Scientific Works. Series C. Veterinary Medicine. Vol. LXXI (1), 2025
ISSN 2065-1295; ISSN 2343-9394 (CD-ROM); ISSN 2067-3663 (Online); ISSN-L 2065-1295

COMPARATIVE STUDY OF THE USE OF AMNIOTIC MEMBRANE SUSPENSION (EYEQ AMNIOTIC EYE DROPS®) IN NON-VASCULARIZED AND VASCULARIZED INDOLENT CORNEAL ULCERS IN DOGS

Iuliana IONAȘCU[1*], Jacqueline MOCANU[1]

[1]University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine, 105 Splaiul Independentei, 5th District, 050097, Bucharest, Romania

*Corresponding author email: iuliana.ionascu@usamv.ro

Abstract

Indolent corneal ulcers in dogs, also known as canine spontaneous chronic corneal epithelial defects (SCCEDs), represent a significant challenge for veterinarians due to their frequency and tendency to recur, particularly in brachycephalic breeds. Debridement plays a crucial role in the healing process of indolent corneal ulcers in dogs. Over time, combinations of antibiotic eye drops and corneal healing agents have been employed.
This study compared the effectiveness of an amniotic membrane suspension (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) in 22 dogs diagnosed with non-vascularized and vascularized indolent corneal ulcers following multiple debridement procedures. The results of the study demonstrated that the presence of corneal vascularization reduces the healing period compared to non-vascularized indolent corneal ulcers.

Key words*: indolent corneal ulcer, amniotic membrane suspension eye drops, debridement, dog.*

INTRODUCTION

Indolent corneal ulcers in dogs that fail to heal and are refractory to conventional therapy are common in veterinary practice. Known as canine spontaneous chronic corneal epithelial defects (SCCEDs) can be superficial characterized by loss of corneal epithelium and exposure of corneal stroma without stromal loss (Gelatt et al., 2013; Eaton et al., 2017) or can be deep corneal ulcers and involve stromal defect (Bentley, 2005; Gellat et al., 2021).
Clinically, patients present ocular pain, blepharospasm, epiphora, corneal oedema peripheral to the lesion and the fluorescein test is positive (Maggs et al., 2013). Examination with a magnifying glass reveals a non-adherent anterior corneal epithelium under which fluorescein stain test is positive (Figure 1). Debridement of the non-adherent epithelium is a mandatory procedure before initiating local therapy. Cotton-tip debridement, scalpel blade debridement and superficial grid keratotomy (Boutin et al., 2020; Ionașcu, 2023) are inexpensive and efficient methods for the treatment of SCCEDs, performed under local anaesthesia.
In many cases (Figure 2), the anterior corneal epithelium is removed over a significant surface area.
Landrevie et al. (2023) utilized combinations of cotton-tip epithelial debridement and corneal thermal cautery, with or without diamond burr debridement, in the treatment of this condition.

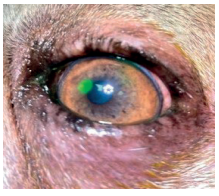

Figure 1. OS Four-years-old French Bulldog with central indolent corneal ulcer, bordered by a lip of non-adherent epithelium

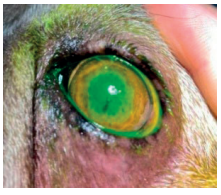

Figure 2. OS Previous case after cotton-tip debridement

After debridement, local treatment is carried out using antibiotic eye drops and corneal healing agents, administered 3-4 times per day (Maggs et al., 2017).

In indolent corneal ulcers, following debridement, daily disposable human contact lenses (Acuvue Oasys®) or bandage lenses specifically designed for dogs (An-Vision, GmbH®) can be used. These lenses protect the cornea, reduce pain, and consequently shorten the healing time (Ionașcu, 2021; Ionașcu, 2023). Another study demonstrates that a cross-linked, modified HA hydrogel provides further benefit by accelerating time to corneal wound closure compared to a non-cross-linked HA solution (Williams et al., 2017).

