Neurogenic KCS
From the ophthalmologist perspective

Màrian Matas Riera LV FHEA PgCertVetEd DipECVO MRCVS
EBVS® European Specialist in Veterinary Ophthalmology
RCVS Specialist in Veterinary Ophthalmology
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Summary

- Diagnosis of NKCS
- Treatment of NKCS
- Literature review
- Recap of autonomic data of the eye

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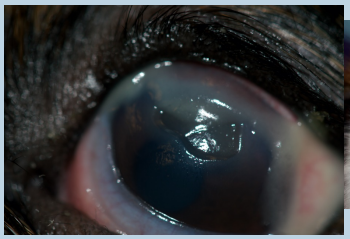
Larry, 8 yold MN, 10kg



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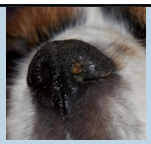
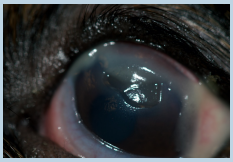
Larry

- Non-healing corneal ulcer left eye for 10 days
- Mucopurulent discharge
- Discomfort left eye
- Red left eye
- Sneezing and rubbing nose
- Conjunctival hyperhemia
- Blepharospasm OS
- STT 18-0mm/1min OD/OS respectively
- No changes intraocularly
- Xeromycteria





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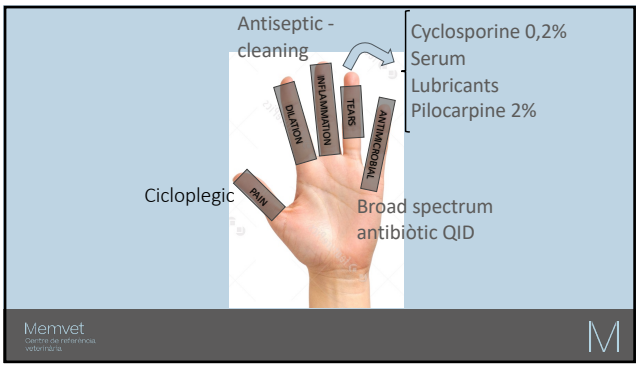

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Neurogenic dry eye - treatment

- Antiseptic - cleaning
  - Povidone iodine 1:50
  - N-acetilcysteine
- Cycloplegic BID
- Topical lubricants OS
- Serum (heterologous) 4x
- Broad spectrum antibiotic
- Cyclosporine 0,2% BID OS
- Pilocarpine 2%: 1 drop every 10kg, twice daily

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Treatment discussion

- Antiseptics
- Serum
- Antibiotics
- Cyclosporine

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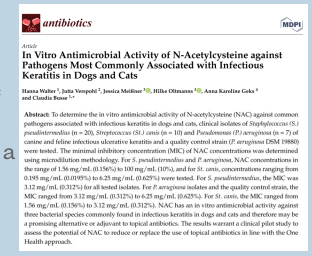
Antiseptics

- N-Acetilcysteine:
  - Antiseptic for ophthalmic pathogens
    - Anticollagenase activity
- Use of pov.iodine 1:50 as a cleaning product ?



antibiotics

MDPI

Article

In Vitro Antimicrobial Activity of N-Acetylcysteine against Pathogens Most Commonly Associated with Infectious Keratitis in Dogs and Cats

Hanna Walter [†], Jutta Verspohl [†], Jessica Meilinor [†], Hilke Ottmanns [†], Anna Karoline Geks [†] and Claudia Busse [†,*]

Abstract: To determine the in vitro antimicrobial activity of N-acetylcysteine (NAC) against common pathogens associated with infectious keratitis in dogs and cats, clinical isolates of *Staphylococcus (S.) pseudintermedius* (n = 20), *Streptococcus (St.) canis* (n = 10) and *Pseudomonas (P.) aeruginosa* (n = 7) of canine and feline infectious ulcerative keratitis and a quality control-strain (*P. aeruginosa* DSM 1988) were tested. The minimal inhibitory concentration (MIC) of NAC concentrations was determined using microdilution methodology. For *S. pseudintermedius* and *P. aeruginosa*, NAC concentrations in the range of 1.56 mg/mL (0.156%) to 100 mg/mL (10%), and for *St. canis*, concentrations ranging from 0.195 mg/mL (0.0195%) to 6.25 mg/mL (0.625%) were tested. For *S. pseudintermedius*, the MIC was 3.12 mg/mL (0.312%) for all tested isolates. For *P. aeruginosa* isolates and the quality control strain, the MIC ranged from 3.12 mg/mL (0.312%) to 6.25 mg/mL (0.625%). For *St. canis*, the MIC ranged from 1.56 mg/mL (0.156%) to 3.12 mg/mL (0.312%). NAC has an in vitro antimicrobial activity against three bacterial species commonly found in infectious keratitis in dogs and cats and therefore may be a promising alternative or adjuvant to topical antibiotics. The results warrant a clinical pilot study to assess the potential of NAC to reduce or replace the use of topical antibiotics in line with the One Health approach.

