Thoughts and Recommendations on Metaphylaxis in Commercial Feedyard Settings with an Emphasis on Drug Selection and Post-Metaphylaxis Intervals

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Abstract

Various antimicrobial drugs are approved for metaphylaxis in cattle at high risk for developing BRD. Although many can be used successfully, some antimicrobials appear to have superior comparative effectiveness across a broad range of BRD risk levels. Practitioners should familiarize themselves with the available literature to understand which antimicrobial(s) best meet the needs of their clients and the cattle they manage. Once a practitioner has selected an antimicrobial for metaphylaxis purposes, it is also recommended they familiarize themselves with the literature pertaining to Post Metaphylaxis Intervals. In general, extending PMI beyond what is traditionally regarded as prudent, results in reduced BRD treatments without deleterious effects on BRD mortality or growth performance. Additional considerations in selecting metaphylaxis agents and PMIs are discussed herein.

Key words: feedyard, feedlot, metaphylaxis, antimicrobial, Post Metaphylaxis Interval, Post Treatment Interval

Introduction

Metaphylaxis is the use of an antimicrobial drug for control of respiratory disease in a groupof cattle at high risk for developing Bovine respiratory disease (**BRD**). Metaphylaxis typically occurs at arrival processing and has been demonstrated as an effective tool for reducing BRD morbidity, mortality and other negative healthand performance indices.[1,2]A general 'rule of thumb' is that metaphylaxis reduces BRD morbidity and mortality by half. Antimicrobials labeled for metaphylaxis belong to one of four drug classes: 1) cephalosporin, 2) fluoroquinolone, 3) florfenicol, or 4) macrolide. Notable differences exist in terms of effectiveness, convenience of use in the field, and price. Although price is outside the scope of this discussion, effectiveness in large pen trial settings as well as perspectives from the field will be summarizedherein.

Package Inserts (*i.e.*, Labels) provide useful information regarding Indications, Dosage and Administration, and Residue Warnings (*i.e.*, 'withdrawal'), but they do not provide information regarding appropriateperiod of time before subsequent antimicrobial therapy should be considered (colloquially, Post Metaphylaxis Interval or PMI). Incidentally, Post Treatment Interval (**PTI**) garners the same definition but within the context of *treatment* rather than metaphylaxis.Although PMI has been estimated from pharmacological properties of the drug,[3,4]large clinical trials are needed to determine the optimum PMI. The following discussion serves to summarize my experience and the available literature with regards to selection of metaphylaxis drug and PMI.

Drug Selection for Metaphylaxis

Choosing the 'right' antimicrobial for metaphylaxis starts with selecting a product that has been approved for this purpose (Table 1). Although there are many options available, a handful comprise the lion's share used for metaphylaxis in commercial feedyards. Perhaps the most important characteristic of a metaphylaxis drug is its ability to control BRD and, arguably more important, is its comparative effectiveness for controlling BRD. While a comprehensive review of the literature as it pertains to metaphylaxis is outside the scope of this discussion, readers are directed to explore areview article published in 2010.[2]Additionally, a meta-analysis revealed macrolide class drugs tended to have lesser odds of BRD morbidityoccurrence compared to a control (no metaphylaxis; Figure 1a).[5]Macrolides (*i.e.*, tulathromycin[a] and tilmicosin[b]) also had lesser odds of BRD mortality occurrence compared to a control with the odds of BRD mortality being four timesgreater for tilmicosincompared to tulathromycin(Figure 1b).These results tend to correspond with results from large pen comparative effectiveness trials we've conducted at Five Rivers Cattle Feeding. For instance,more than 10,000 calves and short yearlings were enrolled in two studies designed to measure comparative effectiveness of tulathromycin and tilmicosin metaphylaxis compared to a control with no metaphylaxis (Five Rivers Cattle Feeding; data on file). In this study, BRD morbidity was lowest ($P< 0.001$) for tulathromycin (8.28%), intermediate for tilmicosin(10.8%), and greatest for nometaphylaxis Control group (20.3%). Additionally, BRD mortality was lowest ($P< 0.01$) for tulathromycin (0.63%), intermediate for tilmicosin(1.12%), and greatest forControl (1.40%).

Although tulathromycin seems to stand out as superior in metaphylaxiscomparative effectiveness, trial results vary. This can be a result of a study lacking in statistical poweror it can be a result of differences in the conditions under which metaphylaxis treatments were applied.

