Acute corneal hydrops is an incompletely understood complication of keratoconus, characterized by marked corneal edema caused by a break in Descemet membrane, allowing aqueous to enter the corneal stroma and epithelium. Although usually self-limiting, with clinical signs of edema typically resolving after 3 months, it often leaves a vision-impairing scar, necessitating and expediting the need for corneal transplantation. Studies have identified risk factors for developing acute hydrops. Modern imaging modalities such as ultrasound biomicroscopy, anterior segment optical coherence tomography, and in vivo confocal microscopy have enlightened us to the microstructural changes that take place during acute hydrops, the factors that influence its duration, and sequelae. Newer treatment regimens have seen a reduction in the duration of corneal edema during acute hydrops, and have improved the survival of corneal grafts after transplantation for resolved hydrops.

Potential conflict of interest: None.

Accepted for publication Jan 21, 2014.
From the Department of Ophthalmology, New Zealand National Eye Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand.
Inquiries to Professor Charles N.J. McGhee, Department of Ophthalmology, New Zealand National Eye Centre, Private Bag 92019, University of Auckland, Auckland, New Zealand; e-mail: c.mcghee@auckland.ac.nz
http://dx.doi.org/10.1016/j.ajo.2014.01.017
© 2014 by Elsevier Inc. All rights reserved.
insertion of $\text{C}_3\text{F}_8$ can hasten the first step but not the second.

Although acute hydrops is usually self-limiting and clinical signs of edema typically resolve after 2-4 months,\textsuperscript{9,10} it often leaves a vision-impairing scar (Figure 2), necessitating and expediting the need for corneal transplantation. In some cases, corneal neovascularization may occur (Figure 2, arrow), and this has significant implications for the patient’s future management and prognosis. Previous studies suggest that edema near the limbus and intrastromal cleft formation in cases of acute corneal hydrops may be considered risk factors for stromal neovascularization. Any associated inflammatory response, which may be greater in patients with atopy, has also been suggested as a potential stimulus to neovascularization.\textsuperscript{11}

**EPIDEMIOLOGY AND RISK FACTORS**

The prevalence of keratoconus has been reported to vary in different studies internationally, from 8.8-54.4 per 100 000.\textsuperscript{12} Corneal hydrops is relatively uncommon and is estimated to occur in 2.6%-2.8% of patients with keratoconus.\textsuperscript{13,14} Interestingly, the mean age of onset of corneal hydrops is similar across studies, typically around 25 years of age, with a male preponderance.\textsuperscript{13,15}

Although an ethnic variation in prevalence of keratoconus is well established, few studies have specifically identified ethnic associations with the development of acute hydrops in keratoconus. In a recent study from New Zealand, where keratoconus is the most common indication for corneal transplantation,\textsuperscript{16} the authors noted that Pacific ethnicity is strongly associated with the development of acute hydrops, whereas New Zealand European ethnicity is negatively associated with hydrops development.\textsuperscript{15}

Although other risk factors have been identified in several studies, owing to the relatively small numbers of subjects in most studies it is difficult to isolate the risk factors of hydrops from those risk factors for keratoconus per se. However, 2 retrospective reviews attempted to determine the clinical factors associated with the development of acute hydrops, and each study included over 100 patients. Tuft and associates\textsuperscript{13} identified earlier age of diagnosis, steeper keratometry, and poorer Snellen visual acuity at the time of diagnosis of keratoconus to be strongly associated with subsequent development of corneal hydrops. Corneal hydrops also developed at a greater rate in eyes with severe allergic eye disease. Fan Gaskin and associates\textsuperscript{15} also identified poorer visual acuity at first presentation to the tertiary referral center for keratoconus to be associated with subsequent hydrops development. A history of eye rubbing was also associated with hydrops development—indeed, a history of atopy and contact lens wear (which were not associated with greater likelihood of hydrops). Somewhat paradoxically, subjects who develop hydrops were found to be less likely to have a family history of keratoconus in this study.\textsuperscript{15}

