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Abstract

Case series summary Described are 13 cats diagnosed with deep ulcerative keratitis and successfully managed medically without grafting procedures. Typical treatment involved frequent topical application of serum and antibiotics (usually a fluoroquinolone and a cephalosporin). Seven cats also received systemic antibiotics. Analgesia was achieved using various combinations of topical atropine and systemic buprenorphine, robenacoxib or corticosteroids. Six cats were hospitalized for a median (range) period of 2.5 (1–8) days, typically because of frequent medication administration. Median (range) follow-up time was 41.5 (9–103) days. Median (range) number of recheck examinations was 4 (2–6). Median (range) time to corneal re-epithelialization was 21 (9–103) days. Median (range) topical antibiotic course was 29.5 (16–103) days. Median (range) duration of Elizabethan collar use was 28 (13–73) days. At the time of writing, no further recheck examinations were recommended for 10 cats; median (range) time between initial to final examinations in these cats was 35 (20–103) days. All cats retained the affected globes and were apparently comfortable and visual at the latest recheck examination.

Relevance and novel information These cases reveal that aggressive medical management is highly successful in select cats with deep ulcerative keratitis, and can result in a cosmetically acceptable, apparently comfortable and visual globe. However, therapy is intensive with frequent administration of multiple topical and sometimes systemic medications, and requires multiple veterinary visits over many weeks. Referral to a veterinary ophthalmologist for consideration of surgical stabilization is recommended, as not all cases may be amenable to the medical therapy described here.

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Introduction

Corneal ulcers are commonly diagnosed in feline practice, and caused by feline herpesvirus, trauma, exposure, tear film deficiency, decreased corneal sensitivity or foreign bodies.[1] Most superficial ulcers heal rapidly, but some progress to involve the stroma, which can cause globe rupture with associated vision loss. Corneal stromal loss is typically attributed to bacterial infection with the presence of proteases and collagenases, and usually associated with reflex anterior uveitis. Therefore, deep ulcerative keratitis requires intensive therapy with antibiotics, a cycloplegic and proteinase inhibitors such as serum.[2–4] In addition, surgical techniques such as conjunctival grafts or flaps[3,5–7] or keratoplasties,[8] often supplemented by use of biomaterials,[9–15] are frequently recommended when ulcers extend to >50% corneal thickness.[3] However, surgery is expensive and requires general anesthesia and sometimes neuromuscular blockade, microsurgical instrumentation and suture, an operating microscope, and a surgeon trained in microsurgical techniques. Additionally, grafting may result in notable visual impairment.[3,8,13,15]

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A recent series of patients seen at the University of California-Davis Veterinary Medical Teaching Hospital (UCD-VMTH) with severe ulcerative keratitis, and where surgery was not recommended or not elected, made evident that medical management was sometimes associated with resolution of keratitis and retention of vision. Therefore, the aim of this case series was to demonstrate that intensive medical management can offer a successful alternative to surgical therapy for select cats with severe deep ulcerative keratitis, and can result in a visual and apparently comfortable globe.

Case series description

Materials and methods

Because the goal of this study was not to compare medical with surgical management, but rather to show that medical management in some cases could produce excellent clinical outcomes, cases were selected not by a complete retrospective review of medical records but by a request for veterinarians in the UCD-VMTH Ophthalmology Service to recall cats diagnosed with deep ulcerative keratitis and successfully managed medically. Medical records from UCD-VMTH, and sometimes the referring veterinarian, were reviewed by one author (MGMB), to ensure that all cats had corneal ulceration with at least 40% stromal loss with or without keratomalacia, and that no cats received conjunctival or corneal grafting procedures. For cats meeting these inclusion criteria, data retrieved from the medical record included sex, breed, age, previous ophthalmic or systemic disease, feline leukemia virus (FeLV) and immunodeficiency virus (FIV) status, all current medications at the time of initial presentation, medications administered for ulcerative keratitis prior to presentation, disease duration prior to referral, ophthalmic examination findings, visual status, diagnostic test results, treatment, and disease progression. Anterior uveitis was diagnosed based on the presence of aqueous flare, anterior chamber cell and/or intraocular pressure (IOP) <10 mmHg. Ocular discomfort was assessed based on the presence of one or more of the following clinical signs: blepharospasm, third eyelid protrusion, or miosis.

