

# Diagnosis and Management of Chronic Corneal Epithelial Defects (Indolent Corneal Ulcerations)

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Chronic corneal epithelial defects (CCEs; indolent corneal ulcerations) are the most common refractory ulcerations in veterinary medicine and are diagnosed by their classic appearance. CCEs are superficial ulcerations without stromal involvement and have a nonadherent epithelial border (lip). Fluorescein stain adheres to the exposed stroma and extends below the epithelial border, outlining the epithelial lip. CCEs occur secondary to adnexal disease, keratoconjunctivitis sicca, exposure keratitis, neurotrophic keratitis, and primary corneal disease. In cats, herpes keratitis is associated with the development of CCEs. Bacterial infections are not responsible for the refractory nature of CCEs. Because of the refractory nature of CCEs, treatment can be frustrating for both owner and veterinarian. Current treatment recommendations consist of identifying and treating the underlying cause and performing procedures that stimulate epithelialization and adhesion of the corneal epithelium. Initial treatment of CCEs includes ulcer debridement and grid keratotomy. Superficial keratectomy is indicated in refractory cases. © 2003 Elsevier Inc. All rights reserved.

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Corneal ulceration is one of the most common ophthalmic disorders in veterinary medicine. Corneal ulcers are classified based on depth (superficial, deep, descemetocoele) and ease of healing (complicated, uncomplicated, refractory, progressive). Superficial ulcerations involve the corneal epithelium and basement membrane with minimal or no stromal involvement. Deep ulcerations extend to one half the stromal depth or greater, and descemetocoeles extend to the level of Descemet's membrane. Superficial corneal ulcerations that do not resolve within 5 to 7 days are considered refractory, and ulcers that progress in size or depth are considered complicated.<sup>1</sup> Chronic superficial epithelial defects (indolent ulcerations) are the most common refractory ulcers in veterinary medicine and are persistent, superficial ulcerations with a nonadherent epithelial lip and no stromal involvement. The failure of the anterior epithelium to adhere to the underlying stroma is responsible for their refractory nature. In general, chronic corneal epithelial defects (CCEs) are not progressive in nature.

Within 1 hour of injury, corneal epithelial cells began to migrate across the defect.<sup>2-3</sup> A fibrin and fibronectin mat is deposited in the wound,<sup>4</sup> helping adherence of the epithelium to the stroma.<sup>5</sup> Plasminogen activator is released from the migrating epithelial cells and converts plasminogen into plasmin,

which cleaves old epithelial cell attachments and allows epithelial cells to migrate across the wound.<sup>6</sup> Permanent adhesions between the epithelial cell basement membrane and underlying stroma are formed after epithelization. Focal areas of tight adhesions are formed by hemidesmosomes that extend through the basement membrane to anchor the basal epithelial cells to the basement membrane and the basement membrane to the anterior stroma.<sup>7</sup> If the basement membrane is not disturbed during wounding, then adhesions between the epithelial cells and stroma are completed in 1 week. If the basement membrane has to be regenerated, then it may take as many as 6 weeks for the adhesions to form.<sup>8</sup>

Disorders that interfere with epithelization, basement-membrane formation, or the tight adhesions between the epithelial cells, basement membrane, and stroma, can predispose to CCEs. Epithelization can be delayed by mechanical irritation from adnexal disease, keratoconjunctivitis sicca, or exposure keratitis.<sup>7,9</sup> Proteinases, such as plasmin and metalloproteinase, are associated with persistent corneal epithelial defects (CEDs) and are shown to prematurely destroy the fibrin or fibronectin matrix<sup>10,11</sup> and delay basement-membrane replacement and adhesion,<sup>12</sup> respectively. Primary epithelial disorders,<sup>13,14</sup> decreased numbers of hemidesmosomes,<sup>13</sup> basement-membrane disorders,<sup>13,14</sup> and anterior stromal abnormalities<sup>15,16</sup> are linked to the development of spontaneous CCEs. In cats, development of CCEs is associated with keratitis caused by feline herpesvirus-1.<sup>17</sup>

CCEs are diagnosed by their classic appearance. The failure of epithelial adhesion is responsible for the characteristic findings of a superficial ulceration with a nonadherent epithelial border (epithelial lip) and no stromal involvement. Fluorescein stain adheres to the exposed stroma and extends below the loose epithelial border, outlining the epithelial lip (Fig 1).

The first step in chronic corneal epithelial defect (CCE) treatment is to determine the underlying etiology and, most importantly, whether the refractory ulcer is caused by primary corneal disease or is secondary to other factors. Clinically, the diagnosis of primary corneal disease is made by excluding other factors that could contribute to delayed healing. Therefore, a good history, physical examination, and complete ophthalmic examination are essential before instituting therapy.

## Secondary Ophthalmic Disorders Associated with CEDs

### Infectious Disorders

In cats, CCEs develop secondary to herpes keratitis. La Croix et al reported 72% of cats with CCEs have a history consistent with herpes keratitis and an upper respiratory-tract infection or recurrent conjunctivitis.<sup>17</sup> A viral etiology has not been re-

