Infectious Bovine Keratoconjunctivitis

Dane DeBower, DVM†
James R. Thompson, DVM, MS††

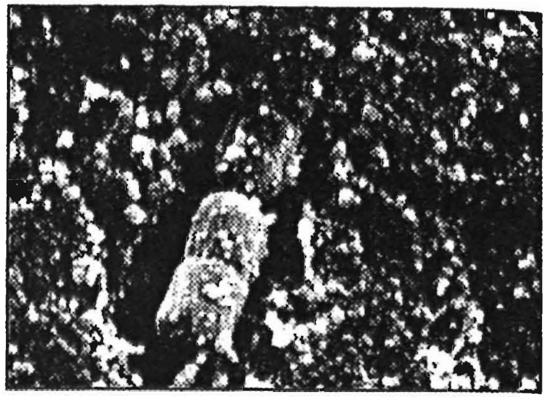
Infectious Bovine Keratoconjunctivitis (IBK) is an internationally recognized ocular disease of cattle. Also known as pinkeye, IBK has a significant economic impact on the cattle industry. The costs come as a result of decreased weight gain, milk discard, decreased show value and costs of therapy.

The etiologic agent of IBK is a bacterial organism, *Moraxella bovis*.[1] *Moraxella bovis* is a Gram negative rod that is spread rapidly by direct contact and by insect vectors such as *Musca domestica*, *Musca autumnalis*, and *Stomoxys calcitrans*. Typical lesions include corneal ulceration with possible perforation, corneal opacity, conjunctival hyperemia and edema.[2] Clinical signs can disappear at any stage but may persist in untreated individuals for 30 days or more. These factors and many more have made epidemiological, clinical, and pathological research of utmost veterinary importance. This article will highlight what is currently known about the etiology, treatment, and prevention of IBK.

Etiology

Moraxella bovis is primarily implicated in the progression of IBK to clinical manifestations.[3] In 60% of cases *M. bovis* isolates are found, whereas in 30% of cases *Brannamella ovis* is isolated.

Important to the pathogenesis of IBK are several predisposing factors. Evidence suggests that concurrent *Mycoplasma bovoculi* and/or Infectious Bovine Rhinotracheitis (IBR) virus infections predispose an animal to IBK.[4] IBR virus may damage corneal and



Scanning EM of *Moraxella bovis* in a "pit" on the surface of corneal epithelium. (Magnification 20,000X)

conjunctival tissues permitting secondary *M. bovis* infection. Clinical diagnoses are often misinterpreted in that conjunctivitis, blepharospasm, and corneal ulceration are common to both IBR and IBK.

Primary irritation of conjunctival or corneal tissues is required for initiation and progression of disease. Irritation can result from windblown dust, desiccation, ammonia-laden air, plant material, feedstuffs, ultraviolet (UV) light, and insects.[1,5] Most significant are plant materials, UV radiation, and insects.

Plant materials pose a greater risk to range cattle where tall grasses such as wild rye and shrubs provide air-borne and mechanical irritation. Feedstuffs, especially hay, pose a similar problem to cattle on feed. Bale feeders are problematic by virtue of design.[6] Cattle given round bales feed primarily from the center, creating a plateau from which hay, dust, and other irritants rain down into the eyes. Additionally, direct contact between animals is high given current feeder design, thereby maximizing the spread of infectious agents.

UV radiation is an environmental problem for range cattle, especially white-faced cattle.[1,5] Non-pigmented conjunctival epi-

†Dr. DeBower is a 1996 graduate of the Iowa State University College of Veterinary Medicine.

††Dr. Thompson is an associate professor in Veterinary Clinical Sciences at the Iowa State University College of Veterinary Medicine.

thelium associated with white-faced cattle allows high amounts of UV radiation to fall upon cells of the cornea and conjunctiva, sensitizing them to inflammation and infection.

