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Keratitis and Current Treatment Methods in Pets

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Abstract: Keratitis is defined as infectious and non-infectious eye disease in human medicine and ulcerative and non-ulcerative disease in veterinary medicine. The corneal epithelium is the transparent anterior part of the eye that covers the iris and pupil. It acts as a transparent membrane that allows light to pass through the eye. A healthy cornea prevents bacteria invasion of the eye via anatomical, mechanical, immunological, and microbiological mechanisms. Failure of these defenses and trauma, immunosuppression, and neurological or iatrogenic factors predispose the cornea to ulcerative keratitis and bacterial eye infections. Inadequate tear secretion and eyelid dysfunction lead to insufficient corneal protection, and the combination of these reasons with endogenous causes triggers excessive epithelial damage.
Keywords: Cornea, keratitis, ocular surface disease

Evcil Hayvanlarda Keratit ve Güncel Tedavi Yöntemleri

Öz: Keratit, insan hekimliğinde enfeksiyöz ve non-enfeksiyöz göz hastalığı, veteriner hekimliğinde ise ülseratif ve non-ülseratif göz hastalığı olarak tanımlanır. Kornea epiteli, iris ve pupillayı örten gözün şeffaf ön kısmıdır. Işığın gözden geçmesini sağlayan şeffaf bir zar görevi görür. Sağlıklı bir kornea anatomik, mekanik, immunolojik ve mikrobiyolojik mekanizmalarla çeşitli bakterilerin istilasını önler. Hastalıklar, travma ve immunsupresyon, nörolojik veya iyatrojenik nedenlerle bu savunmanın yetersiz kalması korneayı ülseratif keratit ve bakteriyel göz enfeksiyonlarına yatkın hale getirir. Eksik gözyaşı salgısı ve göz kapağı disfonksiyonu yetersiz kornea korumasına yol açar ve bu nedenlerin endojen nedenlerle birleşmesi aşırı epitel hasarını tetikler.
Anahtar kelimeler: Keratit, kornea, oküler yüzey hastalığı

Introduction

The transparent front layer of the eye known as the corneal epithelium serves as a transparent membrane to let light pass through while covering the iris and pupil (Leong and Tong, 2015). A healthy cornea is reported to prevent the invasion of various bacteria via anatomical, mechanical, immunological and microbiological mechanisms. Failure of these defenses due to disease, trauma, immunosuppression, neurological or iatrogenic causes has been reported to predispose the cornea to ulcerative keratitis and bacterial infections (Hindley et al., 2015). Ocular surface infections, which can develop due to corneal abrasion, could pose a severe threat to vision by causing ulceration and tissue destruction (Cappiello et al., 2023). The corneal infection could be seen due to contamination of the traumatic ulcer or the introduction of microorganisms from the environment by traumatically micro puncture of the corneal stroma. However, epithelial nonulcerative keratomycosis associated with precorneal tear film instability occurs without predisposing corneal damage. Therefore, a cornea infected with fungi may not initially stain with fluorescein (Mustikka et al., 2020).

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Types of Keratitis

Bacterial keratitis

Bacterial keratitis caused by infectious organisms is a sight-threatening disease. These organisms should be identified early and their antibiotic susceptibility should be known (Hall and Franzco, 2004). Bacterial infections can cause rapid disease progression and loss of the eye due to both bacterial and host-derived factors, including toxins and proteinases (Hindley et al., 2015). It is reported that bacterial keratitis is a clinically significant disease, although it is less common in cats compared to other domestic animals (Goldreich et al., 2020). Refractive corneal surgery and immunosuppression trigger bacterial keratitis (Fleiszig and Evans, 2002; Carion et al., 2018). A combination of direct microscopy and culture on a bacteriological plate medium is recommended for