Signalment and history

Thirteen cats (eight neutered males, four spayed females and one intact male) evaluated between October 2014 and May 2017 were included. There were seven domestic and six purebred cats, three of which were brachycephalic. Age at initial evaluation was recorded for 12 cats; median (range) age was 5.9 (0.3–13.5) years. Six cats spent time indoors and outdoors, three cats were housed only indoors and indoor/outdoor status was not recorded for four cats. Detailed medical history was unavailable for one cat adopted as a stray. All other cats were evaluated by a veterinarian once (n = 7) or twice (n = 5) prior to referral. Median (range) time from initial examination by the referring veterinarian until referral was 2 (0–14) days. The owners of four cats attributed ulceration to suspected (n = 3) or observed (n = 1) trauma from another animal. Neither bacterial culture nor cytology was performed in any cat prior to referral. Prior to referral, cats were treated with topical ophthalmic antibiotics (n = 10), serum (n = 1), atropine (n = 1) or neomycin–polymyxin–dexamethasone (n = 1). Systemic medications administered prior to referral included antibiotics (cefovecin [n = 2] or pradofloxacin [n = 1]), analgesics (buprenorphine [n = 3] or an unknown analgesic [n = 1]) or non-steroidal anti-inflammatory drugs (meloxicam [n = 2]). A third eyelid flap was placed 3 days prior to referral in one cat.

Previous ocular disease was recorded for two cats – surgically reduced traumatic proptosis in the affected eye (n = 1) and dendritic keratoconjunctivitis in the unaffected eye (n = 1). Three cats had previous medical complaints, including periodontal disease (n = 1), traumatic malocclusion and urinary tract obstruction (n = 1), or poor body condition and periodontal disease (n = 1). All cats tested were negative for FeLV (n = 3) and FIV (n = 2).

Examination findings

At initial presentation to UCD-VMTH, deep ulcerative keratitis affected the right eye of eight cats and the left eye of five cats. Corneal ulcer size and shape ranged widely. Median (range) ulcer depth at the deepest point was 75% (40–100%). Corneal perforation had occurred in four eyes. Ulcerated corneal regions were described as axial (n = 5), axial and entire paraxial (n = 3), axial and ventral paraxial (n = 2), temporal paraxial (n = 1), dorsotemporal peripheral (n = 1) or the entire cornea (n = 1). Eleven cats had corneal vascularization, nine had corneal stromal leukocytic infiltrate and four had keratomalacia. Four cats had concurrent ocular disease, including corneal sequestration in the affected eye and non-ulcerative keratitis in the contralateral eye (n = 1), superficial ulcerative keratitis in the unaffected eye (n = 1), medial inferior entropion in both eyes (n = 1) or corneal fibrosis in the unaffected eye (n = 1). Seven cats had anterior uveitis in the affected eye, four had no clinical evidence of anterior uveitis and in two cats the presence of anterior uveitis could not be determined due to corneal changes.

Ocular discomfort was assessed as likely present in all cats, owing to the observation of at least one of the following: blepharospasm (n = 13 cats), third eyelid protrusion (n = 5) or miosis (n = 1). A menace response was present in nine cats, absent in three and could not be assessed owing to blepharospasm in one. Direct pupillary light reflex (PLR) in the affected eye was present in six cats, could not be assessed owing to corneal opacification in five, and was absent as a result of intense miosis in one cat and as a result of mydriasis secondary to atropine administration in another. Consensual PLR from the affected to the unaffected eye was present in all

cats. Dazzle reflex was present bilaterally in 11 cats, inconsistently present in the affected eye in one cat and could not be assessed in another cat owing to blepharospasm. Palpebral reflex was complete bilaterally in 11 cats, incomplete in the affected eye in one and incomplete bilaterally in one.