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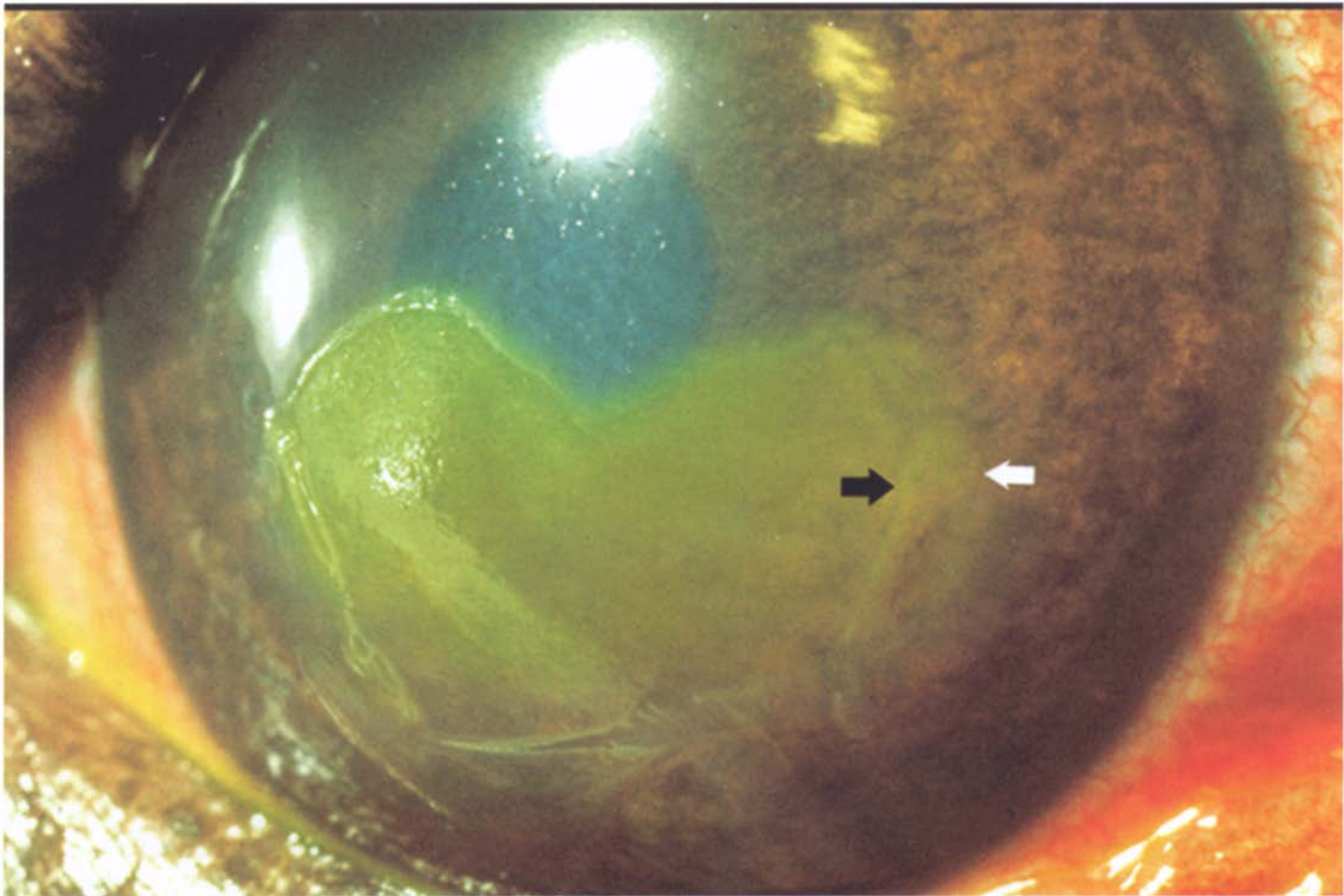
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**Fig 1.** The classic appearance of a CCED (indolent corneal ulceration). CCEDs are superficial ulcerations without stromal involvement. There is a nonadherent epithelial border (epithelial lip). Fluorescein stain adheres to the exposed stroma and extends below the loose epithelial border, outlining the epithelial lip. The black arrow indicates the loose epithelial border. The white arrow indicates the fluorescein stain below the epithelial lip. (Image courtesy of Dr. Cynthia Powell, Colorado State University, College of Veterinary Medicine.)

ported in dogs. Infection by bacteria has not been shown to contribute to the development of CCEDs.

#### Adnexal Disease

Frequently, CCEDs are associated with eyelid abnormalities, such as distichia, ectopic cilia, trichiasis, entropion, eyelid tumors, and lagophthalmos.<sup>7,9</sup> Mechanical irritation related to the abnormal or misdirected hairs interferes with the adhesion of the epithelium to the underlying stroma. Lagophthalmos occurs secondary to exophthalmia, buphthalmia, abnormal eyelid conformation, or cranial nerve deficits, and can predispose to exposure keratitis and secondary CCEDs.

Eyelids should be examined under magnification for abnormal hairs, and the lid margins evaluated for conformation disorders. An ulceration related to a lid abnormality will be in the area of the lid disorder. If exposure keratitis is suspected, then a menace response or palpebral reflex is used to evaluate the ability of the eyelid to close. Because of the potential for blepharospasms, the eyelids are evaluated early in the examination process.

#### Keratoconjunctivitis Sicca (KCS)

Any disorder that interferes with the tear film can predispose to CCEDs.<sup>7,9</sup> Therefore, it is advisable to perform a Schirmer tear test (STT) and a tear break-up time in patients diagnosed with

a refractory corneal ulcer. Dogs with an STT less than 15 mm/min have a decrease in the aqueous component of the tear film.<sup>18</sup> Dogs with a tear break-up time of less than 20 seconds<sup>19,20</sup> have poor tear-film stability secondary to a mucus deficiency.

Initial treatment of KCS consists of cyclosporine 0.2% ophthalmic ointment applied twice daily. In nonresponsive cases, a higher concentration of cyclosporine solution (0.5–2.0%) is used to stimulate tear production, and it is applied to the eye 2 to 3 times a day.<sup>18</sup> The frequency of application may be reduced once the STT values increase above 20 mm/min.<sup>21</sup> In one clinical trial, tacrolimus ointment (0.2–0.3% twice per day) was successfully used to treat KCS in patients not responsive to cyclosporine therapy.<sup>22</sup> Medications such as methylcellulose or sodium hyaluronate that stabilize the tear film are indicated if the tear break-up time is rapid.

#### Exposure Keratitis

Exposure keratitis develops secondary to the inability of the eyelids to close completely over the globe, and can predispose to CCEDs.<sup>7,9</sup> Lagophthalmos develops secondary to lid conformation disorders, cranial nerve VII defects, buphthalmia, or exophthalmia. The ability of the eyelids to completely close over the globe is tested by gently touching the medial or lateral canthus. Treatment for exposure keratitis consists of treating

