Antimicrobial Use in Feedlot Calves: Its Association with Culture Rates and Antimicrobial Susceptibility

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ABSTRACT

Data were collected on antimicrobial usage and health problems, in beef feedlot calves. Although the association between them was not significant, many feedlot owners did not use recommended dosages or duration of treatment and this may have led to a reduced recovery rate.

Injectable tetracyclines were the most frequent antimicrobial for primary treatment of sick calves; whereas chloramphenicol was selected most frequently when the primary treatment appeared to be ineffective. Treatment with antimicrobials reduced the likelihood of isolating both *Pasteurella multocida* and *Haemophilus somnus*. Chloramphenicol therapy reduced the likelihood of isolating *Pasteurella haemolytica*.

Therapy with a particular antimicrobial, in the week prior to death, increased the level of resistance in *P. haemolytica* to that antimicrobial. Treatment with other antimicrobials also increased the level of resistance to that antimicrobial; although to a lesser degree. The lowest levels of resistance were observed in Pasteurella isolated from nontreated cattle. After adjustment for antimicrobial exposure, resistance to penicillin, tetracyclines and chloramphenicol occurred together more frequently than expected by chance alone.

RÉSUMÉ

Cette étude visait à colliger des données sur la relation entre l'utilisation d'antibiotiques et les problèmes de santé, chez des veaux de parcs d'engraissement. Même si cette relation ne se révéla pas significative, le fait que plusieurs éleveurs ne respectèrent ni les doses ni la durée recommandées de l'antibiothérapie pourrait expliquer une baisse du taux de guérison.

Les tétracyclines injectables s'avérèrent l'antibiotique choisi le plus souvent pour le traitement initial des veaux malades. Le chloramphénicol fut par ailleurs le deuxième choix le plus fréquent, à la suite d'un premier traitement infructueux. L'antibiothérapie réduisit les chances d'isoler *Pasteurella multocida* et *Haemophilus somnus*. Le traitement au chloramphénicol réduisit les possibilités d'isoler *Pasteurella haemolytica*.

L'emploi d'un antibiotique particulier, au cours de la semaine qui précéda la mort, augmenta la résistance de *P. haemolytica* à son endroit. L'utilisation d'autres antibiotiques augmenta aussi la résistance à l'endroit de cet antibiotique particulier, mais à un degré moindre. Les taux de résistance les plus bas s'observèrent avec les souches de *Pasteurella* isolées des veaux non traités. Après la détermination de l'antibiotique le plus approprié, une résistance simultanée à l'endroit de la pénicilline, des tétracyclines et du chloramphénicol se produisit plus souvent que prévu par le seul effet du hasard.

INTRODUCTION

In a previous report, the results of a computer model indicated the difficulties in estimating the actual (true) percentage of resistant organisms in a source population from resistance levels (apparent) observed in the diagnostic laboratory (5). Data, from the Bruce County Beef Cattle Project (6), were presented to validate the model results. In particular, there was an association between antimicrobial exposure and the percentage of calf lungs from which putative pathogens were cultured (positive culture rate) as well as the percentage of these putative pathogens that were resistant to selected antimicrobials (apparent resistance level) in the laboratory. (Resistance as used in this paper indicates that the organisms were not killed or unduly restricted in growth by the concentrations of antimicrobials used routinely in the Ontario Veterinary College (OVC) diagnostic laboratory; see Table VII).

This report contains additional data, obtained during 1980-1981, on antimicrobial use, positive culture rates and apparent resistance levels.

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MATERIALS AND METHODS

At the first visit to the feedlot, after arrival of a group of calves, the owner was asked what antimicrobial would be used for initial treatments (first choice) and what antimicrobial he would select (second choice) if poor results were obtained with the first antimicrobial selected. If two antimicrobials were given concomitantly the owner was asked to rank them as most important (first choice) and least important (second choice). The trade name, dosage (total mL), number of injections (administrations) per day and the usual period of treatment (number of days) for each antimicrobial were recorded. In addition, when calves were sent to the OVC for postmortem examination, the owners were asked to list the antimicrobials administered, during the week prior to death.