These considerations are described below. I've tried to list them in order of importance. The order might not be perfect, but it's not arbitrary.

1) Statistical Power – This is the probability of detecting a treatment effect (*e.g.*, a difference in BRD mortality) when in fact it truly exists. Studies lacking in statistical power are at increased risk of making a Type II error (failing to detect a difference when one actually exists). Larger studies (*i.e.*, larger sample sizes) generally increase statistical power and, in general, larger sample sizes increase the ability to detect small differences in mortality. This is important not only from an animal welfare standpoint, but because mortality is arguably the biggest driver in an economic analysis of trial results. Small pen studies and/or studies involving small sample sizes often report relatively large effect sizes (large numerical differences) but with non-significant (high *P*-value) treatment effects.[6] Results from these types of studies are difficult to utilize when making decisions incommercial feedyards.

2) BRD Risk Level – In general, comparative efficacy studies are much less sensitive the lower the inherent BRD risk of the cattle. The lower the BRD risk, the less sensitive a study *could* be whereas the higher the BRD risk, the more sensitive the study could be. Antibiotics having different comparative efficacy in 'reality' could look similar in lower risk populations but could result in markedly different health outcomes when we compare them in high-risk populations. Some studies are designed to measure comparative efficacy in a certain population (*e.g.*, moderate risk). Sometimes you plan for high-risk cattle and the cattle just don't get sick. Regardless,

you should qualify the results of the study with the risk level of the cattle used in the study. You can get a feel for the risk level of the cattle by evaluating BRD morbidity and mortality results.

3) Post Metaphylaxis Interval – As I hope you will discover before the end of this discussion, extending PMI can improve metaphylaxis success independent of the inherent capabilities of the antimicrobial used to control BRD-related morbidity and mortality. A seemingly inferior drug can match or even outperform a superior drug simply because PMI was longer in the inferior drug compared to the superior one. This is *probably* more likely to occur inpopulations in which the BRD burden is relatively low. Depending on the objective of the researchers, the study should utilize identical PMI across the metaphylaxis agents being tested. An example of one such study is available in the public domain.[7]

4) BRD Treatment Regimen – Assuming there's some inherent BRD risk in a study population of cattle and assuming that the PMI of the two antimicrobial drugs being compared are 'reasonable' and the same, first BRD pulls should be a reliable measure of metaphylaxis success. However, BRD mortality *can* be influenced by the BRD Treatment Regimen. As such, a 'good' trial design will compare two metaphylaxis drugs using the same PMI *and* the same BRD Treatment Regimen. Using such a design will allow you to ascribe BRD-related morbidity *and* mortality to the metaphylaxis drugs you're testing. Of course, there's always a random variation term in your statistical model, but the health outcomes aren't confounded by the BRD

treatment regimen. This considerationnotwithstanding, sometimes we do compare Program A to Program B.[4] In such cases, the hypothesis we're testing is different than if we're wanting to compare Drug A to Drug B.

Practical Considerations for Selecting Metaphylaxis Drugs

A noteworthy feature of feedlot clinical practice and research is that we arebeholden to the nuances – both good and bad – of the industry. Labor shortages, lack of experience, speed of commerce, and economics, for example, are important considerations in selecting metaphylaxis drugs. Perhaps the most important consideration is the dose of the drug. Doses for various metaphylaxis drugs in shown in Figure 2 (dose for a 650 lb animal). Dose is important for at least two reasons:

1) Speed of commerce – All other things being equal, products requiring larger volumes of drug require more time and time is money. This is particularly the case if the volume exceeds that set forth by BQA guidelines (*i.e.,* 10 mL per injection site). A product that requires more than a single injection site is costly and represents a big line item across large numbers of cattle receipts. Of course, this will depend on the size of the animal. Occasionally, I throw caution to the wind and recommend administering 11 or 12 mL in a single injection so I can reduce the injection sites in a calf.

2) Injection Site Area – Many of the high risk (and *ultra*-high risk) cattle are lightweight animals. Cattle receiving metaphylaxis are also receiving other health products (*e.g.*,

vaccines, dewormers), so you need to remember that you don't have a lot of injection site 'real estate'. This is an especially important consideration depending on the chute the feedyard is using because you don't always have good access to the injection site triangle. Needless to say, a lower volume dose is preferred because of this.

