Epidemiological Characteristics of a Chicago-area *Acanthamoeba* Keratitis Outbreak

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• PURPOSE: To characterize *Acanthamoeba* keratitis (AK) cases and analyze the geographical distribution within the Chicago-Gary-Kenosha metropolitan area, Chicago, Illinois, USA.

• DESIGN: Retrospective, population-based cohort study.

• METHODS: All AK cases diagnosed at the University of Illinois at Chicago Cornea Service from June 1, 2003, to November 30, 2005, were included in analysis. Patients with keratitis were defined as cases through confocal microscopy, histology, and/or positive cultures. Exploratory analyses were performed to evaluate whether AK cases were unequally distributed geographically. County population data were extracted from US Census 2000 data, and rates were age-standardized to Cook County. Poisson regression analysis was used to estimate the age-standardized rate ratio (RR) between AK cases and county of residence. Current cases (June 1, 2003 to November 30, 2005) were compared with historical cases (June 1, 2000 to November 30, 2002) to determine if the current rate of AK diagnosis differed from historical rates.

• RESULTS: Forty AK cases were diagnosed between June 1, 2003 and November 30, 2005. The average (±SD) age of patients with AK was 28.0 ± 15.0 years (range, 13 to 70 years), 52.5% were men, and 95.0% wore contact lenses. Estimated RR measures demonstrated increased rates for all counties relative to Cook, and were significant for both DuPage County (RR 3.59; 95% confidence interval [95% CI] 1.44, 8.39) and Will County (RR 3.66; 95% CI 1.18 to 9.56). Current AK diagnosis rates were significantly higher than historical rates (RR 6.67; 95% CI 3.05 to 17.52).

• CONCLUSIONS: AK cases are increasing in frequency. The increased rates are unevenly distributed in the study area. Further research is warranted to better understand the increase and unusual geographical distribution. (Am J Ophthalmol 2006;142: 212–217. © 2006 by Elsevier Inc. All rights reserved.)

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ACANTHAMOEBA KERATITIS (AK), FIRST RECOGnized in 1973, is an often severe, painful infection of the cornea that commonly causes corneal scarring and sometimes blindness. AK is caused by the free-living amoeba *Acanthamoeba*, and it is believed to be related to exposure to contaminated water. Of the 208 reported cases of AK in the US between 1973 and 1988, 85% occurred in contact lens wearers,[1,2] and it is generally believed that contact lens use (particularly when lenses are worn while swimming or when users have poor lens hygiene) is a prominent risk factor. In fact, contact lens use was the single best predictor of AK development in the Iowa outbreak after regional flooding during the mid-1990s.[3] Other well-known risk factors include poor lens hygiene, use of certain types of contact lens disinfection products, source water contamination, and even the type of hydrogel lens material; symptom onset may depend on seasonal temperatures.[3–8]

Although AK is extremely rare, with reported US annualized incidence rates ranging between 1.65 to 2.01 cases per million contact lens wearers, it may be up to 15 times more common in the United Kingdom, Europe, and Hong Kong.[4,9–14] The Department of Ophthalmology at the University of Illinois at Chicago (UIC) has recently seen a considerable increase in the number of AK cases. Specifically, we saw 40 cases between June 1, 2003 and November 30, 2005, 38 of which occurred in contact lens wearers (35 of whom were soft contact lens wearers). Before this recent surge, anecdotally, there had been a

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TABLE 1. Expected *Acanthamoeba* Keratitis Cases Based on US Census 2000 Data

Characteristic	Value
US population	281,421,996
Chicago-Gary-Kenosha Metropolitan Statistical Area population	9,157,540
Chicago city population	2,896,016
Approximate contact lens users in United States[15]	34,000,000
Approximate contact lens users in Chicago-Gary-Kenosha	~1,106,000
Annual US AK incidence rate[12]	1.65–2.01 cases per 1,000,000 contact lens users
Expected AK cases annually in Chicago-Gary-Kenosha	1.83–2.22 cases

AK = Acanthamoeba Keratitis.

yearly maximum of only two or three cases over the past couple decades, which is relatively consistent with what is to be expected, assuming approximately 34 million contact lens users in the United States[15] (Table 1).