Diagnostic testing

Samples for cytologic assessment were obtained from eight cats; six had suppurative inflammation (two with squamous epithelial hyperplasia), one had no cytologic abnormalities and one had septic suppurative inflammation with rods. Aerobic bacterial culture and sensitivity was performed in eight cats and yielded notable growth in just two: one grew a coagulase-negative *Staphylococcus* species with broad antimicrobial resistance but susceptibility to ofloxacin; the other grew very small numbers of a broadly susceptible coagulase-negative *Staphylococcus* species and a member of the *Streptococcus viridans* group, along with small numbers of an unidentified bacterial species. In the remaining six cats, there was no growth in three, one grew a single colony of a fastidious but unidentified bacterial species, one grew very small numbers of a coagulase-negative *Staphylococcus* species susceptible to all antibiotics tested and one grew small numbers of a fastidious *Corynebacterium* species. Mycoplasmal culture was negative in all three cats tested. Fungal culture was negative in the one cat tested. Neither corneal cytology nor culture and sensitivity were performed in five cats owing to the fragility of the globe following perforation in one cat and fractious temperament in a second cat; no reason was noted for the remaining three. Median (range) IOP was 11 (2–15) mmHg in the eight cats in which it was recorded. Schirmer tear test 1 was performed in one cat and was 15 mm/30 s in the affected eye and 12 mm/min in the unaffected eye.

Treatment

Surgical stabilization was discussed with the owners of nine cats, but medical management was chosen because a conjunctival flap was expected to excessively limit sight (n = 3), owing to financial constraints (n = 2) or because extensive vascularization at initial examination suggested healing was likely (n = 2); no reason was evident in the medical records for two cats. Five cats were hospitalized at presentation for medical management, owing to owner preference (n = 4) or for an unrecorded reason (n = 1). An additional cat initially treated as an outpatient was hospitalized for 1 day following recheck examination on day 6, owing to progressive keratomalacia and stromal loss. A sample of malacic cornea was trimmed and submitted for aerobic bacterial culture and sensitivity but yielded no growth; a partial temporary tarsorrhaphy was then placed to better protect the malacic cornea. Considering all six cats hospitalized, median (range) duration of hospitalization was 2.5 (1–8) days.

All cats were treated with both topical and systemic medications. All cats received topical antibiotics, including cefazolin (33 mg/ml, compounded from cefazolin [Hospira] and artificial tear solution [LiquiTears; Major Pharmaceuticals]; n = 11; median [range] frequency: 1 drop q2 [2–6] h), 0.3% ofloxacin (n = 10; median [range] frequency: 1 drop q2 [2–6] h) or 0.3% ciprofloxacin (n = 2; median [range] frequency: q3.5 [3–4] h). Ten cats received ofloxacin and cefazolin, one cat received ciprofloxacin and cefazolin, one cat received ofloxacin only and one cat received ciprofloxacin only. Twelve cats received topical serum at a median (range) frequency of 1 drop q2 (2–8) h and 10 cats received topical atropine at a median (range) frequency of 1 drop q18 (12–24) h. Orally administered drugs included prednisolone (n = 5), robenacoxib (n = 2) or antibiotics (n = 7), including amoxicillin-clavulanic acid q12h (n = 2), pradofloxacin q24h (n = 2), cefpodoxime q 24h (n = 1), azithromycin q24h (n = 1) or doxycycline q24h (n = 1). Cefovecin was administered subcutaneously once to two cats. Eight cats received transmucosal buprenorphine q8–12h, and one cat received intramuscular buprenorphine once. An Elizabethan collar was recommended in 12 cats.

Progress and outcome

Median (range) follow-up time was 43 (9–103) days. Median (range) number of recheck examinations was 4 (2–6). Gradual reduction in corneal stromal malacia, cellular infiltrate and vascularization, in conjunction with variable development of corneal fibrosis, occurred in all cats (Figure 1). The corneas of 11 cats no longer retained fluorescein at the latest examination; median (range) time to re-epithelialization was 21 (9–103) days. Transmucosal buprenorphine, oral robenacoxib and oral prednisolone were discontinued at the last examination in all cats; median (range) duration of use was 18 (12–30) days, 8 (3–13) days and 28 (4–33) days, respectively. Topical atropine was discontinued at the last examination in nine cats; the median (range) topical atropine course was 25 (4–73) days. Topical antibiotics were discontinued at the latest examination in 12 cats; the median (range) topical antibiotic course was 29.5 (16–103) days. The patient who received topical antibiotics for 103 days was treated until corneal re-epithelialization had occurred. Elizabethan collar use was discontinued at the latest examination in 10 cats; median (range) duration of Elizabethan collar use was 28 (13–73) days. At the time of writing, no further recheck examinations were recommended for nine cats; median (range) time from initial to final examination in these cats was 35 (20–103) days. Only one cat revisited the UCD-VMTH for recurrent ocular disease – bilateral superficial corneal ulceration 86 days after the initial visit. All 13 cats retained the affected globe. At the latest examination, a menace response was present in 12 cats, and was not assessed in the remaining cat; however, this cat had a consensual