Another practical consideration for selecting an antimicrobial for metaphylaxis might not seem as obvious and that is our ability – or inability as it were – to accurately determine BRD risk. Once upon a time I had a 'top shelf' arrival program whereby the program, and therefore the metaphylaxis drug,varied according to BRD risk (*i.e,.* low, moderate, high). This was a great program on paper, but it failed from time to time and when it did it seemed to fail in a big way. We didn't struggle putting cattle into the low risk 'bucket' and we didn't seem to struggle all that much putting cattle into the high-risk bucket. It was the moderate risk cattle we struggled with. It was literally the adage '80% of your problems come from 20% of your cattle'. We were trying to split hairs at the speed of commerce. We would incorrectly place cattle into the moderate risk bucket when in fact they belonged in the high-risk bucket. Those cattle would receive a lesser drug when in fact they really needed the superior drug. I became disillusioned with that approach and decided to have two risk categories instead: low risk and high risk. I chose the best metaphylaxis drug available, based on trial results, and in doing so had a drug that would work on anything that came through the door. We were also able to pickup some operational efficiency because we weren't having to manage two drugs. One drug in the barn, one drug at end of month inventory, and so on. It's not perfect, but it seems to be better than what we did before. At any rate, I thinkit's a consideration when selecting a metaphylaxis drug for use in a commercial feedyard.

Selection of Post Metaphylaxis Intervals

Veterinary practitioners are likely to implement a PMI when prescribing metaphylaxis. As mentioned previously, the package insert doesn't help much here. Pharmacologic attributes of the drug provide estimate for PMI[8] but do not inform us on the optimum PMI to use in the clinical setting. Therefore, large pen studies have been conducted to ascertain optimum PMI. Owing to the fact thatpublished clinical trial data are limited, available information tends to support the notion that extended PMI does not result in deleterious effects and in some cases better health outcomes. In one study evaluating a 3- or 7-day PMI for ceftiofur crystalline free acid[c],PMI of more than 3 days was not beneficial; however, the study utilized highrisk calves and an antibiotic that, due to pharmacologic attributes, may not lend itself to an extended PMI.[9]In another study, no difference in BRD morbidity (average 9.6%) or mortality (no mortality observed)was noted between PMIs of 3-, 5-, or 7-day when tilmicosinwas used as the metaphylaxis drug.[10] And in a second study by the same researchers, a 10-day PMI resulted in the lowest BRD morbidity compared to 3-, 5-, or 7-day PMIfor tilmicosin metaphylaxis (39.3 and 54.7% for 10-day versus 3-, 5-, and 7-day, respectively; $P < 0.01$). No deleterious effect ($P = 0.64$) on mortality was noted; however, it is important to notethat this study was small and while the effect size for mortality was relatively large, a statically significant treatment effect was not observed.In a more recent study conducted in a large pen commercial feedyard setting, BRD morbidity decreased quadratically ($P = 0.076$) from 4- to 13-dayPMI for tildipirosin[d] metaphylaxis (Figure 3).[11]Mortality due to BRD did not differ ($P = 0.70$;average = 0.73) in this study; however, the lowest numerical BRD mortality (0.64%) was for the 13-day PMI. Likewise, feedlot growth

performance was also not influenced by PMI treatment. With some exceptions, the literature tends to support extended PMI, at least for macrolide class drugs used in moderate risk populations. Although the available literature is limited, results from published PTI studies also tend to support this notion.[12,13]

Admittedly, it seems cavalier to speculate why extended PMI studies tend to yield positive results given these studies were not designed to elucidate such mechanisms. Nevertheless, metaphylaxis seems to provide protection, both on an individualand on a population level, during a time when cattle are processing vaccinal and wild type antigen presented to them leading up to and during the time of arrival processing.[14]Given the pharmacologic attributes of certain antimicrobials – namely the macrolide drugs – extended PMI may provide that protectionwithout the added stress of removing animals from their home pen, moving them through a hospital facility, *et cetera*. Given that BRD mortality tends not to be influenced by extended PMI, it is also plausible that extended PMIhas no *true* effect on BRD morbidity and that 'drug on board' is sufficient for disease resolution without additional antimicrobial therapy. Implicit to this notion is the idea that we are not talented at differentiating between BRD cases that resolve without additional intervention from those that require follow-up therapy.Nevertheless, assuming extended PMI is beneficial, at least in part because it improves recovery from shipping, feedlot arrival, and processing, then it stands to reason that additional management steps that serveto improve comfort, low stress, and relaxation, should also improve health outcomes. When taken in aggregate,such management steps may potentiate improved health outcomes in cattle at risk for developing BRD. That's what we're trying to accomplish at the end of the day. A couple words of caution are worth mentioning. First, the population used in the tildipirosin study was

