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MAJOR REVIEW

Management of Corneal Perforation

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Abstract. Corneal perforation may be associated with prolapse of ocular tissue and requires prompt diagnosis and treatment. Although infectious keratitis is an important cause, corneal xerosis and collagen vascular diseases should be considered in the differential diagnosis, especially in cases that do not respond to conventional medical therapy. Although medical therapy is a useful adjunct, a surgical approach is required for most corneal perforations. Depending on the size and location of the corneal perforation, treatment options include gluing, amniotic membrane transplantation, and corneal transplantation. (**Surv Ophthalmol 56**:522–538, 2011. © 2011 Elsevier Inc. All rights reserved.)

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I. Introduction

Corneal perforation is a cause of ocular morbidity and profound visual loss.[13,119] It is the end result of various infectious and noninfectious disorders that include microbial keratitis, trauma, and immune disorders. Although of low prevalence in the developed world, it accounts for a large number of cases requiring an urgent surgical intervention in developing countries.[111,131] Eyes with corneal perforation need immediate treatment in order to preserve the anatomic integrity of the cornea and to prevent complications such as secondary glaucoma or endophthalmitis. Management of corneal perforation may range from temporary measures, such as application of bandage contact lens and gluing, to definitive treatment such as corneal transplantation.

The selection of an appropriate treatment option is mostly guided by size and location of the perforation and the status of the underlying disease.

II. Disorders Leading to Corneal Perforation

Corneal melting and subsequent perforation is a classic feature of corneal ulcers that do not respond to medical therapy. One of the most important events leading to corneal thinning and perforation is a breach in the corneal epithelium; however, a few organisms such as *Corynebacterium diphtheriae*, *Haemophilus aegyptius*, *Neisseria gonorrhoeae*, and *N. meningitidis*, and *Shigella* and *Listeria* species can penetrate an intact epithelium.[95] Occasionally, keratitis can be established

via the corneoscleral limbus by hematogenous spread. Further alterations in the basement membrane of the epithelial cells may cause persistent epithelial defects. Stromal melting by proteolytic enzymes elaborated by altered epithelial cells and polymorphonuclear leucocytes has been demonstrated in experimental animals and in vitro in human corneas.[51] Descemet's membrane is an effective barrier to microorganisms. When most of the stroma melts away, the Descemet's membrane bulges forward, forming a descemetocele. In conditions like rheumatoid arthritis, there may be altered stromal collagen that contributes to further corneal melting.

The major causes of corneal ulceration leading to corneal perforation can be broadly grouped as infectious, noninfectious (ocular surface-related and autoimmune), and traumatic.

A. INFECTIOUS CORNEAL PERFORATION

Severe and recalcitrant infectious keratitis is a common cause of corneal perforation. Whereas bacterial and fungal corneal infections are frequent in the developing world, recurrent herpetic keratitis causing stromal necrosis is the major cause of corneal perforation in developed countries.[99]

1. Bacterial Keratitis

Bacterial keratitis often produces corneal ulceration leading to corneal perforation.[4,61] Most bacteria require a break in the corneal epithelium to gain access to the corneal tissue. Once bacteria gain access, cytokines such as interleukin 1 and tumor necrosis factor (TNF) are released attracting polymorphonuclear cells. TNF induces the release of pro-inflammatory cytokines from macrophages, polymorphonuclear cells, and T-cells from the corneal epithelium and stroma. In the case of virulent organisms such as *Pseudomonas*, release of enzymes like collagenase accelerates the process of corneal perforation.[65,72,165] The stromal necrosis progresses and the infection extends deeper into the cornea, ultimately causing perforation. The native imbalance between the cytokines contributes to corneal melting even after the bacterial amplification stops.

Infection with *Pseudomonas aeruginosa* generally has a poor outcome, and corneal perforation ensues rapidly.[9,90] Various other organisms that have been isolated include *Staphylococcus* spp, *Proteus* spp, *Streptococcus pneumoniae, Moraxella* spp, and *Salmonella* spp.[22,73,110] A study from north India found that outdoor occupation, trauma with vegetative matter, central location of corneal ulcer, lack of corneal neovascularization, monotherapy with fluoroquinolone, and failure to start timely management were associated with an increased risk of corneal perforation in microbial keratitis. In that study *Staphylococcus epidermidis* was the most common microbe isolated from perforated corneal ulcers.[158]

2. Herpes Keratitis

In herpetic disease corneal perforations are caused by necrosis of corneal stroma. Although active viral replication may be present in some cases, the host immune response is believed to be the principal cause. Destruction of the corneal stroma is largely mediated by matrix metalloproteinases and collagenases from the polymorphonuclear cells and macrophages.[20,42] Recurrent infection with progressive corneal thinning further contributes to corneal perforation.[42] In necrotizing stromal keratitis, the epithelium breaks down over a dense stromal infiltrate, forming a superficial ulcer that may slowly or rapidly deepen, producing a descemetocele and subsequent corneal perforation. Close supervision is crucial because these ulcers may perforate unpredictably with too much topical corticosteroid or antiviral therapy.

3. Fungal Keratitis

Fungal keratitis is more prevalent in the developing world. The rate of progression of fungal keratitis is slow, but available antifungal therapy is not optimal, mainly due to low ocular penetration. Overall, one-third of all fungal infections require surgical intervention because of treatment failures or corneal perforations.[41] Fungi associated with corneal perforation include *Fusarium solani,*[171,172] *Aspergillus fumigatus, Penicillium citrinum, Candida albicans, Cephalosporium,* and *Curvularia*. The rate of corneal perforation in fungal keratitis ranges from 4% to 33%. Lalitha et al reported a perforation rate of 61% in cases with treatment failures (overall 19% perforation rate).[85]

B. NONINFECTIOUS CORNEAL PERFORATION

1. Ocular Surface–Related

Noninfectious corneal perforation usually occurs in diseases that adversely effect the precorneal tear film and other components of the ocular surface.

