

Endophthalmitis After Keratoprosthesis

Incidence, Bacterial Causes, and Risk Factors

Mahmaz Nouri, MD; Hisao Terada, MD; Eduardo C. Alfonso, MD; C. Stephen Foster, MD; Marlene L. Durand, MD; Claes H. Dohlman, MD, PhD

Objectives: To determine the rate of endophthalmitis in a group of patients with keratoprostheses and to analyze possible risk factors.

Methods: A total of 108 patient eyes, operated on between 1990 and 2000 with double-plated keratoprostheses, were analyzed with regard to the surface flora, the incidence and cause of bacterial endophthalmitis or sterile vitritis, the keratoprosthesis design, prophylactic antibiotics, concomitant immunosuppression, and preoperative diagnosis.

Results: Surveillance cultures were obtained from 30 uninfected eyes. The flora was similar to that reported in the normal population and did not vary significantly with time. Thirteen cases of bacterial endophthalmitis occurred 2 to 46 months postoperatively in the patient population that had been followed up for 2 months to 17 years (average, 3 years 4 months). The incidence was

39% in 13 patients with Stevens-Johnson syndrome, 19% in 27 patients with ocular cicatricial pemphigoid, and 7% in 28 patients with ocular burns. Only 1 of the other 40 cases (consisting mostly of repeated graft failures in non-cicatrizing conditions) developed endophthalmitis; this patient had a filtering bleb. All endophthalmitis pathogens were gram positive: *Streptococcus pneumoniae*, 23%; other streptococci, 39%; *Staphylococcus aureus*, 23%; and *Staphylococcus epidermidis*, 15%.

Conclusions: The most important risk factor for endophthalmitis after these keratoprostheses was found to be preoperative diagnosis. The rate of infection was very high in Stevens-Johnson syndrome and ocular cicatricial pemphigoid, moderate in chemical burns, and low in noncicatrizing corneal disease.

Arch Ophthalmol. 2001;119:484-489

From the Departments of Ophthalmology, Massachusetts Eye and Ear Infirmary, and Harvard Medical School, Boston (Drs Nouri, Terada, Foster, Durand, and Dohlman); and Bascom Palmer Eye Institute and University of Miami School of Medicine, Miami, Fla (Dr Alfonso). The authors have no proprietary interest in any device described in this article.

PATIENTS blinded by severe ocular surface diseases or injuries may become sighted again through the placement of a keratoprosthesis (KPro); however, because this device bridges the nonsterile ocular surface and the sterile anterior chamber, the risk of intraocular infection is always present.¹ Although endophthalmitis is known to occur frequently in patients with KPros,^{2,3} the incidence, bacterial causes, and risk factors for KPro-related endophthalmitis have been insufficiently quantified.

Risk factors for any infection that involves a prosthetic device include factors relating to the host, the device design, and the bacteria causing the infection. The specific questions addressed herein were as follows: Are patients with certain underlying ocular diseases at greater risk for KPro-related endophthalmitis? Are some KPro designs associated with a higher incidence of endophthalmitis? What bacteria are the most common causes of KPro-

related endophthalmitis, and are these bacteria more prevalent in uninfected KPro ocular surface flora than in normal eyes?

We report our experience with 108 patient eyes with double-plated KPros, including 13 patients who developed endophthalmitis. We also report the results of surveillance cultures from 30 uninfected eyes.

RESULTS

The results of surveillance cultures in 30 uninfected eyes (28 patients) with KPros are shown in **Table 2**. A second culture, performed several months later in 21 of these patients, showed patterns of microbial growth similar to the first culture. The predominant organisms were coagulase-negative staphylococci (present in more than two thirds of eyes), *Staphylococcus aureus*, *Corynebacterium* species (diphtheroids), and viridans streptococci. Gram-negative bacilli and yeast were uncommon.

