Clinical Characteristics of *Acanthamoeba* Keratitis Infections in 28 States, 2008 to 2011

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Purpose: The aim was to describe a geographically and clinically diverse sample of cases of *Acanthamoeba* keratitis (AK) and establish the risk factors for poor outcomes among patients with this disease.

Methods: We conducted a retrospective, population-based case series of 116 patients with AK identified through a national surveillance network. Data were collected via a medical record review by diagnosing ophthalmologists and by phone interviews with patients. Exact logistic regression modeling was used to determine risk factors for poor visual outcomes.

Results: Among patients with data available on contact lens use, it was found that 93.3% wore contact lenses. The median time from symptom onset to care seeking was 2 days, whereas the median time from symptom onset to diagnosis was 27 days. Keratoplasty was performed in 27 of 81 patients with available outcome data and was more likely in patients >40 years old [odds ratio (OR) 5.25, 95% confidence interval (CI) 1.49–21.92]. When adjusted for age, the risk factors for keratoplasty included the presence of a ring infiltrate (OR 40.00, 95% CI 3.58–447.0) or any sign of stromal invasion (OR 10.48, 95% CI 2.56–55.09). One-third of patients with available data on best-corrected visual acuity had a best-corrected visual acuity <20/200, with the presence of a ring infiltrate as the only significant predictor of this outcome when adjusted for age (aOR 3.45, 95% CI 1.01–12.31).

Conclusions: AK remains challenging to diagnose. Consequently, patients with advanced disease are more likely to have poor outcomes, particularly if they are older. The increasing awareness of AK among general eye care providers may shorten referral times and potentially improve outcomes.

Key Words: *Acanthamoeba*, diagnosis, risk factors

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Acanthamoeba keratitis (AK) is a rare, potentially blinding infection of the cornea caused by a free-living ameba commonly found in the environment. In the United States, AK primarily affects otherwise healthy contact lens wearers (CLWs).[1,2] Previously identified risk factors among CLWs include improper storage or disinfection of lenses and contact with nonsterile water while wearing lenses.[3–5] Among nonCLWs, corneal trauma has been proposed as a primary risk factor for AK infection.[6–8] Clinical outcomes tend to be poor, with substantial proportions of patients requiring keratoplasty or enucleation.[9,10]

AK is difficult to diagnose and treat. Symptoms are often nonspecific and classic signs (eg, perineuritis) are not always present.[6,11,12] Estimates of the sensitivity of culture for detecting *Acanthamoeba* range from 50% to 74%[13–15]; other modalities such as confocal microscopy (CM) and polymerase chain reaction are potentially more sensitive than culture techniques but are less widely available and are less standardized.[13,16] Delays in proper diagnosis have been correlated with more extensive disease at presentation for medical care, greater likelihood of requiring keratoplasty, and worse final visual acuity.[17–19] Treatment is complicated by several factors, including the resistance of *Acanthamoeba* spp in cyst form to many pharmacological agents[20] and the use of topical steroids before diagnosis.[15,21] Although therapy with topical biguanides is considered to be the most effective in treating AK,[15] no evidence-based guidelines exist and practices vary substantially.[22]

The available clinical information about AK has been limited by the fact that most data have been derived from case studies or small case-series investigations that span long periods of time.[9,23–26] These case series have typically been reported from single institutions and therefore may have limited generalizability beyond that select group of patients. We present data on clinical characteristics, risk factors, diagnostic

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modalities, treatments, and outcomes for 116 case patients with AK from 28 US states between 2008 and 2011.

METHODS

Case Definition and Case Ascertainment

We defined a case of AK as eye disease occurring in a person with corresponding clinical signs and symptoms whose infection was diagnosed by an ophthalmologist and confirmed either by laboratory findings (tissue specimen positive by culture or histology) or by CM. We included cases with symptom onset between January 1, 2008, and June 12, 2011. Cases were identified through a surveillance network coordinated by Centers for Disease Control and Prevention (CDC) that includes 14 academic ophthalmology centers and 1 commercial clinical laboratory (see Table, Supplemental Digital Content 1, http://links.lww.com/ICO/A162). Additionally, some state health officials solicited individual case reports through direct communications with ophthalmologists and optometrists.

Data Collection

Data were collected from case patients and diagnosing ophthalmologists. Case patients were interviewed by telephone using a standardized questionnaire to gather data on symptoms, contact lens use, and demographics. Standardized chart abstraction forms were sent to diagnosing ophthalmologists to collect information from medical records. Using this form, ophthalmologists were asked to indicate the presence or the absence of multiple signs and symptoms, the types of modalities used to attempt diagnosis and ensuing results, the types of medications prescribed during the clinical course of infection, and the outcomes of disease, specifically whether the infection resolved with medication, whether keratoplasty was performed or planned and the last known best-corrected visual acuity (BCVA).