AK is a painful and difficult disease to treat; it requires intensive therapy and frequently a corneal transplant. Although it is often initially misdiagnosed, patients with AK are eventually referred to corneal subspecialists, who in turn usually refer the patients to tertiary medical centers. Discussions with community corneal subspecialists suggest that we likely have captured nearly all recent and historical cases, in part because we were the only institution within the catchment area with a confocal microscope (Confoscan 2, Nidek, Gamagori, Japan), or any other noninvasive diagnostic imaging device, between 2000 and 2005.

Between June 1, 2003 and November 30, 2005, only six of 40 AK cases diagnosed at UIC were from the City of Chicago. Other cases were from surrounding areas, with a large percentage originating from the west, southwest, and south suburbs. This referral pattern is not only inconsistent with departmental patient referral patterns, but is also highly inconsistent with expected case locations, given area demographics and the size of the City of Chicago, which is located in Cook County. The purpose of this analysis is to evaluate the geographical distribution of cases, to provide descriptive statistics, and to compare the current and historical rates of AK diagnosis.

METHODS

THE UIC INSTITUTIONAL REVIEW BOARD REVIEWED AND approved this research. The UIC Department of Ophthalmology, located within the Illinois Medical District immediately west of downtown Chicago, serves as a major tertiary referral center for both Chicago and the Chicago-Gary-Kenosha metropolitan area, and together with its associated hospital clinics registers approximately 64,500 outpatient visits annually. A retrospective cohort study design was used to provide descriptive statistics for current cases and to compare current UIC AK diagnosis rates to historical diagnosis rates. Hypothesis testing was conducted to determine whether the current rate of diagnosis at UIC was increased over the historical rate, and whether the current cases were equally distributed throughout the region according to US Census 2000 demographic information.

All cases of AK diagnosed at the UIC Cornea Subspecialty practice between June 1, 2003 and November 30, 2005, were included in the analysis and considered current cases; all UIC AK cases similarly diagnosed between June 1, 2000 and November 30, 2002, were defined as historical cases. Time frames for current and historical cases were identified such that the duration and season at risk were identical between current and historical cases and the potential for AK diagnosis included the availability of a confocal microscope at UIC (available beginning June 1, 2000). Keratitis was defined as AK if one or more of the following conditions were met: (1) identification of highly refractile, 10- to 25-μm ovoid bodies on confocal microscopy; (2) identification of trophozoites or cysts through histology when specimens were stained with Diff-Quick stain after fixation; (3) positive cultures; or (4) definitive clinical presentation that resolved with anti-*Acanthamoeba* treatment. Confocal microscopy was performed by a single clinician (E.Y.T.). Cases were identified through confocal microscopy diagnostic codes, record review, and a search of computer-generated consultation letters containing the word "*Acanthamoeba*."

To evaluate hypothesis strength that current AK cases were not equally distributed throughout the region, AK incidence rates in the general population were calculated by using the US Census Bureau's Census 2000 population data. County population data restricted to the same age range as cases were extracted from US Census 2000 data to determine the number of people at risk per county (aged 13 to 74; as close as possible according to US Census age stratifications), and incidences rates were age-standardized to Cook County using eight age categories (13 to 18, 19 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 69, and 70 to 74). Poisson regression analysis was performed at the county level to model the age-standardized rate ratio (RR) of AK according to county of residence, and was limited to the five-county Illinois region directly surrounding Chi-

TABLE 2. Case Demographic Information for All *Acanthamoeba* Keratitis Cases

Demographic	Value
Number	40
Age (years)	
Mean ± SD	28.0 ± 15.0
Range	13–70
Male gender, n (%)	21 (52.5%)
Race, n (%)	
Caucasian	38 (95.0%)
African-American	2 (5.0%)
Year* (%)	
2003	22.5%
2004	41.6%
2005	35.9%
Season† (%)	
Spring	25.3%
Summer	25.3%
Fall	27.4%
Winter	22.1%
Current contact lens use, n (%)	
All	38 (95.0%)
Soft contact lens use	35 (87.5%)
Rigid contact lens use	3 (7.5%)

*Percentages adjusted to 12-month time period because study period (June 1, 2003, to November 30, 2005) includes unequal time periods per year.

†Seasons defined by meteorological conventions of spring beginning on March 1, summer on June 1, autumn on September 1, and winter on December 1. Percentages were adjusted because study period includes unequal numbers of seasons.

