Lid-Related Keratopathy in Stevens-Johnson Syndrome: Natural Course and Impact of Therapeutic Interventions in Children and Adults

SWAPNA S. SHANBHAG, SAHIL SHAH, MADHU SINGH, CHIRAG BAHUGUNA, PRAGNYA R. DONTHINENI, AND SAYAN BASU

• PURPOSE: To compare the long-term visual outcomes of different management strategies in children and adults with Stevens-Johnson Syndrome (SJS)—induced chronic lid-related keratopathy.

• DESIGN: Retrospective comparative case series.

• METHODS: This study included 705 eyes of 401 patients (81 children and 320 adults) with SJS who presented with chronic lid-related keratopathy between 1990 and 2015. Affected eyes received either conservative therapy [topical medications (n = 363)] or definitive management (n = 342) that included mucous membrane grafting (MMG), prosthetic replacement of the ocular surface ecosystem (PROSE) contact lenses, or both. The primary outcome measure was change in best corrected visual acuity (BCVA) over time. The secondary outcome measure was the odds of developing corneal ulceration or perforation in the first year.

• RESULTS: The treatment subgroups were comparable at baseline in terms of BCVA and previous management ($P > .10$). Over 10 years, children and adults who received conservative therapy lost at least 5 lines of median BCVA and carried a 3 times higher risk of developing corneal ulceration in the first year. Conversely, definitive therapy provided significant benefit by improving median BCVA ($P < .0001$). In children, MMG was more effective than PROSE ($P = .009$), whereas PROSE was more effective than MMG in adults ($P = .028$). However, the combination of MMG followed by PROSE provided the best results in both children and adults ($P < .036$).

• CONCLUSIONS: Both MMG and PROSE changed the natural course and helped in preserving and improving vision in eyes with SJS-induced lid-related keratopathy. Regardless of age, those who received both MMG and PROSE had the best long-term visual outcomes. (Am J Ophthalmol 2020;219:357–365. © 2020 Elsevier Inc. All rights reserved.)

STEVENS-JOHNSON SYNDROME (SJS) IS A BLISTERING autoimmune disease that affects the skin and mucous membranes. Although it is rare, affecting 0.4 to 7 cases per million population annually,[1] SJS and its more severe form, toxic epidermal necrolysis (TEN), can involve the eyes in 40%-84% of cases in the acute phase.[2–6] Unfortunately, 43%-89% of cases progress to long-term ocular complications.[7–10] Chronic visual morbidity in SJS/TEN can be secondary to changes in the ocular surface, like epithelial denudation in the acute phase, and keratopathy in the chronic phase, which can be secondary to dry eye or due to lid margin changes.[11–13] In severe cases, the chronic ocular disease may progress to total limbal stem cell deficiency (LSCD) and ocular surface dermalization. Lid margin changes (eg, posterior migration of the mucocutaneous junction and keratinization) and tarsal changes (eg, scarring and keratinization) cause cumulative blink-related trauma to the delicate ocular surface.[14] Several therapeutic measures have been reported to address these problems, and their specific role in children has been previously described in the literature.[13] In a previous study, these investigators, who used an algorithmic approach, found that appropriate definitive therapy in the eyes of children with chronic ocular sequelae of SJS changed the natural course of the disease and helped to preserve and improve vision.[13] In this study, the investigators compared the role of definitive management strategies, specifically in eyes with chronic lid-related keratopathy in both children and adults, in terms of visual improvement and the risk of corneal complications.

MATERIAL AND METHODS

• STUDY DESIGN, APPROVAL AND PARTICIPANTS: This was a retrospective case series of both adults and children (age 16 years or younger) who presented between January 1, 1990 and December 31, 2015 to LV Prasad Eye Institute, Hyderabad, India with ocular complaints after developing

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Jul 8, 2020.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.07.006