**TABLE 1. Breeds Reported with Spontaneous Corneal Epithelial Defects (Indolent Corneal Ulceration)**

Breed	Numbers reported	Percent reported
Boxers	127	24.56%
Mixed	57	11.03%
Poodle and poodle X	52	10.58%
Golden retriever	35	6.77%
Other	32	6.19%
Corgi	27	5.22%
Labrador retriever	20	3.87%
Springer spaniel	19	3.67%
German shepard and shepardmix	16	3.09%
Keeshound	10	1.93%
Cocker spaniel	10	1.93%
Schnauzer	10	1.93%
Terrier X	9	1.74%
Lhasa apso	8	1.55%
Airedale	7	1.35%
Boston terrier	7	1.35%
Samoyed	7	1.35%
Australian shepard	6	1.16%
Sheltie	5	0.97%
English bull dog	5	0.97%
Beagle	4	0.77%
Jack Russell terrier	4	0.77%
Siberian husky	3	0.58%
Alaskan malamute	3	0.58%
Weimaraner	3	0.58%
Bichon prise	2	0.39%
Shih tzu	2	0.39%
Dalmatian	2	0.39%
Chow chow	2	0.39%
Yorkshire terrier	2	0.39%
Greyhound	2	0.39%
West Highland white terrier	2	0.39%
Norwegian elkhound	2	0.39%
Silky terrier	2	0.39%
Spitz	2	0.39%
Brittany	2	0.39%
Dandie Dinmont terrier	1	0.19%
Cairn Terrier	1	0.19%
Great pyren	1	0.19%
Miniature pinscher	1	0.19%
Germ short haired	1	0.19%
American Eskimo dog	1	0.19%
Old English sheepdog	1	0.19%
Maltese	1	0.19%
Pit bull	1	0.19%

Data compiled from refs. 14,16,24-26,27,29,30,32-34,39,53.

the underlying cause and performing either a temporary tarsorrhaphy or a permanent canthoplasty.

### Neurotrophic Keratitis

Neurotrophic keratitis develops in both dogs and cats after loss of corneal sensation provided by the ophthalmic branch of the trigeminal nerve. Loss of corneal sensation can predispose to chronic epithelial defects and delay healing of ulcerations.<sup>1,7</sup> Corneal sensation is evaluated by touching the peripheral cornea with a cotton-tip applicator or wisp of cotton. A positive blink response or retraction of the globe indicates normal sensation. A temporary tarsorrhaphy is often beneficial in the treatment of neurotrophic keratitis.

### Primary Corneal Disease

Any primary corneal diseases that interfere with the adhesion of the corneal epithelium to the underlying stroma can predispose to CCEDs. Corneal diseases that are associated with CCEDs

**TABLE 2. Mean Duration of Ulceration and Age of Dogs Reported with CCEDs at Time of Referral**

Reference	Mean duration before to referral	Age/years
(29)	NR	7.0
(30)	6.6 weeks	6.6
(14)	NR	9.0
(16)	NR	8.7
(34)	9.22 weeks	9.25
(27)	7.0 weeks	8.3
(33)	5.5 weeks	8.8
(25)	5.0 weeks	9.5
(26)	5.76 weeks	9.1
(24)	6.8 weeks	8.0
(53)	7.15 weeks	
(32)	14.57 weeks	7.86
(39)	NR	7.0
(37)	NR	6.5
(15)	NR	9.0
Mean of all studies	7.51 weeks	8.2 yr

NR = Not reported.

include calcific keratopathy,<sup>7,23</sup> lipid keratopathy,<sup>1</sup> corneal edema,<sup>7,14,24-27</sup> and spontaneous corneal epithelial defects (SCEDs).<sup>7,13-14,16,24-34</sup> Of these, SCEDs are the most common and are diagnosed after eliminating other corneal abnormalities and adnexal disease.

### Spontaneous Chronic Epithelial Defects

The term spontaneous chronic corneal epithelial defects (SCCEDs) is used to describe CCEDs with no discernible cause.<sup>16,34</sup> This condition was first described by Magrane in 1954.<sup>28</sup> Other names used to describe this disorder include rodent ulcers,<sup>28</sup> indolent corneal ulceration,<sup>29</sup> Boxer ulcers,<sup>30-31</sup> persistent corneal ulcerations,<sup>7</sup> persistent corneal erosions,<sup>14,25-27,32</sup> refractory corneal ulcerations,<sup>24</sup> and recurrent corneal erosions.<sup>13,33</sup>

The boxer is the most common breed reported to develop SCCEDs. Although 24.56% of the cases occur in Boxers, SCCEDs are reported to develop in over 45 different breeds, with the mixed breed being the second most common dog to develop this condition (Table 1). A higher number of SCCEDs occur in poodles and poodle crosses, Golden retrievers, Corgis, Labrador retrievers, Springer spaniels, and German Shepards and

**TABLE 3. Percent of Male and Female Dogs Reported with CCEDs**

Reference	Total male	Total female
(29)	21	8
(30)	12	8
(14)	4	6
(16)	23	23
(34)	20	25
(27)	8	8
(33)	8	10
(25)	75	61
(26)	53	39
(24)	7	10
(53)		
(32)	5	9
(39)	86	60
(37)		
(15)		
Total all studies	322	267
Percent all studies	54.67%	45.33%

**TABLE 4. Percent Healing and Post-treatment Times for Single and Multiple Corneal Procedures Reported for the Treatment of CCEDs**

Corneal procedures	% healed (one procedure)	% healed (multiple procedures)	Mean post-treatment time
Chemical debridement (30) <sup>+</sup>		100%	46 days
Debridement (26)	63%	84%	23.4 days
Debridement (25) <sup>++</sup>		34%	24.4 days
Punctate keratotomy (33) <sup>+++</sup>		88%	12.25 days
Punctate keratotomy (25) <sup>+++</sup>		72%	21.5 days
Grid/punctate keratotomy (15) <sup>+++</sup>	53%	Keratectomy performed if not healed	12.0 days
Grid keratotomy (27) <sup>+++</sup>		94.44% grid repeated	9.3 days
Grid keratotomy (26) <sup>+++</sup>		100% grid repeated	13.4 days
Grid keratotomy (37) <sup>+++</sup>	100%		healed within two weeks
Keratectomy (26)	100%		9.3 days
Keratectomy (34)	100%		Not reported
Keratectomy (31)	100%		
Keratectomy (15)	100%		
Thermokeratoplasty (47) <sup>++++</sup>		Keratotomy performed before	16 days
		100%	15.4 days

<sup>+</sup>4-6% aqueous iodine only; repeated every 7-10 days until healed (no debridement); <sup>++</sup>Debrided every 7-10 days; <sup>+++</sup>Debrided before procedure. <sup>++++</sup>Recommended CCED associated with severe corneal edema.

Shepard crosses than other breeds. Murphy et al reported the Keeshond to be over-represented when compared with the general hospital population.