**NATURAL HISTORY OF CORNEAL HYDROPS**

After the rupture of Descemet membrane, it may retract and curl anteriorly to form scrolls, ridges, or strands around attached fragments of stroma.\textsuperscript{7} This is thought to be the reason why acute hydrops takes longer to resolve than localized corneal edema caused by a breach of Descemet membrane during cataract surgery on a keratoconic eye.\textsuperscript{17}

The onset of acute hydrops is usually heralded by marked epiphora, followed by intense photophobia and pain, associated with markedly reduced visual acuity. Most cases of acute corneal hydrops resolve spontaneously over 2-4 months\textsuperscript{9,10} as the adjacent endothelial cells enlarge and migrate to cover the defect.\textsuperscript{18} Secondary flattening of the cornea may facilitate improved contact lens fitting, but central corneal scarring typically mandates corneal transplantation to restore visual function.

Unsurprisingly, greater area of corneal involvement by hydrops corresponds to a longer duration for the edema to resolve, increased risk of neovascularization, and ultimately a poorer visual outcome.\textsuperscript{19} Other complications of acute hydrops include infection, pseudocyst formation, malignant glaucoma, and corneal perforation.\textsuperscript{4,13} A history of hydrops may also predispose patients to greater likelihood of episodes of endothelial graft rejection after penetrating keratoplasty.\textsuperscript{13,20}

![Figure 1. Anterior segment photograph demonstrating severe acute corneal hydrops in a patient with keratoconus. Extensive corneal edema with epithelial bullae is visible and a vertical defect in Descemet membrane is present in the central cornea.](image-url)
IMAGING OF CORNEAL HYDROPS

TRADITIONAL MODALITIES OF ANTERIOR SEGMENT IMAGING in corneal ectasia can be problematic in acute hydrops owing to the difficulty of imaging through an edematous cornea. The advent of ultrasound biomicroscopy (UBM), anterior segment optical coherence tomography (AS-OCT) (Figure 3), and in vivo confocal microscopy (IVCM) (Figure 4) has revealed some of the ultrastructural changes that occur during acute hydrops in vivo.8,10,17,21 Previously such ultrastructural changes could only be extrapolated from ex vivo observations on “resolved” tissue—obtained following corneal transplantation. These new technologies have also improved our ability to predict duration of edema and likelihood of neovascularization and to monitor response to therapy.8,9,17,21

An ultrasound biomicroscopy study has confirmed that intrastromal edema is directly related to rupture of Descemet membrane. Direct visualization of Descemet tear revealed areas of deficiency under the location of maximum stromal edema.21 In the same study, following intracameral C3F8 at week zero, ultrasound biomicroscopy demonstrated a complete unrolling and reapposition of Descemet membrane to the corneal stroma by 3 weeks, with complete resolution of edema in 92.3% of cases by 6 weeks.

In a similar study, Nakagawa and associates assessed a series of 13 consecutive hydrops corneas with ultrasound biomicroscopy and discovered that not only was rupture of Descemet membrane identified in all eyes, but all eyes also exhibited intrastromal clefts.17 In 11 of 13 eyes the clefts were connected with the anterior chamber on the ultrasound biomicroscopy images. The authors hypothesized that severe corneal edema results from the presence of intrastromal clefts by increasing the surface area exposed to the anterior chamber. The gap between Descemet membrane and the stroma may also delay the closure of Descemet membrane and ultimately the resolution of corneal edema.

Basu and associates8 examined 24 eyes with acute hydrops with anterior segment optical coherence tomography and published a retrospective study assessing the serial observations throughout the duration of hydrops. Interestingly, they identified 3 patterns of Descemet membrane appearance during acute hydrops on anterior segment optical coherence tomography: detachment with break and rolled ends, detachment with break and flat ends, and detachment with no break. However, they acknowledged that because anterior segment optical coherence tomography scans are taken at 45-degree intervals, a small planar break could have been missed, as detachment without break would question our present understanding of the mechanism of hydrops development. This study revealed that, without intervention, not only is the duration of edema affected by the size of Descemet membrane break, but also the depth of the Descemet membrane detachment. The third factor to influence duration of clinical edema is intervention with intracameral C3F8 (see next section).

