# Emergency Corneal Grafting in the United Kingdom: A 6-year Analysis of the UK Transplant registry

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**Synopsis:** The information available about emergency corneal graft surgery is limited. In this study, the largest of its kind, we analyzed 6 years of data from UK Blood & Tissue transplant, and found that emergency corneal graft surgery, although less successful than elective corneal graft surgery, is a successful eye and sight saving operation.

**Abstract**

**Background:** Corneal graft (CG) surgery is the most common and successful tissue transplant worldwide. A small and important group of patients are done in emergency situations, typically to save a perforated eye. Our knowledge of the indications and outcomes of emergency corneal grafting (eCG) is limited.

**Methods:** Retrospective, multifactorial analysis of all corneal grafts registered by the United Kingdom Transplant Service from April 1999 to March 2005.

**Results:** A total of 12976 CGs were performed. 1330 (11.4%) were eCGs including 433 regrafts. Actual perforation occurred in 876 (65.9%) patients. 420 (31.5%) grafts were for tectonic purposes alone and 217 (16.3%) were also grafted for visual rehabilitation. The main diagnostic categories were infection (39.4%), non- infectious ulcerative keratitis (32.2%) and other causes (ectasias, previous ocular surgery, injury, dystrophies and opacification). Graft survival of first eCG at one, two and five years was 78%, 66% and 47% respectively. Best corrected visual acuity (BCVA) of surviving grafts at 1 year was: 6/12 or better in 29.9%, 6/18 to 6/60 in 38.4%, CF to LP in 30.6% and NPL in 1%; with worsening of vision in only 8.7% of the patients.

**Conclusion:** This study which is the largest of its kind shows that despite the seriousness of the critical corneal pathology and the surgical challenges that they pose, the outcomes of eCG are favourable with most patients keeping their eyesight and avoiding immediate rejection. These clinical outcomes show the value of eye banking facilities that are developed to support corneal tissue supply for eCG.

**INTRODUCTION**

Corneal allografting is the oldest, most common and successful tissue transplantation procedure worldwide[1-4]. The majority of CG’s are performed under elective conditions, however, a smaller and more critical group of patients are operated in emergency situations. In such cases, emergency corneal grafting (eCG) surgery is often the only solution to stabilize the globe and retain ocular integrity in patients with severe corneal disorders, or persistent infectious and non-infectious keratitis. Failure to act urgently would likely lead to severe visual loss or loss of the eye[5].

Emergency keratoplasty is regarded as high risk surgery in comparison to scheduled keratoplasty, with worse outcomes and higher postoperative complication rates, however, the evidence on the indications, risk factors for graft failure and outcomes of eCG is patchy. There are studies from USA[6-16], Australia[17-20], New Zealand[21-22], UK[23-29], Germany[30-34], France[35], Italy[36], Sweden[37], Israel[38], Turkey[39], Saudi Arabia[40], Taiwan[41-43], China[44-47], India[48-53], Canada[54-58], Hungary[59], Iran[60], and Singapore[61] that have either concentrated on a subtype of eCG or have small number of eCGs, usually grouped under “other” indications. We present a retrospective study with the largest cohort of eCG patients by utilizing the United Kingdom Transplant register, a database with over 30000 patients. The data provide the indications, graft survival and outcomes of this procedure. Such knowledge would benefit patient counselling, clinical management and the planning of eye bank services for eCG.

**MATERIALS AND METHODS**

**Data Collection**

We analysed data from all emergency corneal grafts from April 1999 to March 2005 that were registered with UK Transplant, the United Kingdom’s matching and distribution service. Emergency CG’s are classified by using ‘reasons for grafts’: therapeutic (severe infection, threatened or actual perforation) as selected by the surgeons on the United Kingdom Ocular Tissue Transplant Record form.

Records were submitted by the operating surgeon or doctors involved in the patients’ care at the day of the operation (routine CG registration) and at intervals of 1, 2 and 5 years thereafter until graft failure, loss to follow-up or death of the patient has occurred. Missing data were routinely sought by follow-up letter. Ethical approval was not required as the data is being routinely collected for such purposes.

We analysed information on the graft procedure, indication for surgery, demographics, vision before and after surgery, rejection episodes and graft failure. Additional data include host and surgical factors that could affect outcome such as: the presence of tissue inflammation, ocular surface disease, extent of vascularisation, glaucoma and other coexisting disease including infectious processes when this was not the primary condition leading to the need for a corneal graft. Surgical factors analysed include, suturing technique, graft-host trephine sizes and the development of post-operative complications as indicated in the UK transplant audit follow-up forms.

