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Practice patterns and opinions in the treatment of acanthamoeba keratitis

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Abstract

Purpose—Management of acanthamoeba keratitis remains challenging for ophthalmologists. We conducted a survey of members of the Cornea Society to elicit expert opinions on the diagnosis and treatment of acanthamoeba keratitis.

Methods—An online survey was sent to all subscribers of the Cornea Society kera-net listserv. Descriptive statistics were performed.

Results—Eighty-two participants completed the online survey. Of the 82 respondents, 76.8% included the combination of clinical examination and culture in their diagnostic strategy, and 43.9% used confocal microscopy. Most respondents (97.6%) had used combination therapy with multiple agents to treat acanthamoeba keratitis at some point in the past, whereas a smaller proportion (47.6%) had ever used monotherapy. Respondents most commonly chose PHMB as the ideal choice for monotherapy (51.4%), and dual therapy with a biguanide and diamidine as the ideal choice for combination therapy (37.5%). The majority of respondents (62.2%) reported using topical corticosteroids at least some of the time for acanthamoeba keratitis. Keratoplasty was an option considered by most respondents (75.6%), although most (85.5%) would only perform surgery after medical treatment failure.

Conclusion—There was a wide range of current practice patterns for the diagnosis and treatment of acanthamoeba keratitis. The lack of sufficiently-powered comparative effectiveness studies and clinical trials makes evidenced-based decision making for this disease difficult.

Keywords

monotherapy; combination therapy; corticosteroids; keratoplasty; Bayesian

Introduction

Acanthamoeba keratitis is difficult to treat, with little comparative evidence on which to base treatment decisions. Many aspects of management remain uncertain. For example, confocal microscopy is a frequently described diagnostic modality for acanthamoeba keratitis, but it is unclear how commonly this technique is used for diagnosis.¹ While therapy with multiple agents often forms the basis for treatment of acanthamoeba keratitis, monotherapy with a biguanide antiseptic such as polyhexamethylene biguanide (PHMB) or chlorhexidine has also been shown to be effective.^{2–6} The role of corticosteroids for acanthamoeba has been controversial. Some reports have singled out corticosteroids as the factor most likely to predict treatment failure, but others have demonstrated good outcomes when using topical corticosteroids.^{3, 7–10} The role of keratoplasty to remove acanthamoebal organisms is unclear. Because it is a rare disease, acanthamoeba keratitis has been difficult to study, and much uncertainty remains. The objective of this survey was to assess practice patterns in the treatment of acanthamoeba keratitis, and specifically to assess providers' opinions about the efficacy of different diagnostic methods, single agent versus multiple agent therapy, corticosteroids, and keratoplasty.

Materials and Methods

In January 2010 a survey was distributed to approximately 800 ophthalmologists and vision scientists via the Cornea Society's kera-net and administered via an internet-based survey tool, Survey Monkey (Portland, OR). A reminder was sent two weeks after the initial distribution. The survey was organized into several sections. First, respondents were asked about their current practice patterns regarding use of antimicrobial agents for acanthamoeba keratitis. Specifically, opinions were elicited regarding the use of a single agent (termed monotherapy in this report) versus multiple agents (termed combination therapy in this report) for the treatment of acanthamoeba keratitis. Second, respondents were asked about their ideal antimicrobial regimen, and any factors that prevented use of this ideal regimen. Next, the survey posed questions regarding the use of corticosteroids and surgical treatment. Respondents were then asked about their uncertainty regarding the efficacy of monotherapy versus combination therapy, and regarding the efficacy of steroid therapy versus no steroid therapy. Finally, respondents were asked questions about their practice setting and experience with acanthamoeba treatment.

Descriptive statistics with binomial 95% confidence intervals were used to analyze responses. McNemar's chi square test was used to compare proportions from questions answered by the same respondents. Fisher's exact test was used to compare various diagnostic and treatment practices between experienced and inexperienced clinicians, and between university-based and private practitioners.

We asked three questions to determine the uncertainty of estimates for acanthamoeba clearance time with monotherapy versus combination therapy: (1) which treatment would clear acanthamoeba quicker, (2) how much faster the preferred treatment would clear acanthamoeba organisms, and (3) the chance that clearance times for monotherapy and combination therapy were actually not that different, defined as being within 10% of each other. We modeled the uncertainty of the log odds ratio for each individual responder as a Gaussian distribution, with the first two questions establishing the mean, and the third fixing the standard error (we chose that standard error most likely to result in the observed response). The distributions for all respondents were averaged. A similar procedure was used to construct a distribution for the uncertainty of estimates for the final visual acuity with steroid therapy versus no steroid therapy. The probability that combination therapy (or steroid therapy) would improve results was estimated by integrating the area under the

distribution from 0 to ∞ . Analyses were conducting using Stata version 10.0 (StataCorp, College Station, TX) and Mathematica 7.0 (Wolfram Research Inc., Champaign, IL).

