior and restart.
- Stable in NS, D5W, and a variety of other solutions for 24 hours at room temperature (25°C or 77°F) and 7 days refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3 hours.

Appendix 5

Ceftaroline Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.24 mg/mL

Reconstitution instruction for ceftaroline (Bag A): 60 mg of ceftaroline in 250 mL D5W/NS. Dilute the 600 mg/vial with 20 mL SWFI, mix well, and then withdraw 2 mL = 60 mg to dilute with a 248-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Ceftaroline Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.6 mg (Total 2.5 mL)	0.6 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1.2 mg (Total 5 mL)	1.8 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2.4 mg (Total 10 mL)	4.2 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4.8 mg (Total 20 mL)	9 mg
Step 5	60 Minutes	160 mL/h for 15 minutes	9.6 mg (Total 40 mL)	18.6 mg

II. Start Infusion of Bag B at Concentration of (2.4 mg/mL)

Reconstitution instruction for ceftaroline (Bag B): 600 mg of ceftaroline in 250 mL of D5W/NS. Dilute the 600 mg/vial dilute with 20 mL SWFI, mix well, and then withdraw 20 mL to dilute with 230 mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Ceftaroline Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 6	75 Minutes	20 mL/h for 15 minutes	12 mg (Total 5 mL)	30.6 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	24 mg (Total 10 mL)	54.6 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	48 mg (Total 20 mL)	102.6 mg
Step 9	120 Minutes	100 mL/h for 15 minutes	96 mg (Total 25 mL)	198.6 mg
Step 10	135 Minutes	200 mL/h for 15 minutes	192 mg (Total 50 mL)	390.6 mg

- If step number 10 is tolerated, then start therapeutic dose in 1 hour given over 30 minutes.
  - If any steps between steps 1 and 10 gets interrupted or missed, then return to 2 steps prior and restart.
- Use within 6 hours at room temperature (25°C or 77°F) or within 24 hours if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 2.5 hours.

Appendix 6

Ceftazidime Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction for ceftazidime (Bag A): 20 mg of ceftazidime in 100 mL of D5W/NS. Dilute 500 mg/vial with 10 mL of SWFI, mix well, withdraw 1 mL = 50 mg, dilute with 9 mL of SWFI, and then withdraw 4 mL = 20 mg to dilute with 96-mL D5W/NS.

Infusion Instruction: (Prime Tubing With Ceftazidime Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction for ceftazidime (Bag B): 200 mg of ceftazidime in 100 mL of D5W/NS. Dilute 500 mg/vial with 10 mL of SWFI, mix well, and then withdraw 4 mL = 200 mg to dilute with 96 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Ceftazidime Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	5 mg (Total 2.5 mL)	12.5 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	22.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	42.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	82.5 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	80 mg (Total 40 mL)	162.5 mg

III. Start Infusion of Bag C at Concentration of 20 mg/mL

Reconstitution instruction for ceftazidime (Bag C): 2000 mg of ceftazidime in 100 mL of D5W/NS. Dilute 2 vials of 1000 mg/vial of ceftazidime with 20 mL SWFI, mix well, and then withdraw 20 mL and dilute with 80 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Ceftazidime Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	30 mL/h for 15 minutes	150 mg (Total 7.5 mL)	312.5 mg
Step 11	150 Minutes	60 mL/h for 15 minutes	300 mg (Total 15 mL)	612.5 mg
Step 12	165 Minutes	120 mL/h for 15 minutes	600 mg (Total 30 mL)	1212.5 mg

- If step number 12 is tolerated, then start therapeutic dose in 2 hours.
  - If any steps between steps 1 and 12 get interrupted or missed, then return to 2 steps prior and restart.
- Diluted solution may be stored for 24 hours at room temperature (25°C or 77°F) or for 7 days if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3 hours.

