# Dependence of Elevated Eosinophil Levels on Geographic Location in the VA San Diego Healthcare System

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An investigation of patient records at multiple locations found high eosinophil levels, which may be related to dyslipidemia or *Coccidioides immitis* infection.

A primary care physician in the VA San Diego Healthcare System (VASDHS) clinically observed an unexpected rate of elevated eosinophil levels on routine blood tests of patients residing in inland areas of San Diego County and Imperial County. The majority of the affected patients did not present with symptoms or associated pathology, leaving the significance of these laboratory results unclear and creating question of what intervention, if any, might be most appropriate for these patients. A preliminary chart review of clinic visits at community-based clinic sites confirmed higher rates of elevated eosinophil levels compared with those of patients seen at the San Diego-based medical center. Based on this finding, a more formal investigation was initiated.

Eosinophils are leukocyte components of the cell-mediated immune response and may be elevated in conditions that include hypersensitivity reactions, adrenal insufficiency, neoplastic disorders, and parasitic infections, among others.[1] An elevated percentage of eosinophils can be attributed to a variety of causes, and isolated elevations in a particular individual may not necessarily reflect an underlying pathology. Furthermore, elevated eosinophil levels alone do not necessarily indicate eosinophilia, as the latter is defined by absolute eosinophil counts. However, the occurrence of elevated eosinophil levels that remain unexplained at the population level raises the possibility of a common exposure and warrants further investigation. If such a phenomenon appears to be geographically distributed, as was noted by VA physicians in San Diego and Imperial County, it becomes important to consider what exposures might be unique to a particular site.

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## *Coccidioides immitis*

The soil fungus *Coccidioides immitis* (*C immitis*) is a growing public health concern for inland areas of San Diego County and Imperial County. While its presence in the northern California San Joaquin Valley has been of particular research interest and has gained traction in public discourse, the organism also is endemic to much of southern California, Arizona, New Mexico, and Texas, with its range extending as far north as parts of Nevada and Utah.[2] Although *C immitis* has been identified as endemic to the dry climate of Imperial County, the precise degree of its endemicity and clinical significance are less clear.

From 2006 to 2010, Imperial County reported a comparatively low incidence rate of coccidioidomycosis (*C immitis* infection) compared with that of similar adjacent climates, such as Yuma, Arizona. A 2011 Imperial County survey found that only 23% of clinicians considered coccidioidomycosis a problem in California, and only 43% would consider the diagnosis in a patient presenting with respiratory problems.[3] These findings have raised the concern that cases are being missed either from failure to diagnose or from underreporting. Furthermore, in light of a 1997 study that found intestinal parasites in about 28% of the population in Mexico, there is concern that given the close proximity to northern Mexico (where *C immitis* also is found), rates of *Strongyloides stercoralis*, *Giardia*

*lamblia*, *Entamoeba histolytica*, *Cryptosporidium*, *Ascaris lumbricoides*, and other parasitic infections might be higher in border counties, such as Imperial County, compared with other sites in California.[4]