RESULTS

Tetracyclines were used for initial treatments in 59% of cattle groups. Chloramphenicol was used for initial treatments in 29% of groups and were selected in 51% of groups when the initial antimicrobial selected did not appear to work. The extensive use of both of these drugs was apparent in the calves sent for postmortem; 44% of which had been treated with tetracyclines and 50% with chloramphenicol in the week prior to death. Approximately 25% of the 114 calves sent for postmortem in 1980-81 had been treated with both these antimicrobials in the week prior to death (Table I).

Many of the owners used treatment regimes that appeared to be inadequate in dosage rates and/or total days treated (Table II). Based on recent recommendations (3), owners using the 50 mg/mL tetracyclines underdosed their animals (6.3 mg/kg); whereas those using the 100 mg/mL preparation used the correct dose, but 81% of them treated for less than three days. Owners using chloramphenicol for initial treatments, used recommended dosage rates, frequency and duration of therapy. Those using penicillin gave adequate levels (15 000 μ/kg), but most routinely treated their calves for less than three days. Owners using tetracyclines as the second choice antimicrobial tended to use too low a dosage and over half those using chloramphenicol as the second choice routinely treated for less than the recommended minimum of four days. The differences in mortality rates, morbidity rates or treatment costs, classified by antimicrobial initially used for therapy, were not significant by one-way analysis of variance (8). However, the owners using 50 mg/mL tetracyclines had intermediate morbidity rates (24.5%), the highest mortality rates (0.9%), and the highest per head treatment costs ($3.56) in their calves. Case fatality rates were lowest in groups of calves initially treated with chloramphenicol (500 mg/mL) or penicillin (Table III).

Eighty-three of the 287 (28.9%)

TABLE I. The Number of Groups of Feedlot Calves and Necropsied Calves, Treated with Antimicrobials. Data from Bruce County Beef Project 1980-81

Antimicrobial	Number of Groups of Calves: First Choice Antimicrobial[a] No. (Percent)	Number of Groups of Calves: Second Choice Antimicrobial[a] No. (Percent)	No. of Necropsied Calves Given Antimicrobials in Week Prior to Death No. (Percent)
Penicillin	12 (11)	4 (4)	15 (13)
Tetracycline			
— 50 mg/mL	27 (25)	11 (12)	
— 100 mg/mL	37 (34)	12 (13)	51[b] (44)
Chloramphenicol			
— 200 mg/mL	28 (25)	46 (49)	
— 500 mg/mL	4 (4)	2 (2)	57[b] (50)
Sulfonamides (oral)	2 (2)	15 (16)	19 (17)
Potentiated Sulfonamides	0	1 (1)	7 (6)
	110	94	114

[a]The first choice represents the initial antimicrobial used to treat sick calves. The second choice was the antimicrobial that would be used if the first antimicrobial was ineffective. Oral sulfonamides were never used singly, and most of the feedlot owners ranked them second in importance to the other antimicrobials used concomitantly

[b]Concentration of antimicrobial not specified

Table II. Descriptive Data on Antimicrobial Use in Feedlot Calves. Data from Bruce County Study 1980-81

First Choice[a] Antimicrobial		Average Dosage (mL)	Number of Groups with Calves Treated: > once per Day	Number of Groups with Calves Treated: for < 3 Days
Penicillin[b]		15.2 14,900 μ/kg	3/12	8/12
Tetracycline	50 mg/mL	25.5 6.3 mg/kg	3/27	6/27
	100 mg/mL	23.4 11.5 mg/kg	3/27	30/37
Chloramphenicol	200 mg/mL	22.8 21.78 mg/kg	22/28	4/28
	500 mg/mL	10.5 25.7 mg/kg	3/4	1/4
Second Choice[a] Antimicrobial				
Tetracycline	50 mg/mL	16.2 3.8 mg/kg	3/11	7/11
	100 mg/mL	16.7 8.3 mg/kg	5/10	7/10
Chloramphenicol	200 mg/mL	23.3 22.7 mg/kg	7/46	28/46