Dry eye syndrome is a major contributor to chronic epithelial defects. Corneal xerosis in conditions like keratoconjunctivitis sicca results from the depletion of goblet cells. Loss of goblet cells and accessory lacrimal glands leads to alteration of tear composition and severe dry eye. Chronic epithelial defects combined with poor healing may lead to sight-threatening infectious corneal ulceration, sterile thinning, and/or perforation. Corneal perforation has been reported to occur in Sjögren syndrome.[27]

Corneas in Sjögren syndrome are predisposed to stromal degradation, ulceration, and consequent perforation as a result of diminished tear secretion, corneal epithelial breakdown, and enzymatic degradation of collagen by inflammatory cells.[44] Other systemic conditions associated with xerosis include vitamin A deficiency, erythema multiforme, and benign mucous membrane pemphigoid.[11,23,67,133,137]

2. Autoimmune Causes

Collagen vascular diseases such as rheumatoid arthritis, systemic lupus erythematosus, temporal arteritis, Wegener granulomatosis, sarcoidosis, and inflammatory bowel disease may be associated with corneal melting.[56,121,143] Peripheral ulcerative keratitis (PUK) is a rare inflammatory disease of the peripheral cornea, usually associated with rheumatoid arthritis, that may lead to rapid perforation of the globe and visual failure.[148] Corneal melt in patients with rheumatoid arthritis heralds systemic vasculitis in more than 50% of cases, carries a high mortality, and needs early and aggressive treatment.[148] In corneas affected by PUK, a local imbalance exists between levels of a specific collagenase (MMP-1) and its tissue inhibitor (TIMP-1) that been suggested is responsible for the rapid keratolysis which is the hallmark of PUK.[127]

Severe pain and photophobia are the main symptoms of PUK. Slit lamp examination reveals a noninfiltrating ulcer near the limbus with surrounding inflammatory infiltrate and conjunctival injection. Keratoconjunctivitis sicca is common. PUK has also been described with primary Sjögren syndrome, polyarteritis nodosa, Wegener granulomatosis, and relapsing polychondritis.

A rare cause of corneal perforation, Mooren ulcer, is an idiopathic form of PUK.[101] The etiology is uncertain, and previous reports describe the presence of inflammatory cells, immunoglobulin, and increased expression of human leukocyte antigen class 2 molecules in the involved areas.[43,174] Perforation is common in the "malignant" form of Mooren ulcer, up to 36% of cases in one series.[176] Patients in whom Descemet's membrane has a minimal overlying stroma may be predisposed to perforation either spontaneously or following minor trauma.[53,171,176,177]

3. Traumatic Corneal Perforation

Corneal trauma can result from a penetrating or perforating eye injury, although an urgent surgical intervention is not always required. Eyes with previous cataract surgery and refractive surgery are more prone to corneal damage and melting following blunt trauma, especially when associated with dry eye

syndrome.[46,66,68,69,83,89,96,110,123,160] Corneal melting may also occur with chemical injuries of the eye.[8,97] Chemical burns cause extensive limbal and conjunctival cell destruction.[5] Persistent inflammation prevents epithelialization and accelerates ulceration and melting with globe perforation. Increase in the activity of the enzyme collagenase along with ischemia leads to corneal melting and is often associated with a poor prognosis.

III. Approach to Management of Corneal Perforation

A. HISTORY AND CORNEAL WORK-UP

Corneal perforation requires prompt management. Most patients with corneal perforation experience a sudden drop in visual acuity with associated ocular pain. Relevant ophthalmic history includes ocular trauma, ocular surgery, contact lens use, herpetic eye disease, dry eyes, or use of topical corticosteroids. All patients should be asked about rheumatoid arthritis, lupus, and immunosuppression as it is imperative that systemic medications be administered in the setting of systemic autoimmune disease.[143]

Care should be taken to minimize pressure on the the eye, and patients should be instructed not to squeeze their lids. Iris prolapse is diagnostic of corneal perforation. A positive Seidel test with 2% fluorescein is also conclusive (Fig. 1). The suspect area is painted with fluorescein, and the site of perforation is seen as a bright yellow spot as the dye is diluted. When the corneal perforation is small or self-sealing, gentle pressure may cause the leakage of aqueous that confirms the site of perforation (pressure Seidel test). The size and location of the perforation as well as the extent of stromal involvement are important parameters in determining management. Small corneal perforations may be amenable to conservative treatment with bandage contact lens or corneal gluing, whereas large perforations may require a primary repair or corneal transplantation in the form of patch graft or tectonic keratoplasty. Impending perforations may be heralded by folds in Descemet's membrane. Systemic antibiotics may be advised when bacterial keratitis is complicated by scleritis or there is a risk of endophthalmitis.[95] The patient should be instructed to use an eye shield.

B. LABORATORY DIAGNOSIS

In cases with concurrent keratitis, a gentle corneal scraping is required for microbiological diagnosis. This should be submitted for Gram stain, Calcofluor white preparation, chocolate agar, Sabouraud
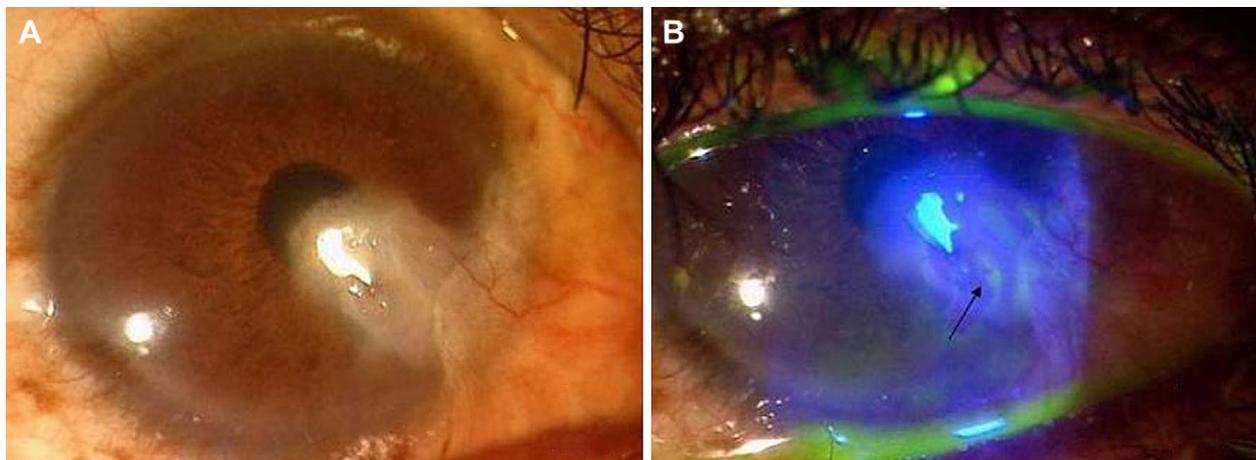
Fig. 1. Slit-lamp photograph of a corneal perforation (*A*) with a positive Seidel test (*arrow, B*).

dextrose agar, and thioglycollate broth. Calcofluor white is very useful in detecting both fungi and *Acanthamoeba*. In cases with high index of suspicion, a non-nutrient agar may be used for detection of *Acanthamoeba*. A swab is taken for the detection of herpes virus whenever applicable. In cases with contact lens–related microbial keratitis, contact lens cases and cleaning solutions may be cultured.[33] It is prudent to start antimicrobial therapy while waiting to take the patient to the operating room.

