

## Letter to the Editor

### Allergen immunotherapy: No evidence of infectious risk

*To the Editor:*

Allergic rhinitis affects approximately 15% to 30% of the US population and accounts for more than 22 million health care visits annually.<sup>1,2</sup> Allergic rhinitis treatments were estimated to cost \$11.2 billion in 2005, which was a near doubling over a 5-year period.<sup>1</sup> Additionally, this condition accounts for significant indirect costs, with approximately 6 million lost work days each year.<sup>3</sup>

Subcutaneously administered allergen immunotherapy (AIT) is a cost-effective and disease-modifying treatment that has been used for the past century to successfully treat allergic rhinitis, allergic conjunctivitis, asthma, and Hymenoptera venom allergy.<sup>4</sup> AIT is administered to 2.6 million persons in the US each year, resulting in approximately 16 million annual injections.<sup>5</sup>

AIT is thought to be a safe treatment, with large local reactions (0.7% to 4% of injections) and systemic allergic reactions (0.2% of injections) being the most common adverse sequelae.<sup>4</sup> Data on the risk of infection from AIT are scant. There are no identifiable reports of infection resulting from AIT in the literature, and a single study evaluated this issue and demonstrated no risk of local infection after AIT injection.<sup>6</sup>

Proposed US Pharmacopeia (USP) guideline changes currently under consideration would result in a drastic restriction in the availability of AIT. For this reason, we sought to further explore the safety of current AIT practices. Our objective was to examine the historical risk of infection from AIT in a large patient population in an integrated health care system with electronic health record (EHR) data.

We analyzed data from the Partners Research Patient Database Repository, a repository of all EHR data within a health system that includes Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH). We identified all AIT injections administered by using Current Procedure Terminology codes 95115 and 95117 over a 10-year period from November 1, 2005, through October 31, 2015. We included patients who received AIT at one of 2 main allergy practices at MGH or BWH. Patients' demographic information, such as age, sex, and self-reported race/ethnicity, were also obtained from the Partners Research Patient Database Repository.

The primary outcome of this analysis was skin and soft tissue infection (SSTI) or systemic infection within 5 days after AIT injection. We identified infections using previously validated codes from the International Classification of Diseases, Ninth Edition (ICD-9; see [Table E1](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).<sup>7,8</sup> We included codes billed from either an inpatient or outpatient location at any hospital or clinic affiliated with MGH or BWH. Each identified infection was followed by a comprehensive electronic chart review by at least 1 board-certified allergist/immunologist (D.S.B., A.B., and A.A.L.) to determine whether the injection could be reasonably deemed to have caused the identified infectious process. Criteria for association of infection with AIT administration were the presence of an infectious process in the skin or soft tissue contiguous to the site of AIT injection or a bloodstream infection that did not have an obvious origin elsewhere. Ethical

clearance for this study was provided by the Partners Human Research Committee.

Among 3,242 patients, we identified 136,322 episodes of AIT injection during the 10-year study period ([Table I](#)). The median number of injections per patient was 30 (interquartile range, 13-54). The median patient age at first injection was 38 years (interquartile range, 28-50 years). Most patients were female (60%) and white (75%).

Within this data set, 66 patients had 86 episodes of billing for infections occurring within 5 days of receiving an AIT injection. Thirty-seven (43%) infections were classified as SSTIs, and 49 (57%) infections were classified as systemic infections. After review of the original medical record, all of the SSTIs were found to be at sites remote from the AIT administration and unrelated. Likewise, none of the systemic infections were attributed to AIT (details are provided in [Table II](#)).

In this large retrospective cohort study of 136,322 AIT injections over a 10-year period at 2 large academic medical centers, we identified no findings of SSTI or systemic infection attributable to AIT injection. These data come from 2 of the largest allergy/immunology practices in Massachusetts, with MGH having 20 allergists on staff, and BWH having 29 allergists on staff.