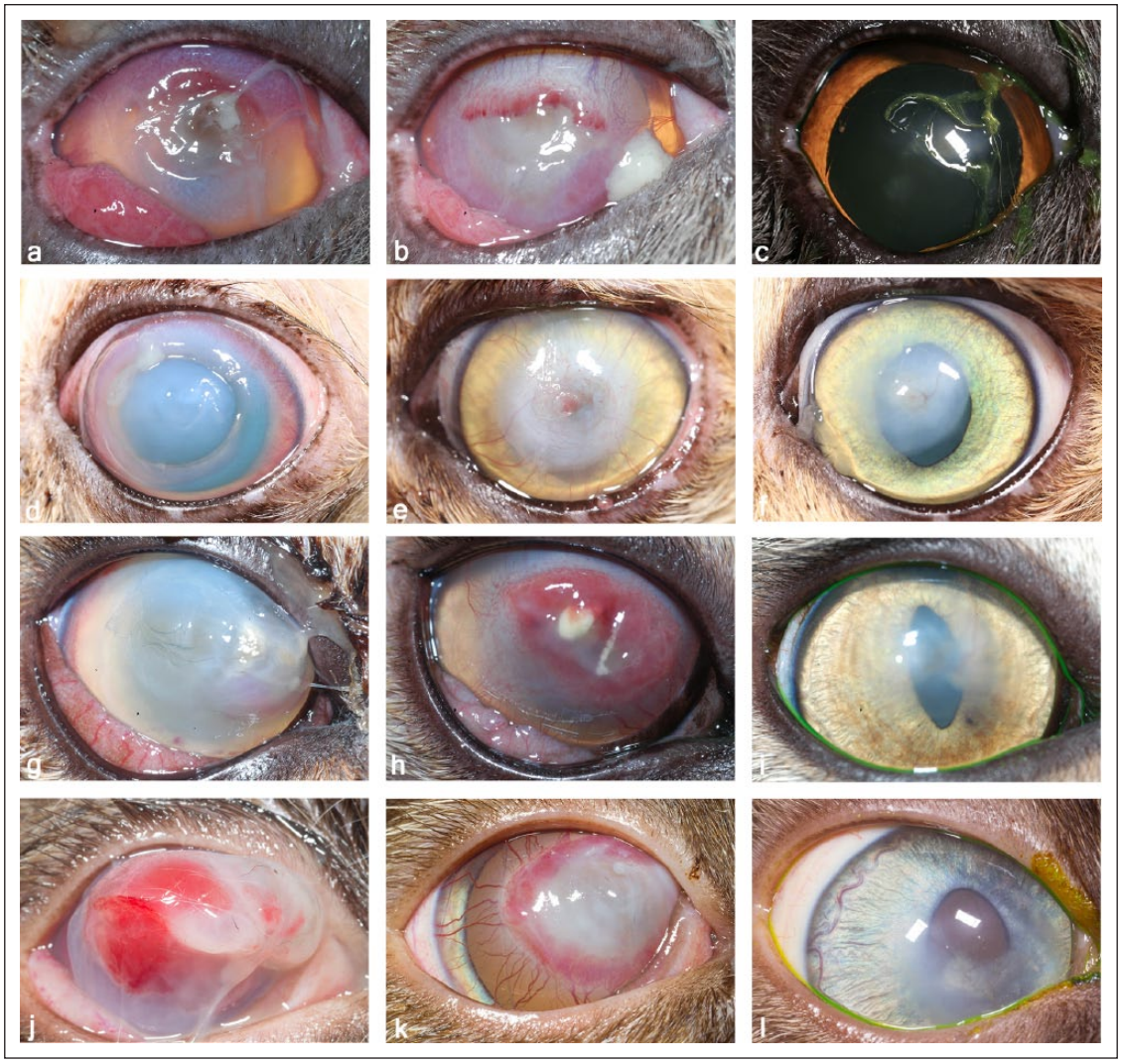

Figure 1 External photographs showing clinical progress of four cats with medically-treated deep ulcerative keratitis. (a–c) Right eye of a 7-year-old male castrated Persian cat at (a) presentation, and on days (b) 11 and (c) 73 of medical therapy. The linear structure on the corneal surface on Day 73 (c) is a mucus strand stained with fluorescein. Aerobic bacterial culture and sensitivity in this cat yielded growth of small numbers of a fastidious *Corynebacterium* species. (d–f) Left eye of a 6.5-year-old male castrated Persian cat at (d) presentation, and on days (e) 29 and (f) 35 of medical therapy. Aerobic bacterial culture and sensitivity, as well as fungal and mycoplasmal culture, in this cat yielded no growth. (g–i) Right eye of a 4-year-old male castrated Savannah cat at (g) presentation, and on days (h) 36 and (i) 103 of medical therapy. Aerobic bacterial culture and sensitivity in this cat yielded a coagulase-negative *Staphylococcus* species with broad antimicrobial resistance but susceptible to ofloxacin. (j–l) Right eye of an 8-month-old male intact Siamese cat with a full-thickness corneal rupture at (j) presentation, and on days (k) 28 and (l) 68 of medical therapy. Dyscoria was noted on (l) day 68. Aerobic bacterial, fungal and mycoplasmal cultures were not performed in this cat

PLR from the affected to unaffected eye, and a direct PLR and dazzle reflex in the affected eye.

Discussion

To our knowledge, this is the first case series detailing medical management of deep ulcerative keratitis in cats. Because successful management was an inclusion criterion for the present study, the prognosis for cats managed medically vs those managed with combined medical and surgical techniques was not