Over the past few years, a new type of matrix therapy agent named ReGeneraTing Agent (RGTA®) has provided encouraging results, accelerating the healing of chronic skin ulcers of diabetic or vascular origin (Martinez et al., 2019). RGTA® is a set of molecules, chemically engineered polymers, that are specifically designed to replace degraded heparan sulphate molecules in the injured matrix compartment. Therefore, they are considered as heparan sulphate mimetics based on their chemical structures and functions. RGTA® protects naturally existing structural and signalling proteins, and in doing so, creates a cellular microenvironment favourable to healing, thereby enhancing the speed and quality of tissue repair (Barritault et al., 2017; Hayek et al., 2016*)*.

In the domain of ophthalmology, an RGTA® family compound named OTR4120, a heparan sulphate mimetic, has been reported to show encouraging results for the treatment of corneal ulcers and dystrophies of various aetiologies (Chebbi et al., 2008).

The amniotic membrane (AM) has a long history of use in the treatment of various diseases of the ocular surface in human. It contains pluripotent cells, highly organized collagen, anti-fibrotic and anti-inflammatory cytokines, immune-modulators, growth factors, and matrix proteins (Murri et al., 2018). Recently, AM extract and AM extract eye drops have been successfully used in clinical applications, including dry eye and chemical burns in human (Murri et al., 2018). This is due to its ability to preserve the biochemical properties of the corneal material while delivering essential extracellular matrix components to the damaged cornea (Guo et al., 2011; Ledbetter et al., 2006).

Using the results obtained in the treatment of corneal conditions in humans with eye drops containing amniotic membrane suspension as a reference, a new product (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) has been developed for use in veterinary ophthalmology in recent years.

In the specialized literature, experimental studies have been conducted using amniotic membrane eye drops (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) in cases of superficial corneal ulcers in horses (Lyons et al., 2020) and stromal ulcers in rats (Lee et al., 2024).

The studies conducted by Lyons, 2020 aimed to evaluate the effect of amniotic membrane extract on re-epithelialisation of equine corneal ulcers compared with ulcers treated with antibiotic, antifungal and mydriatic medical therapy alone, and to evaluate equine corneal healing after experimentally induced superficial ulceration.

Lee et al., 2024 conducted a comparative study on the effect of topical amniotic membrane suspension (AMS) and ReGeneraTing Agent (RGTA) on surgically induced deep stromal ulcers in rats.

To the best of our knowledge, there are no studies investigating the efficacy of amniotic membrane suspension in non-vascularized and vascularized indolent corneal ulcers in dogs. The aim of this study is to present the clinical efficacy of amniotic membrane suspension (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) in superficial and deep indolent corneal ulcer in dogs.

MATERIALS AND METHODS

A total of 22 dogs were presented at the Veterinary Teaching Hospital (Faculty of Veterinary Medicine Bucharest) for nonhealing corneal ulcers after failure of primary treatment by the referring veterinarian, usually by epithelial debridement, without evidence of defect resolution for several weeks to months. A total of 22 dogs (22 eyes) were evaluated in these case reports. All dogs were privately owned pets. Owners reviewed and signed an informed consent form before samples were

collected, as well as providing consent for the use of (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) after debridement of indolent corneal ulcer.

To assess the efficacy of EyeQ Amniotic Eye drops®, Vetrix, Cumming, GA, a total of 22 dogs referred for non-healing ulcers were enrolled in this study.

All dogs underwent complete clinical evaluation and 10 dogs were diagnosed with superficial non-vascularized indolent corneal ulcer (Figures 3 and 4), 5 dogs were diagnosed with deep non-vascularized indolent corneal ulcers (Figure 6), and 7 dogs were diagnosed with deep vascularized indolent corneal ulcers (Figure 8).