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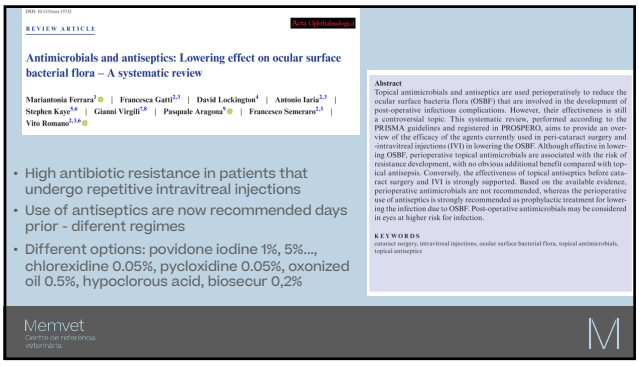

REVIEW ARTICLE

Acta Ophthalmologica

Antimicrobials and antiseptics: Lowering effect on ocular surface bacterial flora – A systematic review

Mariantonia Ferrara[1] | Francesca Gatti[2,3] | David Lockington[4] | Antonio Iaria[2,3] | Stephen Kaye[5,6] | Gianni Virgili[7,8] | Pasquale Aragona[1] | Francesco Semeraro[2,3] | Vito Romano[2,3,6]

Abstract

Topical antimicrobials and antiseptics are used perioperatively to reduce the ocular surface bacteria flora (OSBF) that are involved in the development of post-operative infectious complications. However, their effectiveness is still a controversial topic. This systematic review, performed according to the PRISMA guidelines and registered in PROSPERO, aims to provide an overview of the efficacy of the agents currently used in peri-cataract surgery and -intravitreal injections (IVI) in lowering the OSBF. Although effective in lowering OSBF, perioperative topical antimicrobials are associated with the risk of resistance development, with no obvious additional benefit compared with topical antisepsis. Conversely, the effectiveness of topical antiseptics before cataract surgery and IVI is strongly supported. Based on the available evidence, perioperative antimicrobials are not recommended, whereas the perioperative use of antiseptics is strongly recommended as prophylactic treatment for lowering the infection due to OSBF. Post-operative antimicrobials may be considered in eyes at higher risk for infection.

KEYWORDS

cataract surgery, intravitreal injections, ocular surface bacterial flora, topical antimicrobials, topical antiseptics

- High antibiotic resistance in patients that undergo repetitive intravitreal injections
- Use of antiseptics are now recommended days prior - diferent regimes
- Different options: povidone iodine 1%, 5%..., chlorexidine 0.05%, pycloxidine 0.05%, oxonized oil 0.5%, hypoclorous acid, biosecur 0,2%

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What about serum?

Topical blood products modulate the effects of ophthalmic antibiotics against common bacterial pathogens in dogs with infectious keratitis

Melissa A. Kubai[1*], Mackenzie M. Roy[1], Chloe C. Stinman[2], Danielle E. Kenne[2], Rachel A. Allbaugh[1] and Lionel Sebbag[1,3*]

[1]Department of Veterinary Clinical Sciences, Iowa State University, College of Veterinary Medicine, Ames, IA, United States, [2]Veterinary Diagnostic Laboratory, Iowa State University, College of Veterinary Medicine, Ames, IA, United States, [3]Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel

