Ophthalmol Ther (2025) 14:1369–1383
https://doi.org/10.1007/s40123-025-01152-9

REVIEW

The Natural History of *Acanthamoeba* Keratitis: A Systematic Literature Review

Vincenzo Papa · Danielle H. Bodicoat · Angela Arteaga Duarte · John K. G. Dart · Maria De Francesco

Received: January 27, 2025 / Accepted: April 17, 2025 / Published online: May 5, 2025

ABSTRACT

***Introduction*:** *Acanthamoeba* keratitis (AK) was first identified in 1972 and the first patient cured with propamidine was reported in 1985. Treatment outcomes, before the advent of the first effective anti-amoebic treatment, were known to be poor and often required therapeutic keratoplasty (TK) but have not been evaluated in detail. Analysis of these outcomes has value for several reasons: it gives an historical perspective, describes the natural history of AK when the disease was minimally modified by the early treatments and provides a benchmark against which current treatments can be compared and how these have changed the therapeutic results.

***Methods*:** We conducted a systematic literature review for the period 1970–1995 using PRISMA guidelines. The population of interest comprised patients with AK treated without products having established anti-amoebic activity against both trophozoites and cysts (biguanides or diamidines). The outcomes of interest were medical cure, TK and enucleation. Proportions and 95% confidence intervals were estimated.

***Results*:** Fifty-six case reports were eligible. Risk factors for AK were reported in 44/56 patients: contact lens wear in 30/44 (68.2%) and trauma in 14/44 (31.8%). The mean time from presentation to diagnosis was 7.3 weeks (standard deviation 9.3 weeks); 13/56 (23.2%) were diagnosed within 4 weeks. Topical treatments given to patients included corticosteroids (85.2%), antibiotics (85.2%), antivirals (72.2%) and antifungals (51.8%). Final visual acuity was ≥ 20/40 in 17/33 (51.5%) patients with no missing data. Medical cures were reported in 11/56 patients (19.6%), TK in 38/56 (67.9%), other surgery in 4/56 (7.1%) and enucleation in 3/56 (5.4%).

***Conclusion*:** This study suggests that, before the availability of propamidine as the first effective treatment for AK, the clinical outcome of these patients was poor with only a few patients cured without surgery. These findings should be interpreted with caution because they rely on case reports and series that are subject to inherent bias.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-025-01152-9.

V. Papa (✉)
SIFI S.P.A., 36, Via Ercole Patti, 95025 Aci S. Antonio, Catania, Italy
e-mail: Vincenzo.Papa@sifigroup.com

D. H. Bodicoat · A. A. Duarte · M. De Francesco
HEOR Value Hub, Brussels, Belgium

J. K. G. Dart
Moorfields Eye Hospital NHS Foundation Trust, London, UK

J. K. G. Dart
National Institute of Health Research (NIHR) Moorfields Biomedical Research Centre, London, UK

Keywords: *Acanthamoeba*; Infectious keratitis; Keratoplasty

Key Summary Points

Why carry out this study?

Acanthamoeba keratitis (AK) is a serious disease. Its natural history in absence of an effective treatment is not well known.

This systematic literature review investigated the outcome of AK before the availability of the first effective medical treatment (propamidine).

What was learned from the study?

The review identified 56 case reports of patients with AK treated with medicine with no established anti-amoebic effect.

Only 11/56 (19.6%) patients were cured without surgery.

This compares with the approximately 60% cure rate reported with current off-label treatments and with the 85% cure rate reported with the first medicinal product approved for the treatment of AK.

INTRODUCTION

Acanthamoeba keratitis (AK) is a rare, but serious, ocular infection caused by several *Acanthamoeba* species, which can result in severe visual impairment, including blindness [1–3]. AK is associated with contact lens wear, ocular trauma and exposure to contaminated soil and water [4]. Its incidence in the general population is estimated to be 2.34 (95% CI 0.98–5.55) per million per year [5]. The clinical course of AK depends on the stage of the disease and has been extensively described elsewhere [1–3, 6]. Currently, no drugs have been licenced for the treatment of AK outside the European Union where a preservative-free ophthalmic solution containing polihexanide (PHMB) 0.08% [7] was recently approved. First-line therapy to date has consisted of various unlicensed anti-amoebic treatments (AAT), such as PHMB, chlorhexidine, propamidine and hexamidine, often given in combination [6, 8, 9].

AK is a relatively new disease first identified as a distinct clinical entity in 1972 in the US [10] and further described in 1974 in the UK [11]. Being a new and ultra-rare cause of microbial keratitis, both difficult to culture, with clinical appearances like those of herpes keratitis and, at that time, without the availability of diagnosis by DNA detection using polymerase chain reaction or using in vivo confocal microscopy, AK was usually misdiagnosed or late diagnosed.

For these patients, the treatment commonly given was based on a mix of corticosteroids, antivirals, antibiotics and antifungals [12], but, in most cases, therapeutic keratoplasty (TK) was used to control the infection. Approximately a decade after its identification, Wright reported the first patient with AK cured with medical therapy using propamidine isethionate [13]. Unlike the available antimicrobials, antifungals and antivirals in use at that time as well as anti-helminthic and anti-malarial drugs, this diamidine was shown to have good anti-amoebic trophozoicidal and cysticidal properties [13]. Thereafter, most patients with AK were treated with Brolene®, when available, as the first effective topical anti-amoebic drug, which was often combined with neomycin. Since then, benzalkonium chloride, an excipient of Brolene®, has also been shown to be an effective anti-amoebic [14] providing additional anti-amoebic effects to the commercial preparation of propamidine. The importance of the elimination of the more treatment-resistant cyst form of *Acanthamoeba*, as opposed to the more susceptible trophozoite, was becoming evident following the introduction of Brolene®, although the requirement to eliminate viable cysts for effective medical treatment was not clearly stated until 1991 [15]. The analysis of the outcomes of treatment for AK without Brolene®, and before the subsequent introduction of other effective anti-amoebics, can be expected to provide an approximation of the natural history of untreated AK. This is an approximation because AK outcomes were modified, to a limited extent, by the anti-trophozoicidal effects of some of the antibiotics and antifungals in use at that time [13].