Appendix 7

Ceftolozane/Tazobactam Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.015 mg/mL

Reconstitution instruction for ceftolozane/tazobactam (Bag A): 1.5 mg of ceftolozane/tazobactam in 100 mL of D5W/NS. Dilute 1.5 g ceftolozane/tazobactam vial with 10 mL of SWFI, mix well, withdraw 1 mL = 150 mg, dilute with 9 mL of SWFI, withdraw 1 mL = 15 mg, dilute with 9 mL of SWFI, and then withdraw 1 mL = 1.5 mg to dilute with 99 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Ceftolozane/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.0375 mg (Total 2.5 mL)	0.0375 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	0.075 mg (Total 5 mL)	0.1125 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	0.15 mg (Total 10 mL)	0.263 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	0.3 mg (Total 20 mL)	0.563 mg

II. Start Infusion of Bag B at Concentration of 0.15 mg/mL

Reconstitution instruction for ceftolozane/tazobactam (Bag B): 15 mg of ceftolozane/tazobactam in 100 mL of D5W/NS. Dilute 1.5 g ceftolozane/tazobactam vial with 10 mL of SWFI, mix well, withdraw 1 mL = 150 mg, dilute with 9 mL of SWFI, and then withdraw 1 mL = 15 mg to dilute with a 99-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Ceftolozane/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	0.375 mg (Total 2.5 mL)	0.938 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	0.75 mg (Total 5 mL)	1.688 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	1.5 mg (Total 10 mL)	3.188 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	3 mg (Total 20 mL)	6.188 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	6 mg (Total 40 mL)	12.188 mg

III. Start Infusion of Bag C at Concentration of 1.5 mg/mL

Reconstitution instruction for ceftolozane/tazobactam (Bag C): 150 mg of ceftolozane/tazobactam in 100 mL of D5W/NS. Dilute 1.5 g ceftolozane/tazobactam vial with 10 mL of SWFI, mix well, and then withdraw 1 mL = 150 mg to dilute with a 99-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Ceftolozane/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	20 mL/h for 15 minutes	7.5 mg (Total 5 mL)	19.688 mg
Step 11	150 Minutes	40 mL/h for 15 minutes	15 mg (Total of 10 mL)	34.688 mg
Step 12	165 Minutes	80 mL/h for 15 minutes	30 mg (Total of 20 mL)	64.688 mg
Step 13	180 Minutes	160 mL/h for 15 minutes	60 mg (Total of 40 mL)	124.688 mg

IV. Start Infusion of Bag D at Concentration of 15 mg/mL

Reconstitution instruction for ceftolozane/tazobactam (Bag D): 1500 mg of ceftolozane/tazobactam in 100 mL of D5W/NS. Dilute 1.5 g ceftolozane/tazobactam vial with 10 mL SWFI, mix well, and then dilute with 90 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Ceftolozane/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 14	195 Minutes	10 mL/h for 15 minutes	37.5 mg (Total of 2.5 mL)	162.188 mg
Step 15	210 Minutes	20 mL/h for 15 minutes	75 mg (Total 5 mL)	237.188 mg
Step 16	225 Minutes	40 mL/h for 15 minutes	150 mg (Total 10 mL)	387.188 mg
Step 17	240 Minutes	80 mL/h for 15 minutes	300 mg (Total 20 mL)	687.188 mg
Step 18	255 Minutes	160 mL/h for 15 minutes	600 mg (Total 40 mL)	1287.188 mg

- If step number 18 is tolerated, then start therapeutic dose in 2 hours.
  - If any steps between steps 1 and 18 get interrupted or missed, then return to 2 steps prior and restart.
- Diluted solution may be stored for 24 hours at room temperature (25°C or 77°F) or for 7 days if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 4.5 hours.