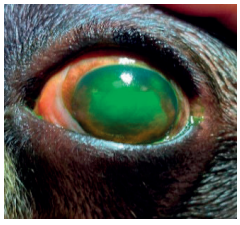

Figure 3. OS Seven-years-old French Bulldog with superficial non vascularized indolent corneal ulcer

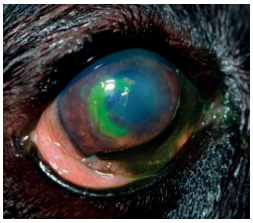

Figure 4. OD Eleven-years-old Terra Nova with superficial non vascularized indolent corneal ulcer

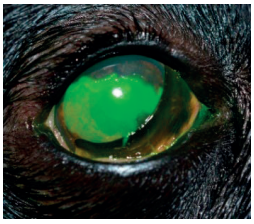

Figure 5. Case from figure 4, eleven-years-old Terra Nova with superficial non vascularized indolent corneal ulcer, clinical aspect after cotton-tip debridement

All dogs underwent sterile cotton-tip debridement under local anaesthesia with oxybuprocaine hydrochloride 0.4% (Benoxi®, Unimed Pharma).

The cotton-tipped swab was passed over the ulcer in multiple circular motions, removing the non-adherent epithelium (Figure 5, Figure 7, and Figure 9).

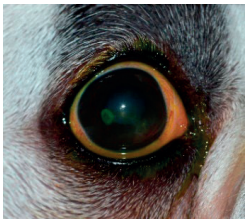

Figure 6. OD Nine-years-old English Bulldog with deep non vascularized indolent corneal ulcer

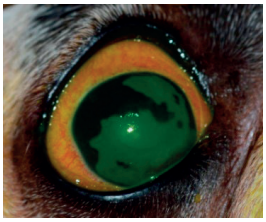

Figure 7. Case from figure 6, nine-years-old English Bulldog with deep non vascularized indolent corneal ulcer, clinical aspect after cotton-tip debridement

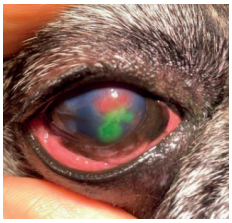

Figure 8. OD Ten-years-old English Bulldog with deep vascularized indolent corneal ulcer

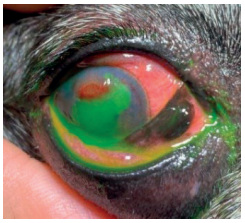

Figure 9. Case from figure 6, ten-years-old English Bulldog with deep vascularized indolent corneal ulcer clinical aspect after cotton-tip debridement

After debridement, the dogs were locally treated with Tobramycin eye drops (Tobrom®, 3 mg/ml, Rompharm Company SRL) și EyeQ

Amniotic Eye drops®, Vetrix, Cumming, GA, three times a day. The patients were examined every 7 days for a period of 2 months, and debridement of the ulcers was performed when the fluorescein test revealed the denuded anterior epithelium.

The corneal ulcers were considered healed when the cornea showed a negative fluorescein test and there was no evidence of blepharospasm or ocular discharge.

The data were analyzed for breed, age, duration of clinical signs before referral, number of cotton-tip debridements, number of weeks before corneal vascularization appeared, number of weeks before healing was achieved, and any and complications.

RESULTS AND DISCUSSIONS

The corneal ulcers had been treated by referring veterinarians for a median of 13 weeks (range 2 weeks - 24 weeks) prior to enrollment in this study. Medical treatment consisted of topical and systemic antibiotics, as well as topical artificial tear solutions containing hyaluronic acid.

Dog breeds included French Bulldog (n=5), Shih-Tzu (n=3), English Bulldog (n=2), Bichon (n=2), Pug (n=2), Pekingese (n=2), crossbreds (n=2), Terra Nova (n=1), Samoyed (n=1), Jack Russel Terrier (n=1), Amstaff (n=1). The median age was 7 years, with a range between 1 year and 13 years. Eight patients were female (36.36%) and 14 were male (63.64%). Ten patients were treated in the right eye (45.45%) and 12 in the left eye (54.55%).

From the total number of dog patients (n=22), 5 dogs (22.72%) were diagnosed with non-vascularized deep indolent corneal ulcers (DN), 10 dogs (45.45%) with non-vascularized superficial indolent corneal ulcers (SN) and 7 dogs (31.82%) with vascularized deep indolent corneal ulcer (DV). The number of debridements varied: 3 dogs underwent 1 debridement, 5 dogs had 2 debridements, 10 dogs had 3 debridements, 2 dogs had 4 debridements, 1 dog had 5 debridements, and 1 dog had 6 debridements (Table 1).

