Outcomes of treatments for keratomalacia in dogs and cats

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Outcomes of treatments for keratomalacia in dogs and cats: a systematic review of the published literature including non-randomised controlled and non-controlled studies

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Objectives: The aim of this review was to interrogate the evidence base for treatment of keratomalacia in dogs and cats, through examination of the applicable literature.

Materials and Methods: Studies were screened for evidence to answer the following question Which of the treatment options for keratomalacia in dogs and cats offers the best chance of globe survival, the fastest time to resolution with globe survival, and the best visual outcome. The search utilised the PubMed (http://www.pubmed.gov/) and ISI Web of Science (http://wok.mimas.ac.uk/) databases. Databases were searched using the following terms: (keratomalacia OR corneal melt OR corneal malacia) AND (dog OR canine OR canid OR cat OR feline OR felid) AND (treatment OR outcome OR morbidity OR complications). Studies were assessed by one author (CH) and excluded if they related to less than three keratomalacia cases, experimental treatments, in vitro studies, or did not provide information regarding outcome. Studies were classified to a level of evidence according to the system described by the Oxford Centre for EvidenceBased Medicine.

Results: Eighteen (18) studies were identified as providing information to answer the proposed question, one as level 3, 10 as level 4 and seven as level 5 evidence. Only one study compared two treatments, the remaining were prospective or retrospective case series of a single treatment intervention. Study design was highly variable with respect to population size, followup and outcome assessment, making direct comparison difficult, and metaanalysis was not applied.

Clinical Significance: Overall, the evidence for improved outcome of one proposed treatment over another proposed treatment for keratomalacia in dogs and/or cats is very weak.

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INTRODUCTION

Keratomalacia is a serious ocular disease capable of causing corneal perforation and loss of the globe. It is also referred to as "corneal melting" due to the typical appearance of a gelatinous collagenolysis encountered in these cases resulting from enzymatic degradation of the corneal stromal collagen. Collagenases and proteinases (matrix metalloproteinases, MMPs) are responsible for this corneal destruction and are liberated from bacteria and/or fungi, corneal and conjunctival epithelial cells and leucocytes. Collagenases and proteinases are normally present within the tear film and cornea in a fine balance with their endogenous tissue

inhibitors and are required for normal homeostasis of the ocular surface. Imbalance of these enzymes with their inhibitors leads to over-zealous collagen destruction and corneal degradation. Pre-existing and ocular surface co-morbidities may increase the risk of keratomalacia, including keratoconjunctivitis sicca, neurotrophic keratitis, exposure keratitis due to lagophthalmos and bacterial or fungal keratitis.

Anti-collagenase treatment is instigated to try to mitigate collagen loss and retain as much corneal tissue as possible. Anti-collagenase treatments used in veterinary ophthalmology include: topical: serum, plasma, fresh frozen plasma (FFP), freeze–thaw cycled plasma (FTCP), platelet-rich plasma (PRP), ethylenediaminetetraacetic acid (EDTA), acetylcysteine and tetracyclines (topical and/or oral). Additionally, most cases require antimicrobial treatment appropriate to any identified infections (by cytology, culture and sensitivity or PCR testing) as well as analgesic treatments including oral non-steroidal anti-inflammatory drugs and/or opioid-based analgesia and/or paracetamol (dogs only) and atropine. Any other ocular co-morbidities may require additional treatments (e.g. eyelid surgery, tear replacement and/or stimulation etc.)

Surgical debridement of necrotic corneal tissue may be appropriate and help to stabilise the malacic area by debulking the enzyme-rich malacic tissue. In some cases, the degree of corneal tissue loss is substantial and tectonic support may be required. Surgical treatments described in dogs and/or cats include: conjunctival pedicle grafting, corneal grafting (fresh or frozen; homologous or heterologous tissue), corneoconjunctival transposition (CCT), collagen biomatrix grafts [e.g. porcine intestinal (BioSIS) or bladder (ACell) submucosa, bovine pericardium (Tutopatch) and equine pericardium, without or without additional third eyelid flap (TELF)], amnion grafting (homologous or heterologous), cyanoacrylate glue application, keratectomy with TELF and collagen cross-linking.

A systematic review of the current literature was undertaken to determine the evidence base for the various treatments of keratomalacia described in dogs and cats. The aim of this review was to assess the evidence base and identify recommended treatment(s) based on globe survival, visual outcome, and time to resolution (while maintaining a globe).

MATERIALS AND METHODS

The following question was designed to establish the evidence base for the treatment of keratomalacia in dogs and cats: "Which of the treatment options for keratomalacia in dogs and cats offers the best chance of globe survival, the fastest time to resolution with globe survival, and the best visual outcome."

An on-line literature search was undertaken 5 October 2020 for studies and case series/reports related to treatment (both medical and surgical) of keratomalacia in dogs and cats. The search criteria were restricted to the English-language publications over the last 30 years (1990 to 2020).