Finally, insects can be especially irritating as they feed on lacrimal secretions. The face fly *Musca autumnalis*, the housefly *Musca domestica*, and the biting fly *Stomoxys calcitrans* are all important irritating agents as well as vectors for *M. bovis*.[1,3] These vectors, most prevalent in late summer, feed on lacrimal and mucosal secretions on the face of all cattle. *Moraxella bovis* can survive on the body surface and in the salivary organs of these vectors for up to 72 hours. The relatively limited circulating radius of these flies, however, does help limit spread from herd to herd.[7]

Virulence Factors

Once host defense mechanisms are compromised, *M. bovis* has many virulence factors that enable it to establish infection. Even though there is no bacterial collagenase production, collagen is broken down in the disease process through host neutrophil action. Host neutrophils release hydrolytic enzymes on the surface of the cornea and cause breakdown of the corneal collagen matrix. The importance of recognizing this is that corneal damage can be decreased by lowering the immune response with corticosteroid therapy.

The lack of collagenase is by no means indicative of a total lack of *M. bovis* enzymes. A large number of enzymes are present, including fibrinolysin, phosphatase, hyaluronidase, and aminopeptidase. These enzymes are all important in breaking down corneal epithelial cell matrices and allowing colonization. Equally important are hemolysins, leukotoxins, proteases, pili, and a distinctive lipopolysaccharide (LPS).[8]

The presence and type of pili seem to play a highly important role in virulence. Colonies of *M. bovis* that appear rough have been characterized as virulent, piliate organisms, whereas smooth colonies are considered to be avirulent, non-piliate organisms.[9] The pili of *M. bovis* are filamentous homopolymers of protein subunits. Two types of pili have been identified from *M. bovis*, namely type I and type Q.[10] Type I pili have been associated with the ability to maintain persistent infection by invading deeper tissues. Type Q pili have been shown to enhance the ability of *M. bovis* to adhere to corneal epithelium. Interestingly, *M. bovis* has the ability to switch phase from type I to type Q thereby enhancing infectivity. Concurrently, heterogeneity and resistance to host defenses associated with type I pili are conferred.

Lipopolysaccharide also appears to play a role in virulence associated with O antigens.[8-11] A full complement of O antigen in LPS confers smooth colonies of *M. bovis* whereas areas absent in antigen denote rough colonies. The effects of the *M. bovis* LPS are dramatic. LPS introduced into rabbits elicits pyrogenicity, dermal Shwartzman reaction, tumor necrosis factor (TNF) and Interleukin-1 (IL-1). Significantly, TNF has been implicated as the primary mediator of LPS biological activity, namely the release of IL-1. The release of IL-1 has a great impact on the response to *M. bovis* in bovine ocular tissues, especially regarding chemotaxis of phagocytes to the area.

Host Response

Once *M. bovis* has adhered to epithelial cells of the cornea, the sequence of events associated with an immune response are initiated.[7] Neutrophils attracted to the area can be found in the intercellular spaces of edematous tissue occasionally containing phagocytized bacteria. In unresolved inflammation, the cells of the stratum spinosum necrotize and detach from the underlying stratum basale, leaving erosions. On the site of the erosion, continued invasion of bacteria progressing through the basement membrane into the propria leads to corneal ulceration. This process will allow 3 mm diameter lesions to form within 72 hours. Lesion resolution includes fibroblast proliferation, fibrinous exudate, and serofibrinous infiltration of surrounding tissues. Histopathological examination of diseased periorbital tissues shows accumulation of lymphoid tissue with marked hyperplasia in the sub-epithelial conjunctival tissue.[1,7,12] In chronic ulcerated regions of the cornea, intensive neovascularization and iridocyclitis develop. These areas of

Scanning electron micrograph of *Moraxella bovis* colonizing a corneal ulcer. (Magnification 3,240X)

neovascularization with young capillaries proceed from the limbus toward the ulcer.

Clinically the affected animal exhibits excessive lacrimation, redness of periorbital tissues and corneal opacity.[13] Additionally the animal will be photophobic, blepharospastic, and anorexic. These signs are often good initial clues in diagnosing IBK.

