Pathogenesis and Clinical Management of Infectious Bovine Keratoconjunctivitis

Lisle W. George, *D.V.M.*
George Kagonyera, *D.V.M.*
Department of Veterinary Medicine
University of California
Davis, California 95616

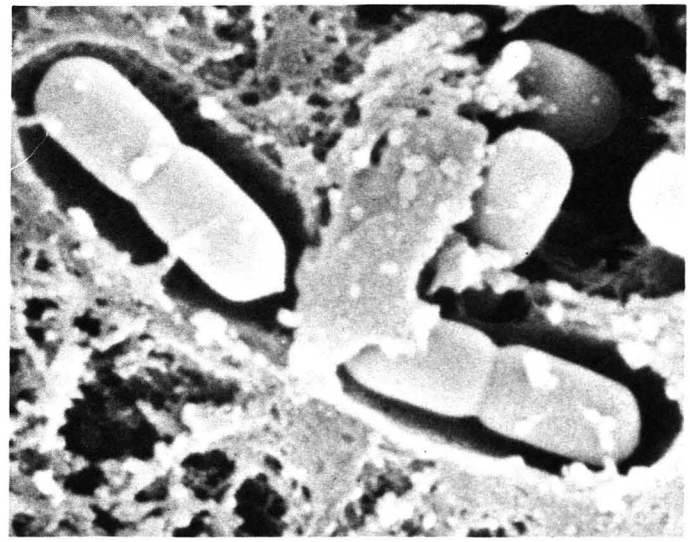
Infectious bovine keratoconjuctivitis (IBK) is a widespread ocular disease of cattle which is caused by the bacterium *Moraxella bovis (M. bovis).*[1,2] The annual losses in the United States are estimated to be approximately $200,000,000.[3] Specific economic losses include decreased growth rates, lower purchase prices for cattle with scarred eyes, reductions of post-weaning weight gains and treatment associated costs.[4,5] The case attack rate of IBK in yearling cattle may range between 20 and 100%.[5,6,7] New cases occur over the entire summer, and epizootics may last for as long as 4 months.[6,7] The economic significance of IBK and the commercial development of vaccines has stimulated recent studies into the pathogenesis and treatment of IBK.

Pathogenesis of *M. bovis* Infection

Serial changes of the early corneal lesions in *M. bovis* infected calves have been described.[6,7] By 24 hours, bacteria resembling *M. bovis* are lying upon the surface of the corneal epithelial cells.[8,9] Corneal ulcers measuring <1.0 mm in diameter are commonly observed (figure 1). The cells surrounding the ulcer crater appear necrotic, and are vacuolated. By 1 day post infection, bacteria resembling *M. bovis* are present in the corneal stroma. These bacteria are surrounded by clear "lacunae," and appear to be lying in excavated pits (figure 2).[8,9,10] The characteristic microscopic appearance of the corneal stroma by 8 days post-infection is depicted in figure 3. The changes include necrosis of stromal collagen, infiltration by neutrophils and macrophages, edema, and neovascularization. Bacteria resembling *M. bovis* are infrequently seen in the corneal stroma at this time. Pathologic corneal changes which may occur after day 8 include neovascularization, inflammatory cell infiltration, corneal perforation iris prolapse, proliferation of granulation tissue, and scar formation.

FIGURE 1. Corneal ulcer of a calf 24 hours after exposure to M. bovis. (X250).

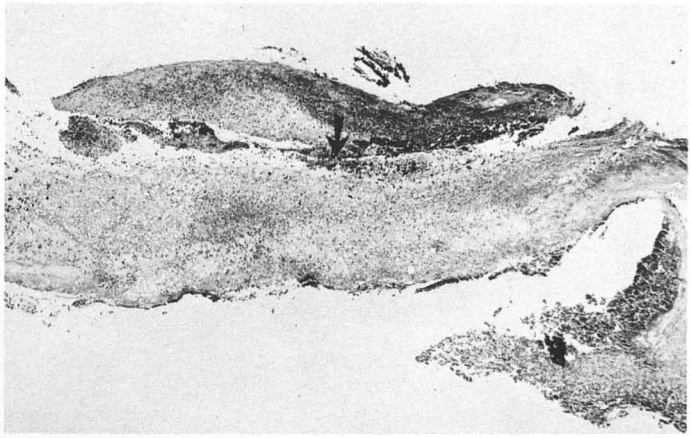
FIGURE 2. Scanning electron photomicrograph of cornea from a calf 24 hours post infection. Bacteria resembling M bovis are located in pits upon the corneal surface. (X1200).