Appendix 8

Ceftriaxone Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction: 10 mg of ceftriaxone with 50 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL SWFI, mix well, withdraw 1 mL = 100 mg, dilute with 9 mL of SWFI, and then withdraw 1 mL = 10 mg to dilute with a 49-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Ceftriaxone Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction: 100 mg of ceftriaxone in 50 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL SWFI, mix well, and then withdraw 1 mL = 100 mg to dilute with 49 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Ceftriaxone Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	5 mg (Total 2.5 mL)	12.5 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	22.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	42.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	82.5 mg

III. Start Infusion of Bag C at Concentration of 20 mg/mL

Reconstitution instruction: 2000 mg of ceftriaxone in 100 mL of D5W/NS. Dilute 2 vials of 1000 mg/vial with 20 mL SWFI, mix well, and then dilute with an 80-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Ceftriaxone Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 9	120 Minutes	10 mL/h for 15 minutes	50 mg (Total 2.5 mL)	132.5 mg
Step 10	135 Minutes	25 mL/h for 15 minutes	125 mg (Total 6.25 mL)	257.5 mg
Step 11	150 Minutes	50 mL/h for 15 minutes	250 mg (Total 12.5 mL)	507.5 mg
Step 12	165 Minutes	100 mL/h for 15 minutes	500 mg (Total 25 mL)	1007.5 mg

- If step number 12 is tolerated, then start therapeutic dose in 5 hours.
  - If any steps between steps 1 and 12 gets interrupted or missed, then return to 2 steps prior and restart.
- For concentrations 10-40 mg/mL reconstituted in D5W, NS, or SWFI, stable for 2 days at room temperature (25°C or 77°F) or for 10 days if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3 hours.

Appendix 9

Imipenem-Cilastatin Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.4 mg/mL

Reconstitution instruction for imipenem-cilastatin (Bag A): 100 mg of imipenem-cilastatin in 250 mL of D5W/NS. Dilute 500 mg/vial with 10 mL of SWFI, mix well, and then withdraw 2 mL = 100 mg to dilute with 248 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Imipenem-Cilastatin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	1 mg (Total 2.5 mL)	1 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	2 mg (Total 5 mL)	3 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	4 mg (Total 10 mL)	7 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	8 mg (Total 20 mL)	15 mg

II. Start Infusion of Bag B at Concentration of 4 mg/mL

Reconstitution instruction for imipenem-cilastatin (Bag B): 1000 mg of imipenem-cilastatin in 250 mL of D5W/NS. Dilute 2 vials of 500 mg/vial with 20 mL of SWFI, mix well, and then dilute with 230 mL of D5W/NS.

Infusion Instruction: (Prime Tubing With Imipenem-Cilastatin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	10 mg (Total 2.5 mL)	25 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	20 mg (Total 5 mL)	45 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	40 mg (Total 10 mL)	85 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	80 mg (Total 20 mL)	165 mg
Step 9	120 Minutes	100 mL/h for 15 minutes	100 mg (Total 25 mL)	265 mg
Step 10	135 Minutes	200 mL/h for 15 minutes	200 mg (Total 50 mL)	465 mg

- If step number 10 is tolerated, then start therapeutic dose in 1 hour.
  - If any steps between steps 1-10 get interrupted or missed, then return to 2 steps prior and restart.
- Reconstituted solution is stable for 4 hours at room temperature (25°C or 77°F) or 24 hours when refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 2.5 hours.

Appendix 10

Levofloxacin Desensitization Protocol

I. Start Infusion of Bag A at Concentration of (0.02 mg/mL)

Reconstitution instruction for levofloxacin (Bag A): 5 mg of levofloxacin in 250 mL of D5W. Withdraw 1 mL (5 mg) from the 500 mg/100 mL D5W levofloxacin premixed bag and inject into a 249 mL of D5W.

Infusion Instruction: (Prime Tubing With Levofloxacin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.05 mg (Total 2.5 mL)	0.05 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	0.1 mg (Total 5 mL)	0.15 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	0.2 mg (Total 10 mL)	0.35 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	0.4 mg (Total 20 mL)	0.75 mg

II. Start Infusion of Bag B at Concentration of (0.5 mg/mL)

Reconstitution instruction for levofloxacin (Bag B): 50 mg of levofloxacin in 100 mL of D5W. Withdraw 10 mL (50 mg) from the 500 mg/100 mL D5W of levofloxacin premixed bag and inject into 90 mL of D5W.