**Statistical Analyses**

All statistical analyses were performed using SAS (version 9.1, SAS Institute Inc., Cary, NC). Kaplan-Meier survival curves were used to illustrate univariate differences in graft survival and a Cox regression model was fitted to investigate which factors affected graft survival. Chi-squared tests were used to investigate differences in categorical variables and t-tests were used to investigate differences in continuous variables between emergency and all other corneal grafts.

To enable comparison of a homogeneous group, graft survival, rejection and visual acuity were limited to first eCG. Post-operative visual acuity and refractive data was limited to assessments between 8 and 16 months from the day of eCG surgery for one year outcomes and between 18 and 30 months for two year outcomes.

**RESULTS**

A total of 12,976 corneal grafts performed between April 1999 and March 2005 have been reported to UK Transplant, 11646 (88.6%) of which were done under elective conditions and 1330 (11.4%) under emergency circumstances. Records were submitted by a total of 498 surgeons from 273 centres, approximately half of which were involved in eCG surgery [244 (48%) surgeons from 147 (54%) centres]. All operation registration UKT forms were returned whereas the completion rate of follow up audit forms was 90% at year one, 85% at year two and 74% at year 5. Detailed information on transplants was not available prior to April 1999. The mean age of eCG recipients at the time of transplantation was 60 years (SD 20) compared with 56 (SD 22) for corneal grafts performed under routine conditions and varied from less than one year to more than 98 years (Figure 1). Approximately equal numbers of women (51%) and men (49%) had received an eCG. The proportion of eCGs that were HLA matched was only 3% (44/1330) compared with 7% (823/11646) for elective CGs. Recipients of 147 grafts (11%) were known to have died, and 84 grafts (6%) had been lost to follow-up. Two patients recorded as lost to follow up had actually died.

**Indications / Diagnosis**

These were similar for both first time eCG (897 patients, 67.4%) and repeat eCG surgery (433 patients, 32.6%). The main diagnostic categories for first eCG were infection (353 patients, 39.4%), non-infectious ulcerative keratitis (289 patients, 32.2%) and other including ectasias (7%), previous ocular surgery (5.7%), injury (4.1%), dystrophies (2.6%) and opacification (1.9%). For repeat eCG the diagnostic categories were graft failure (230 patients, 53.1%) infection (84 patients, 19.4%), non-infectious ulcerative keratitis (61 patients, 14.1%) and other including ectasias (1%), previous ocular surgery (2.5%), injury (2.8%), dystrophies (1%) and opacification (0.7%) (Table 1).