We performed a systematic literature review (SLR) of these historical data to identify this cohort of "untreated" patients with AK. This was carried out with several aims: (1) to provide an historical perspective, (2) to describe the natural history of AK in patients untreated with effective anti-cystic anti-amoebic drugs and (3) to provide a benchmark against which current treatments can be compared and the resulting changes in therapeutic outcomes compared to this "untreated" cohort.

METHODS

Search Strategy

A SLR was performed according to a protocol following the PRISMA-P guidance [16]. Databases were searched (PubMed, Cochrane Library, Prospero, Clinicaltrial.gov) using the following search terms: "*Acanthamoeba* keratitis" OR (Amoebic AND keratitis) OR (*Acanthamoeba* keratitis [MeSH Terms]). The search was initially limited to the period 1970–1990 (search performed 26th November 2023) and then extended to include the period 1991–1995 (search performed 2 December 2023). No language restrictions were placed on the articles; however, for non-English language articles only the abstract was used for data extraction.

Eligibility Criteria

- Population of interest: patients of any age with a confirmed diagnosis of AK not receiving treatment with products with an established anti-amoebic activity, i.e. PHMB, chlorhexidine, propamidine or hexamidine [6, 8, 9].
- AK diagnosis: only cases with clinical findings, consistent with AK, associated with at least one of the following were evaluated: (1) positive culture from corneal tissues; (2) identification of *Acanthamoeba* in smears or histology; (3) perineural infiltrates or a positive culture from contact lens paraphernalia.
- Outcome of interest: medical cure, TK, enucleation.
- Data source: Clinical trials, observational studies, case reports and case series were all eligible for inclusion. If a paper included a mixture of untreated and treated patients, it was considered eligible for inclusion only if data were reported separately for untreated patients. Originally, the inclusion dates were set as 1970 to 1990, as it was expected that there would be no untreated cases beyond 1985 when propamidine became available. However, during the screening, multiple papers published in 1990 were eligible. As a result, the search was extended to 1995. Only a single eligible paper was published in 1995; therefore, the search dates were not extended any further.

Data Screening and Additional Searching

Studies from all sources were combined, duplicate publications removed and titles/abstracts and then the full texts screened by two independent reviewers. Backward and forward citation chasing was conducted for eligible articles using the CitationChaser Shiny App (https://estech.shinyapps.io/citationchaser/) to ensure that eligible articles not indexed in the searched databases were identified. Any potentially eligible articles identified through citation chasing went through the same process of eligibility checking, followed by citation chasing if eligible. This circular process was repeated until no new articles were identified. Duplicate papers were identified and removed automatically on import into Covidence software (https://www.covidence.org/) before title/abstract screening. In case of duplication of cases in multiple papers, data were obtained from all reports to get as complete a dataset as possible.

Data Extraction

Data extraction was undertaken in Microsoft Excel by one reviewer based on the published information available. Where data were not

available in the published report, they were marked as missing, and no attempt was made to obtain these data. A second reviewer then checked the extracted data against the original publication. Any conflicts were discussed and agreed between the reviewers.

Quality Assessment

The strength of the overall body of evidence was assessed using the GRADE framework as very low, low, moderate or high [17]. In addition, a risk of bias assessment was conducted by one reviewer using the Institute of Health Economics quality appraisal of case series studies checklist [18]. As per the tool guidance, irrelevant questions were removed before the assessment was conducted. These mainly pertained to the intervention of interest or statistical analyses (which were not conducted in any study).

Statistical Analysis

The main effect measures were binary (yes/no) for whether an outcome had occurred. For each outcome, proportion with 95% confidence interval (CI) was estimated with the CI based on binomial proportion. Analyses were conducted using Stata software v18.0. All eligible cases and studies were included in the analyses. There were no missing outcome data as an outcome of interest was required as part of the eligibility criteria.

Ethics Compliance

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Literature Search and Study Selection

A PRISMA diagram showing the flow of studies through the literature search is shown in Fig. 1. In brief, 573 records were identified from all sources. After removing 235 duplicates, 335 titles and abstracts were screened, 107 of which progressed to full text screening. During the full text screening, 70 studies were excluded, of which 33 were excluded because of the use of an ineligible treatment (mainly propamidine). Finally, 37 articles met the eligibility criteria [10–12, 19–52].

Patient Characteristics

Across the 37 selected articles, 56 case reports were eligible [10–12, 19–52]. Individual characteristics, treatments and outcomes are displayed in Table 1. Details of all treatments used are shown in Table S1 in the electronic supplementary materials. Summary data, derived from Table 1 and Table S1, are given in Table 2 and summarised here. Most cases were reported in the US ($n = 31$; 55.4%). Probable risk factors for AK were reported in 44/56 patients and included contact lens wear in 30/44 (68.2%) and ocular trauma in 14/44 (31.8%). The mean and standard deviation (SD) time from presentation to diagnosis ranged from 1 to 25 (mean ± SD = 7.3 ± 9.3) months and only 13/56 (23.2%) patients were diagnosed within 1 month of symptom onset. Patients were treated with several topical or, less frequently, systemic agents. Topical treatments included corticosteroids (46/54 = 85.2%), antibiotics (46/54 = 85.2%), antivirals (39/54 = 72.2%) and antifungals (28/54 = 51.8%). The most used systemic medicines were corticosteroids (20/54 = 37.0%) and antifungals (17/54 = 31.5%). For two patients, the treatments used were not recorded. Final visual acuity (VA) was reported in 33 of the 56 patients of whom 17/33 (51.5%) had a final VA of ≥ 20/40.