diagnosing bacterial keratitis (Schonheyder et al., 1997). Gram-negative and gram-positive bacteria such as *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., and *Serratia* spp. are mostly isolated from patients with bacterial keratitis (Fleiszig and Evans, 2002). The traditional clinical protocol for bacterial keratitis is the topical application of broad-spectrum antibiotic eye drops. However, delay in laboratory testing for appropriate antibiotic selection may alter the course of the disease and high doses of antibiotics may cause toxicity. Therefore, new therapeutic approaches such as metal nanoparticles, cationic species, photothermal and photodynamic therapy are being investigated (Fan et al., 2023). *Pseudomonas aeruginosa* is an opportunistic, gram-negative pathogen commonly associated with bacterial keratitis (Carion et al., 2018). This pathogen, which causes significant destruction and loss of stromal tissue, typically presents as a rapidly progressive, suppurative stromal infiltrate and prominent mucopurulent exudate. Necrosis surrounded by inflammatory epithelial edema and stromal ulceration is reported to be characteristic of this disease (Hazlett, 2004). In *Pseudomonas aeruginosa* infections, glucocorticoids with potent strong anti-inflammatory and immunosuppressive properties are recommended to be used with intensive topical antibiotic use (Murugan et al., 2016; Yang et al., 2018).

Zhu et al. (2020) created four groups with the *P. aeruginosa* keratitis model in their study. They administered TobraDex (0.3% tobramycin + 0.1% dexamethasone) in the first group, Tobrex (0.3% tobramycin) in the second group, 0.1% dexamethasone in the third group and standard saline solution in the fourth group four times in a day. As a result of the study, they reported that neutrophil infiltration decreased in the Tobrex group, severe neutrophil infiltration and bacterial load decreased in the Dexamethasone group, and the amount of neutrophils and bacterial load decreased more in the TobraDex group than in other groups. In conclusion, they emphasized that the mice treated with TobraDex and Tobrex exhibited mild corneal damage; converserly, the mice treated with dexamethasone exhibited very severe corneal damage, and clinical findings supported these conditions.

Clinically, small abscess-like lesions with a mostly grey-white appearance, minimal epithelial edema and stromal infiltrates had been reported in *Staphylococcus spp.* in keratitis. It is emphasized that intrastromal abscesses and perforation may occur in chronic *Staphylococcus* keratitis (Shrestha et al., 2020). In their study, Bello et al. (2023) compared the effects of Genipin extract which was obtained from *Gardenia Jasminoides Ellis* in *S. auerus* and *P. aeruginosa* keratitis in their study. They reported that Genipin treatment reduced the bacterial load and alleviated the severity of keratitis by suppressing neutrophil infiltration. In addition, they reported that Interleukin-1, Interleukin-6, Interleukin-8, Interleukin-15, and Tumour Necrosis Factor- α values decreased significantly in Genipin treatment. As a result of the study, they offered that Genipin could be used in bacterial keratitis.

Ulcerative keratitis

Ulcerative keratitis, which exposes the corneal stroma and causes blepharospasm, photophobia, lacrimation, conjunctival hyperemia, and corneal edema, is one of the most common ocular surface diseases (Iwashita et al., 2020). The inadequate corneal protections due to the lack of tear volume and eyelid dysfunction with endogenous causes trigger excessive epithelial damage. Eyelid, eyelash, and tear film dysfunctions are more common in dogs, especially in brachycephalic breeds (Iwashita et al., 2020; Packer et al., 2015). Numerous etiologies, including morphological and neurological abnormalities of the eyelids, abnormal eyelashes or facial hair, quantitative or qualitative tear film abnormalities, corneal innervation deficiencies, foreign bodies, and bacterial infections, can cause corneal ulcers (Ledbetter et al., 2006). The eye can be examined with white or cobalt blue light to diagnose ulcerative keratitis after fluorescein staining. In addition, it is reported that bacterial and fungal cell culture, cytology and Polymerase Chain Reaction (PCR) can be used to determine the causative agent of ulcers (Edman et al., 2019). It is reported that most superficial ulcerative keratitis can heal rapidly, but progressed keratitis to the stroma may cause visual loss. Corneal stroma damage is typically attributed to bacterial infection by the presence of proteases and collagenases and is reported to be associated with anterior uveitis. Therefore, deep ulcerative keratitis is an ocular disease that requires intensive treatment with antibiotics, and cycloplegic and proteinase inhibitors (Bustamente et al., 2018). Topical corticosteroids are reported to be contraindicated (Hartley, 2010).