Drug sensitivity tests form an important part of laboratory evaluation. The increased recovery of staphylococcal isolates and decreased effectiveness of fluoroquinolones against these pathogens presents an important therapeutic challenge.[1,47] Methicillin resistant organisms, especially *Staphylococcus aureus*, may be encountered.[6,93]

C. SYSTEMIC WORK-UP

Cases with a history or signs of associated systemic diseases require a medical consult. Most commonly these patients have a collagen vascular disease such as rheumatoid arthritis and lupus. Adjustment in the dose of immunosuppressive agents is usually helpful as a part of overall management.

IV. Management of Corneal Perforations

A. NON-SURGICAL MANAGEMENT

1. Treating the Infectious Cause

When microbial infection is suspected as a cause of corneal perforations, rapid diagnosis and treatment are essential to increase the success of surgery. Monotherapy with fluoroquinolones has been shown to result in shorter duration of intensive therapy and shorter hospital stay when compared with traditional combined fortified therapy.[64,105,109,155] The newer generation fluoroquinolones offer enhanced transcorneal penetration without any apparent disadvantages.[30,55,79,134] The fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, have a greatly lowered resistance rate while providing better Gram-positive activity than previous-generation fluoroquinolones.[80] Several recent clinical trials have shown that their topical application is effective in the treatment of bacterial keratitis caused by commonly encountered organisms.[64,105,155] Caution should be exercised because there have been a few reports of corneal melting associated with the use of topical fluoroquinolones.[45,91] Even when the corneal perforation is suspected to be noninfectious, prophylactic topical antibiotic therapy should be given. In addition, cycloplegia is also advised to increase patient comfort and minimize inflammation and adhesions.

2. Antivirals

In cases of melting disorders suspected to be associated with herpetic stromal keratitis (HSK), acyclovir is the mainstay for treatment and prevention of recurrent herpetic eye disease.[44] Suppressive oral antiviral therapy may be beneficial in reducing the rate of recurrent herpes simplex virus epithelial keratitis and stromal keratitis.[44,163] Systemic antivirals include acyclovir, valacyclovir, and famciclovir. Topical trifluridine 1% is more commonly used in the United States, and more recently ganciclovir has been approved for the treatment of herpetic eye disease.

It is important to distinguish necrotizing and non-necrotizing stromal HSK. Necrotizing stromal disease is in part due to replicating virus in the stroma that must be adequately treated with antivirals to allow concurrent treatment with steroids in order to prevent stromal melting.[58] The Herpetic Eye Disease Study Group showed that a combination of steroid and antivirals reduces duration of herpetic stromal

keratitis.[8,170] A faster recovery and an improved outcome more often occurs with acyclovir and dilute corticosteroids than with acyclovir alone.[29,107]

If a perforation has occurred in a case of HSK, switching to oral acyclovir may be considered. Moorthy et al, however, reported no benefit of systemic acyclovir in preventing the occurrence of corneal perforation in HSK.[99]

3. Anti-glaucoma Drugs

Pharmacologic suppression of aqueous production encourages wound healing and reduces pressure that may cause extrusion of intraocular contents. If the anterior chamber is formed, anti-glaucoma medications should be considered.[18]

4. Anti-collagenases

Although collagenases have been implicated in the occurrence of corneal ulceration and thus topical and systemic collagenase inhibitors have been used by some corneal specialists as adjunctive therapy, there is no clear evidence of their clinical benefit.

Ulceration of the rabbit cornea has served as a model system to study the effects of collagenases and its inhibitors. Enzymes from the rabbit and human cornea have been seen to be inhibited by metal-binding agents of the ethylenediaminetetra-acetic acid (EDTA) type, by thiols, and by the human serum antiprotease alpha-2-macroglobulin. Thiols are thought to inhibit corneal collagenases by binding to or removing an intrinsic metal cofactor (Zn), and/or possibly by reducing one or more disulfide bonds.[16]

Calcium-EDTA, cysteine, and acetylcysteine given as eye drops are able to prevent or retard ulceration in the alkali-burned rabbit cornea. Topical acetylcysteine (more stable than cysteine) used four to six times daily may be beneficial in some patients. Both disodium edetic acid and acetylcysteine have been used to inhibit collagenase activity, particularly in *Pseudomonas* corneal infections.[72] Topical citrate has a favorable effect on the incidence of corneal ulceration and perforation after alkali burning in rabbit eyes, but the inhibition of corneal ulceration may not be related to its anti-collagenase action.[17,114]

Additional enzyme inhibitors to target the metalloproteinases are under investigation. The increased expression and elevated activity of a wide range of matrix metalloproteinases in melted corneal samples confirm that these enzymes contribute to tissue destruction.[14]

Systemic tetracyclines hasten corneal re-epithelialization in rabbits after alkali burns.[17,113] In human corneal limbal epithelium, doxycycline inhibits corneal matrix metalloproteinase activity, chelating the metal ions.[145,146] This may explain why doxycycline helps to stabilize corneal breakdown and prevent subsequent perforation.[34,36,75,94,145]

5. Anti-inflammatory Therapy

The inflammatory reaction can be as damaging to the cornea as the infection,[115] and judicious use of topical steroids may be beneficial in the management of bacterial keratitis. The organism and sensitivities should be known before starting steroid treatment after 2–5 days of appropriate antibiotic treatment.[26] If the chosen antibiotic is effective against the organism, then the concurrent use of steroids will not inhibit the bactericidal effect of the antibiotic.[39,149]

Steroids should not be used in the initial treatment of posttraumatic and contact lens–related ulcers, in part because they may be fungal. Also, if a perforation is suspected to be related to HSK, the use of corticosteroids is best avoided. If steroids are given, the smallest possible dose in conjunction with an antiviral agent should be used. The overuse of antiviral agents and or antibiotics will inhibit re-epithelization. Steroids are generally avoided in cases of exposure, neurotrophic keratitis, or dry eyes. In more advanced conditions, medroxyprogesterone acetate 1% may be considered as it does not inhibit collagen synthesis, partly related to its suppressive effects on the production of tissue collagenase.[102]

a. Use of Steroid-sparing Agents

Systemic immunosuppressive medication may be beneficial in unresponsive severe noninfectious corneal inflammatory disease or to prevent post-operative corneal melting syndromes.[10,37] It is important that these patients be co-managed by a medical physician who understands the process of keratolysis. Immunosupressive drugs have significant adverse effects, including bone marrow suppression, and inappropriate use or dosages can be devastating.