The mean duration of CCEDs before referral is 7.5 weeks (Table 2). SCCEDs occurs in middle-aged to older dogs, with a mean age of 8.2 years (Table 2). The number of cases reported in male dogs (54.67%) is slightly higher than in female dogs (45.33%; Table 3), but there does not appear to be a sex predisposition.<sup>13-16,27,34</sup>

The cause for development of SCCEDs is still under investigation. Initially, investigators proposed an endocrine or senile etiology.<sup>29</sup> Recent studies suggest that an abnormality in the adhesion process between the cornea's anterior epithelium, basement membrane, and stroma may be responsible.<sup>13-16</sup>

Abnormalities with the corneal epithelium,<sup>13-16</sup> basement membrane,<sup>13,15-16</sup> hemidesmosomes,<sup>13</sup> anterior stroma,<sup>13,15-16</sup> and corneal innervation<sup>34</sup> are reported in dogs with SCCEDs. Because of the presence of epithelial dysplasia and epithelial degeneration, early reports classified SCCEDs in dogs to be an epithelial dystrophy.<sup>13,14</sup> Based on abnormal basement-membrane architecture<sup>13-14</sup> and decreased numbers of hemidesmosomes in the area of the ulceration,<sup>13</sup> other investigators suggested the etiology to be a primary basement-membrane disease.<sup>7,13-14</sup> Recently, Bentley et al reported that the basement membrane is normal in the areas of the cornea not associated with the epithelial defect, and implied that SCCED are not a basement-membrane dystrophy but rather an age-related condition.

A hyaline acellular zone located in the anterior stroma of patients with SCCEDs<sup>15,16</sup> is suggested to be responsible for the refractory nature of SCCEDs.<sup>16</sup> This hyaline acellular zone is composed of collagen and prevents the corneal epithelium from adhering to the stroma.<sup>16</sup> Recently, Murphy et al identified abnormalities in corneal nerve density, distribution, and morphology in dogs with SCCEDs. A circumscribed area of hyperinnervation is present in the subepithelial stroma and epithelium surrounding the epithelial lip. The level of the neurotransmitter substance P in the epithelial lip is 3 times that of normal corneas. These findings suggest that substance P also may play a role in the pathogenesis of SCCEDs.

#### Corneal Edema

Cornea edema develops secondary to anterior corneal epithelial or posterior corneal epithelial dysfunction, and it can predis-

pose to CCEDs. Fluid accumulation in the anterior stroma results in the development of bullous keratopathy and in spontaneous epithelial defects that are recurrent and refractory.<sup>7,14,24-27</sup> Edema interferes with the adhesion of the epithelium to the underlying stroma. Topical hyperosmotic agents, such as 5% sodium chloride, are used with limited success to reduce the edema and improve epithelial adhesion.<sup>7,1</sup>

#### Anterior Stromal Calcific Keratopathy and Lipid Keratopathy

Subepithelial deposits of calcium<sup>7,23</sup> or lipid<sup>1</sup> can be associated with CCED. The epithelium over these areas is often poorly adhered to the underlying stroma, predisposing to refractory ulcers. Calcium deposition occurs in response to severe keratitis,<sup>7</sup> age-related calcific keratopathy,<sup>23</sup> systemic hypercalcemia, or hyperadrenocorticism.<sup>35</sup> Topical disodium ethylenediaminetetraacetic acid solution (EDTA; 1-5%, 2-3 times a day) is used to treat calcific keratopathy. In severe cases, a superficial keratectomy is recommended to remove the calcium.<sup>1,23</sup> Lipid keratopathy develops secondary to hyperlipemia, diet, or chronic keratitis and is treated by correcting the underlying cause.

#### Treatment of CCEDs

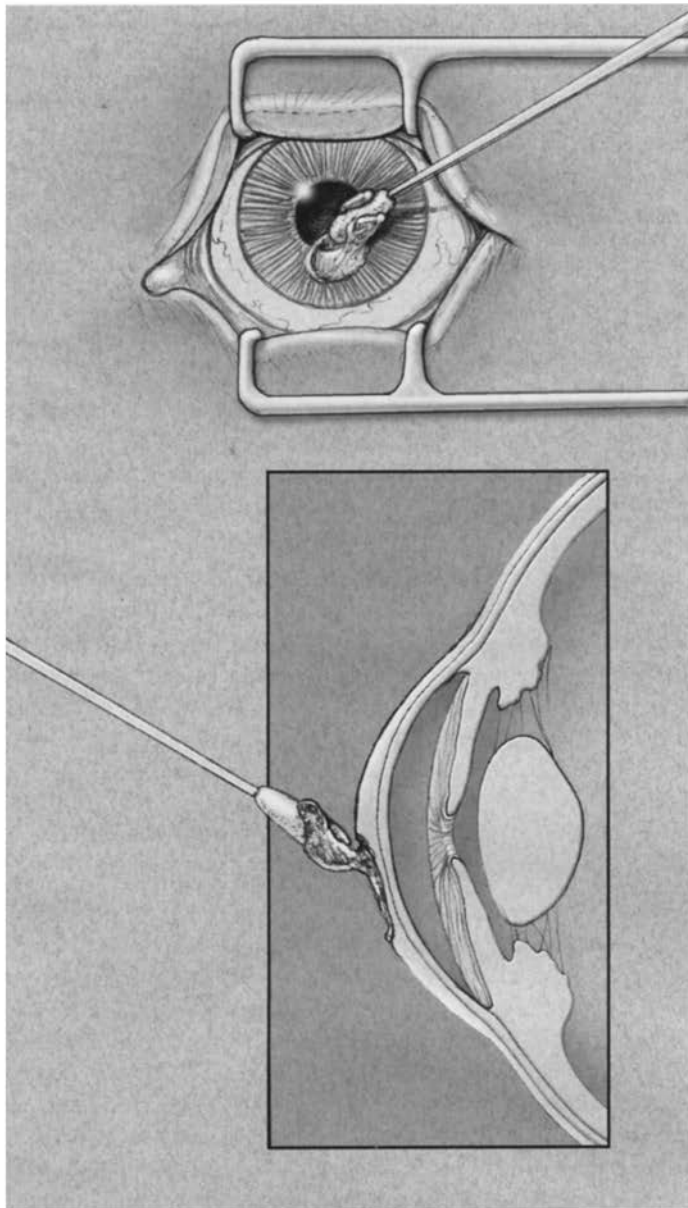
The first step in treating CCEDs is to determine the cause and correct any condition that is associated with the ulceration. Failure to correct an underlying condition, such as KCS or adnexal disease, will prevent the ulceration from responding to treatment. A number of therapies are described that promote healing and are directed at stimulating epithelialization and promoting epithelial adhesion.