The search utilised the PubMed (http://www.pubmed.gov/) and Institute for Scientific Information (ISI) Web of Science (http://wok.mimas.ac.uk/) databases. Databases were searched using the following terms: (keratomalacia OR corneal melt* OR corneal malacia) AND (dog OR canine OR canid OR cat OR feline OR felid) AND (treatment OR outcome OR morbidity OR complications). A further search for (cornea* graft*) AND (dog OR canine OR canid OR cat OR feline OR felid) was undertaken on PubMed and cross-referenced against original search to exclude duplicates and assess if grafts undertaken for keratomalacia (grafting for other diseases excluded).

The protocol for this review has not been published on a repository or in another journal, although follows the same principles out-lined in Tivers *et al.* 2017.

Studies were assessed by one author (CH) and excluded if they were studies relating to non-keratomalacia disease, related to species other than dogs or cats, had less than three keratomalacia cases included, were conference abstract only publications, were review articles with no new data, were experimental treatments or in vitro studies or were duplicated.

Studies were reviewed and assigned a level of evidence base as described in the Oxford Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group 2017), as summarised in Table 1. Each study was assessed for type of study described (e.g. retrospective, prospective, controlled, random/non-random, cohort study, case series/study), the number of animals included, criteria for assessing outcome (e.g. vision, corneal clarity, anatomic repair) and duration of follow up and time to resolution (see Tables 2 and 3).

Statistical analysis of the data from included studies in this review was not submitted for statistical synthesis (meta-analysis) as study design differences were considered to have made direct comparison of data misleading.

RESULTS

A total of 76 studies were identified in the initial search of ISI Web of Science databases. Studies were excluded if they related to species other than dogs or cats (four), less than three kera-

Table 1. Excerpt from Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (OCEBM Levels of Evidence Working Group 2017)

Question	Step 1 (level 1†)	Step 2 (level 2†)	Step 3 (level 3†)	Step 4 (level 4†)	Step 5 (level 5)
Is this intervention/ treatment beneficial?	Systematic review of randomised trials or n of one trial	Randomised trial or observational study with dramatic effect	Non-randomised controlled cohort/ follow-up study	Case series, case–control studies or historically controlled studies‡	Mechanism-based reasoning

†Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), inconsistencies between studies or because the absolute effect size is very small. Level may be upgraded if there is a large or very large effect size.
‡As always, a systematic review is generally better than an individual study.

Table 2. Summary of studies providing evidence for the treatment of keratomalacia in dogs and cats

Level of evidence (OCEBM)	Type of study	Papers included
Level 3	Non-randomised controlled cohort/follow-up study	Pot *et al*. (2014)
Level 4	(a) Non-randomised prospective cohort study	Speiss *et al*. (2014) Famose (2014) Famose (2015)
	(b) Non-randomised retrospective cohort study. Case series – describing outcome for one treatment method with no control group	Vanore *et al*. (2007) Goulle (2012) Dulaurent *et al*. (2014) Balland *et al*. (2016) Costa *et al*. (2019) Guyonnet *et al*. (2020) Demir *et al*. (2020)
Level 5	Case series – not providing good information on outcome specific to keratomalacia	Hansen & Guandalini (1999) Soontornvipart *et al*. (2003) Watte *et al*. (2004) Dorbandt *et al*. (2015) Chow et al (2016) Lacerda *et al*. (2017) Maini *et al*. (2020)

tomalacia cases (two), studies relating to non-keratomalacia disease (41), were conference abstract only publications (two), were review articles with no new data (four), experimental treatments or in vitro studies (four) or were duplicated (one). The initial PubMed database search revealed a total of 35 studies and 24 were excluded as studies relating to non-keratomalacia disease (14), less than three keratomalacia cases (three), experimental treatments or in vitro studies (three) or were review articles with no new data (four). The final PubMed search (cornea* graft*) AND (dog OR canine OR canid OR cat OR feline OR felid) yielded 67 studies of which 59 were excluded as studies relating to non-keratomalacia disease (32), or related to species other than dogs or cats (nine) less than three keratomalacia cases (three), experimental treatments or in vitro studies (nine), were review articles with no new data (three) or were duplicated (one).

Eighteen (18) studies were identified as providing information to answer the proposed question. One study was classified as providing level 3 evidence, 10 as level 4 evidence (three 4(a) and seven 4(b)) Tivers *et al*. 2012) and seven as level 5 evidence (summarised in Table 2). The findings of these 18 studies with respect to number of animals included duration of follow up, time to epithelial healing (fluorescein negative staining), anatomical outcome, vision and corneal clarity outcomes for keratomalacia cases are summarised in Table 3.

Direct comparison of different treatments

Only one study compared the outcome of two different treatments for keratomalacia (Pot *et al*. 2014). This was a prospective, non-randomised, controlled cohort study of 49 eyes (35 dogs and 11 cats) over a 3-year period (2009 to 2012) and was classified as level 3 evidence.