Deepika et al. (2023) randomly divided 20 dogs with deep ulcerative keratitis into two groups and treated the first group with 0.1% Tacrolimus, 0.5% moxifloxacin and oral doxycycline and dietary nutritional supplements. The second group was treated with 0.1% cyclosporine, 0.5% moxifloxacin, oral doxycycline and dietary nutritional supplements. At the end of the one month they reported that there was a significant difference between clinical findings and ulcer healing in Group 1 compared to Group 2. They reported that tacrolimus is more effective in the treatment of ulcerative keratitis. It has immunomodulatory effects similar to cyclosporine, suppresses T-cell proliferation and is a good lacrimomimetic.

Bayley et al. (2018) investigated the effect of superficial keratectomy in non-healing corneal ulcers associated with primary corneal endothelial degeneration.

They reported that superficial keratectomy was effective in 47 of 89 dogs with painful, non-healing corneal ulcers associated with primary corneal endothelial degeneration. However, Dalmatians had a high risk for corneal ulcer development. Mezzadri et al. (2021) performed surgical treatment in descamatocele, perforated corneal ulcer, and deep corneal ulcer with autologous buccal mucosa membrane graft in cats and dogs in their study. In 12 cats (13 eyes) and 14 dogs (14 eyes), autologous buccal mucosa grafts were applied; they reported that there were no intraoperative complications, 24 of the 27 eyes healed, and 22 eyes regained effective visual function. They emphasized that an otology buccal mucosa graft can be considered an alternative treatment method for ulcerative keratitis.

Mycotic keratitis

Mycotic keratitis, which is usually a result of corneal injury in farm environments or environments with plant materials, is a slowly developing ocular disease that occurs in immunosuppressed conditions such as overuse of broad-spectrum antibiotics, indiscriminate use of corticosteroids, and diabetes (Shukla et al., 2008). *Aspergillus* spp. and *Fusarium* spp. are the most common causative agents of mycotic keratitis. *Alternaria, Curvularia, Helminthosporium, Penicillium,* and *Candida* are also reported to cause mycotic keratitis. (Raj et al., 2021). It is reported that topical use of 5% natamycin is effective in treatment, and topical amphotericin B 0.3-0.5% can be used as an alternative, but its use is limited because of toxicity (Austin et al., 2017). In addition, voriconazole, which has high ocular penetration capability, has gained popularity in treating fungal keratitis (Hariprasad et al., 2008). Many limitations in treating fungal keratitis, include delayed diagnosis, limited availability of systemic and topical agents, poor drug penetration, toxicity, corneal thinning, recurrence, and corneal perforation (Ler et al., 2022). Wei et al. (2022) investigated the efficacy of standard corneal cross-linking. They accelerated corneal cross-linking in treating an experimental fungal keratitis model caused by *Aspergillus fumigatus* in 26 New Zealand rabbits. In Group 1, the cross-linking time was set as 10 min, the irradiation parameters were 9 mW/cm^2, and 0.1% riboflavin was added every 3 min for 30 min. In Group 2, the cross-linking time was set as 30 min, irradiation parameters were 3 mW/cm^2, and 0.1% riboflavin was added every 5 min. They treated the rabbits in both groups medically with 1% voriconazole and concluded that both cross-linking models can prevent ulcer progression and promote ulcer healing. At the same time, they emphasized that the rapid cross-linking model can control infection faster and is superior to standard cross-linking in ulcer healing.