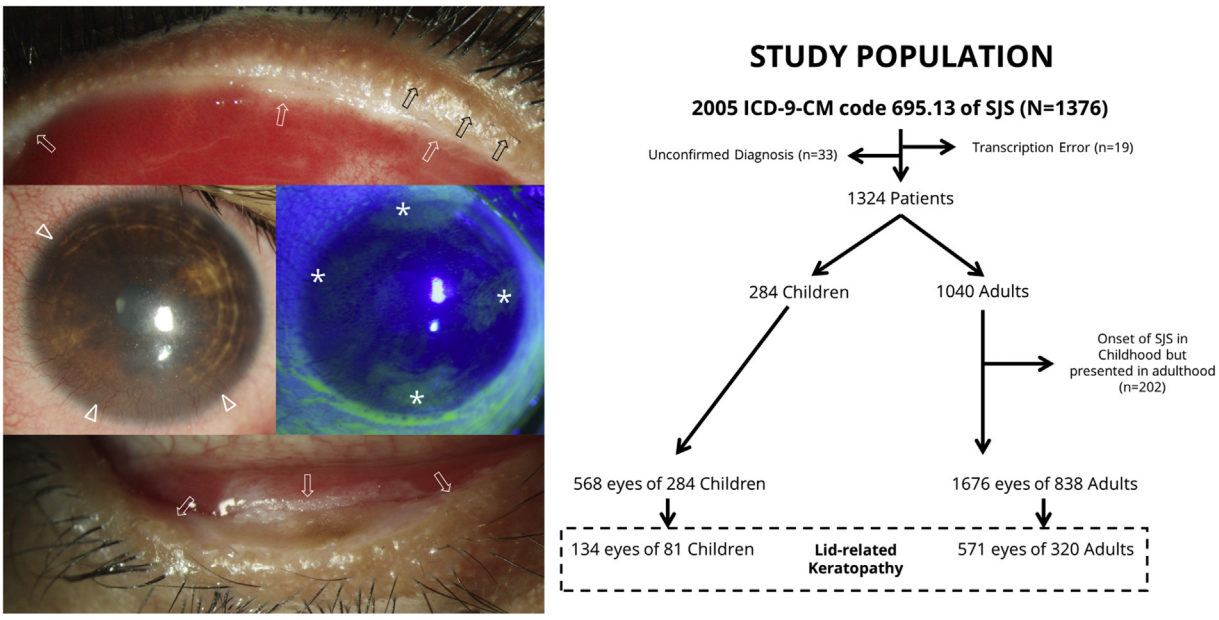

FIGURE 1. Inclusion criteria and patient selection for the study. (Left panel) Lid-related keratopathy was defined as presence of upper lid and/or lower lid margin keratinization (white arrows) with or without distichiatic lashes (black arrows) with corresponding areas of keratopathy in the form of corneal vascularization (white arrows), scarring, and fluorescein-staining (asterisks). (Right panel) Flowchart describing the final selection of 705 eyes of 401 patients with lid-related keratopathy for the study. ICD-9 = International Classification of Diseases-9th Revision; SJS = Stevens-Johnson Syndrome.

SJS. Using the 2005 International Classification of Diseases-9th Revision-Clinical Manifestation code 695.13 for SJS, the medical records of 1,376 patients were identified and retrieved. After carefully going through each record, 52 cases were excluded, either because they did not have a documented medical diagnosis of SJS (n = 33) or had unrelated pathologies that were incorrectly transcribed as SJS (n = 19). Another 202 records of patients who had SJS in childhood but presented later in adulthood were also excluded.

Finally, the records of 284 children and 838 adults were screened to select for cases who had lid-related keratopathy. Of these patients, 134 eyes in 81 children and 571 eyes in 320 adults with lid-related keratopathy were finally included in this study. The flowchart describing the selection of cases for the study is presented in Figure 1. The criteria for defining lid-related keratopathy were described previously[13] and are reiterated in Figure 1. Only eyes that had keratopathy (presence of corneal fluorescein staining, epitheliopathy, or superficial scarring and vascularization) that corresponded to the areas of lid-margin keratinization were selected for this study. Eyes without keratopathy or with non-lid–related keratopathy were excluded from this study.[13] In addition, eyes with end-stage keratopathy with corneal conjunctivalization or dermalization and severe forniceal shortening or symblepharon were excluded from the study. The ethics committee of the LV Prasad Eye Institute, Hyderabad, India, approved this study, which was conducted in strict adherence to the tenets of the Declaration of Helsinki.

• **DATA COLLECTION:** Data were extracted manually and entered in a predesigned spreadsheet. Medical records were reviewed to identify the demographic and clinical data at presentation and at subsequent time points. The treatment modalities in the form of medical or surgical management, postoperative complications, and duration of follow-up, were also collected in detail. The lid, conjunctival, and corneal changes at presentation were then graded according to Sotozono's classification.[15]