|  |  |  |
| --- | --- | --- |
| **Indication for eCG** | **1st Graft** | **ReGraft** |
| **No (S/T/A)\*** | **%** | **No (S/T/A)\*** | **%** |
| **Ectasias** | **63 (11/53/19)** | **7.0** | **4 (1/2/2)** | **0.9** |
| * **Keratoconus**
 | 53 (11/47/15) | 5.9 | 2 (1/1/1) |  |
| * **Keratoglobus**
 | 3 | 0.3 | - |  |
| * **Other Ectasias**
 | 7 (0/6/4) | 0.8 | 2 (0/1/1) |  |
| **dystrophies** | **23 (15/12/7)** | **2.6** | **4 (0/4/0)** | **0.9** |
| * **Fuchs' dystrophy**
 | 16 (12/9/4) | 1.8 | 4 (0/4/0) |  |
| * **Other Dystrophies**
 | 7 (3/3/3) | 0.8 | - |  |
| **Previous ocular surgery** | **51 (20/27/14)** | **5.7** | **11 (2/5/5)** | **2.5** |
| * **Pseudophakic corneal oedema**
 | 30 (13/19/4) | 3.3 | 3 (1/0/0) |  |
| * **Aphakic corneal oedema**
 | 9 (5/5/3) | 1.0 | - |  |
| * **Complications of refractive surgery**
 | 1 | 0.1 | -  |  |
| * **Other previous ocular surgery**
 | 11 (2/3/7) | 1.2 | 8 (1/5/4) |  |
| **Infection** | **353 (150/59/217)** | **39.4** | **84 (46/22/44)** | **19.4** |
| * **Viral infection**
 | 99 (25/23/67) | 11.0 | 18 (3/6/13) | 4.2 |
| * **Bacterial infection**
 | 187 (108/33/139) | 20.8 | 52 (35/12/29) | 12.0 |
| * **Fungal infection**
 | 19 (17/3/11) | 2.1 | 10 (8/4/2) | 2.3 |
| * **Protozoan infection**
 | 24 (19/9/4) | 2.7 | 2 (2/0/1) | 0.5 |
| * **Other infection**
 | 24 (14/5/16) | 2.7 | 2 (1/0/1) | 0.5 |
| **Injury** | **37 (1/9/30)** | **4.1** | **12 (1/2/11)** | **2.8** |
| * **Mechanical injury**
 | 17  | 1.9 | 4 | 0.9 |
| * **Chemical injury**
 | 12 | 1.3 | 6 | 1.4 |
| * **Other injury**
 | 8 | 0.9 | 2 | 0.5 |
| **Ulcerative keratitis** | **289 (16/28/262)** | **32.2** | **61 (5/9/54)** | **14.1** |
| * **Rheumatoid arthritis**
 | 134 (6/9/127) | 14.9 | 19 (1/0/19) | 4.4 |
| * **Other ulcerative keratitis**
 | 155 (10/19/135) | 17.3 | 42 (4/9/35) | 9.7 |
| **Graft failure** |  |  | **230 (80/94/119)** | **53.1** |
| * **Rejection**
 |  |  | 32 (10/21/13) | 7.4 |
| * **Primary failure**
 |  |  | 16 (5/9/3) | 3.7 |
| * **Endothelial failure**
 |  |  | 8 (4/4/1) | 1.8 |
| * **High astigmatism**
 |  |  | 1 (1/1/1) | 0.2 |
| * **Endophthalmitis**
 |  |  | 5 (4/1/3) | 1.2 |
| * **Other cause of failure**
 |  |  | 168 (56/58/98) | 38.8 |
| **Opacification\*** | **17 (3/14/4)** | **1.9** | **3 (2/3/0)** | **0.7** |
|  |  |  |  |  |
| **Other** | 56 (8/15/45) | 6.2 | 20 (4/2/16) | 4.6 |
| **Unknown / Not reported** | 8 (2/3/3) | 0.9 | 4 (2/2/2) | 0.9 |
|  |  |  |  |  |
| **Total** | **897 (259/234/621)** |  | **433 (146/145/255)** |  |
| \*S/T/A: Severe infection/ Threatened perforation/ Actual perforation.  |

 Overall, severe infection (S), threatened (T) and actual (A) perforation were reported in 405 (30.5%), 379 (28.5%) and 876 (65.9%) patients respectively. Of note, many patients had a combination of pathologies i.e. severe infection with threatened perforation 84 (6.3%); severe infection with actual perforation 15 (1.1%); severe infection with threatened perforation that perforated 40 (3%); threatened perforation that perforated 151 (11.4%). Additionally, some patients were operated with no visual expectation (for cosmetic and tectonic reasons) and only 217 (24.8%) were having good visual potential.

The patients’ mean age at time of surgery per indication were: 59 (SD, 19) for severe infection, 54 (SD, 24) for threatened perforation and 62 (SD, 19) for actual perforation. There was significant age difference per indication when comparing threatened with actual perforation (p<0.0001), severe infection with threatened perforation (p=0.02) but not when comparing severe infection with actual perforation (p=0.9).

**Type of operation & Techniques**

The majority of eCGs were done with a full thickness Penetrating Keratoplasty (1132 patients, 85.1%) followed by Deep Anterior Lamellar Keratoplasty (6%) and Superficial Lamellar Keratoplasty (4%), with other types of graft accounting for less than 5% of eCGs. Interrupted suturing was the most frequently performed suturing technique (82%), followed by continuous (9%) and mixed (7%). The size of the majority of routine grafts were between 7.00mm and 8.25mm; 78% compared with 43% of eCG. Only 1% and 2% of routine grafts had a trephine diameter of less than 7.00mm or greater than 8.75mm respectively, compared with 10% and 23% of eCG. The majority of eCGs were over-sized by 0.25mm (19%) and 0.50mm (45%), with 19% same-size grafts and 4% over-sized by more than 0.50mm.

**Repeat eCGs**

A third of all emergency grafts were regrafts; 33% (433/1330) compared with 18% (2063/11646) of routine grafts. The main indication for these was graft failure, recorded in 53% (230/433) of redo-eCG compared with 74% (1520/2063) of the routine regrafts. The other diagnostic categories for repeat eCG were infection (19%), ulcerative keratitis (14%), rejection (7%), and endophthalmitis (1%). Of the 84 patients that were regrafted due to infection, 52 (62%) were for a bacterial infection. Most of the redo-eCGs had regrafts in the same eye while fewer eCG patients had previously received grafts in the other eye (33% compared with 18%, p< 0.0001).