Definition of Terms

Based on the known pathophysiology of AK[27] and previously published classifications of the stages of infection,[15,18,19] we categorized the severity of disease at presentation to the diagnosing ophthalmologist as early ($\geq$1 of the following signs only: epithelial or subepithelial infiltrate, epithelial ulceration, punctate keratopathy), middle (some signs of stromal invasion—including focal/multifocal stromal infiltrate; anterior chamber cells; and flare without hypopyon, radial perineuritis, linear keratopathy, hypopyon—but without signs of advanced infection) or advanced ($\geq$1 of the following signs: ring infiltrate, diffuse stromal infiltrate, stromal abscess, nodular, or diffuse scleritis). Time intervals related to care seeking and diagnosis were defined as follows: care-seeking time (number of days from symptom onset to first consultation with any health care provider), referral time (number of days from the first consultation with any health care provider to presentation at the physician who diagnosed AK), diagnosis time (number of days from presentation to the diagnosing physician until confirmed diagnosis of AK), and total time to AK diagnosis (number of days from symptom onset to confirmed diagnosis of AK, that is, the composite interval of care-seeking time, referral time and diagnosis time). Poor visual outcome was defined as requiring keratoplasty or having a BCVA of $<$20/200 in the affected eye; these outcomes were analyzed separately.

Data Analysis

Data from case-patient interviews and chart abstraction forms were entered into a database using mrInterview software (International Business Machines, Armonk, NY) and analyzed using SAS 9.3 (SAS Institute Inc, Cary, NC). To analyze relationships between patient age and other variables, we categorized patients into those 40 years of age or below and those above 40 years of age, based on a median age of 40 among case patients. The Wilcoxon rank-sum test was used to compare distributions among populations. The χ^2 and Fisher exact tests were used to test associations between categorical variables. The kappa statistic was used to compare the agreement between culture and CM results. Exact logistic regression models were used to calculate crude and age-adjusted odds ratios (ORs) to assess risk factors associated with the need for keratoplasty and poor BCVA. For all the tests, results were considered statistically significant at $P < 0.05$.

Human Subject Protection

Data for this case series were collected as part of a 2011 multistate investigation of AK cases initiated in response to persistently elevated numbers of reported AK cases after a multistate outbreak investigation in 2007.[5] Because the purpose of the investigation was to identify, characterize, and control disease in response to an immediate public health threat, it was determined to be a nonresearch public health emergency response and was exempted from a CDC IRB review. This investigation was conducted in a manner that adhered to the tenets of the Declaration of Helsinki and was compliant with US government regulations for protecting patient privacy.

RESULTS

Clinical Presentation

During the multistate investigation, completed chart abstraction forms were returned for 116 case patients from 28 states (see Table, Supplemental Digital Content 2, http://links.lww.com/ICO/A163); 90 case patients (77.6%) also completed telephone interviews. The remaining patients could not be contacted or refused an interview.

Among the 116 case patients, common symptoms at presentation to the diagnosing ophthalmologist included eye pain (91.4%), eye redness (82.8%), blurred vision (81.0%), photophobia (80.2%), and tearing (62.1%) (Table 1). The most common presenting signs on eye examination were an epithelial or subepithelial infiltrate (56.0%), punctate keratopathy (52.6%), and epithelial ulceration (49.1%). Ring infiltrate and radial perineuritis were only present in 34 (29.3%) and 25 (21.6%) case patients, respectively. Overall, 58 patients

TABLE 1. Frequency of Common AK Symptoms and Signs at Presentation to Diagnosing Ophthalmologist (N = 116)

	n	%
Symptoms		
Eye pain	106	91.4
Eye redness	96	82.8
Blurred vision	94	81.0
Photophobia	93	80.2
Tearing	72	62.1
Foreign body sensation	52	44.8
Eye discharge	27	23.3
Physical signs		
Epithelial or subepitheial infiltrate	65	56.0
Punctate keratopathy	61	52.6
Epithelial ulceration	57	49.1
Diffuse stromal infiltrate	35	30.2
Focal/multifocal stromal infiltrate	35	30.2
Ring infiltrate	34	29.3
Anterior chamber cells without hypopyon	26	22.4
Radial perineuritis	25	21.6
Linear keratopathy	24	20.7
Hypopyon	15	12.9
Stromal abscess	4	3.5
Nodular or diffuse scleritis	2	1.7
Status of disease at first presentation to diagnosing physician		
"Early" AK (epithelial involvement only)*	28	24.1
"Middle" AK (signs of stromal invasion)†	30	25.9
"Advanced" AK (severe infection)‡	58	50.0

*The patient presented only with ≥1 of the following signs: epithelial or subepithelial infiltrate, epithelial ulceration, punctate keratopathy.

