Successful rapid liposomal amphotericin B desensitization in pediatric case series

Cankat Genis, M.D., Zeynep Sengul Emeksiz, M.D., Sule Buyuk Yaylatokgil, M.D., Tayfur Ginis, M.D., Candan Islamoglu, M.D., and Emine Dibek Misirlioglu, M.D.

ABSTRACT

Background: *Liposomal amphotericin B (LAMB) is a crucial agent in the treatment of invasive fungal diseases caused by a wide variety of yeasts and molds. In the presence of an infection caused by a fungal agent resistant to alternative antifungal drugs, desensitization may be the only option to continue treatment. However, there is insufficient information and consensus with regard to amphotericin B desensitization protocols in the pediatric age group.*

Objective: *We present our experience with five cases of patients in whom successful desensitization protocols were applied with LAMB, along with a review of the literature on pediatric cases. We also provide a sample desensitization protocol that we successfully applied.*

Methods: *Pediatric patients who continued their treatment with the successful rapid desensitization protocol conducted at the Paediatric Allergy and Immunology Clinic of the Ministry of Health Ankara City Hospital between September 2019 and September 2023 were examined. Desensitization protocols were applied based on Castells' desensitization protocol.*

Results: *Five patients ages between 5 and 12 years were referred to us due to the development of anaphylaxis during their treatment with LAMB. Anaphylaxis is diagnosed clinically, according to the European Academy of Allergy and Clinical Immunology guidelines: anaphylaxis (2021 update). A 16-step desensitization protocol was prepared by using LAMB solutions at four different dilutions (0.001, 0.01, 0.1, and 1 mg/mL). Each solution consisted of four steps, with a 15-minute infusion for each step. The patients were premedicated with 1 mg/kg/dose methylprednisolone and an antihistamine.*

Conclusion: *The data we present on the successful application of a sample protocol to five cases, particularly in a pediatric setting, are noteworthy valuable contributions to the field, which demonstrates the feasibility and success of rapid desensitization with LAMB in pediatric patients. This can provide important insights and potentially serve as a reference for medical professionals working with similar cases in the future.*

(Allergy Asthma Proc 45:201–206, 2024; doi: 10.2500/aap.2024.45.240008)

Liposomal amphotericin B (LAMB) is a crucial agent in the treatment of invasive fungal diseases caused by a wide variety of yeasts and molds. In addition to marked nephrotoxicity, amphotericin B has several adverse effects, including hepatotoxicity, hypokalemia, and infusion-related reactions (fever, chills, myalgia, nausea, vomiting, tachycardia, and hypertension).[1] This has accelerated the development of less toxic new formulations. LAMB is a form of amphotericin B that preserves its antifungal activity while markedly reducing its toxicity.[1,2]

LAMB is a treatment option for which allergic and anaphylactic reactions are rarely observed. In a study that evaluated reactions related to 141 LAMB treatment courses applied to 84 pediatric patients over 3 years, two cases of patients with anaphylaxis (1.4%) were reported.[3] When such reactions occur, it is generally preferable to continue treatment with other antifungal drugs, such as caspofungin or voriconazole. However, in the presence of an infection caused by a fungal agent resistant to such alternative antifungal drugs, zygomycetes infections, kala-azar, and children experiencing anaphylaxis with LAMB during the course of neutropenic fever, desensitization may be the only option to continue treatment.[4]

Although desensitization protocols have been successfully applied in case series for commonly used antibiotics (*e.g.*, penicillin and cephalosporins), chemotherapeutic agents, antituberculosis drugs, nonsteroidal anti-inflammatory drugs, monoclonal antibodies, and vaccines), according to the literature, there are limited data on desensitization protocols for LAMB, which is essential for the treatment of invasive fungal sepsis.[5] In this study, we present our experience with five cases of patients for whom a successful desensitization protocol was applied with LAMB, along with a review of the literature on pediatric cases. We also provide a sample desensitization protocol that we successfully applied.