assessed. However, this series does provide some striking examples of how well even vision-threatening and globe-threatening keratitis can be managed without corneal surgery in select patients. All 13 cats in the present series retained an apparently comfortable and visual globe at the final recheck examination. This suggests that medical management can serve as an alternative to enucleation, or conjunctival or corneal grafting procedures, and may even be a preferred option in some cats. Although not assessed in the present study, a number of factors should be assessed when considering the relative merits of globe salvaging grafting, enucleation, or medical management

alone. These include consideration of the size and depth of the corneal defect (both jointly and as independent factors), owner finances and motivation to medicate, and access to a veterinary ophthalmologist. Although increasing depth is typically seen as an important motivation for graft or flap placement (with surgical management typically reserved for patients with >50% stromal loss[3]), surface area or geographic size of the ulcer must also be considered. Ulcers that occupy the majority of the cornea may not be good surgical candidates as the required conjunctival graft or flap will be so large as to be essentially blinding. The present study did not compare outcomes achieved with medical therapy alone versus those achieved with medical therapy in conjunction with surgery; however, we believe that some of the outcomes in this series are superior to those we typically achieve surgically, given the severity of the presenting signs. Future studies prospectively comparing medical vs combined medical and surgical management of deep ulcerative keratitis in cats would be worthwhile.

