Purpose: To analyze the characteristics and long-term outcomes of patients that underwent pediatric penetrating keratoplasty (PPK) for herpes simplex virus (HSV) keratitis.

Design: Retrospective, interventional, consecutive case series.

Methods: Observational report of outcomes and findings for 9 patients with history of HSV keratitis that underwent PPK and were followed in a single institution. Difference between the median preoperative and final best-corrected visual acuity (BCVA) was assessed and the outcomes are reported.

Results: We included 9 eyes; median age at the moment of the PPK was 14 years. The median initial BCVA was 20/400 (range 20/60 to hand motion) and final was 20/50 (range 20/30 to 20/400) \((P < .05)\). Follow-up was a median of 94 months. Complications in these patients included glaucoma (1), graft rejection (1), recurrence of disease (1), and amblyopia (3). No graft failures were present.

Conclusion: The long-term outcomes with PPK for HSV keratitis in children provide improvement in BCVA when not compromised by amblyopia. (Am J Ophthalmol 2017;173:139–144. © 2016 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)
presentation was recorded as epithelial keratitis, stromal keratitis (either immune mediated or necrotizing), and endotheliitis (linear, disciform, or diffuse) or a combination of the above. When available, the number of recurrences was also recorded. History of systemic disease was investigated, specifically atopic skin disease, asthma, and other allergies; disease status was classified as active either if inflammation at the cornea was present or if perforation was present or imminent, and inactive if a corneal scar was present in the absence of inflammation. Visual acuity was measured with Allen picture figures, LEA symbols test, HOTV, illiterate E, or Snellen visual charts depending on age. BCVA before PPK and at the final follow-up was measured with rigid contact lens over-refraction; time of prophylactic acyclovir and complications are reported.

Prophylactic oral acyclovir was indicated for at least 6 months before surgery and continued postoperatively indefinitely: a dose of 400 mg/d in those older than 2 years, divided in 2 doses, and 400 mg 2 times daily when the patients were able to take pills. Tolerance to medication was recorded, and for patients with long-term prophylaxis, kidney and liver functions tests were routinely ordered biannually.

All patients were treated with a PPK performed at our institute, based on rehabilitation for optical purposes. Surgeries were performed under general anesthesia, with the use of a Flieringa ring and donor grafts oversized by 0.5-1.0 mm. Sixteen 10-0 nylon interrupted sutures were used in all patients. At the end of the surgery, all patients were given topical steroids and antibiotics. Postoperatively, topical prednisolone acetate 1% was administered 4-6 times a day initially and then in tapering doses, with topical antibiotic drops for 1 month. Occlusion therapy was undertaken in patients suspected to have amblyopia. Suture removal was performed in all cases at the slit lamp owing to patient cooperation, and it was completed in most cases by 1 year.

Ocular hypertension was defined as intraocular pressure greater than 21 mm Hg as measured with applanation tonometer in 2 different measurements, or if patients had antihypertensive drops. Glaucoma was defined as ocular hypertension and increased cup-to-disc ratio and abnormal optic nerve, optical coherence tomography, or automated visual fields. Graft rejection was considered by the biomicroscopic appearance of an anterior chamber reaction with keratic precipitates exclusively on the donor endothelium, by an endothelial or epithelial rejection line, or by graft edema with associated new keratic precipitates.11 Herpetic recurrences were considered as keratitis with edema confined to the endothelial precipitates adhering to both the donor and host endothelium, and iritis.12 In both cases, patients were treated with systemic acyclovir and topical corticosteroids. Graft failure was defined as corneal edema in the absence of inflammation that did not respond to steroids.

NINE PATIENTS WITH UNILATERAL PPK WERE INCLUDED. Five patients were female and 4 were male; in 7 cases the left eye was affected. The delay from the onset of symptoms to presentation for consultation was a median of 24 months (range 1 day to 7 years). The median age of the patients at presentation was 9 years (range 3-17 years) and the median age at the moment of the PPK was 14 years (range 7-17 years). The median BCVA before the surgery was 20/400 (range 20/60 to hand motion). Corneal sensitivity was decreased in all patients. Five patients presented with interstitial keratitis and 4 with a disciform keratitis, resulting in a central scar over the visual axis in all of them. The disease was quiescent before surgery for at least 6 months in all cases. The detailed characteristics of the patients are presented in the Table.