Bacterial keratitis is a common and serious condition that often leads to vision impairment and potential loss of the eye if not treated promptly and adequately. Topical blood products are often used concurrently with topical antibiotics, helping to mitigate corneal 'melt' from proteases released on the ocular surface. However, blood products are rich in albumin and could affect the efficacy of antibiotics due to drug–protein binding. In this study, serum and plasma samples were harvested from 10 healthy dogs and 10 healthy horses, obtaining fresh and frozen (1 month at −20°C) aliquots for *in vitro* experiments. Albumin levels were quantified using species-specific ELISA kits. Thirty bacteria (10 *Staphylococcus pseudintermedius*, 10 *Streptococcus canis*, 10 *Pseudomonas aeruginosa*), isolated from canine patients with infectious keratitis, were each tested with blank plates as well as commercial susceptibility plates (Sensititre™ JOEYE2) to assess the minimal inhibitory concentration (MIC) of 17 different antibiotics in the absence (control) or presence of eight test groups: serum or plasma (fresh or frozen) from canines or equines. Albumin concentrations ranged from 13.8–14.6 mg/mL and 25.9–26.5 mg/mL in canine and equine blood products, respectively. A direct antimicrobial effect was observed mostly with equine vs. canine blood products (specifically serum and to a lesser degree plasma), and mostly for *Staphylococcus pseudintermedius* isolates. MICs generally increased in the presence of blood products (up to 10.8-fold), although MICs also decreased (down to 0.25-fold) for selected antibiotics and ocular pathogens. Median (range) fold changes in MICs were significantly greater ($p = 0.004$) with the canine blood products (2 (0.67–8.1)) than the equine blood products (2 (0.5–5)). In practice, clinicians should consider equine over canine blood products (lesser impact on antimicrobial susceptibility), serum over plasma (greater antimicrobial effects), and administering the blood product ≥15 min following the last antibiotic eyedrop to minimize the amount of albumin–antibiotic binding in tear film.

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[1]Department of Veterinary Clinical Sciences, Iowa State University, College of Veterinary Medicine, Ames, IA, United States, [2]Veterinary Diagnostic Laboratory, Iowa State University, College of Veterinary Medicine, Ames, IA, United States, [3]Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel

- Consider protein-free alternatives (NAC, EDTA)
- Equine Vs canine
  - Impact on antibiotics was lesser for equine
- Serum over plasma
  - Impact on bacterial growth was greater in serum
  - No differences on albumin concentration
- Fresh Vs frozen: the same
- Recommendation: serum 15min after the antibiotic

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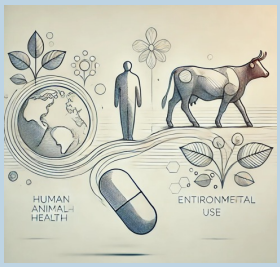
Antibiotic use ?

- Should we use it in:
  - SCCEDs?
  - Neurogenic dry eye?
  - KCS superficial ulceration?
- Legalities behind antibiotic use in superficial corneal ulceration?



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Cyclosporine?

what fungi is cyclosporine extracted from?

Cyclosporine is extracted from the fungus *Tolypocladium inflatum*. This fungus was discovered in a soil sample from Norway, and it produces cyclosporine as a secondary metabolite. Cyclosporine is widely known for its immunosuppressive properties, which are used in organ transplantation to prevent rejection.

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Cyclosporine?

- Selective T-helper lymphocyte suppression inhibiting calcium-dependent phosphatase calcineurin
- CsA also inhibits fibroblast proliferation and has direct lacrimostimulatory properties
- Significant goblet cell stimulation and increased mucous secretion are also reported with topical CsA therapy
- This effect also makes topical CsA a useful therapy for the qualitative tear film disorders that develop secondary to mucin deficiency

Moore CP, McHugh JB, Thorne JG, Phillips TE. Effect of cyclosporine on conjunctival inflammation in a canine keratoconjunctivitis sicca model. Invest Ophthalmol Vis Sci 2001;42: 653–9.

B.H. Grahn, E.S. Storey / Vet Clin Small Anim 34 (2004) 739–753

Kaswan RL, Salisbury MA, Ward DA. Spontaneous canine keratoconjunctivitis sicca: treatment with cyclosporine eye drops. Arch Ophthalmol 1989;107:1210–6.

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Ketorolac as NSAID?

