Ocular Immunology and Inflammation

ISSN: 0927-3948 (Print) 1744-5078 (Online) Journal homepage: www.tandfonline.com/journals/ioii20

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**To cite this article:** Shiao W. Wong, Fiona Carley & Nicholas P. Jones (2021) Corneal Decompensation in Uveitis Patients: Incidence, Etiology, and Outcome, Ocular Immunology and Inflammation, 29:4, 771-775, DOI: 10.1080/09273948.2019.1698747

**To link to this article:** https://doi.org/10.1080/09273948.2019.1698747

OCULAR IMMUNOLOGY AND INFLAMMATION
2021, VOL. 29, NO. 4, 771–775
https://doi.org/10.1080/09273948.2019.1698747

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ORIGINAL ARTICLE



# Corneal Decompensation in Uveitis Patients: Incidence, Etiology, and Outcome

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**ABSTRACT**

**Purpose**: To identify the prevalence, etiology, management and visual outcomes of treatment in uveitis-related corneal decompensation.

**Patients and methods**: This is a retrospective study of patients with corneal decompensation identified from a large cohort with uveitis in a tertiary referral clinic setting.

**Results**: Between March 1991 and May 2018, 4132 new patients with uveitis were seen in Manchester Uveitis Clinic. Of these, 25 patients (0.6%) were identified with corneal decompensation of which 9 (0.2%) were affected bilaterally (total 34 eyes). The mean interval between uveitis diagnosis and decompensation was 23 months (range 0-117 m). Ten patients (41%) had associated glaucoma. Seventeen eyes (50%) had undergone intraocular surgery prior to decompensation. For eyes with no history of raised intraocular pressure or intraocular surgery, keratouveitis (presumed autoimmune or tuberculous) was the most common cause of corneal decompensation. Fourteen eyes (41%) required corneal graft and of these, five required repeat grafting.

**Conclusions**: Corneal decompensation in eyes with uveitis is a rare but significant complication. Direct endothelial inflammation may alone cause decompensation, but in most eyes with uveitis, prior raised intraocular pressure or intraocular surgery are required to precipitate the cornea into decompensation. Outcomes of corneal transplantation in this group may be disappointing.

**ARTICLE HISTORY**
Received 3 April 2019
Revised 25 September 2019
Accepted 25 November 2019

**KEYWORDS**
Cornea; corneal decompensation; corneal graft; corneal oedema; corneal transplant; endothelium; uveitis

## Introduction

Corneal involvement in uveitis is uncommon but well recognized and includes band-shaped keratopathy and various forms of keratitis. Uveitis is a substantial risk factor for keratopathy in general.[1] Chronic or recurrent uveitis typically causes inflammatory cell deposition on the corneal endothelium and permanent endothelial cell loss can result.[2] Secondary ocular hypertension and glaucoma are common complications[3] that may also damage endothelial cells. Some forms of anterior uveitis including herpetic keratouveitis, presumed autoimmune corneal endotheliitis, and chronic cytomegalovirus-associated uveitis with endotheliitis[4] may also cause endothelial cell loss. Eyes with uveitis frequently undergo cataract extraction, glaucoma surgery and other intraocular interventions which may contribute further to reduced endothelial cell counts. It is therefore surprising that despite studies identifying lower endothelial cell counts in patients with uveitis,[5] clinically observed corneal decompensation in uveitis (CDU) appears very uncommon and to our knowledge, the prevalence and etiology have not previously been reported. This study aims to identify the risk factors for CDU and its prevalence, to describe outcomes of treatment and to suggest means of prevention.

## Patients and Methods

The Manchester Uveitis Clinic (MUC) database prospectively records data on each new patient attending, and for those continuing to attend, records significant changes in manifestations, diagnosis, and management. This includes a field for CDU. From the patients identified, data were retrospectively collected from clinical records, including demography, cause and duration of uveitis, type of preceding intraocular surgery if any, pattern of corneal decompensation, types and frequency of corneal transplantation and visual results.