†The patient presented with some signs of stromal invasion (focal/multifocal stromal infiltrate, anterior chamber cells, and flare without hypopyon, radial perineuritis, linear keratopathy, and hypopyon) but not signs of severe infection (ring infiltrate, diffuse stromal infiltrate, stromal abscess, nodular, or diffuse scleritis).

‡The patient presented with ≥1 of the following signs: ring infiltrate, diffuse stromal infiltrate, stromal abscess, nodular, or diffuse scleritis.

(50.0%) presented with at least 1 physical sign suggesting advanced *Acanthamoeba* infection.

Diagnosis

Acanthamoeba spp were isolated in culture from 88 of 100 cases (88.0%) and seen by CM in 52 of 72 cases (72.2%) (Table 2). In 54 of the 116 total cases (46.6%), culture was the only diagnostic modality positive for AK (other test findings were either negative or not performed), whereas in 23 cases (19.8%), CM was the only modality positive for AK. In addition, 2 cases were confirmed by tissue histology alone (both culture and CM were negative), and the results of the remaining 37 cases were found to be positive by multiple test modalities. Only 16 cases were not cultured—their results were all found to be positive by CM. In 47 of the 116 total cases (40.5%), data on diagnosis were available for both culture and CM; comparative results are presented in Table 3.

Treatment

Treatment information was available for 112 case patients (96.5%). In 55 cases (49.1%), the initial treatment

TABLE 2. Test Methods and Results Used to Diagnose Case Patients With AK

Test Type	Patients Tested (N = 116)		Patients Tested Positive	
	n	%	Frequency	%
Culture	100	86.2	88/100	88.0
CM	72	62.1	52/72	72.2
Histology/smear/stain	57	49.1	11/57	19.3
Polymerase chain reaction	5	4.3	2/5	40.0
At least 2 of the above methods	76	65.5	37/76	48.7

prescribed by the diagnosing ophthalmologist was an antiamebic therapy, including chlorhexidine, polyhexamethylene biguanide, and/or hexamidine. The first medication prescribed was an antibiotic in 34 cases (30.4%), an antiviral medication in 10 cases (8.9%), an antifungal agent in 3 cases (2.7%), and a steroid in 6 cases (5.4%). A total of 37 patients (33.0%) were prescribed steroids at any point during the course of treatment; the diagnosing ophthalmologist in 14 of these cases (37.8%) prescribed steroids before making a diagnosis of AK.

Care Seeking and Diagnosis Intervals

For the 116 case patients, the median total time to AK diagnosis was 27 days (range: 0–296 days; Fig. 1). Among CLWs, the median was also 27 days (range: 2–60 days), compared with 50 days (range: 2–120 days) for patients who were not CLWs ($P < 0.001$). Patients presenting with signs of advanced AK had a median total time to AK diagnosis of 35 days (range: 1–296) compared with 19 days (range: 0–187) for patients whose presentations did not include these signs ($P < 0.01$). Median total time to AK diagnosis for patients aged 40 years or below was 22 days (range: 0–187) compared with 34 days for patients aged above 40 years (range: 0–296) ($P = 0.02$). Other demographic factors were not statistically associated with total time to AK diagnosis.

Among all the case patients, the median care-seeking time was 2 days (range: 0–120 days). Median care-seeking time was 2 days (range: 0–60 days) for CLWs versus 30 days (range: 2–120 days) for non-CLWs ($P < 0.01$). There were no statistically significant differences in care-seeking time

TABLE 3. Results Where Diagnostic Confirmation of AK Was attempted by Both Culture and Confocal Microscopy (N = 47)

	CM		
Culture	*Acanthamoeba* spp Visualized	*Acanthamoeba* spp Not Visualized	Total
Acanthamoeba spp isolated	26	10	36
Acanthamoeba spp not isolated	10	1	11
Total	36	11	47

$\kappa = -0.19$, $P = 0.10$.

