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# The Complications After Keratoplasty

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## 1. Introduction

Keratoplasty is the medical term that refers to a cornea transplant. There are some differences between the definitions of keratoplasty, commonly it is mentioned for corneal transplant, Lamellar Keratoplasty, which is a partial thickness corneal grafting and penetrating keratoplasty: is a full-thickness corneal grafting. The indications for keratoplasty include: optical (to improve visual acuity by replacing the opaque host tissue by a healthy donor or pseudophakic bullous keratopathy), tectonic (in patients with stromal thinning and descemetocelles, to preserve corneal anatomy and integrity), therapeutic (removal of inflamed corneal tissue refractive to treatment by antibiotics or antiviral drugs) or cosmetic (in patients with corneal scars giving a whitish opaque hue to the cornea).

The most frequent causes of corneal alterations leading to keratoplasty are keratoconus, bacterial infections, poor hygienic contact lens wear (Buehler et al. 1992, Chalupa, 1987, Holden, 2003) or trauma. Among microbial infections, bacterial infections are the most frequent and are mainly caused by *Staphylococcus sp.*, *Streptococcus sp.* or *Pseudomonas sp.*

Some side effects of keratoplasty can be infection (keratitis on the new transplanted cornea or endophthalmitis), transplant rejection, vision fluctuation, glaucoma and bleeding, among others less reported. Infection is one of the most frequent complications after keratoplasty, which can cause endophthalmitis. Infection after keratoplasty, can result from inappropriate healing or like a complication during the transplant (Confino and Brown, 1985 and Dana, 1995). even though the area around the eye is completely sterilized the day of the surgery and the face is covered with sterile drapes. Despite these actions to keep the surgical area clean, infections still may occur.

On the other hand, transplant rejection is one of the hardest complications after keratoplasty. It occurs when the body rejects the new cornea. But it can occur from days to several years after surgery. Symptoms that show that the immunological system has rejected the cornea may be redness of the eye, an extreme sensitivity to light and pain, autoimmune diseases, infiltrates and also unknown causes. Signs of rejection may occur anywhere from one month to several years after the transplant surgery. On these cases, keratoplasty can be repeated when the transplant is rejected and oral immunosupresor drugs must be taken for long time to reduce the rejection. Some authors are reported also vision fluctuation after keratoplasty, frequent symptoms are poor vision and fluctuations for up to several months or years. Not until the vision has reached a constant and the sutures have been removed can the individual be given a prescription for eyeglasses or special contact lenses.

Other reports refer to glaucoma like a potential complication after keratoplasty. Glaucoma is a buildup of pressure in the eye that can cause a complete loss of vision. Keratoplasty increases the chances of pressure buildup during the surgical procedure that may lead to glaucoma for metabolism changes on the stroma or perhaps can be caused for immunological reactions or metabolic associations. It depends of the clinical history of each patient, not all cases are the same, by this reason must be studied independently. Additionally, may appear bleeding and pain after keratoplasty, sometimes the blood vessels may leak, which would result in bleeding from the eyes. In these cases, sitting upright will encourage the blood to settle. Pain after the keratoplasty is a common side effect oftentimes due to dry eyes. In theory the dry eye contribute with corneal infection, probably due to the opportunistic microbes, which invade the tissue, also is the same with the use of contact lenses for long periods due to hypoxia (low oxygen) (Mertz G. 1980) and to hypercapny (increase of carbon dioxide CO<sub>2</sub>). Patients usually feel pain and discomfort when they move the eye at all for weeks after surgery.

Ocular infection occurs mostly in immunosuppressed patients, prior diabetes mellitus, hypertension, hypoadrenalism, taking oral corticosteroids, atopic dermatitis; prolonged use and low hygienic conditions with contact lenses (soft lenses are more frequent than RGP contact lenses) , opportunistic microorganisms which interfered with normal flora, dry eye and a low percentage for contamination of the surgical team. The etiology of keratoplasty in cases of microbial infection has been reported by several authors, as well as the findings on postoperative keratoplasty, one of the main causes is keratoconus and previous corneal graft rejection. The most common microbiological findings correspond to bacteria such as *Staphylococcus sp.*, *Pseudomonas sp.*, *Pneumococcus sp.* *Serratia marcescens*, *Streptococcus pneumoniae*, *Streptococcus viridians*, *Bacillus sp.*, *Corynebacterium sp.* primarily and other microorganisms such as fungi (*Candida sp.* *Candida glabrata*, *Aspergillus sp.*, *Fusarium sp.*), among the viruses that are mostly found associated with keratoplasty are the *herpes simple*.

In the reports of eye infection as a complication after keratoplasty, the finding of organisms corresponds in most cases to opportunistic bacteria of the normal ocular flora. In a prospective study conducted in 2004 by a team of researchers in Japan (Wakimasu et al. 2004). They found in a retrospective study among 753 eyes with microbial keratitis after keratoplasty, 14 had bacterial and 13 fungal infections. The time intervals between transplantation and the onset of infection averaged were seven months on average for bacteria and 24 for fungus. In many cases unexpected occasions are to be studied independently and allow further studies regarding the appropriate surgical protocol and the use of antibiotic and steroid therapy to prevent such cases in future.

Even reports of mixed infections are: bacteria-bacteria, fungus or bacteria. Associated with these findings should be taken into account the presence of bacterial endotoxins are another complication of keratoplasty of microbial origin, producing toxic anterior segment syndrome (TASS), which has been attributed to the use of intracameral antibiotics, reusable cannulas, cleaning the instrumental use of detergents or non-ionized water, among others (Maier et al. 2010). Moreover, the time of onset of infection can vary from weeks to years of development after transplantation. The associated risks are contaminated sutures, persistent epithelial defects. The clinical appearance of TASS is typically characterized by intense early postoperative inflammation of the anterior ocular segment. Sometimes it can be accompanied by fibrin formation, corneal edema, without periocular pain. For diagnosis

of this pathology it is important to make routine microbial tests: (culture of microorganisms, mycobacteria, polymer chain reaction (PCR), mycoplasma, Chlamydia, simplex virus, adenovirus and endotoxins (limulus amebiocyte lysata, QCL 1000, Cambrex Bio Science).