• **MANAGEMENT ALGORITHM:** Because treatment modalities like lid margin mucous membrane grafting (MMG; 2008 onwards) and prosthetic replacement of the ocular surface ecosystem lenses (PROSE; Boston Foundation for Sight, Needham, Massachusetts, USA; 2005 onwards) were available at different points in time, there was a large group of eyes that received conservative and/or palliative management in the form of topical lubricants and occasional steroids, epilation, electrolysis, and punctal cautery. This group was important for the following reasons: 1) they had the longest follow-up and therefore were illustrative of the natural history of the disease; and 2) they served as a control group against which the efficacy of other definitive treatment modalities (eg, lid margin MMG and PROSE) could be compared. The details of these treatment

TABLE 1. Demographic Characteristics of Patients Presenting With Chronic Lid-Related Keratopathy in SJS

Category	Children (n = 81; 134 eyes)	Adults (n = 320; 571 eyes)	*P* Value
Sex (%)			
Male	50 (60.2)	130 (40.6)	<.0001
Female	31 (39.8)	190 (59.4)	
Etiology of SJS (%)			
Drugs	57 (69.7)	233 (72.8)	<.0001
Antibiotics	10	42	
Sulpha drugs	14	58	
NSAIDs	7	20	
Antiepileptic	4	14	
Antimalarial	1	9	
Unknown drug	21	91	
Exanthematous fever	11 (14.1)	15 (4.8)	
Unknown Etiology	13 (16.2)	72 (22.4)	
Delay in presentation (%)			
1.5-3 mos	12 (14.8)	70 (22)	<.0001
3-6 mos	8 (9.9)	44 (13.8)	
6-12 mos	8 (9.9)	56 (17.4)	
>1 y	53 (65.4)	150 (46.8)	
Amniotic membrane grafting in acute stage of SJS (%)			
Yes	1 (1)	4 (1.2)	.9
No	80 (99)	316 (98.8)	
BCVA at presentation (%)			
20/20 to 20/60	54 (40.1)	226 (39.5)	.13
20/70 to 20/399	64 (47.5)	259 (45.4)	
20/400 or worse	16 (12.5)	86 (15.1)	
Schirmer's test I: mm of wetting at 5 min without anesthesia (%)			
0-5	9 (6.7)	108 (18.9)	.034
6-10	16 (11.9)	81 (14.2)	
11-15	23 (17.2)	63 (11)	
>15	75 (55.9)	247 (43.3)	
Not recorded	11 (8.3)	72 (12.6)	
Treatment received in chronic stage (%)			
Conservative	82 (61.2)	281 (49.2)	.438
MMG	19 (14.2)	81 (14.2)	
PROSE	13 (9.7)	77 (13.5)	
MMG + PROSE	20 (14.9)	132 (23.1)	

BCVA = best-corrected visual acuity; MMG=mucous membrane grafting; NSAIDs = nonsteroidal anti-inflammatory drugs; PROSE = prosthetic replacement of ocular surface ecosystem contact lenses; SJS = Stevens-Johnson syndrome.

modalities, including patient selection, technique, and postoperative care, were provided in previous review articles.[16,17]

• **OUTCOME MEASURES AND STATISTICAL ANALYSIS:** The main outcome measure was the change in best corrected visual acuity (BCVA) following each type of intervention. The secondary outcome measure was the chance (relative risk and/or odds ratio) of ocular complications in terms of the rate of at least 1 episode of corneal ulceration and/or perforation in the first year of treatment. The first year was counted from presentation in those who received conservative therapy, postoperatively for the MMG group, after dispensing of the contact lenses for the PROSE group, and after MMG was performed and PROSE lenses were dispensed in the group that received both. MedCalc software, version 19.2.5 (MedCalc Software Limited, Ostend, Belgium) was used for statistical analysis. Analyses of descriptive statistics were conducted for the variables of interest: continuous variables (median and 95% confidence intervals) and categorical variables (frequency and percentage). The χ^2 test was used to compare the baseline data in different groups. Wilcoxon's signed-rank test was used to calculate the change in BCVA in each group over time. The Mann-Whitney U test was used to compare the BCVA between different groups at each time point. A 2-tailed *P*-value <.05 was considered statistically significant.

