ZIEMIŃSKA, Daria, MOTOLKO, Karina, BURCZYK, Rafał, DUSZYŃSKI, Konrad, and TOKARCZYK, Elżbieta. Advancements in Corneal Transplantation: Addressing Rejection Risks, Innovations and Challenges. Quality in Sport. 2024;35:56443. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.35.56443
https://apcz.umk.pl/QS/article/view/56443

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.11.2024. Revised: 05.12.2024. Accepted: 16.12.2024. Published: 16.12.2024.

Advancements in Corneal Transplantation: Addressing Rejection Risks, Innovations and Challenges

Daria Ziemińska

Szpital św. Wincentego a Paulo w Gdyni

ul. Wójta Radtkego 1, 81-348 Gdynia

dziemin98@wp.pl

ORCID: 0009-0001-8240-2593

Karina Motolko

Specjalistyczny Szpital Miejski im. M. Kopernika w Toruniu

ul. Stefana Batorego 17/19, 87-100 Toruń

karinamotolko@gmail.com

ORCID: 0009-0001-9971-6687

Rafał Burczyk
Szpital Uniwersytecki nr 2 im. dr J. Biziela
ul. Ujejskiego 75, 85-168 Bydgoszcz
raimer001@gmail.com
ORCID: 0000-0002-1650-1534

Konrad Duszyński
Studenckie Koło Naukowe Okulistyki
Gdański Uniwersytet Medyczny
ul. Marii Skłodowskiej-Curie 3a, 80-210 Gdańsk
konrad.duszynski9000@gmail.com
ORCID: 0009-0006-5524-8857

Elżbieta Tokarczyk
Szpital św. Wincentego a Paulo w Gdyni
ul. Wójta Radtkego 1, 81-348 Gdynia
elzbieta.tokarczyk96@wp.pl
ORCID: 0009-0003-9683-7699

Abstract

Introduction and Objective:

Corneal transplantation is an increasingly common surgical procedure, with lamellar keratoplasty now favored over penetrating keratoplasty due to its advantages in outcomes and precision.

Review methods:

A literature review utilizing databases like Scopus, Google Scholar, and PubMed, with keywords such as "corneal transplantation rejection" and "high risk of rejection," underscores the need for advancements in understanding and managing graft rejection.

Brief knowledge status:

Key insights highlight the importance of deeper exploration into the immunological mechanisms of rejection to refine therapeutic strategies. The development of bioengineered materials like acellular porcine corneal stroma (APCS) offers a promising solution to the global donor shortage, though further validation of their clinical utility is needed. Complementary

therapies such as amniotic membrane transplantation show promise in mitigating graft failure and treating corneal surface disorders due to their anti-inflammatory and regenerative properties. Moreover, comparative studies suggest that advanced keratoplasty techniques, such as Descemet Membrane Endothelial Keratoplasty (DMEK), may achieve lower rejection rates compared to alternatives like Descemet Stripping Automated Endothelial Keratoplasty (DSAEK).

Discussion:

Future priorities include advancing drug delivery systems, ensuring the feasibility and accessibility of bioengineered materials, and conducting large-scale multicenter trials to validate novel treatments and surgical methods across diverse populations.

Summary:

Addressing these challenges is particularly crucial for high-risk and pediatric patients, with the ultimate goal of reducing graft failure rates and the necessity for repeat interventions.

Keywords: corneal transplantion rejection, corneal transplant rejection, corneal graft rejection, pathophysiology of corneal graft rejection, bioengineered corneal materials

1. Introduction

Corneal transplantation is a surgical procedure that continues to gain popularity. Globally, as many as 100,000 such operations are performed annually, with 40,000 of them taking place in the United States alone [1]. In recent years, lamellar keratoplasty has become the preferred method, largely replacing penetrating keratoplasty in cases where only part of the cornea requires replacement. This shift has contributed to a reduced risk of graft rejection [2].