Results

Demographics

Eighty-two respondents participated in the survey (10% of those on the listserve), with 85.4% of respondents identifying themselves as practicing cornea specialists. While 87.8% of respondents reported being involved in the care of at least one case of acanthamoeba keratitis in the preceding 5 years, there was a spectrum of experience: 15.9% reported seeing more than 20 cases, 12.2% reported seeing 11 to 20 cases, 29.3% reported seeing 6 to 10 cases, and 30.5% reported seeing 1 to 5 cases. The majority of respondents reported being from the United States or Canada (61.0%), followed by Asia (12.2%), Latin America (12.2%), and Australia (4.9%). Respondents were evenly distributed between academic institutions (45.1%) and private practice (45.1%); 9.8% of respondents did not identify their practice setting.

Current Practices

Respondents used a variety of methods for the diagnosis of acanthamoeba keratitis (Table 1). The majority of respondents (63/82; 76.8%) used a diagnostic strategy that included at least a clinical examination and culture, and almost all respondents (79/82; 96.3%) used either clinical examination or culture. Confocal microscopy was a diagnostic modality used by 36 (43.9%) respondents, though 91.7% of respondents who used confocal microscopy did so in combination with a culture and/or smear. Only 3 (2.4%) respondents reported using confocal microscopy as the sole means of diagnosis. Use of confocal microscopy was more common among university-based respondents (21/37; 56.8%) compared to those not at a university (15/45; 33.3%), $p=0.05$.

Of the 82 respondents, 39 (47.6%) had used monotherapy in the past. As shown in Table 2, the most frequent choices of monotherapy were one of the biguanide antiseptic agents. In contrast, 80 (97.6%) respondents had used combination therapy in the past, in 52 different combinations. Of respondents who reported use of combination therapy, 29 (36.3%) reported 1 combination of medications, 20 (25%) reported 2 different combinations, 10 (12.5%) reported 3 different combinations, and 23 (28.8%) reported 4 different combinations of medications. Biguanides and diamidines were the agents most commonly included in the reported combinations (Table 3). The most common combinations were PHMB/propamidine (11.0%), chlorhexidine/propamidine (9.4%), chlorhexidine/PHMB (7.3%), and PHMB/propamidine/neomycin (6.8%). In general, the most commonly reported combination was that of dual therapy with a biguanide and diamidine (35.1%), though a sizable number consisted of these two classes of medications plus the addition of a topical or oral azole (12.6%), or neomycin (11.0%), or both an azole and neomycin (6.8%). Respondents most often used a 2-drug combination, though some used 5 or more drugs (Table 3). Only one respondent reported the use of a medication not listed in Table 3; this respondent reported using IV pentamidine in combination with topical therapy.

The vast majority of respondents (92.8%) preferred combination therapy over monotherapy for treatment of acanthamoeba keratitis. In fact, 90.2% of the 82 respondents reported using combination therapy “most of the time” or “always”, but only 6.1% did so with monotherapy ($p<0.00001$). When asked how effective each of the treatments were, 34.1% of the 82 respondents found monotherapy moderately or completely effective, compared to 90.2% for combination therapy ($p<0.00001$).

Ideal practices

Respondents were asked which agents they would use for *acanthamoeba* keratitis in an ideal world, where cost and availability were not a problem. Only 37 respondents selected an ideal agent for monotherapy; of those, most chose PHMB or chlorhexidine (Table 2). In comparison, 72 respondents selected an ideal regimen for combination therapy. The vast majority of these (68/72; 94.4%) would include one of the biguanides in combination therapy (Table 1). The most common ideal combination regimen consisted of dual therapy with a biguanide and diamidine (37.5%); other common ideal regimens would include these 2 medications plus a topical/oral azole (13.9%), or neomycin (9.7%), or both an azole and neomycin (5.6%). When asked why they would not use monotherapy, the most common answers among the 82 respondents were lack of effectiveness (54.9%) and insufficient evidence (22.0%); common reasons for not using combination therapy were poor patient compliance (23.2%), lack of availability (22.0%), cost (20.7%), and adverse events (19.5%).