[a]See Table I

[b]Assumes penicillin-streptomycin combination at 200 000 units per mL

Table III. The Association between Initial Treatment of Individual Calves and Subsequent Health Status of Feedlot Calves. Data from Bruce County Beef Project 1980-81

Initial Antimicrobial Used to Treat Sick Calves		Morbidity Rate (%)	Mortality Rate (%)	Case Fatality Rate (%)	Treatment Costs per Head ($)
Penicillin	200 000 μ/mL	17.3	0.21	1.2	1.82
Tetracycline	50 mg/mL	24.5	0.91	3.7	3.56
	100 mg/mL	26.1	0.59	2.2	2.40
Chloramphenicol	200 mg/mL	22.2	0.56	2.5	2.94
	500 mg/mL	38.9	0.20	0.5	2.75
Significance of differences (p-value)		p = 0.42	p = 0.14	not tested	p = 0.48

Table IV. The Distribution of Cause of Death in Treated and Nontreated[a] Feedlot Calves. Data from Bruce County Beef Project 1979-81

Cause of Death (Diagnosis)	Treated calves	Nontreated Calves
Fibrinous pneumonia	95	22
Bronchopneumonia	17	7
Interstitial pneumonia	19	5
Infectious bovine rhinotracheitis	8	0
Infectious thromboembolic meningoencephalitis	14*	23
Bloat	5*	5
Urinary calculi	6	2
No diagnosis	6*	4
Iatrogenic	7*	6
Other diseases	27	9
Total	204	83

[a]Calves not receiving antimicrobials within one week prior to death
$X^2 = 34.7$ $p < 0.0001$ (The major differences are due to a relative excess of nontreated calves in the four diagnostic catagories marked with asterisk)

calves sent for postmortem examination had not received antimicrobials in the week prior to death (Table IV). In these calves, four diagnostic categories suggestive of sudden death; namely, infectious thromboembolic meningoencephalitis (ITEME), bloat, iatrogenic disease and "no diagnosis", occurred significantly more frequently than in treated calves.

The effect of antimicrobial exposure on positive culture rates of *Pasteurella* and *Haemophilus* species from lung tissue is shown in Table V. On average, antimicrobial exposure had no effect on isolating *P. haemolytica*, tended to reduce the likelihood of isolating *P. multocida* and significantly reduced the likelihood of isolating *H. somnus*. Although this ordering persisted when specific antimicrobial exposure was examined (Table VI), chloramphenicol reduced the probability of isolating all organisms, including *P. haemolytica*, to a greater extent than other antimicrobials.

The effect of antimicrobial exposure on antimicrobial resistance in *Pasteurella* species is shown in Table VII. Exposure to an antimicrobial increased the likelihood of bacterial pathogens being resistant to that antimicrobial and exposure to other antimicrobials appeared to produce a nonspecific increase in resistance. (Nonspecific is used in the sense that resistance to antimicrobial A was produced by exposure to antimicrobial B.)

The patterns of multiple resistance after adjustment for exposure to specific antimicrobials are shown in Table VIII. In *P. haemolytica* the only significant resistance pattern was joint resistance to penicillin and tetracycline. In *P. multocida*, multiple resistance to chloramphenicol, penicillin and tetracycline occurred more frequently than expected by chance alone. All *P. haemolytica* were resistant to sulfonamides and thus the association with resistance to other antimicrobials could not be tested. Resistance to trimethoprim did not appear to be associated with resistance to other antimicrobials.

