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15 years of allergen immunotherapy vial sterility testing

The prevalence of allergic rhinitis, atopic dermatitis, and asthma is increasing and is associated with significant morbidity and increasing health care costs. Current treatment options for allergic rhinitis are broad and generally begin with pharmacotherapy and, when practical, allergen avoidance. In the general population, approximately one-third of children and two-thirds of adults report partial or poor relief with pharmacotherapy alone.[1] The next step in treatment is often initiation of subcutaneous allergen immunotherapy (AIT). Adverse AIT effects include local reactions (estimated frequency 26–82%) and systemic reactions (from <1% in conventional therapy to >34% in some studies of rush immunotherapy). There have been no reported infections associated with AIT injections.[2]

Allergen immunotherapy extracts are prepared based on the recommendations of 4 guiding documents: the Allergen Immunotherapy Extract Preparation Manual,[3] the Revised 797 US Pharmaceutical (USP) Compounding Guidelines,[4] the Food and Drug Administration's Guidelines for Mixing, Diluting, or Repackaging Biological Products,[5] and the allergen extract package inserts. In 2006, the USP Compounding Guidelines were changed and an exception was allotted for allergen extracts such that allergen extracts were not subject to the personnel, environmental, and storage requirements as other compounded sterile preparations when certain criteria were met. In September 2015, the USP proposed revoking all exceptions. This change has raised significant concerns regarding the availability of AIT to the general population and highlights the importance of rigorously evaluating the safety of our current AIT practice. There are only 2 published articles that reported on monitoring bacteriostasis in allergen extract mixing; however, in these studies, the extracts were not prepared in accordance with the current mixing guidelines and cultures were performed on a limited set of vials.[6,7] To validate our current vial preparation practice, we report the results of 15 years of bacterial and mold cultures performed on 12,209 AIT prescription vials.

The US Centralized Army Extract Laboratory (USACAEL; Silver Spring, Maryland) prepares most allergen extracts for all branches of the military, the Veteran's Administration, and many civilian practices. Although in existence since 1976, the USACAEL started formally tracking and documenting sterility testing of new vial sets in October 2000 to the present (Table 1). From October 2000 through September 2015, the USACAEL compounded a total of 508,284 allergen extract vials representing some 112,952 individual new patient extract prescriptions. Extracts for AIT are obtained from Greer Laboratories (Lenoir, North Carolina). During this period, the USACAEL performed sterility testing on 2.4% (12,209 of 508,284) of all extract vial sets prepared during this 15-year period (Table 1).

The sterility procedure was performed by testing new treatment sets, which consisted of 4 or 5 vials that were aseptically prepared under a laminar air flow hood in accordance with current USP 797 guidelines for allergen extract preparation. Using an aseptic technique, a single syringe was used to withdraw samples from vials with the lowest to the highest concentration, for a total of 1 mL. The contents of the syringe were mixed to ensure uniform distribution of the different vial concentrations. Sterility tests were performed using 2 types of recommended culture media: trypticase soy broth (TSB) and thioglycollate medium (TM). One half of the 1-mL sample was injected into the appropriately designated TSB tube and the other half was injected into the TM tube. The TM tubes were incubated at 33°C to 37°C to evaluate for possible bacterial contamination. The TSB tubes were incubated at 22°C to 25°C to evaluate for possible mold contamination including *Candida* species, *Aspergillus* species, and *Bacillus subtilis*. The TSB and TM tubes were incubated for 14 days. The racks of TSB and TM tubes were visually inspected for evidence of growth on days 3, 7, and 14. This procedure was adopted from the 2001 Food and Drug Administration's Code of Federal Regulations recommendation for sterility testing of bulk material as described in Title 21, Subchapter F, Part 610.12.[8]

From 2001 through 2015, sterility testing was performed on a total of 12,209 patient prescription vials. During this period, there was only 1 recorded positive result (representing <0.008% of all cultures). This vial set was again sterility tested using the previously described procedure and the result was negative. This most likely indicates that the positive culture result was due to contamination of the medium during the sterility testing procedure and not to contamination of the treatment set. Although the positive culture result was most likely due to contamination during the sterility procedure, no shots were administered from this patient's vial set and the prescription was remixed. During this period, there were no reports to the USACAEL of infections resulting from the 508,284 distributed vials.