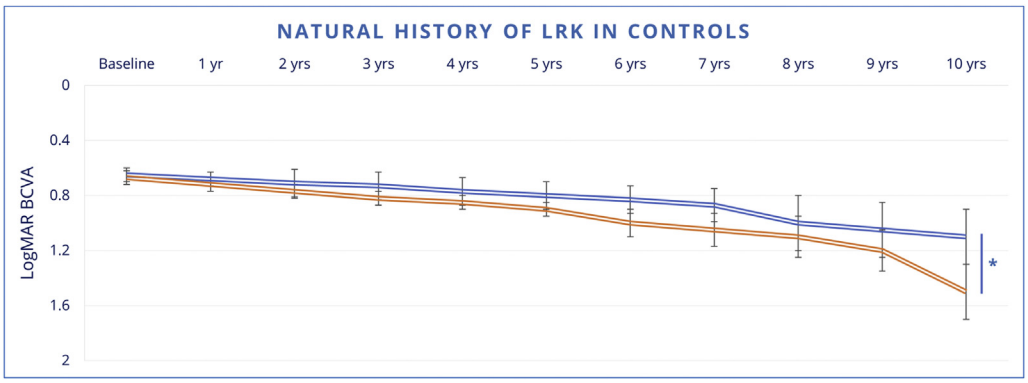

FIGURE 2. Natural history of lid-related keratopathy in patients with Stevens-Johnson syndrome. The median best-corrected visual acuity (BCVA) over 10 years of follow-up is displayed graphically for children and adults. There was a significant deterioration in BCVA over time in both groups, which was comparatively worse in adults (P = .0018). *Statistically significant difference (Mann-Whitney U test). LogMAR = logarithm of minimal angle of resolution; LRK = lid-related keratopathy.

RESULTS

• **DEMOGRAPHICS:** This study included 705 eyes of 401 patients (81 children and 320 adults). The baseline demographic characteristics are detailed in Table 1. Affected eyes either received conservative therapy (n = 363) or definitive management (n = 342), including lid margin MMG and PROSE contact lenses, or both. There were significant differences among the children and adults in terms of: 1) greater proportion of patients being male in children and female in adults; 2) exanthematous fever being the more commonly reported etiology in children; 3) greater proportion of children presenting more than a year after the acute episode of SJS compared with adults; and 4) greater severity of dryness (as measured by Schirmer I) in adults compared with children. However, both children and adults were comparable in terms of: 1) 99% not having received amniotic membrane transplantation (AMT) during the acute stage; and 2) BCVA at baseline (20/80 to 20/100). The treatment subgroups were also comparable at baseline in terms of BCVA (P = .13) and previous management (P = .9). Among children and adults, the proportion of eyes in each of the 4 groups (conservative, those who underwent MMG, those who received PROSE, and those who received MMG+PROSE) were comparable (P = .438).

• **CONSERVATIVE THERAPY FOR LID-RELATED KERATOPATHY:** The change in BCVA over 10 years in patients managed conservatively is provided in Figure 2. BCVA decreased significantly over time, dropping from a median of 20/80 to 20/500 over a 10-year period (363 eyes; P = .0017). This loss of median BCVA was attributable to deterioration in corneal clarity in 23 (28%) eyes and 104 (37%) eyes of children and adults, respectively. The degree of deterioration of median BCVA was significantly greater (P = .018) in adults (281 eyes; 20/90 to 20/632; P < .0001) compared with that in children (82 eyes; 20/90 to 20/320; P = .0033).

• **PROSE VERSUS MMG FOR LID-RELATED KERATOPATHY:** Overall, there was improvement in BCVA from baseline with MMG (P = .003) and PROSE (P = .009) over 5-years of follow-up (Figure 3). At 5 years, among children, there was a significantly greater improvement in BCVA with MMG (Figure 4), from a median of 20/100 to 20/30 (19 eyes) compared with BCVA of 20/60 with PROSE (13 eyes; P = .01), and BCVA of 20/126 in the control group (82 eyes; P < .0001). However, in adults, PROSE lens wear resulted in significantly greater improvement of BCVA (Figure 4), from a median of 20/100 to 20/40 (77 eyes) compared with BCVA of 20/60 with MMG (81 eyes; P = .028) and BCVA of 20/160 (281 eyes; P < .0001) with conservative therapy. One of the reasons for this difference was noncompliance in PROSE lens wear, with discontinuation seen in 3 (23%) eyes, all of which were in children younger than 8 years of age. The final median BCVA at 5 years with MMG was significantly better in children compared with adults (P = .0001), whereas with PROSE, it was significantly better in adults compared with children (P = .0018) (Figure 3).