Outcomes of medically managed deep ulcerative keratitis are reported in dogs and horses. One study compared recovery rates in 34 dogs whose ulcerative keratitis was managed medically or surgically.[16] Recovery was defined as corneal re-epithelialization and preservation of vision. Although all seven dogs with superficial stromal ulcers recovered with medical management, only 2/7 or 0/2 dogs with a deep stromal ulcer or descemetocele, respectively, recovered with medical management. By contrast 7/7 dogs with descemetoceles and which received conjunctival flaps recovered. In a separate study,[17] outcomes of 66 horses with 70 *Pseudomonas*-infected corneal ulcers were reviewed. Although ulcer depth was not accurately defined, 51 ulcers were subjectively classified as 'severe' and 11 were classified as 'moderate' based on diameter, depth, location and a number of other factors. Sixty-nine were aggressively medically managed and one received conjunctival and third eyelid flaps. Of these, 51 (73%) healed with excellent vision and minimal scarring, 13 (19%) were enucleated, three (4%) became blind and phthisical and two (3%) healed with peripheral vision only; one horse (1%) was euthanized. Another retrospective study[18] reported visual outcome and ocular survival in horses treated for ulcerative keratomycosis. Favorable visual outcome was documented in all 20 horses treated medically vs 16/19 (84%) of horses treated medically and surgically. Retention of a cosmetically acceptable, non-painful globe was achieved in all 20 horses treated medically and in 17/19 (89%) of horses treated medically and surgically. Taken together, data from cats in the present study, and from horses and dogs in previous studies suggest that aggressive medical management in appropriately selected patients frequently can result in retention of a comfortable, apparently visual globe.

A typical treatment protocol in the present case series included topical application of a fluoroquinolone and a cephalosporin, serum and atropine. Approximately half of the cats in this series also received systemically administered antibiotics, anti-inflammatory agents and/or analgesics. Treatment regimens were intensive, with antibiotics and serum typically applied every 2–4 h at first. This required hospitalization in approximately half of the cases we describe, but is consistent with reports in other species,[16–18] although horses were typically treated with the aid of sub-palpebral lavage systems and with the addition of an antifungal agent.

Topical and systemic antibiotic use must always be judicious and with appropriate consideration of antimicrobial stewardship guidelines. However, antibiotics play an essential role in the management of deep ulcerative keratitis presumed or proven to be infectious. Empirical topical antibiotic therapy providing coverage for gram-negative rods and gram-positive cocci is recommended while culture and cytology results are pending.[19,20] As a result, all cats in the present series received topically applied antibiotics – most commonly very frequent application of a fluoroquinolone and cephalosporin – to ensure broad-spectrum bactericidal antibiosis. However, the use of such a combination should be reserved for ulcers in which there is confirmed or suspected bacterial infection, and not used for prophylaxis in apparently uninfected ulcers. In addition, antibiotics were administered systemically in nine cats in the present series.

The topical and systemic use of antibiotics in these cats and in the treatment of keratitis in general warrants further discussion. While consideration of general principles of antimicrobial stewardship are appropriate, a number of unique features of corneal disease should be realized. The cornea is a unique tissue in that it is non-vascularized, which renders it highly susceptible to degradation due to collagenase activity unopposed by serum anticollagenases, and makes it generally not amenable to systemic therapy. The cornea is less than 1 mm thick and yet protects a vital sensory organ requiring that clinical decision-making is rapid and effective. Unlike internal organs, the cornea can be directly examined using high magnification, and pathology interpreted with great reliability. Finally, corneal culture and cytology do not reliably detect sepsis in all patients, especially when a specimen considered adequate elsewhere cannot reliably or safely be collected from the fragile cornea owing to concerns about causing globe rupture. In addition, culture results may be affected by previous antibiotic use (as was potentially the case in 10 cats in the present series). As a result of all of these factors, ophthalmologists ten dot suspect bacterial involvement whenever there is corneal stromal loss (as was present in all cats in the present series), corneal malacia (present in four cats) or leukocytic infiltration (present in nine cats).[3]

The systemic use of antibiotics also requires some special thought in keratitis. Systemic antibiotics are warranted in patients with corneal perforations (present in 4/9 cats receiving systemic antibiotics in the present series), as perforation permits exposure of the intraocular contents to infectious agents and normal corneal flora.[3,4] While not always essential in deep but non-perforating ulcerative keratitis, systemic antibiotics may be wise if they are likely to achieve meaningful concentrations in the cornea through delivery via pathologic vascularization of the cornea, breakdown of the blood–ocular barrier as occurs in uveitis, or via the tear film as occurs with some drugs in non-inflamed eyes, and likely more drugs in inflamed eyes. For example, orally administered doxycycline has anti-inflammatory[21] and antimalacic properties,[22] as well as its better-understood antimicrobial properties. It also achieves notable concentrations in the pre-corneal tear film of dogs,[23] horses[24] and northern elephant seals,[25] but not cats without ocular inflammation.[26] Therefore, the use of doxycycline in the single cat in the present study relied on doxycycline reaching the cornea through the aqueous humor, corneal blood vessels or possibly via tears if inflammation permits tear drug concentrations to increase. By contrast, pradofloxacin does achieve useful concentrations in the pre-corneal tear film of cats following oral administration,[26] and may be an effective choice in infectious keratitis if susceptible organisms are present. All of these factors should be considered when selecting the types, number, frequency, route, and duration of antibiotic therapy in eyes with ulcers believed or proven to be infected; however, consideration must also be given to appropriate antibiotic stewardship.