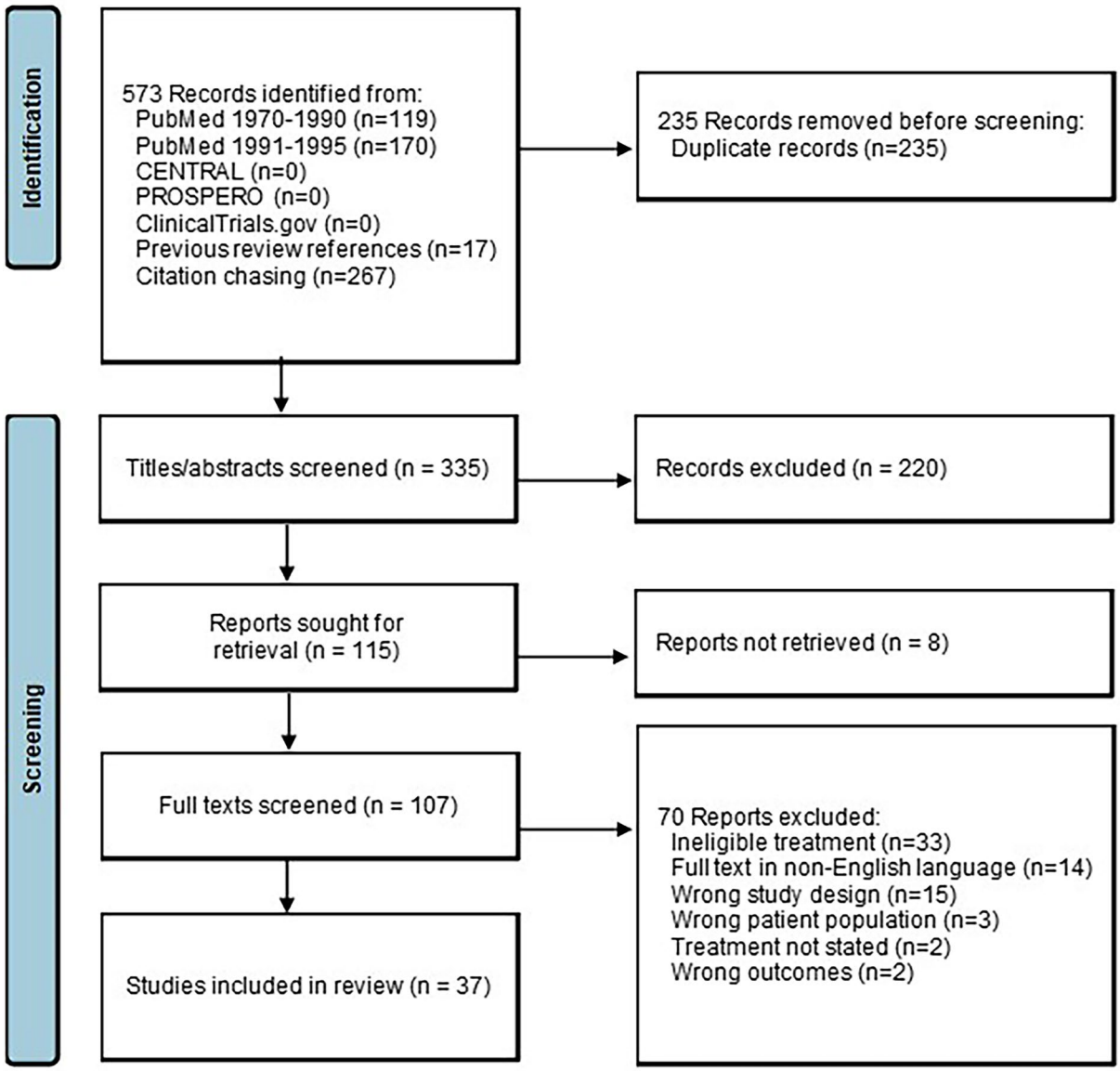

Fig. 1 PRISMA diagram showing the flow of studies for the systematic literature review

Clinical Outcome

Table 3 summarises the clinical outcomes for these patients. Eleven of 56 patients (19.6%) were cured without any surgical intervention. In 4/56 (7.1%), a cure was obtained after extensive epithelial debridement aimed at removing as much infected corneal epithelium as possible; this is a minor surgical procedure as opposed to the limited epithelial debridement that is done as a part of diagnostic procedures. TK was performed in 38/56 patients (67.9%) and 3/56 patients (5.4%) had enucleation. One patient (case no. 2 in Table 1) was subjected first to keratoplasty and then enucleated; this patient was considered censored after the first event (keratoplasty) and was not included in the enucleation category.