Based upon these pathologic studies, it appears that there are 4 discrete pathologic stages in *M. bovis* infection. These include: 1.) bacterial attachment to the corneal epithelium, 2.) epithelial cell destruction, 3.) stromal excavation, and 4.) corneal fibroplasia.

Attachment Phase—Attachment of the *M. bovis* to the corneal epithelium appears to be a prerequisite for the development of IBK.[11] Pathogenic isolates of *M. bovis* produce pili which bind to one or more corneal epithelial cell receptors.[12,13] Pili are separated from *M. bovis* by mechanical agitation of the bacterial cells and precipitation in buffers of high ionic strength. The pili are composed of repeating protein subunits named pilin. The amino acid sequence of

FIGURE 3. Hematoxylin and Eosin stained corneal section from a calf infected with M. bovis for 8 days. The stroma is not covered by epithelium. There is extensive stromal invasion by neutrophils, macrophages, and plasma cells. There also is extensive corneal edema and a posterior synechia (arrow). (X75).



pilin has been determined. The sequence of the first 50 amino acid residues is the same as in pilin from Neisseria, Pseudomonas, and Bacteriodes. *Moraxella bovis* produces 2 types of pilin (a and b).[12] The molecular weights of the a and the b pilins are 20,000 and 17,000 respectively. As measured by competitive ELISA assays, there is approximately 60% shared antigenicity between the 2 types of pilin. The gene for the b pilin has been cloned, and has been determined to have a similar sequence to that of *Neisseria gonrrheae.*[14] A single bacterium can produce a or b pilin or can shift pilin production from a to b or vice versa. A single translocation of the nucleotides of the pilin genes in the 5′3′and 3′5′DNA strands produces the shift from a to b pilin production.[12] This translocation occurs spontaneously. Bacteria thus may produce solely a or b pilins, or may produce both types at the same time.

The functional aspects of switch from b to a pilin types have been studied.[13] Cultures of *M. bovis* which produced either a or b pilin were inoculated into susceptible calves. The infectivity and pathogenicity of each isolate was examined. The calves were housed in isolation to prevent cross infection by the heterologous isolate. Of the 6 calves that were given *M. bovis* producing the b pilin, 3 developed corneal ulcers and 4 became persistently infected. Conversely, *M. bovis* infection and IBK developed in only 1 of the 8 calves that were given the a pilin producing cultures. The isolates that were recovered from the ocular secretions of this animal produced the b pilin. This indicated that the production of the b pilin appears to be related to the development of IBK. The switch from b to the a pilin production may occur randomly, and may serve to vary the surface antigenicity of the *M. bovis.* Thus, the host may respond to the initial corneal colonization with the production of b pilin antibodies. The spontaneous conversion of a to b pilin production would offer a heterogeneous antigen to the host's immune system and provide a mechanism for bacteria survival in the face of an overwhelming host immune response. The relationship between this phenomenon and the development of the chronic carrier state of *M. bovis* is unclear. These and other studies which related to the antigenic structure of the *M. bovis* pili indicate that pilin vaccinal products should possess both the a and b epitopes.