Parasitic keratitis

Acanthamoeba keratitis is a rare parasitic disease characterized by acute infection with trophozoites of the opportunistic protozoan *Acanthamoeba castellani* (Cooper et al., 2021). In vivo confocal microscopy (IVCM) is generally accepted as the first method to confirm the diagnosis of *Acanthamoeba* keratitis cases, because it is rapid and has high specificity and sensitivity for amoeba detection (Ledbetter, 2021). Although eye pain and photophobia are usually seen as clinical symptoms, they may cause blindness (Morales et al., 2015). In the IVCM image of *Acanthamoeba* keratitis, cysts and trophozoites are seen in the corneal stroma in clusters or in a chain arrangement (Ledbetter, 2021). There is no standard treatment option for *Acanthamoeba* keratitis. However, diamidine (propamidine-isethionate, hexamidine-isethionate), biguanide (polyhexanide, 0.02% chlorhexidine) and neomycin sulfate that can show antiamoebic effect was indicated in literature (Larkin et al., 1992; Reinhard and Baumans, 2006; Szentmary et al., 2020). At the same time, the compound of 1% povidone-iodine, antileischmaniatic (miltefosine), antifungal (miconazole, clotrimazole, voriconazole, natamycin) can be used for the treatment was recorded (Szentmary et al., 2020). *Onchocerca spp.* and other microfilarial parasites cause keratitis in humans, horses, and dogs. The inflammatory response due to the migration of microfilariae into the cornea and their subsequent death causes keratitis in most cases (Edelmann et al., 2017).

Non-ulcerative keratitis

Keratitis is classified as infectious and non-infectious in human medicine and ulcerative and non-ulcerative in veterinary medicine. Non-ulcerative keratitis is usually caused by mechanical irritation (pigmentary keratitis) or immune-mediated (Kecova et al., 2004). In pigmentary keratitis, corneal inflammation, vascularization and corneal edema are observed with progressive pigmentation on the corneal surface (Sebbag and Sanchez, 2022).

Superficial pigmentary keratitis

Pigmentary keratitis, which is described as the development of corneal pigmentation associated with chronic inflammation, is an ocular surface disease. It causes significant visual impairment and blindness in severe cases. Pigmentary keratitis is caused by migrating melanocytes from the limbal and perilimbal regions and their accumulation in the corneal epithelium and anterior stroma (Azoulay, 2013). Corneal pigmentation has also been reported as a feature of inflammatory corneal pathologies such as keratoconjunctivitis sicca, chronic superficial keratitis, and ulcerative/non-ulcerative keratitis. It is reported that pigmentary keratitis develops more rapidly and efficiently in brachycephalic breeds, especially in pugs

(Maini et al., 2019). The factors causing pigmentary keratitis are chronic distichiasis, nasal fold trichiasis, medial entropion and macroblepharon (Labelle et al., 2013). In addition, limbal stem cell deficiency or genetic factors may cause pigmentary keratitis in pugs (Maini et al., 2019).

Azoulay (2013) applied cryogen consisting of 95% dimethyl ether, 3% isobutane, and 2% propane to the pigmented area of the cornea under anesthesia in 9 dogs with unilateral or bilateral corneal pigmentation and investigated its effect. The pigmented area mostly healed within 5-15 days after cryosurgery in three dogs, as well as corneal edema, inflammation in the cornea and conjunctiva, and superficial corneal ulceration were recorded as postoperative complications. In conclusion, they emphasized that cryotherapy is a suitable adjunctive treatment method for severe corneal pigmentation and that further studies are needed to evaluate its safety and effectiveness.