Table 1 List of patients with AK included in the systematic literature review

Case no.	Author year, (reference)[a]	Risk factors	Age (years)	Sex	Country	Diagnosis	Time to diagnosis (months)	Treatments[b]				Cure with no surgery	TPK	Enucleation	Final visual acuity
								Antibiotics	Antivirals	Antifungals	Steroids				
1	Naginton 1974 [11]	Unknown	32	F	UK	Histology	6	Yes	Yes	No	Yes	No	Yes	No	NA
2	Naginton 1974 [11]	Trauma	59	M	UK	Microbiology	25	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
3	Jones 1975 [10]	Trauma	59	M	USA	Microbiology	1	Yes	Yes	Yes	Yes	No	Yes	No	CF
4	Jones 1975 [10]	Unknown	23	F	USA	Microbiology	8	Yes	Yes	Yes	Yes	Yes	No	No	20/100
5	Lund 1978 [19]	Trauma	22	M	Germany	Histology	2	Yes	No	No	Yes	No	Yes	No	NA
6	Hamburg 1980 [20]	Trauma	67	M	Netherland	Histology	4	Yes	No	Yes	Yes	No	No	Yes	NA
7	Key 1980 [21]	Unknown	27	M	USA	Histology	4	Yes	Yes	Yes	Yes	No	No	Yes	NA
8	Ma 1981 [22]	Trauma	67	M	USA	NA	NA	NA	NA	NA	NA	No	Yes	No	NA
9	Ma 1981 [22]	Trauma	42	M	USA	Histology	2	Yes	Yes	Yes	Yes	Yes	No	No	3/200
10	Bos 1981 [23]	Uknown	36	M	Netherland	Histology	8	Yes	No	Yes	Yes	No	Yes	No	20/50
11	Olson 1984 [24]	CLW	16	M	USA	NA	NA	NA	NA	NA	NA	No	Yes	No	NA
12	Witschel 1984 [25]	CLW	63	F	Germany	Histology	3	Yes	Yes	Yes	Yes	No	Yes	No	NA
13	Blackman 1984 [26]	CLW	23	F	Philippines	Histology	2	Yes	No	Yes	Yes	No	Yes	No	20/30
14	Hirst 1984 [26]	CLW	48	F	USA	Histology	3	Yes	Yes	Yes	Yes	No	Yes	No	20/40
15	Samples 1984 [27]	CLW	42	M	USA	Histology	4	Yes	Yes	Yes	Yes	No	Yes	No	CF
16	Moore 1985 [28]	CLW	25	M	USA	Histology	12	No	Yes	Yes	Yes	No	Yes	No	HM
17	Moore 1985 [28]	CLW	13	F	USA	Microbiology	13	Yes	Yes	Yes	Yes	No	Yes	No	20/20

Table 1 continued

Case no.	Author year, (reference)[a]	Risk factors	Age (years)	Sex	Country	Diagnosis	Time to diagnosis (months)	Treatments[b]				Cure with no surgery	TPK	Enucleation	Final visual acuity
								Antibiotics	Antivirals	Antifungals	Steroids				
18	Hanssens 1985 [29]	Trauma	34	M	Belgium	Histology	9	Yes	Yes	No	Yes	No	Yes	No	NA
19	Roussel 1985 [30]	Trauma	31	M	Australia	Microbiology	3	Yes	Yes	No	Yes	No	Yes	No	NA
20	Theodore 1985 [31]	Trauma	28	F	USA	Histology	4	Yes	Yes	No	Yes	No	Yes	No	LP
21	Theodore 1985 [31]	Uknown	45	M	USA	Microbiology	1	Yes	Yes	Yes	Yes	No	Yes	No	LP
22	Theodore 1985 [31]	Trauma	20	M	USA	Microbiology	4	Yes	Yes	Yes	Yes	No	Yes	No	20/25
23	Cohen 1985 [32]	CLW	18	F	USA	Microbiology	5	Yes	Yes	No	Yes	No	Yes	No	20/25
24	Cohen 1985 [32]	CLW	32	M	USA	Histology	10	Yes	Yes	No	Yes	No	Yes	No	20/30
25	Cohen 1985 [32]	Uknown	61	F	USA	Histology	36	Yes	Yes	No	Yes	No	Yes	No	20/30
26	Cohen 1985 [32]	Trauma	56	F	USA	Histology	36	Yes	No	Yes	Yes	No	Yes	No	20/400
27	Baum 1985 [33]	CLW	29	F	USA	Histology	NA	Yes	No	No	Yes	No	Yes	No	NA
28	Wilhelmus 1986 [34]	CLW	25	M	USA	Histology	1	No	Yes	Yes	Yes	No	Yes	No	20/40
29	Wilhelmus 1986 [34]	Trauma	40	M	USA	Microbiology	1	Yes	No	No	Yes	No	No	Yes	NA
30	Mannis 1986 [35]	CLW	38	M	USA	Histology	2	Yes	Yes	No	Yes	No	Yes	No	20/200
31	Mannis 1986 [35]	CLW	39	F	USA	Histology	36	Yes	Yes	No	Yes	No	Yes	No	20/25
32	Jackson 1986 [36]	CLW	19	M	Australia	Microbiology	4	Yes	Yes	Yes	Yes	Yes	No	No	20/60
33	Moore 1987 [37]	CLW	31	F	USA	Histology	4	Yes	Yes	No	Yes	No	Yes	No	NA
34	Moore 1987 [37]	CLW	40	F	USA	Microbiology	3	Yes	Yes	No	Yes	No	Yes	No	20/20