TABLE 3. *Acanthamoeba* Keratitis Cases and Cohort Data per Five-county Illinois Area Surrounding Chicago*

County	No. of Cases	US Census 2000 Population
DuPage	8	684,059
Lake	2	478,840
McHenry	2	192,328
Will	5	372,455
Cook	14	4,051,601
Total	33	5,779,283

*Cases were diagnosed between June 1, 2003, and November 30, 2005.

TABLE 4. Age-standardized Rate Ratios for *Acanthamoeba* Keratitis per Five-county Illinois Area Surrounding Chicago*

County	Rate Ratio	95% Confidence Limit		χ^2	*P* Value
		Lower	Upper		
DuPage	3.59	1.44	8.39	8.33	.004
Lake	1.31	0.21	4.68	0.13	.723
McHenry	2.69	0.42	9.63	1.71	.190
Will	3.66	1.18	9.56	6.20	.013
Cook	1.00	1.00	1.00	—	—

*Based on US Census 2000 population data.

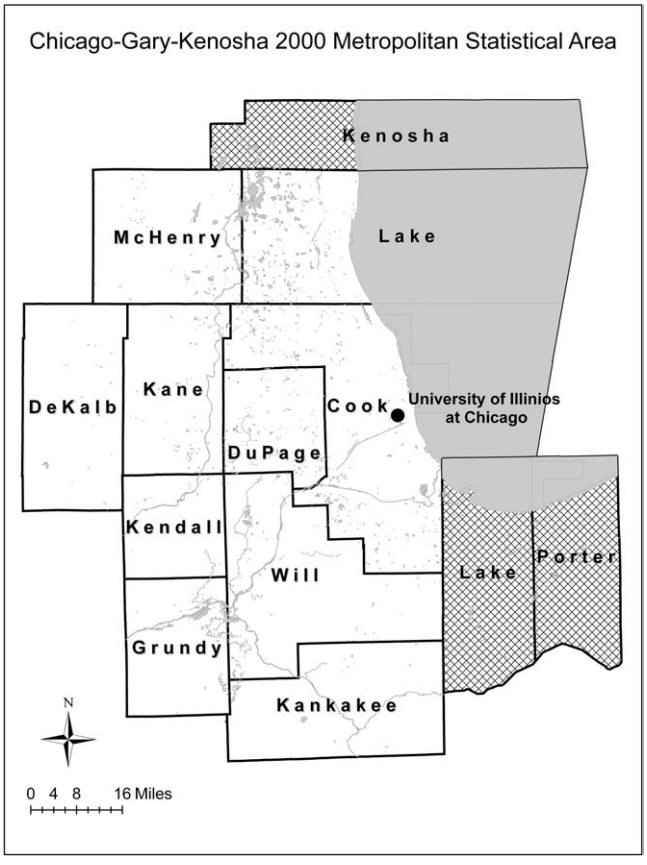

FIGURE. Map of Chicago-Gary-Kenosha 2000 Metropolitan Statistical Area detailing 14-county area including Lake Michigan and local water features. Shaded counties (Kenosha, Lake, and Porter) represent Wisconsin and Indiana. Only five Illinois counties were analyzed for geographical distribution to ensure adequate *Acanthamoeba* keratitis (AK) cases per county, including DuPage, Lake, McHenry, Will, and Cook Counties.

cago to ensure adequate AK cases per county. Descriptive statistics were calculated for basic demographic and clinical information, including age, gender, race, contact lens use, year, and season.

To evaluate the hypothesis that current rate of AK diagnosis at UIC was increased over the historical rate, Poisson regression was used to estimate RR of AK diagnosis for all counties comparing the current time period (June 1, 2003 and November 30, 2005) to an historical time period (June 1, 2000 and November 30, 2002). The six-month time period between December 1, 2002 and May 31, 2003, in which one AK case was diagnosed was excluded to

TABLE 5. Diagnosed *Acanthamoeba* Keratitis Cases and Rate Ratios Per Time Period*

Time Period	No. of Cases Diagnosed	Rate Ratio	95% Confidence Limit		χ^2	*P* Value
			Lower	Upper		
June 1, 2003 to November 30, 2005	40	6.67	3.05	17.52	18.78	<.0001
June 1, 2000 to November 30, 2002	6	1.00	1.00	1.00	—	—

*Based on US Census 2000 population data.

maintain consistency between the current and historical time periods for both seasonality and time at risk.