Nineteen eyes (19 animals, 12 dogs and seven cats) were treated with corneal collagen cross-linking in addition to standard medical treatment (topical antibiotics, topical and systemic collagenase inhibitors, ±topical atropine 1%, systemic meloxicam and buprenorphine) (CXL group). Thirty eyes (27 animals, 23 dogs and four cats) were treated with standard medical treatment alone (control group). Allocation was dependent on clinician and owner discretion. Cases with corneal perforation or descemetocoele were excluded.

Corneal cross-linking (CXL) was performed under general anaesthesia with the eye positioned in a horizontal plane. Application of 0.1% iso-osmolar riboflavin drops (in 20% dextran solution) was performed every 3 minutes for 30 minutes followed by irradiation for 30 minutes with 365-nm ultraviolet A light (irradiance 3 mW/cm^2, UV-X Peschke Meditrade, Cham, Switzerland) with continued riboflavin drop application every 3 minutes during this period. Irradiation of the limbus was avoided.

Cases were re-examined at days 7, 14 and 28, and thereafter at various time points in long-term follow up. The primary end point was stabilisation of the keratomalacia, and the requirement for surgical/rescue stabilisation (or enucleation) was considered treatment failure. Rescue treatment [CXL, or conjunctival pedicle graft (CPG) or TELF] was recommended if greater than or equal to 20% additional stroma was lost during follow up.

Rescue treatment was undertaken in nine of 30 control group eyes and five of 19 CXL group eyes, which was not statistically different between groups (for total cases or for dog/cat cases separated). Rescue CXL was undertaken in seven of nine eyes in the control group, and CPG in one of nine and declined by owner in one of nine. Rescue CPG was undertaken in four of five eyes in CXL group and TELF in one of five. The ulcer size and depth was greater in the canine CXL group compared to the canine control group, but not in the feline groups. Although rescue treatment was not more significant in either group, the canine ulcers in the CXL group were deeper and larger than those in the control group at initial presentation. Overall stabilisation rate after CXL was 74% (14/19), and 100% (6/6) for rescue CXL.

Ulcer deepening during the follow-up period was seen in both CXL and control groups, but this was greater in the control group (mean 35% stromal loss >50% stromal loss) than the CXL group (50% >55%). The time to epithelial healing (negative fluorescein staining) (P=0.02) and the time to stabilisation of the corneal stroma was longer in the canine CXL group compared to the canine control group, but there was no statistical significance between the feline groups. The depth of stromal thinning at the site of previous ulceration was greater in the canine control group (20%) compared to the canine CXL group (2.5%), but this effect was not seen in the feline treatment groups.

Prospective studies reporting the outcome for one treatment

Three prospective studies were designed to assess the treatment of CXL (Speiss *et al*. 2014) and accelerated CXL (Famose 2014 and Famose 2015) for the treatment of keratomalacia in dogs and cats (Speiss *et al*. 2014), dogs (Famose 2014) and cats (Famose 2015). These were non-controlled, non-randomised unmasked studies and classified as level 4 (4a, Tivers *et al*. 2012) evidence.

Table 3. Summary of articles reporting outcome of treatments for keratomalacia in dogs and cats