Epithelial Cell Necrosis Phase—The production of corneal epithelial cell necrosis by pathogenic isolates of *M. bovis* has been demonstrated.[8 15 16] Monolayers of bovine corneal epithelium were exposed to culture filtrates from *M. bovis*, or to whole living cells. The corneal cells were lysed after 30 minues of incubation with the living bacteria (figures 4a and 4b).[15] Incubation of the cells with the culture filtrates produced cellular vacuolation, and separation at the intercellular junctions (figure 5). These *in vitro* changes also were observed in the corneas of experimentally infected calves.[8] Whole cultures of *M. bovis* and culture filtrates also were cytotoxic for bovine neurophils.[16] The cytotoxicity was calcium dependent, and could be eliminated by inactivation of the *M. bovis* with formalin, sodium azide, or heat. The necessity of ionized calcium for cytotoxic activity indicates that this factor may be a metalloprotein enzyme. The cytotoxic activity also lysed bovine neutrophils (figure 6). The filtrates did not kill human neutrophils. *Moraxella bovis* produces a large number of proteolytic factors and a hemolysin.[16 17 18] The relationship between the cytotoxin and the hemolysin are unclear. Like the cytotoxin, the hemolysin requires the presence of ionized calcium for activity. Hemolytic isolates of *M. bovis* are cytotoxic for bovine neutrophils, whereas non hemolytic isolates lack this trait.[16] Additionally, the pathogenicity of *M. bovis* is dependent upon the production of hemolysin.[19] In field infected cattle, antihemolysin titers increased in cattle with severe cases of IBK.[20] The hemolysin is associated closely with the cell wall, but can be extracted by filtration of culture supernatants through polycarbonate membranes.[18] These also are characteristics of the cytotoxin. Although unpublished observations in our laboratory have suggested that the hemolytic and cytotoxic activities in culture supernatants can be separated using gel-filtration chromatography, the specific relationships between the proteolytic, hemolytic, and cytotoxic activities in *M. bovis* remain unclear.

Stromal Liquefaction Phase—The pathogenesis of the stromal damage is not known, however it appears to be produced by an interaction between the corneal neutrophils, the *M. bovis*, and the stromal components.[8] Lacrimal secretions from calves with severe corneal ulcers do not contain collagenase. *Moraxella bovis* does not produce a collagenase *in vitro.*[17] These data may indicate that the denaturation of corneal stroma may occur either via non specific denaturation of the stromal collagen, or destruction of the stromal ground substance. *Moraxella bovis* produces numerous proteolytic enzymes which are capable of denaturing the stromal ground substance.[17] Such denaturation, could result in fibrillation of stroma collagen. Such collagen

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FIGURE 4a. Scanning electron photomicrograph of normal cultured bovine corneal epithelial cells. (X1250).

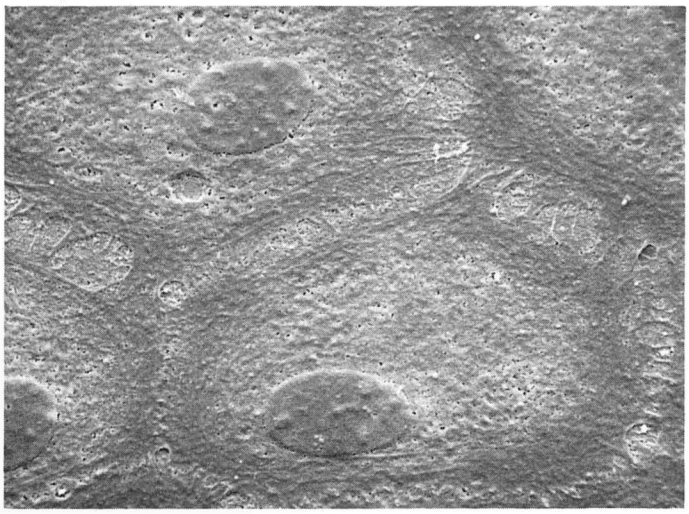


FIGURE 4b. Scanning electron photomicrograph of cultured bovine corneal epithelial cells 30 minutes after inoculation of living M. bovis. (X1250).

