

Injectable immunotherapy: recommendations for safe allergen vial preparation in the office setting

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**Current Opinion in Otolaryngology & Head and
Neck Surgery** 2009, 17:223–225

Purpose of review

To review the proper technique for preparing allergen vials to be used in subcutaneous immunotherapy in the office setting, examine the potential for bacterial contamination during mixing and handling and associated risk factors and review the data relevant to contamination during vial mixing.

Recent findings

Existing literature on the subject of safe vial preparation suggests that the incidence of bacterial contamination of allergen vials is very low. Historically, there is no report of bacterial infection for subcutaneous immunotherapy using vials prepared in the office setting or otherwise when using the proper sterile technique.

Summary

In-office compounding of vials is a safe practice with literature to support continuing this practice of preparation.

Keywords

allergen, contamination, preparation, sterile, vial

Curr Opin Otolaryngol Head Neck Surg 17:223–225
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1068-9508

Introduction

The diagnosis and treatment of allergy in the field of otolaryngology is important. Many of the disease processes seen in otolaryngology clinics such as otitis media, chronic rhinitis, chronic sinusitis, and even Ménière's disease have allergies as an exacerbating factor. The best chance for cure of allergies is immunotherapy, which in the United States is usually subcutaneous injectable immunotherapy (SCIT). There are no reported cases of infection from SCIT, though the possibility exists. It is essential that proper preparation and handling techniques be employed when administering injectable immunotherapy. This article reviews the literature examining safe practices of injectable immunotherapy.

Current in-office immunotherapy practices

The last several years have shown a surge of activity in otolaryngic allergy practices across the country. Allergen-specific immunotherapy (SIT) is implemented usually in the form of SCIT. When attempts at medical management with avoidance, oral antihistamines, nasal irrigations, and nasal steroids are inadequate or only partially successful, allergen-SIT significantly improves a patient's symptom profile and is the only intervention which can potentially cure the patient making it an essential part of any allergy physician's practice. The otolaryngologist can identify patients with potential allergy, who may not know they have allergy and save

the patient the expense of traveling to another physician's office for allergy management. By offering allergy evaluation and therapy, the otolaryngologist provides a maximum value, 'a one stop shop' for many patients with ear, nose, and throat disorders, which have an allergic component. The demand is quite high and growing in the field of otolaryngology. Some 10 million patients are treated annually with SCIT in the United States alone [1•].

Chronic rhinosinusitis, Eustachian tube dysfunction, and chronic otitis media are just a few of the diseases seen in otolaryngology clinics associated with environmental allergies [2]. Safe allergy management is as important as effective allergy management. Safety of allergy immunotherapy requires not only that the antigen dosage be appropriate, but also that the vial and the administration be sterile. This article will review safe and sterile allergy vial preparation.

The incidence of anaphylaxis is 0.005% of allergy shots among otolaryngic allergists. The presentation and treatment algorithm for anaphylaxis is well described in the literature [2]. A less frequently considered adverse event following an allergy shot is infection. The issue of sterility in the preparation of allergen vials has been discussed nationally among pharmacists, otolaryngologists, and medical allergists for the last several years. In 2003, United States Pharmacopeia (USP) made recommendations regarding the compounding of medications that

would place onerous burdens on the practices of the physicians treating allergy patients. In the Pharmacopeial Forum, chapter 797, the guidelines for medication compounding in office recommended clean rooms, ventilated hoods, air sampling, and other safety measures. While it did not specifically cite allergen vial preparation, a translation to vial preparation was easily apparent. In 2006 the USP, after weighting the input of various allergy societies, undertook a revision that stated allergen vial preparation in the office setting was reasonable and did not require the ventilated hoods and air sampling required of compounding medications in a hospital or pharmacy. This revision is now in print in the updated 2007 version of chapter 797 [3]. So then, what is considered proper handling of materials and sterile technique for preparing vials?

What is sterile preparation?

King and Mabry [4] outlined a practical protocol for mixing allergen vials in an office setting. This same protocol was used in prospective studies looking for rates of bacterial contamination. The steps are as follows:

- (1) A counter top in the allergy clinic is designated as the mixing space and is prepped topically with 70 isopropyl alcohol or clinical germicide.
- (2) When prepping the mixing area and arranging vial materials, nonsterile gloves are worn. Proper hand washing occurs prior to gloving.
- (3) Vials of hermetically sealed allergen are mixed in vials using hermetically packaged syringes and diluent.
- (4) Several different antigens may be injected into these vials and diluted with sterile 0.4 percentage phenolated saline buffered to pH 7.4. Then, 25 or 50% glycerin is injected into the patient vial to bring the glycerin content to a minimum of 10%.
- (5) Once the vials are prepared, they are stored in refrigerator at approximately 38 F for no longer than 3 months.
- (6) For administration, the allergen is drawn into a small-gauge syringe (27 G) after prepping the rubber stopper top with 70% isopropyl alcohol and administered subcutaneously after the skin is prepped with 70% isopropyl alcohol.
- (7) All disposable materials, such as syringes and needles, are handled and used only once, then discarded in the appropriated receptacles.
- (8) Vials are typically remixed once every 5–10 weeks while in the buildup phase of immunotherapy, and all vials are marked in with a 3-month expiration date.
- (9) Vials are discarded after the 3-month storage period.

