ARTICLES

Comparison of Penicillin, Oxytetracycline, and Trimethoprim-Sulfadoxine in the Treatment of Acute Undifferentiated Bovine Respiratory Disease

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Abstract

Penicillin, oxytetracycline, and a trimethoprim-sulfadoxine combination were compared as first choice antibiotics for the treatment of acute bovine respiratory disease in weaned beef calves. There was no statistical difference in the mortality losses due to respiratory disease; however, the case fatality rate in the trimethoprim-sulfadoxine treatment group (3%) was markedly lower than in the penicillin (10%) and oxytetracycline (8%) treatment groups. The trimethoprim-sulfadoxine group also had statistically fewer treatment days compared to the penicillin and oxytetracycline groups ($p < 0.05$). Inclusion of mortality costs in the calculation of treatment costs demonstrated that treatment of the trimethoprim-sulfadoxine group was appreciably less costly than treatment of the other groups. Temperature response abnormalities, defined as either an elevation in temperature or a failure of temperature to drop from one treatment day to the next, were associated with a relapse rate of approximately 50%. *In vitro* antibiotic sensitivity testing of *Pasteurella haemolytica* isolated from pretreatment nasal swabs was not a useful predictor of treatment success of antimicrobials.

Résumé

Comparaison de la pénicilline, de l'oxytétracycline et d'une combinaison de triméthoprime et de sulfadoxine, pour le traitement des maladies respiratoires aiguës bovines indifférenciées

Cette expérience consistait à comparer l'oxytétracycline, la pénicilline et une combinaison de triméthoprime et de sulfadoxine, comme antibiotiques de premier choix, pour le traitement des maladies respiratoires aiguës, chez des veaux de boucherie sevrés. On n'enregistra pas de différence statistique relative aux mortalités imputables à ces maladies. Leur taux se révéla toutefois beaucoup plus faible chez les veaux traités avec la combinaison précitée, où il n'atteignit que 3% comparativement à 10%, chez les veaux traités à la pénicilline, et à 8%, chez ceux qui reçurent de l'oxytétracycline. Les veaux traités au triméthoprime et à la sulfadoxine affichèrent aussi un nombre significativement moins élevé de jours de traitement, du point de vue statistique ($p < 0,05$), que ceux auxquels on donna de la pénicilline ou de l'oxytétracycline. L'inclusion des pertes dues aux mortalités dans le calcul du coût des traitements démontra que le traitement avec la combinaison précitée s'avéra beaucoup moins onéreux qu'avec la pénicilline ou l'oxytétracycline. Les écarts de température, soit une simple hyperthermie ou sa persistance d'un traitement à l'autre, s'accompagnaient d'un taux de rechute d'environ 50%. L'antibiogramme réalisé avec *Pasteurella haemolytica* isolée des écouvillons nasaux prélevés avant l'antibiothérapie, ne se révéla pas utile pour en prédire le succès.

Can Vet J 1988; 29:

Introduction

Respiratory disease is the most common cause of sickness and mortality in the feedlot (1,2,3). The selection of an appropriate antibiotic and the evaluation of its success in the treatment of respiratory disease is an important consideration to the feedlot owner and his veterinarian. Many antimicrobials have been used in the treatment of respiratory disease and have been evaluated to some extent (4). Initial field trials with a potentiated sulfonamide suggested a high level of efficacy in the treatment of bacterial diseases of cattle and pigs (5).

In this study, we compared the efficacy of penicillin, oxytetracycline, and a trimethoprim-sulfadoxine combination in the treatment of acute undifferentiated bovine respiratory disease (AUBRD).

Materials and Methods

The trial was conducted in a commercial feedlot at Strathmore, Alberta. The animals utilized in the study were fall calves between 250 and 320 kg in weight. The calves were primarily recently weaned auction market-derived calves and were delivered to the feedlot by truck. Upon arrival at the feedlot, they were processed in a standard manner. Each calf was eartagged, branded, given an injection of vitamins A and D,

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treated for warbles and lice (pour-on insecticide), and vaccinated against infectious bovine rhinotracheitis, clostridial diseases, and *Haemophilus somnus* infection. The calves were placed in pens with capacities of about 300 head.