Characteristic clinical symptoms of graft rejection include edema and inflammatory cells circulating in the anterior chamber of the eye [3]. Low-risk transplant recipients have up to a 90% chance of 2-year graft survival [4], whereas the chances for high-risk recipients drop to 50%, even with the maximum doses of immunosuppressive drugs [5]. One of the most significant factors predisposing to corneal graft rejection is considered to be the degree of

neovascularization in the host's bed. Despite promising results, the primary cause of transplant failure remains immunological rejection [6].

2. Aim of the study

In our work, we aim to explore the issues related to corneal transplantation and present the latest information on effective methods to prevent graft rejection. The following article addresses various aspects of the graft rejection mechanism itself, as well as the challenges faced by patients at elevated risk of rejection. Additionally, it discusses the future challenges ahead, providing insights into the current state of the common situation.

3. Materials and methods

For the purpose of this paper, electronic databases such as Scopus, Google Scholar, and PubMed were searched. A literature review was conducted using the following keywords: *corneal transplantation rejection, corneal transplant rejection, corneal graft failure, corneal graft rejection, high risk of rejection, children corneal transplantation*. The focus was placed on articles addressing the prevention of corneal graft rejection, presenting cases of high-risk patients, and outlining the current state in pediatric patients. Original research studies, case reports, and review articles were utilized. The search was limited to publications in Polish and English.

4. Corneal transplant rejection mechanism

Corneal transplantation is among the most successful types of solid organ transplants [7]. Unlike other tissues or organs, the cornea is considered a relatively privileged site for transplantation in its healthy state, primarily due to the lack of blood and lymphatic vessels (except for the marginal corneal arcades) and the limited presence of mature antigen-presenting cells [8]. Despite this, immune rejection remains a significant cause of corneal graft failure [7]. A disruption of corneal immune privilege can trigger the host immune system to react against antigens in the donor corneal button. This immune response may result in the destruction of donor tissue, driven by cells and mediators of both innate and adaptive immunity. The host immune response consists of two components: the afferent arm and the effector arm [9]. T lymphocytes play a central role in both, significantly influencing the outcome of allografts [7]. In the afferent arm of the immune response, allospecific T cells are activated through two main pathways: the direct pathway, where T cell receptors interact with intact allogeneic major histocompatibility complex (MHC) molecules on donor cells, and the indirect pathway, where

donor peptides are presented by self-MHC molecules on recipient antigen-presenting cells (APCs), such as dendritic cells [9,10]. Following corneal transplantation, the previously quiescent corneal environment becomes inflammatory. This inflammation induces the expression of MHC-II on central dendritic cells (DCs), upregulates costimulatory molecules such as CD80, CD86, and CD40 on both central and peripheral DCs, enhances the expression of adhesion molecules crucial for T cell activation, and promotes the release of cytokines including IL-1, IL-6, and IL-12 [9].

The effector arm of graft rejection is predominantly mediated by T cells. Allo-sensitization and activation of T cells occur in the draining lymph nodes and subsequently migrate to the cornea. There, they recognize donor MHC antigens, triggering inflammation and tissue destruction. The primary cellular mediators of graft rejection are CD8+ cytotoxic T lymphocytes (CTLs) and CD4+ T-helper lymphocytes, which are key drivers of delayed-type hypersensitivity (DTH) responses [9]. The involvement of both CD4+ and CD8+ T cells in recognizing alloantigens is critical to the initiation of rejection, with CD4+ T cells playing a particularly central role in allograft rejection [7].

T-helper cells secrete IL-2, IFN-gamma, and lymphotoxin, which promote inflammation and initiate an attack on donor antigens. These cytokines also recruit leukocytes and other immune cells to the inflamed cornea. Additionally, alloreactive T cells facilitate the formation of memory T cells, which are responsible for the heightened immune response observed upon re-exposure to the same antigen, as seen in cases of regraft [9].

The survival of corneal allografts relies on a delicate balance between immune and inflammatory responses, which help maintain the cornea's relative immune privilege [7].