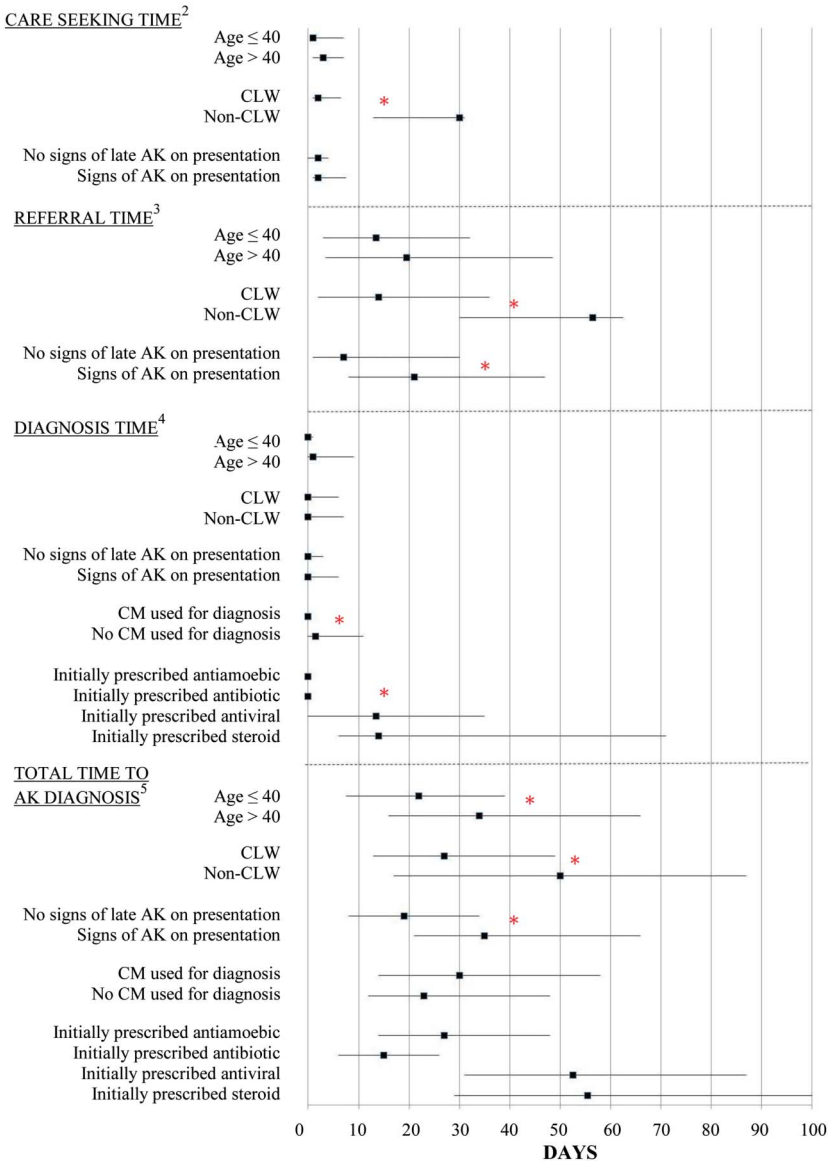


FIGURE 1. Median times with interquartile ranges for care seeking and diagnosis among selected subgroups of patients with Acanthamoeba keratitis (AK). N = 90 for age and contact lens wearer (CLW), N = 116 for signs of late AK/confocal diagnosis, and N = 106 for medication types. [2]Defined as the interval between symptom onset and first presentation to any medical facility. [3]Defined as the interval between first presentation to any medical facility and first presentation to the diagnosing ophthalmologist. [4]Defined as the interval between first presentation to diagnosing ophthalmologist and diagnosis of AK. [5]Defined as the composite interval of care-seeking time, referral time, and diagnosis time. *Statistically significant difference between median times within subcategories, at $P < 0.05$. CM, confocal microscopy.

when analyzed by gender, age group, race, ethnicity, or severity of infection at presentation.

Among all the case patients, median referral time was 14.5 days (range: 0–229 days); this was significantly longer (21 days, range: 0–229) for patients with signs of advanced AK at first presentation to the diagnosing physician compared with those without these signs (7 days, range: 0–56, $P < 0.01$). Among CLWs, the median referral time was 14 days (range: 0–163 days), compared with 57 days (range: 4–68 days) for patients who were not CLWs ($P < 0.01$). Comparisons of referral time by gender, age group, race, and ethnicity were not statistically significant.