PATIENTS AND METHODS

PATIENTS

A total of 108 patient eyes in 103 patients with various preoperative diagnoses had a KPro implanted between March 1990 and January 2000. Ninety-six eyes were operated on at the Massachusetts Eye and Ear Infirmary in Boston and 5 were operated on outside the United States (by C.H.D.). In addition, 7 patients were operated on at the Bascom Palmer Eye Institute in Miami, Fla (by E.C.A.). The patients were divided into 4 broad categories based on preoperative diagnosis. Twenty-seven patient eyes had ocular cicatricial pemphigoid (OCP), 13 had Stevens-Johnson syndrome (SJS), and 28 had been burned (27 chemical burns and 1 thermal burn). The remaining 40 patient eyes (other) had a variety of noncicatrizating ocular conditions such as repeated graft failures from degenerations, dystrophies, herpes simplex, herpes zoster, bacterial infection, aniridia, rheumatoid arthritis, or graft-vs-host disease. As a rule the last group had minimal intraocular inflammation in the past but had had repeated corneal graft failures. The mean duration of follow-up for the total population was 3 years 4 months (range, 2 months to 17 years).

Bacterial endophthalmitis was recognized by sudden onset of ocular pain, intensely inflamed eyes, and rapid reduction of vision. There was early severe turbidity in the anterior chamber or the vitreous. Of the 13 patients who had endophthalmitis, 9 received prompt therapy, including intravitreal antibiotics. Therapy included intravitreal vancomycin, 1 mg; amikacin, 0.4 mg; dexamethasone, 0.4 mg; and topical and systemic antibiotics (intravenous vancomycin plus ceftazidime, tobramycin, or ciprofloxacin). In 2 patients (1 and 5) no intravitreal antibiotics were given before loss of vision, and in 2 others (3 and 4) intravitreal therapy was delayed by at least 24 hours.

The institutional review boards had approved the project, and informed consent was obtained from all participating subjects.

PROSTHESIS

The KPros were of the Dohlman-Doane design, which comes in 2 types (**Figure 1**).⁴ Type I has a collar button shape with a front plate diameter of 5.5 to 7 mm, a stem diameter of 3.2 or 3.5 mm, an interplate distance of 0.75 or 1.0 mm, and a back plate ranging from 7.0 to 11.0 mm. The type II prosthesis has the same dimensions but with an additional 2-mm nub added to the front plate for protrusion through the eyelid skin in end-stage dry conditions. The type I keratoprosthesis was used in 65 eyes and type II in 43 eyes. In 57 cases the back plate had holes to improve nutrition, fluid flow, fixation, and anchorage by means of scar tissue formation. Fifty-one cases used a later design, the "no holes" KPro, and nearly all (96%) such KPros were placed after October 1, 1996.

SURGICAL PROCEDURE

The surgical techniques have been previously described in detail.⁵

ANTIBIOTICS, CORTICOSTEROIDS, AND IMMUNOSUPPRESSIVES

The patients routinely were given 1.0 g of cefazolin intravenously (except in penicillin-allergic patients) at the start of the KPro operation. Topical 10% povidone-iodine was used as a preoperative antiseptic. Intraoperatively, a topical combination product of trimethoprim and polymyxin B was administered periodically. Postoperatively, the patients received oral cephalexin, 500 mg, 2 to 3 times daily by mouth for 2 to 3 weeks and topical gentamicin, ofloxacin, or trimethoprim-polymyxin B. These were given 4 times a day initially and gradually reduced to twice daily for 2 months. This regimen was then continued indefinitely. Usually topical antibiotics were alternated every 3 months.

In the type I KPro, a temporary conjunctival flap was often used, and this was opened centrally after 2 months.⁶ Before this opening, the antibiotics were given as indicated, accompanied by 1% prednisolone acetate 2 to 4 times daily. Following exposure of the KPro, whether from the time of surgery or after some time, the prednisolone was switched to 1% medroxyprogesterone suspension 4 times daily. Standard long-term dosage was twice daily. Only rarely was prednisolone given once the prosthesis had been exposed.