Table 1 continued

Case no.	Author year, (reference)[a]	Risk factors	Age (years)	Sex	Country	Diagnosis	Time to diagnosis (months)	Treatments[b]				Cure with no surgery	TPK	Enucleation	Final visual acuity
								Antibiotics	Antivirals	Antifungals	Steroids				
35	Cohen 1987 [38]	CLW	34	F	USA	Histology	2	Yes	No	Yes	Yes	No	Yes	No	20/25
36	Davis 1987 [39]	Unknown	27	M	USA	Histology	12	Yes	Yes	Yes	Yes	No	Yes	No	HM
37	Brincker 1988 [40]	CLW	16	M	Denmark	Histology	5	Yes	Yes	No	Yes	No	Yes	No	20/30
38	Brincker 1988 [40]	CLW	19	M	Denmark	Histology	3	Yes	Yes	Yes	Yes	No	Yes	No	20/40
39	Florakis 1988 [41]	CLW	16	M	USA	Histology	3	Yes	Yes	Yes	Yes	No	Yes	No	NA
40	Lindquist 1989 [42]	CLW	71	F	USA	Histology	15	No	No	No	Yes	No	Yes	No	NA
41	Lindquist 1990 [43]	Unknown	34	F	USA	Histology	21	No	Yes	No	Yes	No	Yes	No	20/20
42	Sharma 1990 [44]	Trauma	18	M	India	Microbiology	< 1	Yes	No	No	No	Yes	No	No	NA
43	Sharma 1990 [44]	Unknown	21	M	India	Microbiology	< 1	Yes	Yes	No	No	Yes	No	No	NA
44	Sharma 1990 [44]	Unknown	26	F	India	Microbiology	1	Yes	No	Yes	No	Yes	No	No	20/200
45	Sharma 1990 [44]	Uknown	40	M	India	Microbiology	< 1	Yes	No	Yes	No	Yes	No	No	LP
46	Peterson 1990 [45]	CLW	23	F	USA	Histology	3	Yes	Yes	No	Yes	No	Yes	No	NA
47	Ishibashi 1990 [46]	CLW	23	M	Japan	Microbiology	1	Yes	Yes	Yes	Yes	No[c]	No	No	20/30
48	Ishibashi 1990 [46]	CLW	19	F	Japan	Amoeba in contact lens paraphernalia	1	Yes	Yes	Yes	Yes	No[c]	No	No	20/16
49	Ishibashi 1990 [46]	CLW	37	F	Japan	Microbiology	3	Yes	Yes	Yes	Yes	No[c]	No	No	20/40
50	Girija 1992 [47]	Trauma	38	F	India	Microbiology	< 1	Yes	No	No	No	No	Yes	No	NA

Table 1 continued

Case no.	Author year, (reference)[a]	Risk factors	Age (years)	Sex	Country	Diagnosis	Time to diagnosis (months)	Treatments[b]				Cure with no surgery	TPK	Enucleation	Final visual acuity
								Antibiotics	Antivirals	Antifungals	Steroids				
51	Reuber 1992 [48]	CLW	68	F	Germany	Microbiology	< 1	Yes	No	No	No	Yes	No	No	NA
52	Nakagawa 1993 [49]	CLW	NA	NA	Japan	Microbiology	NA	No	Yes	Yes	Yes	Yes	No	No	NA
53	Nakagawa 1993 [49]	CLW	NA	NA	Japan	Amoeba in contact lens paraphernalia	NA	No	Yes	Yes	Yes	Yes	No	No	NA
54	Srinivasan 1993 [50]	CLW	40	F	India	Microbiology	< 1	Yes	No	Yes	Yes	Yes	No	No	NA
55	Brooks 1994 [51]	CLW	27	F	Australia	Presence of perineural infiltrates	2	No	Yes	No	Yes	No[c]	No	No	20/20
56	Perry 1995 [52]	Unknown	38	F	USA	Histology	2	No	Yes	No	Yes	No	Yes	No	20/30

AK Acanthamoeba keratitis, *NA* not available, *CF* counting fingers, *F* female, *HM* hand movements, *LP* light perception, *M* male; *TPK* therapeutic perforating keratoplasty, *CLW* contact lens wear

[a]Some cases are included in multiple papers. Only the first report is referenced

[b]A list of topical and systemic drugs used in each patient is shown in Table S1 (available in the electronic supplementary materials)

[c]These patients were cured after an extensive (subtotal) epithelial debridement which is considered (Table 3) a minor surgery procedure

Table 2 Summary of data included in Table 1 and Table S1 (available in the electronic supplementary materials) for 56 patients with AK

Country	***n*** **(%)**
US	31 (55.4)
India	6 (10.7)
Japan	5 (8.9)
Australia	3 (5.4)
Germany	3 (5.4)
UK	2 (3.6)
The Netherlands	2 (3.6)
Denmark	2 (3.6)
Belgium	1 (1.8)
Philippines	1 (1.8)
Final visual acuity	***n*** **(%)**
≥ 20/40	17 (51.5)
< 20/40	16 (48.5)
Missing	23
Risk factors	***n*** **(%)**
Contact lens wear	30 (68.2)
Trauma	14 (31.8)
Missing	12
Topical treatments	***n*** **(%)**
Corticosteroids	46 (85.2)
Antibiotics	46 (85.2)
Antivirals	39 (72.2)
Antifungals	28 (51.8)
Missing	2
Systemic treatments	
Corticosteroids	20 (37.0)
Antibiotics	10 (18.5)
Antivirals	3 (5.5)
Antifungals	17 (31.5)
Missing	2
Time from presentation to diagnosis, weeks	
Mean (SD)	7.3 (9.3)
Range	2–25

Table 2 continued

AK Acanthamoeba keratitis, *SD* standard deviation

Quality Assessment

The GRADE quality of evidence for reported clinical outcome was rated as "low" because of the risk of bias inherent with case reports. Table S2 in the electronic supplementary materials shows the results of the risk of bias assessment. The main potential sources of risk were that, in all/nearly all studies, it was unclear whether the study was conducted prospectively or retrospectively, whether patients were recruited consecutively, what eligibility criteria were employed (if any), whether patients entered the study at a similar point in their disease and whether relevant outcome measures were established a priori.