Article	Number of patients	Treatment	Follow-up period	Time to resolution (fluorescein negative) of keratomalacia cases	Outcome (anatomical) of keratomalacia cases	Outcome (vision) of keratomalacia cases
Guyonnet *et al*. (2020)	53 dogs (57 eyes) (all keratomalacia)	Medical – topical tobramycin + equine serum (q2 to 4 hours) ± topical atropine and systemic meloxicam (0.1 mg/kg q24 hours)	15 days- chosen end point at which cases were considered as success or failure Median follow-up period for successful medically treated cases=2.5 months (7 days to 2 years) Median follow up for failed medical treated cases=4 months (3 weeks to 3 years)	Median 6 days (2 to 15 days)	31 (52%) of 57 healed with medical treatment 26 (48%) of 57 eyes required surgical intervention (medical treatment failure=progression of stromal loss >20%)	30 of 31 successful medically treated eyes were visual at day 15 14 of 15 eyes followed to day 60 were visual: corneal opacity mild nine of 15, moderate three of 15 and severe three of 15 22 of 26 surgically "rescued" cases were visual (three enucleated, one lost to follow up)
Soontornvipart *et al*. (2003)	78 dogs 10 cats (25 keratomalacia and recurrent ulcerations cases grouped together, not stated if how many of each or how many of each species)	Conjunctival pedicle grafting	Not given, but minimum 3 months	Keratomalacia cases not separated from recurrent ulcerations so not possible to draw conclusions	Keratomalacia cases not separated from recurrent ulcerations so not possible to draw conclusions	Keratomalacia cases not separated from recurrent ulcerations so not possible to draw conclusions
Demir *et al*. (2020)	20 cats (all keratomalacia cases)	Lamellar keratectomy and third eyelid flap (flap removed 4 to 5 weeks postoperatively)	Not given, but minimum 1 to 1.5 months	All cases fluorescein negative at removal of third eyelid flap at 4 to 5 weeks	All globes retained	Vision in all cases (at 1 to 1.5 months postoperatively) Scarring – transparent six (30%) of 20. mild six (30%) of 20, thick and vascularised eight (40%) of 20
Vanore *et al*. (2007)	Five dogs Two cats (all keratomalacia cases)	Surgical repair with porcine small intestinal submucosa (SIS) with third eyelid flap for 2 weeks (2 cases perforated at surgery)	6 months	All cases fluorescein negative at removal of third eyelid flap at 15 days	Globes retained in all cases	Vision in all cases Graft "opalescent" at 4 weeks in all cases At 2 to 3 months two of seven cases (one cat and one dog) had endothelial scars from perforation and two of seven (one cat and one dog) cases had neovascularisation still present At 6 months five of seven cases had complete corneal transparency
Goulle (2012)	60 dogs (42 keratomalacia) 42 cats (7 keratomalacia)	Surgical repair with porcine small intestinal submucosa (SIS; mean four layers) with third eyelid flap for 3 weeks	3 months for all cases (20 dogs and three cats follow up at >3 months)	Data not given - but 97 of 106 eyes had full biomaterial integration with epithelial healing, which is presumed to mean these cases were fluorescein negative. Specific reference to keratomalacia cases not given	Globes retained in all cases	Dog cases with keratomalacia: Vision in all (42/42) cases at 3 months Transparent/discrete scar 27 (64%) of 42 Mild scar in four (10%) of 42, marked scar 11 (26%) of 42, faint pigmentation eight (19%) of 42, mild pigmentation five (12%) of 42 Vision impairment in five of 20 dogs with keratomalacia at follow up greater than 3 months due to pronounced corneal pigmentation Discrete/transparent scar nine of 20 (45%), mild pigmentation two (10%) of 20 Cat cases with keratomalacia: Vision in all cases at 3 months Transparent/discrete scar three(43%) of seven, mild scar in three (43%) of seven, marked scar one (14%) of 7, sequestrum formation one (14%) of seven

Table 3. (Continued)

Article	Number of patients	Treatment	Follow-up period	Time to resolution (fluorescein negative) of keratomalacia cases	Outcome (anatomical) of keratomalacia cases	Outcome (vision) of keratomalacia cases
Balland *et al*. (2016)	27 dogs (10 keratomalacia) 3 cats (none keratomalacia)	Surgical repair with porcine urinary bladder acellular matrix (ACell, one to two layers) with third eyelid flap for 18 days	90 days	Nine of 10 fluorescein negative at 18 days Last case fluorescein negative at day 45 check	Globes retained in all cases	All cases visual All cases scarring/fibrosis graded as moderate
Chow *et al*. (2016)	37 dogs (4 keratomalacia and deep ulceration) – however in discussion states "majority of dogs presented with collagenolytic processes typically associated with infection" 41 cats (none keratomalacia)	Surgical repair with porcine urinary bladder acellular matrix (ACell, one layer) with bandage contact lens and temporary tarsorrhaphy	Data not given	Data not given	No specific data ref keratomalacia cases, nine of 82 cases died following surgery (unrelated causes) Five of 82 cases globe lost to phthisis or enucleation Excluding deaths 68 of 73 globes retained (93%)	No specific data ref keratomalacia cases Excluding cases with phthisis, enucleation or lost to follow up 22 of 30 dogs visual and 37 of 38 cats visual Excluding deaths and globe loss 59 of 68 vision retained (87%)
Dorbandt *et al*. (2015)	69 dogs (number of keratomalacia cases not stated – categorised according to ulcer depth only and variables considered were lesion size, location of ulcer in cornea, surgical time, time to stop anti-proteolytic or antibiotics and patient age)	Surgical repair with porcine acellular submucosa and conjunctival pedicle graft *versus* conjunctival pedicle graft alone	Data not given	Data not given	Unknown - number of keratomalacia cases not stated; hence, follow-up data not available Considering all cases, five of 73 eyes enucleated (68/73 globes retained, 93%)	Unknown - number of keratomalacia cases not stated hence follow up data not available Considering all cases, 93% visual; perforated globes had 89% success, descemetocoeles 95% and deep stromal ulcers 100% visual No difference in success rates between CPG and CPG+biomaterial graft
Dulaurent *et al*. (2014)	Three dogs (all keratomalacia) Three cats (none keratomalacia)	Surgical repair using bovine pericardium (Tutopatch)	2 months	2 weeks	Progressive keratomalacia in one of three dogs required second surgery (conjunctival bridge graft)	Graft was opalescent in two of three dogs at 4 weeks and both were visual. At 2 months, both were translucent with only focal scar Graft opaque in one of three dogs that had bridge graft and dog was blind
Hansen & Guandalini (1999)	18 dogs (all had keratomalacia *or* descemetocoele) 12 cats (nine had keratomalacia *and* descemetocoele)	Surgical repair using frozen lamellar corneal graft with third eyelid flap for 15 days	6 months	Data not given	Canine keratomalacia and descemetocoele cases not separated Globes retained in all cases	Canine keratomalacia and descemetocoele cases not separated All eyes visual at 60 days Granulation tissue invaded graft day 30 and vessels started to clear day 45 Scarring of graft in all cases but usually translucent