Cyclosporine (CSA) is a specific modulator of T-cell function and an agent that depresses cell-mediated immune responses. It binds to cyclophilin, an intracellular protein, which in turn prevents formation of interleukin-2 and the subsequent recruitment of activated T-cells.[131] Oral and topical CSA (1% or 2%) can be tried in melting stromal ulcers and post-operative corneal melts.[49,153] Oral CSA has been used, with apparent efficacy, to treat corneal melting syndromes such as Mooren ulcer and that associated with Wegener granulomatosis.[10,81]

A recent development in immunosuppression involves inhibition of various effector cells, targeting

cell products such as cytokines or their receptors.[98] Rituximab, a chimeric monoclonal antibody against B-cells has been used in peripheral ulcerative keratitis associated with Wegener granulomatosis.[63] Infliximab, a monoclonal antibody directed against TNF-α has been used found to be effective in rapidly arresting the progression of a sterile PUK in rheumatoid arthritis.[106,156]

6. Optimizing Epithelial Healing

Maintenance of the tear film is important for epithelial healing. This can be achieved by replenishing the eye's moisture with preservative-free artificial tears and ointment and by delaying evaporation. Punctal or intracanalicular plugs prevent drainage of the tear film and maximize its contact duration with the ocular surface.[7] These can reduce dependency on tear supplements in patients with dry eye.[15] In cases of dry eyes, patients with punctal occlusion may benefit from adjunctive topical cyclosporine A.[128] In addition to preservative-free tear and ointment supplements and topical cyclosporine, autologous serum drops have been applied in cases of persistent epithelial defects and keratoconjunctivitis sicca with some success.[117,175]

Whenever possible, preservative-free topical medications are preferred. Preservatives such as benzalkonium chloride, thimerosal, and EDTA have been shown to retard epithelial healing of cornea in animal models.[28,57]

In cases of small corneal perforations and progressive melting, soft contact lenses may be helpful. A hydrophilic bandage contact lens is used to promote epithelial resurfacing and to reduce patient discomfort. Injuries may seal with a large soft contact lens. After 48 hours persistent leakage can often be assessed by gently sliding the lens to the side.[70]

B. SURGICAL MANAGEMENT

1. Corneal Gluing

a. Cyanoacrylate Glue

Cyanoacrylate glue, in use since the late 1960s,[167] is highly effective, easy to use, and can delay the need for urgent corneal transplantation. The use of cyanoacrylate glue has been associated with lower enucleation rate and better visual results.[61] In high-risk perforations (e.g., those associated with infection or trauma) the delay in penetrating keratoplasty with the use of corneal glue usually leads to better outcomes. Gluing is advocated in any noninfected, progressive corneal thinning disorder before perforation. In such cases, not only has gluing been showed to arrest the thinning process, but application is also easier in a nonperforated eye.[71]

The goal of tissue glues is to urgently restore the tectonic integrity of the globe with the understanding that a more definitive procedure may be required at a later stage. Corneal gluing is not a panacea for all types of corneal perforations. In a study of perforations and descemetoceles in 44 eyes by Leahy et al, only 32% of eyes required no further treatment after application of tissue adhesive. A corneal transplantation had to be performed in nearly half (45%) of the eyes after gluing.[86]

Cyanoacrylate adhesive works best for small (<3 mm) concave central defects.[50,74,142] In peripheral ulcers the glue can easily dislodge as it does not adhere well to conjunctiva. Cyanoacrylate glue prevents re-epithelialization into the zone of damaged and naked corneal stroma in cases with infective keratitis and thus prevents the development of the critical setting for corneal melting via the production of collagenase enzymes. Interruption of the melting process is most successful when applied early in the course before overwhelming numbers of polymorphonuclear neutrophils have accumulated.

Available preparations of corneal glue for clinical use include the following:

- Indermil (butyl-2-cyanoacrylate; Sherwood, Davis and Geck, St Louis, MO, USA)
- Histoacryl (butyl-2-cyanoacrylate; BBraun, Melsungen, Germany)
- Histoacryl Blue (N-butyl-2-cyanoacrylate; BBraun)
- Nexacryl (N-butyl-cyanoacrylate; Closure Medical, Raleigh, NC, USA)
- Dermabond (2-octyl-cyanoacrylate; Closure Medical)

Histoacryl glue D-3508 and isobutyl-2-cyanoacrylate are the two most commonly used tissue adhesives.[126] Dermabond (2-octyl-cyanoacrylate) is also used successfully for skin and cornea adhesion.[154] Commercially available "super glue" (methyl-2-cyanoacrylate) has also been used, but appears to be more toxic than the other acrylate derivatives.

b. Surgical Techniques for Corneal Gluing

Glue should be applied with the smallest amount possible in a controlled manner, avoiding excessive spillage. Fogle et al demonstrated that direct early application of cyanoacrylate adhesive to the ulcer bed and adjacent basement membrane plus a bandage contact lens was effective in the interruption of progressive corneal stromal melting related to herpes simplex, keratoconjunctivitis sicca, alkali burns, radiation keratitis, rheumatoid arthritis and Stevens-Johnson syndrome.[40] Moschos et al created a mesh with 10-0 nylon sutures at the site of corneal perforation before the application of glue.[100]

We prefer to use an operating microscope in a sterile environment. A 2-mm dermatological punch is first used to trephine a single disc from a sterile disposable drape. A small amount of sterile ophthalmic ointment is placed on the flat end of a cotton-tipped applicator, and the disc is then stuck onto the ointment and placed aside. A few drops of topical anesthesia are applied to both eyes. A non-compressing lid speculum (e.g., Jaffe) is used to separate the lids. The perforation site is inspected, and loose epithelium and necrotic tissue are removed carefully. Epithelium 1–2 mm surrounding the ulcer is removed as well as any vitreous, foreign matter, or lens material. After debridement the perforation site should be as dry as possible, otherwise the glue will not stick. If the anterior chamber is totally flat a small amount of air or viscoelastic may be injected to form the chamber to avoid incarceration of iris or other tissue to the adhesive. One drop of adhesive is then applied to the 2-mm trephine drape, and with further drying, the adhesive is directly applied to the area of perforation. The polymerization process will take place in several minutes. If a small leak remains, additional applications adjacent to the existing plug may be needed or the initial plug can be simply removed and reapplied. Multiple re-applications are not recommended because this will enlarge the defect. After solidification the area should be inspected and dried examining for further leaks and a bandage contact lens applied. The patient should be examined a few minutes later to ensure the glue/disc contact lens complex has not moved and the anterior chamber is deepening, and then an hour later to look for further deepening.