Treatment

Antimicrobial susceptibility studies have shown *M. bovis* to be susceptible to penicillin, streptomycin, gentamicin, tetracycline, cephalosporin, nitrofurans and sulfanilomides.[2,7] Unfortunately, susceptibility and efficacy are not synonymous. The lack of effective treatment is due to short tear half-life of topical antimicrobials and the limited ocular presence of parenterally administered drugs.[2] Long-acting oxytetracycline is effective for treatment of infected calves. Following deep muscle parenteral administration of long-acting oxytetracycline, conjunctival levels remain at 2 mg/mL or greater for 72 hours.[2] This amount has proven efficacious for treatment of infected animals.

Subconjunctival administration provides pharmacological advantages over deep muscle administration. Most importantly, lower dosages may be used which yield higher ocular concentrations. Difficulty of subconjunctival administration is a drawback which must be considered. Penicillin and aminoglycosides are the most commonly used subconjunctival preparations.[14] Although these drugs result in high ocular concentration, healing rates are not markedly different from deep muscle parenteral oxytetracycline.[2] Despite desirable healing rates, subconjunctival penicillin results in more corneal ulcer recurrence and increased shedding of *M. bovis* when ineffective.

Topical administration of antimicrobials has been insufficiently studied. What is known is that topical preparations do not remain in the eye due to excessive lacrimation, thereby minimizing their effect. Topical preparations such as Furazolidone spray reduce the numbers of *M. bovis* that are shed as well as reduce ulcer sizes. Neomycin-tylosin spray results in activity mimicking that of Furazolidone.

Showing much promise for topical administration is benzathine cloxacillin. Oilbased formulations of benzathine cloxacillin reduce the shedding of *M. bovis* and hasten the resolution of corneal ulcers.[14,15] Two doses of benzathine cloxacillin 72 hours apart yield up to 10 mg/mL ocular concentration for seven days. Should FDA approval be forthcoming, a 375 mg topical dose has been suggested as very effective. High efficacy, low cost, and short withdrawal times would make benzathine cloxacillin an appealing alternative.

What is evident in looking at antimicrobial therapy is that it is costly and not always effective. Treatment is costly due to drug expense, labor costs, and weight gain losses. As is true with so many diseases, prevention is the ultimate goal which on many levels surpasses the best xenobiotic therapy.

Photograph of a bovine eye infected with *Moraxella bovis*. Clinically affected animals typically exhibit signs of excessive lacrimation, redness of periorbital tissues, and corneal opacity.

Prevention

With annual losses of $150 million estimated in the U.S., IBK has a profound economic impact.[6] Efforts are being concentrated on prevention of this disease in an effort to minimize these costs. Primary prevention efforts have centered on immunologic research. It is known that an active IgA response is necessary to prevent IBK. Studies have shown that upon recovery from infection with *M. bovis*, cattle show high levels of IgA on mucosal surfaces thereby lending resistance to reinfection. Most vaccines that have been recently tested elicited an IgG response which has not proven effective in preventing infection. Recent efforts have included both heat and formalin killed bacterins, such as Addison Biologics' product, adjuvant and pilus vaccines by Schering-Plough, Smith Kline Beacham, and others. None of these vaccines have proven successful.[13] Pilus vaccines currently on the market have some producers convinced of their efficacy; however, when quantitatively compared to non-vaccinates, no appreciable difference can be noted.

Perhaps the producer is left with what may prove to be the best medicine for the future: management. A revolution is in progress which exemplifies the benefits of total herd management. By maintaining an optimal environment, disease frequency among all production animals decreases.[16] Preventative approaches of this kind have often proved more economically feasible than contemporary treatment practices.

With respect to IBK specifically, several management–related means of control should be considered. Attempts to reduce mechanical irritation should be implemented. Tall grasses, noxious weeds, and shrubs should be cleared from pastures. Modifying bale feeders by increasing head space from 9 to 15 inches decreases exposure of the animal to hay stems and also to nearby individuals who may be carriers.[6] Irritation due to face flies should be limited as much as possible. Insecticide ear tags, dust bags and Insect Growth Regulator–containing rations can be of some help in this area. The amount of stress on the animal should be limited to reduce the incidence of disease. By recognizing and dealing with stresses such as shipping, high fly populations, or excessive sunlight, intervention may be preventative. For instance, prior to shipping to pasture, a prophylactic dose of long-acting oxytetracycline may override the critical post–shipping stress period, allowing native defenses to recover. As with any infectious disease and especially with IBK, infected animals should be isolated, preferably in a dark area, to minimize contact with other animals and UV radiation. By thus managing early breaks, spread can be limited.