Within each of these institutions, allergen extracts are mixed separately by using aseptic techniques based on current USP chapter <797> guidelines but not consistent with proposed USP changes. Most commercial extracts are 50% glycerinated, and dilutions are made with sterile saline containing phenol. Studies of the sterility of allergen extracts have demonstrated that bacterial contamination is extremely rare (1 in 2,085).<sup>9</sup> There have been no case reports in the published literature of infections resulting from AIT injections. To our knowledge, only 1 prior study, that by Lay et al,<sup>6</sup> examined infectious risk and AIT. This retrospective study examined 26,795 injections administered to 272 patients over a 6-year period and found that no patients experienced fever or SSTI at the site of injection. Additionally, they found that no patients required antibiotics or other medical treatment for infection. Our study examined a significantly larger population of patients across 2 large allergy practices.

The strengths of this study include the large sample size (>130,000 AIT injections in >3,000 patients), the 10-year study period, and use of high-quality EHR data, which reduces the possibility of misclassification. Although we do not have a closed health system, our methods would have identified infections that might have been diagnosed in other practices within our health care system (eg, urgent care clinics or primary care office).

A potential limitation is that minor localized infections might have gone unreported and would not be captured in this analysis; however, any major complications would have been captured. Another limitation is that these data were collected retrospectively from the EHR using ICD-9 codes. Although ICD-9 codes have been validated to identify SSTIs,<sup>8</sup> identification of systemic infections with ICD-9 codes are less clear. However, we used a broad array of ICD-9 codes and adapted codes used from a prior study (Stevenson et al<sup>7</sup>) to identify postoperative systemic infections. Ultimately, we reviewed all suspected cases with a formal chart review. A final limitation is that racial/ethnic minorities might have been underrepresented in our cohort.

**TABLE I.** Baseline characteristics of the cohort (136,322 injections among 3,242 patients)

| Characteristic                              | No. (%)    |
|---------------------------------------------|------------|
| Age at first injection (y), median (IQR)    | 38 (28-50) |
| Male sex                                    | 1,285 (40) |
| Race/ethnicity                              |            |
| White                                       | 2,442 (75) |
| Black                                       | 169 (5)    |
| Hispanic                                    | 246 (8)    |
| Other                                       | 385 (12)   |
| No. of injections per patient, median (IQR) | 30 (13-54) |

IQR, Interquartile range.

**TABLE II.** Infections identified in the cohort within 5 days after AIT injection (86 infections among 66 patients)

| Type of infection (ICD-9 code)               | No. (%) |
|----------------------------------------------|---------|
| Viral pneumonia, unspecified (480.9)         | 1 (1)   |
| Bacterial pneumonia, unspecified (482.9)     | 6 (7)   |
| Bronchopneumonia, organism unspecified (485) | 2 (2)   |
| Pneumonia, organism unspecified (486)        | 38 (44) |
| Influenza with pneumonia (487.0)             | 1 (1)   |
| Cellulitis and abscess of finger (681.00)    | 1 (1)   |
| Cellulitis and abscess of toe (681.1)        | 1 (1)   |
| Impetigo (684)                               | 6 (7)   |
| Folliculitis (704.8)                         | 25 (29) |
| Hidradenitis (705.83)                        | 4 (5)   |
| Bacteremia (790.7)                           | 1 (1)   |

In conclusion, in this large retrospective cohort study of risk of infection with AIT, we did not find any cases of SSTIs or systemic bacterial infections from AIT injections. These findings suggest that the sterility and safety practices in place during the study

period are adequate to prevent adverse infectious outcomes related to the preparation and administration of AIT.