(Continued)

Table 3. (Continued)

Article	Number of patients	Treatment	Follow-up period	Time to resolution (fluorescein negative) of keratomalacia cases	Outcome (anatomical) of keratomalacia cases	Outcome (vision) of keratomalacia cases
Lacerda *et al*. (2017)	50 dogs (number of keratomalacia cases not stated)	Surgical repair using fresh or frozen corneal grafts (homologous and heterologous)	34 days – 6 years (median 0.55 year=201 days)	Unknown – number of keratomalacia cases not stated hence follow up data not available	Unknown – number of keratomalacia cases not stated hence follow up data not available (43/50 cases 86%) 13 of 50 (26%) cases had second rescue surgery (conjunctival graft)	Unknown – number of keratomalacia cases not stated; hence, follow-up data not available (41/43 cases 95% visual; overall 41/50 82% visual) Transparent graft three (10.3%) of 29, mild opaque five (17.2%) of 29. moderately opaque six (20.7%) of 29, severely opaque five (17.2%) of 29, completely opaque 10 (34.5%) of 29
Costa *et al*. (2019)	111 dogs (51 keratomalacia cases)	Surgical repair using cryopreserved amniotic membrane (heterologous – human or bovine)	21 to 400 days (mean 99 days)	Data specific to keratomalacia cases not given Overall 15 to 45 days (mean 26 days)	Data specific to keratomalacia cases not given except that keratomalacia cases had 'complications' in 9 of 51 cases (18%)	Vision of keratomalacia cases: "good" 46 of 51 (90%), poor/absent five (10%) of 51. Corneal opacity grade 0 to 2 30 (59%) of 51, grade 3 to 4 21 (41%) of 51 [Overall (all cases) vision "good" in 105/114 eyes (92%). Corneal opacity grade 0 6/113 (5%), grade 1 21/113 (19%), grade 2 33/113 (29%), grade 3 40/113 (35%), grade 4 13/113 (12%)]
Watte *et al*. (2004)	28 dogs (seven keratomalacia cases) Nine cats (three keratomalacia cases)	Management using butyl-2-cyanoacrylate adhesive		Data not given [glue retention time in keratomalacia cases 14 to 86 days (mean 35 days)]	All globes retained (n=10)	Data on vision not given Corneal pigmentation in four of seven dogs, lipid deposition in one of seven dogs
Maini *et al*. (2020)	40 dogs five cats (15 keratomalacia cases – not stated how many of each species)	Surgical repair using low-temperature vacuum-dehydrated amnion (Omnigen)	2 to 1046 days (median 84 days)	8 to 67 days (median 19 days)	Data specific to keratomalacia cases not given [Overall graft failure 10/46 eyes (21.7%), enucleation 3/46 eyes (6.5%), persistent malacia 2/46 (4.3%), corneal perforation under graft 1/46 (2.2%)]	Data specific to keratomalacia cases not given [Overall 31/33 eyes (94%) visual at last exam, excluding 10 cases where vision stated not recorded]
Pot *et al*. (2014)	35 dogs (23 control, 12 CXL) 11 cats (four control, seven CXL) (all keratomalacia cases)	Management using corneal cross-linking (CXL) – control group with no CXL	Control group 0.1 to 1.2 months (median 1 month) CXL group 0.25 to 22.5 months (median 3 months)	Control group dogs 5.8 to 37 (median 14) days Cats 14 to 45 (median 15) days CXL group dogs 13 to 84 (median 33) days cats 7 to 60 (median 20) days	Five of 19 CXL eyes required rescue treatment – four of five conjunctival pedicle graft and one of five eyes had third eyelid flap 74% success rate on CXL treatment (not statistically significant from control group 70%) Nine of 30 control eyes required rescue treatment – seven of nine eyes CXL, one of nine conjunctival pedicle graft and recommended but declined in one of nine Intervention (treatment failure) recommended if stromal loss greater than20% than at presentation No significant difference in failure rate between CXL and control groups	All eyes visual (including those with rescue therapy) Pigmentation seen in 11 of 26 dog eyes (eight brachycephalics, seven pugs) in control group, four of 12 dog eyes (two pugs) n CXL group Bullous keratopathy in one dog in each CXL and control group Sequestrum formation developed in one cat eye in control group and two cat's eyes in CXL group