## Results

Between March 1991 and May 2018, 4132 new patients with uveitis were seen in MUC. Of these, 25 patients were identified with CDU of which 9 had bilateral decompensation (total 34 eyes). This gives CDU an approximate prevalence of 0.6% in this (predominantly tertiary referral) patient population. For affected patients, the mean age at uveitis onset was 32 years (range 3–84 years), at presentation to MUC 34 years, and 52% were female; 52% had unilateral uveitis and 48% bilateral uveitis. These data were not significantly different from that of the total clinic population.[3] The most common etiologies associated with CDU were sympathetic ophthalmia and Fuchs' heterochromic uveitis (FHU). Table 1 shows all causes, Table 2 compares risks for all diagnoses using total numbers recorded in MUC.

Eight eyes (24%) developed CDU without any history of ocular hypertension, glaucoma or intraocular surgery. Of these, four were presumed to be caused by "autoimmune

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**Table 1.** Diagnoses associated with corneal decompensation in uveitis (CDU).

| Diagnosis of uveitis | CDU (patients, %) | CDU (eyes, %) | Focal CDU (eyes,%) | Prior IOS (eyes, %) | IOS type |
|---|---|---|---|---|---|
| Fuchs' heterochromic uveitis | 6 (24) | 6 (17.6) | 5 (83) | 3 (50) | 3: Phaco + IOL<br>1: IOL explant |
| Sympathetic ophthalmia | 5 (20) | 6 (17.6) | | 5 (83) | 5: Phaco + IOL<br>1: IOL explant<br>1: Secondary IOL<br>1: PI |
| Idiopathic chronic anterior uveitis | 3 (12) | 5 (14.7) | 2 (40) | 2 (40) | 2: Phaco + IOL<br>1: Vitrectomy |
| Autoimmune endotheliopathy | 3 (12) | 5 (14.7) | 4 (80) | 0 (0) | |
| JIA-associated chronic anterior uveitis | 2 (8) | 4 (11.8) | 2 (50) | 3 (75) | 3: Phaco + IOL<br>1: AC washout<br>1: Vitrectomy |
| HLA B27-associated anterior uveitis | 2 (8) | 3 (8.8) | 1 (33) | 2 (67) | 2: Phaco + IOL<br>2: Trabeculectomy<br>1: Bleb needling |
| Tuberculosis-associated keratouveitis | 1 (4) | 2 (5.9) | 2 (100) | 0 (0) | |
| VZV-associated chronic panuveitis | 1 (4) | 1 (2.9) | | 0 (0) | |
| Idiopathic chronic panuveitis | 1 (4) | 1 (2.9) | | 1 (100) | 1: Baerveldt tube<br>1:3 AC reformation |
| Post-surgical chronic anterior uveitis | 1 (4) | 1 (2.9) | | 1 (100) | 1: Baerveldt tube<br>1: Phaco + IOL |
| Totals | 25 | 34 | 16 | 17 | |

Abbreviations: JIA = juvenile idiopathic uveitis; VZV = varicella-zoster virus; IOS = intraocular surgery; IOL = intraocular lens; Phaco = phacoemulsification; PI = peripheral iridotomy; AC = anterior chamber

endotheliopathy" (but now would be analyzed for viral anterior uveitis); two by tubercular keratouveitis, one HLA-B27 related anterior uveitis and one juvenile idiopathic arthritis-related chronic anterior uveitis. The mean delay between uveitis onset and CDU was 23 months (range 0–117 months). Seventeen affected eyes (half of the total) had undergone a total of 38 intraocular surgical procedures prior to CDU (7 eyes, 1 procedure; 4 eyes, 2 procedures; 5 eyes, 3 procedures; 1 eye, 4 procedures). Cataract surgery (performed in 16 of 17 eyes undergoing surgery) was the most common operation performed. Twelve affected eyes had prior ocular hypertension or glaucoma. Of these, five had undergone glaucoma surgery (3 mitomycin- or 5FU-enhanced trabeculectomy, and 4 Baerveldt tube implantation).