Of the 9 eyes, 4 were considered to be inactive on arrival and remained inactive during the complete follow-up, 3 had their first episode at presentation in our institution, and 2 were considered to be a recurrence of a previous episode. For the 3 patients with the first active disease diagnosed in our center, 2 had a documented single recurrence in the follow-up (Patients 2 and 9) before surgery; therefore, from the complete group of patients, 5 eyes were of recurring nature (Table). Four patients had mild corneal neovascularization limited to 1 quadrant preoperatively.

No concomitant systemic diseases were found in these case series. All patients requiring a PPK received prophylactic oral acyclovir after the surgery for at least 6 months (range 6-33 months). None of these patients presented an adverse effect owing to the systemic acyclovir in the follow-up. One patient (Patient 3) presented an interstitial recurrence of HSV keratitis in the recipient cornea after interrupting prophylaxis 8 months post PPK, again requiring oral acyclovir in treatment dose; unfortunately, the recurrence led to a corneal opacity in the graft (Figure 1).

One of the patients (Patient 6) developed glaucoma 1 year after corneal transplantation, requiring a glaucoma drainage device, achieving an adequate control of the intraocular pressure after the surgery. Patient 9 presented with graft rejection 15 years after surgery, and was successfully treated with systemic acyclovir and topical corticosteroids (Figure 2).
Median final BCVA after PPK at last follow-up was 20/50 (range 20/30 to 20/400), showing significant improvement compared with preoperative BCVA ($P = .001$). Two patients (Patients 3 and 5) with preoperative BCVA of 20/100 or worse had no improvement in vision after surgery, and this was attributed to amblyopia; Patient 3 had a residual corneal opacity after the episode of herpetic recurrence in graft and poor adherence to amblyopia therapy, and Patient 5 had a 5-year delay from onset of symptoms to presentation at our institution.

We compared BCVA between patients receiving PPK at age 12 years or younger with those >13 years. Preoperative values (median 20/3000 and 20/400, respectively, $P = .387$) and postoperative results (median 20/80 and 20/40, respectively, $P = .131$) were not significantly

![FIGURE 1](image1.png)  
**FIGURE 1.** Eye of a 9-year-old female patient that underwent pediatric penetrating keratoplasty for herpes simplex virus keratitis, showing a corneal opacity in the center of the graft after recurrence of herpetic keratitis.

![FIGURE 2](image2.png)  
**FIGURE 2.** Eye of a 17-year-old female patient that underwent pediatric penetrating keratoplasty for herpes simplex virus keratitis, after successful treatment of graft rejection, showing a large vessel where the rejection episode started.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Eye</th>
<th>Age at Presentation/Age at PK (Years)</th>
<th>Type of Keratitis</th>
<th>Status of the Disease</th>
<th>BCVA Previous to PK</th>
<th>BCVA After PK</th>
<th>Complications</th>
<th>Time of Follow-up After PK (Months)</th>
<th>Complete Time of Follow-up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/R</td>
<td>15/16</td>
<td>Interstitial</td>
<td>Inactive on arrival</td>
<td>20/2000</td>
<td>20/50</td>
<td>None</td>
<td>21.8</td>
<td>28.3</td>
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<tr>
<td>2</td>
<td>M/L</td>
<td>9/16</td>
<td>Disciform</td>
<td>First episode</td>
<td>20/60</td>
<td>20/40</td>
<td>None</td>
<td>24.2</td>
<td>111.8</td>
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<tr>
<td>3</td>
<td>F/L</td>
<td>6/9</td>
<td>Disciform</td>
<td>Recurrence</td>
<td>20/200</td>
<td>20/100</td>
<td>Recurrence of herpetic keratitis in graft; amblyopia</td>
<td>112.6</td>
<td>117.8</td>
</tr>
<tr>
<td>4</td>
<td>F/R</td>
<td>13/14</td>
<td>Interstitial</td>
<td>Inactive on arrival</td>
<td>20/1000</td>
<td>20/50</td>
<td>None</td>
<td>35.2</td>
<td>53.9</td>
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<tr>
<td>5</td>
<td>F/L</td>
<td>7/7</td>
<td>Interstitial</td>
<td>Inactive on arrival</td>
<td>HM</td>
<td>20/400</td>
<td>Amblyopia</td>
<td>140.7</td>
<td>148.1</td>
</tr>
<tr>
<td>6</td>
<td>M/L</td>
<td>16/16</td>
<td>Disciform</td>
<td>Recurrence</td>
<td>20/400</td>
<td>20/40</td>
<td>Glaucoma related to PK; required valve implant</td>
<td>24.6</td>
<td>40.5</td>
</tr>
<tr>
<td>7</td>
<td>M/L</td>
<td>3/8</td>
<td>Disciform</td>
<td>First episode</td>
<td>20/400</td>
<td>20/30</td>
<td>None</td>
<td>49.1</td>
<td>94.2</td>
</tr>
<tr>
<td>8</td>
<td>F/L</td>
<td>17/17</td>
<td>Interstitial</td>
<td>Inactive on arrival</td>
<td>20/400</td>
<td>20/40</td>
<td>None</td>
<td>143.3</td>
<td>30.6</td>
</tr>
<tr>
<td>9</td>
<td>F/L</td>
<td>5/7</td>
<td>Interstitial</td>
<td>First episode</td>
<td>HM</td>
<td>20/80</td>
<td>Graft rejection 15 years after PK</td>
<td>190.7</td>
<td>215.1</td>
</tr>
</tbody>
</table>