#### Client Communication

Client communication is an essential part of the treatment for CCEDs. The refractory nature, potential for reoccurrence, and spontaneous nature can be frustrating for owners. No matter the cause or treatment, it may take days to weeks for more refractory cases to resolve.

#### Antibiotic Therapy and Cycloplegia

Although chronic epithelial defects are not associated with bacterial infections, a broad-spectrum topical antibiotic, such as



**Fig 2. Debridement of a CCED. A dry, cotton-tip applicator is used to move the loose corneal epithelium. Frequently, the area of nonadherent epithelium extends several millimeters beyond the ulcer's edge. (Reprinted with permission from Miller WW: Evaluation and management of corneal ulcerations: A systematic approach. Clin Tech Small Anim Pract 16:51-54, 2001.)**

neomycin/polymyxin B/bacitracin ophthalmic solution, is indicated to help prevent secondary infections. To prevent toxic changes to the epithelium, topical antibiotics that are epithelial toxic, such as gentamycin,<sup>36</sup> are avoided, and solutions are used at a low frequency (3-4 times a day) in place of ointments.<sup>1,9</sup> Topical atropine 1% ophthalmic solution (2-3 times a day) is indicated if severe ocular pain and miosis are present. Generally, atropine is indicated for 3 to 5 days after debridement/keratotomy or keratectomy procedures.

#### Corneal Debridement

Mechanical debridement,<sup>25,26</sup> with or without chemical debridement,<sup>13</sup> is recommended in the treatment of CCEDs. Debridement is used to stimulate corneal healing by removing the abnormal corneal epithelium and basement membrane, as well

as debris from the exposed stroma. Debridement stimulates proliferation of adjacent epithelium and promotes epithelial attachment, but as the sole treatment, debridement has a prolonged post-healing time when compared with the combination of debridement and punctate or grid keratotomy. Debridement alone has an average post-treatment healing time of 23 to 24.4 days (Table 4).<sup>25,26</sup>

#### Mechanical Debridement

The defect is debrided every 7 to 10 days until epithelization is complete. After the application of a topical anesthetic, a dry, cotton-tipped applicator is used to remove the abnormal epithelium and debris from the stromal surface (Fig 2). If needed, fine corneal forceps are used to facilitate removal of loose epithelium. The defect is aggressively debrided until epithelium no longer dislodges easily from the stroma. The epithelium is removed to at least 1 to 2 mm past the margin of the fluorescein-stained area.<sup>1,9</sup> If the area of abnormal epithelium is extensive and extends across the cornea surface, a larger epithelial defect may be created by debridement (Fig 3). In general, it is difficult to remove healthy epithelium with a cotton-tip applicator.

#### Chemical Debridement

Tincture of iodine, dilute povidone-iodine, trichloroacetic acid, and phenol are used for chemical debridement.<sup>1</sup> Iodine is the most common agent used and is theorized to alter the anterior stromal surface, allowing for epithelial adhesion.<sup>1,9</sup> After chemical debridement, the average post-healing time of CCEDs is 46 days.<sup>13</sup> Chemical debridement is not recommended by most clinicians, and if used, it is not used alone but rather in conjunction with mechanical debridement.