The calves were checked twice daily and those judged to be sick by the pencheckers were removed from the pen ("new pulls") to a hospital facility for evaluation. A diagnosis of AUBRD was made based on depression, increased respiratory rate, and lack of rumen fill. To be placed into a treatment group the calf could not have a rectal temperature lower than 40.5°C (105°F), could not have been treated previously for any disease, and could not have been involved in a mass medication program. Calves exhibiting clinical signs that could be attributed to other organ systems were not included in the trial. Prior to treatment, a deep nasal swab was collected from each animal, placed into Amies transport medium (Starplex, Mississauga, Ontario) and sent to the Diagnostic Bacteriology Laboratory at the Western College of Veterinary Medicine for bacterial culture and sensitivity. The nasal swabs were cultured in routine fashion and all *Pasteurella* isolates were tested by a standard disk agar diffusion test (Kirby-Bauer test).

If a new pull fulfilled the requirements for being entered into the trial, it was placed into a treatment group. The calves were alternatively placed into an antibiotic treatment group in blocks of three as they were presented. In essence, there was a systematic rotation through the three antibiotics — penicillin, oxytetracycline, and trimethoprim-sulfadoxine. Each antibiotic treatment group was comprised of 100 animals.

The dosages for the three antibiotics were as follows: 65,000 IU/kg procaine penicillin G (Ethacilin, rogar/STB, London, Ontario), IM once daily; 20 mg/kg oxytetracycline (Liquamycin LP, rogar/STB, London, Ontario) IM once daily; and 16 mg/kg trimethoprim-sulfadoxine (Trivetrin, Coopers Agropharm Inc., Willowdale, Ontario) IM once daily. The trial animals were given their assigned antibiotics for three days regardless of response.

On the third day, if the calf had shown clinical improvement and if its temperature was below 39.7°C (103.5°F), it was returned to the home pen after the third injection. If its temperature was still elevated on the third day, it was given its third treatment and put back into the hospital pen. If, on day four, the temperature was normal (< 39.7°C), it was given a fourth treatment of the same antibiotic and sent back to its home pen. If, however, the temperature remained elevated, treatment was switched to erythromycin (Erythro-200, P.V.U., Victoriaville, Quebec) at 20 mg/kg IM once daily. Additional alternative antibiotics were used if erythromycin failed to achieve clinical improvement as measured by temperature response. The trial animals were followed for 60 days after the first treatment for AUBRD. A successful treatment was defined as three days of therapy with no relapses over the 60 day study period. Twenty calves in the trial were released on the third day of the trial following their third treatment despite the presence of rectal temperatures above 39.7°C. This premature release was based on visual assessment ("eye-balling") which suggested that the calves required no further treatment.

The three treatment groups were evaluated with respect to: 1) initial response; 2) number of treatment days; 3) relapse rate; 4) case fatality rate; and 5) cost of treatment. Treatment costs included cost of initial treatment plus any cost incurred in treating a relapse. There was no control over the selection of antibiotics in the treatment of relapses.

All animals that died were examined at postmortem by the attending feedlot veterinarian and the diagnosis was confirmed by the Regional Diagnostic Laboratory at Airdrie, Alberta. Samples of lung tissue were submitted to the laboratory for histological confirmation of the character and age of the lesion.

Chi-square analysis was used to compare the treatment length, relapse and case fatality data in the three groups.

Results

The trimethoprim-sulfadoxine group had the highest number of calves treated successfully. However, when compared to the total number of calves successfully

TABLE 1
Animals Successfully Treated with the Same Initial Antibiotic for Three or Four Days with no Relapse (100 animals per treatment group)

Treatment Days	Penicillin (n)	Oxytetracycline (n)	Trimethoprim-Sulfadoxine (n)
3	43	45	54
4	7	5	5
Total	50	50	59

TABLE 2
Number of Animals Relapsing After Initial Treatment for Acute Undifferentiated Respiratory Disease

Number of Times an Animal Relapsed	Penicillin (n)	Oxytetracycline (n)	Trimethoprim-Sulfadoxine (n)
1	29	26	27
2	6	7	11
3	6	2	0
Total	41	35	38