Corticosteroids

A majority of the 82 respondents reported that they use corticosteroids, with 52.4% reporting use “some of the time,” 9.8% reporting use “most of the time,” and the remainder reporting “never.” Of the 51 respondents who used corticosteroids, 56.9% institute steroid therapy in the setting of persistent inflammation, and 41.2% do so when they are confident of microbial cure. Many (31.4%) wait until after 1 month of treatment before starting corticosteroids; just 5.9% use steroids after only 2 weeks of treatment..

Surgery

The majority (62/82, 75.6%) of respondents thought that keratoplasty could play a role for a patient with *acanthamoeba* keratitis and with no imminent perforation. Of the 62 clinicians who would perform surgery as part of *acanthamoeba* treatment, most would operate after treatment failure (85.5%), followed by after clinical resolution (9.7%) or after some specified time (4.8%).

Uncertainty

Figure 1A shows the mean of the respondents' distributions for the relative efficacy of steroid therapy versus no steroid therapy in terms of the final visual acuity. The area under the curve (AUC) can be calculated for different ranges of the x-axis to provide information regarding the respondents' uncertainty of various scenarios. For example, the AUC for values of the x-axis greater than zero (59%) indicates that on average, respondents thought there was a 59% probability that corticosteroids would result in better visual acuity compared to no steroids. Similarly, the AUC to the right of $x=2$ reflects the perceived probability that corticosteroids would result in visual acuity 2 lines better than no steroids (32%), and the AUC to the left of $x=-2$ reflects the perceived probability that using steroids would result in a visual acuity 2 lines worse than no steroids (17%). Figure 1B shows the distribution of the respondents' opinions regarding the relative efficacy of combination therapy versus monotherapy in terms of *acanthamoeba* clearance time. AUCs can be calculated similarly as for Figure 1A; in this case, respondents felt there was a 75% chance that combination therapy would clear *acanthamoeba* faster than monotherapy, and a 51% chance that combination therapy would clear *acanthamoeba* twice as fast as monotherapy.

Experience

We compared responses from clinicians with more experience treating *acanthamoeba* keratitis, defined as being involved with >10 cases in the past 5 years, compared to those who had treated 10 or fewer cases in the past 5 years. There were some apparent differences in diagnosis and treatment depending on experience level, though none were statistically

significant (Table 1). Those with more experience were more likely to use all forms of diagnostic modalities compared to those who treated 10 or fewer cases in the past 5 years, and were also more likely to work in a university-based practice. In addition, respondents with more experience tended to include PHMB more frequently in their combination therapy, were more likely to include a biguanide and diamidine in their combination therapy, and were more likely to use steroids and surgery for treatment of acanthamoeba keratitis. Conclusions from this analysis did not change if the threshold for experience was changed to >5 cases in the past 5 years (data not shown).

Discussion

In this survey, respondents overwhelmingly preferred combination therapy to monotherapy for treatment of acanthamoeba keratitis, although considerable uncertainty remained regarding this choice. This preference for combination therapy mirrors many of the recent case series that describe combination treatment for acanthamoeba keratitis.^{11–14} This preference is also consistent with case reports of acanthamoeba keratitis that failed monotherapy but subsequently responded to multiple agents.¹⁵ Traditionally, combination therapy has been advocated due to the belief that multiple agents were more effective, and selected for less resistance.² In general, survey respondents agreed with this assessment. However, combination therapy has the potential disadvantages of epithelial toxicity, cost, and compliance,^{16, 17} all of which were commonly identified as reasons why survey respondents would refrain from using combination therapy. Given the excellent *in vitro* susceptibility profile of the biguanide medications for acanthamoeba, monotherapy with one of these medications could be sufficiently effective while avoiding the disadvantages of combination therapy.¹⁸ The lack of randomized clinical trials comparing combination therapy with monotherapy for acanthamoeba keratitis makes an evidenced-based decision difficult. Nonetheless, concern for poor outcomes, regardless of which particular treatment is used, may lead some clinicians to use more rather than fewer medications, even if the evidence base for this decision is limited.