DISCUSSION

Before the introduction of propamidine as the first effective anti-amoebic in 1985 [13], the clinical progression of AK was close to what would be expected as the natural history of the disease in untreated patients, often requiring TK, and usually terminating in blindness or significant visual disability and, in some cases, eye removal. This analysis of clinical outcomes, before effective treatments were available, has not been done before. We believe describing the natural history of AK in patients untreated with effective drugs has value for historical purposes and for a benchmark against which current treatments can be compared. In the present study, we performed a SLR aimed at analysing the outcome of patients with AK not treated with products with an established effect on *Acanthamoeba* trophozoites and cysts. Although an assumption is usually made that only drugs that are cysticidal in vitro can be expected to be effective as therapy [6], in vitro results do not necessarily relate to an in vivo response. This issue has been little explored in published studies [53] and bears further investigation given the positive

Table 3 Outcomes of patients with AK not treated with anti-amoebic products

Outcome	*N* (%)	Proportion (95% CI)[c]
Cured without surgery	11/56 (19.6%)	0.20 (0.10, 0.32)
Cured with minor surgery[a]	4/56 (7.1%)	0.07 (0.02, 0.17)
Therapeutic keratoplasty	38/56 (67.9%)	0.68 (0.54, 0.80)
Enucleation[b]	3/56 (5.4%)	0.05 (0.02, 0.16)

AK Acanthamoeba keratitis, *CI* confidence intervals

[a]These patients did not have therapeutic keratoplasty and were cured after a subtotal epithelial debridement

[b]One patient (case no. 2 in Table 1) was enucleated after keratoplasty. In the present analysis, this patient was considered censored after the first event (keratoplasty) and is not included in the enucleation outcome category

[c]CI interval based on binomial proportion

response of AK in some patients to treatment with oral miltefosine [2], which contrasts with the poor in vitro cysticidal activity of the drug [54, 55]. However, there is a current consensus that only biguanides (PHMB and chlorhexidine) and diamidines (propamidine and hexamidine) are effective topical first-line anti-amoebic treatments [2, 6, 56]. Therefore, in the analysis, the SLR included all "historical" patients with AK not treated with a biguanide with or without a diamidine. This study offers a unique opportunity to understand the unmodified natural history of AK. Such knowledge is invaluable for contextualizing the progress achieved with actual treatments and for identifying the gaps that remain in managing this challenging disease.

To our knowledge, this is the first report describing the natural history of "untreated" patients with AK. We found 37 reports published in the period 1970–1995 describing the outcome of 56 patients not receiving an established AAT [10–12, 19–52]. Such reports were all case reports or case series. As expected, the overall outcome of these patients was poor. Indeed, only 11/56 (19.6%) of patients were considered cured using available medical treatments, such as antibiotics, antifungals and antivirals, which were largely ineffective. Remaining patients required TK in 38/56 (67.9%), deep epithelial debridement (minor surgery) in 4/56 (7.1%) and enucleation in 3/56 (5.4%).

This study has limitations. First, all reports are very old and not necessarily indexed in databases. In addition, such data are potentially subjected to bias due to the nature of case reporting. However, the SLR methods, particularly the citation chasing, are likely to have found most untreated cases as cross-citations between papers, which were exhaustively searched and reached saturation. Additionally, these methods are unbiased, and the sample size is large enough that a small number of unidentified cases are unlikely to have a substantial impact on the cure rate estimates.

CONCLUSIONS

The poor outcomes observed highlight the significant challenges posed by AK, particularly its resistance to available therapies and its potential for severe, vision-threatening complications. In addition, such information provides a robust base for evaluating the efficacy of new treatments. By comparing untreated cases with those treated successfully after the introduction of effective therapies, physicians can better assess how far therapeutic advancements have come and identify areas where further innovation is needed. Indeed, the proportion of patients cured medically without surgery has increased from 0.20 (95% CI 0.10; 0.32), as shown in the present study, to 0.61 (95% CI 0.54; 0.67) using off-label treatments [57] and to 0.85 (95% CI 0.74; 0.92) with the first drug licensed for the treatment of AK [7].

Author Contribution. Vincenzo Papa, Danielle H Bodicoat, Angela Arteaga Duarte, John KG Dart and Maria De Francesco contributed to the study conception and design. Acquisition of data and analysis were performed by Danielle H Bodicoat, Angela Arteaga Duarte and Maria De Francesco. Data interpretation was performed by all authors. The first draft of the manuscript was written by Vincenzo Papa and all authors commented on previous version of the manuscript. All authors read and approved the final manuscript.

Funding. Sponsorship for this study and the journal's rapid service fee were funded by SIFI SpA (Italy).

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Vincenzo Papa is an employee of SIFI SpA (Italy). John KG Dart and Maria De Francesco received a consultant honorarium from SIFI SpA (Italy). Danielle H Bodicoat and Angela Arteaga Duarte have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Lorenzo-Morales J, Khan NA, Walochnik J. An update on *Acanthamoeba* keratitis: diagnosis, pathogenesis and treatment. Parasite. 2015;22:10. https://doi.org/10.1051/parasite/2015010.

2. Kaufman AR, Tu EY. Advances in the management of *Acanthamoeba* keratitis: a review of the literature and synthesized algorithmic approach. Ocul Surf. 2022;25:26–36. https://doi.org/10.1016/j.jtos.2022.04.003.

3. Petrillo F, Tortori A, Vallino V, et al. Understanding *Acanthamoeba* keratitis: an in-depth review of a sight-threatening eye infection. Microorganisms. 2024;12(4):758. https://doi.org/10.3390/microorganisms12040758. (**PMID:38674702;PMCID:PMC11052265**).

4. Radford CF, Minassian DC, Dart JK. *Acanthamoeba* keratitis in England and Wales: incidence, outcome, and risk factors. Br J Ophthalmol. 2002;86(5):536–42. https://doi.org/10.1136/bjo.86.5.536.