Once seen by the diagnosing ophthalmologist, median diagnosis time was 0 days (range: 0–162 days). Case patients who were older than 40 years had a median diagnosis time of 1 day (range: 0–71 days) compared with 0 days for patients 40 years or below (range: 0–162 days) ($P = 0.02$). Patients whose infections were diagnosed by CM had a median diagnosis time of 0 days (range: 0–40 days) compared with 1.5 days (range: 0–162 days) when CM was not used for diagnosis ($P < 0.01$). Median diagnosis time differed when analyzed by the initial choice of medication as follows: amebicidal medication (median: 0 days, range: 0–27 days), antibiotic (median: 0 days, range: 0–86 days), steroid (median: 14 days, range: 1–119 days), and antiviral medication (median: 14 days, range: 0–162 days) ($P < 0.01$). There were no statistically significant differences in the diagnosis time among patients when analyzed by other clinical or demographic variables.

Outcomes

Twenty-three of 116 patients (19.8%) were still undergoing pharmaceutical treatment at the time of data collection and 12 (10.3%) had no available outcome data. Of the remaining 81 (69.8%) case patients with known final

treatment outcomes, 54 (66.7%) had infections that resolved with pharmaceutical therapy alone, whereas 27 (33.3%) underwent a penetrating keratoplasty or were awaiting keratoplasty at the time of data collection. In univariate analysis, keratoplasty was more likely to be performed on patients who were older than 40 years (OR 5.25, 95% confidence interval [CI] 1.49–21.92), who presented to their diagnosing ophthalmologist with ring infiltrate (OR 7.27, 95% CI 2.05–28.74) or other signs of advanced disease (OR 7.92, 95% CI 2.56–27.36), or whose diagnosis was made >30 days after symptom onset (OR 3.60, 95% CI 1.20–11.50). Patients who were initially prescribed steroids were also more likely to undergo a keratoplasty, although this result had a borderline statistical significance (OR 8.76, 95% CI 1.29–∞; $P = 0.06$). When adjusted for age using logistic regression modeling, only advanced disease at presentation to the diagnosing ophthalmologist remained significantly associated with the need for undergoing a keratoplasty. The effect of ring infiltrate was modified by age. Among patients older than 40 years, those with a ring infiltrate were significantly more likely to undergo a keratoplasty (aOR 40.0, 95% CI 3.58–447.03) than those without a ring infiltrate. Crude and age-adjusted ORs are presented in Table 4.

Of the 100 patients (85.6%) whose BCVA was reported, 33 (33.0%) developed a BCVA worse than 20/200 in the affected eye. When adjusted for age, patients with this outcome were more likely to present to the diagnosing ophthalmologist with a ring infiltrate (aOR 3.45, 95% CI 1.01–12.31). No other factors reached statistical significance. ORs (crude and age-adjusted) are presented in Table 5.

Demographics and Contact Lens Uses

Data on demographics and contact lens use were available for the 90 case patients who were interviewed by telephone. The majority were female (n = 56, 62.2%), non-Hispanic (n = 82, 92.1%), White (n = 79, 87.8%), and CLWs (n = 84, 93.3%). The median age was 40.3 years, with a bimodal distribution of patient ages (Fig. 2). Of 84 CLWs, 69 (82.1%) wore soft lenses. Seven CLWs (10.1%) reported using daily disposable lenses, 38 (55.1%) reported using daily lenses (intended to be removed every night and replaced every 2–4 weeks), and 21 (30.4%) reported using extended-wear lenses (intended to be worn continuously for up to 30 days). Fifteen CLWs (17.9%) wore rigid gas-permeable lenses. The majority of CLWs (54 or 64.3%) reported using a multipurpose solution to clean their lenses; other solutions used included saline (23.8%), daily cleaner, (22.6%), rewetting solution (16.7%), and peroxide (8.3%). Of 68 patients with available data, 37 (54.4%) reported rinsing their lenses

TABLE 4. Associations Between Demographic, Clinical, Diagnostic, and Treatment Factors and Need for keratoplasty* Among Patients With AK With Known Final Outcomes on Pharmaceutical Therapy (N = 81)