large butnarrowly defined to include only moderate risk cattle. It is plausible that the PMIeffects observed in this study do not reflect what would be observed in different cattle populations (*i.e.*, cattle with a higher BRD burden: high and ultra-high risk populations). Although not discussed in detail here, populations of ultra-high risk cattle in which concomitant metaphylaxis has been utilized challenges the idea that extended PMI works uniformly across all populations. After all, if concomitant metaphylaxis yields superior results compared to single metaphylaxis, then perhaps some populations might benefit from additional antimicrobial therapy even though they have already drug on board. Second and perhaps more obvious, it does not seem wise to extrapolate results from a study evaluating a class of antibiotic different than the one you're using.This is because of the potential differences in pharmacological properties from one drug to another.

Summary

Literature exists which helps guide practitioners in selecting antimicrobials for metaphylaxis purposes and while the literature is sparse, it does exist for helping practitioners become more comfortable with extended PMI. Additional considerations as well as caveats exist when developing a program for metaphylaxis. As always, components of the production system (*e.g.*, vaccines, nutrition, husbandry) also play important roles in realizing a favorable health outcome in cattle at risk for developing BRD.

Endnotes

a. Draxxin; Zoetis Inc., Kalamazoo, Michigan

b. Micotil; Elanco US, Inc., Greenfield, Indiana

c. Excede; Zoetis Inc.

d. Zuprevo; Merck Animal Health, Rahway, New Jersey

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1

Table 1. Antimicrobials labeled for metaphylaxis

Trade Name	Drug	Drug Class	Label Dosage, mL/100 lbs[x]	Meat Withdrawal, days
Advocin	Danofloxacin	Fluoroquinolone	2.0	4
Baytril 100	Enrofloxacin	Fluoroquinolone	3.4	28
Draxxin	Tulathromycin	Macrolide	1.1	18
Excede	Ceftiofur	Cephalosporin	1.5	13
Micotil 300	Tilmicosin	Macrolide	1.5 to 3.0	42
Noromycin 300 LA	Oxytetracycline	Tetracycline	4.5	28
Nuflor	Florfenicol	Florfenicol	6.0	38
Zactran	Gamithromycin	Macrolide	1.8	35
Zuprevo 18%	Tildripirosin	Macrolide	1.0	21

[x]Subcutaneous administration.

2

3

4

Figure 1. Forest plots of odds ratio (with 95% credibility intervals) comparison between metaphylaxis drugs and control (no metaphylaxis) for BRD morbidity (a) and mortality (b).[5] An odds ratio less than 1 indicates the odds of the eventoccurance are greater for the control compared to the antimicrobial. All but trimethoprim sulfa (**TMS**) had lesser odds than the control for BRD morbidity; the 'upper tier' treatment arm included tulathromycin and 'middle tier' treatment arm included tildipirosin,gamithromycin, ceftiofur, tilmicosin, and oxytetracycline. Tulathromycin and tilmicosin had lesser odds of BRD mortality occurrence compared to no metaphylaxis.[5]