A custom vial is prepared for each patient based on allergy skin or in-vitro testing results. Doses range in volume

from 0.05 to 0.5 ml. The injections are administered subcutaneously to patients by trained healthcare personnel after preparing the skin with alcohol while wearing gloves. Current recommendations for vial mixing emphasize the importance of listing the name of one specific patient, with a beyond-use date and storage temperature range that is assigned based on manufacturers' recommendations or peer review publications (www.usp.org). The addition of bacteriostatic substances to the vials such as 0.25% phenol or 20% glycerin is also recommended [5[•]]. Although glycerin has shown some bacteriostatic properties, it has not been clearly quantified, so it is used largely as a preservative [6]. The concentrations of phenol and glycerin vary depending on manufacturer, physician preference, and desired shelf life of the vial being used. The above method was used in three studies recently published on safe vial preparation and bacterial contamination [1[•],7^{••},8^{••}].

Factors that may increase the risk of infection when handling vials in the clinic

Longfield, Bawden, Melnyk, and Thompson [9–12] in four separate studies cited handling techniques that increase risk of infection. These included increased number of punctures, a lack of resealability of rubber closure, lack of aseptic technique, injection of air into the vial before removal of the solution, prolonged length of storage, and reduced antimicrobial activity of bacteriostatic agents used in preparation and administration. The antimicrobial and preservatives used in these studies were variable, including 0.4% phenol, 0.9% benzyl alcohol, 0.1% methylparaben, 0.01% propylparaben, and others. The conclusion of these articles uniformly was that the incidence of contamination was quite low, from 0.004 to 0.5% [11]. These studies were not on allergen vials specifically; however, their conclusions are applicable to allergy vials.

Commercial preparation

In 2001, Wohlfarth *et al.* [13] of Antigen Laboratories, Inc., described the advantages of commercially produced vials such as assured sterility. In the article, the conditions for compounding included clean room environs, air sampling, vial sampling with cultures, and preparation under a ventilated hood. These measures, though undoubtedly very effective, were duplicated in a recent study conducted at Southern Illinois School of Medicine. Vials prepared under ventilated hoods in a pharmacy were cultured and compared with vials prepared in the office setting with no significant difference in rates of bacterial contamination. Of the vials cultured in the pharmacy under the ventilated hood, one tested positive for *Escherichia coli*, and those prepared in the office revealed two cultures that were positive for

coagulase-negative *Staphylococcus* and an alpha-*Streptococcus*. Repeat cultures of these vials revealed no bacteria suggesting that these were simply handler contaminants rather than originating from the vials themselves. In Wohlfarth *et al.*'s article, positive cultures were found in random sampling of the vials prepared in the setting of a clean room under ventilated hood and disposed of appropriately. A long safety record with no documented infections strongly suggests that there is no difference in overall sterility of vials for SCIT whether prepared in the traditional manner in the office without a hood or in the hospital setting clean room with a hood.

Comparison of commercial and office preparation of vials

In Lay *et al.*'s retrospective study and literature review, there were no cases of bacterial infection from SCIT [1•]. In a recent prospective study by the same authors, vials were prepared in the office setting and under a ventilated hood in a microbiology lab, and no significant difference in contamination rates was found between the two arms. A total of 537 vials were prepared and cultured; 320 vials were arbitrarily assigned to in-office preparation and 217 to under-hood preparation. A total of two (0.6%) positive cultures occurred in vials prepared in-office and one (0.5%) from under-hood preparation. This outcome yielded an odds ratio of 1.36 with a 95% confidence interval of 0.12–15.08 ($P=0.8$). The sample size (537) used in this experiment was large enough to detect a significant difference of 4% (13 of 320) versus 0.5% (one of 217) with a power of 80%, which was judged to be within clinically acceptable limits [7••].

Preparing allergy vials in the physician allergist office is convenient and cost-effective. Each patient has his or her own unique combination of allergens and dosing requirements, which can be changed in real time in the office setting.

Conclusion

SCIT has enjoyed a long and apparently infection-free history of treatment. Allergy patients rely on us as allergy physicians to maintain this track record of safe preparation and administration of SCIT. Using simple sterile

technique in the office setting with appropriately prepared areas by trained staff is the standard.

Acknowledgements

I would like to thank Dr Richard Bass and Dr Stephen Chadwick for their guidance in writing this article.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 247).

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