Visual Impairment in Fungal Versus Bacterial Corneal Ulcers 4 Years After Successful Antimicrobial Treatment

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• PURPOSE: To compare longitudinal outcomes of visual acuity after fungal corneal ulcers with those of bacterial ulcers.
• DESIGN: Prospective cohort study.
• METHODS: This study was conducted in a tertiary eye hospital in South India. The population consisted of 100 of 152 individuals whose fungal or bacterial keratitis had been diagnosed 4 years prior and had been enrolled in 1 of 2 concurrent randomized trials. Causative organisms of infectious keratitis were either bacterial or fungal. Presenting visual acuity consisted of best spectacle corrected visual acuity (BSCVA) and hard contact lens-corrected visual acuity (CLVA).
• RESULTS: Fifty study participants with prior fungal keratitis and 50 with prior bacterial keratitis were enrolled. Four years after treatment for keratitis, participants' presenting vision in the better eye was worse than 20/60 for 12 individuals (24.0%) in the fungal group and 10 individuals (20.0%) in the bacterial group. Median BSCVA in the affected eye at the 4-year visit in the fungal group was similar to that in the bacterial group (Snellen equivalent, 20/32 for each), although vision worse than 20/400 was more common in the fungal ulcer group after spectacle correction (odds ratio [OR] 4.19; 95% confidence interval [CI], 1.11-15.8) and contact lens correction (OR, 5.74; 95% CI, 1.37-24.1).
• CONCLUSIONS: In this South Indian population with a previous episode of fungal or bacterial keratitis, correctable bilateral visual impairment was common. Although long-term visual outcomes were, on average, similar between fungal and bacterial ulcers, fungal ulcers were more likely to produce severe visual impairment. (Am J Ophthalmol 2019;204:124–129. © 2019 Elsevier Inc. All rights reserved.)

INFECTIOUS KERATITIS REMAINS A MAJOR CAUSE OF visual impairment worldwide.[1–3] In tropical environments, fungal keratitis makes up a large proportion of keratitis cases.[4,5] Relative to bacterial corneal ulcers, fungal ulcers are typically thought to be more difficult to treat and to result in worse outcomes.[6] The present authors previously reported that, at 3 months after diagnosis, fungal ulcers were more likely to have a larger scar size and to have perforations than bacterial ulcers but did not have significantly worse best spectacle corrected visual acuity (BSCVA).[7] In a separate report, it was found that bacterial corneal ulcers experienced significant improvements in BSCVA after 3 months.[8] Thus, it is possible that the differences between bacterial and fungal ulcers that were observed at 3 months could change with longer follow-up. As an attempt to better describe the long-term visual outcomes of bacterial and fungal corneal ulcers, a subset of study participants from the earlier comparative study were interviewed at a 4-year follow-up visit. The current study compared presenting visual acuity, BSCVA, and hard contact lens corrected visual acuity (CLVA) in bacterial and fungal ulcers to better understand the natural history of infectious corneal ulcers.

SUBJECTS AND METHODS

• STUDY DESIGN: This was a prospective cohort study that drew participants from 2 randomized clinical trials conducted at Aravind Eye Hospital in Madurai, India, one of which enrolled fungal corneal ulcers and one of which enrolled bacterial ulcers. The two trials overlapped in time and had similar inclusion and exclusion criteria and outcomes, which allowed a direct comparison. The first trial was a multicenter therapeutic exploratory trial that randomized participants with smear-positive fungal keratitis to topical natamycin, 5%, or topical voriconazole, 1% (Therapeutic Exploratory Study of Comparing Natamycin and Voriconazole to Treat Fungal Corneal

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TABLE 1. Enrollment Characteristics of Study Participants and Those Lost to Follow-up (LTFU) at Four Years