Table 3. (Continued)

Article	Number of patients	Treatment	Follow-up period	Time to resolution (fluorescein negative) of keratomalacia cases	Outcome (anatomical) of keratomalacia cases	Outcome (vision) of keratomalacia cases
Speiss *et al.* (2014)	Three3 dogs Three cats (all keratomalacia)	Management using CXL	2 to 22.5 months (median 9.5 months)	7 to 40 days (median 16.5 days)	All globes retained	Data on vision not given Complications in three of six6 animals – sequestrum, bullous keratopathy and corneal pigmentation but long term outcome in these three cases reported to be good
Famose (2014)	Eight dogs (all keratomalacia cases)	Management using accelerated CXL	30 days	7 to 15 days (median 15 days)	All globes retained	All eyes visual Fibrosis varied from mild to marked in eight of eight. Corneal pigmentation present in two of eight at 30 days
Famose (2015)	10 cats (all keratomalacia cases)	Management using accelerated CXL	30 days	8 to 15 days (median 8 days)	All globes retained	All eyes visual Variable fibrosis at 30 days

Speiss et al. reported a prospective pilot study using the same CXL procedure described in Pot et al. on three dogs and three cats with keratomalacia. This small series had a longer follow-up period than Pot et al. with a median follow up of 9.5 months, and complications in three of six cases of bullous keratopathy, sequestrum formation and corneal pigmentation. Interestingly, examining the Pot et al. study for these complications demonstrated no statistically significant difference in rate of the control group *versus* the CXL group, suggesting the underlying keratomalacia might be responsible for complications rather than the CXL procedure.

Accelerated CXL was used as a treatment for keratomalacia in eight dogs (Famose 2014) and 10 cats (Famose 2015) utilising 0.1% isotonic riboflavin (in 20% dextrose solution, Vibex) applied every 2 minutes for 30 minutes irradiation for 3 minutes with 370-nm ultraviolet A light (irradiance 30 mW/cm^2, KXL Avedro, Waltham, MA, USA). Both studies showed faster median epithelialisation at 15 days in dogs and 8 days in cats, compared to 33 days in dogs and 20 days in cats in the Pot et al. study. Variable degrees of corneal fibrosis were noted in both cats and dogs, and corneal pigmentation was noted in two of eight dogs at 30 days post-treatment, although all cases were reportedly visual.

Retrospective case studies reporting the outcome for one treatment

Seven retrospective case studies reported the outcome for single treatments including lamellar keratectomy, porcine acellular biomaterials (SIS or ACell), or bovine pericardium (Tutopatch) with TELF for varying lengths of time (2 to 5 weeks), or cryopreserved amniotic membrane (human or bovine) or medical treatment alone. These studies were classified as level 4 (4b, Tivers *et al.* 2012) evidence.

Three studies (Vanore *et al.* 2007, Goulle 2012, Balland *et al.* 2016) reported retrospective data for porcine acellular biomaterials [porcine small intestinal submucosa (SIS) and porcine urinary bladder acellular matrix (ACell)]. Vanore et al. described the successful use of SIS in two cats and five dogs with keratomalacia. In all but one dog, a TELF was used for 15 days postoperatively to protect the underlying graft. Vision and globe maintenance was reported in all cases, with all cases fluorescein negative at 15 days postoperatively (when TELF removed), and at 6 months only two of seven had residual corneal scarring (not graded). Both of these cases had suffered corneal perforation and the remaining five of seven had not perforated.

Balland et al. described the use of ACell with a TELF for 18 days in 10 dogs with keratomalacia as part of a retrospective study of 27 dogs and three cats undergoing corneal reconstruction with this biomaterial. In all keratomalacia cases, the postoperative corneal scarring (opacity) was subjectively graded as moderate, although the grading system (mild, moderate, severe) was not described in detail. *Re*-epithelialisation (fluorescein negative staining) was complete at 18 days in nine of 10 keratomalacia cases and one of 10 at 45 days.

Goulle 2012 reported a much larger retrospective study of 106 cases of corneal reconstruction using SIS biomaterial and a TELF

for 3 weeks, of which 42 dogs and seven cats had keratomalacia. Time to fluorescein negative staining (epithelial healing) was not given. Successful anatomical repair was reported in all canine cases, with corneal transparency or a discrete scar at 3 months in 27 (64%) of 42 keratomalacia cases. A mild scar was reported in four (10%) of 42, a marked scar in 11 (26%) of 42, faint pigmentation in eight of 42 (19%) and mild pigmentation in five (12%) of 52. Twenty canine cases were followed for more than 3 months, and of these, five (25%) of 20 developed visual impairment as a result of marked corneal pigmentation. The feline cases were all visual at 3 months postoperatively, with corneal transparency or discrete scar in three (43%) of seven, a mild scar in three (43%) of seven, a marked scar in one (14%) of seven and sequestrum formation in one cat (14%). The corneal opacity grading system (discrete, mild, marked) was not described in detail.