Risk Factors for Keratoplasty	n	OR (95% CI)	*P*	aOR (95% CI)†	*P*
Demographics/clinical history					
Bilateral AK	9	0.22 (0.01–1.83)	0.26	0.19 (0.00–1.27)‡	0.15
Age >40 yrs	36	5.25 (1.49–21.92)	0.01	—	
History of potential AK medical risk factor§	22	0.68 (0.19–2.20)	0.67	0.72 (0.16–3.03)	0.86
Used contact lenses	58	0.85 (0.09–10.99)	>0.99	0.93 (0.08–13.73)	>0.99
Presenting signs					
Late/severe disease at presentation¶	34	7.92 (2.56–27.36)	<0.001	10.48 (2.56–55.09)	<0.001
Ring infiltrate at presentation	23	7.27 (2.05–28.74)	<0.001		
Ring infiltrate >40 yrs of age‖				40.0 (3.58–447.03)	0.02
Ring infiltrate ≤40 yrs of age‖				1.00 (0.09–11.59)	>0.99
Radial perineuritis at presentation	15	0.75 (0.11–3.79)	>0.99	0.73 (0.06–5.77)	>0.99
Diagnosis					
Care-seeking time** >1 wk	14	1.13 (0.27–4.33)	>0.99	1.48 (0.29–7.50)	0.82
Referral time†† >1 wk	39	2.44 (0.87–7.21)	0.10	1.79 (0.51–6.59)	0.45
Diagnosis time‡‡ >1 d once seen by diagnosing physician	30	1.52 (0.52–4.43)	0.54	1.45 (0.38–5.46)	0.73
Total time from onset to diagnosis >30 d	32	3.60 (1.20–11.50)	0.02	3.31 (0.87–14.06)	0.09
Diagnosis with CM	35	1.68 (0.60–4.77)	0.38	2.10 (0.60–7.62)	0.29
Treatment					
Initially treated with amebicidal agent	34	1.02 (0.35–2.96)	>0.99	0.72 (0.18–2.75)	0.80
Initially treated with steroids	3	8.76 (1.29–∞)‡	0.06	8.15 (1.07–∞)‡	0.09
Received steroids before AK diagnosis	11	0.58 (0.09–3.49)	0.76	0.40 (0.03–3.53)	0.62

*Twenty-seven of 81 patients required keratoplasty.
†Age-adjusted ORs.
‡Maximum likelihood estimate does not exist, median unbiased estimate reported.
§Includes previous eye trauma, previous eye surgery, previous eye infection, previous keratopathy, history of diabetes mellitus, or history of immune deficiency.
¶Includes patients presenting with ≥1 of the following signs: ring infiltrate, diffuse stromal infiltrate, stromal abscess, nodular or diffuse scleritis.
‖Significant interaction with age, stratified estimates reported.
**Defined as the interval between symptom onset and first presentation to any medical facility.
††Defined as the interval between the first presentation to any medical facility and the first presentation to diagnosing ophthalmologist.
‡‡Defined as the interval between the first presentation to the diagnosing ophthalmologist and diagnosis of AK infection.

TABLE 5. Associations Between Demographic, Clinical, Diagnostic, and Treatment Factors and BCVA <20/200* Among Patients With AK With Known Final BCVAs (N = 100)

Risk Factor for BCVA <20/200	n	OR (95% CI)	*P*	aOR (95% CI)†	*P*
Demographics/clinical history					
Bilateral AK	13	0.57 (0.09–2.46)	0.63	0.30 (0.01–3.04)	0.51
Age >40 yrs	38	2.66 (0.92–8.21)	0.08	—	
History of potential AK medical risk factor‡	23	1.41 (0.47–4.10)	0.64	1.04 (0.27–3.75)	>0.99
Used contact lenses	73	0.16 (0.00–2.08)	0.22	0.15 (0.00–2.06)	0.21
Presenting signs					
Late/severe disease at presentation§	47	2.73 (1.07–7.22)	0.03	2.52 (0.85–7.85)	0.10
Ring infiltrate at presentation	28	2.57 (0.90–7.47)	0.08	3.45 (1.01–12.31)	0.05
Radial perineuritis at presentation	23	0.44 (0.09–1.70)	0.30	0.70 (0.10–4.14)	0.95
Diagnosis					
Care-seeking time¶ >1 wk	18	1.81 (0.55–5.82)	0.39	1.73 (0.46–6.41)	0.51
Referral time‖ >1 wk	52	1.67 (0.67–4.31)	0.32	1.45 (0.49–4.45)	0.61
Diagnosis time** >1 d once seen by diagnosing physician	36	2.08 (0.80–5.50)	0.15	1.50 (0.48–4.72)	0.59
Total time from onset to diagnosis >30 d	41	2.50 (0.96–6.70)	0.06	2.04 (0.68–6.28)	0.24
Diagnosis with CM	42	0.71 (0.27–1.79)	0.56	0.96 (0.31–2.88)	>0.99
Treatment					
Initially treated with amebicidal agent	45	1.02 (0.39–2.63)	>0.99	1.45 (0.46–4.69)	0.65
Initially treated with steroids	6	4.91 (0.66–57.34)	0.14	5.33 (0.66–66.98)	0.14
Received steroids before AK diagnosis	14	3.57 (0.69–20.95)	0.15	2.45 (0.32–21.49)	0.53