Table V. The Positive Culture Rate of *Pasteurella* and *Haemophilus* Species, from the Lungs of Beef Calves at Post Mortem, According to History of Antimicrobial Use. Data from the Bruce County Beef Project

No. calves given Antimicrobials[a]	No. Calves with No Significant Growth on Culturing (NSG)	Number of Calves[b] Positive for		
		P. haemolytica	*P. multocida*	*H. somnus*
Yes: 204	108 42 NC	41	13	2
No: 83	32 20 NC	11	9	13
		52	22	15
Odds Ratio and chi-square compared to NSG group		1.08/0.00	0.41/2.39	0.06/21.66

NC = Not cultured — not counted in NSG group
[a]One or more antimicrobials within one week of death
[b]Two calves had both *P. multocida* and *H. somnus*, one had both *P. haemolytica* and *H. somnus*

DISCUSSION

Based on the treatment regimes reported by the owner, it appears that many owners require more information regarding appropriate therapeutic methods, although the impact of inadequate therapy is difficult to assess with the data at hand. Morbidity and mortality rates, as well as treatment costs were not significantly different amongst groups defined by antimicrobials used. Also, the data represent only the owner's

general choice of therapy and the numbers of animals treated with each antimicrobial are unknown. Nonetheless, perusal of the data in Tables II and III suggests that adequate dosage of antimicrobial might be more important than duration of treatment or antimicrobial used, in enhancing the recovery of diseased calves. As expected, the use of antimicrobials was less frequent in calves dying from diseases suggestive of acute death, than in calves dying from other causes, most frequently respiratory tract diseases.

Table VI. The Association Between Treatment with Antimicrobials and the Positive Culture Rate from Lungs of Calves at Necropsy, for *Pasteurella* and *Haemophilus* spp. Data from The Bruce County Beef Project

Antimicrobial used	Isolate		
	P. haemolytica	*P. multocida*	*H. somnus*
Penicillin	1.77[a]	0.44	0.20
Tetracycline	1.62	0.97	0.18[s]
Chloramphenicol	0.43[s]	0.27[s]	0.09[s]
Sulfonamides (oral)	1.60	0.29	0.13
Potentiated sulfonamides	0.90	0.28	0.40

[a]Odds-Ratios. If greater than one, an increased positive culture rate was observed when the antimicrobial was administered in the week prior to death. If less than one, a decreased positive culture rate was observed, relative to animals not treated with that antimicrobial

[s]The odds ratio is significantly different from one ($p < 0.05$). (See Ref. #2)

Table VII. The Association Between Antimicrobial Resistance and Antimicrobial Use in Feedlot Calves. Data from Bruce County Beef Project 1979-81

P. haemolytica Antimicrobial	No. Resistant[b]/No. Isolates (Percent)		
	Treated with antimicrobial	Treated with other antimicrobials	Not treated
Penicillin[a]	10/11 (91)	24/30 (80)	4/10 (40)
Tetracycline[a]	25/32 (78)	7/9 (77)	3/10 (30)
Chloramphenicol	4/17 (24)	2/24 (8)	0/10 (0)
Sulfonamides	14/14 (100)	27/27 (100)	10/10 (100)
Potentiated sulfonamides	2/3 (67)	14/38 (37)	2/10 (20)
P. multocida			
Penicillin	0/1 (0)	1/12 (8)	0/9 (0)
Tetracycline	2/11 (18)	0/2 (0)	0/9 (0)
Chloramphenicol	1/5 (20)	0/8 (0)	0/9 (0)
Sulfonamides	1/1 (100)	10/12 (83)	7/9 (78)

[a]The level of resistance to these antimicrobials was significantly different ($p < 0.05$) among the treatment groups as determined by chi-square test

[b]The concentration of antimicrobials in the discs used for testing resistance was 10 units, 5 mcg, 30 mcg, 0.25 mg (23.8 mcg and 1.25 mcg) for penicillin, tetracycline, chloramphenicol, sulfonamides and potentiated sulfonamides respectively