	Fungal		Bacterial	
Enrollment Characteristic	Included n = 50	LTFU n = 22	Included n = 50	LTFU n = 30
Female, n (%)	20 (40.0)	6 (27.3)	25 (50)	10 (33.3)
Median age (IQR)	48 (33-58)	55 (48-60)	45 (38-60)	56 (37-65)
Median logMAR BSCVA (IQR)[a]	0.61 (0.30-1.7)	0.80 (0.24-1.8)	0.65 (0.36-1.6)	1.36 (0.64-1.7)
Median infiltrate size (mm) (IQR)	3.5 (2.2-5.1)	3.6 (2.7-4.8)	2.5 (1.9-3.7)	3.2 (1.9-5.1)
Organism, n (%)				
Fusarium species	17 (34.0)	6 (27.3)	-	-
Aspergillus species	6 (12.0)	3 (13.6)	-	-
Bipolaris species	6 (12.0)	0 (0)	-	-
Curvularia species	4 (8.0)	3 (13.6)	-	-
Other fungus, n (%)	17 (34.0)	10 (45.5)	-	-
S. pneumoniae, n (%)	-	-	21 (42.0)	15 (51.7)
Nocardia species, n (%)	-	-	14 (28.0)	4 (13.3)
P. aeruginosa, n (%)	-	-	12 (24.0)	7 (23.3)
Other bacteria, n (%)	-	-	3 (6.0)	4 (13.3)

Values are n (%) or median (IQR).
IQR = interquartile range; LTFU = lost to follow-up.
[a]Best spectacle corrected visual acuity was assessed using the logarithm of the minimum angle of resolution (logMAR) units.

Ulcer [MUTT-TE]; NCT00557362).[9] The second trial was the multicenter Steroids for Corneal Ulcers Trial (SCUT; NCT00324168), which randomized participants with culture-positive bacterial keratitis who had been treated with at least 48 hours of moxifloxacin, 0.5%, to either topical prednisolone sodium phosphate, 1%, or topical placebo.[10] Aside from the causative organism, inclusion and exclusion criteria for the trials were similar. In both trials, patients with no light perception vision in the affected eye or BSCVA worse than 20/200 in the unaffected eye were excluded.[9,11] In both trials, BSCVA was assessed at enrollment and at 3 months. For the present study, any study participants who had been enrolled for either trial at Aravind Eye Hospital Madurai from October 8, 2007, to August 18, 2008, were invited for a 4-year follow-up visit. Note that comparison of the two trials was facilitated by restricting cases to only those enrolled at a single study site and to only those enrolled during a common time window. The study received ethical approval from the Aravind Eye Hospital Institutional Review Board and the University of California, San Francisco, Committee on Human Research.

• **ASSESSMENT:** We used methods for the current study that were similar to those for the original trials, including refraction protocols and slit lamp examination protocols.[9,11] Certified refractionists assessed the presenting visual acuity (ie, visual acuity corrected with the participant's current eyeglasses or uncorrected visual acuity if the participant did not use eyeglasses) and BSCVA for each eye in logMAR units with an Early Treatment Diabetic Retinopathy Study visual acuity chart.[12] Refractionists evaluated subjects with visual acuity worse than logMAR 1.6 (Snellen equivalent, 20/800) for counting fingers, hand motions, light perception, or no light perception visual acuity, which were assigned a logMAR of 1.7, 1.8, 1.9, or 2.0, respectively. Affected eyes with a BSCVA worse than logMAR 0.22 (Snellen equivalent, 20/32) underwent hard contact lens over-refraction. Slit lamp biomicroscopy and dilated fundus examinations were performed in all study participants. Refractionists were masked to the treatment allocation at each visit and to the causative organism at the 4-year visit.

• **STATISTICAL ANALYSIS:** Descriptive statistical analysis was performed. Comparisons were made between the fungal keratitis group and the bacterial keratitis group using the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. The proportion of participants meeting the World Health Organization threshold for visual impairment (visual acuity worse than 20/60) was compared between the fungal and bacterial groups in a logistic regression adjusted for baseline visual acuity. Similar methods were used to compare the proportion of participants meeting the threshold for blindness (visual acuity worse than 20/400). All visual acuity analyses were conducted with logMAR acuities, but Snellen equivalents were used when describing the results.[13] Scar size was reported as the geometric mean of the largest scar diameter and its perpendicular width; eyes that had undergone

TABLE 2. Visual Impairment in Eyes With Fungal and Bacterial Keratitis Four Years Following Diagnosis and Treatment

	Fungal n = 50	Bacterial n = 50	OR (95% CI)[a]	*P* Value
Presenting vision				
Worse than 20/60	32	30	1.18 (0.48-2.86)	0.72
Worse than 20/400	13	4	5.00 (1.30-19.2)	0.02
BSCVA				
Worse than 20/60	16	12	1.54 (0.54-4.43)	0.42
Worse than 20/400	12	4	4.19 (1.11-15.8)	0.04
CLVA				
Worse than 20/60	14	7	2.71 (0.85-8.59)	0.09
Worse than 20/400	12	3	5.74 (1.37-24.1)	0.02

BSCVA = best spectacle-corrected visual acuity; CI = confidence interval; CLVA = hard contact lens-corrected visual acuity; OR = odds ratio.