The postoperative treatment includes topical antibiotic therapy and an aqueous suppressant. A protective shield should be placed. In cases of infectious perforations, patients should continue their medications. Ideally the glue should remain in position for as long as possible, but careful monitoring is required because the risk of glue dislodgement and re-perforation is high.

c. Cyanoacrylate Glue: Outcomes and Complications

Application of cynoacrylate glue allows timely management of small corneal perforations with a good outcome. Several studies have shown a clear benefit of the early use of cyanoacrylate glue.[86,168] Hirst et al have shown improved visual outcomes with reduced enucleation rate (6%vs 19%).[62] Corneal glue has been found to be advantageous in cases with frank as well as impending perforations. Successful corneal gluing may obviate the need for other surgical treatment. Forty-four percent of the cases

in a series by Weiss et al[168] and 32% of cases in another study by Leahey et al[86] did not require any further intervention. Treatment with corneal gluing alone has been shown to be definitive in as many as 86% of cases.[138]

In cases that are refractory to corneal gluing, either a repeat gluing can be performed or, in severe cases, an urgent corneal transplantation undertaken to preserve the integrity of the globe. Lekskul et al used Histoacryl glue in 15 eyes with non-traumatic corneal perforations.[87] Overall, 53% had to be reglued for recurrent leaks or glue dislodgment within several days, and 7% needed a penetrating keratoplasty for refractory leaking.[87] Moorthy et al evaluated the success of cyanoacrylate tissue adhesive in the management of corneal perforations associated with herpetic keratitis. Glue application could heal corneal perforations in only 37% of eyes. More than 30% of eyes required multiple applications of tissue adhesive and a therapeutic keratoplasty had to be performed in 57%.[99]

Complications arise from the tissue adhesive or from the original perforation and include cataract formation, worsening of infectious keratitis,[138] granulomatous keratitis, glaucoma,[86] papillary conjunctivitis,[19] and symblepharon formation.[168]

d. Fibrin Glue

Fibrin tissue adhesives offer several advantages over cyanoacrylate-based tissue adhesives in that they solidify quickly, apply easily, and cause less discomfort.[138] Similar to cyanoacrylate glue, fibrin glue has been successfully used in cases with impending as well as frank corneal perforations.[84] Bernauer et al employed fibrin glue in cases with corneal perforations related to rheumatoid arthritis and achieved a successful outcome in 84%.[10]

The main disadvantage of biological glues is that they start to degrade much faster than cyanoacrylate, have no bacteriostatic effects (like cyanoacrylate), and there is a risk of transmission of prion/viral diseases with the use of bovine products in its constituents.[21,38,84,144,169] Currently most corneal surgeons use fibrin glue mainly to secure amniotic membrane grafts.[74]

2. Conjunctival Flaps

Conjunctival flaps are used in cases with indolent progression and corneal thinning.[48,52] A conjunctival flap brings in superficial blood vessels to promote healing of corneal ulcers therefore preventing the occurrence of corneal perforation. The flaps also control pain, eliminate the use of frequent medications, and may provide an alternative to invasive surgery.[2,51,52,130] A conjunctival flap is not appropriate

for active suppurative keratitis with marked stromal thinning[92] or in eyes with frank perforation because the leak will continue under the flap. A modified conjunctival flap procedure, referred to as superior forniceal conjunctival advancement pedicle, has been described.[132]

3. Amniotic Membrane Transplantation and Its Variants

Amniotic membrane transplantation (AMT) is used as a treatment for corneal perforation to restore corneal stromal thickness so that urgent penetrating keratoplasty can be avoided.[120] AMT is a good alternative to penetrating keratoplasty, especially in acute cases in which graft rejection risk is high.[129] Amniotic membrane patches can be secured over the perforation with either sutures or glue.[150] Both cyanoacrylate and fibrin glue have been used, but fibrin glue allows sealing of larger perforations and gives better results.[35,58] A single layer or a multilayered amniotic membrane (AM) may be used depending on the depth of involvement (Fig. 2). A single-layered AMT is done in cases of persistent epithelial defects, and a multilayered AMT is done in cases of associated corneal thinning or corneal melts.[54,120]

Amniotic membrane can successfully treat a refractory corneal epithelial defect by promoting epithelial healing and thus prevent corneal perforation. Rodríguez-Ares et al reported successful multilayered amniotic membrane transplantation in 73% of cases and concluded that multilayered AMT was effective for treating corneal perforations with diameter < 1.5 mm.[129]

Hick et al evaluated the efficacy of amniotic membrane with fibrin glue in corneal perforations refractory to conventional treatment. Overall
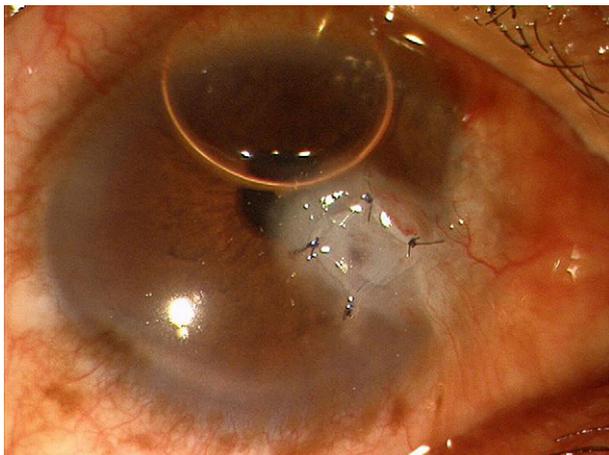

Fig. 2. Slit-lamp photograph of repaired corneal perforation with amniotic membrane graft.