Azathioprine or cyclosporine was given for a short time after the surgery in 3 patients with a diagnosis of SJS. Similarly, azathioprine or dapsone was given in 3 patients with OCP. In 4 patients systemic prednisone was also administered for some time after the operation. At the time of infection, however, corticosteroids and immunosuppressives were only administered as indicated in **Table 1**.

CULTURES

In a subset of 30 of the Massachusetts Eye and Ear Infirmary patient eyes with KPros, we studied the microbial flora of the tissue around the device (conjunctival in type I, lid skin in type II), obtaining cultures at various times postoperatively. Patients had between 1 and 5 cultures taken at random time points. The samples were placed on blood agar, chocolate agar, Sabouraud agar, ANA agar, or in thioglycolate broth. The cultures were obtained after 1 drop of topical anesthetic was applied.

In patients with endophthalmitis, samples of aqueous humor and/or vitreous were cultured for bacteria and fungi.

STATISTICS

All analyses were performed using the χ^2 test and Fisher exact test. All tests were 2-sided with a .05 level of significance.

Bacterial endophthalmitis occurred in 13 patients (Table 1, **Figure 2**). Possible risk factors, such as preoperative corneal diagnosis, type of KPro, size of back plate, and presence or absence of holes in the back plate, are listed. Patients' medication at the time of infection and the causative organism are also shown. The interval

between surgery and infection varied between 2 and 46 months (average, 18 months).

The endophthalmitis rate in the total cohort was 12% (**Table 3**). The patients with SJS had a 39% incidence; the patients with OCP, 19%; the burn patients, 7%; and other, 2%. χ^2 Analysis of the disease categories revealed

significant difference ($P = .001$). Further analyses showed significance regarding SJS vs burn ($P = .02$) and SJS vs other ($P = .001$). There was also statistical significance between OCP and other ($P = .03$). Although the difference in infection rate between OCP and SJS appeared to be clinically important, it failed to meet statistical significance ($P = .13$). The same held for OCP vs burn ($P = .20$).

With regard to other possible risk factors for endophthalmitis, there was no significant difference in patients who had a type I vs type II KPro (7/65 or 11% vs 6/43 or 14.0%, respectively, $P > .05$). Patients who had KPros with back plate holes had a higher rate of endophthalmitis than those with the “no holes” design (9/57 or 16% vs 4/51 or 8%), but this difference was not statistically significant ($P > .05$). In addition, any difference in these rates may be ascribed to the shorter duration of follow-up in patients with the “no holes” design. Patients who had KPros with a larger back plate diameter (≥ 9.5



Figure 1. Designs of keratoprosthesis. Left, Collar button-shaped device used in eyes with functioning tear secretion and blink mechanism (type I). Right, Model with an added nub to protrude through the lid skin in end-stage dry eyes (type II). In some back plates the holes have been eliminated.

mm) had a higher rate of endophthalmitis than those with back plate diameter of 8.5 mm or less (7/47 or 15% vs 6/61 or 10%), but this difference also was not statistically significant. Thus, the only significant risk factor for endophthalmitis was preoperative diagnostic category (SJS, OCP, burn, or other). Of note, the only 2 burn patients who developed endophthalmitis had alcohol and compliance problems. Finally, in the other group, the only patient who developed an infection also had a glaucoma filtering bleb, a known risk factor.

The pathogens that caused endophthalmitis in our patients with KPros are listed in Table 1. All endophthalmitis cases were due to gram-positive cocci. In most cases, endophthalmitis resulted in loss of useful vision (Table 3). In 3 cases some vision was retained at the 20/400 to 20/200 level. In 2 of these patients, the pathogen was *Staphylococcus epidermidis* and the third case was caused by viridans streptococci (*Streptococcus mitis*). This patient was seen within 6 hours of symptom onset.

Several patients developed vitreous inflammation without pain or conjunctival injection and responded to topical steroid therapy alone. They were diagnosed as having sterile endophthalmitis (Table 3).