[a]Logistic regression was adjusted for BSCVA at baseline. The odds ratio compares fungal relative to bacterial ulcers.

TABLE 3. Visual Acuity 4 Years After Treatment for Infectious Keratitis

	Median logMAR Visual Acuity (IQR)	
	Fungal n = 50	Bacterial n = 50
Presenting visual acuity[a]		
Affected eye	0.7 (0.3-1.5)	0.6 (0.3-1.0)
Fellow eye	0.3 (0-0.78)	0.3 (0-0.48)
Better Seeing eye	0.19 (0-0.48)	0.3 (0-0.48)
BSCVA		
Affected eye	0.16 (0.02-0.78)	0.22 (0.02-0.42)
Fellow eye	0 (0-0.18)	0.1 (0-0.2)
Better seeing eye	0 (0-0.18)	0.05 (0-0.2)

BSCVA = best spectacle corrected visual acuity; IQR = interquartile range.

[a]Presenting visual acuity is defined by the World Health Organization as visual acuity obtained with currently available refractive correction, if any. Here, 5 participants in the fungal group and 4 participants in the bacterial group had visual acuity tested with their eyeglasses and the remaining participants were tested without eyeglasses.

keratoplasty had scar sizes imputed by using the last observation carried forward (ie, the 3-month visit for all eyes).

RESULTS

• **STUDY POPULATION:** Between October 8, 2007, and August 18, 2008, Aravind Eye Hospital Madurai enrolled 80 study participants with bacterial keratitis and 72 study participants with fungal keratitis into the respective trials. Of these participants, a 4-year follow-up examination was conducted in 50 participants (62.5%) with bacterial keratitis and 50 participants (69.4%) with fungal keratitis. The baseline characteristics of study participants with fungal keratitis who were lost to follow-up were not significantly different from those who had a 4-year follow-up visit in terms of age, sex, visual acuity, or scar size. As reported elsewhere, the study participants with bacterial keratitis who were lost to follow-up had worse visual acuity at enrollment than those who returned for the 4-year visit.[14] Baseline characteristics are shown in Table 1. Visual acuities between bacterial and fungal ulcers were similar, but fungal ulcers tended to be larger.

• **PRESENTING VISION:** Of the 100 study participants who had 4-year follow-up examinations, 9 were wearing eyeglasses at the time of the study visit (5 in the fungal keratitis group and 4 in the bacterial keratitis group). The median presenting logMAR visual acuity (ie, acuity with current spectacle correction for those with eyeglasses and uncorrected visual acuity for those without eyeglasses) at 4 years in the affected eye was 0.7 (Snellen equivalent, 20/100; interquartile range [IQR], 0.3, 1.5 logMAR units) for the fungal keratitis group and 0.6 (Snellen equivalent, 20/80; IQR, 0.3, 1.0 logMAR units) for the bacterial keratitis group. Blindness of the affected eye, defined as visual acuity worse than 20/400, was more common in the fungal group than in the bacterial group (Table 2). The median logMAR presenting vision in the fellow eye at 4 years was 0.3 (Snellen equivalent, 20/40) for both the fungal and bacterial groups. Bilateral visual impairment, defined as presenting visual acuity worse than 20/60 in the better-seeing eye, was present in 12 individuals (24.0%) in the fungal group and 10 individuals (20.0%) in the bacterial group.