Some factors to take into account to protect the cornea in these surgeries are prophylactic antibiotic treatment, asepsis eye with an appropriate antiseptic prior to surgery, postoperative antibiotic treatment, age, nutrition and immunosuppressant of the patient and to be taken considered minimizing the risk of postsurgical infection. Before this surgical procedure should be performed before the control protocol for signs or symptoms of eye infection and make an effective and timely microbiologic diagnosis. In the case of mixed microbial infections reported leading to keratoplasty (bacteria-bacteria or bacteria-fungi) (Garcia et al.2004, Delgado et al.2008), it should be clear which is the microorganism more dangerous to invade cornea (fungus or bacteria) to inhibit it with the indicated treatment (antimycotic or antibiotic agent, respectively) , knowing the physiopathology of the infection, the mechanisms of adhesion (biofilm formed for bacteria or hyphaes for fungus) and reflect on the use of corticosteroids in ocular infection, because it which may exacerbate the corneal infection in most cases with corneal compromise. Asepsis previous eye surgery, irrigating with povidone-iodine a day before surgery, has proved a good choice to prevent infection after the keratoplasty (Nash et al. 1991).

Corneal complications due to other ophthalmic surgeries like post intraocular implants relation have been associated with edema. It occurs for many reasons, but it is often a sequel of intraocular surgery, called either pseudophakic bullous keratopathy (PBK) or aphakic bullous keratopathy (ABK). Knowledge of the structure of the cornea and the proper functioning of its layers is fundamental to understanding corneal edema. Authors suggest that the endothelium becomes increasingly unable to act as a pump to deturgesce the cornea, it causes the stroma begins to swell, especially in the central cornea. As the stroma swells, the cornea thickens and folds are seen in the Descemet membrane. The edema may fluctuate in response to changing intraocular pressure with higher pressures leading to more edema. At this point, maintenance of intraocular pressure at a low level is important. The combination of variable endothelial function and variable intraocular pressure determines the extent of corneal edema (Aquavella et al, 2010).

This chapter is a description of microbial complications in keratoplasty, to understand the physiology and behavior of these microorganisms in the surgical process, the relationship with the ocular immune system at the time of surgery, knowing the clinical findings to identify whether a bacterial infection, viral or fungal infection may be present. Another factor to evaluate the postoperative course of keratoplasty is the type of antibiotic used after keratoplasty and should be evaluated according to clinical evidence, since in many cases is not time for microbiological culture fungal or bacterial infection alone is assessed, but fungi attack the corneal stroma, being more aggressive with corneal tissues:

Microbial complications post-keratoplasty may even become worse on endophthalmitis and in the worst cases enucleating of some inevitable cases. In vitro studies, it have shown that the anatomy of corneal tissue which allows the invasion of microorganisms in and its biochemical composition. The corneal stroma lamellar structure composed of collagen fibrils which contribute to corneal transparency, being invaded by microorganisms allows rapid entry stromal inflammatory cells, predisposing to ulcers. Crystalline keratopathy caused by *Streptococcus sp.* should not confuse with a fungal infection because it form a crystalline forms similar to mycotic hyphaes. (Butler et al.2001).

## 2. Statistical methods

### 2.1 Method

For the analysis of the data, the following sources were consulted for this paper: Expert opinion, clinical case reports and specialized databases. In the first case, it was a survey with ophthalmologists skilled in corneal surgery, yielding six National specialists which are located geographically in Colombia. An unstructured interview was used for this. For the clinical reports, we reviewed the clinical cases of the service of ophthalmic consult of Fundación Universitaria del Área Andina Seccional Pereira and the reports made by specialists.

### 2.2 Databases

Three bibliographic databases were searched: Medline, Ebsco, Hinary. To facilitate the search, the connector used was “and”. In total 78 Articles were reviewed and 37 were chosen for the report.

### 2.3 Keywords

Keratoplasty, ophthalmology, ocular and immunology, keratoplasty and complications, microbiological infections and cornea.

### 2.4 Criteria for inclusion

First, personal meeting with experts (ophthalmologist cornea specialists) was conducted for the review. Second, we reviewed clinical cases of the optometric clinical of Fundación Universitaria del Área Andina Seccional Pereira and private ophthalmologist consult. Additionally, the inclusion criteria respond to the search of articles and reports of work based on post keratoplasty infection, immunological and post-keratoplasty complications, astigmatism and post-keratoplasty using End Notes. The clinical cases selection was made by ophthalmological consult of control with complications post-keratoplasty. Three cases were included.

### 2.5 Criteria for exclusion

Articles with the topic of ocular infections which did not require keratoplasty, and immunological diseases without corneal compromises, were rejected.

## 3. Clinical pearls on microbial complications after and before keratoplasty

The most microbial reported associated with microbial keratitis which required keratoplasty are bacterial associations (Driebe and Stern 1983) following by mycotic and herpetic infections and less often, *Acanthamoeba sp.* The complications are more dangerous if there is an association with corneal stroma because the cornea needs respiration (Hill, 1976). Several factors contribute to adherence (Miller, 1987) by bacteria: extracellular bacterial products such as alkaline proteases, protease IV, exotoxin A, exo-enzyme B and a recent small protease, called PASP (*P. aeruginosa* small protease) are been reported and contributes to epithelial erosions in keratitis caused by this agent. Recently, a group of molecules bacterial signaling, known as N-acilhomoserina lactones (AHLs), has also been reported as important factors in virulence of same bacterias (Marquart et al., 2005). The correlation between these factors of adherence and virulence, as the production of signals of molecular and expression of phenotypic characteristics including the production of enzymes, has studied by chromatography and bioassay in recent years. Moreover, the lack

of tear that low lubrication caused by widespread use is a factor that should be taken into account users contact lenses (Kwong, 2007), because the tear is carrier lysozyme, lactoferrin, and immunoglobulins @-lysine that being dehydrated lens facilitates molecular adhesion of *P. aeruginosa* (Zhu et al. 2002).