success was observed in 80% (27/33 eyes) of cases. Grafts with fibrin sealant demonstrated a better success rate compared with grafts secured with sutures (92.9% vs 73.7%). In patients with severe limbal damage, a success rate of only 20% (1/5) was observed. These techniques lead to rapid reconstruction of the corneal surface and can give a good final functional result or allow keratoplasty to be done under more favorable conditions.[59]

a. Hyperdry Amniotic Membrane Patching Attached Using a Tissue Adhesive

A hyperdry amniotic membrane with tissue adhesive or a fibrin glue–assisted augmented amniotic membrane may be used to seal corneal perforations. Kitagawa et al used hyperdry amniotic membrane and a tissue adhesive for corneal perforations. In three eyes, corneal perforations were treated with a single-layer patch of dried AM using a biological tissue adhesive. The dried AM was prepared with consecutive far-infrared rays and microwaves (hyperdry method) and was sterilized by gamma-ray irradiation. This was then cut to the desired size and shape, and the tissue adhesive was applied to the amniotic epithelial side of the dried membrane. After this, the dried membrane with glue was applied to the site of corneal perforation lesion using forceps.[77]

b. Fibrin Glue–Assisted Augmented Amniotic Membrane Transplantation

Kim et al analyzed the efficacy of fibrin glue–assisted augmented amniotic membrane transplantation in 10 patients with corneal perforations more than 2 mm in greatest dimension. A 5- or 7-ply augmented amniotic membrane was constructed by applying fibrin glue to each sheet of AM to repair the corneal perforation. The augmented AM was designed 0.5 mm larger than the diameter of the perforation and was transplanted onto the perforation site with 10-0 nylon suture. If needed, additional overlay AM was sutured on top. The mean ulceration diameter was 2.7 ± 0.95 mm (range, 2–5 mm). All had well-formed deep anterior chambers, and 90% completely epithelialized over the AM. No eyes showed evidence of infection or recurrent corneal melting during the follow-up period.[74]

4. Corneal Transplantation

A large corneal perforation (≥ 3 mm diameter) is not amenable to corneal gluing and requires therapeutic keratoplasty along with management of the underlying condition. Depending on the size

of the perforation, a small diameter patch graft or large diameter keratoplasty is performed, either full thickness or lamellar depending on the depth of involvement.[31,32,104,122,124,139,147,166] In a case with infectious corneal perforation, therapeutic keratoplasty also replaces the infected cornea and reduces the infective load (Fig. 3).

When the perforations are not too large, a small tectonic corneal transplantation preserves the integrity of the globe. Tectonic grafts, also called patch grafts, are either lamellar or perforating, and cover corneal stromal defects, restoring the structure of the cornea or sclera. Patch grafts can be used temporarily for central corneal perforations (for future optical penetrating keratoplasty) or permanently to repair peripheral perforations and descemetoceles.

a. Surgical Technique

The timing of corneal grafting can depend on the etiology of the perforation. In some cases with infectious keratitis with coexisting corneal perforation, temporary management with corneal gluing can be tried while intensive antimicrobial treatment is being used in order to control the infection. Another technique described by Kobayashi et al employs the use of custom designed hard contact lens along with ethyl-2-cyanoacrylate adhesive. A penetrating keratoplasty is performed after the anterior chamber stabilizes.[78]

Surgical manipulation, especially mechanical trephination with a free-hand trephine or with suction trephines, is challenging to perform during tectonic penetrating keratoplasty as there is a risk of extrusion of intraocular contents. The ocular surface is marked with a trephine followed by free-hand cutting starting through the perforation. Use of excimer laser trephination has also been described in order to obtain customized cuts.[82]

Delay in performing therapeutic corneal transplant may be advantageous in some cases with fulminant corneal infections. Nobe et al have reported that if penetrating keratoplasties were performed for infectious corneal perforation, grafts had a better chance to remain clear if surgery could be delayed for some time (2–5 days).[103] However, if the surgeon feels that medical management or corneal gluing won't stop the aqueous leak from the site of perforation, a tectonic patch graft or large therapeutic graft should be performed at the earliest time possible. In cases with posttraumatic corneal perforation, primary closure should occur as soon as possible in order to prevent the development of ocular infection. In large posttraumatic perforations that may not be amenable to primary closure, standby donor corneal tissue must be made available in case a need for tectonic graft arises during the surgery.

In some cases with long-standing perforated corneal ulcers, the iris tissue plugs the perforated cornea with overlying epithelialization. This may be particularly common in the developing world where patients present late. Routine therapeutic keratoplasty in such cases leads to mechanical damage to the iris, resulting in severe bleeding and large surgical coloboma during the removal of the host corneal button. Vajpayee et al have described a technique of "layer-by-layer" keratoplasty for the effective management of such cases. A preliminary lamellar separation is performed in order to excise the superficial portion of the corneal button thereby reducing the bulk of the corneal tissue.[162]

Other variations of therapeutic keratoplasty have been described such as the use of a corneal allograft combined with relocation of a crescent of autologous corneal tissue.[24] This technique may be useful in corneal perforations sparing a healthy portion of the cornea that can be relocated in between the allograft
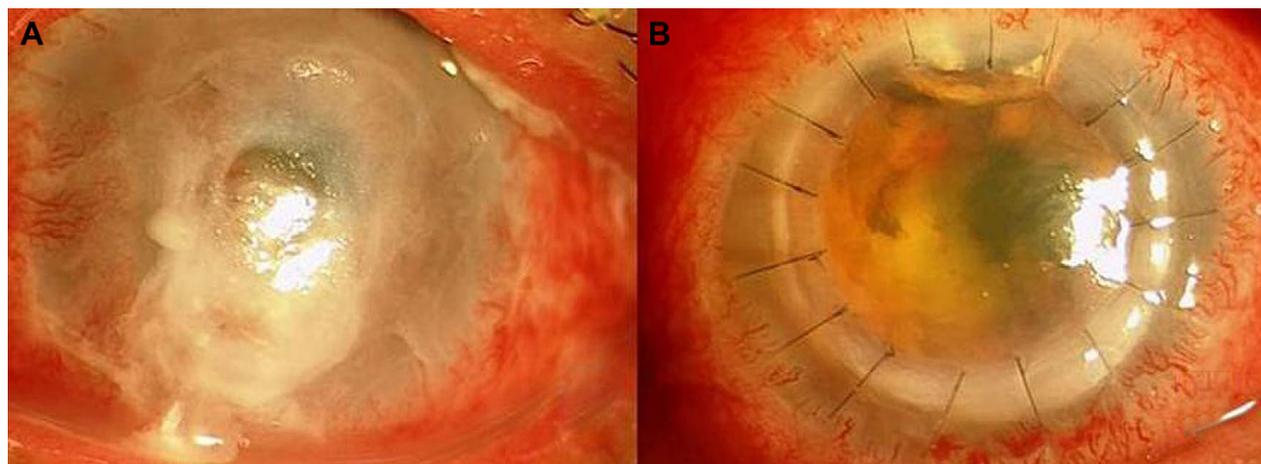

Fig. 3.   Slit-lamp photograph showing corneal melting (*A*) and postoperative photograph after therapeutic keratoplasty (*B*).