From the Department of Paediatric Allergy and Immunology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey
No external funding sources reported
The authors have no conflicts of interest to declare pertaining to this article
Supplemental data available at www.IngentaConnect.com
Address correspondence to Cankat Geniş, M.D., Department of Paediatric Allergy and Immunology, University of Health Sciences, Ankara City Hospital, Ankara 06800, Turkey
E-mail address: cankatgenis@gmail.com
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METHODS

In this retrospective study, pediatric patients who continued their treatment with the successful rapid desensitization protocol conducted at the Paediatric Allergy and Immunology Clinic of the Ministry of Health Ankara City Hospital, Turkey, between September 2019 and September 2023 were examined. An anaphylaxis diagnosis was established according to the diagnostic criteria of the European Academy of Allergy and Clinical Immunology (EAACI).[6] Patients ages >18 years, those who did not meet the EAACI[6] diagnostic criteria for anaphylaxis, and those whose rapid desensitization was unsuccessful were excluded from the study.

The medical records of the included patients were examined to gather information on demographic characteristics, medical history, diagnoses, criteria that led to anaphylaxis diagnosis, treatments administered for anaphylaxis, the desensitization protocols applied, and the number of successful doses of amphotericin B administered after desensitization. Amphotericin B was administered to all the patients as an intravenous infusion of 5 mg/kg/dose from the same LAMB brand.

In this study, protocols were performed based on Castells' desensitization protocol.[7] The researchers recommend a 12-step protocol with three dilutions for most patients but a 16-step protocol with four dilutions for individuals who are highly sensitive.[7] According to the study by Broyles *et al*.[8] recommended desensitization protocol for immediate reactions, a 16-step protocol should be applied to patients who experience grade 3 reactions, including anaphylaxis, who are at a higher risk during desensitization. Our patients' reactions were classified as grade 3 in severity, according to the grading system for generalized hypersensitivity by Brown.[9] Hence, the 16-step desensitization protocol was applied to all the individuals.

In this study, the primary outcome was the success of the rapid desensitization protocol, whereas the secondary outcomes were evaluated based on the number of amphotericin B doses administered without issues after the protocol. Approval for the study was obtained from the ethics committee of the Ministry of Health Ankara City Hospital, Republic of Turkey (approval E2-23–5047).

RESULTS

Between 2019 and 2023, five patients ages between 5 and 12 years, three with hematologic malignancies, one with tuberculosis meningitis, and one with chronic granulomatous disease were referred to us due to the development of anaphylaxis during their LAMB treatment. Anaphylaxis was diagnosed clinically when considering the EAACI criteria.[6] Due to the absence of alternative drugs after anaphylaxis, the initiation of amphotericin B desensitization created a clinical urgency for treatment continuation and this circumstance prevented additional tests. Hence, we were unable to conduct nonirritant prick and intradermal tests with amphotericin B to confirm immunoglobulin E related hypersensitivity reactions. Rapid amphotericin B desensitization proved successful in all the patients, and they completed their treatments with a total of 28–70 doses of amphotericin B. None of the patients required readministration of amphotericin B after completing the treatment. In addition, all the patients had severe chronic illnesses; therefore, they were not subjected to challenges to confirm anaphylaxis.

All the patients underwent a comprehensive evaluation for infectious diseases, and it was determined that alternative antifungal agents would not provide sufficient efficacy in the treatment of the current infection. The emphasis on amphotericin B being the sole option in the treatment indicated the necessity of continuing treatment with this drug. Given the history of anaphylaxis with amphotericin B in all the patients, desensitization was the only appropriate option, and continuation of treatment with a rapid desensitization protocol was planned. The clinical characteristics of the patients are summarized in Table 1.

Before the procedure, all the patients' parents were informed about the treatment, and their written consent was obtained. Desensitization was conducted in a suitable environment with the necessary emergency intervention conditions and under the direct supervision of health-care personnel trained to manage reactions.