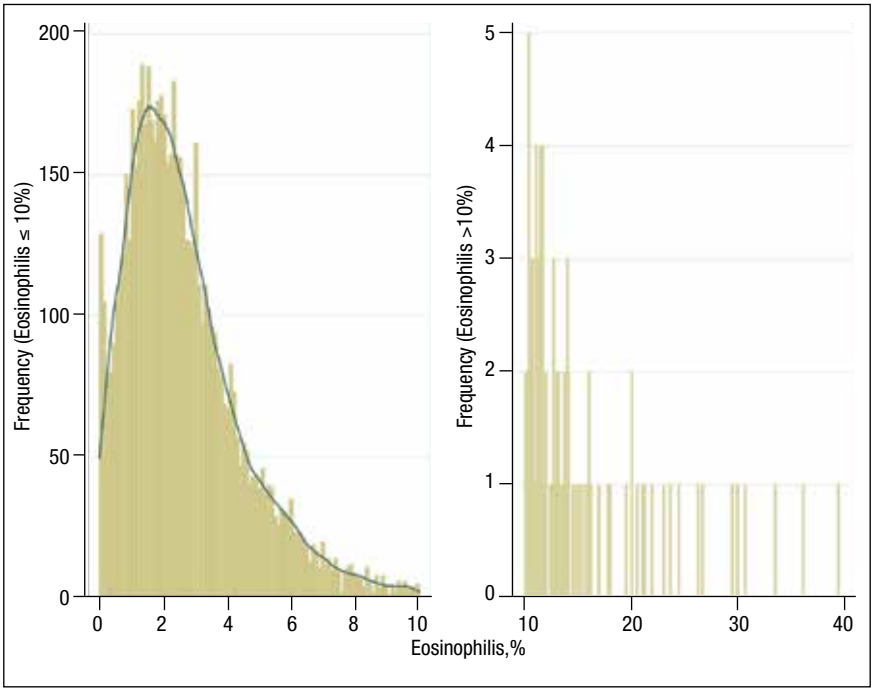
While coccidioidomycosis and parasitic infections are potential causes of the elevated eosinophil levels at VASDHS, recent studies have demonstrated an association between cardiovascular risk factors, such as dyslipidemia and diabetes mellitus, and eosinophil count.[5] The association between dyslipidemia and elevated eosinophil levels is not well understood, although recent studies have described it as likely multifactorial with contributing mechanisms involving oxidative stress, endothelial dysfunction, and inflammatory changes.[6] Consideration of these cardiovascular risk factors is of particular importance in this population because of its high rate of overweight and obesity. According to the 2011-2012 California Health Interview Survey, 71% of Imperial Valley adults were found to be either overweight or obese compared with the California state average of 55% and the San Diego County average of 57%.[7,8]

This investigation aimed to identify whether geographically distributed elevated eosinophil levels can be identified using population-level data, whether eosinophil levels are found to be elevated at a particular site, and whether such observations might be explained by known characteristics of the patient population based on existing patient data.

## METHODS

The percentage of eosinophils on complete blood counts (CBCs) were acquired for all VASDHS patients who had laboratory visits from May 1 to June 30, 2010, based on patient records. For patients with multiple laboratory visits during the period, only data from the earliest visit were included for this investigation. Initially, patients were sorted according to the site of their laboratory blood draw: Chula Vista, Escondido, Imperial Valley, La Jolla, Mission Valley, and Oceanside. Descriptive statistical analyses were carried out for each specific site as well as with patients from all sites pooled.