Understanding the immunopathogenesis of corneal graft rejection is crucial for recognizing the protective mechanisms and factors contributing to rejection episodes. This knowledge aids in the early diagnosis and effective management of graft rejection [9].

5. Knowledge status

Among meta-analyses dedicated to corneal graft rejection, several main research directions stand out, receiving significant scientific attention:

5.1. Identification of High-Risk Patients

The literature describes many high-risk factors, the most well-known being ocular surface inflammation, retransplantation, corneal neovascularization and neolymphangiogenesis, glaucoma, and previous ocular surgeries. The role of HLA matching in corneal transplantation remains controversial and is not used in routine practice. However, some authors suggest that

HLA matching in high-risk corneal transplants could be beneficial[11, 12]. High-risk patients with corneal neovascularization demonstrate significantly elevated levels of pro-inflammatory cytokines in tears and aqueous humor. Furthermore, it is known that corneal transplantation in such patients may trigger reactivation of underlying inflammatory processes[13, 14].

A deeper understanding of the mechanisms of corneal rejection could help identify warning signs and establish monitoring indicators for therapy.

Analyzing the pathophysiology of corneal diseases treated with transplantation, the impact of these diseases on rejection risk, and identifying parameters for asymptomatic or minimally symptomatic patients who may develop corneal diseases requiring transplantation could benefit those requiring rapid intervention. Understanding the mechanisms underlying corneal diseases requiring transplants may help identify at-risk groups, enhance knowledge of connections between ocular conditions, and improve diagnostics and treatments, thereby reducing corneal graft rejection rates.

Fuchs' Endothelial Corneal Dystrophy (FECD) is one of the most common corneal dystrophies. In a genomic study conducted by Gorman et al., several new loci associated with the disease were identified, including LAMA5, LAMB1, COL18A1, SSBP3, THSD7A, RORA, PIDD1, and HS3ST3B1, alongside the confirmation of previously discovered loci such as TCF4, KANK4, LAMC1, and ATP1B1. Furthermore, strong pleiotropic effects of the TCF4 gene were observed, including elevated levels of bicarbonates and potassium, as well as decreased chloride levels in the blood[15, 16].

5.2. Examining the Causes of Excessive Immunization Leading to Rejection in Light of Widespread Vaccination

In recent years, cases of acute graft rejection following vaccination (e.g., for COVID-19 or influenza) have been reported, particularly among high-risk groups such as multiply transplanted patients with corneal neovascularization and neolymphangiogenesis. In these cases, the anterior chamber loses its immune-privileged status [17,18,19].

A thorough understanding of post-vaccination immunization processes could influence vaccination guidelines for corneal graft recipients.

5.3. New Directions in Immunosuppressive Therapy for Corneal Transplants

The anterior chamber of the eye, being an immunologically privileged site, presents pharmacodynamic challenges due to limited drug penetration. Current immunosuppressive therapy often proves ineffective, with up to 20% of corneal transplants resulting in rejection. Innovative methods for drug delivery are under active development to address these gaps [20].

Given the shortage of donor tissues for treating corneal blindness, bioengineering and xenotransplantation of the cornea have seen significant advancements. Acellular porcine corneal stroma (APCS) has been clinically used since 2012 [21]. However, APCS transplants may not be suitable for peripheral corneal diseases [22]. Graft failure can occur with Acellular Porcine Corneal Stroma (APCS) transplants, similar to human corneal transplants. In 2019, two successfully treated cases of graft rejection following APCS transplantation were reported in patients with fungal corneal ulcers [23]. In this case, for the first time during the COVID-19 pandemic, amniotic membrane transplantation combined with cauterization of neovascularization was successfully used to treat APCS graft failure. This approach was unconventional, as the common treatments for APCS graft failure typically involve tacrolimus, glucocorticoids, antiviral medications, or repeat transplantation [24,25].