and the recipient bed. The chances of an immunologic rejection are theoretically lessened by intercalating a crescent of autologous tissue between the allograft and the limbal vessels. Also, the combination of an allograft with a crescent of autologous corneal tissue minimizes the disadvantages associated with eccentric or oversized trephination.[24]

b. Corneal Patch Grafts

Tectonic grafting is best suitable for cases with peripheral corneal perforations and descemetoceles (Fig. 4). It effectively restores the integrity of the eye and allows acceptable visual rehabilitation.[164] Traditionally, corneas preserved in media such as McCarey Kaufman or Optisol are used for these procedures; however, for tectonic purposes even glycerin-preserved corneas may be maintain the integrity of the globe. Yao et al used cryopreserved corneas in 45 patients with corneal perforations secondary to severe fungal keratitis. Infection was successfully eradicated in 87% of cases, and about 50% of cases received subsequent optical keratoplasty. The rate of corneal allograft rejection was reported to be very low (<4%), thereby offering a major advantage over conventional therapeutic keratoplasty.[173] Shi et al reported no allograft rejection in a series of 15 eyes with therapeutic keratoplasty performed using cryopreserved corneal tissues.[140]

Utine et al described the use of gamma-irradiated corneal tissue for management of partial-thickness corneal defects.[161] The tissues (VisionGraft Sterile Cornea) selected for processing include tissues that are not suitable for penetrating keratoplasty, but have clear and uncompromised stroma. They have
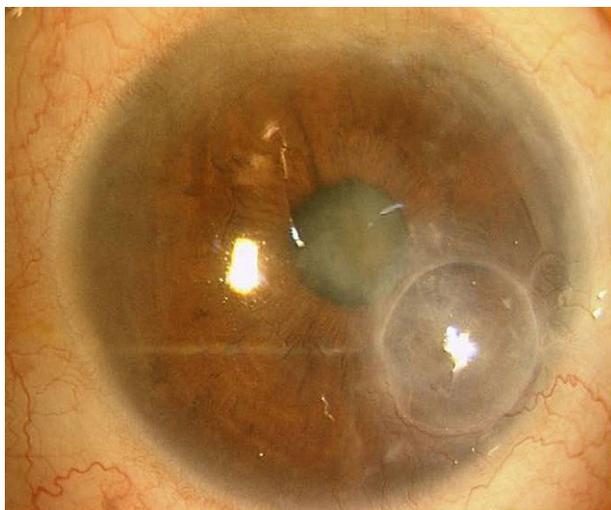

Fig. 4. Slit-lamp photograph showing operated therapeutic patch graft in a case with corneal perforation.

a shelf life of 1 year at room temperature and are available in customized shape and size.[161] Utine et al proposed that these corneas should be considered in lieu of fresh donor corneas or cryopreserved or glycerin-preserved tissues for corneal patch grafts because of easy availability, lack of immunogenicity, and decreased risk of infection.

c. Lamellar Keratoplasty

Lamellar keratoplasty is used as a tectonic measure to patch the cornea in cases corneal perforations or descemetoceles[141] and is preferred over a full-thickness graft because the latter will often lead to immunological rejection or endothelial decompensation. Lamellar keratoplasty, however, also has disadvantages such as occurrence of intralamellar neovascularization or incomplete removal of pathogens in the case of deep infectious ulcers. Lamellar corneal transplantation can be performed as deep lamellar crescentic lamellar or epikeratoplasty.[11]

i. Deep Lamellar Keratoplasty. The advantages of lamellar keratoplasty over a full thickness graft include absence of endothelial rejection as well as potential intraocular complications.[3] A superficial or deep lamellar keratoplasty may be performed depending upon the depth and severity of the corneal pathology. It is also possible to achieve complete eradication of corneal infection especially when using the big bubble deep anterior lamellar keratoplasty technique. However, it may be difficult to use the big bubble technique in cases with frank perforations. Instead, a manual superficial lamellar keratoplasty may be performed successfully (Fig. 5). In cases with descemetoceles a careful separation of the overlying corneal stroma can be achieved with balanced salt solution or viscoelastic, therefore baring the Descemet's membrane. In cases with deep suppurative lesions it is very important to irrigate the recipient bed with antibacterials or antifungals to decrease the load of organisms before suturing the corneal graft. Amebicidal drugs should be avoided in such scenarios due to their potential endothelial toxicity.

Another advantage of using lamellar technique is reduction in the chance of intraocular spread of infection, especially in cases of recurrent infection. Anshu et al reported 50% incidence of endophthalmitis in cases of recurrent infection after therapeutic penetrating keratoplasty in contrast to no cases of endophthalmitis in the therapeutic deep lamellar keratoplasty group.[3]

In order to circumvent the difficulties in dissection during deep lamellar keratoplasty, Por et al used intracameral injection of fibrin glue (Tisseel VH; Baxter Healthcare Corp, Deerfield, IL, USA).
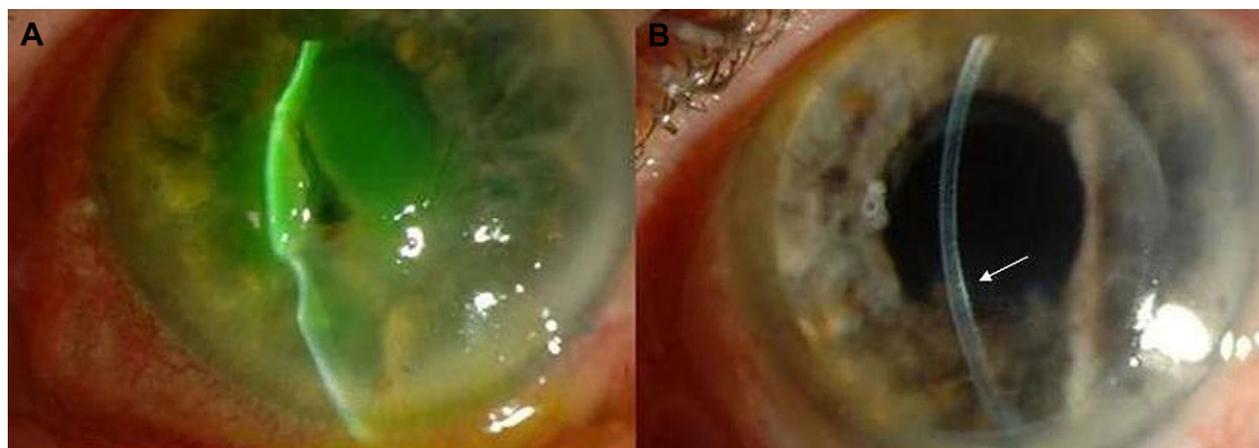
Fig. 5. Slit-lamp photograph showing a central corneal perforation (*A*) and postoperative picture after a deep lamellar keratoplasty (*B*). Arrow represents the site of rupture of Descemet's membrane.