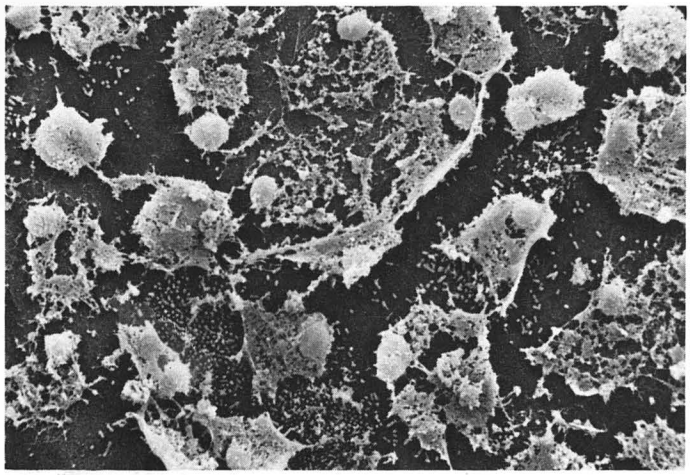


FIGURE 5. Scanning electron photomicrograph of cultured bovine corneal epithelial cells 30 minutes after inoculation of sterile M. bovis culture filtrate. (X1250).

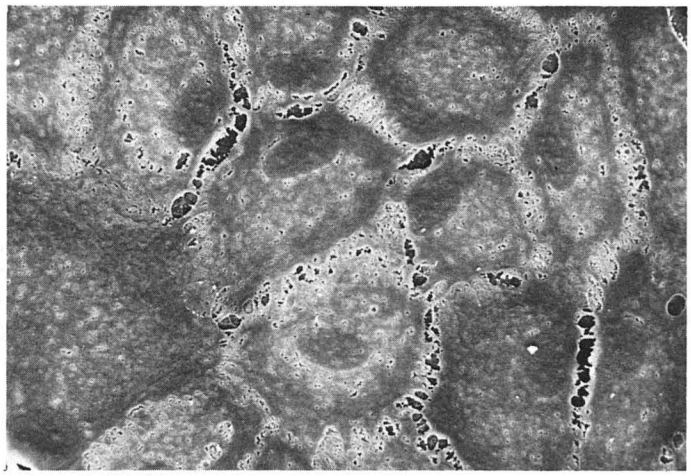
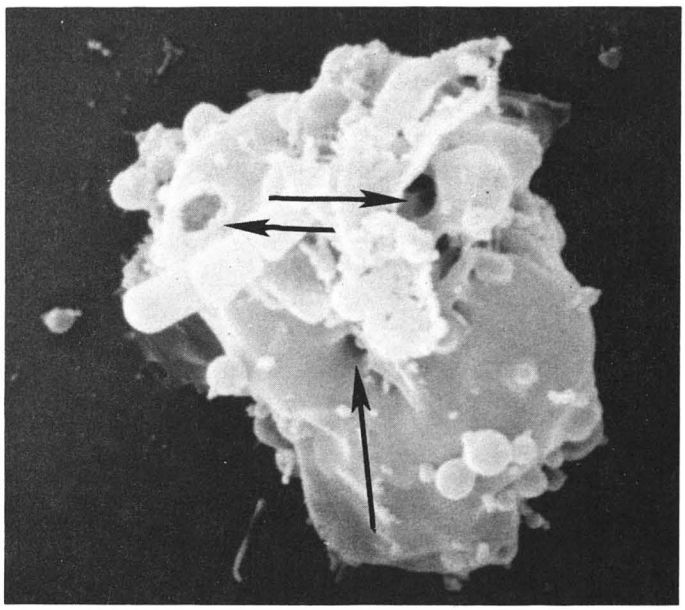


FIGURE 6. Scanning electron photomicrograph of a bovine neutrophil 10 minutes after incubation with living M. bovis. The arrow points to holes in the cell membranes. (X1000).



would be accessible to hydrolysis by non specific proteases produced by *M. bovis* and neutrophils. The corneal stromal excavation is probably produced by the consonant activities of *M. bovis* and the host's inflammatory cells.

The importance of the bovine neutrophil to the genesis of the corneal ulcer was demonstrated by treating calves with hydroxyurea and then infecting them with *M. bovis*.[8] Hydroxyurea treatment resulted in profound neutropenia. The corneal ulcers of the hydroxyurea treated calves were more shallow than those of the controls, indicating a synergism between the neutrophil and stromal lysis.