### 3.1 Differential diagnosis between keratitis caused by microbes

There are a lot of reason for make microbial culture collection in all protocols to identify the type of microbial keratitis pre or post keratoplasty: Signs are similar in bacterial keratitis, exist mixed infections which required different treatments, there are several signs can help to make the differential diagnosis prior to the results of the microbiological findings, some of these are:

SIGNS	BACTERIAL KERATITIS	MYCOTIC KERATITIS	HERPES KERATITIS	ACANTHAMOEBA KERATITIS
Hyperemy	Yes	Yes	Yes	Yes
Satellite lesion	No	Yes	No	No
Pain	Yes	Yes	Yes (Active lesion)	Yes
Lesion borders	Regular	Diffused and irregulars, Feathery borders or hyphate edges	Dendritic ulcers	Regular
Hypopyon	Yes or no	which appears dry, rough, and leathery	No	No
Color infiltrates	White, cream, yellow	infiltrates appear grayish-white or yellowish-white, and the base of the ulcer is often filled with soft, creamy, raised exudates, dematiaceousfungi: brown or black pigmentation on the surface of the ulcer.	White	White or grey
Frequent Causes	corneal foreign body, contact with non-sterile water, bullous keratopathy, neurotrophic keratopathy, herpes simplex keratitis, radial keratotomy, swimming and scuba diving, basement membrane dystrophy, contact lens wear and bacterial keratitis	Vegetal origin foreign body contamination, dirty case lenses storage, immunosuppression.	Immuno-supression	Contaminated water, dirty contact lens case contaminated
Micro-organisms	<i>Staphylococcus sp.</i> , <i>Streptococcus sp.</i> , <i>Pseudomona sp.</i> <i>Mycobacterium sp.</i>	<i>Aspergillus sp.</i> , <i>Fusarium sp.</i> , <i>Candida sp.</i> (Muzaliha et al.,2010)	<i>Herpes simple</i>	<i>Acanthamoeba sp.</i> ( McCulley,2000) (Varga et al.1993)
Stromal immunologica l ring	No	No	No	Immunological ring at the limbus

Table 1. Microbes finding on clinical pearls of keratitis complications associated with corneal infections after keratoplasty and common treatment.

Some infections are caused by more than one microorganism of different species, some of the normal flora or another opportunistic microbes like different bacteria species and in even and rare cases fungi and bacteria. It has been reported more frequently in contact lens wearers in widespread use without improper lubrication, as in the case of Figure 1, a case reported by our research group, where the patient also had a cosmetic tattoo in her eyes. On these cases perhaps an alteration of the normal flora associated with corneal dehydration can contribute to the eye injury. Some cases of contamination should be detected early and obligatorily required to perform a microbial culture using PCR techniques to detect it in less time and be very cautious with antibiotic and steroid therapy in these special patients. Steroids may get worse the damage still unknown causes and antibacterial antibiotics do not work against fungi. The review of these protocols and prior detection signs is the key to the success of a good corneal transplant.



Fig. 1. Infection before keratoplasty caused by Mixed flora: Bacterial keratitis and *Aspergillus sp.*, six days evolution. (Delgado, Chile. 2008, Photograph Personal Album: Márquez & Durán).

In the microbial ocular infections, those with bacterial association respond in most cases if the lesion is peripheral, if the lesion is central and affects optical zone, are more likely to result finally in keratoplasty, perhaps the periphery limbal vessels contribute to improved immune performance, while in central corneal recovery is slower and microbial invasion penetrates more easily to the stroma. But in the case of fungal infections, those fungal cases are caused in most cases for vegetal origin, inappropriately use of contact lenses or unknown causes. In China, in a study performed from 2000 to 2008 with 899 patients, they found no recovery when the treatment was made combined conjunctiva or intracamerular fluconazol. (Shi et. al. 2010). By the other hand, therapy with silver sulfadiazine ointment, natamycin is a better prognosis in cases of microbial infections of fungal origin. Another authors include cyclosporine to prevent graft rejection beginning 2 weeks after penetrating keratoplasty (PKP) and avoid steroids (Xie et al., 2001). Steroids for unknown cause in the case of fungus and bacteria like *Pseudomona* are not a good choice for treatment and cannot be administrated for the security of the corneal integrity. More studies are required in a future for new options of immunosuppressor against immunological mediator of inflammation. It is important to check any graft rejection, clarity of the graft, visual acuity, and surgical complications after surgery in all cases.

### 3.2 Treatment of microbial infections after keratoplasty

The successful treatment of microbial infections requires of the experience of an interdisciplinary team: corneal experts ophthalmologists, immunologists and microbiologists

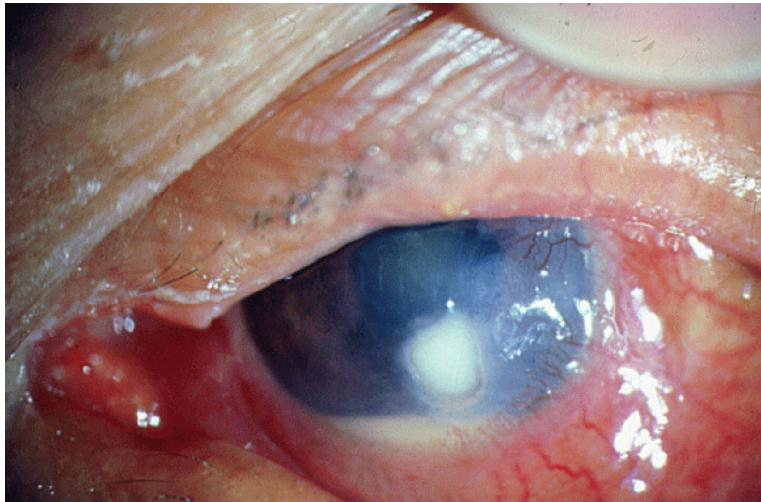


Fig. 2. Keratitis and posterior endophthalmitis infection caused by *Staphylococcus sp.* (Courtesy: Ophthalmologist Emilio Méndez.M.D. Personal Atlas).

and the cooperation of the patient. It is important to act fast and certainly. The use of antibiotics like last generation fluoroquinolones is the best option and it is recognized around the world in the case of bacterial complications. With the fungus infections it is not easy, due that it is hard to have the microbiological findings on time. For these reason the clinical pearls are so important to choice the best therapy.