Sixteen eyes (47%) developed focal decompensation primarily in the corneal periphery, but reaching the visual axis in three eyes; 11 of 16 primarily affected the inferior cornea. Peripheral (predominantly inferior) edema was seen in five of six eyes affected by FHU but four eventually required corneal surgery. Six of seven eyes with keratouveitis secondary to presumed autoimmune endotheliopathy or presumed tuberculosis also showed peripheral edema. The remaining 18 eyes had diffuse corneal edema (see Table 1).

Fourteen of 34 eyes (41%) with CDU (0.25% of the whole uveitis cohort) underwent corneal transplantation (11 penetrating keratoplasty [PK], 3 Descemet-stripping automated endothelial keratoplasty [DSAEK]). Of those undergoing PK, five (45%) required repeat PK, three required a third, and one, a fourth. The reasons for repeat transplantation are shown in Table 3. Six out of 14 eyes (42.9%) which underwent corneal graft had vision worse than 6/60 at the final visit. Only two eyes (14.3%) had a vision of 6/12 or better after corneal graft at final visit (1 PK and 1 DSAEK). Ten eyes had comorbidity permanently affecting vision: four with amblyopia, four with macular scarring secondary to chronic macular edema or disciform degeneration; one with end-stage glaucoma and one with phthisis. The changes in visual acuity (VA) between the first presentation to MUC and the latest measurement are shown in Figure 1. When last seen, six eyes (17.6%) had a perception of light or worse (2 chronic idiopathic anterior uveitis, 1 chronic uveitis with juvenile idiopathic arthritis, one autoimmune endotheliopathy [but blinded by glaucoma], 1 sympathetic ophthalmia, 1 chronic pan uveitis secondary to Varicella Zoster). Seven others (20.6%) had acuity of count fingers or worse, and nine (26.5%) had 6/12 Snellen or better. For the three eyes undergoing DSAEK, the latest VAs were 6/9, 6/15, and 6/18. Overall at the latest visit, 24 of 34 eyes (70.6%) had worse VA than at presentation to MUC, and 4 patients were registered vision-impaired. Severe visual loss was experienced in a range of diagnoses, with none, in particular, appearing as high-risk.

**Table 2.** The risk of corneal decompensation for each diagnosis, comparing with the total cohort in Manchester Uveitis Clinic.

| Diagnosis of uveitis | Patients with CDU | Total in MUC | Risk % |
|---|---|---|---|
| Fuchs' heterochromic uveitis | 6 | 397 | 1.5 |
| Sympathetic ophthalmia | 5 | 40 | 12.5 |
| Idiopathic chronic anterior uveitis | 3 | 293 | 1.0 |
| Autoimmune endotheliopathy | 3 | 5 | 60.0 |
| JIA-associated chronic anterior uveitis | 2 | 114 | 1.75 |
| HLA B27-associated anterior uveitis | 2 | 197 | 1.0 |
| Tuberculosis-associated keratouveitis | 1 | 3 | 33.0 |
| VZV-associated chronic panuveitis | 1 | 3 | 33.0 |
| Idiopathic chronic panuveitis | 1 | 251 | 0.4 |
| Post-surgical chronic anterior uveitis | 1 | 2 | 50.0 |
| Subtotals | 25 | 1305 | 1.9 |
| Other diagnoses | 0 | 2827 | 0.0 |
| Grand totals | 25 | 4132 | 0.6 |

Abbreviations: CDU = corneal decompensation in uveitis; JIA = juvenile idiopathic uveitis; VZV = varicella-zoster virus

## Discussion

The data on CDU presented here do not represent a point–prevalence study; diagnoses were made over a 27-year period