COMMENT

With our KPros and our techniques, endophthalmitis is now clearly the main obstacle to a safe outcome. It used to be that glaucoma was the most feared long-term problem, especially in the chemical burn category. However, with the addition of the simultaneous implantation of a glaucoma valve shunt, the threat of pressure damage has receded.⁷

In our series, the major risk factor for endophthalmitis was a preoperative diagnosis of SJS or OCP. The reason for this is not clear. One possibility is that pa-

Table 1. Bacterial Endophthalmitis in Patients With Keratoprosthesis*

Patient No.	Diagnosis	Type of Keratoprosthesis	Back Plate Diameter, mm	Back Plate Holes	Interval, mo	Repair Melt Retract	Gross Leak
1	OCP	II	11.0	+	8	+	+
2	SJS	II	9.5	+	10	+	-
3	SJS	I	9.5	+	13	+	+
4	SJS	I	9.5	+	14	+	-
5	OCP Behçet	II	9.5	+	25		
6	Burn	II	9.5	+	39	+	+
7	OCP	II	9.5	+	3	+	-
8	OCP? Atopy	I	8.5	+	36	+	-
9	OCP	I	8.5	-	28	+	-
10	SJS	I	8.5	-	2	+	-
11	SJS	II	8.5	-	6	-	-
12	Graft failures Filtering bleb	I	7.5	-	2	-	-
13	Burn	I	8.5	+	46	+	+

*OCP indicates ocular cicatricial pemphigoid; SJS, Stevens-Johnson syndrome; plus sign, present; minus sign, absent; and ?, unknown.

†These 2 patients were also given oral doxycycline, 100 mg/d.

‡The type was further identified as *Streptococcus mitis*.

tients with these conditions have an increased rate of tissue breakdown (“melt”) around the KPro (**Figure 3**). In most of the endophthalmitis cases, however, there was no visible leak of aqueous humor at the time of infection and intraocular pressure was normal. Microscopic bacterial contamination of the aqueous humor most likely occurs in all KPro patients, and perhaps patients with SJS and OCP, in whom ocular immunity may be altered, are less able to fight this microbial invasion.

The term *vitritis*, in contrast to endophthalmitis of clearly bacterial origin, requires some comment. Can we be certain that patients with vitritis are sterile? Admittedly not, but they constitute a strikingly different category in that the eye is not red or painful and that vision, with the aid of corticosteroids, returns to the previous level within a few months. There are reasons to believe that some of these patients ignored the recommendation to wear a protective shield during the night and probably rubbed their unprotected eyes, causing a “spill” into the anterior chamber of necrotic material that frequently accumulates between the 2 KPro plates. The holes in the back plate may play a role here, and because of this suspicion, the back plates are now made solid.

All endophthalmitis cases in our series were due to streptococci or staphylococci, but KPro patients with SJS and OCP in our surveillance culture group did not have a higher rate of colonization with these organisms than other KPro patients. Some pathogens were not found in the surveillance cultures, and it is likely that once colonization with these intrinsically virulent organisms occurs, infection follows rapidly. This seemed to be true for *Streptococcus pneumoniae* and β -hemolytic streptococci, organisms not found in surveillance cultures. Indeed, 1 patient (patient 4) in the surveillance group developed pneumococcal endophthalmitis 3 weeks after a

surveillance culture grew only α -streptococci (*S mitis*) and coagulase-negative staphylococci.

Endophthalmitis due to streptococci or *S aureus* is associated with a poor outcome in postcataract endophthalmitis.⁸ All 10 of the patients with endophthalmitis in our series infected with these organisms lost all vision in the affected eye.