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**Table E1.** ICD-9 codes used to identify infections

| ICD-9<br>Code                                      | Description                                                   |
|----------------------------------------------------|---------------------------------------------------------------|
| <i>Skin and Soft Tissue Infections<sup>1</sup></i> |                                                               |
| 680                                                | Carbuncle and furuncle                                        |
| 681.00                                             | Cellulitis and abscess of finger                              |
| 681.01                                             | Cellulitis and abscess of toe                                 |
| 681.90                                             | Cellulitis digit, NOS                                         |
| 682                                                | Other cellulitis and abscess                                  |
| 684                                                | Impetigo                                                      |
| 704.8                                              | Folliculitis                                                  |
| 705.83                                             | Hydradenitis                                                  |
| 771.5                                              | Neonatal infective mastitis                                   |
| 675.1                                              | Breast abscess                                                |
| 675.2                                              | Nonpurulent mastitis                                          |
| <i>Systemic Infection<sup>2</sup></i>              |                                                               |
| 038.0                                              | Streptococcal septicemia                                      |
| 038.10                                             | Staphylococcal septicemia, unspecified                        |
| 038.11                                             | Methicillin susceptible Staphylococcus aureus septicemia      |
| 038.19                                             | Other staphylococcal septicemia                               |
| 038.2                                              | Pneumococcal septicemia [Streptococcus pneumoniae septicemia] |
| 038.3                                              | Septicemia due to anaerobes                                   |
| 038.40                                             | Septicemia due to gram-negative organism, unspecified         |
| 038.41                                             | Septicemia due to hemophilus influenzae [H. influenzae]       |
| 038.42                                             | Septicemia due to escherichia coli [E. coli]                  |
| 038.43                                             | Septicemia due to pseudomonas                                 |
| 038.44                                             | Septicemia due to serratia                                    |
| 038.49                                             | Other septicemia due to gram-negative organisms               |
| 038.8                                              | Other specified septicemias                                   |
| 038.9                                              | Unspecified septicemia                                        |
| 790.7                                              | Bacteremia                                                    |
| 995.9                                              | Systemic inflammatory response syndrome (sirs)                |
| 995.91                                             | Sepsis                                                        |
| 995.92                                             | Severe Sepsis                                                 |
| 480.0                                              | Pneumonia due to adenovirus                                   |
| 480.1                                              | Pneumonia due to respiratory syncytial virus                  |
| 480.2                                              | Pneumonia due to parainfluenza virus                          |
| 480.3                                              | Pneumonia due to SARS-associated coronavirus                  |
| 480.8                                              | Pneumonia due to other virus not elsewhere classified         |
| 480.9                                              | Viral pneumonia, unspecified                                  |
| 481                                                | Pneumococcal pneumonia                                        |
| 482.0                                              | Pneumonia due to Klebsiella pneumoniae                        |

|        |                                                                |
|--------|----------------------------------------------------------------|
| 482.1  | Pneumonia due to Pseudomonas                                   |
| 482.2  | Pneumonia due to Hemophilus influenzae                         |
| 482.30 | Pneumonia due to Streptococcus, unspecified                    |
| 482.31 | Pneumonia due to Streptococcus, group A                        |
| 482.32 | Pneumonia due to Streptococcus, group B                        |
| 482.39 | Pneumonia due to other Streptococcus                           |
| 482.40 | Pneumonia due to staphylococcus, unspecified                   |
| 482.41 | Methicillin susceptible pneumonia due to Staphylococcus aureus |
| 482.82 | Pneumonia due to escherichia coli [E. coli]                    |
| 482.83 | Pneumonia due to other gram-negative bacteria                  |
| 482.84 | Pneumonia due to Legionnaires' disease                         |
| 482.89 | Pneumonia due to other specified bacteria                      |
| 482.9  | Bacterial pneumonia, unspecified                               |
| 483.0  | Pneumonia due to mycoplasma pneumoniae                         |
| 483.1  | Pneumonia due to chlamydia                                     |
| 483.8  | Pneumonia due to other specified organism                      |
| 485    | Bronchopneumonia, organism unspecified                         |
| 486    | Pneumonia, organism unspecified                                |
| 487.0  | Influenza with pneumonia                                       |
| 482.49 | Other Staphylococcus pneumonia                                 |
| 482.81 | Pneumonia due to anaerobes                                     |

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