• **PROSE AND MMG FOR LID-RELATED KERATOPATHY:** The best results in both children and adults were seen in eyes that received both MMG and PROSE (Figure 3). In 20 eyes of children and 132 eyes of adults, BCVA improved from a median of 20/100 to 20/25 (Figure 3; P < .0001). The final BCVA at 5 years with MMG and PROSE was comparable in adults and children (Figure 3; P = .23). There were no compliance issues in either children or adults in this group, and no patient discontinued PROSE lens wear. At 5 years of follow-up (Figure 4), children who received MMG + PROSE had significantly better BCVA than MMG alone (P = .036), PROSE alone (P = .0002), or conservative therapy (P < .0001). Similarly, adults who received MMG + PROSE had significantly better BCVA than MMG alone (P = .012), PROSE alone

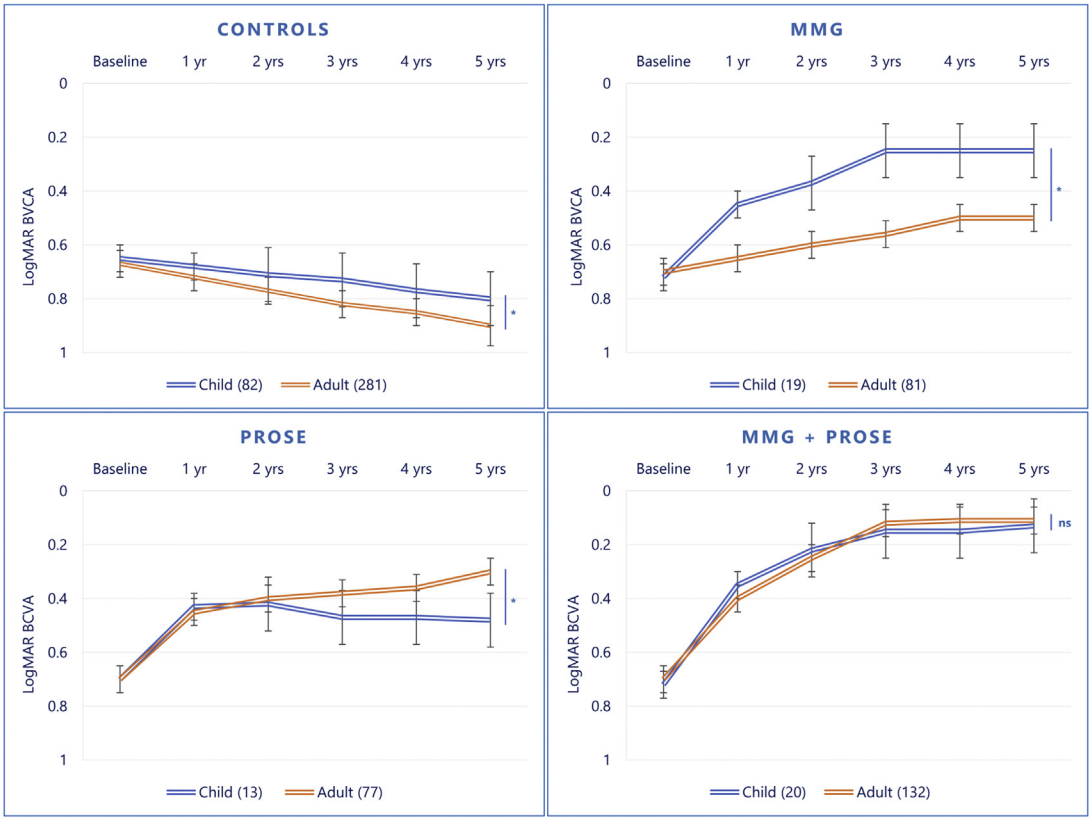

FIGURE 3. Visual outcomes of conservative and definitive therapies in children and adults with lid-related keratopathy after developing Stevens-Johnson Syndrome. The control group that received conservative medical management showed significant worsening of best corrected visual acuity (BCVA) over a 5-year period. Lid margin mucous membrane grafting (MMG; top right) significantly improved BCVA and was more effective in children compared with adults. Prosthetic replacement of ocular surface ecosystem (PROSE) lenses (bottom left) was also beneficial but more effective in adults compared with children. Finally, the combination of MMG and PROSE was equally effective in children and adults (bottom right). *Statistically significant difference (Mann-Whitney U test). LogMAR = logarithm of minimal angle of resolution.

($P = .0043$), or conservative therapy ($P < .0001$). The improvement in the ocular surface in terms of corneal clarity and staining patterns after using a combined approach of MMG and PROSE lenses is depicted in Figure 5.