5. Aiello F, Gallo Afflitto G, Ceccarelli F, et al. Perspectives on the incidence of *Acanthamoeba* keratitis: a systematic review and meta-analysis. Ophthalmology. 2025;132(2):206–18.

6. Dart JK, Saw VP, Kilvington S. *Acanthamoeba* keratitis: diagnosis and treatment update 2009. Am J Ophthalmol. 2009;148(4):487-499.e2. https://doi.org/10.1016/j.ajo.2009.06.009.

7. Dart JKG, Papa V, Rama P, et al. The orphan drug for *Acanthamoeba* keratitis (ODAK) trial: a Phase3 trial of PHMB (polihexanide) 0.08% with placebo versus PHMB 0.02% with propamidine 0.1%. Ophthalmology. 2024;131(3):277–87. https://doi.org/10.1016/j.ophtha.2023.09.031.

8. Maycock NJ, Jayaswal R. Update on *Acanthamoeba* keratitis: diagnosis, treatment, and outcomes. Cornea. 2016;35(5):713–20. https://doi.org/10.1097/ICO.0000000000000804.

9. Oldenburg CE, Acharya NR, Tu EY, et al. Practice patterns and opinions in the treatment of *Acanthamoeba* keratitis. Cornea. 2011;30(12):1363–8. https://doi.org/10.1097/ICO.0b013e31820f7763.

10. Jones DB, Visvesvara GS, Robinson NM. Acanthamoeba polyphaga keratitis and Acenthamoeba uveitis associated with fatal meningoencephalitis. Trans Ophthalmol Soc U K (1962). 1975;95(2):221–32.

11. Naginton J, Watson PG, Playfair TJ, McGill J, Jones BR, Steele AD. Amoebic infection of the eye. Lancet. 1974;2(7896):1537–40.

12. Hirst LW, Green WR, Merz W, et al. Management of *Acanthamoeba* keratitis. A case report and review of the literature. Ophthalmology. 1984;91(9):1105–11.

13. Wright P, Warhurst D, Jones BR. *Acanthamoeba* keratitis successfully treated medically. Br J Ophthalmol. 1985;69(10):778–82.

14. Heaselgrave W, Hamad A, Coles S, Hau S. In vitro evaluation of the inhibitory effect of topical ophthalmic agents on *Acanthamoeba* viability. Transl Vis Sci Technol. 2019;8(5):17.

15. Osato MS, Robinson NM, Wilhelmus KR, Jones DB. In vitro evaluation of antimicrobial compounds for cysticidal activity against Acanthamoeba. Rev Infect Dis. 1991;13(Suppl 5):S431–5.

16. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1. https://doi.org/10.1186/2046-4053-4-1.

17. Siemieniuk R, Guyatt G. What is GRADE? BMJ. 2022. https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/. Accessed 30 Sept 2022.

18. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about. Accessed 20 Mar 2025.

19. Lund OE, Stefani FH, Dechant W. Amoebic keratitis: a clinicopathological case report. Br J Ophthalmol. 1978;62(6):373–5.

20. Hamburg A, De Jonckheere JF. Amoebic keratitis. Ophthalmologica. 1980;181(2):74–80.

21. Key SN, Green WR, Willaert E, Stevens AR. Keratitis due to Acanthamoeba castellani. A clinicopathologic case report. Arch Ophthalmol. 1980;98(3):475–9.

22. Ma P, Willaert E, Juechter KB, Stevens AR. A case of keratitis due to Acanthamoeba in New York, New York, and features of 10 cases. J Infect Dis. 1981;143(5):662–7.

23. Bos HJ, Völker-Dieben HJ, Kok-van Alphen CC. A case of *Acanthamoeba* keratitis in The Netherlands. Trans R Soc Trop Med Hyg. 1981;75(1):86–91.

24. Olson SP, Weidner N Acanthamoeba keratitis associated with soft contact lens use. The American Society of Clinical Pathologists 1984; Anatomic Pathology I1 No.52: 373-37 AP I1 84-8 (AP 11-92). Cited in Jackson et al 1986 (ref no. 36)

25. Witschel H, Sundmacher R, Seitz HM. Amebic keratitis: clinico-histopathologic case report. Klin Monbl Augenheilkd. 1984;185(1):46–9.

26. Blackman HJ, Rao NA, Lemp MA, Visvesvara GS. Acanthamoeba keratitis successfully treated with penetrating keratoplasty: suggested immunogenic mechanisms of action. Cornea. 1984;3(2):125–30.

27. Samples JR, Binder PS, Luibel FJ, Font RL, Visvesvara GS, Peter CR. Acanthamoeba keratitis possibly acquired from a hot tub. Arch Ophthalmol. 1984;102(5):707–10.

28. Moore MB, McCulley JP, Luckenbach M, Gelender H, Newton C, McDonald MB, et al. Acanthamoeba keratitis associated with soft contact lenses. Am J Ophthalmol. 1985;100(3):396–403.

29. Hanssens M, de Jonckheere JF, de Meunynck C. *Acanthamoeba* keratitis. A clinicopathological case report. Int Ophthalmol. 1985;7(3–4):203–13.

30. Roussel TJ, Badenoch PR, Chandraratnam E, Coster DJ. Acanthamoebic keratitis in a healthy Australian man. Med J Aust. 1985;143(12–13):615–7.

31. Theodore FH, Jakobiec FA, Juechter KB, Ma P, Troutman RC, Pang PM, et al. The diagnostic value of a ring infiltrate in acanthamoebic keratitis. Ophthalmology. 1985;92(11):1471–9.

32. Cohen EJ, Buchanan HW, Laughrea PA, Adams CP, Galentine PG, Visvesvara GS, et al. Diagnosis and management of *Acanthamoeba* keratitis. Am J Ophthalmol. 1985;100(3):389–95.