**TABLE.** Characteristics of the Patients With Penetrating Keratoplasty in the Pediatric Population With Herpes Simplex Virus Keratitis

**BCVA** = best-corrected visual acuity; **F** = female; **HM** = hand motion; **L** = left; **M** = male; **PK** = penetrating keratoplasty; **R** = right.
Patients' median follow-up from presentation to the final visit was 94 months (range 28-215 months) and corneal transplant median follow-up was 49 months (range 22-190 months); no graft had failed by the end of the follow-up (Figure 3).

DISCUSSION

HSV INFECTION IS AN IMPORTANT ANTERIOR SEGMENT DISEASE in children that is often late diagnosed or misdiagnosed, with prompt recognition and adequate treatment needed to reduce the probability of permanent vision loss.5,6 In pediatric patients, epithelial dendritic and interstitial keratitis are frequent forms of the disease, and a high rate of recurrent disease is present, with 50% of recurrences presenting around 13-15 months after the initial episode.5,6 Herpetic keratitis in young patients could theoretically be more common in developing countries, as the seroconversion rates for HSV-1 in children are higher in lower socioeconomic classes.13

The prognosis after pediatric corneal transplantation is often age dependent, with younger patients having worse outcomes. Other factors that also affect survival rate of the graft in children include the clinical diagnosis for which the graft was performed, active ocular inflammation at the time of transplantation, history of intraocular surgery, corneal vascularization, occurrence of rejection episode, need for operative procedure post graft, and refractive surgery to the graft.4

Reported indications for PPK vary in different parts of the world. In developing countries, healed or active infection is the most common indication for keratoplasty, while in the developed world congenital opacities like anterior segment dysgenesis or corneal dystrophies are the most common indications within this age group.14,15

Our study highlights the importance of antiviral prophylaxis after PPK in HSV keratitis. Oral administration of acyclovir significantly reduces the risk of HSV recurrence, decreases the episodes of rejection, and gives better overall graft survival when compared with placebo in adults.11,16 Oral acyclovir was administered daily in all our patients, with only 1 recurrence in a patient that discontinued prophylaxis medication. However, dosage and duration of prophylactic acyclovir treatment for PPK post HSV in this specific population is still an issue for debate.

Prophylaxis in children is especially important, because the probability of disease recurrence is directly proportional to the number of recurrences, based on large series of patients.5 Tissue damage after HSV keratitis is attributable to both direct viral damage and immune reaction; therefore, and given the prolonged life expectancy in children and the strength of the immune response, it is possible to speculate that this age group is more prone to more recurrences with greater severity.