In corneal perforations up to 4 mm in greatest dimension, the defect is sealed externally with cyanoacrylate adhesive or fibrin sealant. An air bubble is then injected into the anterior chamber, followed by intracameral Tisseel fibrin sealant. Subsequently a manual deep lamellar keratoplasty is performed.[118] Because fibrin sealant is a biological, it resorbs completely in a few days.

Deep lamellar keratoplasty has been successfully performed with corneal melting secondary to gonococcal ocular infection.[12,141,159] In these cases a gentle exposure of deep corneal stroma is achieved using a hydrodissection approach rather than using the big bubble technique. In a series of 92 eyes undergoing therapeutic corneal transplantation, Ti et al performed lamellar keratoplasty in 12 eyes with corneal stromal suppurations and descemetoceles.[157] Irrigation of the corneal bed was done with antibacterial or antifungal drugs after stromal dissection before suturing the graft.

ii. Crescentic Lamellar Keratoplasty. Crescentic lamellar keratoplasty has been described in the past for cases with corneal perforation associated with pellucid marginal degeneration.[125,135,136,152] Parmar et al performed biconvex and crescentic grafts in eight eyes with peripheral infected corneal ulcer, rheumatoid arthritis–associated peripheral corneal melt, and Mooren ulcer. Both tectonic and visual results were encouraging in all cases included in this retrospective review.[112]

The advantages of small eccentric grafts over large grafts include lower risks of graft rejection, peripheral anterior synechiae formation, and secondary glaucoma. A good visual acuity may be achieved despite graft failure because of eccentric location. Furthermore, a future optical penetrating keratoplasty is not precluded. Although the technique of shaped eccentric grafting in peripheral corneal

disorders is technically challenging, surgical outcomes are good.

d. Tectonic Epikeratoplasty

During tectonic epikeratoplasty (TEK), a glycerine-preserved corneal button is used to seal the perforation. A 360-degree peritomy is performed, and the graft is sutured to the recipient sclera upon the melted cornea with silk sutures. The graft is left in place for a few weeks to allow complete healing of the perforated cornea. Lifshitz et al have reported good outcomes after TEK performed in six eyes with frank, and three eyes with impending, perforations secondary to ocular surface diseases, including Steven-Johnson syndrome, dry eye, relapsing herpetic keratitis, posttraumatic corneal thinning, and local anesthetic abuse.[88]

TEK is a viable surgical option in cases with large corneal perforations. Although it is considered a temporizing measure, it may obviate the need for a subsequent corneal transplantation in a few cases. There is a potential risk of epithelial downgrowth, however, because of the presence of epithelium in the perforation bed with an overlying graft.

e. Outcomes and Prognosis

The outcome and prognosis of keratoplasty depends on the etiology, site, and size of the perforations. Therapeutic keratoplasties performed for infectious conditions carry a better prognosis as compared to those performed for immunologic conditions like corneal melting secondary to ocular pemphigoid, both in terms of visual gain and graft survivals.[25] The postoperative course is complicated by various factors affecting the ocular surface. The type of surgical procedure, the predominant

pathogenic mechanism, and the perioperative immune status influence the outcome. The control of corneal melting and the prevention of surface infection are critical for graft survival.[10] Killingsworth et al reported that in patients with severe keratoconjunctivitis sicca, although anatomical success was achieved in 83% of eyes, all grafts failed.[73] Pleyer et al performed therapeutic keratoplasty in 16 eyes with corneal perforations or descemetoceles secondary to rheumatoid arthritis. Anatomical success could be achieved in all eyes. Postoperative complications included epithelial keratopathy (50%), corneal ulceration (31%), fistulation (25%), loose sutures (25%), and graft rejection (13%). Regrafts were required in 31% of eyes because of recurrence of corneal melting or persistent deep stromal defects.[116] In a similar review by Palay et al, of cases with corneal perforations secondary to rheumatoid arthritis that underwent an urgent keratoplasty, 52% required repeat penetrating keratoplasties.[108]

f. Complications

Performing corneal transplantation on an inflamed eye along with a disrupted blood–aqueous barrier is not only challenging, but also is associated with a high rate of intraoperative as well as postoperative complications.[60,76] The incidence of postoperative complications such as allograft corneal graft rejection and high intraocular pressure is higher in penetrating keratoplasty when compared to lamellar.[171] Besides, there is always a risk of recurrence of infection, more common after fungal keratitis than bacterial keratitis.[171]

Although there is no endothelial graft rejection after lamellar corneal transplant, there is a potential risk of leaving the infection in the deeper corneal layers. This is especially important in cases with deep corneal infiltrates and coexisting corneal perforations. In such cases, careful deep corneal dissection may be helpful in eradicating the corneal infection. Also, as mentioned previously, irrigating the corneal bed with antibacterial or antifungal drugs may be useful in decreasing the load of infectious organisms before suturing of the donor graft.

Xie et al evaluated the complications and therapeutic effects of penetrating keratoplasty in the treatment of corneal perforations in fungal keratitis in 52 eyes. The complications reported were graft rejection (38.5%), recurrence of infection (15.4%), complicated cataract (19.2%,) and secondary glaucoma (13.5%).[171] Sukhija et al found glaucoma to be the most common complication after therapeutic corneal transplantation, occurring in 22% of eyes with presurgical perforated ulcers.[151]

V. Conclusion

Corneal perforation results from a variety of infectious and noninfectious disorders and requires prompt management. Successful medical and surgical treatment also rely upon control of ocular surface disease, neurotrophic factors, and systemic autoimmune conditions when present. Although small perforations respond reasonably well to corneal gluing techniques, peripheral perforations can be best managed with a partial conjunctival flap or tectonic keratoplasty. Large perforations and those unresponsive to other measures may need urgent corneal transplantation.

VI. Method of Literature Search

PubMed was queried with combinations not limited to the following search terms: *corneal perforation, corneal gluing, corneal transplantation, management, keratoplasty, therapeutic keratoplasty,* and *epidemiology*. A review of the search results was performed and relevant articles to the topics of clinical manifestations and treatment were included. Relevant articles to the management of corneal perforations in various conditions were also included. Case reports without additional value over another report of the same condition were not included. References related to pathogenesis and treatments were selected by the authors.

VII. Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Outline

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