**Figure 1.** Distribution of Eosinophil Levels (n = 6,777)



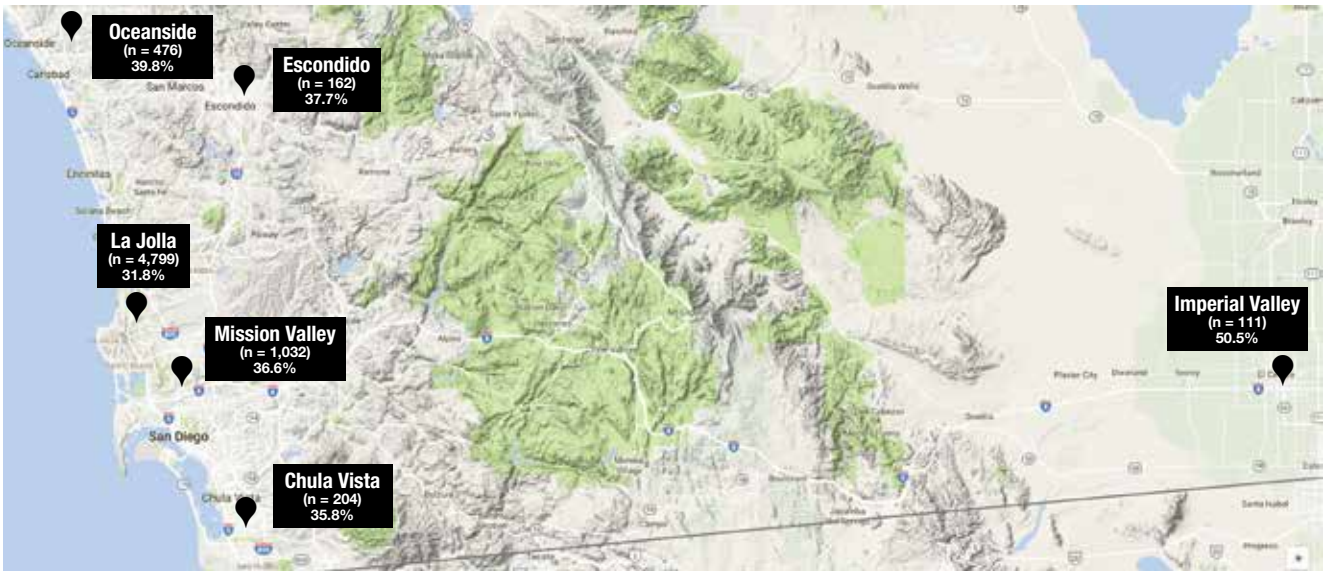

Using VA Clinical Laboratory standards reporting eosinophil percentages > 3% as elevated, 33.7% of VA San Diego patients studied have eosinophil percentages above this cutoff.

### Sites With Elevated Eosinophil Levels

In addition to descriptive statistics, Pearson $\chi^2$ tests were initially performed to determine whether the proportions of elevated eosinophil levels at inland VASDHS sites in San Diego and Imperial counties deviated significantly from the expected levels at the coastal La Jolla hospital comparison site. Additional Pearson $\chi^2$ tests were performed subsequently to compare all sites involved in the study against all other sites. The goal of these Pearson $\chi^2$ tests was to identify potential sites for further investigation with no adjustment made for multiple testing. Sites with eosinophil levels significantly higher or lower than the expected levels when compared with the other sites included in the study were investigated further with a chart review.

Based on the VA Clinical Laboratory standards, a peripheral eosinophil percentage > 3% was considered elevated. Absolute eosinophil levels also were calculated to determine whether elevated eosinophil levels were associated with absolute counts reflective of eosinophilia. Counts of 500 to 1,499 eosinophils/mL were considered mild eosinophilia, 1,500 to 4,999 eosinophils/mL considered moderate eosinophilia, and ≥ 5,000 considered severe eosinophilia.[9]

**Figure 2.** Percentage of Sample Population With Elevated Eosinophil Levels at 6 Sites[a]




[a]Map generated using Google Maps.

### Site-Specific Subgroup Analysis

A structured chart review was conducted for all patient notes, laboratory findings, studies, and communications for sites identified with elevated eosinophil levels. Demographic information was collected for all subjects, including age, race, occupation, and gender. Each record was systematically evaluated for information relating to possible causes of eosinophilia, including recent or prior data on the following: CBC, eosinophil percentage; HIV, *C immitis*, or *Strongyloides stercoralis* serology, stool ova and parasites, diagnoses of dyslipidemia, diabetes mellitus, malignancy, or adrenal insufficiency; and histories of atopy, allergies, and/or allergic rhinitis. In addition, given the unique exposures of the veteran population, data on service history and potential exposures during service, such as to Agent Orange, also were collected.

A multivariate analysis using logistic regression was conducted to determine whether conditions or exposures often associated with eosinophilia might explain any observed elevations in eosinophil levels. For the logistic regression model, the response variable was eosinophil levels > 3%. Explanatory variables included parasitic infection diagnosis, including *C immitis*, dyslipidemia diagnosis, malignancy diagnosis, allergy and/or atopy diagnosis, and HIV diagnosis. In addition, the analysis controlled for demographic variables, such as age, sex, race, period of service, and Agent Orange exposure and were included as explanatory variables in the model. Categorical variables were coded as 0 for negative results and 1 for positive results and were identified as missing if no data were recorded for that variable. Statistics were performed using Stata 13 (College Station, TX).