Treatment of IBK

The susceptibility patterns of *M. bovis* have been investigated.[21] The bacterium is susceptible to many antibiotics and antimicrobials including penicillin, kanamycin, gentamicin, tetracycline, trimethoprim/sulfa, ormetoprim/sulfa, and nitrofurazone. The minimum inhibitory concentration (MIC) of tylosin for *M. bovis* was >=125 ug/ml. Some differences in the susceptibility of *M. bovis* to cloxacillin have been reported. In one study, the mean MIC of cloxacillin was >=125 ug/ml, but in another study was <=4 ug/ml. This may have been due to regional susceptibility differences in the *M. bovis* isolates. Such data indicate the necessity for performing susceptibility tests upon *M. bovis* prior to formulation of treatment recommendations for IBK.

Most outbreaks of IBK affect a large number of animals over the entire summer.[6 18] In most cases, the epizootic persists through the entire summer. The prolonged nature of the epizootic and the large number of cattle that may develop IBK results in costly and time consuming treatment. Optimally, therapeutic agents therefore should eliminate *M. bovis*

from the eye after a limited number of applications. Studies have indicated that one bulbar subconjunctival administration (100 mg) of kanamycin eliminated *M. bovis* from the eyes of experimentally infected calves.[22] This effectiveness appeared to be more related to the high peak concentrations of kanamycin than to the short (4 hour) persistence of the drug in the lacrimal fluids.

Both laboratory and field studies have shown that the OTC-LA is an effective therapeutic agent for treatment of IBK.[23] [24] Pharmacokinetic studies indicated that the oxytetracycline was selectively deposited in the conjunctival and the corneal epithelium, but did not appreciably diffuse into the tears.[25] Infection of the calves with *M. bovis* did not appreciably enhance the diffusion of oxytetracycline into the lacrimal fluid. In an unpublished field study performed at the University of California, we found that calves treated subconjunctivally with procaine penicillin G (150,000 I.U. daily for 3 days) had significantly greater frequency of post-treatment *M. bovis* infections than did calves treated with a long-acting oxytetracycline formulation (OTC-LA; 20 mg/kg IM,). The OTC-LA was administered 2 times. The injections were spaced 72 hours apart. The beneficial effect of the OTC-LA treatments was enhanced by feeding oxytetracycline (2.0 gm/calf/day) to the animals. The calves that were treated with subconjunctival penicillin had more favorable clinical responses than the controls, but had greater lesion severity and a higher rate of recurrent ocular *M. bovis* infections than the OTC-LA treatment group calves. In a separate field study performed at The University of California, parenteral injection of the OTC-LA also was superior to the topical administration of furazolidone spray to naturally infected calves.[24] The beneficial effects of 3 daily bilateral topical applications of furazolidone spray were limited to smaller corneal ulcer size on days 13, and slightly smaller corneal ulcer opacities by 60 days. The study was conducted during the months of June, July, and August. During this study, the times required for administration of the 2 drugs, for examination of the cattle on pasture, for sorting affected animals and for putting the animals through the squeeze chute was measured. The labor costs then were calculated (based upon a cost of $10.00 per hour), and added to the actual drug costs. The losses were estimated as veterinary costs for enucleation of eyes with panophthalmitis, and $0.05 per lb for calves with large opacities in 1 or both eyes. Large opacities were defined as those which covered at least 1/3 of the corneal surface. All of the calves were weighed prior to the beginning of the study and then weekly thereafter until the final observation on August 6. During the study, all roundups and cattle sorts were performed by 2 people on horseback. Treatments were dispensed from a table located 15 feet from the front of the squeeze chute. A diagrammatic plan of the cattle handling facilities is depicted in figure 7. There were 103 calves in the study. Calves were prospectively and randomly distributed into the 3 treatment groups. This represented OTC-LA group, furazolidone treatment group and controls. Table 1 describes the specific costs that were incurred during the study. No differences in weight gain or mean weights were observed. The total costs are given in table 2. The highest total cost (costs + losses due to scars) was observed in the OTC-LA group. This was due to the high purchase price of the antibiotic, and the large IM dosage that was administered. The labor costs in the OTC-LA and furazolidone treatment groups were similar. During the study, ocular secretions were collected and were cultured. The statistical analyses indicated that the retreatment with the OTC-LA was unnecessary provided that the specific *M. bovis* infection was eliminated.