Discussion

In a severely competitive economic climate, the beef producer and veterinarian alike must work to prevent costly diseases such as IBK. Current therapies provide an adequate means for treating IBK if it is detected prior to corneal ulceration, yet the costs inherent are substantial. An effective vaccine is needed to nullify the expense of treatment of disease. Lack of such a vaccine has ensured that carriers and relapses will potentiate IBK over time. Lack of death losses disguises IBK as an unimportant disease, and this does not help the cause for research dollars. Regardless, the cattle producer and veterinarian need adequate tools to deal with this menace of the bovine eye.◆

References

1. Brown JF, Adkins TR. Relationship of feeding activity of face fly (*Musca autumnalis* DeGreer) to production of keratoconjunctivitis in calves. *Am J Vet Res* 1972;33:2551-2555.

2. George LW. Antibiotic treatment of infectious bovine keratoconjunctivitis. *Cornell Vet* 1990;80:229-235.

3. Powe TA, Nusbaum KE, Hoover TR, et al. Prevalence of nonclinical *Moraxella bovis* infections in bulls as determined by ocular culture and serum antibody titer. *JVet Diagn Invest* 1992;4:78-70.

4. Rosenbusch RF. Influence of mycoplasma preinfection on the expression of *Moraxella bovis* pathogenicity. *Am J Vet Res* 1983;44:1621-1624.

5. Hughes DE, Pugh GW, McDonald TJ. Ultraviolet radiation and *Moraxella bovis* in the etiology of bovine infectious keratoconjunctivitis. *Am J Vet Res* 1965; 26:1331-1338.

6. Maxwell K. Prevention and cure of pinkeye. *Pinkeye Practicum* 1993;1:1-2.

7. Nagy A, Vandermissen E, Kapp P. Further data to the aetiology, pathogenesis and therapy of infectious bovine keratoconjunctivitis. *Comparative Immunology, Microbiology and Infectious Disease* 1989; 12:115-127.

8. Johansen KA, Wannemuehler MJ, Rosenbusch RF. Biological reactivity of *Moraxella bovis* lipopolysaccharide. *Am J Vet Res* 1990;51:46-51.

9. Wilt GR, Wu G, Bird RC, et al. Plasmid content of piliated and nonpiliated forms of *Moraxella bovis*. *Am J Vet Res* 1990;51:171-173.

10. Reuhl WW, Marrs CF, George LW, et al. Infection rates, disease frequency, pilin gene rearrangement, and pilin expression in calves inoculated with *Moraxella bovis* pilin-specific isogenic variants. *Am J Vet Res* 1993;54:249-253.

11. Kagonyera GM, Munn R, George LW. Cytopathic effects of *Moraxella bovis* on cultured bovine neutrophils and corneal epithelial cells. *Am J Vet Res* 1989;50:10-17.

12. Bateman KG, Leslie KE, Scholl TP. A field trial of a piliated *Moraxella bovis* bacterin for the prevention of infectious bovine keratoconjunctivitis. *Can Vet J* 1986;27:23-27.

13. Smith PC, Blankenship T, Hoover TR, et al. Effectiveness of two commercial infectious bovine keratoconjunctivitis vaccines. *Am J Vet Res* 1990;51:1147-1150.

14. Abeynayake P, Cooper BS. The concentration of penicillin in bovine conjunctival sac fluid as it pertains to the treatment of *Moraxella bovis* infection. *J Vet Pharm* 1989;12:25-30.

15. Diagneault, George LW. Topical benzathine cloxacillin for the treatment of experimentally induced infectious bovine keratoconjunctivitis. *Am J Vet Res* 1990;51:1 153-1156.

16. Caley HK. Pinkeye. Cooperative Extension Service, Kansas State University 1991;983:1-2.