In vivo confocal microscopy is a technology that has revolutionized imaging of the cornea in recent years. Lockington and associates conducted a prospective study of
acute hydrops in keratoconus as assessed by in vivo confocal microscopy. This study revealed the presence of presumed inflammatory cells, in 4 of the 10 eyes studied, and postulated these may be associated with neovascularization. These cells were hyper-reflective, with round cell bodies (Figure 4, Left) present in the epithelium and anterior to mid-stroma. In 2 eyes, these cells persisted throughout the duration of hydrops, beyond clinical resolution. In these 2 cases, other unique cellular structures were also identified: elongating cells with small cell bodies were noted in the anterior stroma at 2-3 months (Figure 4, Middle) and at 3 months after presentation, both of these corneas also exhibited unusual stromal cells with large, round, speckled cell bodies and elongated cells with branching cell processes (Figure 4, Right). Both corneas developed stromal neovascularization and were the only corneas to do so during the study.

Contemporary imaging modalities have enabled significantly greater insight into the pathophysiology of corneal hydrops. However, in a clinical setting, UBM and IVCM require more technical skills and operator experience. Notably, although the latter has increased our understanding of hydrops at the microstructural level, currently IVCM has a minimal role in management. In contrast, AS-OCT is easier to capture than UBM or IVCM and therefore might more readily assist in ascertaining whether certain interventions may be beneficial (see next section).

TREATMENT OF CORNEAL HYDROPS

HISTORICALLY A VARIETY OF METHODS HAVE BEEN USED TO treat acute corneal hydrops, including the excision of a vertical ellipse of cornea, a conjunctival flap, medial tarsorrhaphy, paracentesis, ocular hypotensive treatment, chemical or thermal cauterization of the cornea, injection of autologous blood into the anterior chamber, and emergency penetrating keratoplasty. However, advocacy of some earlier treatments was based on a lack of understanding of the natural history of hydrops.

Acute hydrops is a condition that generally resolves without intervention over 2-4 months, during which time the sight and comfort of the patient is significantly compromised. Longer duration of edema is also more likely to lead to complications such as neovascularization. Therefore many therapeutic options are aimed at safely facilitating speedier recovery. Other forms of treatment are targeted at minimizing or eliminating complications of hydrops.

Treatment regimens can be divided into conservative, medical, and surgical options.

Most conservative treatment includes observation and topical lubrication for comfort. Pressure patching and bandage contact lens have also been advocated to reduce edema.

Medical therapy usually encompasses topical hypertonic saline (5%) to reduce intrastromal edema, topical corticosteroids to reduce inflammation and prevent neovascularization, and cycloplegic agents to reduce pain. Unfortunately, the evidence behind any of these regimens remains limited, case-based, and largely anecdotal.

Theoretically, topical corticosteroids may reduce the risk of corneal neovascularization or lessen the extent of progression should neovascularization occur. However, there is little evidence in the literature to support this theory. Indeed, although widely used in clinical practice, some studies have found topical corticosteroids to be entirely ineffective in arresting the progression of stromal neovascularization in corneal hydrops.
As the clinical indications for use of anti–vascular endothelial growth factor (anti-VEGF) agents in corneal diseases increase, future studies may investigate their potential role in the management of intractable neovascularization after acute corneal hydrops.

In the last 10 years, intracameral injection of air or expansile gas has been advocated as a treatment for acute hydrops. Proponents of this therapy advocate that the presence of air/gas in the anterior chamber encourages reapposition of Descemet membrane to the corneal stroma and thus promotes reattachment, thereby speeding up the resolution of stromal edema. The air/gas also acts as a mechanical barrier, preventing further egress of aqueous humor into the stroma. The procedure involves the formation of paracentesis to inject air/gas with or without an accompanying surgical iridectomy/iridotomy to avoid pupil block glaucoma.