Dulaurent *et al.* 2014 reported on the outcome of a retrospective study of the use of bovine pericardium (Tutopatch) for corneal reconstruction in three dogs with keratomalacia, as well as three feline cases of corneal sequestrum. This was successful in two of three dogs with epithelial healing at 2 weeks, an opalescent scar at 4 weeks and translucent with a focal scar at 2 months in both cases. The remaining dog underwent a rescue surgery of conjunctival bridge graft placement and was blind in this eye. It is difficult to draw any conclusions on the suitability of bovine pericardium grafting for keratomalacia with such a small sample size.

Costa *et al.* 2019 published a larger multicentre retrospective study using cryopreserved amniotic membrane for corneal reconstruction in 111 dogs, of which 51 had keratomalacia. Data specific to the keratomalacia cohort was not given except that nine of 51 keratomalacia cases suffered complications (e.g. suture dehiscence, graft failure, graft pigmentation) but the specific complications were not reported. The authors reported epithelial healing in a mean of 26 days (15 to 45 days) over all 111 dogs but was not reported for the keratomalacia cases in isolation. Vision in the keratomalacia cases was described as good in 46 (90%) of 51 and poor or absent in five (10%) of 51, which was not statistically different from the overall rate of 92% vision and 8% poor or absent vision. Corneal opacification was graded as 0 to 2 in 30 (59%) of 51 and 3 to 4 in 21 (41%) of 51 of keratomalacia cases, which was similar to the overall grade 0 to 2 (53%) and 3 to 4 (47%). Grading was subjectively ascribed as 0 – transparent, 1 – faint opacity, 2 – mild opacity, 3 – moderately opaque and 4 – severely opaque. The authors noted that those cases that had longer epithelial healing times (mean 26 days) had less opacity than those with shorter healing times (mean 22 days). The authors also found that larger defects, those with concurrent ocular disease (e.g. anterior uveitis, keratoconjunctivitis sicca, trichiasis, distichiasis etc), those with perforations or descemetocoeles and those utilising human amniotic membrane (rather than bovine) had higher complication rates, but specific data relating to the keratomalacia cohort were not given. The authors also noted that larger defects were significantly associated with poor or absent vision (visual eyes median 5 mm *versus* poor/absent vision median 9 mm).

Demir *et al.* (2020) reported a retrospective study utilising lamellar keratectomy with TELF in place for 4 to 5 weeks for the treatment of 20 cats with keratomalacia. All corneas were fluorescein negative at removal of the TELF, and all animals were reported to be visual. Scarring was graded at 1 to 1.5 months as transparent (6/20, 30%), mild (6/20, 30%) or thick and vascularised (8/20, 40%). Follow up was reported to have continued periodically (monthly) thereafter but these data were not given.

Guyonnet *et al.* 2020 reported the outcome of 57 eyes of 53 dogs with keratomalacia treated with medical therapy alone. Medical treatment consisted of topical tobramycin and equine serum each q2 to 4 hours, with topical atropine as deemed appropriate, and systemic meloxicam. Cases were considered as successful or failures at day 15 dependent on fluorescein staining (negative=successful) and whether rescue surgical intervention (conjunctival graft, porcine SIS graft, porcine ACell graft, ovine amniotic membrane graft or enucleation) was required (if required=failure). Thirty one keratomalacic eyes were successfully treated with medical treatment (52%). Median time to fluorescein negative staining was 6 days (range 2 to 15 days). Rescue surgical intervention was undertaken in 26 (48%) of 57 eyes where greater than20% progression of stromal loss was witnessed. Twenty two eyes in this rescue group were visual (three enucleated, one lost to follow up), although the degree of corneal opacity "varied greatly depending on the surgical technique." Of the successfully medically treated group, 30 of 31 eyes were visual at day 15, and 14 of 15 eyes followed to day 60 were visual. At this point, corneal opacity was graded as mild (9/15, 60%), moderate (3/15, 20%) or severe (3/15, 20%).

Seven level 5 studies were identified reporting retrospective case series of single treatments for corneal reconstruction where keratomalacia cases were not easily separated from other cases. Additionally, in four level 5 studies (Chow & Westermeyer 2016, Dorbandt *et al.* 2015, Hansen & Guandalini 1999, Watte *et al.* 2004) data on time to epithelial healing or vision were not overtly stated so these outcome parameters were less easily compared with other studies.

DISCUSSION

This systematic review of the literature pertaining to the treatment of keratomalacia in dogs and cats reveals that the evidence base for recommending any one type of treatment is very weak. In recommending the most effective treatment, the decision should be based on the most reliable evidence available. The Oxford Centre for Evidence-Based Medicine system to rank evidence has been revised by the OCEBM Levels of Evidence Working Group in 2017. The revision sought to reflect clinical decision making and was simplified whilst avoiding making definitive recommendations. This allows this system to be used when no systematic reviews are available, and is more appropriate for application to the veterinary literature (Tivers *et al.* 2012, Tivers *et al.* 2017).