TABLE VIII. The Association between Resistance to Selected Antimicrobials in *P. haemolytica* (and *P. multocida*) after Adjustment[a] for Antimicrobial Exposure. Data from Bruce County Beef Project 1979-81

Antimicrobials	Penicillin	Tetracycline	Chloramphenicol	No. Resistant/ No. Isolates
Penicillin	—	0.90 (s)	ns (0.94)	38/51(2/22)
Tetracycline	0.91 (s) ns (0.70)	—	ns (0.94)	35/51(2/22)
Chloramphenicol	ns (0.70)	ns (0.70)	—	6/51(1/22)

[a]The adjustment was made using discriminant analysis techniques. (See Ref. #7) The significant standardized discriminant function coefficients are shown. s indicates that unconditionally, there was a significant association between the antimicrobials. ns indicates no unconditional or conditional association. Resistance to sulfonamides was not statistically associated with resistance to any of the other antimicrobials

In a previous report (5), it was argued that apparent resistance rates derived from routine diagnostic data should not be used to estimate true resistant rates. The data presented here, validate that argument at least qualitatively. Certainly, treatment with an antimicrobial influenced what pathogens were isolated, as well as the resistance of the pathogen to that and other antimicrobials. Nonetheless, the relative standings in terms of resistance rates were stable irrespective of what if any antimicrobial was used for therapy.

Given the limitations of available data and the lack of random sampling, resistance rates are best estimated using the proportion resistant in organisms isolated from nontreated calves; however, larger numbers of organisms are needed to increase the precision of these estimates. For example, a 95% confidence interval for the percentage resistant to chloramphenicol, given that in ten organisms none were observed resistant, is 0% to 27% and 8 to 62% for tetracycline (8). In strains of *Pasteurella* isolated from untreated calves, in one feedlot in California, 37.1%, 10.4% and 22.3% were resistant to tetracycline, sulfathiazole and penicillin respectively (3). In general, a well designed prospective probability sample would be a more desirable way of estimating resistance rates, than using diagnostic laboratory data.

The majority of "resistance" noted in this study was probably plasmid mediated (9), and the dual coding of resistance to penicillin and tetracycline previously reported could explain the association reported herein. There does not seem to be other biological reasons (3) for the multiple resistance patterns noted in this study. Other authors (1) have proposed reasons for the occurrence of multiple resistance in *Pasteurella*, but no data

on antimicrobial exposure were presented in their paper. Our data indicate that interpreting resistance patterns in bacteria isolated from animals exposed to antimicrobials may be misleading because of the pronounced effect of treatment on observed resistance rates and patterns.

The major problem confronting the practitioner is the choice of antimicrobials for therapy. Most recommendations, in this regard, are based on observed minimum inhibitory concentration studies and serum levels of antimicrobials subsequent to treatment; together with experience (3). One report cites a 81.9% response rate to sulfamethazine at 2.2 g/kg; a 70.8% response rate to tetracyclines at 12.5 mg/kg and a 78.6% response rate to penicillin at 66 000 μ/kg (3). Sulfonamides are not widely used in Ontario and the high dosage of penicillin requires an extended withdrawal time. We have contrasted chloramphenicol at 15 mg/kg to an experimental antimicrobial in a trial, on three farms, where sick cattle were sequentially assigned to receive one of these drugs. No calves required additional treatment, in the first four days, in the chloramphenicol group and only 5/45 (11%) of the treated calves subsequently relapsed. These rates were significantly lower than those in the experimental antimicrobial group, which had compared favorably with tetracycline in field trials in California feedlots.

Thus, although there is some qualitative agreement among the effects of antimicrobials on culture rate, resistance rate and therapeutic value, neither culture rate or resistance rate may be good predictors of the latter. Field trials of antimicrobial efficacy under a variety of management regimes, including culture and sensitivity of a random sample of the cattle, prior to and following treatment are needed. These would be of great value in assisting the selection of antimicrobials for therapy as well as clarifying the role of antimicrobial sensitivity testing in this regard.

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