FIGURE 7. Schematic drawing of the cattle handling facilities at the Sierra Foothills Field Station. The arrow denotes the site from which the medications were dispensed.

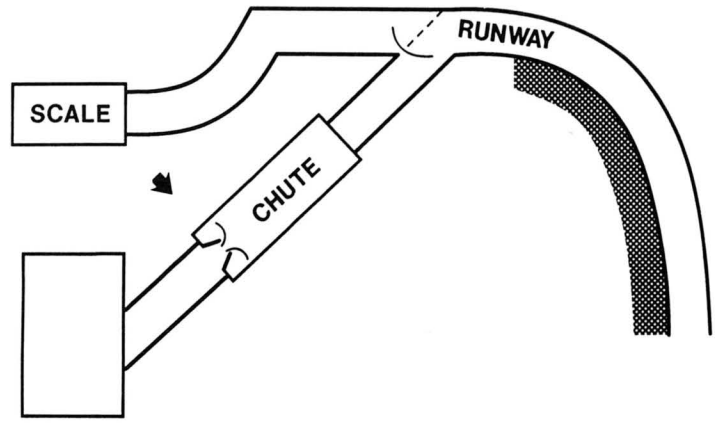


TABLE 1. Cost analysis of 2 different treatments for infectious bovine keratoconjunctivitis.

Group	Treatment Cost	Labor Cost (Treatment)	Labor Cost (Handling)	Total Losses
OTC (n=33)	$196.84	$10.30	$109.16	—$0—
NFZ (n=35)	$32.50	$10.30	$109.16	$100.00
Controls (n=35)	—$0—	—$0—	—$0—	$250.00

OTC = OTC-LA treated group
NFZ = Furazolidone treated group
Labor costs were based upon 2 people at an hourly rate of $10.00 per hour.

TABLE 2. Total costs of 2 treatments for infectious bovine keratoconjunctivitis.

Group	Total Cost
OTC (n=33)	$316.30
NFZ (n=35)	$251.96
Controls (n=35)	$250.00

OTC = OTC-LA treated group
NFZ = Furazolidone treated group

In another study (unpublished), topical benzathine cloxacillin (BC) was as effective as OTC-LA for treatment of experimental IBK. In this experimental study, single topical dosages of 250 and 375 mg BC per eye were significantly more efficacious than formulations containing lower dosages. These findings were recently confirmed in a field study. Pharmacokinetic studies (unpublished) indicated that a single topical administration of BC produced lacrimal fluid concentrations of cloxacillin that peaked at >=400ug/ml and remained >=4.0 ug/ml for 6 hours. This was markedly different from previous reports which demonstrated lacrimal fluid cloxacillin concentrations >=4 ug/ml for 56 hours after a single topical administration of BC. The reason for the difference between the 2 studies is unknown. It is important to recognize that the dosage of BC used in these studies was markedly greater than that which is commercially available in mastitis formulations.

