Infectious bovine keratoconjunctivitis (IBK) is one of the most common diseases of cattle and is of major economic importance. If the primary aetiological agent, *Moraxella bovis*, is successfully eliminated from ocular tissues corneal ulcers heal at a constant rate. If treatment is unsuccessful ulcer reoccurrence may follow initial healing. Appropriate antimicrobial selection requires knowledge of antimicrobial sensitivities and distribution in ocular tissues and tears. Drugs may be delivered to the eye in several ways: subconjunctival injection, topical application and systemic administration. While therapeutic efficacy is affected by the frequency and mode of drug delivery, variations between intensive and extensive enterprises dictate the practical method of antimicrobial delivery. Specific recommendations for antimicrobial therapies targeting Australian IBK outbreaks are dependent upon antimicrobial pharmacokinetics, drug regulations and associated costs.

**Key words:** Bovine, keratoconjunctivitis, *Moraxella bovis*, antimicrobial, pinkeye


**CCFA** Ceftiofur crystalline-free acid  
**IBK** Infectious bovine keratoconjunctivitis  
**IM** Intramuscular  
**MIC** Minimum inhibitory concentration  
**SC** Subcutaneous

Infectious bovine keratoconjunctivitis (IBK) or ‘pinkeye’ is a common and highly contagious ocular disease affecting cattle worldwide that is caused by the Gram negative bacterium *Moraxella bovis*. Although *M bovis* is the most commonly isolated pathogen from IBK, the occurrence and clinical severity is mediated by various factors such as the environment, season, *M bovis* strain and host immune response. Concurrent pathogens such as *Moraxella ovis* have also been implicated as contributors to IBK pathogenesis. Tremendous economic losses stem from inappetance and poor weight gain in affected animals suffering from ocular pain and visual impairment. An Australian postal survey recorded that 81.3% of participating cattle owners reported the occurrence of IBK, and 75% observed a reduction in the weight gain of affected cattle. Other major losses resulting from IBK include the direct costs of repetitive drug treatments, loss of value of show animals, and reduced milk production from infected dairy animals. As early as 1979 in Australia, losses due to reduced production were estimated to reach 22 million dollars, with 1.5 million dollars spent for treatment.

Ideally, treatment of IBK will achieve elimination of *M bovis* infection. If IBK is treated successfully corneal ulcers heal at a constant rate; however, if *M bovis* is not eliminated from ocular tissues ulcer reoccurrence may follow initial healing. Studies conducted in the United States have demonstrated in vitro *M bovis* antimicrobial susceptibility to ampicillin, cephalosporin, nitrofurans, penicillin, sulfonamides, tilmicosin, and variable in vitro susceptibility to cloxacillin, erythromycin, gentamicin, oxytetracycline and streptomycin. Resistance has been demonstrated to tylosin and lincomycin. Appropriate antimicrobial selection for the treatment of cattle infected with *M bovis* requires knowledge of the minimum inhibitory concentration (MIC) for the bacterium, as well as an understanding of antibiotic distribution into ocular tissues and tears following administration. Drugs may be delivered to the eye in several ways: subconjunctival injection, topical application and systemic administration.

Antimicrobial susceptibility testing of Australian *M bovis* isolates suggests that antimicrobial resistance is uncommon in Australian field isolates. Despite this, the variable antimicrobial susceptibility observed in the United States indicates that antimicrobial resistance could develop and antimicrobial susceptibility testing should be conducted in the event of treatment failure. Therapeutic decisions are influenced by numerous factors such as efficacy, cost, animal husbandry implications, labour requirements and availability, withholding times, availability and quality of facilities, and availability of veterinary support. Therefore the best therapeutic strategy for a particular herd is dependent on the final analysis of the current situation. This review discusses comparative efficacy data for a number of antimicrobials available world-wide for IBK treatment. Our recommendations of several treatment options pertain only to those drugs with labelling for treatment in Australia.

**Subconjunctival treatment**

Subconjunctival administration of antimicrobials aims to reduce treatment costs and total dosages of drug while achieving higher ocular drug concentrations. Subconjunctival injections probably
lead to some direct diffusion across the sclera and choroid; alternatively, the drug may gradually leak from the injection site, entering the tear film and eventually the eye via the cornea as if it were applied topically. Although subconjunctival drug dosages are variable, they are generally given in volumes up to 1 ml and typically maintain therapeutically effective tear concentrations for 24 hours or longer. Nonetheless, the elimination of an ocular *M. bovis* infection may be more dependent on achieving therapeutic drug concentrations in infected ocular tissues rather than tears.14–16