TABLE 3
Time in Days After Initial Treatment Regime when First Relapse Occurred

Days	Penicillin	Oxytetracycline	Trimethoprim-Sulfadoxine	Total
1–6	32	17	16	65
7–15	6	10	16	32
16–30	3	4	3	10
> 30	0	4	3	7

TABLE 4
Comparison of Relapse Rates in Calves Contracting AUBRD in the First Six Days Postarrival to those Treated for the Disease Seven or More Days Postarrival

Days Post-arrival	Penicillin	Oxytetracycline	Trimethoprim-Sulfadoxine	Total
< 7	18/36 (50%)	18/42 (43%)	17/37 (46%)	52/113 (46%)
≥ 7	19/61 (31%)	13/52 (25%)	20/61 (33%)	54/117 (31%)
p	NS	< 0.05	NS	< 0.05

TABLE 5
Mortality by Treatment Group

Drug	Respiratory Diseases	Other Causes	Total	No. in Treatment Group
Penicillin	10	2[a]	12	100
Oxytetracycline	8	1[b]	9	100
Trimethoprim-Sulfadoxine	3	1[c]	4	100

$\chi^2 = 3.715$, $p < 0.20$
[a]Death due to bloat in one case and clostridial disease in another
[b]Death due to multicentric lymphosarcoma
[c]Death due to bloat

treated where alternative antimicrobials were used, there were no differences among the three treatment groups (Table 1).

There are no statistical differences in the relapse rates among the three treatment groups (Table 2). Examination of the number of relapses in the first six days after the initial treatment period reveals that treatment with penicillin resulted in a statistically higher (χ^2, $p < 0.02$) number of relapses than did treatment with oxytetracycline or trimethoprim-sulfadoxine (Table 3).

There was a statistically higher relapse rate (χ^2, $p < 0.01$) in calves initially treated less than seven days postarrival compared to those initially treated seven days or later postarrival (Table 4).

The total number of treatment days for each treatment group includes length of initial treatment and days necessary for treating relapses during the 60-day study period. The total number of treatment days were 545, 506 and 467 for penicillin, oxytetracycline, and trimethoprim-sulfadoxine respectively. The total treatment days were different from each other (χ^2, $p < 0.05$).

There was a higher mortality rate in the penicillin and oxytetracycline treated groups; however, this difference was not significant (Table 5). Fibrinous pneumonia was the primary cause of mortality in all cate-

TABLE 6
The Cost of Treatment and Mortality, per Treated Animal, by Treatment Group

	Mean	
Drug	Drug Costs	Drug and Mortality Cost[a]
Penicillin	$10.40	$60.40
Oxytetracycline	9.75	49.75
Trimethoprim-Sulfadoxine	14.42	29.42

[a]Figure is calculated on basis of drug cost and a purchase price of $500.00 (Cdn) per calf

TABLE 7
Number of Animals in which Temperature Increased or Failed to Decline during Initial Treatment by Antibiotic Group

	Penicillin	Oxytetracycline	Trimethoprim-Sulfadoxine
No relapse	26	28	8
Relapse	19	23	8

gories. The cost of drugs and mortality is presented in Table 6.

Temperature decline during the initial treatment regime was examined in all three treatment groups when animals were categorized by unexpected changes in temperature (either an elevation in temperature or a failure to drop from one day to the next). A greater proportion ($p < 0.001$) of animals (40/88) relapsed if they had a temperature greater than 39.7°C on the last day of treatment when compared to a conventional temperature decline (66/192). There were fewer such temperature aberrations in the trimethoprim-sulfadoxine treatment group (Table 7). The percentage of calves with temperature aberrations from which *Pasteurella haemolytica* was isolated from pretreatment swabs was 53%, 65% and 20% in the penicillin, oxytetracycline, and trimethoprim-sulfadoxine treatment groups respectively.

Pasteurella haemolytica was isolated from 121 (40%) of the pretreatment nasal swabs. These isolates were evenly distributed among the three treatment groups. In addition, 19 isolates (6%) of *P. multocida* were made simultaneously with *P. haemolytica*. Eighty-four *P. haemolytica* isolates and 19 *P. multocida* isolates were submitted for Kirby-Bauer testing (Table 8).