A 16-step desensitization protocol was prepared by using LAMB solutions at four different dilutions (0.001, 0.01, 0.1, and 1 mg/mL). Each solution consisted of four steps, with a 15-minute infusion for each step. The desensitization protocol was successfully implemented without any adverse events, which allowed the patients to complete their treatment without any observed allergic reactions. An example of a successful desensitization protocol applied to a 10-year-old, 33-kg patient diagnosed with Burkitt lymphoma is provided in Table 2. The patient received a total of 45 doses of LAMB without any reaction and successfully completed the treatment. The patient was premedicated with 1 mg/kg/dose of methylprednisolone and an antihistamine. The desensitization protocol for the other four patients involved adjusting the methylprednisolone dose from the existing treatment protocol to before desensitization and adding an antihistamine as part of the premedication process. Each vial of LAMB contains 50 mg in 12.5 mL, which means that it has a concentration of 4 mg/mL. The

Table 1 **Clinical characteristics of patients undergoing desensitization**

Patient No.	Gender	Age, y	Diagnosis	Clinical Symptoms of Anaphylaxis	Treatment Applied for Anaphylaxis	Success of Desensitization Protocol	No. Successful Doses After Desensitization
1	Male	12	Tuberculosis meningitis	Hypotension, vomiting, sudden urgency for defecation (on the second day, the 10th minute of the dose)	Adrenaline, methylprednisolone, and an intravenous saline solution fluid load	Successful	33
2	Female	10	Burkitt lymphoma	Urticaria, dyspnea, desaturation (on the first day, the 5th minute of the dose)	Adrenaline	Successful	45
3	Male	5	Aplastic anemia	Urticaria, vomiting, shortness of breath, tachypnea (on the fifth day, the 10th minute of the dose)	Adrenaline	Successful	70
4	Male	10	Chronic granulomatous disease plus miliary tuberculosis plus intracranial aspergillosis	Angioedema, desaturation, shortness of breath, tachypnea (on the first day, the 5th minute of the dose)	Adrenaline, methylprednisolone, antihistamine	Successful	46
5	Male	10	Acute lymphoblastic leukemia	Urticaria, shortness of breath, coughing (on the first day, the 3rd minute of the dose)	Adrenaline, methylprednisolone, antihistamine	Successful	28

Table 2 **Sample desensitization protocol**

Step No.	Solution*	Dilution	Infusion Rate, mL/hr	Administered Volume, mL	Duration, minutes	Administered Dose, mg	Cumulative Dose, mg
1	A	1/1000	4	1	15	0.001	0.001
2	A	1/1000	8	2	15	0.002	0.003
3	A	1/1000	16	4	15	0.004	0.007
4	A	1/1000	32	8	15	0.008	0.015
5	B	1/100	8	2	15	0.02	0.035
6	B	1/100	16	4	15	0.04	0.075
7	B	1/100	32	8	15	0.08	0.155
8	B	1/100	64	16	15	0.16	0.315
9	C	1/10	8	2	15	0.2	0.515
10	C	1/10	16	4	15	0.4	0.915
11	C	1/10	32	8	15	0.8	1.715
12	C	1/10	64	16	15	1.6	3.315
13	D	1/1	16	4	15	4	7.315
14	D	1/1	32	8	15	8	15.315
15	D	1/1	64	16	15	16	31.315
16	D	1/1	90	133,6	89	133,685	165
Total					5 hr, 14 min		165

**Solution A: 0.001 mg/mL, 1/1000 dilution; solution B: 0.01 mg/mL, 1/100 dilution; solution C: 0.1 mg/mL, 1/10 dilution; solution D: 1 mg/mL, 1/1 dilution.*

desensitization protocol was performed with LAMB at a dose of 5 mg/kg.

DISCUSSION

Desensitization is a procedure that induces temporary tolerance to a medication that may cause severe hypersensitivity reactions, *e.g.*, anaphylaxis, when there are no alternative treatments available or when existing alternatives are not as effective as the responsible drug.[10] Due to the high-risk nature of desensitization, it is recommended to prioritize protocols that are already available in the literature and that have been successfully applied in at least 10 patients. This ensures that the selected protocol has a well-documented track record of safety and effectiveness, which mitigates the risks associated with the procedure.[11] A review of the literature revealed that there is a limited number of rapid desensitization sample protocols conducted with LAMB, and they vary in terms of application characteristics. In addition, only a small fraction of these cases involved pediatric patients (Supplemental Table 1).

From a review of the pediatric cases in the literature, we identified a study with four pediatric patients (average age, 11.5 years).[12] All the patients had hematologic disorders; three had fungal opportunistic infections and one started amphotericin B due to febrile neutropenia. Two of the patients underwent desensitization due to anaphylaxis related to amphotericin B used during their current hospitalization: one due to a history of amphotericin B anaphylaxis and the other due to discontinuation of amphotericin B treatment in infancy, which leads to widespread urticaria. A seven-step desensitization protocol was successfully applied to all the patients. Although three patients received premedication with methylprednisolone and an antihistamine before desensitization, the last one did not undergo premedication.