Miyata and associates performed a retrospective study comparing the efficacy and safety of intracameral injection of air (0.1 mL) with conventional medical therapy in the treatment of acute hydrops in keratoconus. Conventional therapy in this study included no therapy, ofloxacin ointment and patching, sodium chloride eye drops (5%), or dexamethasone ointment (0.1%). They noted that those eyes that received intracameral air injections recovered more rapidly compared with those that did not. However, 7 out of the 9 eyes in the treatment group required 2 or more repeated injections of air. Patients were asked to remain supine for as long as possible following the injection of air and patients in the treatment group were also given acetazolamide 750 mg per day for 3 days to prevent ocular hypertension, thus potentially confounding the possible mechanism for the faster recovery. The visual acuity following recovery was not superior in the group treated with air compared to conventional treatment.

In order to avoid repeated injections in clinical practice, other investigators have experimented with longer-lasting gases, such as sulphur hexachloride (SF6) and perfluoropropane gas (C3F8). Panda and associates investigated the use of sulfur hexafluoride (SF6) in the management of corneal edema caused by acute corneal hydrops secondary to keratoconus. They compared intracameral injection of 0.1 mL of 20% SF6 treatment in a prospective study, with stored data of patients previously treated with conventional therapy. Patients who received intracameral SF6 were also administered 250 mg of acetazolamide 3 times daily and asked to remain supine until the gas bubble was resorbed. Conventional treatment included sodium chloride (5%) eye drops every 4 hours, twice-daily sodium chloride (6%) ointment, tropicamide (1%) eye drops, and ciprofloxacin (0.3%) eye drops, until resolution of corneal edema and formation of corneal scar. There were 9 patients in each group. Despite the use of SF6 rather than air, 2 or more injections were still required in 6 of the 9 patients. Corneal edema began to resolve in the injection group at 3 weeks but did not begin to do so in the (historic) conventional group until 12 weeks. The 12-week best spectacle-corrected visual acuity (BSCVA) was correspondingly poorer in the conventional group (mean logMAR BSCVA: 0.39 in injection group and 0.24 in conventional group, P = .016).

Traditionally, perfluoropropane has not been advocated for intracameral use as it is thought to be toxic to the corneal endothelium. However, its successful use has been reported for the reattachment of Descemet tear following complicated cataract surgery. Shah and associates subsequently reported a single case report of rapid resolution of edema following 2 injections of intracameral C3F8. The first injection was 0.1 mL of 10% nonexpansile concentration of C3F8. However, after 1 week the gas bubble had significantly reduced in size and the edema had not improved. Therefore a second injection was made, this time of 0.2 mL 14% perfluoropropane. Day 1 following the second injection found complete resolution of corneal edema with closure of the intrastromal cleft. The vision had also improved and was consistent with the final visual acuity 8 weeks later.

Basu and associates, in a retrospective study of acute corneal hydrops in keratoconus, PMCD, and keratoglobus, compared 62 eyes treated with 14% nonexpansile, intracameral C3F8 with 90 eyes that served as controls. There was significantly faster resolution of clinical edema in the keratoconus group treated with intracameral C3F8 than controls (67.6 ± 39.2 vs 110.6 ± 51.6 days; P < .0001). However, 10 of the study eyes (16%) developed acute glaucoma secondary to pupillary block compared to none of the control eyes (P < .0001). This incidence of pupil block glaucoma prompted the investigators to perform surgical iridectomy in subsequent eyes treated with intracameral C3F8. In a subgroup of 21 study eyes and 19 control eyes no statistical difference was identified in terms of endothelial cell density, polymorphism, or polymegathism following resolution of edema. Similar to other studies, no difference in the final best-corrected visual acuity was identified between the 2 groups.

In a separate, smaller study, Basu and associates assessed eyes with hydrops before and after intracameral C3F8 with AS-OCT and noted that C3F8 made little difference in the speed of resolution of hydrops in 3 out of 13 eyes treated with intracameral perfluoropropane. The average diameter of the Descemet tear in these 3 eyes was 2.1 ± 0.4 mm and the depth was 1.7 ± 0.1 mm, whereas, the average diameter of tear in all 24 hydrops corneas included in the study was 1.1 ± 0.8 mm with a mean depth of 0.9 ± 0.6 mm. The authors postulated that in eyes with large and deep tears, intracameral gas injection may in fact impede reattachment of Descemet membrane and thus slow recovery.