**Table 3.** Reasons for repeat corneal grafts.

| Patient | Diagnosis | No. of grafts and year | Reasons for repeat |
|---|---|---|---|
| 1 | JIA-associated chronic anterior uveitis | 4 PK's (1991, 2000, 2010, 2014) | 1. Graft rejection<br>2. Endothelial decompensation following glaucoma surgery<br>3. Primary graft failure |
| 2 | Sympathetic ophthalmia | 3 PK's (1990, 2000, 2001) | 1. Endothelial decompensation (multiple uveitis recurrences)<br>2. Persistent epithelial defect |
| 3. | Tuberculosis associated keratouveitis | 3 PK's (1998, 2010, 2014) | 1. Graft rejection<br>2. Graft rejection |
| 4. | Fuch's heterochromic uveitis | 2 PK's (2010, 2016) | 1. Graft rejection |
| 5. | Fuchs heterochromic uveitis | 2 PK's (2015, 2018) | 1. Graft rejection |
| 6. | HLA B27-associated anterior uveitis | 2 DSAEKs (2012, 2017) | 1. Endothelial decompensation (uncontrolled glaucoma) |

Abbreviations: PK = penetrating keratoplasty; DSAEK = Descemet-stripping automated endothelial keratoplasty

and the suggested overall figure of 0.6% prevalence must be an approximation. Nevertheless, it is clear that permanent CDU in this uveitis population is rare. It is however striking that all 25 patients with CDU are contained within a small list of diagnoses (Table 1) representing only a small proportion of the diverse causes of uveitis previously reported in this patient group.[6] A significant proportion of these goes on to permanent visual loss. Thirteen eyes (38.2% of those affected by CDU) had visual acuity worse than 6/60, and a recent publication from this center found that CDU was a contributing factor in 4 of 76 patients registered with vision impairment over an 11-year period.[7]

Perhaps more strange than the data presented here is that which is absent: the MUC database has recorded a total of 33 patients with keratouveitis, of whom only 4 appear here; in particular, none of 23 with presumed herpetic keratouveitis do so. A study reported marked pleomorphism of endothelial cells and lowered central endothelial cell density in eyes with herpetic keratouveitis compared to the healthy fellow eye.[8] However, there has been no literature to date describing irreversible corneal edema in patients with keratouveitis.

Corneal edema in all 34 eyes of 25 patients in this study precluded endothelial cell measurement. Nevertheless, endothelial cell loss has been identified in uveitis in general,[5] comparably more so in anterior uveitis,[9] and in some specific entities including recurrent uveitis in Behçet's disease[10] and FHU.[11] However, uveitis-induced cell loss appears not enough *per se* to cause decompensation and it seems that additional insult including intraocular surgery or glaucoma is necessary for the majority. Despite this, no corneal edema was reported after long-term follow-up of cataract surgery in 72 eyes with uveitis.[12] In this series, only eight eyes with CDU had no previous intraocular surgery, raised intraocular pressures or glaucoma; of these, six had underlying corneal endothelitis to explain the decompensation.

The diagnosis causing CDU in most patients in this study is FHU. However, most eyes with FHU showed persistent peripheral decompensation, with central decompensation seen only in a minority. This phenomenon has previously been reported,[13] with peripheral deep stromal haze seen in 7% of a cohort of 103 patients (111 eyes) with FHU, and decompensation in 2.7%. The phenomenon is unexplained.