Pain management is also critical in the holistic treatment of ulcerative keratitis and reflex uveitis in all species; however, systemic analgesic options for cats are somewhat limited in the USA, especially when these cats are treated at home by their owners. Pain in keratitis would be expected to arise from corneal nociceptors, as well as from ciliary body spasm as a consequence of reflex anterior uveitis seen commonly with ulcerative keratitis. As a result, 11 cats in the present series received at least one systemically administered analgesic or anti-inflammatory drug, including buprenorphine (n = 8), robenacoxib (n = 2) or corticosteroids (n = 5). In addition, 10 cats in the present study received topically applied atropine. Buprenorphine is an opioid partial mu agonist which, in the USA, can be dispensed for transmucosal use and provides long-acting moderate analgesia in cats,[27] and is believed to be superior to and with fewer side effects than other opioids.[28] However, it is expensive when compared with similar agents and there can be variability in its efficacy among cats. Non-steroidal anti-inflammatory drugs (NSAIDs), such as meloxicam or robenacoxib, provide superior postoperative analgesia in cats when administered concurrently with buprenorphine than can be achieved with buprenorphine alone.[29,30] While NSAIDs are efficacious analgesic and anti-inflammatory agents and part of the standard of care for deep ulcerative keratitis in dogs at our institution, their use in cats is limited owing to the lack of medications labeled for long-term use in the USA.[31] These limitations seriously constrained use of NSAIDs in patients described in the present series; however, based on their value in treating infectious keratitis in other species, they should likely be used in cats treated in countries where licensed NSAIDs exist.

Orally administered corticosteroids at an anti-inflammatory dose are an appropriate anti-inflammatory and analgesic treatment for uveitis of known origin,[3,4] and – in the present series – were administered to five cats not receiving NSAIDs. Three cats had corneal perforations with concurrent anterior uveitis, and one had corneal lesions precluding visualization of the pupil or anterior chamber. Corticosteroids are contraindicated in patients concurrently receiving NSAIDs and those with diabetes mellitus, cardiovascular disease, chronic renal disease, ulcerative gastrointestinal disease, or systemic fungal or rickettsial disease.[32]

In the present report, median (range) follow-up time was 43 (9–103) days, number of recheck visits was 4 (2–6) and time from admission to re-epithelialization was 21 (9–103) days, consistent with data generated in other species. In horses, median (range) treatment duration was 48 (31–192) days; however, this included surgically and medically managed cases.[18] Time from admission to epithelialization was 6–70 (mean 29) days in horses,[17] and 28–40 days in dogs whose descemetoceles or perforations were treated with medical therapy and a conjunctival graft/flap.[16]

Conclusions

Collectively, data from the present study in cats and previous studies in horses and dogs suggest that select patients with vision- and/or globe-threatening keratitis can be managed without surgical intervention provided that intensive and appropriate medical management is provided.[16–18] Ideally, management should be guided by culture and sensitivity testing, as well as cytologic examination of corneal samples. Cat owners should be advised that a cosmetic and visual globe is a reasonable expectation, but that this will typically require topical and sometimes systemic administration of multiple medications, some as frequently as every 2 h, and that medical treatment (although not always at this intensity) will typically be required for about 1 month, with about four veterinary visits required. Referral to a veterinary ophthalmologist is still strongly recommended for all patients with deep stromal keratitis, as these patients' clinical signs may worsen rapidly; however, results of the present study provide guidelines for patients in which referral is not possible or declined.

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