## RESULTS

A total of 6,777 VASDHS patient records were acquired. Two records included CBC without differentials and were omitted from the study. Among those included, the median eosinophil percentage was 2.3% (SD 2.51). Eosinophil percentages ranged from 0% to 39.3%. The 25th percentile and 75th percentile eosinophil levels were 1.3% and 3.6%, respectively. Nine percent of patients had percentages below 11.6%, and 4 patients had eosinophil percentages ranging from 30% to 39% (Figure 1).

Grouping the records by clinic, 30% to 40% of patients had elevated eosinophil levels at all sites except for Imperial Valley (Figure 2). At the Imperial Valley site, 50.5% of patients had elevated eosinophil levels, which was statistically higher than those of all other sites (Figure 3).

The authors tested the null hypothesis that there is no association between geographic location and the proportion of the population with elevated eosinophil levels. A Pearson $\chi^2$ test of the proportion of elevated eosinophil level ($P < .001$) indicated that the observed differences in elevated eosinophil levels were unlikely due to chance. Further sets of

exploratory $\chi^2$ tests comparing only 2 sites at a time identified Imperial Valley as differing significantly from all other sites at $\alpha = .05$. Eosinophil proportions at the Mission Valley ($P = .003$) and Oceanside ($P < .001$) sites also were found to differ significantly from the La Jolla site. In contrast, eosinophil proportions at the Escondido ($P = .199$) and Chula Vista ($P = .237$) sites did not differ significantly from those of the La Jolla site using $\chi^2$ testing.

### Imperial Valley Clinic

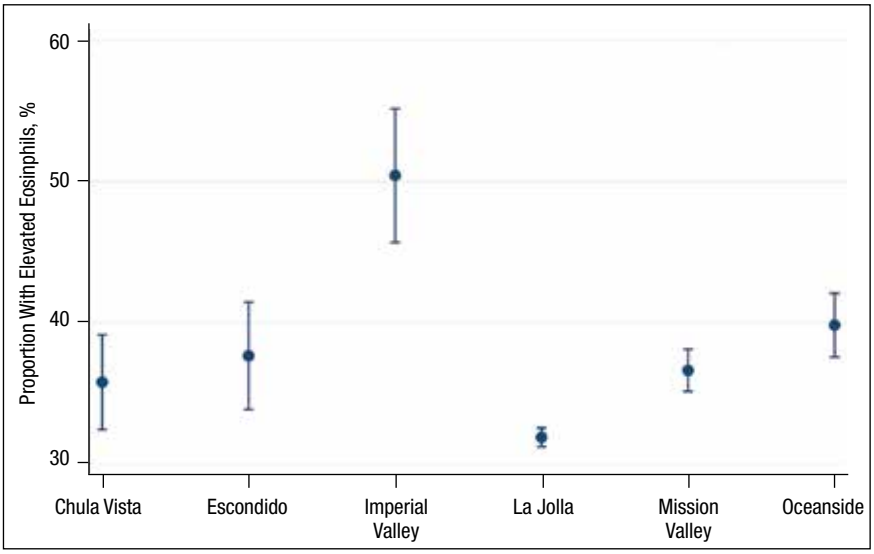
Records were acquired for 109 patients at the Imperial Valley clinic (107 male and 2 female). Fifty-five patients (50.5%) were identified as having elevated eosinophil levels. However, only 5 patients were classified as having mild eosinophilia. No patients were found to have moderate or severe eosinophilia (Table 1).

On review of the data for Imperial Valley patients, 68 had a diagnosis of dyslipidemia and 17 had asthma, atopic dermatitis, allergic rhinitis, and/or atopy not otherwise specified diagnoses. Three patients were identified with diagnoses of malignancies or premalignant conditions, including 1 patient with chronic lymphocytic leukemia, 1 patient with renal cell carcinoma with metastasis to the lungs, and 1 patient with myelodysplastic syndrome. No patients were identified with a diagnosis of HIV. There were no diagnostic laboratory tests on record for *C immitis* serology, stool ova and parasites, *Strongyloides stercoralis* serology, or clinical diagnoses of related conditions.