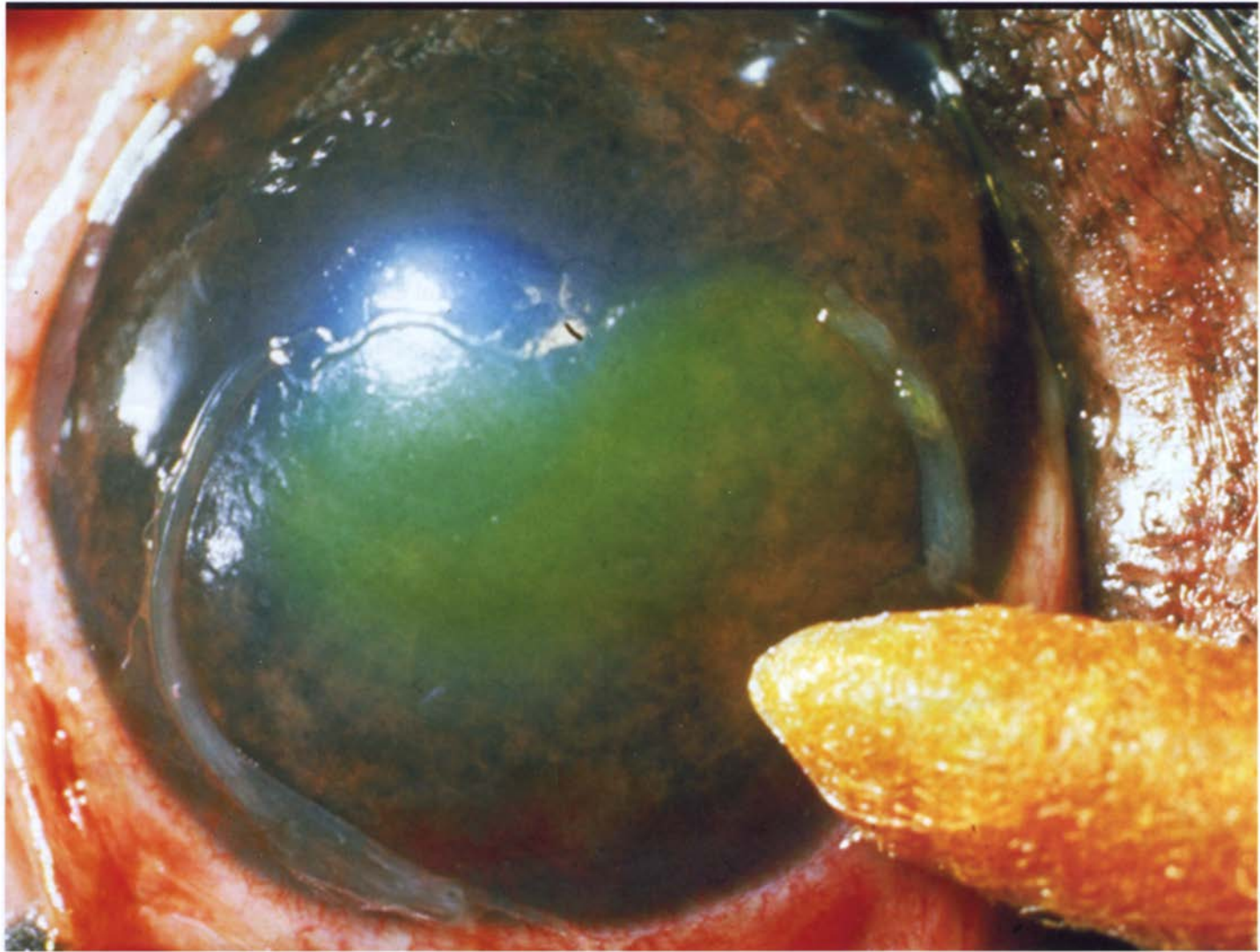
#### Grid/Punctate Keratotomy

When compared with debridement alone, the combination of debridement and a grid or punctate keratotomy increases the healing rate<sup>25-27,33</sup> and decreases the post-treatment healing times for CCEDs (Table 4).<sup>15,26-27,33</sup> Of the 2 procedures, grid keratotomy has the highest healing rate and lowest average post-treatment healing time.<sup>26,27</sup> If multiple grids are performed, the healing rate for CCEDs ranges from 94% to 100%,<sup>26,27,37</sup> with an average post-treatment healing time of 9.3 to 13.4 days.<sup>15,26-27</sup> Both grid and punctate keratotomy procedures increase healing by penetrating the acellular zone of hyaline collagen in the superficial stroma, providing an area of healthy stroma for epithelial adhesion.<sup>26</sup>

#### Punctate Keratotomy

After topical anesthesia and debridement, superficial punctures are made into the anterior stroma with the use of a 20- to 23-gauge disposable hypodermic needle.<sup>25,27,33</sup> The needle is placed perpendicular to the corneal surface and superficial punctures are made into the anterior stroma at 0.5- to 1.0-mm intervals throughout the debrided area.<sup>25,33</sup> Topical anesthesia with sedation or general anesthesia is used in fractious animals. Because of the lower healing rate,<sup>25,33</sup> frequent need for sedation,<sup>33</sup> and potential for deep stromal puncture,<sup>38</sup> punctate keratotomy is performed less frequently than grid keratotomy.





**Fig 3. CCED from Fig 1 after loose epithelium has been pushed back with a cotton-tipped applicator. Note the limit of fluorescein-stain uptake that depicts the size of the ulcer before debridement.**

### *Grid Keratotomy*

After topical anesthesia and debridement, a 25- to 27-gauge<sup>1,26-27,37,38</sup> needle or a 64 beaver blade<sup>38</sup> is used to make linear corneal incisions in a grid pattern. The liner incisions are made at 1- to 2-mm intervals across the ulcers surface and extend 1 to 2 mm past the edge of the ulceration (Fig 4). The liner corneal incisions extend approximately one fourth of the way into the healthy, superficial, anterior stroma. A grid keratotomy breaches the acellular zone of hyaline collagen in the anterior stroma better than a punctate keratotomy. This may be responsible for the higher success rate and shorter post-treatment healing time of a grid keratotomy than a punctate keratotomy. Topical anesthesia with sedation or general anesthesia is used in fractious animals.

### *Keratotomy*

Superficial keratectomy results in the highest success rate and shortest post-treatment healing time of all the procedures used to treat CCEDs (Table 4). A 100% success rate<sup>15,26,31,34</sup> and post-treatment healing time of 9.3 days has been reported.<sup>26</sup> Superficial keratectomy removes the acellular zone of hyaline collagen in the anterior stroma, eliminating the barrier to epithelial healing; thereby, increasing the success rate.<sup>15,26</sup>

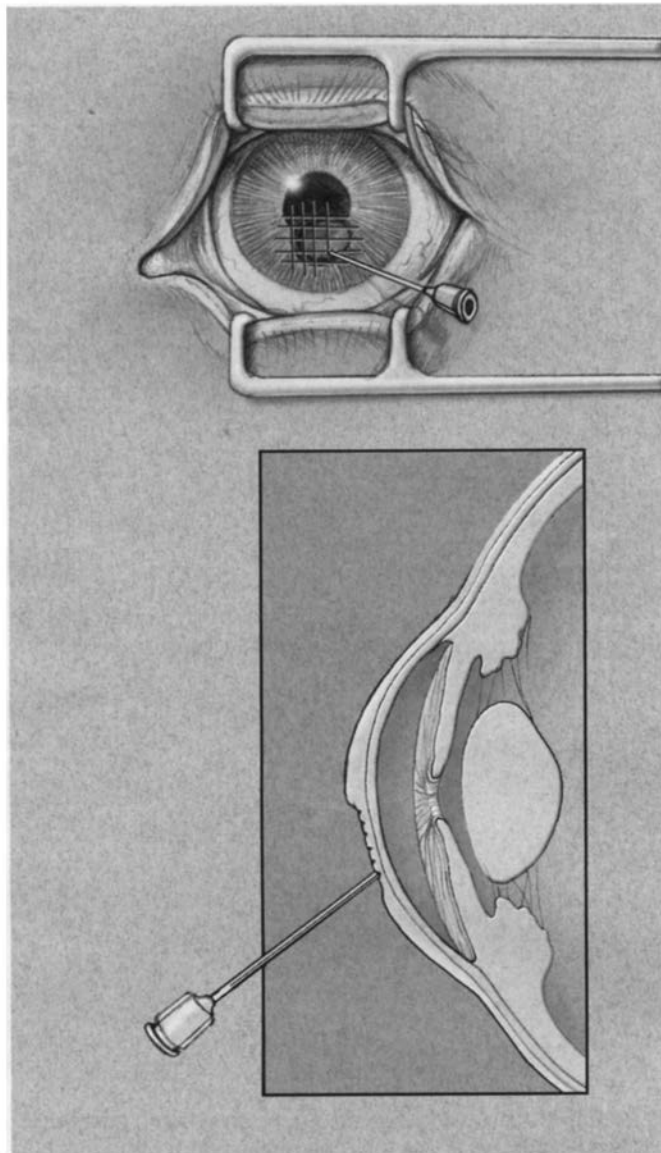
Keratectomies are the most expensive procedure to perform, requiring general anesthesia and experience in microsurgery. With the aid of an operating microscope, a number 64 beaver blade or a corneal trephine is used to outline the epithelial defect. The cornea is incised to approximately one fourth to one third of the stromal depth. A 64 beaver blade or a Matinez corneal dissector is used to separate the cornea lamellae. The procedure is described in detail in Dr. Hollingsworth's chapter on "Corneal Surgical Techniques."