In calves given a bulbar subconjunctival injection of a conventional (100 mg/ml) oxytetracycline formulation, the antibiotic concentration in tears was above MIC for 24 hours.8,17 Although a single subconjunctival dose of a long-acting oxytetracycline formulation achieved tear concentrations above MIC for longer than 72 hours, severe tissue necrosis at the injection site includes such therapy.8 The reported efficacy of subconjunctival penicillin administration is variable, with notable differences in efficacy reported between superior palpebral subconjunctival and bulbar conjunctival routes of administration. Following a single administration of procaine penicillin (3 × 10⁷ IU) into the superior palpebral subconjunctival tissues, therapeutic drug levels within the conjunctival sac fluid were maintained for 35 hours. However, injecting a larger volume of penicillin (6.25 × 10⁷ IU) resulted in therapeutically effective tear concentrations for 40 hours, increasing to 67.6 hours if injected into the skin of the eyelid.16 Nevertheless, the efficacy of penicillin may not be as good as pharmacokinetic data suggest. Three daily injections of beef calves with procaine penicillin G (3 × 10⁷ IU) or a combination of procaine penicillin G and dexamethasone (4 mg) into the superior palpebral subconjunctiva did not affect the outcome of naturally developing IBK when compared to no treatment.15

In contrast, comparisons between calves naturally infected with IBK and treated with bulbar subconjunctival penicillin versus parenteral long-acting oxytetracycline have shown similar reductions in corneal ulcer healing times, but increased corneal ulcer recurrence and a greater post-treatment shed of *M. bovis* in ocular secretions from the bulbar subconjunctival penicillin treated calves.5 Similarly, administration of two bulbar subconjunctival treatments of procaine penicillin G (300,000 IU, 48 to 72 hours apart) has comparable therapeutic efficacy to parenteral treatment with a long-acting oxytetracycline formulation (20 mg/kg IM, repeated at 72 hours if corneal ulcers were present on days 1 or 2) when administered in tandem with feeding lucrene pellets containing oxytetracycline (1 g/0.45 kg of pellets) at a dosage of 2 g per 250 kg calf daily. Although corneal ulcer healing time was equally reduced, calves treated with oxytetracycline had a lower prevalence of IBK and fewer recurrences of corneal ulcers together with a lower frequency of *M. bovis* isolation.18

**Subconjunctival treatment options**

**Procaine penicillin G**

Procaine penicillin G is at present not labelled within Australia for the treatment of IBK. Any use of such would be considered an off-label application. Bulbar subconjunctival dosages of 1 to 2 ml should be administered at 36 hour intervals for 2 to 3 treatments. Both eyes should be treated even if only a single eye is clinically affected. Unaffected eyes should be treated prior to affected eyes and procedures should be in place to limit transmission between animals, such as changing gloves between treatments. Blanket administration of the drug to all animals simultaneously may not prove a practical or economic means for reducing IBK incidence. The cost of the drug is low, but the labour involved with moving, restraining and treating animals may prove expensive. Although this treatment reduces healing time and ocular scarring, the incidence of IBK is not reduced due to relapses and the failure to eliminate the carrier state. There are anecdotal recommendations for subconjunctival administration of corticosteroids in tandem with penicillin. However, the single study reported above15 suggests that such a combination has no significant effect on the outcome of naturally developing IBK.

**Topical treatment**

Topical administration of antimicrobial formulations has been recommended as a potentially cost-effective and less labour intensive method for treatment of IBK.5 However, topically applied aqueous antimicrobial suspensions have a short tear half-life. Antimicrobials sprayed into the eye may prove irritating and remain only a few minutes before tears wash them away. Although topical application of oxytetracycline aerosol or powder is potentially effective based on MIC data,11 application is required three to four times daily for 4 to 7 days.14