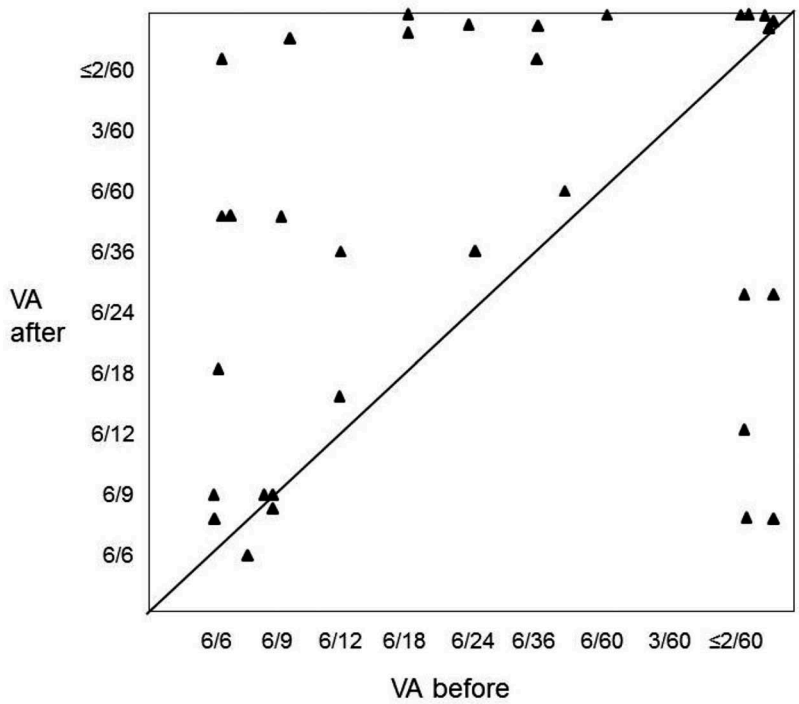


**Figure 1.** Snellen best-corrected visual acuity at first presentation and at final follow-up.

There is increasing interest in the effect of chronic viral anterior uveitis. Endothelial cell loss can be problematic in cytomegalovirus (CMV)-related Posner-Schlossman syndrome[14] and corneal graft failure is more likely in chronic CMV anterior uveitis.[15] A viral etiology for FHU has now been found in these patients.[16] Coincident herpetic uveitis is a high risk for ongoing endothelial cell loss after the corneal graft.[17] It seems clear that viral anterior uveitis targets corneal endothelium, leading to higher rates of cell loss.

Nine eyes with CDU underwent PK and were followed up for 5 years or more. At 5 years, the survival rate was only 30%. This is significantly lower than overall 5-year graft survival in the United Kingdom (which is 73% after a first PK.[18]) For the two eyes which underwent DSAEK and had follow-up of two or more years, the graft survival rate was 50%. This is also much lower compared to 2-year DSAEK survival rates which are 86% and 77% for Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy, respectively (NHS Blood & Transplant, Statistics & Clinical Studies, Stoke Gifford, Bristol). Clearly, the graft failure rate in this group of patients with uveitis and CDU is high. The presence of intraocular inflammation at the time of corneal grafting has been reported to be associated with reduced graft survival[19] and therefore more stringent control of perioperative inflammation may enhance endothelial survival.

Corneal allograft rejection has been reported to be as high as 70% when grafting into 'high risk' recipient beds with the presence of stromal blood vessels, pre-operative glaucoma, prior graft rejection episodes, or active ocular inflammation.[20] This is explained by the imbalance in pro-inflammatory, angiogenic and lymphangiogenic mediators which leads to a breakdown in corneal immune privilege with a consequent host response against the donor graft.[20] Out of 10 repeat grafts from our study, 5 eyes had irreversible corneal graft rejection, 1 eye had endothelial decompensation secondary to uncontrolled glaucoma, and 1 eye had endothelial decompensation secondary to uncontrolled inflammation. Prior glaucoma or uveitis has been reported to increase the risk of failure without an immune allograft reaction with an adjusted relative risk estimate of 3.1[21]

In conclusion, corneal decompensation severe enough to require corneal transplantation is a rare complication of uveitis. Direct endothelial inflammation may alone cause decompensation, but in most eyes with uveitis, prior raised intraocular pressure or intraocular surgery are required to precipitate the cornea into decompensation. Outcomes of corneal transplantation in this group may not be straightforward, and visual results are disappointing; prevention by stringent control of inflammation may prevent some progressing to require surgery.

## Acknowledgments

This research was facilitated by the Greater Manchester Local Clinical Research Network.

## Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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