### *Bandaging Procedures*

A number of bandaging procedures are recommended to protect the cornea after debridement/keratotomy of CCEDs, including contact lenses,<sup>25,39,40</sup> collagen shields,<sup>15,25</sup> cyanoacrylate tissue adhesives,<sup>24</sup> temporary tarsorrhaphies,<sup>1,26,41</sup> third eyelid flaps,<sup>1,25,41,42</sup> and conjunctival flaps.<sup>1,43</sup>

### *Contact Lens/Collagen Shields*

After debridement, the use of contact lenses or collagen shields has varying degrees of success in the treatment of CCEDs.<sup>15,25,39,40</sup> Contact lenses are beneficial in 61.5% to 95.0% of the cases,<sup>25,39,40</sup> with an average post-treatment healing time of 24.8 days.<sup>25</sup> The highest success rates are reported



**Fig 4. Grid keratotomy.** A 20- to 25-gauge needle is used, beveled surface up, to make multiple small corneal incisions in a grid pattern. The incisions are made at 1- to 2-mm intervals across the ulcer's surface and extend 1 to 2 mm past the edge of the ulceration. The incisions are made to the depth of the anterior one fourth of the cornea's stroma. (Reprinted with permission from Miller WW: Evaluation and management of corneal ulcerations: A systematic approach. *Clin Tech Small Anim Pract* 16:51-54, 2001.)

when the contact lens remains in place for 7 to 10 days (Table 5).<sup>39</sup> However, 61.5% of the lens dislodge before 7 days. Collagen shields do not improve the healing rate of CCEDs and have a 44% heal rate. The 72-hour dissolution rate of collagen shields is suggested to be responsible for their low success rate.<sup>25</sup> Studies evaluating the effectiveness of a grid keratotomy, followed by placement of a contact lens or collagen shield, on the healing rate of corneal epithelial defects have not been performed; however, this treatment combination is commonly used.

#### *Cyanoacrylate Tissue Adhesive*

Success rates of up to 100% have been reported with the use of isobutyl cyanoacrylate tissue adhesive (BCTA) in the treatment of CCEDs. The average post-treatment healing time is 23.8 days (Table 5).<sup>24</sup> Tissue adhesive enhances corneal healing by stim-

ulating corneal neovascularization<sup>24,44-46</sup> and chemically debriding the cornea by removing abnormal epithelium and basement membrane,<sup>1</sup> and possibly altering the anterior stroma.

Before applying the BCTA, the ulcer is debrided with a cotton-tipped swab, and the ulcer bed is thoroughly dried by using a second swab. A hyperdermic needle (27-25 gauge) is used to draw up a small amount of the BCTA into the tip of a 1-ml syringe. The needle is removed and adhesive is pushed up to the end of the syringe tip. The syringe is inverted and a thin layer of BCTA is applied to the ulcer bed, with a small amount extending over the edge of the defect.<sup>24</sup> The lids are held open or an eyelid speculum is used to prevent accidental gluing of the eyelids and nictitating membrane. Topical anesthesia can be used alone in most patients to apply BCTA.

#### *Temporary Tarsorrhaphies, Third Eyelid Flaps, and Conjunctival Flaps*

Temporary tarsorrhaphies,<sup>1,26,41</sup> third eyelid flaps,<sup>1,25,41</sup> and conjunctival flaps<sup>1,43</sup> are used alone or in combination with other therapies in the treatment of CCEDs. After a keratectomy or debridement and a keratotomy, temporary tarsorrhaphies serve as a natural bandage that protects the corneal surface. Tarsorrhaphies are particularly beneficial when treating corneal epithelial defects associated with neurotropic keratitis or exposure keratitis. Third eyelid flaps are not beneficial in stimulating healing of corneal epithelial defects, whether used as the sole treatment<sup>25,43</sup> or in combination with a keratotomy<sup>26,37</sup> or keratectomy (Table 5).<sup>26</sup> The inability to observe the ulcer during the healing process and the inability to repeatedly debride or perform keratectomies make third eyelid flaps a poor choice for the treatment of CCEDs.

#### *Conjunctival Flap*

Conjunctival flaps are advocated by some clinicians for the treatment of refractory CCEDs.<sup>1,43</sup> Conjunctival flaps promote corneal healing by providing a direct blood supply and a source of epithelium,<sup>1</sup> but they require general anesthesia, have longer healing times, and produce more scarring than other treatments.<sup>1</sup> Therefore, conjunctival flaps are usually reserved for deep progressive ulcers or ulcers that extend to Descemet's membrane.

#### *Thermokeratoplasty*

Thermokeratoplasty is more beneficial than a grid keratotomy in the treatment of CCEDs associated with bullous keratopathy and severe corneal edema.<sup>47</sup> CCEDs associated with severe corneal edema that are treated by grid keratotomy have a slower healing rate and longer healing time than those not associated with corneal edema.<sup>26,27</sup> Cases with severe corneal edema that have had a grid keratotomy performed before a thermokeratoplasty have a longer post-treatment healing time than those in which a thermokeratoplasty alone is performed (Table 4).<sup>47</sup>

Before performing thermokeratoplasty, debridement is performed to remove the poorly adhered epithelium. A variable low-temperature, fine-tip ophthalmic cautery unit is used with minimal probe temperature. The cautery is applied to the area of exposed stroma in a circular pattern at 2-mm intervals until a mild superficial stromal contracture and opacity is formed, but not a focal burn. Because the probe temperature cannot be

**TABLE 5. Percent Healing and Post-treatment Times for Bandaging Procedures and Topical Medications Reported for the Treatment of CCEDs**

Bandaging Procedures	% Healed	Mean Post-Treatment Time	Note
Soft contact lens (25)	61.5%	24.8 days	
Soft contact lens (39)	73%	NR	92% healed if lens remained for 7-10 days
Soft contact lens (40)	95.0%	NR	Epithelialized in 2 weeks
Collagen shield (25)	44.0%	15 days	
Collagen shield (15)	NR	NR	No improvement in healing rate
Third eyelid (25)	68.0%	17.9 days	
Cyanoacrylate tissue adhesive (24)	100%	23.8 days	Epithelialized/adhesive sloughed in 3.4 weeks ( $\pm$ 1 week)
Topical Medications	% Healed	Mean Post-tx	
Aprotinin <sup>+</sup> (25)	38.8%	23.7 days	
SP <sup>++</sup> (34)	70%	18.62 days	
SP/IGF-1 <sup>++</sup> (34)	75%	22.19 days	
Epidermal GF <sup>+</sup> (53)	80%	NR	
Polysulfated glycosaminoglycan <sup>+</sup> (32)	83%	11.97 days	

+ = Debrided before application; ++ = no debridement.