Chronic superficial keratitis

Chronic superficial keratitis, also known as Uberreiter Syndrome is a common idiopathic non-ulcerative corneal disease characterized by progressive lymphoplasmacytic infiltration of the anterior corneal stroma (Balicki et al., 2021; Pereira et al., 2022). Although the etiology of chronic superficial keratitis is unknown, immune-mediated etiology is suspected to be the reason for it (Jokinen et al., 2011). Chronic superficial keratitis is most common in German shepherd dogs (82%), although it is also seen in other breeds (Balicki et al., 2021). The main symptom of chronic superficial keratitis is depigmentation of the margin of the membrane nictitans and rarely erosion and thickening of the medial central third eyelid (Balicki, 2012). Pereira et al. (2022) conducted a pilot study on the subconjunctival effect of allogeneic mesenchymal stem cells in eight German shepherd dogs with chronic superficial keratitis. They formed a conventional treatment group with topical 1% prednisolone and an experimental group with allogeneic mesenchymal stem cell transplantation. At the end of the 110 days, they reported no local or systemic side effects in the mesenchymal stem cell group, However, the healing was better in the conventional treatment group than the mesenchymal group. They also emphasized that more studies are needed to evaluate the efficacy of stem cells in ulcerative keratitis treatment.

Neurogenic keratitis

Neurogenic keratitis is a degenerative corneal injury due to damage to the trigeminal innervation. Corneal nerves play an essential role in tear production and maintenance of normal metabolism and function of the ocular surface (Versura et al., 2018). Various ocular and systemic diseases can cause damage to the fifth cranial nerve at different levels, from the trigeminal nucleus to the corneal nerve endings. Common causes include herpetic keratitis, diabetes, chemical or surgical damage and neurosurgical procedures (Bonini et al., 2000; Hsu and Modi, 2015). Among these common causes, viral infections especially herpetic infections cause damage to ganglion cells and ganglion sensory fibers (Hsu and Modi, 2015). Acyclovir, a thymidine nucleoside analog is a widely available antiviral agent used to treat of Herpes simplex virus infections (Williams et al., 2005). Jegou et al. (2014) investigated the effectiveness of superficial keratectomy as a surgical procedure in 36 cats with chronic ulcerative keratitis. They did superficial lamellar keratectomy to 41 eyes in 36 cats with ulcerative keratitis due to feline herpes virus-1, calicivirus, *Chlamidophylae felis* and *psittaci*, and they said that 32.5% of the ulcers were cured. They stated that most patients recovered within two weeks after the operation, and 85% recovered completely within four weeks. They explained that the mean healing time was 22.1 days and excellent corneal transparency was gained in a mean follow-up period of 8.9 months. However, recurrence was seen in nine cases, and superficial keratectomy was performed again. In conclusion, they emphasized that superficial keratectomy is an effective treatment method for treating chronic ulcerative keratitis that is resistant to medical treatment in cats.

Superficial spotted keratitis

Superficial spotted keratitis is an ocular disease characterized by punctate staining on fluorescein staining due to the loss of individual cells of the superficial cell layer of the corneal epithelium, including corneal epithelial defects such as corneal erosion and permanent epithelial defects (Kagawa et al., 2013). In a study conducted by Kim et al. (2023), the effect of 0.03% tacrolimus (an immunosuppressant) on the treatment of a dog with superficial spotted keratitis was investigated by spectral domain-optical coherence tomography (SD-OCT). They emphasized that use of 0.2% cyclosporine for an extended period in the treatment of immune-mediated superficial spotted keratitis, is insufficient for treatment. In conclusion, they said that tacrolimus is effective in providing corneal clarity early and continuous treatment with topical immunosuppressants required, and to obtain useful structural information in immune-mediated keratitis and monitor the response of treatment SD-OCT can be used.

Conclusion

Keratitis is still a common disease in domestic animals. Ocular surface infections, which may develop due to corneal abrasion, cause ulceration and tissue destruction and pose a severe visual threat unless untreated. For this reason, it was concluded that this

review would be helpful to determine the etiology of keratitis and providing effective and updated the treatment options.

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