Topical ointments can achieve an increased ‘contact’ time due to increased viscosity and sustained release of drug from small droplets that settle into the inferior cul-de-sac after application. Oil-based benzathine cloxacillin applied topically either once57 or twice18 (72 hour interval) has proven efficacy against *M. bovis* infections. Calves affected with naturally occurring IBK treated with two topical applications of benzathine cloxacillin (250 mg, 72 hours apart) had a similar reduction in corneal lesion healing times and *M. bovis* isolations to those treated with a single dosage of cloxacillin. However, the early treatment of corneal ulcers was a prerequisite for therapeutic efficacy in that initiating treatment on corneal ulcers ≤ 0.5 cm as opposed to >0.5 cm led to significantly shorter healing times.19 Although one US study demonstrated an MIC for cloxacillin (≥ 2 µg/ml) the uniform resistance of all *M. bovis* isolates,11 others have shown lacrimal fluid cloxacillin concentrations exceeding this MIC for 31 hours.20 Another study determined lower MIC levels (0.6–1.25 µg/ml) that were surpassed by lacrimal fluid cloxacillin concentrations up to 86 hours after a single topical administration of 125 mg of oil-based benzathine cloxacillin.17 In a separate study, topical application of a single 250 or 375 mg dose of oil-based benzathine cloxacillin maintained tear cloxacillin concentration above the established MIC (3.13 µg/ml) for *M. bovis* isolate Tifton 1, for 8 and 10 hours respectively. No cloxacillin activity was detectable in the lacrimal fluid by 36 hours after topical administration and no cloxacillin was detected in serum at any time after drug administration.21 Following the treatment of
cattle with a single topical dose of benzyl penicillin in a paraffin ointment (5000 IU). Concentration profiles for formulations of procaine penicillin and benzathine penicillin in an ointment base equated to durations of therapeutic concentration (5 X MIC) in conjunctival sac fluid of 37 and 56 hours respectively. As the antimicrobial action of cloxacillin and penicillin are time dependent it is evident that the duration of therapeutic efficacy achieved with ophthalmic ointments containing these drugs is dependent on the MIC of the infecting strain and the drug concentration of the formulation. In the experimental studies cited therapeutic drug concentrations were maintained for 8 to 86 hours. There is limited information comparing the efficacy of topical formulations to subconjunctival or parenteral treatments. Two topical administrations of oil-based formulations of benzathine cloxacillin (250 or 375 mg, 72 hours apart) reduced the shedding of *M. bovis* in ocular secretions and hastened the healing of corneal ulcers in experimentally induced IBK. This treatment was as effective as two intramuscular (IM) dosages of the long-acting oxytetracycline formulation (20 mg/kg, 72 hours apart) and there was no significant difference between treatments in the number of *M. bovis* isolations at any sample collection interval. This study indicated that elimination of *M. bovis* from ocular tissues may require the maintenance of a lacrimal fluid cloxacillin concentration above the MIC for *M. bovis* rather than a high peak concentration of short duration.

### Topical treatment options

**Oxytetracycline hydrochloride aerosol and powder**

Oxytetracycline hydrochloride ophthalmic aerosol or powder in a puffer pack are registered in Australia for treatment of IBK. No efficacy trials have been published relating to this mode of drug delivery. Material sprayed into the eye remains for only a few minutes before tears wash it away. Directions for use mandate three daily applications of the aerosol or two to three daily applications of the powder to affected eyes. These products provide an alternative choice of treatment on properties lacking the necessary facilities to restrain animals for the application of topical ointment or injection of parenteral drugs. However, they require significant labour for an as yet uncertain outcome. An advantage is that there are nil withdrawal periods for both these products.

**Benzathine cloxacillin ointment**

Benzathine cloxacillin ointment is registered for topical treatment of IBK in Australia using a pre-packed plastic application syringe. Two doses of topical benzathine cloxacillin (minimum of 250 mg up to 375 mg, 72 hours apart) should be administered to affected cattle early in the disease process. Both eyes should be treated even if only a single eye is clinically affected and, preferably, unaffected eyes should be treated prior to affected eyes. Procedures should be in place to limit transmission between animals. Again, blanket administration of the drug to all animals simultaneously may not prove a practical or economic means for reducing IBK incidence. Advantages of this therapeutic regime include nil meat and milk withdrawal times.

### Systemic treatment

Systemic antimicrobial therapy has been recommended as a means of targeting *M. bovis* located within lacrimal glands and nasal passages. Drugs administered systemically may enter the eye via the tear film or through the perilimbal or intraocular circulation. Generally, lipophilic drugs achieve higher intracorneal and intraocular concentrations and are more effective at penetrating the blood:tear barrier than hydrophilic drugs. Nonetheless, the attainment of bacteriostatic tear concentrations is not necessarily predictive of efficacy. Trimethoprim and erythromycin are non-polar, basic, lipophilic drugs that concentrate within tears following parenteral injection yet are not used commercially due to either poor activity against *M. bovis*, the production of excessive tissue inflammation, or cost.

Elimination of *M. bovis* in calves with IBK has been demonstrated following parenteral treatment with oxytetracycline or florfenicol. Oxytetracycline is an amphoteric molecule that should theoretically diffuse into tears; however, parenteral administration of long-acting oxytetracycline leads to a tear concentration less than 1 μg/ml although conjunctival levels are >2 μg/ml for 72 hours. The efficacy of parenterally administered oxytetracycline in the treatment of IBK is likely linked to these higher tissue levels. Substantial conjunctival concentrations of oxytetracycline are present for as long as 20 hours after a single 20 mg/kg IM injection. The drug is shown to localize within the lacrimal gland, conjunctiva, and cornea but not within tear film or aqueous humor. Treatment with two doses of long-acting oxytetracycline (20 mg/kg, 72 hours apart) has been shown to ameliorate clinical signs of naturally occurring IBK through a reduction in *M. bovis* ocular infection and consequent decrease in corneal ulcer healing time and recurrence. Similarly, treatment of all herdmates with IM long-acting oxytetracycline followed by daily feeding of oral oxytetracycline (2 g per 250 kg calf) daily for 10 days has been shown to reduce IBK incidence to 3% within a season.