The 3 patients who had some salvage of vision had either *S epidermidis*, an organism associated with a good

Table 2. Results of Surveillance Cultures of Ocular Surface Flora Taken at 2 Time Points in 30 Uninfected Eyes With Keratoprotheses*

	Time 1 (30 Eyes), No. (%)	Time 2 (21 Eyes), No. (%)†
Gram-positive cocci		
<i>Staphylococcus aureus</i>	6 (20)	3 (14)
Coagulase-negative staphylococci	22 (73)	14 (67)
Micrococci	2 (7)	1 (5)
Viridans streptococci	5 (17)	1 (5)
<i>Corynebacterium</i> species	6 (20)	1 (5)
Gram-negative bacilli		
<i>Moraxella</i> sp	1 (3)	0
<i>Pseudomonas fluorescens</i>	1 (3)	0
<i>Klebsiella</i> sp	0	1 (5)
<i>Flavobacterium</i> sp	0	1 (5)
Anaerobes		
<i>Propionibacterium acnes</i>	3 (10)	0
Other anaerobes	2 (7)	0
Yeast	3 (10)	1 (5)
No growth	2 (7)	3 (14)

*Many eyes had more than 1 microbial isolate. Percentages refer to the percentage of total eyes cultured at a given time point that had that microbial isolate.

†Twenty-one patients (21 keratoprothesis eyes) had a second culture done an average of 7 months (range, 0.5-30 months) after the first culture.

Topical Prophylactic Antibiotics	Corticosteroids	Immunosuppressives	Organism
Gentamicin twice daily	–	–	<i>Staphylococcus aureus</i>
Polymyxin B–trimethoprim 4 times daily; tetracycline 4 times daily	1% Prednisolone 4 times daily	–	<i>S aureus</i>
Ciprofloxacin twice daily	1% Medroxyprogesterone twice daily	–	<i>Streptococcus pneumoniae</i>
Ofloxacin	Prednisone, 20 mg/d	–	<i>S pneumoniae</i>
?	–	–	group A streptococci
Polymyxin B–neomycin–bacitracin ointment	–	–	<i>S aureus</i>
Polymyxin B–trimethoprim twice daily	1% Medroxyprogesterone twice daily	–	viridans streptococci
Polymyxin B–trimethoprim twice daily†	1% Medroxyprogesterone twice daily	–	viridans streptococci‡
Erythromycin ointment	–	–	viridans streptococci
None for 3 d (ciprofloxacin earlier)	Triamcinolone sub-Tenon, 40 mg, twice daily earlier	–	group B streptococci
Ofloxacin twice daily†	1% Medroxyprogesterone twice daily, prednisone, 5 mg/d	Oral azathioprine oral cyclosporine	<i>Staphylococcus epidermidis</i>
Polymyxin B–trimethoprim once daily	1% Prednisolone every day	–	<i>S epidermidis</i>
Ofloxacin twice daily	1% Prednisolone twice daily	–	<i>S pneumoniae</i>

outcome in postcataract endophthalmitis, or presented very early (within 6 hours of symptom onset).

Postoperative endophthalmitis is clearly a major obstacle in patients with SJS and OCP. In fact, the results in our patients with SJS have been so poor that we are

hesitant to perform KPro surgery in this category at the present time. On the other end of the spectrum, the burn patients and, particularly, the graft failures have shown infection rates that are quite low, considering the often severe conditions. Under any circumstances, the search for more effective preventive measures must be intensified. Pneumococcal vaccination may prevent some of the pneumococcal endophthalmitis cases (E. Hohmann, MD, oral communication, 1999). Since all of the infections were due to gram-positive cocci, topical vancomycin may be indicated instead of, or in addition to, other antibiotics. Swabbing around the type II KPro periodically with hydrogen peroxide or with povidone-iodine may also reduce organism colonization and the need for topical prophylaxis. When tissue melt is threatening the integrity of the device, repair surgery should be effectuated