Effects of topical ketorolac tromethamine on tear parameters, meibography, goblet cell density, and conjunctival oxidative stress in healthy dogs

Dáhila Araújo Sonego[1] | Alexandre Pinto Ribeiro[1] | Nathalie Moro Bassil Dower[2] | Bianca Eidt Rodrigues[1] | Suelem Aparecida de França Lemes[1] | Anderson de Oliveira Souza[1] | Elaine Cristina de Lara Spada[1] | Fernando Henrique Furlan[1] | Douglas Ramalho Lisboa[1] | Jadyellen Rondon e Silva[1]

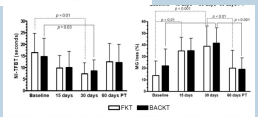

FIGURE 1 Mean ± SD of lipid layer thickness (LLT), non-invasive tear film breakup time (NI-TFBT), and meibomian gland loss (MG loss) assessed during four points in the eyes that received preservative-free ketorolac tromethamine (FKT) and benzalkonium chloride preservative ketorolac tromethamine (BACKT).

Abstract

Objectives: The objective of the study was to evaluate whether a twice-daily instillation of 0.4% preservative-free ketorolac tromethamine (FKT) or 0.4% benzalkonium chloride-preserved ketorolac tromethamine (BACKT), every 12h for 30 days may affect tear film parameters and the meibography in healthy dogs. Additionally, we assessed whether the same treatments irritated the ocular surface, affected goblet cell density (GCD), and the levels of oxidative-stress biomarkers (OSB) in the conjunctiva of the same dogs.

Procedures: Experimental and masked comparison study. In 11 healthy dogs baseline values of the lipid layer thickness, tear meniscus height, non-invasive tear breakup time (NI-TFBT), and the meibomian gland (MG) loss were assessed by OSAvet®. For each dog, one eye received 40 µL of BACKT, while the other received 40 µL FKT, every 12 h for 30 consecutive days. Tear parameters and meibography were repeated 15, 30, and 60 days post-treatments. Conjunctival hyperemia and blepharospasm were monitored at the same time points. At baseline and Day 30, a conjunctival biopsy was collected for GCD and OSB determination.

Results: Conjunctival hyperemia and blepharospasm were not observed. At Day 15, the MG loss increased only in FKT-treated eyes ($p < .001$). On Day 30, both treatment groups showed increased MG loss, shortened NI-TFBT, and reduced GCD and canalase ($p < .05$). At Day 30, BACKT-treated eyes showed lower levels of superoxide dismutase (SOD) ($p = .006$) and higher levels of malondialdehyde (MDA) ($p = .02$). Differences between treatments were not observed for any parameter at any time point ($p > .05$). 60 days after treatment, OSAvet® parameters tended to return to values assessed at baseline; however, significant differences remained for MG loss ($p < .05$).

Conclusions: Twice-daily instillation of KT, containing or not BAC, for 30 consecutive days shortened NI-TFBT, decreased GCD, and increased the MG loss in healthy dogs. KT should be used with caution when prescribed for long periods, particularly in patients with tear film abnormalities. However, future controlled studies using KT, BAC, and other topical NSAIDs are indicated to further support this finding.

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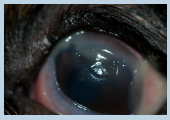
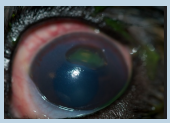
Larry

- Pov. Idodine flush twice daily (0.2%)
- Chloramphenicol eye ointment BID
- Cyclosporine 0.2% BID
- Serum 4x
- Pilocarpine 2%
  - 1drop am – 1 drop pm : 3days
  - 1 drop am – 2 drops pm : 3 days
  - 2 drops am – 2 drops pm : 3 days





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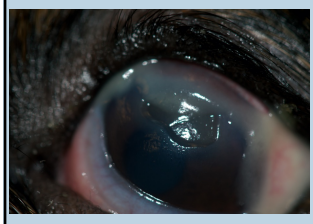
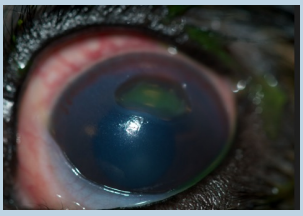
3 days latter after treatment





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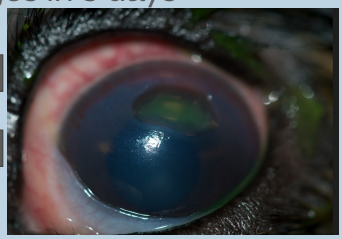
Changes in 3 days