These are the antibiotic therapies recommended for experts:

MICROORGANISMS	ANTIBIOTICS FOR TREATMENT	ANTIMICOTICS AGENTS
<i>Staphylococcus sp.</i> <i>Streptococcus sp.</i>	Vancomicine, Moxifloxacin, Ciprofloxacin	No
<i>Mycobacterium sp.</i>	Amikacin,cefoxitin, clarithromycin	No
<i>Fusarium sp.</i>	No	Amphotericin B or Natamycin or silver sulfadiazine, intrastomal variconazole.
<i>Fusarium sp.</i> + <i>Pseudomona sp.</i>	Ciprofloxacin, Moxifloxacin, Gatifloxacin, Vancomicine (against <i>Pseudomona sp.</i> )	Amphotericin B or Natamycin or silver sulfadiazine (against <i>Fusarium sp.</i> ), intrastomal variconazole.
<i>Candida sp.</i>	No	Amphotericin B or Natamycin or silver sulfadiazine, intrastomal variconazole.

Table 2. Microbes finding on keratitis complications associated with corneal infections after keratoplasty and common treatment.

In the case of infection caused by *Acanthamoeba sp.*, propamidine isethionate 0.1% ophthalmic solution administrated concomitantly with neomycin-polymyxin B gramicidin ophthalmic solution has shown best results. Against neovascularization, another therapy

has been used, topical bevacizumab, a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor A (VEGF-A). VEGF-A is a chemical signal that stimulates the growth of new blood vessels (angiogenesis) in graft rejection (Saxena, 2009). The scientists reported successfully results in one case of graft rejection 6 months following penetrating keratoplasty (triple procedure) in the left eye. With the administration of topical bevacizumab (4 mg/4 mL) in a dose of one drop twice a day for 15 days, she improved her vision and this short topical bevacizumab therapy, may potentially offer a safer and more effective alternative in treating graft rejection after penetrating keratoplasty. The administration must be subconjunctival also, and it is in study for side effects.

### 3.3 Immunological findings after keratoplasty

One of the major complications associated with corneal graft rejection post-keratoplasty associations are immune from the donor and recipient. The therapy with immunomodulators before and after treatment required an individual protocol like a great option to prevent such rejection. Corneal transplantation is a continuous release of antigens in the different corneal layers of specific immune response against the donor cornea. This rejection may occur soon after surgery or month and years later. The following table specifies the associated warning signs in case of rejection and to be taken into account in the post-operative:

Studies in animal models (mice) based on corneal transplantation have shown that the main mediators of the immune response implicated in cases of graft rejection are CD4 cells Th1, Th2, CD4+, CD25+ and recently and hypothesis that Th17 play a crucial role in allograft rejection (Cunnusamy, 2010). Also, eosinophils secrete an array of cytotoxic granule cationic proteins such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophile peroxidase (EPO), eosinophil-derived neurotoxin (EDN) which are capable of inducing tissue damage and dysfunction (Gleich et al, 1993) and after this findings new chemical mediators are involved in this toxicity like eotaxin, a chemokine that attracts eosinophils to bind to its specific receptor, could induce the proliferation of fibroblasts, leading to the excretion of collagen. Fibroblasts also secrete eotaxin when stimulated by IL-4 and tumor necrosis factor (TNF) ( Kumagai et al, 2005). Additionally, one might think in the research based on inhibition of those toxins for therapy pre and post-keratoplasty in a future to minimize their toxic effects, which ones contribute to graft rejection. Some like the studies on mice in recent years, which are trying to use IFN- $\gamma$  for inhibit eotaxin expression at both: protein and mRNA levels, in cultured human corneal fibroblasts. This effect of IFN- $\gamma$  may contribute to the inhibition of eosinophil infiltration into the cornea. Exogenous IFN- $\gamma$  thus represents a potential new therapeutic agent for the treatment of corneal disorders associated with inflammatory ocular diseases such as vernal keratoconjunctivitis.(Fukuda et al. 2002). Some patients present immunological events of rejection after years of POP, perhaps to systemic immunological complications that must be studied in each case with immunological analysis.

TYPE OF FAILURE OF THE IMPLANT	PRIMARY FAILURE	LATE FAILURE
Time of occurrence	Graft failure after first days of postoperative	Graft failure after months or years after postoperative
Signs	Edema after surgery, low transparency during the firsts weeks	Gradual diffuse edema, increase corneal infiltrates, corneal vascularization

Epithelial failure	<p>Occurs in two forms that respond to steroid use. The patient is asymptomatic or has minimal skin irritation. It is self-limiting and does not change in the visual acuity (V.A.).</p> <ul style="list-style-type: none"> <li>• The first type is characterized by elevated epithelial rejection line that stains with fluorescein or rose bengal. Progresses rapidly in days to 2 weeks and may take the form of a ring concentric to the limbus, peripheral to the interface area and subsequently shrinks to the center. The line represents an area of destruction of donor epithelium, which is covered by host epithelium.</li> <li>• The second type is characterized by the presence of subepithelial infiltrates, which contain lymphocytes. They are similar in appearance to those produced by adenovirus. Can change shape, location and disappear by themselves.</li> </ul>
Stromal failure	<p>It is accompanied usually of endothelial rejection. It is characterized by a haze peripheral full-thickness, limbal injection in a previously clear corneal button. Infiltration can be identified in the peripheral interface progresses centrally</p>
Endothelial failure	<p>A classic rejection presents with endothelial rejection line (Khodadoust, 2008), which usually begins in a vascularized portion of the interface and progresses, if untreated, through the endothelial surface over several days. It consists of mononuclear white cells damage the endothelium. This line is made up of mononuclear cells (white blood cells that appear at the vascularized edge of the recently transplanted cornea, if untreated, the line of white blood cells move across and damage the endothelial cells of the cornea. There may be a reaction of moderate to severe CA. The damaged endothelium cannot maintain adequate dehydration of the button and the swells in the posterior to the line, while before it is transparent. Another variant of endothelial rejection presents with diffuse keratic precipitates and anterior chamber reaction, stromal edema localized but not widespread and limbal injection.</p>
Risk factors	<p>Vascularization on the base layers of the recipient corneal. It is the only factor whose relationship to the increased incidence of rejection has been demonstrated. It is believed to be due to loss of immune privilege of the cornea due to normal avascularity</p> <ul style="list-style-type: none"> <li>Large and eccentric grafts</li> <li>Incompatibility of HLA-A, HLA-B and ABO group</li> <li>History of previous rejection of any kind</li> <li>Bilateral Keratoplasty</li> <li>Preservation transportation media and corneal tissue pre - transplantation</li> <li>Age</li> <li>Presence of epithelium in a donor transplant</li> <li>Association with atopic dermatitis, allergy and asthma</li> </ul>