Shadur *et al.*[12] reported applying a seven-step desensitization protocol by using seven solutions of different concentrations in four patients, three of whom experienced anaphylaxis and one who had widespread urticaria. Three of the patients were in the pediatric age group, whereas one was 18 years old. The initial dose was set as a diluted concentration of amphotericin B, which corresponded to 1/1,000,000 of the total amount that should be administered to the patient.[12] Doses were then increased 10-fold at each step, with administrations occurring at 1- to 2-hour intervals.[12] Three of the four patients were premedicated with antihistamines and hydrocortisone.[12]

Ay *et al.*[4] conducted a similar desensitization protocol for a 13.5-year-old male patient who developed anaphylaxis while receiving LAMB treatment for aplastic anemia, invasive pulmonary aspergillosis, and nasal zygomycosis. This protocol was also administered in seven steps: the first five steps involved 10-minute infusions, the sixth step involved 30-minute infusions, and the seventh step involved 4-hour infusions.[4]

By conducting a review of desensitization protocols applied to adult patients, we identified a 57-year-old

patient who developed anaphylaxis during LAMB treatment for mucormycosis and was subjected to a seven-step desensitization protocol with a 2-hour interval between steps. In this case, only antihistamines were used for premedication and the patient successfully completed the protocol without any complications.[13] In the case of a 22-year-old patient diagnosed with acute lymphoblastic leukemia, a 12-step desensitization protocol with three different dilutions was applied at 15-minute intervals. The procedure was successfully completed without any complications.[14] A 39-year-old patient with acute myeloid leukemia who also experienced sinus mucormycosis received amphotericin B at an initial concentration of 1 ng/mL. It was infused at a rate of 2 mL/minute, and the concentration was increased threefold every 30 minutes, reaching 1 mg/mL. A total of 12 increments were applied, and the infusion was successfully completed in 11 hours.[15] In a 39-year-old patient with cryptococcal meningitis, the initially attempted 14-step cumulative dose desensitization protocol at 300 mg (5 mg/kg/dose) was unsuccessful. Subsequently, follow-up desensitization was achieved with a 10-step cumulative dose of 54 mg (0.7 mg/kg/dose).[16]

The clinical details, according to the literature, of pediatric and adult patients who have undergone successful rapid desensitization with amphotericin B are provided in chronological order in Supplemental Table 1. If there is no standardized protocol available in the literature, then it is recommended to consider the Castells' desensitization protocol.[7,8] a 12-step protocol with three dilutions for most patients and a 16-step protocol with four dilutions for patients who are highly sensitive. This ensures that the selected protocol has a well-documented track record of safety and effectiveness, mitigating the risks associated with the procedure.[17] The initial dose is planned based on the severity of the reaction and can range from 1/100 to 1/1,000,000. Dose intervals are typically set between 15 and 60 minutes, with dose increases not exceeding 2.5 times the previous dose. These dose increases are recommended based on *in vitro* studies to avoid mast cell degranulation. When depending on the reaction and patient characteristics, dose modifications can be made as needed. This approach allows for flexible, patient-specific adjustment of the desensitization protocol.[18] We successfully conducted desensitization with this 16-step protocol for all our patients.

The achieved tolerance is temporary and lasts as long as the medication is used. When the dose range exceeds twice the half-life of the drug, the tolerance status diminishes; however, if the dose is administered within a period of twice the half-life of the medication, then desensitization may not need to be repeated.[10] Our patients successfully received amphotericin B treatment without the need for repeated desensitization, owing to our effective desensitization protocol, with durations ranging from 28 to 70 days.

CONCLUSION

The data we present on the successful application of a sample protocol to five cases, particularly in a pediatric setting, is a noteable and valuable contribution to the field, which demonstrates the feasibility and success of rapid desensitization with LAMB in pediatric patients. This can provide important insights and potentially serve as a reference for medical professionals working with similar cases in the future. Expanding current knowledge in this area is crucial to improving patient care and outcomes.

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