• **RISK OF COMPLICATIONS:** The risk of developing at least 1 episode of corneal ulceration or perforation in eyes with post-SJS lid-margin keratopathy with conservative therapy in the first year after presentation was 18.3% (15/82) in children and 23.8% (67/281) in adults. With PROSE alone within the first year of use, this risk was reduced to 7.7% (1/13) in children ($P = .799$) and 9.1% (7/77) in adults ($P = .0086$). With MMG alone, the risk was reduced to 5.3% (1/19) in children ($P = .161$) and 11.1% (9/81) in adults ($P = .023$). However, the greatest benefit was seen in eyes which received both PROSE and MMG, where the risk was 5% (1/20) in children ($P = .14$) and 5.3% (7/132) in adults ($P < .0001$). The overall risk for eyes in the definitive treatment group was 5.7% (3/52) in children ($P = .034$), and 7.9% (23/290) in adults ($P < .0001$). The overall relative risk reduction was 68.8% (18.3% to 5.7%) in children and 66.8% (23.8% to 7.9%) in adults. The statistics in terms of odds ratios is presented in Table 2. Those who received conservative therapy had a 2.61 (82/363 vs 26/342) times greater risk and 3.54 times (82/281 vs 26/316) greater odds of developing corneal ulceration and/or perforation within the first year compared with those who received definitive therapy.

DISCUSSION

OCULAR INVOLVEMENT DURING THE ACUTE STAGE OF SJS in the form of denudation of the lid margin, corneal, limbal, and conjunctival epithelium can lead to chronic sequelae that are potentially blinding.[4,12] Most of the visual morbidity in patients with chronic ocular sequelae of SJS is due to progressive keratopathy, which, in turn, results from lid-margin keratinization.[14] In this study, the authors described the long-term visual morbidity in eyes with lid-

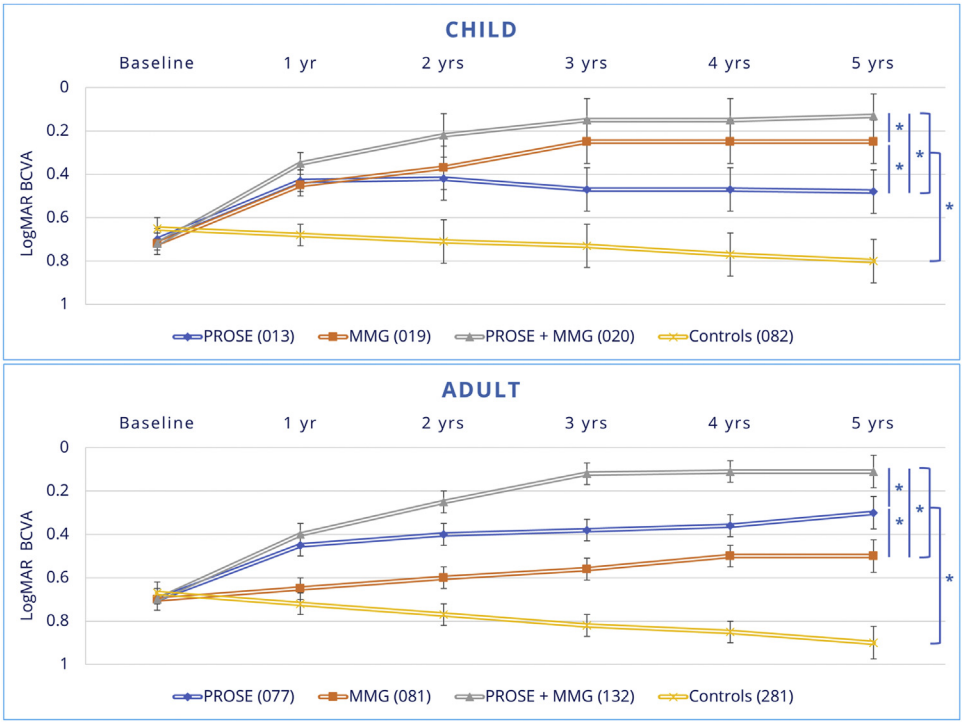

FIGURE 4. Relative impact of definitive therapies on best corrected visual acuity (BCVA) in eyes with lid-related keratopathy after developing Stevens-Johnson syndrome. In both children (top) and adults (bottom) best outcomes were seen with a combination of prosthetic replacement of ocular surface ecosystem (PROSE) lenses and lid margin mucous membrane grafting (MMG). In children at 5 years of follow-up, MMG + PROSE had significantly better BCVA than MMG alone (P = .036), PROSE alone (P = .0002), and conservative therapy ($P < .0001$). Similarly, in adults, MMG + PROSE had significantly better BCVA than MMG alone ($P = .012$), PROSE alone ($P = .0043$), and conservative therapy ($P < .0001$). *Statistically significant difference (Mann-Whitney U test). LogMAR = logarithm of minimal angle of resolution.