Rajaraman and associates proposed the use of compression corneal sutures in addition to intracameral perfluoropropane in the treatment of acute hydrops in a retrospective case series of 17 patients (16 keratoconus and 1 PMCD). Patients received 0.2 mL of isoexpansible...
mixture of 14% C3F8 either alone or with compression sutures. The decision to introduce compression sutures was made only after injection of the gas if (1) a stromal cleft was noted after gas tamponade, or (2) tracking of gas through the stroma was noted during gas injection. Fifteen of the patients underwent intracameral C3F8 with sutures and only 2 eyes underwent intracameral gas injection alone. The average persistence of the bubble in the anterior chamber was 10.75 ± 2.62 days. Corneal edema resolved faster in eyes with C3F8 and compression sutures than in eyes with pneumatic tamponade alone (8.87 ± 4.98 days and 27.5 days, respectively); however, the numbers are too small to be conclusive.

Histopathology of resolved hydrops in 8 eyes treated with intracameral C3F8 injection showed greater attachment of Descemet membrane to the posterior stroma and "burial" of the rolled or folded Descemet membrane in the stroma. This appearance may reflect compression effects of the gas bubble on Descemet membrane. Separation between the split ends of Descemet membrane suggests that end-to-end reapproximation of Descemet membrane may not be possible because of the elastic coiling and retraction of Descemet membrane after rupture. There were no signs of endothelial attenuation in eyes that received C3F8 on histology.

Although adverse events occur uncommonly in the above series, many anterior segment experts still advocate using isoexpansible gases with caution, largely owing to associated serious complications such as pupil block glaucoma, intrastromal migration of gas, Urrets-Zavalia syndrome, and potential complications such as cataract and endothelial cell loss. Additionally, not every patient can adhere to the posturing regimen required as part of this treatment. Indeed, every study on intracameral gas injection for acute hydrops has prescribed supine positioning post injection for a significant period, up to 2 weeks. This could pose potential compliance issues for many patients. The use of intracameral gases also dictates more frequent follow-up as it is important to ensure that complications such as malignant glaucoma and intrastromal migration of the gas do not occur. If a gas other than perfluoropropane is to be used, then close observation is recommended, as repeated injections are frequently necessary.

The definitive benefit gained from intracameral gas across studies is approximately a 1 month faster resolution of hydrops, but no significant difference in terms of final best-corrected visual acuity or need for corneal transplantation. Therefore, it may be advisable to first measure the dimensions of the Descemet tear with AS-OCT, and if the tear is of appropriate dimensions then the procedure might be recommended for individuals who are highly compliant and motivated for faster resolution from hydrops and possibly earlier corneal transplantation. The limited evidence suggests that intracameral perfluoropropane may be the gas of choice as it requires the least number of reinjections and it has also been demonstrated by both in vivo and ex vivo studies to be safe in the context of endothelial preservation. Further studies are required to validate the area and depth of the tear, beyond which intracameral gas injection is unhelpful. From a personal perspective, owing to issues of patient compliance, pupil block glaucoma, reinjection of gas, and lack of benefit in terms of final visual acuity or reduction in need for transplantation surgery, the authors have abandoned intracameral gas injection.

Traditionally, penetrating keratoplasty (PKP) has been employed for patients following acute hydrops as the resultant stromal scar was thought to preclude successful lamellar keratoplasty. Keratoconus has been shown to have one of the best outcomes for PKP. There are various reports as to the success of PKP following acute hydrops. Akova and associates reported no significant difference in the rate of endothelial graft rejection in 35 eyes with a history of hydrops compared to 74 eyes without, despite a higher rate of vernal keratoconjunctivitis in the hydrops group. However, Tuft and associates, in a larger study with a longer period of follow-up, reported that the success of PKP reduces in patients post hydrops owing to presence of neovascularization and the higher prevalence of vernal conjunctivitis. Basu and associates conducted a similar study more recently that generally supported the study by Tuft and associates, but using multivariate analysis identified that the risk of endothelial rejection episodes was greater in eyes with longer duration of corneal hydrops and coexistent ocular allergy.