• **BEST SPECTACLE CORRECTION VISUAL ACUITY:** The visual acuity in the affected eye improved after spectacle correction for most participants in the fungal group (median, 1.9-line improvement over presenting visual acuity; IQR, 0, 4.4) and bacterial group (median, 2.8-line improvement over presenting visual acuity; IQR, 1.0, 4.6) at the 4-year study visit ($P = 0.27$ comparing fungal with bacterial ulcers). As shown in Supplemental Figure 1 (Supplemental Material available at www.ajo.com), spectacle correction was generally not effective for those whose presenting vision was worse than 20/400. Supplemental Figure 2 shows the BSCVA in the affected eye for each study participant at enrollment, at 3 months, and at 4 years. Although the median BSCVA in the fungal group was similar to that in the bacterial group (median Snellen equivalent, 20/32 in each; $P = 0.90$) (Table 3), the fungal ulcer group was more likely to have BSCVA worse than 20/400 at the 4-year follow-up visit (12 of 50 fungal ulcers compared with 4 of 50 bacterial ulcers; odds ratio [OR], 4.19; 95% confidence interval [CI], 1.11-15.8; $P = 0.03$,

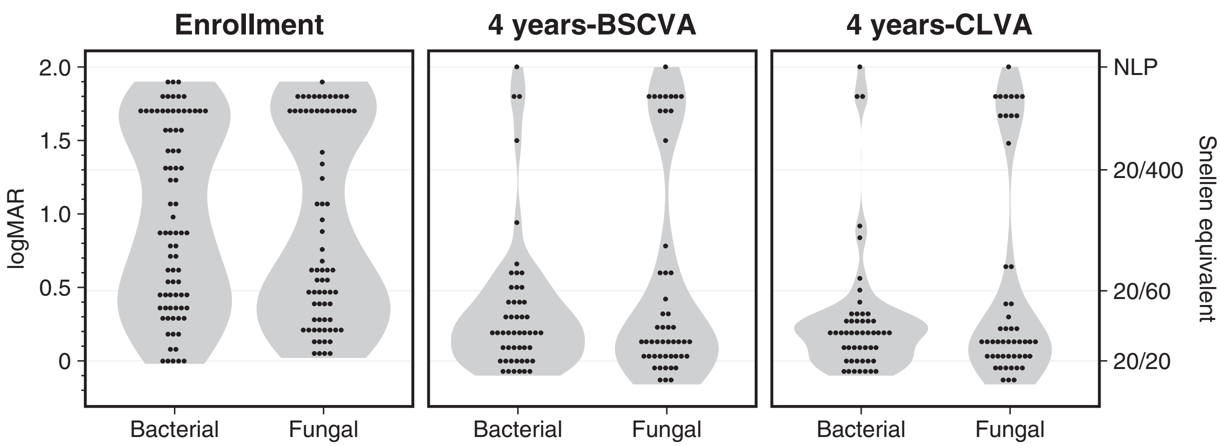

FIGURE. Presenting visual acuity, BSCVA, and CLVA at 4 years in eyes with fungal versus bacterial keratitis. The distribution of logMAR visual acuity is shown for each vision outcome as a dot plot superimposed on a violin plot, stratified by the causative organism. Each point represents the visual acuity of a single eye. CLVA was assessed only for eyes with a BSCVA worse than logMAR 0.22. For the purposes of this graph the BSCVA was substituted for eyes not undergoing CLVA. BSCVA = best spectacle-corrected visual acuity; CLVA = contact lens-corrected visual acuity.

logistic regression adjusting for BSCVA at enrollment) (Table 2, Figure). Appropriate eyeglasses would reduce the number of bilaterally visually impaired (ie, worse than 20/60) study participants to 4 (8.0%) in the fungal group and zero in the bacterial group (*P* = 0.06, Fisher exact test).

• HARD CONTACT LENS-CORRECTED VISUAL ACUITY: Contact lens over-refraction was performed for affected eyes with a logMAR BSCVA of >0.22 (Snellen equivalent, 20/32; n = 21 in fungal group and n = 21 in bacterial group). Of these contact lenses improved visual acuity beyond BSCVA in 10 eyes (47.6%) in the fungal keratitis group and 14 eyes (66.7%) in the bacterial keratitis group. Among eyes that underwent contact lens over-refraction, contact lens visual acuity improved on the BSCVA by a median of 0 lines (IQR, 0, 0.8 lines) in the fungal group and 0.8 lines (IQR, 0, 2.4) in the bacterial group. After contact lens over-refraction, 32 study eyes (64.0%) from the fungal group and 33 eyes (66.0%) from the bacterial group had a corrected visual acuity of logMAR 0.22 (Snellen equivalent, 20/32) or better (*P* = 0.96, logistic regression adjusted for baseline BSCVA). As shown in Table 2, more eyes in the fungal group had hard CLVA worse than 20/60 at 4 years (14 participants vs. 7, respectively; *P* = 0.09 after adjusting for enrollment BSCVA) and CLVA worse than 20/400 at 4 years (12 participants vs. 3, respectively; *P* = 0.02 after adjusting for enrollment BSCVA).