margin keratinization and tried to discern the impact that definitive therapies in the form of MMG and PROSE had on the natural course of the disease. The 2 most important findings of this study were the following: 1) there was a notable decline in visual acuity, in both children and adults managed conservatively with topical lubricants and occasional steroids, epilation, electrolysis, and punctal cautery; and 2) in contrast, interventions like PROSE contact lens and MMG were clearly effective in long-term preservation or improvement in vision. The results also provided more subtle insights into how factors like age and compliance influenced the outcomes of individual interventions, and how combining 2 different interventions like MMG and PROSE could provide supplemental or synergistic benefits. Finally, the knowledge of the relative risk of potentially blinding corneal complications within the first year in patients who experience chronic lid-margin disease will allow physicians to explain the importance of timely therapy to their patients in more relatable terms.

Among the various organs affected in SJS/TEN, chronic ocular sequelae are arguably the most disabling, greatly affecting the quality of life of patients.[18] There is enough evidence in literature to suggest that early AMT mitigates the chronic ocular sequelae to a significant extent.[19–23] However, this practice is not universally prevalent for multiple and complex reasons, the most common being the absence of an adequately trained ophthalmologist as an essential part of the acute care team.[24] Hence, patients often present late without having received adequate ocular care in the acute phase, as was seen in the current cohort, in which 65% of children and 47% of adults presented a year after the acute episode. In addition, many patients are still treated conservatively with medical therapy and minor procedures (eg, repeated epilation and punctal cautery).[13,25] Unfortunately, conservative measures do not specifically address the blink-related microtrauma perpetrated by the keratinized lid margins. As this study showed, those treated conservatively continued to lose vision over time due to progressive keratopathy.[13] Fortunately, in the present day, more definitive interventions such as MMG and PROSE lenses are available to patients with lid-margin keratinization.[25–27] While MMG directly addresses the eyelid pathology and restores near-normal anatomy, PROSE lenses act as a physical barrier, protecting the vulnerable corneal surface from being traumatized by the posterior lid-margin, in addition to providing a fluid

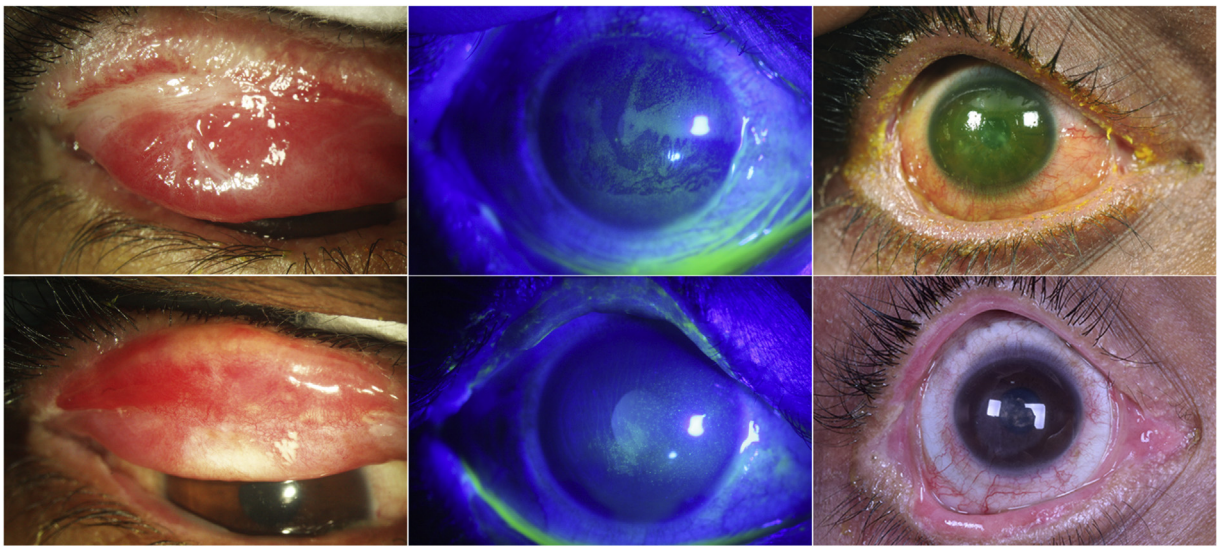

FIGURE 5. Clinical images of lid margin mucous membrane grafting (MMG) and use of prosthetic replacement of ocular surface ecosystem (PROSE) lenses in eyes with lid-related keratopathy after developing Stevens-Johnson syndrome. (Top left) Upper lid margin keratinization preoperatively with (top middle) fluorescein staining on the cornea suggestive of lid-related keratopathy. (Bottom left) Postoperative appearance of the lid margin post MMG showing the smooth contour of the upper lid with (bottom middle) improved fluorescein staining of the cornea. Pre- (top right) and post-operative (bottom right) appearance of the right eye of a young man with lid keratinization and corneal scarring, whose vision improved to 20/25 after MMG and PROSE lenses.

