

Chronic Superficial Keratitis in Dogs

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Chronic superficial keratitis (CSK)—also known as *German shepherd pannus*, *Überreiter's syndrome*, or *degenerative pannus*—is a progressive, usually bilateral, and potentially vision-threatening disease of the canine cornea.^{1,2} It is characterized by chronic inflammation of the corneal epithelium and anterior stroma, which results in neovascularization, pigmentation, and opacification.¹ Atypical pannus (ie, plasmoma), an inflammatory process of the nictitating membrane, has also been described.²

Clinical History & Signalment

Large breeds—in particular German shepherd dogs, shepherd crossbreeds, border collies, and greyhounds—are predominantly affected; however,

CSK can occur in dogs of any size and breed.² Age of onset is an important prognostic indicator. The condition typically progresses rapidly in young dogs (ie, 1-5 years of age); lesions may be less severe in animals affected later in life (ie, >4-5 years of age).²

Physical Examination Findings

CSK manifests initially at the temporal or inferior temporal limbus as a hyperemic, vascularized conjunctival lesion.² Early changes in the cornea are characterized by limbal neovascularization and pigmentation, which advance centrally as the disease course continues.² Chronic tissue changes are characterized by progressing moderate-to-severe corneal neovascularization, with infiltration of fleshy granulation tissue into the anterior stroma and proliferation of limbal melanocytic pigment invasion (**Figure 1**, next page).^{2,3} Lipid infiltrates may also be noted in the clear cornea 1 to 2 mm in front of the leading edge of the lesion.²

CSK = chronic superficial keratitis

As the disease advances, neovascularization often begins at the temporal limbus and extends centrally (**Figure 2**).² The dorsal limbus is only involved late in the disease process; however, the entire cornea may eventually become vascularized, pigmented, and opaque, which can lead to visual impairment.^{2,4,5}

TREATMENT AT A GLANCE

Mild-to-Moderate Cases²

- Long-term topical cyclosporine (0.2%-2% q12h) or tacrolimus (0.02%-0.03% q12h)
 - With or without an additional topical corticosteroid (eg, dexamethasone [0.1%], prednisolone acetate [1%] q6-8h) slowly tapered over few weeks to months²

Moderate-to-Severe Cases^{2,4,10}

- Topical medications as for mild-to-moderate cases; consider higher frequencies
- Subconjunctival corticosteroid injections
- Advanced treatments with strontium-90, soft x-rays (15 kV), and/or keratectomy

Histopathologic Diagnosis & Pathogenesis

The clinical lesion is histopathologically characterized by fibrovascular tissue in the corneal stroma that is accompanied by lymphocytes and plasma cells as well as migration of limbal pigmented cells.² Infiltrating CD4+ lymphocytes are the predominant cells found in patients with CSK, which suggests that CSK has an immune-mediated pathogenesis.¹

An increase in major histocompatibility complex class II antigen expression has been identified in the central corneal epithelium and stroma in dogs with CSK and is indicative of an autoimmune nature of the disease.⁶ In another study, an identified major histocompatibility complex class II risk haplotype was found to be strongly associated with chronic CSK in German shepherd dogs; animals with the risk haplotype were 2.7 times more likely to develop CSK, and animals that were homozygous for this specific haplotype were 8 times more likely. This further suggests that CSK is an immune-mediated disease with a genetic basis.⁷



▲ **FIGURE 1** Left eye of a 9-year-old neutered male German shepherd dog. Thickened nictitans (ie, plasmoma) and lateral corneal infiltration can be visualized (**A**). Right eye of the same dog; nictitans swelling and lateral invasion of cornea can be noted (**B**). Photos courtesy of Tammy Miller Michau, DVM, MS, MSpVM

High altitude and increased exposure to sunlight appear to intensify clinical signs in dogs that may have a genetic predisposition for developing CSK, as ultraviolet radiation may modify cornea-specific antigens, which initiate the cell-mediated inflammation.^{3,8}

Clinical Diagnosis

In most cases, signalment and clinical appearance of the corneal lesions are sufficient for CSK diagnosis. However, major differential diagnoses can include pigmentary keratitis, keratoconjunctivitis sicca, chronic irritation, and/or chronic granulation tissue from previous corneal wounds.²

Treatment & Long-Term Management

CSK can generally be controlled through medical or surgical means (see *Treatment at a Glance*), but it cannot be cured. A standard treatment protocol has not been established, and the goal for all described therapies is to stall disease progression.^{2,8,9} Owners should be advised that lifelong therapy is necessary and that disease severity and

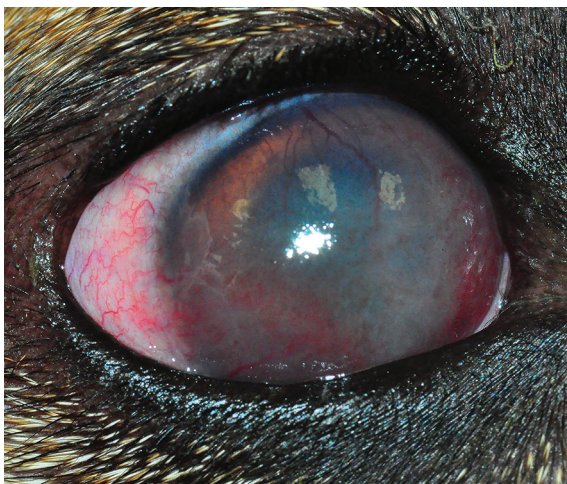
prognosis are also dependent on factors such as age of onset, altitude, sun exposure, and genetic predisposition.^{2,8}