Table 3. Types of corneal transplant failure

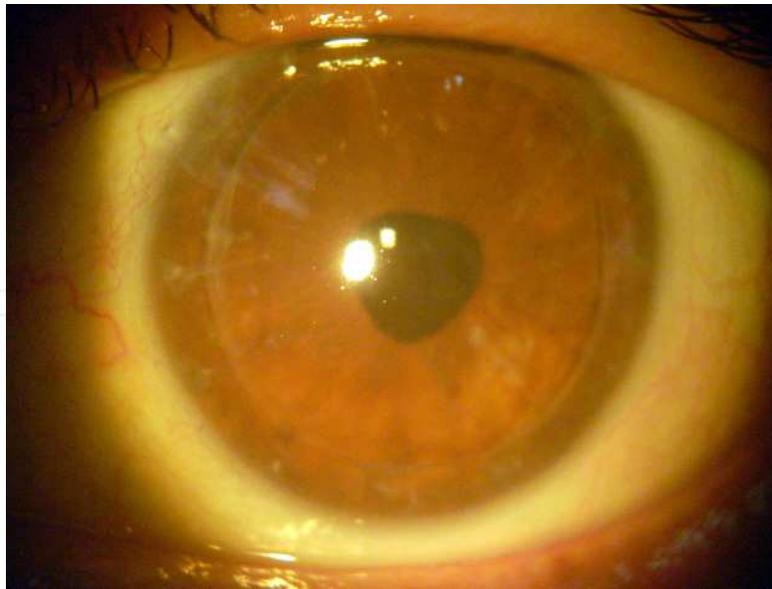


Fig. 3. Keratitis infiltrates post-keratoplasty after 13 year of postoperatory of the keratoplasty. (Cortesy: Mayra Cáceres O.D.)

Another chemical mediator of immune response (Awadi, 2011) are metalloproteinases, collagenase, stomelysin and gelatinase. These matrix of metalloproteinases are inhibited by specific endogenous tissue inhibitors of metalloproteinases (TIMP1, TIMP2, TIMP3, TIMP4), like batimastat and marimastat. Modulation of metalloproteinase activity may thus help to model and minimize scarring such as that occurring in ketatoconus or after traumatic or surgical injury to the cornea (See Chapter Modeling of corneal healing and corneal inflammatory response). Those findings will be so useful to performer better protocols for receptors and immunological exam before and after surgery.

Recent research on bovine serum- free corneal cell and wounded organ cultures were developed with a range of concentrations of TGF-  $\beta$ 1, - $\beta$ 2, and - $\beta$ 3; IL-10; and neutralizing human monoclonal antibodies (mAbs) against TGF- $\beta$ 1 in order to watch the inhibition of TGF- $\beta$  for reduce the myofibroblast differentiation and fibrosis in the cornea, this results may contribute in a future to determined the actions of distinct TGF- $\beta$  isoforms and their inhibitors during early corneal wound healing is an essential step in guiding therapeutic intervention. The found that TGF-  $\beta$ 1 delayed re-epithelialization, increased repopulation of the stroma, increase proliferation and was the only isoform to promote myofibroblast differentiation. Additionally, IL-10 promoted corneal re-epithelialization at low doses but inhibited this response at high doses. Stromal repopulation was prevented by all doses of IL-10. TGF- $\beta$ 2 or the anti-TGF- $\beta$ 2 mAb, CAT-152 had little effect on any repair parameter. Treatment with the anti-TGF- $\beta$ 1 accelerates corneal re-epithelialization but reduces cell repopulation of the stroma. The cytokines TGF- $\beta$ 3 and IL-10 have opposing actions to that of TGF- $\beta$ 1. (Carrington L. et al. 2006).

By the other hand, the evolution of new surgical techniques have been improving for keratoplasty, as well as treatment protocols and prevention of graft rejection, beginning with the removal of sutures to secure the graft, in 1956, using a posterior approach, first reported for Tillett, in 1998, Dr. Gerritt Melles et al. described posterior lamellar keratoplasty (PLK) technique that uses air instead of sutures, placement of the graft to the recipient cornea. Their technique required initial lamellar dissection of the donor and recipient cornea, excision of a 7.5 mm diameter recipient posterior stroma 7.0 button with attached

endothelium and the insertion of a posterior donor button size similar through a limbal incision mm-9. Later, Melles et al. then doubled the donor graft that could be inserted through an incision of 5 mm. Another technique used to simplify the procedure was published by Dr. Goroyov, using a microkeratome to harvest the donor graft, a variation known as Descemet's endothelial keratoplasty automated extraction (DSAEK). Besides reducing the technical difficulty of the general procedure, descemetorhexis and microkeratome donor dissection was also softer surface receptor and donor, resulting in more satisfactory visual results. In 2006, Melles al. et al reported a success with a new variant called Descemet membrane endothelial keratoplasty (DMEK) involved in transplanting endothelium naked DM - a specific disease true form of keratoplasty with minimal trauma.