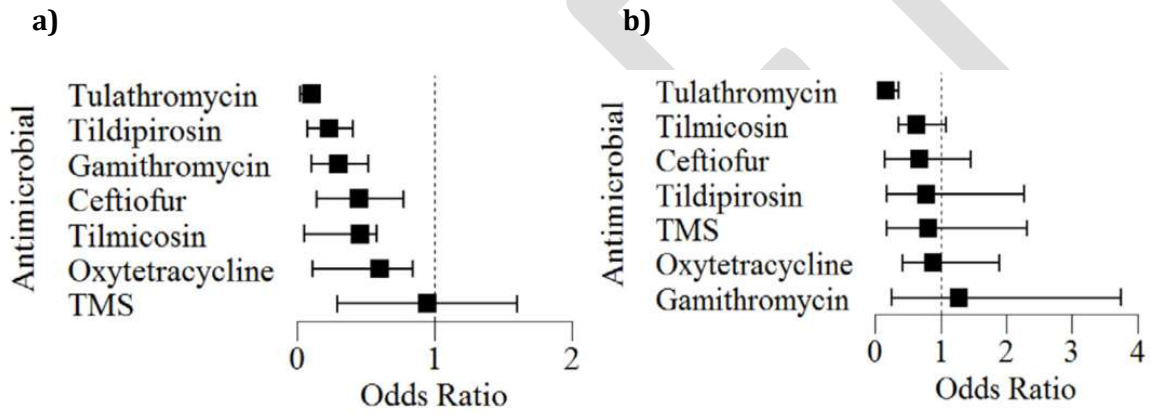

Figure 2. Dose per 650 lbsof antimicrobials approved for control of BRD.

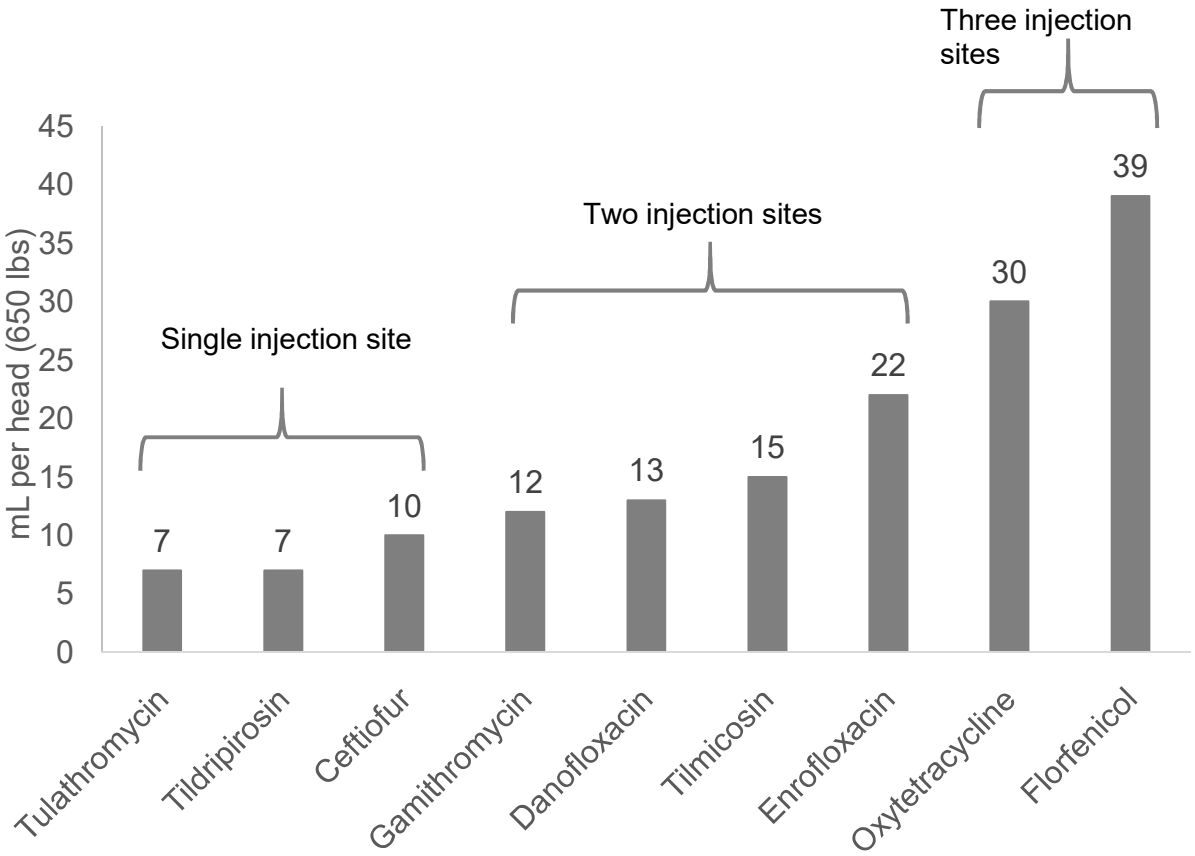

Figure 3. Cumulative bovine respiratory disease morbidity of 4-, 7-, 10-, or 13-day post metaphylaxis intervals for tildipirosin metaphylaxis.[11]