Although respondents favored combination therapy over monotherapy, almost half had used monotherapy in the past, with the most popular choice being PHMB, followed by chlorhexidine. Likewise, if asked to choose an ideal medication for use as monotherapy, over half would choose PHMB, and over three-quarters would choose either PHMB or chlorhexidine. This preference is not surprising, given *in vitro* and clinical studies of the various medications for acanthamoeba keratitis. Reports have shown that both PHMB and chlorhexidine have *in vitro* minimum cysticidal concentrations (MCCs) of roughly 2–3 µg/mL, much lower than the concentrations usually used in clinical practice (0.02% for each).¹⁸ Case reports and series have suggested that single-agent treatment with chlorhexidine^{19, 20} or PHMB^{21–23} may be successful. A clinical trial comparing chlorhexidine monotherapy with PHMB monotherapy found that these two treatments had similar efficacy for acanthamoeba keratitis, with visual acuity improving in the majority of patients taking each medication.⁴ Monotherapy with other agents has been even less well characterized, although it has been well established that the *in vitro* susceptibility profile of the diamidines, neomycin, and azoles is inferior to that of the biguanides.^{11, 18, 24, 25}

While the vast majority of respondents used combination therapy, there was little consensus on exactly which agents to use. The most common combination, PHMB and propamidine, accounted for only 11% of all reported regimens of combination therapy. There was broader consensus on classes of medications, with over 65% of reported combinations including a biguanide and diamidine. This is consistent with many recent reports advocating the use of these two classes of medications, with or without other agents.^{3, 11–13} Choices of combination therapy regimens in an ideal world were not substantially different. This may

indicate that clinicians generally have adequate access to their choices of mediations, or alternately could reflect the lack of comparative research regarding acanthamoeba treatment. Over one-third of respondents would include neomycin and/or an azole in their ideal choice of combination therapy, despite *in vitro* evidence that these medications have poor activity against acanthamoeba^{18, 25} and the potential for corneal toxicity.^{26, 27} The continued use of these agents may be influenced more by their wide availability than by their perceived effectiveness.

Respondents were divided on the use of corticosteroids, with little over half of respondents using corticosteroids in the treatment of acanthamoeba keratitis. The use of steroids in the management of acanthamoeba keratitis is controversial. Animal models have shown that in the absence of anti-acanthamoeba therapy, corticosteroids promote excystment of acanthamoeba cysts and proliferation of trophozoites.²⁸ While some authors have recommended against using corticosteroids during active infection,^{29, 30} others believe steroid therapy may be useful for control of pain and inflammation when given in combination with adequate anti-acanthamoeba therapy.^{3, 7, 10}

More than 75% of respondents viewed keratoplasty as a viable treatment modality for acanthamoeba keratitis, but most clinicians would only perform keratoplasty after medical treatment had failed. This is consistent with most reports of therapeutic keratoplasty for acanthamoeba, which have found acceptable cure rates, but often in the setting of multiple surgeries and poor visual outcomes.^{16, 31–35}

Almost half of respondents reported using confocal microscopy for the diagnosis of acanthamoeba keratitis, although almost all who did so also used more traditional methods such as smear and culture. Some reports have suggested a favorable sensitivity and specificity of confocal microscopy when compared to culture and smear.^{36, 37} Nonetheless, this survey suggests that respondents who do use confocal microscopy have not used it as a replacement for smear and culture, but instead are using confocal microscopy as an additional testing modality for a disease that remains difficult to diagnose.

We suspected that respondents may be uncertain about some of their opinions, given the lack of evidence. Eliciting both an estimate and the confidence in that estimate allowed us to assess the uncertainty of the group, as a distribution (Figure 1). We observed relatively wide distributions for each of the two questions, indicating a high level of uncertainty. These distributions suggest the equipoise necessary for a clinical trial to be considered, and also could be considered as the prior distributions for a Bayesian analysis of a future clinical trial.^{38–40}

This study was limited by factors common to many surveys: low response rate, possibility of recall bias, focus solely on specialists, and unclear generalizability to the underlying study sample. However, we believe the number of respondents was adequate to gauge the preferences of practicing cornea specialists, who likely provide treatment for the majority of patients with acanthamoeba keratitis. The survey asked general questions by design, and did not specify definitions for all terms used. For example, terms like “treatment failure” and “clinical resolution” were left to the judgment of the respondent. Nearly 60% of respondents had seen 10 or fewer cases of acanthamoeba keratitis in the past 5 years. Given the low volume of cases, some respondents may never have encountered a case that failed monotherapy or required steroids, which could alter their practice patterns.