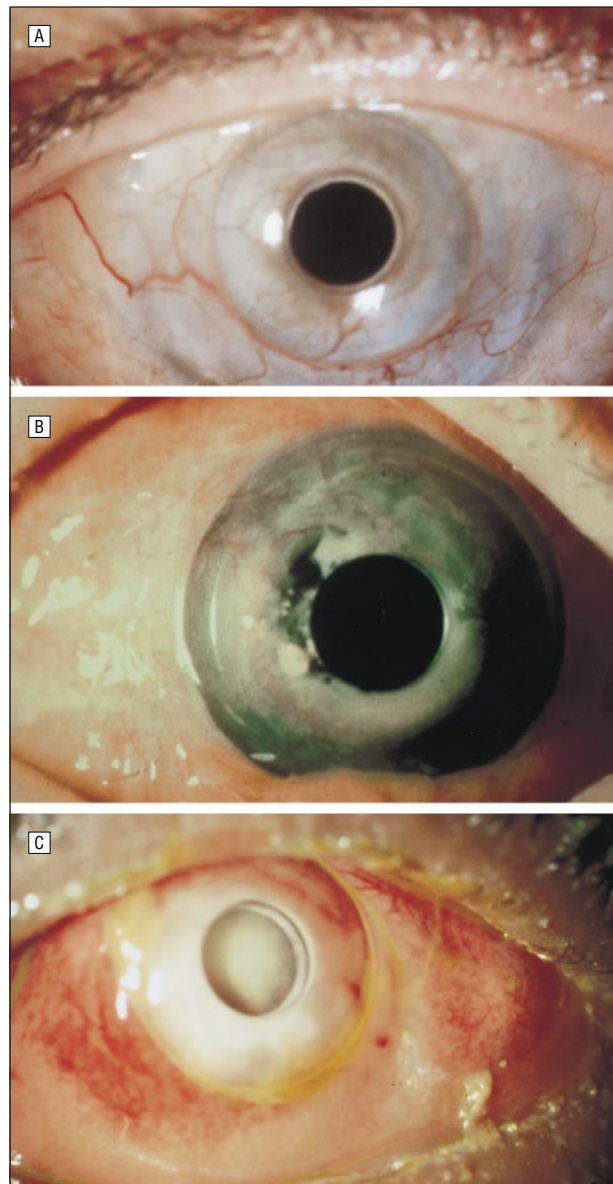


Figure 2. Examples of type I keratoprosthesis. A, Successful outcome, 20/25 vision. B, Beginning necrosis and melt of cornea between the plates. C, Severe, sudden endophthalmitis in a patient with Stevens-Johnson syndrome with a 2-day history, which resulted in enucleation.

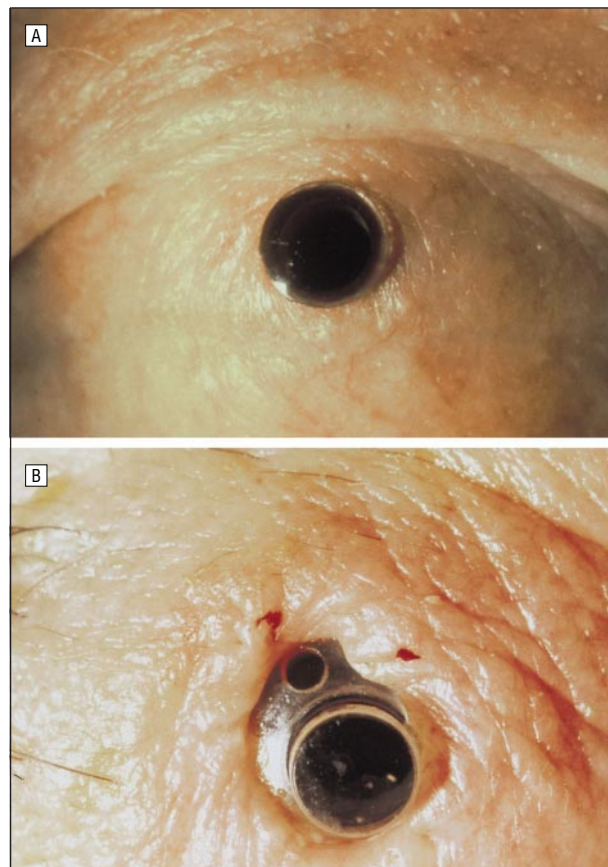


Figure 3. Examples of type II keratoprosthesis. A, Stable situation after 6 years in a patient with ocular cicatricial pemphigoid and 20/30 vision. B, Beginning skin retraction.