Conjunctival hyperhaemia

Uneven epithelium / Epitheliopathy



Stromal loss

Re-epithelisation of the defect walls

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Neuro pathways

- The facial nerve contains:
  - sensory
  - Motor
  - parasympathetic fibers
- Originates in the rostral part of the medulla oblongata
- Preganglionic parasympathetic fibres synapse with the post-ganglionic fibers at the level of the pterygopalatine ganglion
- Post-ganglionic parasympathetic fibers innervate the lacrimal and nictitans glands, lateral and mucosal nasal glands, and palatine glands

- A lesion affecting the preganglionic parasympathetic nerve fibers anywhere from the rostral medulla oblongata to the pterygopalatine ganglion can result in neurogenic KCS (NKCS) with ipsilateral xeromycteria and xerostomia

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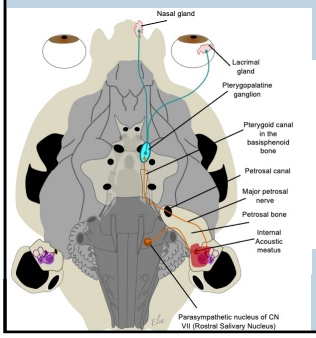
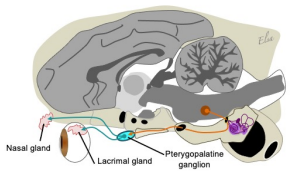
Parasympathetic innervation to the nasal and lacrimal glands





Thank you Elsa Beltran!!!!

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ORIGINAL REPORT

Neurogenic keratoconjunctivitis sicca in 34 dogs: A case series

Amy P. Galley | Elsa Beltran | Roser Tetas Pont

Royal Veterinary College (RVC), Queen Mother Hospital for Animals (QMHA), London, UK

Correspondence:
Amy P. Galley, Department of Clinical Sciences and Services, Royal Veterinary College, University of London, Hawkshead Lane, North Mymms, London, Hertfordshire AL9 7TA, UK.
Email: mmas@rvc.ac.uk

Abstract

Objective: To describe the clinical findings, imaging features, underlying conditions, treatment, and progression of dogs presented between 2010 and 2018 with neurogenic keratoconjunctivitis sicca (NKCS).

Methods: Dogs diagnosed with NKCS were searched in the clinical database. Inclusion criteria were STT-1 readings <15 mm/min, clinical signs of KCS with concurrent ipsilateral xeromycteria.

Results: Thirty-four cases were identified. Mean age at presentation was 8.2 years, median 8.9 years (0.3–14.7). Twenty dogs were male, and 14 dogs were female. Concurrent neurological deficits included facial neuropathy (*n* = 13, 38%), peripheral vestibular syndrome (*n* = 10, 29%), and Horner's syndrome (*n* = 5, 15%). Advanced imaging was acquired in 53% of cases (*n* = 18). Etiologies included idiopathic (*n* = 18, 53%), endocrinopathy (*n* = 6, 18%), otitis interna (*n* = 4, 12%), head trauma (*n* = 3, 9%), iatrogenic (post-TECA-LBO, *n* = 1, 3%), brainstem mass (*n* = 1, 3%), and an area of inflammation in the pterygopalatine fossa (*n* = 1, 3%). Treatment for NKCS was initiated in most cases (*n* = 30, 88%) including: oral pilocarpine 2% and lacrimostimulant (*n* = 19), oral pilocarpine 2% only (*n* = 3), or lacrimostimulant only (*n* = 8). A mean time follow-up of 3.7 months, median 3 months (1–14) was available in 23 cases (68%). Eleven cases with follow-up were responsive (48%) with resolution of the clinical signs in a median time 4 months (1–10), and all of them were treated with oral pilocarpine (±lacrimostimulant).

Conclusions: Most cases presented as idiopathic NKCS; in others, an underlying cause of facial neuropathy was identified. All responsive cases were treated with oral pilocarpine 2%.