Systematic reviews of randomised controlled trials are considered to provide the most reliable evidence on which to base recommendations for treatment(s). Sadly, randomised controlled trials are infrequent in the veterinary literature, and this review only identified one non-randomised controlled trial classified as level 3 evidence, and no level 1 or 2 studies on the outcome of

treatments for keratomalacia in dogs and/or cats. Most studies were level 4 evidence reporting the outcome of a single treatment, with three prospective studies (4a) and seven retrospective studies (4b). The remainder were level 5 evidence providing minimal evidence to answer the question posed in this review. This is not a criticism of those studies, but merely noting that they did not provide good evidence for answering this particular question.

The best evidence available for the treatment of canine and/or feline keratomalacia exists for the use of CXL in the management of keratomalacia but is limited to one level 3 study (Pot *et al.* 2014). This study demonstrated no statistically significant difference in outcome either anatomically or with regards to vision between CXL and control groups. However, seven of nine treatment failures in the control group were successfully rescued with CXL treatment (cross-over for selected patients). The limitations of this study include small treatment groups (based on this preliminary data and assuming the same patient recruitment rate, a power calculation suggested the study would need to run for 10 years to demonstrate a statistically significant difference in outcome between groups) and selection bias (non-randomisation; clinicians/owners appearing to favour CXL treatment for larger and deeper ulcers in dogs) and unmasked cases (potential bias in follow up assessment). The follow-up period was also relatively short in this study, particularly in the control group patients (control group median follow up 1 month, CXL group median follow-up 3 months). This study had a high risk of bias due to clinician allocation of cases to treatment groups. Additionally deep keratomalacia cases (descemetocoeles and perforations) were excluded due to the nature of the collagen cross-linking treatment considered contraindicated for these cases.

Level 4 evidence in the form of studies reporting on outcome following a single treatment provide significant information but are less able to distinguish a leading treatment in terms of time to epithelial healing, anatomical and vision outcomes. Assessment of vision in dogs and cats remains crude, using the menace response in the studies considered in this review as a positive indication of vision. It is therefore not surprising that differences in vision outcome were elusive given this low bar. Corneal clarity might be indirectly indicative of visual compromise; however, a standardised objective measurement of this was not established in any of the studies, and relied on author grading (e.g. transparent, mild, moderate, marked/severe) that conceivably would vary between studies, making comparison between studies challenging.

Studies in this current review had small to modest numbers of canine keratomalacia cases (range 3 to 53 dogs, median 9 dogs), and small numbers of feline cases (range 3 to 20, median 8 cats), with two studies not separating cases based on species (15 to 25, median 20 animals). These small case numbers make the likelihood of identifying statistically significant differences slim unless dramatic effect(s) of treatment were present.

Length of follow up varied between studies, and given that corneal remodelling may continue for an extended period (months) it is also possible that differences in corneal clarity may have been more obvious with longer follow-up periods. In two prospective studies (Famose 2014, Famose 2015), the follow up was only 30 days. Both studies reported on the outcome of accelerated CXL on keratomalacia cases in dogs (Famose 2014) and cats (Famose 2015). In both studies, corneal opacity was described as variable between cases, and data on grades of opacity were not given.

Goulle 2012 demonstrated an apparent increased corneal opacity severity in the feline keratomalacia cases, which is somewhat at odds with the general consensus that the feline cornea scars less than the canine cornea in response to surgery. However, the number of feline keratomalacia cases was small and only three of seven were followed for longer than 3 months. It is possible that a longer follow-up period may have demonstrated further corneal clearing in the feline cases.

Demir *et al.* 2020 reported corneal scarring as transparent in 30%, mild in 30% or thick and vascularised in 40% at 1 to 1.5 months follow up. Follow up was reported to have continued periodically (monthly) thereafter but these data were not given. It seems likely that some of the cats with thick or vascularised scars at 1 to 1.5 months would have had significant clearing at later follow up examinations.

In conclusion, the evidence for recommending any one treatment for keratomalacia in dogs and/or cats over another is very weak. As it stands, a combination of the treatments outlined in this review may be the most appropriate (medical and surgical) depending on the individual case. Whilst no study exists comparing no treatment to any one treatment (for understandable ethical reasons), level 5 evidence (based on physiology and first principles, i.e. mechanism based reasoning) would suggest that medical treatment with anti-collagenase treatment is a minimum requirement for these cases to prevent globe loss through perforation (with attendant pain and suffering). Future studies that are randomised and controlled would be warmly welcomed to expand the evidence base in this field.

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Conflict of interest

The author of this article has no financial or personal relationship with other people or institutions that could inappropriately influence or bias the content of this paper.

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