Infusion Instruction: (Prime Tubing With Levofloxacin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	1.25 mg (Total 2.5 mL)	2 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	2.5 mg (Total 5 mL)	4.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	5 mg (Total 10 mL)	9.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	10 mg (Total 20 mL)	19.5 mg

III. Start Infusion of Bag C at Concentration of (5 mg/mL)

Reconstitution instruction: premixed levofloxacin 500 mg/100 mL D5W

Infusion Instruction: (Prime Tubing With Levofloxacin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 9	120 Minutes	10 mL/h for 15 minutes	12.5 (Total 2.5 mL)	32 mg
Step 10	135 Minutes	20 mL/h for 15 minutes	25 mg (Total 5 mL)	57 mg
Step 11	150 Minutes	50 mL/h for 15 minutes	62.5 mg (Total 12.5 mL)	119.5 mg
Step 12	165 Minutes	100 mL/h for 15 minutes	125 mg (Total 25 mL)	244.5 mg
Step 13	180 Minutes	200 mL/h for 10 minutes	166 mg (Total 33 mL)	410.5 mg

- If step number 13 is tolerated, then start therapeutic dose in 6 hours given over 60 minutes.
  - If any steps between steps 1 and 13 gets interrupted or missed, then return to 2 steps prior and restart.
- Diluted solution (5 mg/mL) is stable in NS and D5W for 72 hours when stored at room temperature (25°C or 77°F) and for 14 days if refrigerated. Protect from light.
- Total time for desensitization is 3.25 hours.

Appendix 11

Meropenem Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.4 mg/mL

Reconstitution instruction for meropenem (Bag A): 100 mg of meropenem in 250 mL of NS. Dilute 500 mg/vial with 10 mL of SWFI, mix well, and then withdraw 2 mL = 100 mg to dilute with a 248-NS bag.

Infusion Instruction: (Prime Tubing With Meropenem Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	1 mg (Total 2.5 mL)	1 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	2 mg (Total 5 mL)	3 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	4 mg (Total 10 mL)	7 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	8 mg (Total 20 mL)	15 mg

II. Start Infusion of Bag B at Concentration of 4 mg/mL

Reconstitution instruction for meropenem (Bag B): 1000 mg of meropenem in 250 mL of NS. Dilute 2 vials of 500 mg/vial with 20 mL of SWFI, mix well, and then withdraw 20 mL to dilute with 230 mL of NS.

Infusion Instruction: (Prime Tubing With Meropenem Solution).

Step Number	Time	Rate of Infusion	Dosed Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	10 mg (Total 2.5 mL)	25 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	20 mg (Total 5 mL)	45 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	40 mg (Total 10 mL)	85 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	80 mg (Total 20 mL)	165 mg
Step 9	120 Minutes	100 mL/h for 15 minutes	100 mg (Total 25 mL)	265 mg
Step 10	135 Minutes	200 mL/h for 15 minutes	200 mg (Total 50 mL)	465 mg
Step 11	150 Minutes	400 mL/h for 15 minutes	400 mg (Total 100 mL)	865 mg

- If step number 11 is tolerated, then start therapeutic dose in 1 hour.
  - If any steps between steps 1 and 11 get interrupted or missed, then return to 2 steps prior and restart.
- When diluted to 1 to 20 mg/mL in NS, the solution is stable for 1 hour at up to 25°C (77°F) or for 15 hours if refrigerated. Recommended to use NS for desensitization.
- When reconstituted to 50 mg/mL with SWFI, the solution is stable for 3 hours at up to 25°C (77°F) or for up to 13 hours if refrigerated.
- Solution reconstituted with D5W should be used immediately.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 2.75 hours.