*Thirty-three of 100 patients had a visual acuity <20/200.
†Age-adjusted ORs.
‡Includes previous eye trauma, previous eye surgery, previous eye infection, previous keratopathy, history of diabetes mellitus, or history of immune deficiency.
§Includes patients presenting with ≥1 of the following signs: ring infiltrate, diffuse stromal infiltrate, stromal abscess, nodular or diffuse scleritis.
¶Defined as the interval between symptom onset and first presentation to any medical facility.
‖Defined as the interval between the first presentation to any medical facility and first presentation to the diagnosing ophthalmologist.
**Defined as the interval between the first presentation to the diagnosing ophthalmologist and diagnosis of AK infection.

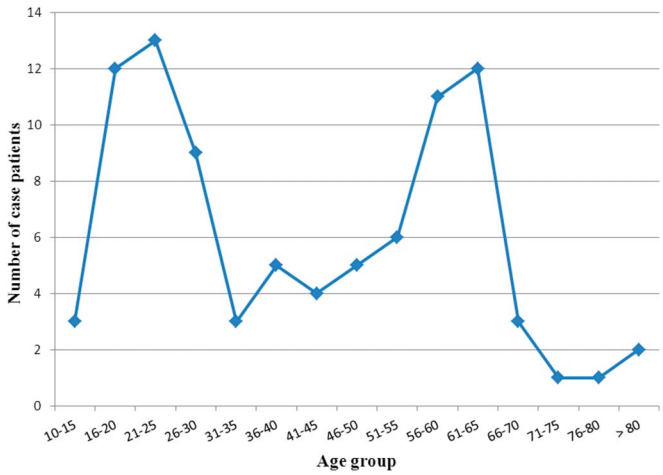
daily, whereas 31 (45.6%) reported rinsing less frequently. Three patients who used daily disposable lenses indicated that they typically reused their disposable lenses 3 to 7 times before replacing them.

Seven of 84 (8.3%) CLWs compared with 5 of 6 (83.3%) patients who did not wear contact lenses had a history of an eye infection, keratopathy (not including trauma or surgery), diabetes, or immune deficiency ($P < 0.001$), comorbidities that have been identified as potential risk factors for the occurrence of other infectious keratitidities, though not explicitly studied in AK.[28,29] None of the 6 non-CLWs had a history of eye trauma or an eye surgery, compared with 12 of 84 (14.3%) CLWs.

DISCUSSION

This article describes the clinical characteristics of 116 patients with AK from 28 states during a 42-month period beginning in January 2008. Although this report includes only those cases that were identified through a limited surveillance network and for which chart abstractions were completed, to our knowledge, it represents the most comprehensive case series of AK in the United States to date.

In agreement with the findings of previous studies,[17,18,21,30] we found that there was a substantial delay from symptom onset to diagnosis of AK and that this delay was associated with poorer clinical outcomes. The most significant contributor to a delay in diagnosis was referral time although this interval was not independently associated with either the need for keratoplasty or poor final visual acuity. The referral times were significantly longer for patients presenting to the diagnosing physician with signs of advanced AK compared with those presenting with less severe infections, whereas the median care-seeking time for both these groups was equal. This finding is in agreement with that of previous research demonstrating



*There were no case-patients younger than 10 years of age

FIGURE 2. Age distribution of patients with AK with available demographic information (N = 90).

a correlation between more extensive disease at presentation and diagnostic delay.[17] The reasons for referral delay are not well understood but may be partly because of the lack of awareness of AK among the health care providers most likely to initially see patients seeking a diagnosis, including community ophthalmologists, optometrists, and emergency room physicians.[31] A significant majority of patients reported common ophthalmologic complaints of pain, eye redness, blurred vision, and photophobia, but signs more specifically associated with AK infections (ie, ring infiltrate, perineuritis) were present in only about one-quarter of case patients. This lack of specific clinical symptoms and signs has been previously reported,[32] and might have contributed to long referral time and to total time to AK diagnosis. However, because we collected data only from diagnosing ophthalmologists, and not first-line providers, we have a limited understanding of the initial clinical presentation and factors that may have contributed to diagnostic delays.