Table 1. Patients' data included in the study

Case number	Breed	Age (years) Sex	Affected eye	Type of ulcer	Number of debridements	Time until vascularization	Healing time (weeks)	Complication
1.	Samoyed	11/M	OD	DN	3	3	8	pigmentation
2.	Bichon	12/F	OD	DN	2	3	5	None
3.	Jack Russel Terrier	13/M	OS	DN	2	3	5	pigmentation
4.	English Bulldog	7/M	OS	DN	4	1	5	pigmentation
5.	Shih Tzu	6/M	OD	DN	3	1	4	None
6.	French Bulldog	7/M	OD	SN	6	4	8	None
7.	English Bulldog	6/M	OS	SN	3	4	6	None
8.	French Bulldog	3/M	OD	SN	3	2	5	None
9.	Terra Nova	11/F	OD	SN	5	5	12	pigmentation
10.	Pug	6/M	OS	SN	3	1	5	None
11.	French Bulldog	7/F	OD	SN	2	1	3	pigmentation
12.	French Bulldog	10/F	OS	SN	3	3	12	pigmentation
13.	French Bulldog	1/F	OS	SN	1	without	2	None
14.	Amstaff	10/M	OS	SN	4	4	6	None
15.	Pug	2/M	OD	SN	1	without	3	None
16.	Bichon	3/F	OS	DV	1	present	3	None
17.	Shih Tzu	12/M	OS	DV	3	present	4	None
18.	Shih Tzu	12/F	OS	DV	3	present	4	None
19.	Pekingese	8/M	OD	DV	2	present	3	None
20.	Crossbreds	9/M	OS	DV	3	present	5	None
21.	Crossbreds	12/M	OD	DV	2	present	4	pigmentation
22.	Pekingese	13/F	OS	DV	3	present	5	None

*SN - superficial non vascularized indolent corneal ulcer; DN - deep non-vascularized indolent corneal ulcer; DV - deep vascularized indolent corneal ulcer.

After 2 weeks of treatment, 4.54% (1/22) of cases with superficial non-vascularized indolent corneal ulcers (SN) healed (Figure 10).

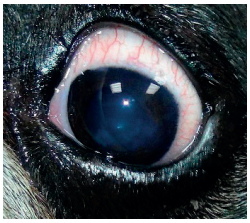

Figure 10. OS One-year-old French Bulldog with superficial non vascularized indolent corneal ulcer (SN) healed after 2 weeks and one debridement

After 3 weeks of treatment 18.18% (4/22) of cases healed, including two with superficial non-vascularized indolent corneal ulcers (SN) and two with deep vascularized indolent corneal ulcers (DV).
After 4 weeks of treatment 18.18% (4/22) of cases healed, including one with deep non-vascularized indolent corneal ulcer (DN) and three with deep vascularized indolent corneal ulcers (DV).
After 5 weeks of treatment 31.81% (7/22) of cases healed, including two with superficial non-vascularized indolent corneal ulcers (SN), three with deep non-vascularized indolent corneal ulcers (DN), and two with deep vascularized indolent corneal ulcers (DV).
After 6 weeks of treatment 9.09% (2/22) of cases, both with superficial non-vascularized indolent corneal ulcers (SN), healed.
After 8 weeks of treatment 9.09% (2/22) of cases healed, including one with superficial non-vascularized indolent corneal ulcer (SN) and one with deep non-vascularized indolent corneal ulcer (DN).
After 12 weeks of treatment 9.09% (2/22) of cases with superficial non-vascularized indolent corneal ulcers (SN) healed.
In patients with superficial non-vascularized indolent corneal ulcer (SN) și deep non-vascularized indolent corneal ulcer (DN) corneal vascularization appeared within a time frame ranging from 1 to 4 weeks. The vascularization was localized at the ulcer's margin (Figure 11) or, in some cases, very abundant, covering the entire surface of the ulcer (Figure 12).