TABLE 2. Risk of Complications in the First Year in Adults and Children With Stevens-Johnson Syndrome With Chronic Lid-Related Keratopathy Among Different Groups

	Ulcer/Perforation	None	Odds	Odds Ratio
Conservative therapy				
Children	15	67	0.22	
Adults	67	214	0.31	
PROSE				
Children	1	12	0.08	0.36
Adults	7	70	0.10	0.32
MMG				
Children	1	18	0.06	0.27
Adults	9	72	0.13	0.42
PROSE + MMG				
Children	1	19	0.05	0.23
Adults	7	125	0.06	0.19

MMG = mucous membrane graft; PROSE = prosthetic replacement of the ocular surface ecosystem lenses.

reservoir to nourish the surface and provide a smoother optical surface for clearer vision. PROSE lenses are worn for only a portion of the day and have a significant off-time, whereas MMG addresses lid-related keratopathy even when PROSE lenses are not worn. Therefore, it is not unusual to find that a combination of these modalities works best, because their mechanisms of action are complimentary to each other.

The challenges in children are unique, and because of noncompliance with PROSE lenses in a few children younger than 8 years of age, the improvement in BCVA was not as impressive as seen with MMG. This was substantiated in a previous paper by Saeed et al., in which they also concluded that children younger than 5 years of age had higher rates of failure to comply with PROSE lenses.[28] Hence, we believe that the threshold to perform MMG in children should be lower, and this should be the first modality offered to children with lid-related keratopathy. It has generally been the authors' experience that following MMG, younger children are usually more comfortable not only in allowing a contact lens trial but are also more compliant in wearing the lenses. In adults, there were no compliance-related issues and the improvement in BCVA with PROSE lenses alone was significantly better compared with MMG. This is understandable and due to the optical property of the contact lenses. However, because most patients are not able to wear PROSE lenses for more than 8-10 hours in a day, the risk of lid-related corneal damage is not completely mitigated by PROSE wear alone. Therefore, the authors strongly believe that both MMG and PROSE lenses should be offered to every patient with SJS and lid-related keratopathy.

The major strengths of this study were the large sample size and the impressive length of the follow-up. The large sample size in our study of patients with chronic sequelae of SJS was the result of AMT in the acute stage not being yet widely adopted in our country, nor in many other locales and countries around the world. Our results will be

important until the use of AMT in the acute setting becomes so universal as to eliminate the chronic sequelae of SJS. This study had several weaknesses that were inherent to its retrospective design. Ideally, different interventions need to be evaluated or compared by performing randomized controlled trials. However, SJS/TEN is an extremely rare condition, and it would take a multicentric approach over several years to do a study of this size.

CONCLUSIONS

IN CONCLUSION, THIS STUDY DESCRIBED THE NATURAL course of lid-related keratopathy in children and adults with SJS and evaluated the role of definitive interventions, such as MMG and PROSE lenses. The study found that both interventions were beneficial, and significantly improved the long-term visual prognosis in such cases. However, the risk of long-term corneal damage and chance of preservation or improvement of vision were best if both modalities were used concurrently. The authors strongly believe that with this study, there will be enough evidence in the literature for MMG and PROSE to become the standard of care for the treatment of lid-related keratopathy in patients with SJS/TEN. The data presented in this study will not only help physicians understand the natural course of lid-related keratopathy but will also guide them in articulating the exact risk of corneal damage and the likely functional loss to their patients, so that both are able to make timely and informed choices together.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

SWAPNA S. SHANBHAG: CONCEPTUALIZATION, METHODology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Sahil Shah:** Investigation, Data curation. **Madhu Singh:** Investigation, Data curation. **Chirag Bahuguna:** Investigation, Data curation. **Pragnya R. Donthineni:** Investigation, Data curation, Writing - review & editing. **Sayan Basu:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization, Supervision.

FUNDING/SUPPORT: THIS WORK WAS FUNDED BY THE HYDERABAD EYE RESEARCH FOUNDATION, HYDERABAD, INDIA. THE sponsoring organization had no role in the design or conduct of this research.

Financial disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. All authors attest that they meet the current ICMJE criteria for authorship.

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