Florfenicol provides a treatment option in *Anaplasma* endemic regions where oxytetracycline use is restricted. Florfenicol has high lipid solubility and low ionic partitioning suggesting that it may distribute well to ocular tissues. Recent work has demonstrated that florfenicol administered subcutaneously (SC) (one dose; 40 mg/kg) or IM (two doses 48 hours apart; 20 mg/kg) is effective for treatment of calves with naturally occurring IBK. Relative to controls, treated calves had smaller corneal ulcers 1 and 2 weeks after treatment and shorter ulcer healing times. Administering the drug to all animals simultaneously would be expected to reduce IBK incidence. Further, another study has demonstrated shorter healing times for eye lesions when calves naturally infected with *M. bovis* were treated twice IM 48 hours apart with florfenicol (20 mg/kg) as opposed to long-acting oxytetracycline (20 mg/kg). Relapses were observed in calves treated with oxytetracycline but not in those calves treated with florfenicol. Antimicrobial examination of *M. bovis* strains isolated from affected calves indicated that 16.67% of the isolates were resistant to oxytetracycline whereas all isolates were sensitive
to florfenicol. Florfenicol is not registered for use in lactating dairy cattle and heifer calves destined to produce milk for human consumption.

Recent studies have evaluated the parenteral treatment of naturally occurring IBK utilizing additional antimicrobials. The lipophilic nature of macrolides allows for concentration at sites of infection. Antimicrobial susceptibility testing has predicted that tilmicosin will favourably control \textit{M. bovis} infections. In fact, tilmicosin administered SC (5 or 10 mg/kg) was effective in resolving corneal lesions associated with an Argentinean outbreak of IBK in Hereford cattle. Cefitofur crystalline-free acid (CCFA) has also been assessed for efficacy against IBK, administration being in the posterior aspect of the ear. The pinna site was chosen due to the reduced risk for tissue residue and the lower potential for injection-site trimming at slaughter. Concentrations of cefitofur metabolites in plasma have been shown to remain well above published \textit{M. bovis} modal MIC values for more than 7 days when administered via this particular route. A single dose of CCFA (6.6 mg of cefitofur equivalents/kg, SC) proved effective in the treatment of IBK in beef calves, resulting in shorter mean healing times, smaller corneal ulcer surface areas, amelioration of ocular discharge and photophobia, and a 50% increase in the percentage of calves healed by day 14. Neither tilmicosin nor cefitofur are registered for treatment of IBK in Australia. Comparative efficacies of tilmicosin and CCFA relative to oxytetracycline or florfenicol have not been established.

**Systemic treatment options**

**Long-acting oxytetracycline**

Long-acting oxytetracycline is registered within Australia for treatment of IBK. Two IM or SC dosages of 20 mg/kg should be administered 72 hours apart. Simultaneous administration of the drug to all animals reduces the incidence of IBK. The long-acting oxytetracycline formulation's extensive milk withdrawal period makes this mode of treatment less desirable for lactating dairy cattle. Antimicrobial resistance to tetracycline has been reported in \textit{M. bovis} isolates in the United States. Blanket systemic treatment with oxytetracycline is not recommended in the \textit{Anaplasma} endemic regions of northern and north-eastern Australia.

Florfenicol

Florfenicol is registered within Australia for treatment of IBK. Two IM dosages of 20 mg/kg 48 hours apart or a single 40 mg/kg SC dosage should be administered to affected cattle. Again, administering the drug to all animals simultaneously would be expected to reduce IBK incidence. This drug is not labelled for dairy cattle, cattle intended for breeding or calves to be processed for veal. Florfenicol provides a treatment option in areas with potential oxytetracycline microbial resistance and/or anaplasmosis.

Ceftiofur and Tilmicosin

Ceftiofur and Tilmicosin are not labelled for the treatment of IBK in Australia.

**Conclusions**

Despite the efficacy of antimicrobial therapy, treatment of affected cattle has many disadvantages and the prevention of IBK is therefore preferable. Affected animals should be segregated from normal cattle and face flies should be controlled using insecticides. If possible, exposure to environmental irritants such as grass awns and dust should be limited. Preventative vaccination may be warranted if an Australian IBK vaccine becomes available. When preventative measures fail, IBK lesions should be treated early in the disease process. Vigilant observation for clinical signs such as increased lacrimation and blepharospasm allows for immediate therapeutic intervention. Treatment failure may reflect delayed therapeutic intervention or inappropriate route or frequency of antimicrobial therapy. Given that variable antimicrobial sensitivity patterns have been reported in other countries, the emergence of antimicrobial resistance should be considered in the future if treatment failures occur in the face of appropriate application of labelled therapeutic drugs.

**References**


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