SP = substance P; IGF-1 = insulin-like growth factor-1; GF = growth factor.

NR = Not reported.

controlled, the probe is applied without pressure and removed immediately.<sup>47</sup>

### Medical Therapy

#### *Aprotinin*

Proteinases prevent basement-membrane replacement and adhesion and may play a role in the development of CCEDs.<sup>12</sup> Aprotinin is an inhibitor of the proteinase plasmin,<sup>7</sup> which has been associated with refractory corneal ulcers.<sup>10,11</sup> An initial report on the topical use of aprotinin to treat CCEDs in dogs was favorable.<sup>48</sup> In a subsequent study, treatment with aprotinin resulted in a healing rate similar to controls at 38.8%, and an average healing time of 23.7 days (Table 5).<sup>25</sup> Aprotinin is currently not recommended for the treatment of corneal epithelial defects in dogs.

#### *Fibronectin*

Fibronectin is a glycoprotein that is normally deposited in the bed of corneal wounds.<sup>7</sup> The topical application of fibronectin is reported to promote the healing of persistent corneal epithelial defects.<sup>49,50</sup> However, recent reports question the efficacy of fibronectin for the treatment of CCEDs in humans.<sup>51</sup>

#### *Substance P/Substance P with Insulin-like Growth Factor-1*

Studies suggest that the neurotransmitter substance P plays a role in the pathogenesis of CCEDs in dogs.<sup>34</sup> Without debridement of the ulceration, the topical applications of substance P or substance P with insulin-like growth factor results in a 70% and 75% healing rate, respectively (Table 5). Substance P is currently not commercially available. Studies evaluating substance P's effect on the healing of CCEDs after debridement and a keratotomy are not reported in the literature.

#### *Epidermal Growth Factor*

Epidermal growth factor (EGF) stimulates mitosis of epithelial cells and protein synthesis,<sup>52</sup> and it is reported to be beneficial in the treatment of CCED in dogs.<sup>53</sup> In one study, topical application of epidermal growth factor (100 g/ml) resulted in an 80% healing rate with a 14-day post-treatment time, com-

pared with a 20% healing rate for controls (Table 5). Additional studies evaluating the effects of EGF are not reported in dogs. However, in horses, EGF is reported not to be beneficial.<sup>54</sup> Currently, EGF is not commercially available.

#### *Serum*

Serum is suggested to be beneficial in the treatment of CCEDs in both dogs<sup>7,27</sup> and people.<sup>55,56</sup> The concentrations of fibronectin, EGF, substance-P, vitamin A, and proteinase inhibitors found in serum may explain its beneficial effects.<sup>56</sup> Controlled studies evaluating serum's effectiveness on CCEDs in dogs has not been reported in the literature.

#### *Polysulfated Glycosaminoglycan*

A correlation between the development of refractory corneal ulcers and plasmin levels is reported in people.<sup>6,10-11</sup> Plasmin is thought to disrupt epithelial cell adhesion.<sup>6</sup> Polysulfated glycosaminoglycan (PSGAG) inhibits plasmin and plasminogen activators and has been shown to be beneficial in the treatment of CCEDs in dogs.<sup>32</sup> A 5% PSGAG (2.5 ml of Adequan<sup>®</sup> intramuscularly with artificial tears to a final concentration of 50 mg PSGAG/ml) applied every 8 hours after debridement resulted in a healing rate of 83%, and an 11.97-day post-treatment healing time (Table 5).

### Hormonal Therapy

A sex predisposition for spayed females and older males was initially reported in Boxers with SCCEDs, and an endocrine or age-related disorder was suggested as a potential etiology.<sup>29</sup> Hormonal supplementations were recommended to stimulate epithelization and to prevent reoccurrence.<sup>57</sup> Recent studies report no sex predisposition for the development of CCEDs,<sup>13-16,34,27</sup> and hormonal therapy has proven not to be beneficial in their treatment.<sup>57</sup> Currently, most ophthalmologists do not recommend hormonal therapy.

### CCEDs in Cats

CCEDs are reported more commonly in domestic short-haired cats, but a predisposition is reported in brachyce-



phalic breeds.<sup>17</sup> The mean age of occurrence is 7 years, 8 months. Associated lid abnormalities include medial canthal entropion and macroblepharon. Herpes keratitis is suspected in 72% of the cases of feline CCEDs.<sup>17</sup>

In cats, treatment by a combination of superficial debridement and grid keratotomy does not decrease the mean healing time when compared with debridement alone, where the mean healing times are 30 days and 42 days, respectively. The incidence of corneal sequestrum formation is higher in cats treated with grid keratotomy than with debridement alone.<sup>17</sup> Because the prolonged healing time and increased incidence of corneal sequestrum formation, grid keratotomy is not recommended in cats with CCEDs.

#### Guidelines for treating CCEDs in dogs:

- Determine and correct any underlying cause of the CCED.
- Debride the CCED with a cotton-tip applicator.
- Perform a grid keratotomy.
- Repeat the debridement and grid keratotomy every 7 to 10 days, until the defect epithelializes.
- Apply neomycin/polymyxin B/bacitracin ophthalmic solution 3 to 4 times a day, and apply atropine 1% ophthalmic solution 2 times a day.
- For refractory cases in dogs:
  - Apply polysulfated glycosaminoglycan 5% in artificial tears every 8 hours
  - Refer for superficial keratectomy.

#### Guidelines for treating CCEDs in cats:

- Determine and correct any underlying cause of the CCED.
- Evaluate the cat for herpes keratitis.
- Treat for herpes keratitis, if indicated.
  - Debride the CCED with a cotton-tip applicator.
  - Do not perform a grid keratotomy.
  - Repeat the debridement every 7 to 10 days, until the defect epithelializes.
  - Apply neomycin/polymyxin B/bacitracin ophthalmic solution or oxytetracycline-polymyxin ophthalmic ointment 3 to 4 times a day.
  - For refractory cases in cats:
    - Refer for superficial keratectomy.

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