**Visual Acuity**

The median best corrected visual acuity (BCVA) improved from hand movements (HM) at the time of transplant to 6/24 (20/80) at two years. The majority of patients (81%) showed an improvement in distance VA following eCG, 11% had no change and only 8% of patients experienced deterioration in distance VA. Figure 2 shows a graph with lines of improvement in the Snellen chart for cases which had completed 1 year follow up with records of preoperative and 1 year postoperative BCVA.

**Rejection, survival and risk of graft failure**

Rejection episodes occurred in 28 (4%) eCGs, of which 24 (86%) went onto fail. The overall graft survival of first eCG at one, two and five years was 78%, 66% and 47% respectively with 88% of the grafts surviving the 1st year being alive at year two. Table 2 shows the factors affecting graft survival for the first eCG.

|  |
| --- |
| **Relative risk of graft failure at five years** |
| Factor | Number | Relative Risk | 95% CI | P |
| Indication for graft (p=0.01) |  |  |  |  |
|  Viral infection | 82 | 1.0 | - |  |
|  Other infections | 195 | 2.2 | 1.3 - 3.6 | 0.003 |
|  Ulcerative keratitis | 195 | 1.8 | 1.1 - 3.1 | 0.03 |
|  Ectasias/dystrophies | 57 | 0.93 | 0.4 - 2.2 | 0.9 |
|  Other indications | 114 | 1.4 | 0.8 - 2.6 | 0.2 |
| Pre-operative acuity (p=0.0002) |  |  |  |  |
|  Better than LP | 466 | 1.0 | - |  |
|  LP, NP | 144 | 1.8 | 1.3 - 2.4 | 0.0005 |
|  Not reported | 33 | 2.1 | 1.3 - 3.7 | 0.006 |
| Graft size (p=0.02) |  |  |  |  |
|  < 9.00mm | 477 | 1.0 | - |  |
|  ≥ 9.00mm | 147 | 1.6 | 1.1 - 2.1 | 0.006 |
|  Not reported | 19 | 1.2 | 0.6 - 2.4 | 0.6 |
| Pre-operative conditions (p=0.02) |  |  |  |  |
|  No | 312 | 1.0 | - |  |
|  Yes | 178 | 1.5 | 1.1 - 2.1 | 0.02 |
|  Unknown | 153 | 1.5 | 1.1 - 2.1 | 0.02 |
| Gender match (p=0.05) |  |  |  |  |
|  F donor / F recipient | 137 | 1.0 | - |  |
|  F donor / M recipient | 134 | 1.1 | 0.7 - 1.8 | 0.6 |
|  M donor / F recipient | 192 | 1.5 | 0.99 - 2.3 | 0.05 |
|  M donor / M recipient | 180 | 1.7 | 1.1 - 2.5 | 0.02 |
| Grafted for visual reasons (p=0.09) |  |  |  |  |
|  Yes | 328 | 1.0 | - |  |
|  No | 246 | 1.3 | 0.99 - 1.8 | 0.06 |
|  Unknown | 69 | 1.5 | 0.95 - 2.4 | 0.08 |

Compared with grafts for viral infection, eCGs performed for non-infectious ulcerative keratitis were 1.8 times more likely to fail at five years (p=0.03). Similarly, the prognosis for grafts with preoperative visual acuity of LP or NLP was poorer than those better than LP; 1.8 times more likely to fail at five years (p= 0.0005). eCGs where the graft size was 9.00mm or greater were 1.6 times more likely to fail at five years, compared with grafts less than 9.00mm in diameter (p= 0.006). Patients with pre-operative conditions that may affect visual acuity were 1.5 times more likely to fail than patients with no reported pre-operative conditions (p=0.02). Gender match of male donor cornea to male recipient was an additional risk of graft failure; 1.7 times more likely to fail than female donor cornea to female recipients.

**DISCUSSION**

The first successful corneal transplant into a human eye [62] was performed over 100 years ago and since then the technique has evolved and become the most widely practised form of clinical transplant worldwide. CG surgery can be performed both as a planned elective operation and as an emergency. Elective CG is usually straightforward and its primary goal is to improve vision in patients that suffer with a stable eye condition like keratoconus, Fuchs’ corneal dystrophy, pseudophakic bullous keratopathy or a corneal scar. Whereas, eCG is performed in patients with trauma, ulceration or a critical corneal thinning/perforation with the aim to restore the structural integrity of the globe with visual improvement, generally a secondary consideration. In patients with severe corneal infection, eCG surgery is also indicated to remove or decrease the microbial load present in the excised tissue.