Logistic regressions assessed whether elevated eosinophil levels > 3% might be explained by predictor variables, such as a history of dyslipidemia, malignancy, or asthma/allergies/atopy (Table 2). As no parasitic infections or HIV diagnoses were identified in the patient population, they were noncontributory in the model. The probability of obtaining the $\chi^2$ statistic given the assumption that the null hypothesis is true equals .027 for the model, suggesting that the overall model was statistically significant at the $\alpha = .05$ level.

Of the key predictor variables of interest, only dyslipidemia was found to predict elevated eosinophil levels. Patients with a diagnosis of dyslipidemia were found to have nearly 4 times greater likelihood of having elevated eosinophil levels compared with patients without dyslipidemia (odds ratio 3.88, 95% confidence interval: 1.04-14.43). Patients with malignancy or a history of asthma, allergy, or atopy were not found to have significantly different odds of having elevated eosinophil levels compared with baseline within the study population.

**Figure 3.** Proportion of Study Population With Elevated Eosinophil Levels[a]




[a]Error bars indicate 95% confidence intervals.

## DISCUSSION

High proportions of elevated eosinophil levels among VASDHS patients were found to be geographically concentrated at sites that included Imperial Valley, Oceanside, and Mission Valley. Although initial exploratory Pearson $\chi^2$ tests did not accommodate for multiple comparisons, a particularly consistent finding was that the proportion of patients with elevated eosinophil levels seemed to be notably high at the Imperial Valley site in particular, which corresponded with the clinical observations made by physicians.

It was initially thought that the elevated eosinophil levels might be due to exposure to geographically distributed pathogens, such as *C immitis*, but there were no clinically diagnosed cases in the population studied. However, it also is true that no *C immitis* serologies or other parasitic serologies were ordered for the patients during the study period. In the context of possible undertesting and underdiagnosis of coccidioidomycosis, it may be possible that these cases were simply missed.

Nonetheless, alternative explanations for elevated eosinophil levels

**Table 1. Demographic Characteristics[a]**

| Characteristics | No. (%) |
|---|---|
| **Gender** | |
| Male | 107 (98) |
| Female | 2 (2) |
| **Age, y** | |
| 20-29 | 10 (9) |
| 30-39 | 14 (13) |
| 40-49 | 9 (8) |
| 50-59 | 11 (10) |
| 60-69 | 30 (28) |
| 70-79 | 21 (19) |
| 80-89 | 12 (11) |
| 90-99 | 2 (2) |
| **Race** | |
| American Indian/Alaskan Native | 2 (2) |
| Asian | 1 (1) |
| Black or African American | 4 (4) |
| White | 94 (93) |
| Hispanic | 48 (51) |
| Non-Hispanic | 46 (49) |
| **Service Era** | |
| World War II | 8 (7) |
| Pre-Korean War | 1 (1) |
| Korean War | 13 (12) |
| Post-Korean War | 5 (5) |
| Vietnam | 43 (39) |
| Post-Vietnam | 7 (6) |
| Persian Gulf War (1990-1991) | 32 (29) |
| **Exposure** | |
| Agent Orange | 1 (1) |

[a]N = 109; due to missing data for individual patients, the total number in each category may not add up to 109.

**Table 2. Odds Ratios From Logistic Regression Modeling of Predictor Variables for Response Variable of Eosinophil Level > 3%**

| Exposure | Odds Ratio | 95% Confidence Interval | *P* Value |
|---|---|---|---|
| Dyslipidemia | 3.88 | 1.04-14.43 | .043[a] |
| Malignancy | 0.88 | 0.04-18.25 | .935 |
| Asthma/allergy/atopy | 0.75 | 0.18-3.18 | .698 |

[a]Indicates $P < .05$. Probability > $\chi^2 = .0268$ for the model; adjusted for age, sex, race, period of service, and Agent Orange exposure.