In 2008, Dr. Pavel Studeny showed a variation of this technique at the American Academy of Ophthalmology annual meeting 2008, which formed a "huge bubble" of air to separate the center of 6 mm or less of the donor, separating the posterior stroma by manual lamellar dissection, removed the stroma during the great bubble and marked central tissue from a donor with the appropriate diameter to create a graft that was naked and central DM endothelium with stroma attached outer edge. This configuration allows easier handling and graft insertion or DSAEK/DMEK anyone. He recently had a variation of this technique called automated keratoplasty endothelial Descemet membrane (DMAEK), in which the donor tissue is first dissected with a microkeratome as DSAEK, a large central bubble is formed, the overlying stroma is removed large bubble, and the fabric is pierced with a drill. All those surgical techniques among others, contribute to reduce the inflammatory response by chemical mediators of inflammation reducing the reject of the implant and are so important for future immunological research and found a long term protocol and also epidemiological studies between those techniques and the relationship with the receptor immunological reject. But it must take in mind each patient's medical history, previous history of atopic dermatitis, systemic and ocular allergies, several dry eye and systemic associations such as diabetes, hypertension and especially those of an autoimmune rheumatoid arthritis, atopic dermatitis, among others to make a very good rating diagnosis before graft itself to the corneal donor. New alternatives based on artificial biopolymers are been introduced in recent researches, and it is mainly important to study the biocompatibility and immune response of these new technologies with the human ocular tissue.

Another new technique to performance keratoplasty is the femtosecond Laser-Assisted Lamellar Keratoplasty, which reduce intraoperative complications, additionally, optimizes postoperative refraction, allows faster visual rehabilitation, and decreases the risk of graft rejection and astigmatism, this technique permits create vertical and lamellar corneal incisions with a variety of shapes and angulations at a precise depth. Combining the advantages of lamellar keratoplasty with the surgical precision of a femtosecond laser enables us new surgical options. Femtosecond laser-assisted lamellar keratoplasty techniques include femtosecond laser-assisted anterior lamellar keratoplasty (FALK), femtosecond laser-assisted deep anterior lamellar keratoplasty (FDALK), and femtosecond laser-assisted endothelial keratoplasty (FLEK), (Yoo,S,Hurmeric V, 2011). The authors recommend performed in patients with deep stromal scarring, keratoconus and ectasia.

Recent research led by scientists from Stanford University with a technique called advance Dolhman-Doane, which consists of a core of plastic biopolymer, transparent and tough, which is surrounded with human tissue and could be an alternative in countries where the corneal donation is not as accequible. For attachment to the rest of the globe, further

chemical engineer Curtis Frank has created an artificial cornea polyacrylic acid and polyethylene nets, achieving a transparent material with high water content 80%. Future research is needed to view and evaluate the biocompatibility in vivo metabolic behavior with other nutrients to the cornea and allow epithelial cells attaching to the surface to prevent risk of infection acting as a layer of protection. Additionally, the bioengineer Jennifer Cochran came up with the addition of collagen to a surface of artificial cornea for better grip and other scientific using the technique of photolithography (manufacture of semiconductor materials) Frank and his team can also create patterns of microscopic pores around the edge of the implant. Thus, when the cornea is implanted in her patient's eye, the cells migrated through the pores by anchoring the cornea in the eye and helping to integrate the artificial material with natural tissue. This process reduces the number of sutures necessary to maintain the artificial cornea into place (Technology Review, MIT). There are major projects being carried out to sensitize the artificial cornea implants as the CORNEA EU project to produce artificial cornea has prompted efforts Joachim Storsberg, the Fraunhofer Institute for Applied Polymer Research IAP in German. His work has led to the creation of new versions of the artificial cornea implants has been shown to have less risk in terms of eye injuries.

### **3.4 Another risk factors of post-keratoplasty complications**

Despite of microbiological and immunological complications are significant to prevent rejection. Those are relationship with the age of the receptor. The allograft rejection has been reported more common in children than in adults, possibly due to a more active immune system in younger patients. On those patients the pediatric transplant sometimes not without clear evidence of endothelial rejection. The rejection may even many years after transplantation. If irreversible failure occurs in patients in the age range amblyogenic, regrafting still may be indicated to advance the patient's visual development. Glaucoma is another common complication on these patients; also ocular hypertension can damage the optic nerve and threaten the survival of the graft and therefore the visual prognosis. The vulnerability of glaucoma in pediatric keratoplasty is potentially affected by the anterior segment abnormal structure or the use of steroids after surgery. Other complications, including endophthalmitis, choroidal hemorrhage, cataract, retinal detachment and phthisis bulbi are relatively rare but do occur.

Another authors reported Suture-related graft infection is a serious complication after penetrating keratoplasty and often leads to serious visual lost attributable to scarring, allograft reactions and also increased astigmatism. To reduce the risk of infection, they propose that it is necessary to ensure at each visit all sutures, that knots are well buried and that the sutures are covered by epithelium (Sonavane A. et al, 2003).

In the case of penetrating keratoplasty, the secondary astigmatism post penetrate keratoplasty (PK) is another complication to consider when using this technique. The first factors that may influence the refractive outcome is PK preexisting pathology in the recipient cornea, such as keratoconus, trauma and other causes of thinning or irregularity, especially peripheral, and therefore persist in the transplanted cornea. In cases of keratoconus, astigmatism may see a gradual change over the years, after an initial refractive result QP correct, due to thinning and corneal ectasy ring at the receiver. Due to scarring, vascularization, the degrees of tension may form irregularities. Additionally, systemic diseases such as diabetes, collagen disease, recipient age, may also affect healing. The more homogeneous it is smaller the astigmatic error. During surgery, there are other parameters

to take into account to prevent complications: compression or deformation of the globe, ocular tone down a narrow cleft interpalpebral a misplaced speculum, a thread tension of the upper rectum or scleral support ring misplaced which can distort the cornea during the trephination and cause a receiver window oval or distorted.