Long-term control of mild-to-moderate cases can often be managed with topical therapy (ie, cyclosporine [0.2%-2% q12h] or tacrolimus [0.02%-0.03% q12h] with or without an additional corticosteroid [eg, dexamethasone 0.1%, prednisolone acetate 1%]). The topical corticosteroid should be started at a higher frequency based on the individual case and case severity, then slowly tapered over time.² One study demonstrated that topical pimecrolimus (1% q8h) may be an effective therapy for moderate-to-total regression of CSK lesions.⁵

For patients with an insufficient or delayed response to topical medication, subconjunctival corticosteroid injections may be necessary to control disease. Patients treated with long-term topical anti-inflammatory drugs should be monitored closely by the owner for signs of ocular discomfort, discharge, redness, and behavior changes and regularly examined by a veterinarian (ie, complete ophthalmic examination) to prevent corneal ulcerations or corneal infections.

Beta irradiation with strontium-90^{2,10} and radiation therapy with soft x-rays (15 kV)⁴ have been described as safe and effective forms of treatment in patients that have severe CSK unresponsive to medical therapy (ie, drop application and subconjunctival injections) alone.

In patients with severe CSK that are unresponsive to medical therapy—and, where available, radiation therapy—surgical intervention may be considered. Superficial keratectomy may be required for



▲ **FIGURE 2** Eye of a 6-year-old spayed German shepherd dog. Diffuse corneal infiltration can be noted. *Photo courtesy of Tammy Miller Michau, DVM, MS, MSpVM*

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patients with blinding disease; however, opacification recurrence should be expected. All of the treatment methods described (ie, medical therapy as well as radiation) should be considered following a keratectomy to prevent or delay recurrence.²

Making husbandry changes such as canine protective eye wear and limiting sun exposure during high UV radiation times should be considered, as ultraviolet-blocking contact lenses have not been shown to be successful or advantageous in CSK treatment.⁹

Conclusion

CSK is an immune-mediated disease process that can be challenging to treat and cannot be cured; delay of disease progression or stabilization of the corneal pathology should be considered a therapeutic success.⁹ A standard protocol has not been determined, but life-long therapy is required.⁹ ■

TAKE-HOME MESSAGES

- CSK is an immune-mediated disease that likely has a genetic basis.⁷
- German shepherd dogs, border collies, and greyhounds appear to be predisposed.²
- CSK can be a potentially blinding disease in severe cases.²
- Onset usually occurs at 3 to 5 years of age but may occur at any age. CSK can be more difficult to control in dogs affected at a young age.²
- UV-light exposure and high altitude may contribute to disease severity.^{3,8}
- Lifelong therapy with immunosuppressive and immunomodulating agents is required.²

CSK = chronic superficial keratitis

See page 82 for references.

Heartgard® (ivermectin/pyrantel) Plus

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

DOSAGE: HEARTGARD® Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Cheewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.

For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer service, please contact Merial at 1-888-637-4251.



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Metacam® (meloxicam)

1.5 mg/mL Oral Suspension (equivalent to 0.05 mg per drop)

0.5 mg/mL Oral Suspension (equivalent to 0.02 mg per drop)

Non-steroidal anti-inflammatory drug for oral use in dogs only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each milliliter of Metacam Oral Suspension contains meloxicam equivalent to 0.5 mg/mL or 1.5 mg/mL and sodium benzoate (1.5 milligrams) as a preservative. The chemical name for Meloxicam is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The formulation is a yellowish viscous suspension with the odor of honey.

Indications: Metacam Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Contraindications: Dogs with known hypersensitivity to meloxicam should not receive Metacam Oral Suspension. Do not use Metacam Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.

Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. **For oral use in dogs only.** As with any NSAID, all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration. Owner should be advised to observe their dog for signs of potential drug toxicity and should be given a client information sheet about Metacam.

Precautions: The safe use of Metacam Oral Suspension in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after administration of the total daily dose of Metacam Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Metacam Oral Suspension has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Metacam Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Adverse Reactions: Field safety was evaluated in 306 dogs.¹ Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetence) were the most common adverse reactions associated with the administration of meloxicam. The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration

Urinary: azotemia, elevated creatinine, renal failure

Neurological/Behavioral: lethargy, depression

Hepatic: elevated liver enzymes

Dermatologic: pruritus

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with use of meloxicam in cats.**

Information for Dog Owners: Metacam, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and should be informed of the clinical signs associated with drug intolerance. Adverse reactions may include vomiting, diarrhea, decreased appetite, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions).** Owners should be advised to discontinue Metacam and contact their veterinarian immediately if signs of intolerance are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

Effectiveness: The effectiveness of meloxicam was demonstrated in two field studies involving a total of 277 dogs representing various breeds, between six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n=109), dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all parameters. In the second field study (n=48), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.¹

Reference: 1. FOI for NADA 141-213 (Metacam® (meloxicam) 0.5 mg/mL and 1.5 mg/mL Oral Suspension).

Manufactured for:

Boehringer Ingelheim Vetmedica, Inc.

St. Joseph, MO 64506 U.S.A.

US Patent 6,184,220

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In addition, no virus transmission—including retroviruses such as human papillomavirus, which can be spread between humans—between pets and humans has been shown to cause cancer in humans.

In fact, reports have shown that pet ownership may actually decrease the incidence of cancer in humans. A population-based case-control study in the San Francisco Bay area showed that pet owners had a reduced risk for nonHodgkin's lymphoma as compared with those who never owned a pet.³ However, this research remains to be confirmed. ■

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