• PERFORATION AND KERATOPLASTY: By the time of the 4-year study visit, perforation had occurred in 8 study participants from the fungal group had 0 from the bacterial group (*P* = 0.01, Wilcoxon rank sum test). Moreover, 7 study participants with fungal keratitis had received a penetrating keratoplasty but none with bacterial keratitis had (*P* = 0.01, Wilcoxon rank sum test). Each perforation and keratoplasty occurred before the 3-month visit. The postoperative vision of eyes undergoing keratoplasty generally remained poor at 4 years. Although 1 participant had a BSCVA of 0.12 logMAR units, the remaining 6 participants had a BSCVA worse than 20/400, and none of these participants achieved substantial improvement with CLVA. Of these, 4 participants had a failed graft, 1 had a dense pupillary membrane, and 1 had a central corneal scar. The other major surgical intervention since enrollment in the respective studies was cataract surgery, which had been performed in the 4-year study interval in 7 (14.0%) of the fungal group and 6 (12.0%) of the bacterial group (*P* = 0.50, Fisher exact test).

• CORNEAL SCARS: The median scar size at the 4-year follow-up visit was 3.3 mm (IQR, 2.1, 5.4) in the fungal group and 2.9 mm (IQR, 1.9, 4.4) in the bacterial group (*P* = 0.20, Wilcoxon rank sum test). Scar size and BSCVA were correlated at the 4-year visit, with each 1-mm increase in size associated with a 2.1-line decrement in vision (95% CI, 1.6-2.6 lines). However, scar size was not significantly different between the 2 groups when accounting for infiltrate size at enrollment (scars in the fungal group were, on average, 0.1 mm smaller; 95% CI, 0.6 mm smaller-0.4 mm larger; *P* = 0.67) (Supplemental Figure 3 shows representative images). On slit lamp examination, a substantial number of study participants had multiple corneal scars in the study eye: 8 (16.0%) in the fungal group and 14 (28.0%) in the bacterial group. Moreover, many study participants had scars in the fellow eye: 21 (42.0%) in the fungal group and 27 (54.0%) in the bacterial group.

Bilateral visual impairment, defined as presenting acuity worse than 20/60 in each eye, was more common in those who also had scars in the fellow eye (13 of 48 participants [27%]) relative to those without scars in the fellow eye (9 of 52 participants [17%]), although the difference was not statistically significant ($P = 0.33$).

DISCUSSION

FOUR YEARS AFTER BEING ENROLLED IN A BACTERIAL OR fungal keratitis trial at a single center in South India, most of the study participants experienced visual impairment in the affected eye, and almost one-fourth experienced bilateral visual impairment. Spectacle correction would greatly reduce the number of bilateral visual impairments, yet only 9% of study participants were wearing eyeglasses at the time of the 4-year follow-up examination. Study participants treated for fungal keratitis were more likely to have counting fingers vision or worse compared with those treated for bacterial keratitis, even after accounting for the worse visual acuity in fungal ulcers at trial enrollment.

Fungal ulcers had worse outcomes than bacterial ulcers in this study, with a greater proportion having visual impairment or blindness after spectacle correction and contact lens correction and a greater proportion experiencing perforation and subsequent therapeutic penetrating keratoplasty. In addition, a greater proportion in the fungal group had bilateral visual impairment after refraction, although this was not statistically significant. A previous study comparing 3-month outcomes in a much larger group of patients from the same set of randomized trials found that fungal corneal ulcers had larger scar sizes and were more likely to perforate relative to bacterial ulcers.[7] The present study found similar results in terms of perforation but not scar size, perhaps because of the limited sample size.