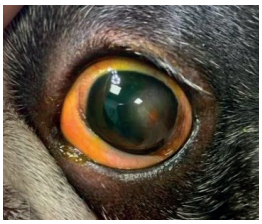

Figure 11. Clinical appearance of the vascularization in superficial non vascularized indolent corneal ulcer (SN) after 5 weeks of treatment

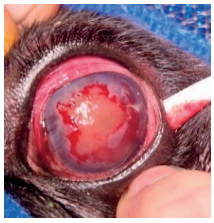

Figure 12. OS Ten-years-old French Bulldog, clinical appearance of the vascularization in superficial non vascularized indolent corneal ulcer (SN) after 6 weeks of treatment

The patients with deep vascularized indolent corneal ulcer (DV) healed at 3 weeks (2/7), 4 weeks (3/7) and 5 weeks (2/7). The cases (Table 2) with superficial non vascularized indolent corneal ulcer (SN) developed vascularization within a time frame ranging from 1 to 5 weeks, and healing occurred at 6 weeks (2/10), at 8 weeks (1/10) and at 12 weeks (2/10).
Two out of ten (2/10) cases with superficial non vascularized indolent corneal ulcer (SN) healed without the appearance of vascularization.

Table 2. Patients' data included in the study

Healing period in weeks	Number of cases with SN	Number of cases with DN	Number of cases with DV
2	1	0	0
3	2	0	2
4	0	1	3
5	2	3	2
6	2	0	0
8	1	1	0
12	2	0	0
TOTAL	10 cases	5 cases	7 cases

Fifteen out of twenty-two (68.2%) had healed without complications (Figure 13). The complications encountered in this case series were corneal pigmentation (Figure 14) in 7 cases (31.81%).

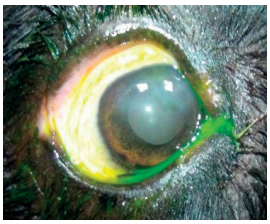

Figure 13. Case from figure 4, OD Eleven-years-old Terra Nova clinical appearance after 12 weeks of treatment for superficial non vascularized indolent corneal ulcer

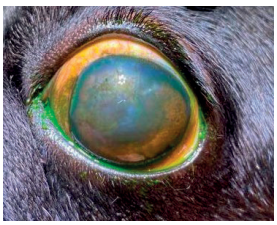

Figure 14. Case from figure 12 OS Ten-years-old French Bulldog, 12 weeks after the treatment. Corneal opacity and mild pigmentation

The local treatment with antibiotics (Tobrom®, 3mg/ml, Rompharm Company SRL) și EyeQ Amniotic Eye drops®, Vetrix, Cumming, GA administered three times a day, along with the debridements, led to the appearance of vascularization in superficial non-vascularized indolent corneal ulcers (SN) and deep non-vascularized indolent corneal ulcers (DN). Corneal vascularization accelerated the healing process.

Amniotic membrane extract eye drops (AMEED) showed a potential benefit in acute corneal injuries when human corneal epithelial cells and human limbal cells treated with AMEED healed faster after mechanical insult. In vitro and in vivo studies reveal that AMEED supports proliferation and differentiation of corneal epithelial cells, enhances epithelial wound healing, and inhibits corneal neovascularization and was as effective as transplanted AM in healing corneal damage in a rabbit model (Murri et al., 2018; Choi et al., 2011).

In addition, amniotic membrane extract (AME) can be combined with umbilical cord (UC) blood as another type of AM-derived solution (Tighe et al., 2017). This combination may be advantageous because the active-matrix component responsible for exerting AM's anti-inflammatory effects (HC-HA/PTX3 complex).

The AM has a long history of use in the treatment of various diseases of the ocular surface. It contains pluripotent cells, highly organized collagen, anti-fibrotic and anti-inflammatory cytokines, immune-modulators, growth factors, and matrix proteins. It is used to promote corneal healing in severely damaged eyes (Murri et al., 2018).

The amniotic membrane has long played a pivotal role in human corneal surgery (Meller et al., 2011), contributing to both the structural fortification of the cornea and the acceleration of the healing process. This is due to its ability to preserve the biochemical properties of the corneal material while delivering essential extracellular matrix components to the damaged cornea (Guo et al., 2011; Shimmura et al., 2002). Additionally, amniotic membrane exhibits antifibrotic and antiangiogenic effects, mitigating corneal scarring and maintaining transparency (Shimmura et al., 2002).