Previous ocular pharmacokinetic studies indicate the following with respect to the treatment of IBK: 1.) For topically applied drugs, the peak lacrimal fluid concentration may be a better indicator of antibacterial efficacy than persistence above the MIC in tears, 2.) For parenterally administered drugs, selective concentration in the ocular tissues may enhance the antibacterial efficacy, 3.) Studies with experimentally infected calves and field observations both should be performed in order to evaluate an ophthalmic drug for the treatment of IBK. Selection of a specific drug for treatment of cattle during an epizootic depends upon the economic constraints imposed by the client, and the susceptibility of the *M. bovis*. Prior to development of a therapeutic plan, the susceptibility of at least 5 *M. bovis* isolates to a library of antibiotics and antimicrobials should be determined. These antibiotics should include penicillin, cloxacillin, gentamicin, nitrofurazone, kanamycin, and tetracycline. If the principal objective of therapy is to minimize corneal ulceration and scarring, all of the susceptible cattle should be treated with OTC-LA (20 mg/kg of body weight; IM). Calves with ulcerated corneas should be retreated 72 hours later. All calves are then given 2.0 gm/calf/day of oxytetracycline in concentrate for 10 days. Calves are then examined every 3rd day during the summer for signs of IBK. They should be retreated only if they develop photophobia, or epiphora, or if existing ulcers worsen. The OTC treatment for IBK is not recommended for use in areas of endemic anaplasmosis.

If treatment cost constitutes the major factor for drug selection, subconjunctivally administered kanamycin (100 mg), or gentamicin (50 mg) are preferred. Retreatments are not administered unless new corneal ulcers occur, or existing lesions worsen. The subconjunctivally administered aminoglycosides will distribute into the udder, and will be detectable in milk. Moreover, they deposit in kidneys for prolonged periods of time. Therefore these drugs should not be administered to lactating dairy animals, or beef cattle within 120 days of slaughter. In strictly commercial cattle rearing conditions, where drug efficacy must be sacrificed in order to achieve a low therapeutic cost, administration of procaine penicillin G subconjunctivally, or nitrofurazone topically should be administered daily for 3 days. Because of the high recurrence rates of ulcers treated with these drugs, retreatments should be administered if the eye has shown no signs of healing by 8 days post treatment. The following clinical scoring system has proved useful for semiquantitative assessment of healing in the field,[24] and in experimentally infected calves: 1=normal; 2=epiphora; 3=corneal ulcer <0.5 cm in diameter; 4=corneal ulcer >0.5 cm in diameter; 6=corneal perforation. Since the proper dosage of BC for treatment of IBK is substantially greater than is currently commercially available, benzathine cloxacillin mastitis formulations should not be used for topical treatment of IBK.

Other ancillary treatments including eye patches, tarsorrhaphy, and 3rd eyelid flaps are of limited benefit for the treatment of IBK.

A study of experimentally infected calves has indicated that administration of corticosteroids to *M. bovis* infected calves ameliorated the inflammation and decreased the amount of painful ocular responses.[8] These beneficial responses were counterbalanced by an increased rate of corneal perforation in the steroid treated eyes, and an increased rate of *M. bovis* shedding in the ocular secretions. Seemingly, ocular corticosteroids should only be administered to cattle after the ocular *M. bovis* infection has been eliminated.

Control of IBK

The control of IBK depends upon reducing the number of carrier animals, fomites, and enhancement factors, segregating affected cattle, and possibly, administering a pilus subunit vaccine. Elimination of the carrier animals is difficult. The *M. bovis* colonized the nasal and respiratory epithelium, where it is not killed by topically applied antibiotics. Parenteral therapy with OTC-LA (20 mg/kg of body weight, 2 times, doses 72 hours apart) has eliminated *M. bovis* from the ocular tissues of calves with chronic ocular infections.[26] Field experience has indicated that the method is expensive (approximately $2.00 per animal, depending upon the body weight), may cause transient myositis at the injection site, and may not completely eliminate the *M. bovis* from the infected animals. The OTC-LA has been more effective for elimination of the asymptomatic *M. bovis* infections in the late, rather than the early summer.

Chemical control of the face fly has proved efficacious for the reduction of *M. bovis* infection and IBK.[27] Effective methods of fly control include backrubbers, sprays, dust bags, and ear tags. Ear tags impregnated with 10% permethrin (Ectrin -Wellcome Animal Health) have been slightly more effective than tags impregnated with 13.7% stirofos (Rabon -SBS Biotech).[28] To control the face fly, the tags must be applied to both ears of all cows. Resistance of the face flies to ear tag insecticides has been reported in the field, and has limited their usefulness in some clinical situations.