All regression analyses were performed by SAS, version 8.02, PROC GENMOD (SAS Inc, Cary, North Carolina, USA). Likelihood-based 95% confidence intervals (95% CI) and *P* values were estimated. Findings were considered to be statistically significant if the *P* value (two-sided) was <.05.

RESULTS

FORTY AK CASES WERE DIAGNOSED AT UIC BETWEEN JUNE 1, 2003 and November 30, 2005. Patient demographic and basic clinical information is presented in Table 2. Not surprisingly, most of the patients used contact lenses, and the use of soft lenses was much more common than the use of rigid gas permeable lenses. Slightly more than half of all cases were men, and the average age was just under 30 years. Table 3 presents the cases as well as US Census 2000 population data used in calculation of relative risks.

Generally, confocal microscopy and microbial analysis (cultures, histology, and/or keratoplasty pathology) were used together to supplement clinical presentation in AK diagnosis. Exceptions included five subjects who were diagnosed with confocal microscopy alone as a result of patient refusal of corneal scraping or insurance issues, and two subjects were diagnosed by microbial analysis alone. Both confocal microscopy and microbial analysis were performed in 33 subjects. All equivocal results for either confocal (n = 3) or microbial analysis (n = 1) were treated as negative test results. For these 33 subjects, the proportion of individuals with disease by microbial analysis with a positive result on confocal microscopy was 92.6%. Likewise, the proportion of cases with a positive test by confocal microscopy that actually had the disease by microbial analysis was 83.3%. Confocal microscopy was positive in all six cases from the historical period, and in 34 (89.5%) of 38 cases for which imaging was performed during the current period.

Poisson regression analysis of cases within the five-county Illinois area surrounding Chicago demonstrated increased age-standardized RRs for AK diagnosis for all counties relative to Cook County. These rates were significantly increased for both DuPage County (RR 3.59; 95% CI 1.44 to 8.39) and Will County (RR 3.66; 95% CI 1.18 to 9.56), which are located to the west and south-southwest of Chicago (Table 4; Figure).

Comparison of all current and historical UIC AK cases demonstrated a marked increase in the rate of AK diagnosis when comparing the current with the historical time period (Table 5). The relative risk for AK diagnosis between June 1, 2003 and November 30, 2005 was nearly seven times greater (RR 6.67; 95% CI 3.05 to 17.52) than between June 1, 2000 and November 30, 2002, suggesting that the rate of AK diagnosis has dramatically increased.

DISCUSSION

OUR DATA REVEAL A STATISTICALLY AND CLINICALLY significant increase in the number of AK cases in recent years. Not only is the rate of AK diagnosis increased, but the age-standardized risk of AK is not consistent across different geographical locations in the Chicago area. As in other reported outbreaks of AK, this Chicago-area outbreak is similar in that nearly all AK cases used contact lenses.

Retrospective cohort studies are subject to certain potential biases, most importantly, the issue of accurately and completely identifying cases. We feel fairly confident in case ascertainment because AK, once symptomatic, is generally not considered a "silent" disease that resolves without treatment or specific anti-*Acanthamoeba* treatment. Furthermore, one clinician (J.S.) has been in the Cornea Service at UIC since 1975 and has historically diagnosed a maximum of two or three AK cases per year since the mid-1980s. Finally, discussions with corneal subspecialists at other Chicago-area academic institutions and within the community suggest we have captured nearly, if not all, historical cases, in part because we were the only institution in the study area with a confocal microscope for noninvasive diagnosis from 2000 to 2005.

Although confocal microscopy may appear to inflate incidence rates as noninvasive diagnostic methods perhaps allow for earlier diagnosis, at which point cases resolve without treatment,[3,16] the temporal inconsistency between confocal microscope acquisition and the Chicago-area

outbreak diminishes the validity of this argument as the source of increased AK diagnosis. Confocal microscopy was used for a full three years at UIC before we saw an increase in cases, with a total of seven cases diagnosed between June 1, 2000 and June 1, 2003. An increase in AK diagnosis would have been expected earlier had this simply been a matter of more sensitive and noninvasive testing tools.