Corneal allografts generally have a low rejection rate occurring in less than 10% of the patients who have not previously received a corneal transplant and who do not have underlying ocular inflammation. Corneal grafts can survive even though HLA typing and systemic immunosuppressive drugs are not employed for the majority of grafts. The success of corneal transplants is due to a combination of anatomical, physiological, and immunological properties that prevent the induction and expression of potentially destructive immune responses to the transplanted tissue[63].

In our study we assessed the indications and outcomes, graft survival, rejection rates and final visual acuity of up to 1330 eCGs. This is the largest cohort of patients with eCG studied to date. Studies from other graft surgery are limited to fewer numbers[6-61].

We found that the most frequent indication for eCG was infection. Subgroup analysis reveals bacterial, viral, acanthamoebal and fungal infections with an incidence of 20.8%, 11%, 2.7% and 2.1% respectively. Previous studies on CG and therapeutic penetrating keratoplasty have shown a broad range of frequencies for bacterial (1.77-40%)[64-70], viral (2.19-35%)[70-79], fungal (0.19-48.1%)[80-85] and acanthamoebal (0.19-13.9%)[86-91] keratitis, and a smaller number for descemetoceles[92-96], corneaoscleral melting[97-100], trauma[101] and repeat grafts[102-113]. This variation may reflect a smaller patient numbers, too broad a definition/inclusion under ‘other diagnosis,’ and the geographical and ethnic variability of these studies. The second most frequent indication in our study was sterile ulcerative keratitis (32.2%), which was either idiopathic (17.3%) or associated with rheumatoid disease (14.9%). Repeat grafts (433) were mainly performed for graft failure (53.1%), infection (19.4%) and ulcerative Keratitis (14.1%).

Emergency graft survival rates were highly dependent on the diagnostic group under the indication for eCG surgery with ulcerative and bacterial keratitis, fairing worse than viral infection (Figure 3). Graft survival was worse for grafts with preoperative visual acuity of LP or NPL, large graft size of >9.00mm, associated preoperative conditions, previous rejection episodes and gender match of male donor cornea to male recipient was an additional risk (Table 2). Emergency regrafts had a worst outcome with 65% of the grafts surviving the first year. Comparison with other studies with regards of survival rate of eCG for a particular diagnostic category is difficult as most of the previous studies in the topic concentrate mainly in one diagnostic category, most of them involving very small samples. Nonetheless our results support that of previous studies where factors such as presence of inflammation, glaucoma, and large diameter grafts are linked to poorer graft survival [6, 27, 35, 39, 42].

Despite the poor prognosis of eCG, overall, graft survival in these high risk transplants was 78% at the end of their 1st year compared to 90% of patients receiving an elective cornea graft operation. Which compares favourably with other organ transplants where 85% of patients receiving a cadaveric kidney, 77% of patients receiving a heart and 65% of patients receiving a liver will have a functioning graft one year after the operation[3, 114].

Patients receiving their first eCG that had not failed were able to achieve visual acuity of 6/12 (20/40) or better in 30 % of the eyes, 6/18 (20/50) to 6/60 (20/200) in 38.4% and only 30.6% had visual acuity of less than counting fingers (CF) at 1 metre. In this group, vision improved in 90% of the patients and in 60% improved by more than 5 Snellen lines with only 1% of patients unable to recover any vision. Overall, following eCG the vision decreased in only 26 patients (8.7%) with both surviving and failing grafts achieving a postoperative improvement in vision.

However in eCG the graft rejection rate is higher and depending on indication it can increase up to 32.1% in 4.4 years[115]. In our study this was 4.2% in the first year. In our study HLA matching was carried out in 823 (7.1%) elective CG and 44 (3.3%) eCG with just over 50% of them performed for regrafts. Previous studies have successfully argued that HLA matching does not appear to have a significant effect on corneal graft survival in elective CG patients[116]. However, there is a strong consensus among clinicians that this may not be the case in eCG where there is a breakdown of corneal immune-privileged status. A vascularised corneal graft bed along with a concurrent corneal infection and/or inflammation, promote the induction of alloimmunity and jeopardizes graft survival. Therefore, there may be a role for HLA matching in eCG surgery. The prolonged use of postoperative systemic/topical immune-suppression and antiviral treatment regimes may be beneficial in eCG however, they need to be evaluated with further studies.

Our study provides demographic, clinical and surgical factors that show the outcome of e­­­­CG surgery and this information can be used to counsel corneal transplant patients about the long-term outcome of their surgery. This study reinforces the importance of eye banking and provision of emergency corneal graft material, confirming that eCG is a successful sight saving operation.

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