Other forms of fly control appear to possess equal efficacy.[27] Dust bags containing insecticidal powders composed of 3% tetrachlorvinphos and backrubbers impregnated with 1% tetrachlorvinphos and 0.25% dichorvinphos have reduced the number of face flies, and the incidence of IBK. Dust bags containing Coumaphos (5%) have been recommended. The bags should be placed in a narrow alleyway and positioned approximately 15 to 18 inches from the ground to ensure that the cattle will spontaneously apply the dust to their faces. Back rubbers containing 11.6% coumaphos (4 quarts per 13 gallons of diesel fuel) has been recommended for use in backrubbers. Permethrin (Expar - Cooper Animal Health; 1 pint per 10 gallons of diesel fuel) has also been recommended for use in back rubbers. As with the dust bags, the backrubbers should be placed in an alleyway, or near water or feed bunks to ensure that the animals adequately contact the insecticide.

The effectiveness of the commercially available pinkeye vaccines is unclear. Some field reports have indicated a lack of vaccine efficacy, while others have shown good protection after vaccination. The reason for this difference is unknown. Vaccines composed of pili, and pili with bacterial enzymes have been licensed for administration to cattle. The comparative efficacy of these 2 products also is unknown.

Other measures that may be useful for the control of IBK may include segregation of cattle with clinical disease from the remainder of the herd, segregation of the younger cattle from the older animals, mowing overgrown pastures, providing at least 1 space per animal at feed bunks, and reductior of dust and plant pollens.

Concurrent administration of modified live infectious bovine rhinotracheitis (MLV IBR) vaccine virus to *M. bovis* infected calves will markedly worsen the corneal disease, and enhance the rate of *M. bovis* shed from the ocular secretions.[29] Therefore, during an IBK outbreak, the modified live virus IBR vaccines should not be administered to calves. If IBR vaccination is necessary during an IBK epizootic, a killed virus vaccine should be used.

Transmission of *M. bovis* on hands and clothing may be important in propagation of field outbreaks. In a previous study,[24] the eyes of naturally infected calves were opened using gloved fingers. The fingers then were press on to bovine blood agar plates immediately thereafter. The gloves then were washed in 1% chlorhexidine, and the fingers were recultured on to new plates. *Moraxella bovis* was isolated from 7 of 10 finger cultures prior to the disinfection, but was not recovered from any of the 10 post disinfection cultures. These data indicate that water repellent garments should be worn during serial treatment and examination of eyes. The garments should be disinfected after the eyes of each animal are examined or treated. Chlorhexidine solution should be an adequate disinfectant for that purpose.

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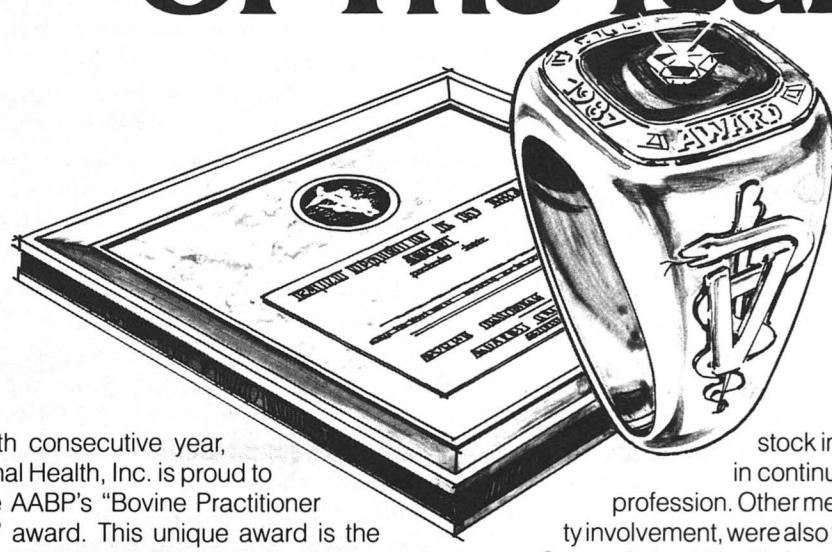

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