At our center, the frequency of positive cultures is even lower than that reported by Letz et al[6] and Lay et al.[7,9] Letz et al performed a similar evaluation of some 2,085 vials of AIT and reported only 1 positive culture result (representing <0.05% of all cultures).[4] Lay et al performed a comparison of bacterial contamination on vials prepared in an office setting using an aseptic technique without a ventilation hood or under an International Organization of Standardization classification 5 vacuum-ventilated hood in a hospital pharmacy. Two of the 320 (representing 0.6%) office-prepared vials and 1 of 217 (0.5%) pharmacy-prepared vials showed positive

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Table 1
US Centralized Army Extract Laboratory[a] Sterility Testing Results From FY 2001 Through FY 2015

FY	Vials tested per month, n												Total, n	Positive, n
	October	November	December	January	February	March	April	May	June	July	August	September		
2001	70	60	60	60	60	60	60	60	60	60	60	60	730	0
2002	60	30	30	60	60	60	60	60	60	60	60	60	660	0
2003	60	60	60	60	60	60	60	60	60	60	60	60	720	0
2004	60	60	60	81	123	107	80	90	121	82	102	91	1057	0
2005	85	92	97	72	45	53	52	88	67	67	57	81	856	0
2006	53	106	94	46	46	71	56	58	58	71	68	101	828	0
2007	75	91	69	72	89	70	77	60	68	78	141	60	950	0
2008	53	58	152	63	70	70	64	130	89	69	62	61	941	0
2009	77	93	70	44	64	70	60	59	58	67	67	63	792	0
2010	59	71	82	81	73	74	72	75	52	90	78	50	857	0
2011	63	63	63	79	63	96	80	80	75	60	93	70	885	0
2012	70	73	82	74	64	63	74	79	71	62	71	72	855	0
2013	71	69	69	78	67	45	69	77	61	61	60	47	774	1
2014	67	60	67	78	81	66	47	58	60	67	69	66	786	0
2015	40	58	53	51	42	42	33	35	36	32	32	64	518	0

Abbreviation: FY, fiscal year.
[a]Extracts were obtained from Greer Laboratories (Lenoir, North Carolina).

culture results for bacterial contamination. The 3 patients who received injections from the vials that demonstrated growth did not develop a clinical infection.[7]

In conclusion, we report a 0% rate of mold and bacterial contamination of AIT vials using the current recommended preparation procedures as stated in the USP 797 Compounding Guidelines and the Allergen Immunotherapy Extract Preparation Manual and up to a 0.008% rate of bacterial contamination resulting from the sterility testing procedure. Our data and those published by Letz et al[6] clearly demonstrate a negligible risk of contamination with the current standards for extract vial preparation. Evaluating this 1 step further, the data presented by Lay et al and Balekian et al[10] who examined AIT injections from these prepared extracts identified no infections associated with injections. We contend that further changes to the current procedures and guidelines for mixing allergen extracts are not indicated at this time.

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First-line treatment of hymenoptera venom anaphylaxis: a 23-year real-life experience

Anaphylaxis represents a significant health care burden and occurs in approximately 1% to 3% of people annually.[1,2] Allergy to hymenoptera venom occurs in 0.15% to 0.8% of children and 0.3% to 8.9% of adults.[3] The complex management of anaphylaxis consists of emergency treatment of acute episodes, follow-up procedures including the prescription of epinephrine, and referral to an allergist. Therefore, it was of interest to investigate the medical care given to patients with systemic reactions after hymenoptera insect stings in Silesia, a southern region of Poland. The subjects of the retrospective cohort study consisted of 2,954 patients allergic to hymenoptera venom who were treated from 1992 through 2015 in Silesia. Review of the recorded data, including primary care history, emergency sheets, paramedic notes, hospital discharge cards, etc, was performed by trained site investigators. Anaphylaxis was diagnosed according to the definition of the World Allergy Oganization.[3] The data were analyzed using Statistica software (StatSoft,

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