Appendix 12

Nafcillin Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction: 20 mg of nafcillin with 100 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL SWFI, mix well, withdraw 1 mL = 100 mg, dilute with 9 mL of SWFI, and then withdraw 2 mL = 20 mg to dilute with 98 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Nafcillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction: 200 mg of nafcillin in 100 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL SWFI, mix well, and then withdraw 2 mL = 200 mg to dilute with 98 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Nafcillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	5 mg (Total 2.5 mL)	12.5 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	22.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	42.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	82.5 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	80 mg (Total 40 mL)	162.5 mg

III. Start Infusion of Bag C at Concentration of 20 mg/mL

Reconstitution instruction: 2000 mg of nafcillin in 100 mL of D5W/NS. Dilute 2 vials of 1000 mg/vial with 20 mL SWFI, mix well, and then withdraw 20 mL to dilute with 80 mL D5W/NS

Infusion Instruction: (Prime Tubing With Nafcillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	25 mL/h for 15 minutes	125 mg (Total 6.25 mL)	287.5 mg
Step 11	150 Minutes	50 mL/h for 15 minutes	250 mg (Total 12.5 mL)	537.5 mg
Step 12	165 Minutes	100mL/h for 15 minutes	500 mg (Total 25 mL)	1037.5 mg
Step 13	180 Minutes	200 mL/h for 15 minutes	1000 mg (Total of 50 mL)	2037.5 mg

- If step number 13 is tolerated, then start therapeutic dose in 1 hour given over 30 minutes.
  - If any steps between steps 1 and 13 gets interrupted or missed, then return to 2 steps prior and restart.
- Solution in NS or D5W is stable for 24 hours at room temperature (25°C or 77°F) and 7 days if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3.25 hours.

Appendix 13

Oxacillin Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.2 mg/mL

Reconstitution instruction: 20 mg of oxacillin with 100 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL SWFI, mix well, withdraw 1 mL = 100 mg, dilute with 9 mL of SWFI, and then withdraw 2 mL = 20 mg to dilute with a 98-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Oxacillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.5 mg (Total 2.5 mL)	0.5 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	1 mg (Total 5 mL)	1.5 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	2 mg (Total 10 mL)	3.5 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	4 mg (Total 20 mL)	7.5 mg

II. Start Infusion of Bag B at Concentration of 2 mg/mL

Reconstitution instruction: 200 mg of oxacillin in 100 mL of D5W/NS. Dilute 1000 mg/vial with 10 mL SWFI, mix well, and then withdraw 2 mL = 200 mg to dilute with a 98-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Oxacillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	5 mg (Total 2.5 mL)	12.5 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	10 mg (Total 5 mL)	22.5 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	20 mg (Total 10 mL)	42.5 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	40 mg (Total 20 mL)	82.5 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	80 mg (Total 40 mL)	162.5 mg

III. Start Infusion of Bag C at Concentration of 20 mg/mL

Reconstitution instruction: 2000 mg of oxacillin in 100 mL of D5W/NS. Dilute 2 vials of 1000 mg/vial with 20 mL SWFI, mix well, and then withdraw 20 mL to dilute with 80 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Oxacillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	25 mL/h for 15 minutes	125 mg (Total 6.25 mL)	287.5 mg
Step 11	150 Minutes	50 mL/h for 15 minutes	250 mg (Total 12.5 mL)	537.5 mg
Step 12	165 Minutes	100mL/h for 15 minutes	500 mg (Total 25 mL)	1037.5 mg
Step 13	180 Minutes	200 mL/h for 15 minutes	1000 mg (Total of 50 mL)	2037.5 mg

- If step number 13 is tolerated, then start therapeutic dose in 1 hour given over 30 minutes.
  - If any steps between steps 1 and 13 gets interrupted or missed, then return to 2 steps prior and restart.
- Solution reconstituted in NS or D5W is stable for 24 hours at room temperature (25°C or 77°F) and 7 days if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3.25 hours.