During surgery it is necessary to have a team that includes appropriate microsurgical instruments apart from the ideal, a proper system illumination and a keratoscope surgical microscope. Postoperatively, many factors can also influence the final astigmatism, age, existing disease into the receiver, local and systemic steroid use local time each suture is kept before being withdrawn, leaving them to favor reports longer. It should be up on the controls to show signs of possible rejection, early withdrawal of sutures, traumatic or spontaneous ectasia, epithelial problems, and secondary infection. We must decide, first, the diameter of the graft and the window. Often it will be a compromise between including all opaque or affected area on one side and try not to reach the peripheral vascularized limb or other areas in order to minimize the risk of rejection.

The suture is probably the main factor that may influence the prevention or induction of astigmatism QP. It is important to correctly position each and every one of the points because one of them misplaced can induce astigmatism may not be discovered until the sutures are removed and can be difficult to correct with a secondary procedure. 10-0 nylon monofilament is still the reference material for the final suture button, but in reality is biodegradable and often breaks into a period of one to three years. The 10-0 polypropylene (Prolene) looks like a really material unchanged, but noted that eventually loses its tensile strength and cracked by the action of UV rays. Polyester (like Dacron, Mersilene) is a truly non-resorbable material, and thickness of 11-0 has a similar strength to nylon 10-0. It is a little less elastic and therefore requires a closer fit with the help of keratoscope (the Mersilene of 10-0 should not be used, it is much rigid). Its hydrophobic behavior also avoids the tendency of nylon to join the cause and viscoelastic "soap films." The mersilene 11-0 is another good choice (Barraquer et al. 2002).

#### **4. Time of rejection of the corneal implant**

According to the evidence of rejection time after surgery the rejection must be classified in hyperacute, acute or chronic rejection. The hyperacute rejection occurs within days after transplantation of the graft. This type of rejection has become rare, affecting less than 1% of transplant recipients due to improved pre-transplant projections. Hyperacute rejection occurs when the host antibodies recognize and bind to antigens of the graft (such as ABO blood group proteins or proteins of major histocompatibility complex). The binding of these antibodies lead to the initiation of the complement cascade, neutrophil recruitment, platelet activation, endothelial cell damage of the graft, and stimulation of coagulation reactions, which in turn lead to rapid thrombosis, loss of vascular integrity, heart tissue, and loss of graft function.

The acute rejection occurs in approximately fifty percent of transplant recipients experience acute rejection (with only 10% progressing to graft loss), which can occur several hours or days (even weeks) after transplantation. The incidence of acute rejection has decreased significantly with the successful use of immunosuppressants such as cyclosporine and azathioprine. The incidence of graft loss was reduced by the latest anti-rejection treatments. Acute rejection occurs when alloantigen-reactive T cells from the host to infiltrate the graft and become activated by contact with foreign proteins, related to the graft presented to

them by antigen presenting cells. These T cells can lead to tissue damage of the graft by the direct elimination of graft cells (killer T cells) or the production of proinflammatory cytokines such as tumor necrosis factor, interleukin-1, and interferon. These cytokines are vasoactive and perpetuate the inflammatory cell recruitment and infiltration. As a result, graft inflammation progresses, leading to tissue distortion, vascular insufficiency, and cell destruction - all of which may eventually compromise graft function.

By the other hand, the chronic rejection occurs in 50% of transplant patients within 10 years after transplantation. This form of rejection is characterized by the development of occlusion of blood vessels luminal progressive thickening of the intima of medium and large artery walls. Chronic rejection is a pathological response of the tissue remodeling that takes place at a variable rate after graft endothelial cells are traumatized by mechanical damage, ischemia, and immune system during and after the transplant. Damaged vascular endothelial cells produce cytokines and tissue growth factors that initiate vascular repair, causing the underlying smooth muscle cells to begin proliferating. Large amounts of intimal matrix occur, leading to vascular wall thickening stop growing. Slowly progressive reduction in blood flow, results in regional tissue ischemia, cell death and tissue fibrosis.

## 5. Conclusion

Keratoplasty is one of the ocular surgeries that contribute with the reinsertion to job and daily activities and quality life of patients. For these reason, it is very important to study the complications and how to protect cornea before and after keratoplasty for visual health and integrity of the eye and to prevent it. There are new diagnostic techniques so useful worldwide (PCR, new chromogenic agar, immunological test, diagnostic test) to identify the microbes and to choice the good therapy. The reports of the type of microorganisms which cause the lesions are not the same in all countries: In Asia, mycotic infections are most frequent than in America, where bacterial reports of microbial infections are most frequent listed on literature.

Protocols to perform microbial sampling to identify not only bacteria, but also fungi, viruses and acanthamoeba and also immunological test should be a requirement for the protocol clinical management of infection after corneal transplantation, as well as the overall health status of the patient habits and systemic associations to prevent corneal damage. More and more cases appear around the world, by one or other reasons, and it is important to take care of the type of microorganism present, the therapeutic protocol: signs, culture and treatment. New therapeutic drugs must be studied, especially for fungus findings, like variconazole, and take special care for mix infections: bacteria-fungus for the differential diagnosis. Dry eye or not lubrication can contribute to microbial infections, because the tears are the immune protection for the cornea and the artificial tears help to remove toxins and mycotic spores. Some cases needs treatment immediately but the use or corticoids it is not recommended because it can decrease the immune response against the infection. There are no therapy against endotoxins that are responsible of the major damage of the stromal tissue, causing toxic anterior segment syndrome (TASS) and new techniques of therapy like the use of intracameral antibiotics, and some recommendations like the use of non-ionized water or detergents during surgery must be evaluated to include in protocols. Another factor to have on mind to prevent infections after keratoplasty is the immunological associations with systemic diseases, and also the maintenance of the cleaning regimen for contact lenses. It is main important for next studies to evaluate if the previous permanent

make up for esthetical reasons around the eye, perhaps it can interfere the microbial equilibrium of normal flora and let the opportunistic flora to colonize the eye and cause infections. Among some aftercare corneal transplant recommendations after this finding around the world it should look the next factors:

- Integrity of sutures
- Epithelization
- Prevention of rejection (immunological exams before surgery donor and receptor)
- More research for therapy protocols
- Non-filtration.