33. Baum JL, Albert DM. Case 10–1985: A 29-year-old native of India with bilateral ulcerative keratitis. N Engl J Med. 1985;312(10):634–41.

34. Wilhelmus KR, Osato MS, Font RL, Robinson NM, Jones DB. Rapid diagnosis of *Acanthamoeba* keratitis using calcofluor white. Arch Ophthalmol. 1986;104(9):1309–12.

35. Mannis MJ, Tamaru R, Roth AM, Burns M, Thirkill C. Acanthamoeba sclerokeratitis. Determining diagnostic criteria. Arch Ophthalmol. 1986;104(9):1313–7.

36. Jackson TN, Heinze JB, Tuxen J, Weiner JM. Successful medical treatment of a corneal ulcer due to Acanthamoeba polyphaga. Aust N Z J Ophthalmol. 1986;14(2):139–42.

37. Moore MB, McCulley JP, Newton C, Cobo LM, Foulks GN, O'Day DM, et al. *Acanthamoeba* keratitis. A growing problem in soft and hard contact lens wearers. Ophthalmology. 1987;94(12):1654–61.

38. Cohen EJ, Parlato CJ, Arentsen JJ, Genvert GI, Eagle RC Jr, Wieland MR, et al. Medical and surgical treatment of *Acanthamoeba* keratitis. Am J Ophthalmol. 1987;103(5):615–25.

39. Davis RM, Schroeder RP, Rowsey JJ, Jensen HG, Tripathi RC. *Acanthamoeba* keratitis and infectious crystalline keratopathy. Arch Ophthalmol. 1987;105(11):1524–7.

40. Brincker P, Gregersen E, Prause JU. *Acanthamoeba* keratitis, clinico-pathological report of 2 cases. Acta Ophthalmol (Copenh). 1988;66(2):210–3.

41. Florakis GJ, Folberg R, Krachmer JH, Tse DT, Roussel TJ, Vrabec MP. Elevated corneal epithelial lines in *Acanthamoeba* keratitis. Arch Ophthalmol. 1988;106(9):1202–6.

42. Lindquist TD, Cameron JD, Havener VR, Rubenstein JB, Lindstrom RL, Doughman DJ. Unsuspected infectious keratitis in host corneal buttons. Surv Ophthalmol. 1989;33(5):359–65.

43. Lindquist TD, Fritsche TR, Grutzmacher RD. Scleral ectasia secondary to *Acanthamoeba* keratitis. Cornea. 1990;9(1):74–6.

44. Sharma S, Srinivasan M, George C. *Acanthamoeba* keratitis in non-contact lens wearers. Arch Ophthalmol. 1990;108(5):676–8.

45. Peterson RJ, Smith ME, Pepose JS. Recurrent *Acanthamoeba* keratitis following penetrating keratoplasty. Arch Ophthalmol. 1990;108(10):1482–3.

46. Ishibashi Y, Matsumoto Y, Kabata T, Watanabe R, Hommura S, et al. Oral itraconazole and topical miconazole with debridement for *Acanthamoeba* keratitis. Am J Ophthalmol. 1990;109(2):121–6.

47. Girija T, Kumari R, Kamath MG, Ramani R, Mohan R, Shivananda PG. *Acanthamoeba* keratitis—a report of two cases. Indian J Ophthalmol. 1992;40(4):124–5.

48. Reuber H, Koch JM. Acanthamoeba keratitis caused by extended wear contact lenses. Klin Monbl Augenheilkd. 1992;200(1):48–50.

49. Nakagawa H, Kazami N, Izai K, Iwasaki M, Uchida Y, Yamaura H, et al. Two cases of early *Acanthamoeba* keratitis. Nippon Ganka Gakkai Zasshi. 1993;97(4):544–50.

50. Srinivasan M, Channa P, Raju CV, George C. *Acanthamoeba* keratitis in hard contact lens wearer. Indian J Ophthalmol. 1993;41(4):187–8.

51. Brooks JG Jr, Coster DJ, Badenoch PR. *Acanthamoeba* keratitis. Resolution after epithelial debridement. Cornea. 1994;13(2):186–9.

52. Perry HD, Donnenfeld ED, Foulks GN, Moadel K, Kanellopoulos AJ. Decreased corneal sensation as an initial feature of *Acanthamoeba* keratitis. Ophthalmology. 1995;102(10):1565–8.

53. Pérez-Santonja JJ, Kilvington S, Hughes R, Tufail A, Matheson M, Dart JK. Persistently culture positive acanthamoeba keratitis: in vivo resistance and in vitro sensitivity. Ophthalmology. 2003;110(8):1593–600.

54. Latifi A, Mohebali M, Yasami S, Soleimani M, Rezaian M, Kazemirad E. Comparing cytotoxicity and efficacy of miltefosine and standard antimicrobial agents against Acanthamoeba trophozoites and cyst forms: an in vitro study. Acta Trop. 2023;247:107009.

55. Mrva M, Garajová M, Lukáč M, Ondriska F. Weak cytotoxic activity of miltefosine against clinical isolates of *Acanthamoeba* spp. J Parasitol. 2011;97(3):538–40.

56. Alkharashi M, Lindsley K, Law HA, Sikder S. Medical interventions for acanthamoeba

keratitis. Cochrane Database Syst Rev. 2015;2015(2):Cd010792. https://doi.org/10.1002/14651858.CD010792.pub2.

57. Papa V, Rama P, Radford C, Minassian DC, Dart JKG. *Acanthamoeba* keratitis therapy: time to cure and visual outcome analysis for different antiamoebic therapies in 227 cases. Br J Ophthalmol. 2020;104(4):575–81. https://doi.org/10.1136/bjophthalmol-2019-314485.