also must be considered. Of the possible explanatory exposures considered, only dyslipidemia was found to be statistically significant in the study population. Patients with dyslipidemia had 4 times greater odds of also having elevated eosinophil levels compared with those who did not have dyslipidemia, which is in line with recent literature identifying conditions such as dyslipidemia and diabetes mellitus as independent predictors of elevated eosinophil levels.[6]

In light of the known high rates of obesity in the Imperial Valley in comparison with rates of obesity in San Diego County from previous studies and questionnaires, the increased levels of dyslipidemia in the Imperial Valley compared with those of the other sites included in the study may help explain the geographic distribution of observed elevated eosinophil levels.[7,8] Although data on dyslipidemia rates among study participants at sites other than Imperial Valley were not collected for this study, this explanation represents a promising area of further investigation.

Furthermore, although about 50% of the population in the Imperial Valley had CBCs with eosinophil levels > 3%, only 5% of the population was found to have eosinophilia based on absolute eosinophil counts, and all such cases were mild. Although excluding infection or other causes of elevated eosinophil levels is difficult, it is reasonable to believe that such low-grade elevations that do not meet the criteria for true eosinophilia may be more consistent with chronic processes, such as dyslipidemia, as opposed to frank infection in which one might expect a more robust response.

## Limitations

The cause of this phenomenon is not yet clear, with the investigation limited by several factors. Possibly the sample size of 109 patients in the Imperial Valley was not sufficient to capture some causes of elevated eosinophil levels, particularly if the effect size of an exposure is low or the exposure infrequent. Of note, no cases of HIV, *C immitis* infection, or other parasitic infections were observed. Furthermore, only 3 cases of malignancy and 17 cases of asthma, allergies, and/or atopy were identified. Malignancy, asthma, and allergy and/or atopy were not statistically significant as predictors of eosinophilia at the $\alpha = .05$ level, although the analysis of these variables was likely limited by the small number of patients with these conditions in the sample population. While all these exposures are known to be associated with eosinophilia in the literature, none were identified as predictors in the logistic regression model, likely due, in part, to the limited sample size.

Given the high proportion of the Imperial Valley population with elevated eosinophil levels compared with those of all other sites investigated, a rare or subtle exposure of the types noted would be less likely to explain such a

large difference. It is important to look more carefully at a number of possible factors—including gathering more detailed data on dyslipidemia and *C immitis* infection rates among other possible contributors—to determine more precisely the cause of the notably elevated eosinophil levels in this and other sites in the region.

## CONCLUSION

Using a convenience sample of the VA population based on routine laboratory testing, this study has established that geographically distributed elevated eosinophil levels can be identified in the San Diego region. However, it is less clear why notably elevated eosinophil levels were found at these sites. Although there was no evidence of a correlation between certain environmental factors and elevated eosinophil levels, this may have been due to insufficiently detailed consideration of environmental factors.

Logistic regression analysis associated dyslipidemia with a notably increased risk of elevated eosinophil levels in the Imperial Valley population, but it would be premature to conclude that this association is necessarily causal. Further research would help elucidate this. Increasing the investigational time frame and a chart review of additional sites could provide informative data points for analysis and would allow for a more in-depth comparison between sites. More immediately, given the possibility that dyslipidemia may be a source of the observed elevated eosinophil levels in the Imperial Valley population, it would be worth investigating the rates of dyslipidemia at comparison sites to see whether the lower rates of elevated eosinophil levels at these other sites correspond to lower rates of dyslipidemia.

In future work, it may be valuable to test the study population for *C immitis*, given the prevalence of the fungus in the area and the concern among many public health professionals of its undertesting and underdiagnosis. Because many cases of *C immitis* are subclinical, it may be worth investigating whether these are being missed and to what degree such cases might be accompanied by elevations in eosinophil levels.

Given that much remains unknown regarding the causes of elevated eosinophil levels in the Imperial Valley and other sites in the region, further study of such elevations across sites and over time—as well as careful consideration of noninfectious causes of elevated eosinophil levels, such as dyslipidemia—may be of important value to both local clinicians and public health professionals in this region. ●

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### *Author disclosures*

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