Appendix 14

Penicillin G Desensitization Protocol

5 million unit = 3000 mg.

I. Start Infusion of Bag A at Concentration of 0.03 mg/mL

Reconstitution instruction for penicillin G (Bag A): 3 mg of penicillin in 100 mL of D5W/NS. Dilute 5 million unit penicillin G vial = 3000 mg with 10 mL of SWFI, mix well, withdraw 1 mL = 300 mg to dilute with 9 mL of SWFI, withdraw 1 mL = 30 mg to dilute with 9 mL of SWFI, and then withdraw 1 mL = 3 mg to dilute with 99 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Penicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	0.075 mg (Total 2.5 mL)	0.075 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	0.15 mg (Total 5 mL)	0.225 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	0.3 mg (Total 10 mL)	0.525 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	0.6 mg (Total 20 mL)	1.125 mg

II. Start Infusion of Bag B at Concentration of 0.3 mg/mL

Reconstitution instruction for penicillin G (Bag B): 30 mg of penicillin in 100 mL of D5W/NS. Dilute 5 million unit penicillin G vial = 3000 mg with 10 mL of SWFI, mix well, withdraw 1 mL = 300 mg to dilute with 9 mL of SWFI, and then withdraw 1 mL = 30 mg to dilute with 99 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Penicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	0.75 mg (Total 2.5 mL)	1.875 mg
Step 5	75 Minutes	20 mL/h for 15 minutes	1.5 mg (Total 5 mL)	3.375 mg
Step 6	90 Minutes	40 mL/h for 15 minutes	3 mg (Total 10 mL)	6.375 mg
Step 7	105 Minutes	80 mL/h for 15 minutes	6 mg (Total 20 mL)	12.375 mg
Step 8	120 Minutes	160 mL/h for 15 minutes	12 mg (Total 40 mL)	24.375 mg

III. Start Infusion of Bag C at Concentration of 3 mg/mL

Reconstitution instruction for penicillin G (Bag C): 300 mg of penicillin in 100 mL of D5W/NS. Dilute 5 million unit penicillin G vial = 3000 mg with 10 mL of SWFI, mix well, and then withdraw 1 mL = 300 mg to dilute with 99-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Penicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 9	135 Minutes	10 mL/h for 15 minutes	7.5 mg (Total of 2.5 mL)	31.875 mg
Step 10	150 Minutes	20 mL/h for 15 minutes	15 mg (Total 5 mL)	46.875 mg
Step 11	160 Minutes	40 mL/h for 15 minutes	30 mg (Total of 10 mL)	76.875 mg
Step 12	175 Minutes	80 mL/h for 15 minutes	60 mg (Total of 20 mL)	136.875 mg
Step 13	190 Minutes	160 mL/h for 15 minutes	120 mg (Total of 40 mL)	256.875 mg

IV. Start Infusion of Bag D at Concentration of 30 mg/mL

Reconstitution instruction for penicillin G (Bag D): 3000 mg of penicillin in 100 mL of D5W/NS. Dilute 5 million unit penicillin G vial = 3000 mg with 10 mL SWFI, mix well, and dilute with a 90-mL D5W/NS bag.

Infusion Instruction: (Prime Tubing With Penicillin Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 14	205 Minutes	10 mL/h for 15 minutes	75 mg (Total of 2.5 mL)	331.875 mg
Step 15	220 Minutes	20 mL/h for 15 minutes	150 mg (Total 5 mL)	481.875 mg
Step 16	235 Minutes	40 mL/h for 15 minutes	300 mg (Total 10 mL)	781.875 mg
Step 17	250 Minutes	80 mL/h for 15 minutes	600 mg (Total 20 mL)	1381.875 mg
Step 18	265 Minutes	160 mL/h for 15 minutes	1200 mg (Total 40 mL)	2581.875 mg

- If step number 18 is tolerated, then start therapeutic dose in 1 hour.
  - If any steps between steps 1 and 18 get interrupted or missed, then return to 2 steps prior and restart.
- After reconstitution, the solution is stable for 24 hours at room temperature (25°C or 77°F).
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 4.5 hours.