Table 3. Visual Outcome

Preoperative Diagnosis	No. of Patients	Cumulative Follow-up (Average per Patient), y	Bacterial Endophthalmitis, No. (%)		Sterile Vitreitis (Vision Recovered), No. (%)
			Loss of Eye	Some Vision Recovered	
Pemphigoid	27	102 (3.75)	4 (15)	1 (4)	2 (7)
Stevens-Johnson syndrome	13	39 (3.75)	4 (31)	1 (8)	3 (23)
Burn	28	106 (3.5)	2 (7)	0	1 (4)
Other (graft failures)	40	107 (3.25)	0	1 (2)	2 (5)
Total	108	354 (3.33)	10 (9)	3 (3)	8 (7)

promptly and the procedures should be refined to make them more simple and effective.

The role of postoperative corticosteroids is not clear, but perhaps their use should be kept at a minimum. In animal experiments, topical corticosteroids reduce the stability of KPros.⁹ These are important issues to resolve since sustained corticosteroid treatment postoperatively in the form of topical drops and sub-Tenon injections are usually required to prevent prolonged intraocular inflammation and formation of retroprosthesis membranes. Clearly, continued efforts to prevent infections after KPro implantation must be given high priority.

Accepted for publication September 27, 2000.

This work was supported by Dysautonomia Foundation, Inc, New York, NY.

The authors are indebted to Balraj Jhawar, MD, for statistical analysis.

Corresponding author: Claes H. Dohlman, MD, PhD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

REFERENCES

1. Cardona H, DeVoe AG. Prosthokeratoplasty. *Trans Acad Ophthalmol Otolaryngol.* 1977;83:271-280.
2. Barnham JJ, Roper-Hall MJ. Keratoprosthesis: a long-term view. *Br J Ophthalmol.* 1983;67:468-474.
3. Alvarez de Toledo J, Barraquer RI, Temprano J, Carreras H, Torres E, Barraquer J. Osteo-odonto-keratoprosthesis: a 30 year retrospective study. *An Inst Barraquer.* 1999;28(suppl):95-100.
4. Doane MG, Dohlman CH, Bearse G. Fabrication of a keratoprosthesis. *Cornea.* 1996;15:179-184.
5. Dohlman CH, Waller SG, Netland PA. Keratoprosthesis surgery. In: Lindquist TD, Lindstrom RI, eds. *Ophthalmic Surgery Update No. 4.* Vol V-L. Chicago, Ill: Mosby-Year Book; 1996:0-32.
6. Al-Merjan J, Sadeq N, Dohlman CH. Temporary tissue coverage in keratoprosthesis. *Middle East J Ophthalmol.* In press.
7. Netland PA, Terada H, Dohlman CH. Glaucoma associated with keratoprosthesis. *Ophthalmology.* 1998;105:751-757.
8. The Endophthalmitis Vitrectomy Study Group. Microbiologic factors and visual outcome in the Endophthalmitis Vitrectomy Study. *Am J Ophthalmol.* 1996;122:830-846.
9. Nouri M, Al-Merjan J, Abad JC, et al. Development of an animal model for a keratoprosthesis to test parameters for survival [abstract]. *Invest Ophthalmol Vis Sci.* 2000;suppl:S-900.

Notice to the Authors of Reports From Clinical Trials

The *Journal of the American Medical Association (JAMA)* and the *Archives of Ophthalmology* function as an editorial consortium.

With one submission and one set of reviews, your clinical trial manuscript will be considered for publication in both *JAMA* and the *Archives of Ophthalmology*.

Submit your paper to the journal of your choice according to the appropriate "Instructions for Authors" and the following guidelines will apply:

1. If your manuscript is accepted by *JAMA*, it will be considered for an editorial or commentary in *JAMA*. Your abstract will also be published in the *Archives of Ophthalmology* with a commentary or editorial.

2. If your manuscript is accepted by the *Archives of Ophthalmology*, it will be considered for an editorial or commentary in the *Archives of Ophthalmology*. Your abstract will also be considered for publication in *JAMA* and may be accompanied by a commentary or editorial in *JAMA*.