In conclusion, surveyed cornea specialists who treat acanthamoeba keratitis used combination therapy more commonly than single-agent therapy, despite uncertainty about the relative effectiveness of the two. The actual and ideal preferred regimens of both monotherapy and combination therapy for acanthamoeba keratitis were similar. PHMB was

the most widely-prescribed medication used in both monotherapy and combination therapy regimens, and the biguanide-diamidine combination was the most common component of combination therapy. Most clinicians believed that corticosteroids and keratoplasty play a role in *acanthamoeba* keratitis treatment. Adjunctive use of confocal microscopy was commonly used for diagnosing *acanthamoeba* keratitis. Clinicians expressed a great deal of uncertainty regarding the benefit of combination therapy and the use of corticosteroids, a finding which is not surprising given that *acanthamoeba* keratitis is a relatively rare event that does not lend itself to comparative effectiveness studies or clinical trials. Nonetheless, the beliefs and practices of cornea specialists are helpful in identifying areas of *acanthamoeba* keratitis treatment which are still controversial, and in need of further study.

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Figure 1. Probability distributions depicting the respondents' uncertainty regarding (A) using corticosteroids versus not using corticosteroids for the outcome of visual acuity, and (B) combination therapy versus monotherapy for the outcome of acanthamoeba clearance time from the cornea.

Table 1

Choices for diagnosis and ideal treatment of acanthamoeba keratitis, stratified by experience level of respondent

	<u>All respondents N=82</u>	<u>More experience[*] N=23</u>	<u>Less experience[*] N=59</u>	
	%	%	%	p-value [†]
Diagnosis				
Use clinical examination	89.0%	78.3%	93.2%	0.11
Use culture	84.1%	91.3%	81.3%	0.33
Use smear	59.8%	60.9%	59.3%	1.00
Use confocal	43.9%	60.9%	37.3%	0.08
Use PCR	7.3%	8.7%	6.8%	1.00
Use contact lens case	50.0%	52.2%	49.2%	1.00
Treatment				
Prefer combination therapy	93.9%	100%	91.5%	0.32
Ideal combination therapy includes:				
Chlorhexidine	51.2%	47.8%	52.5%	0.81
PHMB	61.0%	78.3%	54.2%	0.08
Propamidine	61.0%	78.3%	54.2%	0.08
Hexamidine	8.5%	4.3%	10.2%	0.67
Neomycin	22.0%	26.1%	20.3%	0.57
Topical or oral Azole	34.1%	30.4%	35.6%	0.80
Biguanide + Diamidine	61.0%	78.3%	54.2%	0.08
Did not answer	12.2%	0%	16.9%	0.06
Use steroids	62.2%	73.9%	57.6%	0.21
Use surgery	75.6%	87.0%	71.2%	0.16
University-based practice	45.1%	60.9%	39.0%	0.06

* Inexperienced clinicians reported caring for 0–10 cases of acanthamoeba keratitis in the preceding 5 years; experienced clinicians reported caring for >10 cases.

[†] Fisher's exact test comparing more experienced with less experienced respondents

Table 2

Choices of monotherapy for acanthamoeba keratitis

Responses	N (%)
Used monotherapy in past	39/82 (47.6%)
Past choices for monotherapy*	
Any biguanide	35/39 (89.7%)
Chlorhexidine	21/39 (53.8%)
PHMB	27/39 (69.2%)
Any diamidine	13/39 (33.3%)
Propamidine	13/39 (33.3%)
Hexamidine	2/39 (5.1%)
Ideal choice for monotherapy	
Any biguanide	29/37 (78.4%)
Chlorhexidine	10/37 (27.0%)
PHMB	19/37 (51.4%)
Any diamidine	5/37 (13.5%)
Propamidine	4/37 (10.8%)
Hexamidine	1/37 (2.7%)
Topical azole	3/37 (8.1%)

* Participants asked to list all agents they had ever used as monotherapy, so fractions do not add up to 100%.

Table 3

Choices of combination therapy for acanthamoeba keratitis

All reported combinations N=191	
Responses	%
Combination included:	
Biguanide	94.2%
Chlorhexidine	56.0%
PHMB	68.1%
Chlorhexidine + PHMB	29.8%
Diamidine	70.6%
Propamidine	62.8%
Hexamidine	9.4%
Propamidine + Hexamidine	1.6%
Neomycin	36.1%
Topical or oral azole	34.0%
Common combinations:	
Biguanide + Diamidine	35.1%
Biguanide + Diamidine + Neomycin	12.6%
Biguanide + Diamidine + Azole	11.0%
Biguanide + Diamidine + Neomycin + Azole	6.8%
Number of drugs in combination regimen	
2 drugs	46.1%
3 drugs	35.6%
4 drugs	13.6%
≥5 drugs	4.7%