5.4. Amniotic Membrane Transplantation as Adjuvant Therapy for Infectious Keratitis and Other Keratopathies

Amniotic membrane transplantation is used to treat a wide range of ocular surface disorders, including neurotrophic keratopathy, infectious keratitis, corneal perforations, limbal stem cell deficiency, chemical injuries, radiation keratopathy, and bullous keratopathy. Its anti-inflammatory properties accelerate tissue regeneration and relieve pain [26]. However, there is a lack of data on its use for treating corneal graft rejection [27,28]. Addressing this knowledge gap could lead to new recommendations and preventative measures against repeat surgeries.

5.5. Immunosuppression in Corneal Transplantation

Due to the cornea's immune-privileged status, low- and medium-risk transplants typically use only topical corticosteroids. However, for high-risk patients, some authors advocate modifying treatment regimens to include immunosuppressive drugs such as tacrolimus or cyclosporine, preferably in topical form to avoid systemic side effects [29,30,31].

5.6. Comparing Keratoplasty Techniques

Megnier et al. compared DMEK (Descemet Membrane Endothelial Keratoplasty) and DSAEK (Descemet Stripping Automated Endothelial Keratoplasty). DMEK was associated with fewer graft rejections than DSAEK [32]. Further research is ongoing to compare the safety profiles of DMEK and ultra-thin DSAEK techniques. Other studies have analyzed the impact of graft thickness on outcomes, but significant differences have not been observed [33,34,35,36]. Research on risk factors contributing to graft rejection may be essential for improving corneal transplantation procedures. For instance, Béal et al. compared the outcomes of corneal transplantation using the DSAEK technique across patient groups with grafts of varying

thickness (<80 μm, 80–100 μm, 100–130 μm). The study found no significant differences in outcomes between the groups [37].

5.7 Corneal Transplants in Children

Due to anatomical characteristics of children's eyes, such as low scleral rigidity and high vitreous pressure, corneal transplantation (especially penetrating keratoplasty) carries a high rejection risk. Mohebbi et al. emphasize the need for increased research efforts to address the challenges of diagnosing and treating corneal conditions in pediatric populations. Tailoring procedures to the unique needs of pediatric patients (e.g., issues with adhering to medical recommendations, maintaining hygiene, and postoperative positioning) could reduce rejection rates [38].

6. Discussion

Corneal transplantation remains one of the most successful organ transplant procedures; however, graft rejection continues to present a significant challenge to long-term survival, particularly in high-risk groups and pediatric patients. This discussion has synthesized the insights gained from current research, explored the broader implications of these findings, and highlighted key areas warranting further investigation.

The trends identified emphasize three critical research priorities. First, a deeper understanding of the immunological mechanisms underlying graft rejection is essential to facilitate the development of more precise and targeted therapeutic strategies. Second, advancements in drug delivery systems and bioengineered materials must not only improve therapeutic efficacy but also address challenges related to accessibility and feasibility. Finally, large-scale, multicenter studies are required to validate the safety, efficacy, and applicability of innovative surgical techniques and novel treatment modalities across diverse patient populations.

Corneal transplantation occupies a pivotal position at the intersection of clinical innovation and substantial challenges. Bridging the gaps in knowledge regarding rejection mechanisms, enhancing immunosuppressive strategies, and refining approaches for high-risk and pediatric patients are essential steps toward achieving sustainable graft success and improving the overall quality of life for recipients.

7. Conclusions

The identification and characterization of risk factors for corneal graft rejection, including neovascularization, ocular surface inflammation, and pre-existing ocular conditions, are critical

for improving outcomes. A more comprehensive understanding of the pathophysiology underlying these conditions and the immunological mechanisms driving rejection may facilitate the development of tailored therapeutic strategies, enhanced monitoring protocols, and ultimately, improved transplant success rates.

Emerging evidence underscores a potential association between certain vaccinations, such as those for COVID-19 and influenza, and acute graft rejection, particularly in high-risk patients. A deeper investigation into the immunological processes involved in post-vaccination graft rejection may inform revisions to vaccination guidelines for corneal graft recipients, thereby mitigating adverse outcomes in this population. Current immunosuppressive regimens for corneal transplantation, particularly in high-risk cases, are limited by inadequate drug delivery to the anterior chamber. Innovations in pharmacological delivery systems and the development of novel immunosuppressive agents offer significant potential to enhance therapeutic efficacy and reduce the incidence of graft rejection.