To prevent post surgical infections the disinfection protocols are the main factor to consider for minimize complications: before starting the surgical procedures, all of the recipient eyes (including eyelids and conjunctiva) can be rinsed with povidone iodine solution, 5%, that was allowed to act for 3 to 5 minutes. After drying the periocular surface, the operation field was covered with sterile drapes and PK can be performed as follows: rinsed with sterile solution (balanced salt solution, it is recommended to introduce acetylcholine chloride (like Miochol-E) into the anterior chamber. Prior to donor trephination and the graft's sutural fixation, the donor's endothelium was covered by sodium hyaluronate, 1% (Healon ophthalmic viscosurgical device). To fix the grafts, a double-running cross-stitch suture with 10-0. And the use of an antibiotic ointment administered at the end of surgery.

It is important also instruct patients avoid restrictions and talk about postsurgical care to prevent fails. Some of these are: To take de prescription of antibiotics and drugs, and the restriction recommended by American Ophthalmology Association:

1. Use metal shield nightly or when taking a nap during the day and a cloth pad under glasses during the waking day, for 1 month.
2. Not bend at the waist for more than 10 minutes at a time, but may squat at the knees.
3. Not lift or push anything heavier than 15 pounds, including grandchildren, for 2 weeks.
4. Hair may be gently shampooed by a friend or a beauty shop with the head leaning slightly backwards for 2 weeks.
5. May watch TV
6. No heavy exercise of any kind for 3 weeks
7. No sexual intercourse for 3 days after surgery.
8. No swimming for 3 weeks.
9. Not read for more than 10 minutes at a time for 2 weeks.
10. Walking is permitted.

Other important recommendations to verify are:

Recruitment of donor tissue : de donor must be removed within six hour after death, the viable storage period of the removed cornea-scleral button is two weeks, grafts donors < 12 months or > 70 years are preferably not to be used and for more security it is also important not use corneas from death of unknown causes, certain infectious diseases like Jacob-Creutzfeld, SSPE, progressive multifocal, leuko-encephalopathy (CNS), certain systemic infection (AIDS, septicemia, syphilis, viral hepatitis), leukemia and disseminated lymphoma, intrinsic eye diseases (tumors, active inflammations, previous intra-ocular surgery), with respect to the recipient cornea : absence of corneal sensations, stromal vascularization, corneal thinning at the expected recipient-donor margin, active inflammation) and also it is so important to verify the surgical procedure : decide about graft size, usually graft size is no bigger than 8,5 mm in diameter to avoid post-keratoplasty increase in intra-ocular pressure, anterior synechiae and

vascularization. An ideal size is 7,5 mm. Smaller sizes would give rise to astigmatism due to subsequent tissue tension. Excision of donor tissue consists of trephining the corneo-scleral button previously excised from the cadaver. Trephination (cutting) is performed with the donor graft endothelial side up in a concave Teflon block. The donor button is to be 0,5 mm larger than the planned recipient opening.

For less complications, it is main important also to verify excision of recipient tissue, the size of pupils (miosed pre-keratoplasty to avoid injuring the lens and causing cataract), the sterilization process for trephination if is manual, motorized, or vacuum trephine, rapid decompression of the eye is to be avoided. Partial thickness cut is hence performed first, than full-thickness trephination is performed. Four cardinal interrupted sutures are applied at 12, 3, 6, and 9 o'clock respectively. Interrupted or running sutures are then performed. The anterior chamber volume is reformed by injecting Balanced Salt Solution (BSS). Another post-keratoplasty care treatment is: the use of topical steroids QID and Mydriatic solution BID instilled in the operated eye for the next four weeks. Topical steroids should be continued QD for 6 months, the QOD for another 6 months. Early complications include flat anterior chamber, persistent epithelial defects, and infection. Late complications include glaucoma, astigmatism, late wound separation, cystoid macular edema, and recurrence of the initial disease in the donor graft. Graft failure: Early: Cloudiness of the cornea from the first post-op day. It is usually caused by defective donor endothelium or trauma during surgery. Late: Usually the result of immune graft rejection. 50 % occur in the first 6 months, and the majority occurs in the first year post-operative.

It is equally important to know the history of allergies, systemic diseases and associations that can bring further complications in the recipient and ideally have the donor immunologic and systemic associations to verify their biocompatibility and immunological affinities between donor and receptor of the cornea. Another important issue is to verify early signs of rejection and microbiological differential diagnosis like infiltrates, edema, pain, to respond in time with the antibiotic, antifungal or antiviral indicated as appropriate in each case. Only in this way, it contributes to the success of a surgery that is vital to regain the vision and have no regrets later of rejection and putting at risk the integrity of visual health. Also, join efforts between expert around the world may compromise efforts against the rejection and the injury to prevent any complications and also to find new treatment options for actualize protocols, find new options and improve new technologies applied for medicine, engineering and new applications sciences for better quality life of patients.

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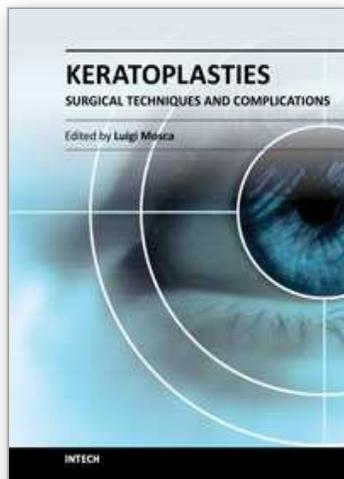
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## **Keratoplasties - Surgical techniques and complications**

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In this book, the authors illustrate different therapeutic and surgical approaches to treating various corneal pathologies. This edition in electronic format allows universal access to everybody regardless of the time of day or setting, portability, and speed of information access. Such features show more feasibility for all readers and reduce the time necessary for research. This book will be a good tool for students as well as specialists working in the field of corneal transplantation, to improve their knowledge of treatment of corneal disease.

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