The *P. haemolytica* isolated from 20 calves was resistant to the antimicrobial in the treatment group (Table 9). However, the initial therapy was successful in 12 calves and only four calves relapsed after the initial therapy. Those animals from which a sensitive *P. haemolytica* was isolated and in which the initial treatment regime was successful are presented in Table 10. Paradoxically, 39 of 102 calves (39%) relapsed when treated with an apparently appropriate antibiotic.

TABLE 8
Sensitivity Patterns of 84 *P. haemolytica* and 18 *P. multocida* Isolates to Selected Antimicrobials

Antimicrobial	*P. haemolytica* % sensitive	*P. multocida* % sensitive
Penicillin	74	100
Tetracycline	67	100
Streptomycin	39	94
Neomycin	73	100
Chloramphenicol	100	—
Nitrofurantoin	96	100
Ampicillin	74	100
Kanamycin	96	100
Polymixin B	98	100
Gentamicin	100	100
Cephalothin	96	100
Triple Sulfa	45	83
Trimethoprim/ Sulfamethoxazole	98	100
Carbenicillin	93	100

Discussion

In vitro effectiveness testing of an antimicrobial against common respiratory pathogens often bears little relationship to the treatment response of clinical "shipping fever" in calves. The only practical method of evaluating an antibacterial takes the form of a field trial utilizing spontaneously occurring bovine respiratory disease. Good field trials comparing various antibiotics in the treatment of bovine respiratory disease are rare in the veterinary literature. The conventional selection of an antibiotic in the field is made on the basis of perceived efficacy, cost, ease of administra-

TABLE 9
Outcome of Animals in which the *P. haemolytica* Isolated from a Pretreatment Nasal Swab was Resistant to the Antimicrobial Used

	Penicillin	Oxytetracycline	Trimethoprim-Sulfadoxine
Treated for 3 days with no relapse	6	5	1
Treated for 4–5 days with no relapse	2	1	0
Relapse after initial treatment	1	3	0
Mortality	0	1[a]	0
Total	9	10	1

[a]Mortality due to fibrinous pneumonia

TABLE 10
Outcome of Treatment in Animals from which a Sensitive *P. haemolytica* was Isolated Prior to treatment

Outcome	Penicillin	Oxytetracycline	Trimethoprim-Sulfadoxine
Treated for 3 days with no relapse	16	15	22
Treated for 4 days with no relapse	7	1	2
Relapse after initial treatment	11	10	18

tion, availability, toxicity, and length of withdrawal.

The higher relapse rate of the penicillin group in the first six days following the initial treatment period may well be related to inadequate duration of treatment. It is known that the highly acid pH which is often present in necrotic material may destroy or reduce the activity of antimicrobials such as penicillin (4,6). There may also be impairment of delivery of penicillin to the sites of chronic infection. The quiescent state of the organism in such a lesion may reduce the effectiveness of penicillin because a rapidly multiplying population of organisms is necessary (7). It may be of importance to ensure that the animal is clinically normal (temperature as well as clinical assessment) for the last two or three days of penicillin therapy. By prolonging the duration of the treatment, it may be possible to achieve a cure and reduce the number of relapses.

Introduction of new cattle into the feedlot is associated with acute UBRD which starts to escalate at about the seventh day postarrival and peaks at about ten to fourteen days (3,8). In this trial, an earlier escalation at three to four days postarrival was observed. Therefore early selection of cattle acutely ill with UBRD was more difficult. It is more common to select cattle in advanced stages of UBRD under these circumstances with a resulting decrease in treatment response and an increase in case fatality rate. The difficulty in selecting animals with respiratory disease in this early period is likely the explanation for the higher relapse rate in animals treated in the period less than seven days postarrival. Recognition of this high-risk situation dictates treatment with the most efficacious antibiotic. In this study, the trimethoprim-sulfadoxine was a better choice of treatment for these animals. There was a significant reduction in total number of treatment days in the 60-day period following initial treatment with the trimethoprim-sulfadoxine. The reduction in mortality observed, while not statistically significant, was a trend in the right direction and when added to drug costs produced an appreciable reduction in the total costs. A prolonged course of treatment, possibly to a minimum of five days, is an alternative method to lower the case fatality rate.