The use of bioengineered materials, such as acellular porcine corneal stroma (APCS), presents a promising alternative to human donor tissues amidst a global shortage. However, the clinical utility of these materials, particularly in peripheral corneal diseases, requires further investigation. Additionally, the integration of complementary therapies, such as amniotic membrane transplantation, has demonstrated potential in addressing graft failure and warrants further exploration. Amniotic membrane transplantation also has shown efficacy in treating various corneal surface disorders, leveraging its anti-inflammatory and regenerative properties. However, its application in the context of graft rejection remains underexplored. Expanding research in this area could provide valuable insights and augment existing therapeutic options to prevent the need for reoperation. Comparative studies of keratoplasty techniques suggest that refined approaches, such as Descemet Membrane Endothelial Keratoplasty (DMEK), may result in lower rejection rates compared to alternatives like Descemet Stripping Automated Endothelial Keratoplasty (DSAEK). Further investigations into the safety and efficacy profiles of these methods are necessary to establish evidence-based recommendations for surgical practice.

In summary, advancing the understanding of corneal graft rejection through focused research on immunological mechanisms, innovative therapeutic strategies, and surgical techniques holds significant promise. Such efforts are particularly critical for improving outcomes in high-risk populations, addressing pediatric-specific challenges, and optimizing the use of bioengineered materials, ultimately reducing the burden of graft failure and the need for repeat interventions.

Authors contribution:

Conceptualization: Daria Ziemińska, Rafał Burczyk, Karina Motolko, Konrad Duszyński, Elżbieta Tokarczyk

Software: not applicable

Verification: Daria Ziemińska, Rafał Burczyk

Formal analysis: Rafał Burczyk, Karina Motolko

Research: Daria Ziemińska, Rafał Burczyk, Karina Motolko, Konrad Duszyński, Elżbieta Tokarczyk

Resources: Daria Ziemińska, Rafał Burczyk, Karina Motolko, Konrad Duszyński, Elżbieta Tokarczyk

Writing-rough preparation: Karina Motolko, Konrad Duszyński

Writing-review and editing: Daria Ziemińska, Rafał Burczyk, Karina Motolko, Konrad Duszyński, Elżbieta Tokarczyk

Visualization: Elżbieta Tokarczyk

Supervision: Konrad Duszyński, Rafał Burczyk

Project administration: Daria Ziemińska, Karina Motolko

Finding acquisition: not applicable

All authors have read and agreed with published version of the manuscript.

Funding statement: This research receive no external founding

Institutional Review Board System: Not applicable

Informed Consent Statement: Not applicable

Acknowledgments: Not applicable

Conflict of Interests Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Bibliography