Ocular hypertension is of concern. Pediatric patients often require increased and prolonged use of topical steroids to control inflammation and to prevent rejection and are more susceptible to developing ocular hypertension associated with topical steroids. Therefore, close follow-up is recommended. Ocular hypertension and glaucoma may also be secondary to HSV trabeculitis, or may develop closed angle glaucoma as children commonly generate anterior synechiae.1 In our series, 1 patient developed glaucoma attributed to PPK but remained with an adequate intraocular pressure after an Ahmed glaucoma valve was implanted.

Poor visual outcome after PPK can be related to frequent graft failures, to optical distortion induced by surface irregularity and irregular astigmatism in the graft, and, most importantly, to amblyopia.3,4,17,18 In patients with PPK attributable to HSV-related disease, some factors might cause amblyopia with lack of improvement in vision, including recurrence of herpetic disease in the graft, poor adherence to amblyopia therapy, graft rejection, and a long delay from the onset of symptoms to the presentation of the patient for treatment.5,6 Up to 20% of the patients in this case series had a BCVA worse than 20/100 attributed to amblyopia, which is consistent with a large proportion of amblyopic patients in a general cohort of HSV disease of the anterior segment.5

Previous authors have reported cases of PPK in HSV with conflicting results. Hsiao and associates described 2 patients older than 8 years who had BCVA of 20/200 after infection and underwent corneal transplantation with 6-month oral valacyclovir prophylaxis; both regained the spectacle BCVA of 20/20.7 On the other hand,
Lowe and associates reported 4 grafts for herpetic eye disease in a group of patients aged 13-19 years; of these, 2 patients required a second corneal graft. From the case series of Beigi and associates, 1 of the children required a full-thickness keratoplasty, without improvement of vision, probably because of amblyopia.5 From the case series of Beigi and associates, 1 of the children required a full-thickness keratoplasty, without improvement of vision, probably because of amblyopia.5 From the case series of Beigi and associates, 1 of the children required a full-thickness keratoplasty, without improvement of vision, probably because of amblyopia.5 From the case series of Beigi and associates, 1 of the children required a full-thickness keratoplasty, without improvement of vision, probably because of amblyopia.5 From the case series of Beigi and associates, 1 of the children required a full-thickness keratoplasty, without improvement of vision, probably because of amblyopia.5

We present here a greater number of patients, the largest series to the authors’ knowledge, that underwent PPK for HSV keratitis and their long-term results, which appear relatively promising. Significant improvement in vision, with a median final BCVA of 20/50, and no graft failures after a median 49 months of follow-up support the benefit of corneal transplantation if required. Even when those patients had some risk factors for immunologic rejection in PK, including the etiology and the young age, it seems that our overall good results were because the selected patients were controlled for the rest of the possible risk factors, such as active inflammation, extensive neovascularization, anterior synechiae, and ocular hypertension. Furthermore, 2 important issues plausibly explain the lack of improvement in BCVA. First and foremost, the delay from the onset of symptoms to presentation at our institution was very prolonged; thus amblyopia is an important problem, even in our relatively old pediatric population. Secondly, children often demonstrate poor compliance with optical aids, including glasses and rigid gas-permeable contact lenses. As most HSV corneal disease is unilateral and the other eye regularly has normal vision, corrective aids are often not indispensable for these patients, leading to refractive amblyopia.

This study has some limitations. HSV keratitis in children is rare, as is the need for transplantation; therefore our sample is small, and because of the retrospective nature our conclusions need to be taken with caution. All the discussions behind the decision to pursue surgery for these patients could not be assessed; therefore, appropriate timing for corneal transplantation in a pediatric patient with HSV keratitis still needs to be studied.

In conclusion, detailed discussion about outcomes and careful follow-up need to be undertaken with the child’s caregiver, with special emphasis on the importance of compliance in prophylaxis, anti-inflammatory treatment, and ocular antihypertensive therapy and the need for close follow-up. In general, we think that careful patient selection in PPK for HSV keratitis allows good long-term results with significant improvement in BCVA and graft survival; however, complications and amblyopia remain frequent and need to be addressed.

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REFERENCES