Fungal keratitis cases were generally worse at study enrollment, which could account for these findings; however, poor visual outcomes were more likely in the fungal group at 4 years even after adjusting for baseline visual acuity. The differences between bacterial and fungal cases could also be due in part to poor outcomes in perforated or nearly perforated eyes. The 7 eyes with fungal keratitis that underwent therapeutic keratoplasty had poor long-term visual outcomes, with only 1 of 7 patients achieving a postoperative visual acuity of better than 20/400 at the 4-year study examination and none improving with a hard contact lens. In contrast, none of the bacterial keratitis cases in this study experienced perforation. Perforation did not explain the entire difference, however, as 6 of the 11 fungal cases with BSCVA worse than 20/400 at the 4-year study visit had not experienced a perforation. Supplemental Figure 2 shows that, even as early as the 3-month visit, the fungal keratitis cases with poor visual acuity at enrollment were less likely to experience improvement in BSCVA over time than were the bacterial cases. This lack of improvement could have been due to inadequate clearance of organisms and/or difficulty managing the host's immune response, both of which are relatively more challenging with fungal keratitis than with bacterial keratitis.

It is notable that many patients with poor visual acuity in this South Indian setting did not pursue optical penetrating keratoplasty once the keratitis had resolved, and over 90% did not wear spectacle correction. This resulted in a considerable amount of correctable visual impairment in this population. Most of the study participants achieved excellent visual acuity with spectacle correction alone and would not require hard contact lenses. This is especially encouraging in a place like India, where it may not be practical for the agricultural workers most at risk for infectious keratitis to wear hard contact lenses. Nonetheless, the low uptake of eyeglasses demonstrated in this study highlights the unmet need for refractive error correction in this population.

Corneal ulcers are thought of as a unilateral condition that does not cause bilateral blindness. However, the present study shows that approximately 20% of study participants with a corneal ulcer had bilateral visual impairment worse than 20/60 4 years after developing the ulcer. This may be due in part to corneal ulcers in both eyes, as almost half of the participants had corneal scars in the nonstudy eye at the 4-year follow-up examination. Participants with scars in the fellow eye were more likely to have bilateral visual impairment at 4 years, although this was not statistically significant. These results are especially noteworthy because an exclusion criterion for both the fungal and bacterial trials was visual acuity worse than 20/200 in the unaffected eye, and many patients excluded from the trials had corneal scars in the unaffected eye.[15] These findings (ie, the high prevalence of bilateral scars and bilateral blindness) suggest that corneal ulceration is frequently a bilateral condition with the potential to cause bilateral visual impairment. While speculative, it is possible that study participants might have been at continued risk for corneal trauma and infection in this South Indian setting as a result of agricultural work.

In this study, cases of fungal keratitis and bacterial keratitis were enrolled in separate clinical trials at a single center during the same time period, allowing us to compare outcomes between the 2 groups 4 years after enrollment. The inclusion and exclusion criteria, study design, and outcomes of the trials were similar, and enrollment occurred during the same time window, making the 2 groups inherently comparable. Moreover, the refractionists were masked to the causative organism, to reduce bias.

Several limitations should be acknowledged. The study had a relatively high rate of loss to follow-up, especially in the bacterial keratitis group. It is possible that participants with bacterial ulcers had less of an incentive to return for a 4-year follow-up examination due to better visual outcomes, although such reasoning is speculative. Patients lost to follow-up appeared to have worse ulcers in both the bacterial and the fungal groups, but the possibility of differential loss to follow-up and subsequent bias cannot be ruled out. The study participants do not form a population-based sample: the most severe ulcers were excluded from the trials. It is possible that one of the groups was worse off at baseline but not enrolled in the respective trial, in which case a larger difference could have been missed between the bacterial and fungal ulcer groups. Contact lens visual acuity tests were not performed for all participants due to logistical constraints, so this outcome could not be compared among all study participants. Because the results come from a single center in India, the generalizability of the findings to other settings with a different spectrum of causative organisms is not clear.

In summary, the present study showed that correctable visual impairment was relatively common in a South Indian population treated for infectious keratitis 4 years earlier. Patients with fungal ulcers were more likely to have counting fingers vision or worse and were more likely to have perforated ulcers than were the patients with bacterial ulcers. These results suggest that early and accurate diagnosis of microbial keratitis, and especially of fungal keratitis, is important to prevent long-term visual impairment. Better treatments for fungal corneal infections and their inflammatory sequelae are needed.

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