1. Edelstein, S. L., DeMatteo, J., Stoeger, C. G., Macsai, M. S., & Wang, C. H. (2016). Report of the Eye Bank Association of America Medical Review Subcommittee on Adverse Reactions Reported From 2007 to 2014. *Cornea*, *35*(7), 917–926. https://doi.org/10.1097/ICO.0000000000000869.
2. Anshu A, Price MO, Price FW Jr. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. Ophthalmology. 2012 Mar;119(3):536-40. doi: 10.1016/j.ophtha.2011.09.019. Epub 2012 Jan 3. PMID: 22218143.
3. Levin, L. A., and D. M. Albert. 2010. Ocular Disease: Mechanisms and Management, 1st Ed. R. Gabbedy and B. Davie, eds. Saunders Elsevier, Philadelphia, PA, p. 65–71.
4. Price FW Jr, Whitson WE, Collins KS, Marks RG. Five-year corneal graft survival. A large, single-center patient cohort. Arch Ophthalmol. 1993 Jun;111(6):799-805. doi: 10.1001/archopht.1993.01090060087029. PMID: 8512481.
5. The collaborative corneal transplantation studies (CCTS). Effectiveness of histocompatibility matching in high-risk corneal transplantation. The Collaborative Corneal Transplantation Studies Research Group. Arch Ophthalmol. 1992 Oct;110(10):1392-403. PMID: 1417537.
6. Dana MR, Streilein JW. Loss and restoration of immune privilege in eyes with corneal neovascularization. Invest Ophthalmol Vis Sci. 1996 Nov;37(12):2485-94. PMID: 8933765.
7. Zhu J, Inomata T, Di Zazzo A et al. Role of Immune Cell Diversity and Heterogeneity in Corneal Graft Survival: A Systematic Review and Meta-Analysis. J Clin Med. 2021 Oct 12;10(20):4667. https://doi.org/10.3390/jcm10204667
8. Downward L, Ahmed M, Hopkinson C et al. Endothelial failure and rejection in recipients of corneas from the same donor. BMJ Open Ophthalmol. 2022 Aug;7(1):e000965. https://doi.org/10.1136/bmjophth-2021-000965
9. Maharana PK, Mandal S, Kaweri L et al. Immunopathogenesis of corneal graft rejection. Indian J Ophthalmol. 2023 May;71(5):1733-1738. https://doi.org/10.4103/IJO.IJO_2866_22
10. Marino J, Paster J, Benichou G. Allorecognition by T Lymphocytes and Allograft Rejection. Front Immunol. 2016 Dec 14;7:582. https://doi.org/10.3389/fimmu.2016.00582

11. Sachdeva, G. S., Cabada, J. P., Karim, S. S., Kahandawa, D. L., Thomas, K. A., Kumar, A., Barry, R. J., & Butt, G. F. (2021). Effectiveness of matching human leukocyte antigens (HLA) in corneal transplantation: a systematic review protocol. *Systematic reviews*, *10*(1), 150. https://doi.org/10.1186/s13643-021-01704-7
12. Jiang, T., Li, M., & Zhang, M. (2022). The correlation between human leucocyte antigen amino acid residue matching before keratoplasty and postoperative rejection: a systematic review and meta-analysis. *Annals of palliative medicine*, *11*(3), 1112–1120. https://doi.org/10.21037/apm-22-268
13. Zhong W, Montana M, Santosa SM, Isjwara ID, Huang YH, Han KY, et al. Angiogenesis and lymphangiogenesis in corneal transplantation-A review. Survey of Ophthalmology [Internet]. 2018 Jul 1 [cited 2022 May 6];63(4):453–79. Available from: https://pubmed.ncbi.nlm.nih.gov/29287709/
14. Yu, K., Lian, X. F., Jiang, X. Y., & Zhou, S. Y. (2021). Efficacy of Immunosuppressants in High Rejection Risk Keratoplasty: A Meta-Analysis of Comparative Studies. *Cornea*, *40*(6), 800–807. https://doi.org/10.1097/ICO.0000000000002709
15. Gorman, B. R., Francis, M., Nealon, C. L., Halladay, C. W., Duro, N., Markianos, K., Genovese, G., Hysi, P. G., Choquet, H., Afshari, N. A., Li, Y. J., VA Million Veteran Program, Gaziano, J. M., Hung, A. M., Wu, W. C., Greenberg, P. B., Pyarajan, S., Lass, J. H., Peachey, N. S., & Iyengar, S. K. (2024). A multi-ancestry GWAS of Fuchs corneal dystrophy highlights the contributions of laminins, collagen, and endothelial cell regulation. *Communications biology*, *7*(1), 418. https://doi.org/10.1038/s42003-024-06046-3
16. Qi, X., Wang, L., Zhang, X., Liu, M., & Gao, H. (2022). Topical administration of tacrolimus and corticosteroids in tapering doses is effective in preventing immune rejection in high-risk keratoplasty: a 5-year follow-up study. *BMC ophthalmology*, *22*(1), 101. https://doi.org/10.1186/s12886-022-02318-w
17. Fujio, K.; Sung, J.; Nakatani, S.; Yamamoto, K.; Iwagami, M.; Fujimoto, K.; Shokirova, H.; Okumura, Y.; Akasaki, Y.; Nagino, K.; et al. Characteristics and Clinical Ocular Manifestations in Patients with Acute Corneal Graft Rejection after Receiving the COVID-19 Vaccine: A Systematic Review. *J. Clin. Med.* **2022**, *11*, 4500. https://doi.org/10.3390/jcm11154500
18. Lockington, D., Lee, B., Jeng, B. H., Larkin, D. F. P., & Hjortdal, J. (2021). Survey of Corneal Surgeons' Attitudes Regarding Keratoplasty Rejection Risk Associated With