Appendix 15

Piperacillin/Tazobactam Desensitization Protocol

I. Start Infusion of Bag A at Concentration of 0.4 mg/mL

Reconstitution instruction for piperacillin/tazobactam (Bag A): 40.5 mg of piperacillin/tazobactam in 100 mL of D5W/NS. Dilute 3.375 g (3375 mg) of piperacillin/tazobactam with 10 mL of SWFI, mix well, withdraw 1 mL = 337.5 mg to dilute with 9 mL of SWFI, and then withdraw 1.2 mL = 40.5 mg to dilute with 98.8 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Piperacillin/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 1	0 Minutes	10 mL/h for 15 minutes	1 mg (Total 2.5 mL)	1 mg
Step 2	15 Minutes	20 mL/h for 15 minutes	2 mg (Total 5 mL)	3 mg
Step 3	30 Minutes	40 mL/h for 15 minutes	4 mg (Total 10 mL)	7 mg
Step 4	45 Minutes	80 mL/h for 15 minutes	8 mg (Total 20 mL)	15 mg

II. Start Infusion of Bag B at Concentration of 4 mg/mL

Reconstitution instruction for piperacillin/tazobactam (Bag B): 405 mg of piperacillin/tazobactam in 100 mL of D5W/NS. Dilute 3.375 g (3375 mg) of piperacillin/tazobactam with 10 mL of SWFI, mix well, and then withdraw 1.2 mL = 405 mg to dilute with 98.8 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Piperacillin/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 5	60 Minutes	10 mL/h for 15 minutes	10 mg (Total of 2.5 mL)	25 mg
Step 6	75 Minutes	20 mL/h for 15 minutes	20 mg (Total 5 mL)	45 mg
Step 7	90 Minutes	40 mL/h for 15 minutes	40 mg (Total 10 mL)	85 mg
Step 8	105 Minutes	80 mL/h for 15 minutes	80 mg (Total 20 mL)	165 mg
Step 9	120 Minutes	160 mL/h for 15 minutes	160 mg (Total 40 mL)	325 mg

III. Start Infusion of Bag C at Concentration of 33.8 mg/mL

Reconstitution instruction for piperacillin/tazobactam (Bag C): 3375 mg of piperacillin/tazobactam in 100 mL of D5W/NS. Dilute 3.375 g (3375 mg) of piperacillin/tazobactam with 10 mL SWFI, mix well, and then dilute with 90 mL D5W/NS.

Infusion Instruction: (Prime Tubing With Piperacillin/Tazobactam Solution).

Step Number	Time	Rate of Infusion	Dose Delivered	Accumulated Dose
Step 10	135 Minutes	10 mL/h for 15 minutes	84.5 mg (Total of 2.5 mL)	409.5 mg
Step 11	150 Minutes	20 mL/h for 15 minutes	169 mg (Total 5 mL)	578.5 mg
Step 12	165 Minutes	40 mL/h for 15 minutes	338 mg (Total 10 mL)	916.5 mg
Step 13	180 Minutes	80 mL/h for 15 minutes	676 mg (Total 20 mL)	1592.5 mg
Step 14	195 Minutes	160 mL/h for 15 minutes	1352 mg (Total 40 mL)	2944.5 mg

- If step number 14 is tolerated, then start therapeutic dose in 1 hour.
  - If any steps between steps 1 and 14 get interrupted or missed, then return to 2 steps prior and restart.
- After reconstitution, the solution is stable for 24 hours at room temperature (25°C or 77°F) or for 48 hours if refrigerated.
- Reconstitution instruction does not take into account overfill volume.
- Total time for desensitization is 3.5 hours.

Authors' Note

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