We found a bimodal age distribution of AK, with peaks in the age groups of 16 to 25 and 56 to 65 years; however, patients above 40 years were more likely to require keratoplasty or end up with poor visual acuity compared with younger patients. Our statistical model detected interactions between patient age and a number of other predictors of both keratoplasty and decreased visual acuity, including severity of disease on presentation and longer diagnosis times. This suggests that older age was a primary driver of poor clinical outcomes among patients in this case series, a finding that is in agreement with that of previous investigations of AK and other infectious keratitidities.[23,33] This may reflect a mix of patient and provider factors, including a higher likelihood of wearing contact lenses longer than prescribed,[34] higher rates of topical steroid use,[35] and a greater number of systemic comorbidities that may predispose to infection.[36]

Once seen by the diagnosing ophthalmologist, a clinical diagnosis tended to be made rapidly, with the large majority of cases being confirmed by culture and/or CM within 3 days. Nearly 25% of the cases were confirmed by CM alone, a proportion consistent with recently published data on diagnostic practices.[22] Ophthalmologists who used CM for diagnosis were able to identify AK more rapidly than those who relied on culture to isolate the parasite. However, we found that there was a poor agreement between CM and culture when both tests were used for diagnosis, suggesting that both modalities might be prone to false negatives. Simultaneous testing for *Acanthamoeba* by >1 method might therefore reduce false negatives and in turn decrease overall diagnosis times for this patient population.

Slightly fewer than half the patients in this case series were initially treated with amebicidal medications, including chlorhexidine, polyhexamethylene biguanide, and/or hexamidine; however, the likelihood of keratoplasty or BCVA <20/200 was not statistically associated with having amebicidal medications drugs prescribed as the initial therapy. In contrast, although only 5% of case patients received steroids as their initial therapy, the diagnosis time (ie, time from presenting to the diagnosing physician to AK diagnosis) was increased in this scenario. Patients who were initially prescribed steroids also had a higher likelihood of keratoplasty, although this result approached but did not achieve statistical significance. Corticosteroids have been shown to increase the pathogenicity of *Acanthamoeba* spp in animal models,[37] and treatment with topical steroids before diagnosis has been implicated as a risk factor for keratoplasty in microbial keratitis,[19] although in this case series, patients who were prescribed steroids before AK diagnosis did not have an increased likelihood of keratoplasty. Steroid use might predict poorer outcomes not necessarily because steroids cause poor results but because their use is more common in severe cases with associated scleritis and more ocular inflammation.[38]

Although CLWs comprise only about 13% of the US population,[34] 93% of patients in this case series for whom such data were available were CLWs, suggesting that contact lens use remains the predominant risk factor for AK in this country. Approximately 10% of CLWs in this study who wore soft contact lenses reported using daily disposable lenses, an interesting finding given previous reports suggesting that such lenses may have a protective effect against AK.[23] This result may be partly because of poor hygiene practices among daily disposable users in our case series. Indeed, other authors have described increased rates of microbial keratitis in daily disposable wearers compared with that in silicone hydrogel wearers,[39] suggesting that factors other than lens storage likely play a role in infection. In contrast to multiple reports in the literature,[6–8] none of the non-CLWs in our case series had a history of previous corneal trauma (including corneal surgery). Although the number of non-CLWs was small, this finding suggests that other risk factors (eg, previous ocular infection) might play a more important role in the development of AK than was previously thought. Care-seeking time was substantially longer among non-CLWs than among patients who used contact lenses, indicating that patients who wear lenses might have readier access to eye care or might be more willing to seek care rapidly for eye problems.

Our analysis had several limitations. Despite inclusion of cases from multiple geographical locations and practice types, our sample may not be generalizable to the US population, because cases were primarily identified from academic medical centers, and data were not available for all AK cases known to have occurred during the period of interest. Moreover, the number of cases included from each state likely reflects differences in reporting variables (ie, access to care, referral networks) in addition to any regional variation in incidence. We were not able to collect as much information on treatment duration or medication selection as we anticipated, limiting our ability to assess how treatment course influenced visual outcome. We were also unable to determine whether keratoplasty, when performed, was secondary to failure to eradicate the infection or for impending corneal perforation. Finally, for some analyses, the small number of cases limited our ability to make strong conclusions regarding associations that we detected.

AK remains challenging to diagnose, with delays in diagnosis leading to poor visual outcomes, particularly in older patients. Our analysis highlights the severity of this disease: 1 out of 3 patients with a known final clinical outcome underwent or was awaiting keratoplasty, and an equal proportion were left with a BCVA of <20/200 in the affected eye. Our data suggest that the greatest opportunity to reduce the total time from symptom onset to diagnosis, and to decrease the severe morbidity associated with AK, is to

shorten the referral time to subspecialty care. This necessitates a greater awareness of AK, its risk factors, and methods for diagnosis among general eye care providers.

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