FIGURE 1 Nine-year-old male entire Lhasa Apso with left NKCS and previously diagnosed bilateral optic nerve neuritis secondary to meningoencephalitis of unknown etiology causing blindness (Table 3, Case 10). Notice the conjunctival hyperemia, corneal pigmentation and ipsilateral xeromycteria at NKCS diagnosis (A) when he was started on oral pilocarpine and topical cyclosporin. Image (B) was taken 4 months after the start of NKCS treatment, the STT-1 reading was reported to have improved above 15mm/min, and there was significant reduction in the corneal pigmentation, with resolution of the xeromycteria

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Neurogenic KCS in dogs

Methods:

- Retrospective review of 34 dogs 9 years
- Inclusion criteria:
  - STT-1 readings <15 mm/min
  - Clinical signs of KCS with concurrent ipsilateral xeromycteria
- Data collected: age, sex, breed, clinical signs, imaging findings, treatment, and follow-up

Results:

- Mean age: 8.2 years;
  - 20 males
  - 14 females

(Results)

- Common concurrent neurological deficits:
  - Facial neuropathy (38%)
  - Vestibular syndrome (29%)
  - Horner's syndrome (15%)
- Advanced imaging:
  - 53% of cases identified various etiologies:
    - Idiopathic (53%)
    - Endocrinopathy (18%) (hypothyroidism, DM)
    - Otitis interna (12%)
    - Head trauma (9%)
    - Others (post TECA-LBO 3%, brain stem mass 3%, inflammation in pterygopalatine fossa 3%)
- Treatment with oral pilocarpine 2% and lacrimostimulants showed a 48% resolution rate of clinical signs.
- Clinical resolution 11 cases follow up: median 4m (1-10m)

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Outcome - time

- n =2 enucleation
- n =2 euthanasia (co-morbidities)
- Tear film replacements were prescribed to all patients
- **Group I**: specific treatment of NKCS: (i) patients receiving a combination of oral pilocarpine 2% and lacrimostimulant (n = 19, 63%)
- **Group II:** patients receiving only oral pilocarpine 2% (n = 3, 10%)
- **Group III**: patients receiving only lacrimostimulants (n = 8, 37%).
- **Lacrimostimulant drugs** included either cyclosporin 0.2% eye ointment or tacrolimus 0.05% compounded oil-based solution at one single time.
- All patients in the first and third treatment group were started on cyclosporin 0.2%; in two cases, the lacrimostimulant was changed to tacrolimus 0.05% due to

- NKCS once maximum dosing was achieved was 3.45 drops 2.45 times daily
- **Seven cases (30%) progressed showing improvement in the STT-1 reading, with a mean time follow-up of 1.7 months, median 2 months (range 1–3 months).**
- Four cases (17%) showed no improvement or deterioration of the NKCS, with a mean time follow-up of 6 months, median 2 months (range 1–20 months).
- Xeromycteria was reported to resolve in 11 cases (48%), including nine of the responsive cases (the remaining two responsive cases had no record of xeromycteria in the follow-up clinical notes), and two cases which showed improvement in the STT-1 readings.

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- **Conclusions:**
- NKCS often presents idiopathically or with underlying neurological conditions
- Effective treatment typically involves oral pilocarpine

TABLE 2 Number of cases with follow-up in each treatment group and their progression

Treatment received	Number of responsive cases (%)	Number of cases improved (%)[a]	Number of cases with no improvement/ deterioration (%)[a]
Oral pilocarpine and lacrimostimulant (n = 15)	9 (60%)	5 (33%)	1 (7%)
Oral pilocarpine only (n = 2)	2 (100%)	0 (0%)	0 (0%)
Lacrimostimulant only (n = 6)	0 (0%)	2 (33%)	4 (67%)

[a]Before being lost to follow-up or is an ongoing case.

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Let's better asses these patients

- Facial neuropathy (38%)
  - Paralysis
  - Paresis
- Vestibular syndrome (29%)
  - Nystagmus
  - Head tilt
- Horner's syndrome (15%)
  - Miosis
  - Ptosis
  - Warmer skin /hyperhaemia (due to vasodilation)

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NKCS – Work up

- Advanced imaging was performed in 18 cases (53%)
  - MRI
  - CT
- Abnormalities were identified n = 13 cases (72%)
- Identification of an etiology in 44% of cases imaged (n = 8)
- Blood work – searching endocrinopathies:
  - T4/TSH
  - Diabetes mellitus: fructosamine

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Case Report

OPEN REPORTS

Feline dry eye syndrome of presumed neurogenic origin: a case report

Lionel Sebbag[1,2], Patricia A Pesavento[3], Sebastian E Carrasco[3], Christopher M Reilly[3,4] and David J Maggs[3]

Journal of Feline Medicine and Surgery Open Reports

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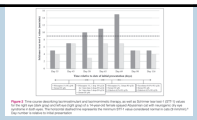
This paper was handled and processed by the American Editorial Office (AAFP) for publication in JFMS Open Reports
SAGE