Vaccinations. *Cornea*, *40*(12), 1541–1547. https://doi.org/10.1097/ICO.0000000000002662

19. Lee, E. H., & Li, J. Y. (2022). Immunization-Associated Corneal Transplantation Rejection: A Review. *Cornea*, *41*(5), 660–663. https://doi.org/10.1097/ICO.0000000000002898
20. Meng T, Zheng J, Shin CS, Gao N, Divya Bande, Hadi Sudarjat, et al. Combination Nanomedicine Strategy for Preventing High-Risk Corneal Transplantation Rejection. ACS Nano. 2024 Jul 29;18(31):20679–93.
21. Decellularization of porcine corneas and repopulation with human corneal cells for tissue-engineered xenografts [Internet]. Google.co.il. 2024 [cited 2024 Nov 25].
22. Li, S., Xiao, P., Deng, Y., Li, M., Wang, Q., & Yuan, J. (2021). Acellular Porcine Corneal Stroma May Not Be Optimal for Peripheral Keratoplasty: Reports of 2 Cases. *Cornea*, *40*(4), 502–505. https://doi.org/10.1097/ICO.0000000000002496
23. Chen, L. N., Hao, J. L., Liu, X. F., Zhou, D. D., Pant, O. P., Liu, X. Y., Liu, H. F., Liu, H. W., & Lu, C. W. (2022). Rejection of Acellular Porcine Corneal Stroma Transplantation During Coronavirus Disease 2019 Pandemic. *The Journal of craniofacial surgery*, *33*(5), 1300–1302. https://doi.org/10.1097/SCS.0000000000008324
24. Zheng, Q., Zhang, Y., Ren, Y., Zhao, Z., Hua, S., Li, J., Wang, H., Ye, C., Kim, A. D., Wang, L., & Chen, W. (2021). Deep anterior lamellar keratoplasty with cross-linked acellular porcine corneal stroma to manage fungal keratitis. *Xenotransplantation*, *28*(2), e12655. https://doi.org/10.1111/xen.12655
25. Zheng, J., Huang, X., Zhang, Y., Wang, Y., Qin, Q., Lin, L., Jin, X., Lam, C., & Zhang, J. (2019). Short-term results of acellular porcine corneal stroma keratoplasty for herpes simplex keratitis. *Xenotransplantation*, *26*(4), e12509. https://doi.org/10.1111/xen.12509
26. Roumeau, S., Dutheil, F., Sapin, V., Baker, J. S., Watson, S. L., Pereira, B., Chiambaretta, F., & Navel, V. (2022). Efficacy of treatments for neurotrophic keratopathy: a systematic review and meta-analysis. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*, *260*(8), 2623–2637. https://doi.org/10.1007/s00417-022-05602-z
27. Baig IF, Le NT, Zaina Al-Mohtaseb. Amniotic membrane transplantation: an updated clinical review for the ophthalmologist. Annals of Eye Science [Internet]. 2023 Jun 1

[cited 2024 Aug 22];8:5–5. Available from: https://aes.amegroups.org/article/view/7312/html