The dosages of penicillin and oxytetracycline used in this trial are greater than normally recommended; however, these dosages are frequently used in the feedlot for the treatment of respiratory disease. The utilization of these dosages has been associated with a greater percentage of clinical cures when compared to using these antibiotics at the lower recommended levels (4). The successful use of trimethoprim-sulfadoxine at the recommended dosage in the treatment of respiratory disease is of importance to the veterinary practitioner. In comparison to the high dosages of penicillin and oxytetracycline, there is less concern with prolonged withdrawal times and the potential of meat residues when using the trimethoprim-sulfadoxine combination at the recommended dose.

The trimethoprim-sulfadoxine combination may be more effective in the treatment of bacterial pneumonia for several reasons. *Pasteurella haemolytica*, the most important pathogen in fibrinous pneumonias, was found to be highly sensitive to the trimethoprim-sulfa combination elsewhere (9) and in this study. The pretreatment isolates of *P. haemolytica* demonstrated a 98% sensitivity to the trimethoprim-sulfonamide combination. Although trimethoprim achieves relatively low concentrations in the plasma, it lends to concentrate in the lungs, which will confer an advantage in the destruction of respiratory pathogens (7,10,11). Trimethoprim is a basic compound and thus tends to accumulate in acidic areas such as necrotic pulmonary tissue, perhaps making it more effective in treating the case of respiratory disease which has some chronicity (7,11).

The use of a thermometer remains our only rapid, objective means of evaluating the calf at chute-side. In general, calves with temperature decline abnormalities in the treatment period relapsed with a 50% probability. A failure of temperature to drop or an elevation in the rectal temperature during treatment should indicate that the duration of treatment be extended. There were several calves in the trial where treatment ceased despite the presence of a rectal temperature above 39.7°C (103.5°F). After three days of treatment, visual assessment of the calf suggested it had recovered. Nine out of the twenty calves in this category relapsed, therefore it can be hypothesized that an objective measurement of body temperature is more valid than visual assessment when treating UBRD.

The isolation of *P. haemolytica* from the nasal cavity and its association with the respiratory disease present remains controversial. *Pasteurella haemolytica* is considered to be part of the basal flora of the bovine respiratory tract (12). Under certain conditions such as weaning, transportation, introduction into feedlots and other stresses, there is an increased frequency of isolation of *P. haemolytica* from the nasopharynx. This has been associated with the development of bovine respiratory disease (13,14,15,16). Hoerlein *et al.* (15) found *Pasteurella* spp. in only 3% of normal calves but in 59.6% of calves with signs of respiratory disease. Corstvet *et al* (16) isolated *P. haemolytica* from 35.6% of animals with clinical signs of respiratory disease but from only 25% of asymptomatic animals. The isolation of *P. haemolytica* from 40% of the test animals falls intermediate among published reports of isolation rates.

It has been postulated that treatment with an antimicrobial increases the resistance demonstrated by *Pasteurella* spp. (17,18). In view of this finding, resistance patterns developed from necropsy material must be held suspect, and testing should be done on *P. haemolytica* sampled from animals prior to treatment. The successful treatment of calves with respiratory disease where the putative pathogen was resistant to the assigned antimicrobial is difficult to explain. Part of the explanation rests with the interpretation of the results from the Kirby-Bauer testing.

The accuracy of the disk diffusion technique for assessing bacterial sensitivity to antibiotics is open to question (19,20,21,22). The Kirby-Bauer procedure is based on human pharmacokinetics and does not take into consideration the blood levels that can be achieved in domestic animals. The Kirby-Bauer method forms a qualitative interpretation of susceptibility in sites

where the drugs are concentrated physiologically. It will also underestimate the concentration of drugs that are achievable at veterinary dosages (4). The concentration of certain antibiotics in diseased respiratory tissues has been demonstrated in cattle (23). Systemic disease may also serve to significantly elevate the concentration of the antibiotic *in vitro* making serum levels achieved in healthy animals inappropriate for determining drug dosage and achievable serum and tissue concentrations (24,25,26). A multiplicity of other factors can make bacterial isolates sensitive at levels below the minimum inhibitory concentration (20,27) and these may explain the clinical cures observed in these cases.

Acknowledgments

We thank the staff of Thiessen Farms Ltd. of Strathmore, Alberta for their willing assistance in this trial. This work was supported by a grant from Coopers Agropharm Inc. CVJ

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