Abstract

Case summary A 14-year-old female spayed Abyssinian cat, which about 1 year previously underwent thoracic limb amputation, radiotherapy and chemotherapy for an incompletely excised vaccine-related fibrosarcoma, was presented for evaluation of corneal opacity in the left eye (OS). The ocular surface of both eyes (OU) had a lacklustre appearance and there was a stromal corneal ulcer OS. Results of corneal aesthesiometry, Schirmer tear test-1 (STT-1) and tear film breakup time revealed corneal hypoesthesia, and quantitative and qualitative tear film deficiency OU. Noxious olfactory stimulation caused increased lacrimation relative to standard STT-1 values suggesting an intact nasolacrimal reflex. Various lacrimostimulants were administered in succession; namely, 1% pilocarpine administered topically (15 days) or orally (19 days), and topically applied 0.03% tacrolimus (47 days). Pilocarpine, especially when given orally, was associated with notable increases in STT-1 values, but corneal ulceration remained/recurred regardless of administration route, and oral pilocarpine resulted in gastrointestinal upset. Tacrolimus was not effective. After 93 days, the cat became weak and lame and a low thyroxine concentration was detected in serum. The cat was euthanized and a necropsy performed. Both lacrimal glands were histologically normal, but chronic neutrophilic keratitis and reduced conjunctival goblet cell density were noted OU.

Relevance and novel information The final diagnosis was dry eye syndrome (DES) of presumed neurogenic origin, associated with corneal hypoesthesia. This report reinforces the importance of conducting tearfilm testing in cats with ocular surface disease, as clinical signs of DES were different from those described in dogs.



- Noxious olfactori stimulation increased the STT relative to Standard
- Oral pilocarpine more efective than topical
but resulted in gastrointestinal upset
- Tacrolimus was not effective
- After 93 day – euthanasia
  - glands histologically normal
  - reduced goblet cells
  - chronic "neurotrophic" keratitis

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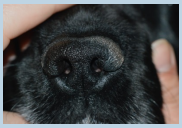
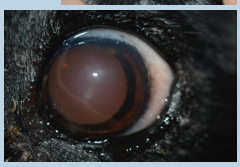
Neurogenic KCS





- Idiopathic
- But check other neuro signs !
  - Work up needed if present
- Ocular suport treatment
  - Lacrimostimulants
    - Cyclosporine
    - Pilocarpine
    - Lubricants
  - Corneal "nutrients"
    - Serum ?
  - Topical antibiotic / Antiseptics
  - Expect improvement 1-3 months

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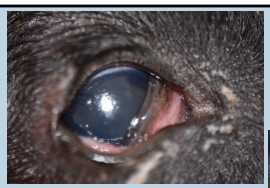

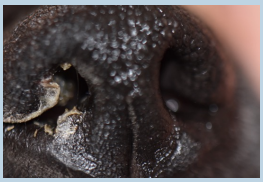

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Disease	Clinical signs	Ganglion	Autonomic	Nerves within the orbit	Function
Neurogenic dry eye	Dry nose/eye	Pterygopalatine	Parasympathetic cnVII	cn.VII (facial) and exits with maxillary and mandibular branches of cn V	Gland production - Lacrimal - Nasal
Horner´s Syndrome	Miosis/TEL protrusion/Ptosis	Cranial cervical ganglion	Sympathetic	cnV (trigeminal)	Dilator iris muscle
Ophthalmoplejia interna	Mydriasis	Ciliary ganglion	Parasympathetic cnIII	cnIII (oculomotor)	Sphincter iris muscle

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Summary

- Diagnosis of NKCS
- Treatment of NKCS
- Literature review
- Recap of autonomic data of the eye

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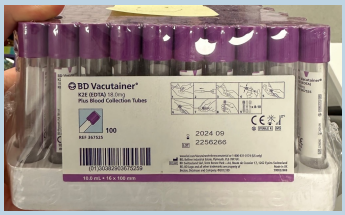

We use K2E EDTA vacutainer tubes (see photo). Add 0.3ml/tube of water for injection/sterile water and mix it well to grab all the crystals around the tube. Then use another 0.3ml for another tube and so on to get 3-5ml enough for a bottle. This "recipe" gives around 3-4% of EDTA which should be strong enough to get rid of the calcium.

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