As such, our results suggest an outbreak of AK in Chicago, with the risk of AK varying on the basis of geographical location. Many factors may be hypothesized as being responsible for this increase in AK diagnosis compared with the historical level of diagnosis, such as clinical or demographic factors, or even organism pathogenicity. New hydrogel lens materials may permit *Acanthamoeba* to adhere better,[6–8] and changes in lens care hygiene, including different solutions[17,18] or the use of no-rub multipurpose solutions—just to name a few—may alter AK risk; however, it is difficult to understand how these or other similar factors alone could account for geographical variation. Because *Acanthamoeba* is a waterborne pathogen, water quality issues need to be considered as a hypothesized cause of increased AK.

In December 1998, the US Environmental Protection Agency (EPA) reduced the allowable amount of carcinogenic disinfection by-products in the water supply with the Stage 1 Disinfectants and Disinfection Byproducts Rule.[19] Disinfection by-products are produced when disinfectants (such as chlorine, ozone, chlorine dioxide, and chloramines) react with organic matter present in the water, and as a result, treatment plants have minimized disinfection by-products by reducing the amount or changing the type of chlorine used, changing the timing of when chlorine is added, or removing organic material from water.[20] EPA compliance deadlines were January 2002 for large surface water systems (for example, Lake Michigan supplies) and January 2004 for small surface water and ground water systems (for example, public aquifer or well supplies).[19] Despite addition of disinfectant residuals throughout the system to protect treated water, most pipes within water distribution systems are colonized by many microorganisms that amoebae graze on as they integrate with biofilms lining pipe surfaces, and chlorine and disinfectant residual levels directly influence the extent of biofilm development.[21–25] As such, disinfection residuals minimize *Acanthamoeba* colonization by reducing available biofilm for *Acanthamoeba* grazing in addition to directly killing trophozoites (cysts are highly chlorine resistant).[26–28] And as a result, biofilms are more highly developed downstream at lower residual chlorine concentrations,[22,25] suggesting that end users further from treatment may be more likely to have *Acanthamoeba* and microorganism-contaminated water. It is plausible that our geographical variation in AK cases may be explained by the distance between water purification and use.

Given the fact that the City of Chicago pumps and treats Lake Michigan water at two treatment plants and provides water to customers within the city and 124 suburbs,[29] most of which are located west, south, and southwest of the Chicago, the hypothesis that recent EPA regulations may have shifted the balance between microbial risk and carcinogenic disinfection by-products must be investigated to understand whether it is related to this increase in AK diagnosis (most suburbs north of Chicago along the lake have their own water treatment facilities and provide water to their neighboring suburbs to the west). This is particularly relevant given the distance between Lake Michigan water treatment and the end user is greater than 35 miles for some patients with AK. Although not all patients with AK received Lake Michigan water supplies, EPA regulations requiring a decrease in disinfection by-products applies to all cases with community water supplies.

If in fact this hypothesis is correct, then it is possible that a similar increase in AK may occur throughout the United States, as was recently described in Philadelphia soon after our outbreak (Rocha FN, AAO E-Abstract PA005, 2005). The EPA compliance deadline for treated water supplies from Lake Michigan and other large surface-water systems was January 2002, two years before compliance deadlines for communities with aquifer-supplied or smaller surface systems.[19] Furthermore, as a result of Chicago demographics and geography, proximity between water treatment and end use for customers receiving Lake Michigan supplies is much greater than distances between water treatment and end use in other parts of the country, potentially allowing the more rapid growth of highly developed biofilms at the end of distribution systems in the Chicago area compared with water distribution systems in smaller cities. As a result, clinicians in other communities need to be alert to the potential for similar AK outbreaks, and surveillance systems should be developed.

In conclusion, this age-standardized exploratory analysis suggests that there is a marked increase in AK compared with the historical rate, and that population data indicate that the geographical distribution of cases is not uniform or random. Although the demographics of the Chicago-area outbreak are similar to that of previously reported cases, including the correlation with contact lens use, the geographical variation and increased risk in AK diagnosis over time appears to be inconsistent with previously understood incidence rates and risk factors. Additional research is warranted to better understand clinical risk factors associated with this recent AK outbreak—and more importantly, to further explore the hypothesis that recent EPA changes to decrease carcinogenic risk from disinfection by-products may have shifted the microbial risk balance, increasing the risk of AK. Finally, clinicians need to be aware that if our hypothesis is correct and the Chicago outbreak is related to recent changes in US EPA

regulations, the potential exists for a similar dramatic increase in AK cases nationally.

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Biosketch

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Biosketch

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