Because of the greater risk of endothelial graft rejection and reduced success of long-term graft survival noted in the preceding studies, and the typically young age of individuals who develop hydrops, recent years have seen the adoption of deep anterior lamellar keratoplasty (DALK) techniques wherever feasible for post-hydrops keratoconus patients. DALK poses technical challenges over those posed by PKP, largely owing to the depth and density of scarring in severe cases and the significant risk of deep perforation at the site of the Descemet membrane rupture. Therefore many of the techniques described for lamellar dissection are contraindicated. Modified dissection techniques have been described in all published case series of DALK following hydrops, most suggesting careful manual dissection down to near-Descemet membrane.

In the largest retrospective noncomparative series of 22 post-hydrops keratoconic eyes treated with DALK, published by Anwar and associates, in which a modified "big bubble" technique was used, the 3-year-postoperative follow-up saw 68.1% of all eyes with a BSCVA of 20/40 or better; 27.2% had 20/30 or better and 9.1% had 20/28 or better. No eyes achieved 20/20. The mean BSCVA at 3 years of follow-up was 20/40. The mean spherical equivalent was −3.53 diopters (D) and the average refractive cylinder was 3.42 D. Six eyes (27%) developed microperforations intraoperatively, but none required conversion to PKP.
In a more recent study conducted by Nanavaty and associates, 36 10 keratoconic eyes of 10 patients underwent DALK post hydrops. Preoperatively BSCVA was 20/80 or worse in all eyes. At 1-year, 100% had BSCVA of 20/40 or better. Intraoperative micro-perforation at the site of previous hydrops occurred in 6 eyes (60%), but none required conversion to penetrating keratoplasty. At latest follow-up, mean spherical equivalent was −2.4 D and refractive astigmatism was 3.42 D. Mean central pachymetry was 572.6 mm. These excellent postoperative values are therefore comparable to results yielded by PKP post hydrops, and with the benefit of longer rejection-free graft survival, DALK may soon become the “standard of care” for post-hydrops visual rehabilitation.

The authors’ current approach to corneal hydrops, which is common and severe in our practice, is to treat with topical lubricants and corticosteroids (the latter to minimize inflammation and neovascularization, not to address edema) until resolution of the hydrops. Topical antibiotics are used where there is epithelial defect or the risk of such is high. We no longer use intracameral gas injection. At the time of corneal transplant our preference is to attempt DALK using a mechanical dissection technique in all cases where the Descemet tear is small (less than 3 mm). Typically in larger tears a penetrating keratoplasty is performed.

CONCLUSIONS

ALTHOUGH RELATIVELY UNCOMMON, ACUTE HYDROPS IN keratoconus is associated with significant morbidity in an otherwise healthy young population. Improved in vivo imaging of the cornea during acute hydrops has led to an enhanced understanding of the pathogenesis and ultrastructural changes of the condition. Anterior segment UBM and OCT in particular have resulted in improved management of the disease. However, despite newer treatment modalities that may shorten the duration of hydrops, ultimately the majority of affected subjects require corneal transplantation for visual rehabilitation.

Effective management of acute corneal hydrops in keratoconus is based on recognizing and addressing the risk factors, treating the acute event effectively and promptly to reduce the duration of edema and its complications, and, ultimately, successful corneal transplantation with acceptable long-term graft survival rates. Unfortunately, as highlighted in this perspective, the evidence base still lags behind surgeons’ enthusiasm for a number of management options, and larger prospective studies are most definitely required to further refine possible prevention and treatment options for this multifaceted disease process.

REFERENCES


Biosketch

Dr Jennifer C. Fan Gaskin has recently completed her Ophthalmology residency at Auckland District Health Board, under the Royal Australian and New Zealand College of Ophthalmologists’ training programme. She is currently conducting her Doctorate of Medicine (MD) research thesis on Complications of Keratoconus and is the recipient of a Health Research Council of New Zealand Career Development Award. She will be embarking on subspecialty training in glaucoma in 2014.
学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。