Most of the beneficial effects of AM are attributed to biomolecules, such as fibronectin, hepatocyte growth factor (HGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF), and collagen types I, III, IV, and V, which are potent sources for corneal regeneration (Mamede et al., 2012). They combine to facilitate migration, adhesion, and differentiation of the model specifically designed to evaluate deep stromal ulcers (Lee et al., 2024).

We must emphasize here the need for careful selection of the patients.

In our study the patients did not show any local or systemic side effects. Owner compliance was very good, except for the fact that the product needs to be stored in the refrigerator between administrations. Some owners reported that the patient keeps its eye closed and exhibits minimal blepharospasm after administration.

This case series is limited by the heterogeneity of the cases and the lack of a comparative control group. Further research is needed using OCT for accurate diagnosis of the depth and extent of the lesions, as well as for assessing the healing process. Further studies are necessary to compare (EyeQ Amniotic Eye Drops®, Vetrix,

Cumming, GA, USA) with other therapies in corneal pathologies in dogs.

CONCLUSIONS

The results of this study suggest that the (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) may be a safe and effective treatment for indolent corneal ulcers in dogs.

The (EyeQ Amniotic Eye Drops®, Vetrix, Cumming, GA, USA) is well tolerated, and the corneal healing is achieved with only 3 administrations per day.

The appearance of corneal vascularization reduces the healing time. In non-vascularized indolent corneal ulcers, the healing period is longer.

Further studies are necessary to determine the clinical efficacy in larger trials using OCT for classifying indolent ulcers based on their depth and extent.

REFERENCES

Barritault D., Gilbert-Sirieix M., Rice K.L., Sineriz F., Papy-Garcia D., Baudouin C., Desgranges P., Zakine G., Saffar J.L., van Neck J. (2017). RGTA® or ReGeneraTing Agents mimic heparan sulfate in regenerative medicine: From concept to curing patients. *Glycoconjugate Journal*, 34:325–338. doi: 10.1007/s10719-016-9744-5.

Bentley, E. (2005). Spontaneous chronic corneal epithelial defects in dogs: A review. *Journal of the American Animal Hospital Association*, Vol. 41, pp. 158–165. https://doi.org/10.5326/0410158

Boutin, M-P., Couterlier, M., Olivier, F. J. (2020). Cotton-tip debridement, scapel blade debridement, and superficial grid keratotomy for treatment of spontaneus chronic corneal epithelial defects (SCCED): A retrospective evaluation of 308 cases. *Veterinary Ophthalmology*, 23(6):979-986. doi:101111/vop.12838

Chebbi, C. K., Kichenin, K., Amar, N., Nourry, H., Warnet, J., Barritault, D., & Baudouin, C. (2008). Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy. *Journal Francais D'ophtalmologie, 31*(5), 465–471.

Choi, J. A., Choi, J.-S., & Joo, C.-K. (2011). Effects of amniotic membrane suspension in the rat alkali burn model. *Molecular Vision, 17*, 404.

Eaton, J. S., Hollingsworth, S. R., Holmberg, B. J., Brown, M. H., Smith, P. J., & Maggs, D. J. (2017). Effects of topically applied heterologous serum on reepithelialization rate of superficial chronic corneal epithelial defects in dogs. *Journal of the American Veterinary Medical Association*, *250*(9), 1014–1022. https://doi.org/10.2460/javma.250.9.1014

Gelatt, K., Ledbetter, E. C., & Gilger, B. C. (2013). *Veterinary Ophtalmology*.

Gelatt, K. N., Ben-Shlomo, G., Gilger, B. C., Hendrix, D. V., Kern, T. J., & Plummer, C. E. (2021). *Veterinary ophthalmology*. John Wiley & Sons.

Guo, Q., Hao, J., Yang, Q., Guan, L., Ouyang, S., & Wang, J. (2011). A comparison of the effectiveness between amniotic membrane homogenate and transplanted amniotic membrane in healing corneal damage in a rabbit model. *Acta Ophthalmologica, 89*(4), e315–e319.