28. Ting, D. S. J., Henein, C., Said, D. G., & Dua, H. S. (2021). Amniotic membrane transplantation for infectious keratitis: a systematic review and meta-analysis. *Scientific reports*, *11*(1), 13007. https://doi.org/10.1038/s41598-021-92366-x
29. Qi, X., Wang, L., Zhang, X., Liu, M., & Gao, H. (2022). Topical administration of tacrolimus and corticosteroids in tapering doses is effective in preventing immune rejection in high-risk keratoplasty: a 5-year follow-up study. *BMC ophthalmology*, *22*(1), 101. https://doi.org/10.1186/s12886-022-02318-w
30. Marques, R. E., Leal, I., Guerra, P. S., Barão, R. C., Quintas, A. M., & Rodrigues, W. (2022). Topical corticosteroids with topical cyclosporine A versus topical corticosteroids alone for immunological corneal graft rejection. *European journal of ophthalmology*, *32*(3), 1469–1481. https://doi.org/10.1177/11206721211023320
31. Din, N., Cohen, E., Popovic, M., Mimouni, M., Trinh, T., Gouvea, L., Alshaker, S., Ong Tone, S., Chan, C. C., & Slomovic, A. R. (2022). Surgical Management of Fuchs Endothelial Corneal Dystrophy: A Treatment Algorithm and Individual Patient Meta-Analysis of Descemet Stripping Only. *Cornea*, *41*(9), 1188–1195. https://doi.org/10.1097/ICO.0000000000002975
32. Magnier F, Dutheil F, Pereira B, Watson SL, Baker JS, Chiambaretta F, et al. Preventive treatment of allograft rejection after endothelial keratoplasty: A systematic review and meta-analysis. Acta Ophthalmologica. 2022 Apr 11;100(5).
33. Dimtsas, G. S., & Moschos, M. M. (2023). Ultrathin-Descemet Stripping Automated Endothelial Keratoplasty *Versus* Descemet Membrane Endothelial Keratoplasty: A Systematic Review and Meta-analysis. *In vivo (Athens, Greece)*, *37*(1), 400–409. https://doi.org/10.21873/invivo.13092
34. Hurley, D. J., Murtagh, P., & Guerin, M. (2023). Ultrathin Descemet Stripping Automated Endothelial Keratoplasty (UT-DSAEK) versus Descemet Membrane Endothelial Keratoplasty (DMEK)-a systematic review and meta-analysis. *Eye (London, England)*, *37*(14), 3026–3032. https://doi.org/10.1038/s41433-023-02467-2
35. Augustin, V. A., Son, H. S., Yildirim, T. M., Meis, J., Łabuz, G., Auffarth, G. U., & Khoramnia, R. (2023). Refractive outcomes after DMEK: meta-analysis. *Journal of cataract and refractive surgery*, *49*(9), 982–987. https://doi.org/10.1097/j.jcrs.0000000000001212

36. Sela TC, Moti Iflah, Khitam Muhsen, Alon Zahavi. Descemet membrane endothelial keratoplasty compared with ultrathin Descemet stripping automated endothelial keratoplasty: a meta-analysis. BMJ Open Ophthalmology [Internet]. 2023 Nov 1 [cited 2024 Nov 25];8(1):e001397–7. Available from: https://bmjophth.bmj.com/content/8/1/e001397
37. Béal, L., Navel, V., Pereira, B., Magnier, F., Watson, S. L., Baker, J. S., Chiambaretta, F., & Dutheil, F. (2022). Efficacy of Thin and Ultrathin Descemet Stripping Automated Endothelial Keratoplasty and Influence of Graft Thickness on Postoperative Outcomes: Systematic Review and Meta-analysis. *American journal of ophthalmology*, *240*, 170–186. https://doi.org/10.1016/j.ajo.2022.03.022
38. Mohebbi, M., Mehrpour, M., Sanij, A. D., Mohammadi, N., & Mirghorbani, M. (2022). Pediatric endothelial keratoplasty: a systematic review and individual participant data meta-analysis. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*, *260*(4), 1069–1082. https://doi.org/10.1007/s00417-021-05459-8