Hayek, S., Dibo, S., Baroud, J., Ibrahim, A., Barritault, D. (2016). Refractory sickle cell leg ulcer: Is heparansulphate a new hope? *Int. Wound Journal*;13:35–38. doi: 10.1111/iwj.12217.

Ionașcu, I. (2021) *Atlas of Veterinary Ophthalmology*, second edition, Curtea Veche, Bucharest, Romania; Chapter 1, pp. 10-18; Chapter 2, pp. 45-47.

Ionașcu, I. (2023) *Chirurgie oftalmologică veterinară,* Curtea Veche, Bucharest, Romania; Chapter 6 pp. 118-124 and pp. 278-284.

Landrevie, C., Marchal, J., Robin, M.C., Douet, J.Y. (2023). Treatment of canine spontaneus chronic corneal epithelial defects (SCCEDs): A retrospective study of 89 cases. *Veterinary Ophthalmology,* 26(4) 280-287. doi:101111/vop.13128

Lee, H., Huang, W-H., Sun, Y.C., Lin, C.T., (2024). Investigation of topical amniotic membrane suspension and regenerating agent on early corneal stromal healing in rats, *Veterinary and Animal Science,*https://doi.org/10.1016/j.vas.2024.100344

Ledbetter, E. C., Munger, R. J., Ring, R. D., & Scarlett, J. M. (2006). Efficacy of two chondroitin sulfate ophthalmic solutions in the therapy of spontaneous chronic corneal epithelial defects and ulcerative keratitis associated with bullous keratopathy in dogs. *Veterinary Ophthalmology*, *9*(2), 77–87. https://doi.org/10.1111/j.1463-5224.2006.00439.x

Lyons, V.N., Townsend, W.M., Moore, G.E., Liang, S. (2020). Commercial amniotic membrane extract for treatment of corneal ulcers in adult horses. *Equine Veterinary Journal,* Vol 53(6), 1268-1276, https://doi.org/10.1111/evj.13399

Maggs, D., Miller, P.E., Ofri, R. (2013). Slatter's Fundamentals of Veterinary Ophtalmology, 6th edition, Elsevier, 213-240

Maggs, D., Miller, P., & Ofri, R. (2017). *Slatter's fundamentals of veterinary ophthalmology E-Book*. Elsevier Health Sciences.

Mamede, A. C., Carvalho, M. J., Abrantes, A. M., Laranjo, M., Maia, C. J., & Botelho, M. F. (2012). Amniotic membrane: From structure and functions to clinical applications. *Cell and Tissue Research, 349*(2), 447–458.

Martinez, J.A., Chiappini, F., Barritault, D., (2019)**.** Case reports for topical treatment of corneal ulcers with a new matrix therapy agent or rgta® in dogs, *Veterinary Sciences,* 6(4):103, doi: 10.3390/vetsci6040103.

Meller, D., Pauklin, M., Thomasen, H., Westekemper, H., & Steuhl, K.-P. (2011). Amniotic membrane transplantation in the human eye. *Deutsches Arzteblatt International, 108*(14), 243.

Murri, M.S., Moshirfar, M., Birdsong, O.C., Ronquillo, Y.C., Ding, Y., Hoopes, P.C. (2018). Amniotic membrane extract and eye drops: a review of literature and clinical aplication, *Clinic Ophtalmology*, 18:12:1105-1112. doi: 10.2147/OPTH.S165553

Tighe, S., Moein.H. R., Chua, L., Cheng, A., Hamrah, P., Tseng, S.C.G. (2017). Topical Cryopreserved Amniotic Membrane and Umbilical Cord Eye drops Promote Re-Epithelization in a Murine Corneal Abrasion Model. *Invest Ophthalmol. Vis Sci* 58(3):1586-1593, doi: 10.1167/iovs.16-20834.

Williams, D. L., Wirostko, B. M., Gum, G., & Mann, B. K. (2017). Topical cross-linked HA-based hydrogel accelerates closure of corneal epithelial defects and repair of stromal ulceration in companion animals. *Investigative Ophthalmology and Visual Science*, *58*(11),4616–4622. https://doi.org/10.1167/iovs.16-20848