MANAGING MYCOPLASMA BOVIS, SALMONELLA, AND BOVINE RESPIRATORY DISEASE IN FEEDLOT HOLSTEIN STEERS

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Mycoplasma bovis

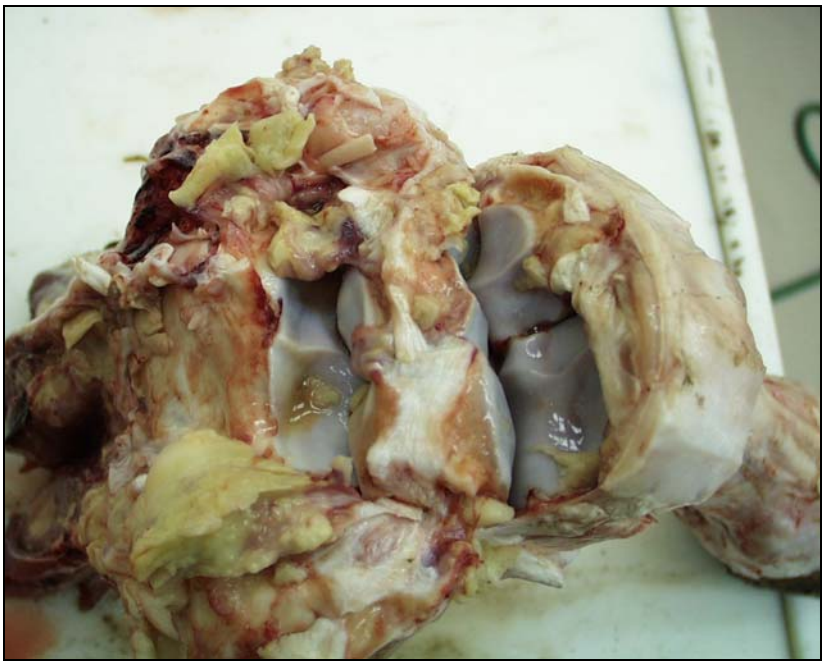
A lot of the questions coming over the phone these days are about prevention and therapy of *Mycoplasma bovis* infections. They are typically in three contexts…

- multiple sites of arthritis following a respiratory outbreak,
- ear infections (usually in small calves), and…
- isolation of *M. bovis* from respiratory mortalities.

Mycoplasma bovis "joint infections" include arthritis and tenosynovitis. Work by Dr. Rosenbusch at ISU suggests that the *M. bovis* strains responsible for arthritis/tenosynovitis may be more phenotypically invasive than strains confined to respiratory infection.[i] Figures 1 and 2 illustrate the clinical and gross necropsy appearance of a calf with *Mycoplasma bovis* related arthritis.

Figure 1: Calf from which *Mycoplasma bovis* was cultured from the joints.

Figure 2: Opened carpus joint of the calf in Figure 2 from which *Mycoplasma bovis* was cultured.



Most of us would agree that this calf was beyond the benefit of modern chemistry. However, what would be an appropriate therapeutic approach for cattle in an earlier stage? One of the problems we face is that *M. bovis* may have an immunosuppressive effect. Experimental inoculation of M. bovis has resulted in suppression of both cell-mediated and humoral immune responses.[ii]

Anti-inflammatory therapy would appear to be indicated, although trying that on a calf in the stage of the one in Figures 1 and 2 would likely be futile unless continued for several weeks. The biggest question is usually what antimicrobials are a good choice for cattle in early stages of joint disease, and what are good choices for therapy of bovine respiratory disease (BRD) if we want to suppress development of *M. bovis* during therapy.

Published antibiotic susceptibility testing data for *M. bovis* must be interpreted with caution due to the lack of standardized techniques or interpretive criteria. However, some general guidance may be obtained by evaluating results for drugs where the minimum inhibitory concentration (MIC) for *M. bovis* approximates the MIC of respiratory pathogens for which clinical efficacy has been demonstrated.[iii,iv,v,vi] These data indicate that oxytetracycline, spectinomycin, florfenicol, and tulathromycin may be appropriate selections for primary *M. bovis* disease. Enrofloxacin and danofloxacin (fluoroquinolones) may also be appropriate choices in cases where *M. bovis* involvement is suspected in respiratory disease due to the primary bovine respiratory pathogens. Any antibiotic used for therapy of primary *M. bovis* disease is being used in an extralabel manner and a valid VCPR is required. Extralabel use of

fluoroquinolones is illegal in food animals in the United States. Therefore, if you use fluoroquinolones (enrofloxacin and danofloxacin) for anything other than bovine respiratory disease in the species indicated on the label, you are breaking the law. This includes the use of fluoroquinolones for diarrhea or scours.

In the author's opinion, one of the most important factors in *M. bovis*-related disease response is duration of therapy. Injectable oxytetracycline therapy may need to be continued for 9-10 days total duration of therapy to give an arthritic animal a chance at recovery. It is recognized that animals in advanced stages of *M. bovis* arthritis have a limited chance of recovery.

A challenge in determining the true contribution of *M. bovis* to bovine respiratory disease is the interpretation of pathogen isolation from chronic cases. We also await clinical data to confirm that any of the available *M. bovis* vaccines are effective.

Therapy of Bovine Respiratory Disease

We have several major decision points in the application of drugs for respiratory disease.

(1) Will we treat the entire group with an antibiotic at the point of origin, on arrival, or in the case of a severe disease outbreak, in the first few weeks after arrival?
(2) What will be the antibiotic for initial therapy of respiratory disease?
(3) What will be the antibiotic for therapy of animals that have not responded to the initial therapy?

Treatment of the entire group for control of respiratory disease.

Antimicrobials labeled for controlling respiratory disease by treating the entire group include tilmicosin (**Micotil**®, Elanco Animal Health), 300 mg/ml oxytetracycline (**Tetradure**®, Merial), ceftiofur crystalline free acid (**Excede**™, Pfizer Animal Health), florfenicol (**Nuflor**®, Schering-Plough Animal Health Corporation), and tulathromycin (**Draxxin**®, Pfizer Animal Health). The time from administration to when you should start treating cattle exhibiting signs of respiratory disease is a critical discussion to have with your veterinarian.

Some producers have tried having the control drug administered at the point of purchase in an attempt to get a jump on the disease progression. Work on comparing this approach to administration on arrival has been done with Micotil.

McClary and Vogel have reviewed some of the metaphylaxis timing literature as well as contributing new data.[vii] They cite one article with equal results between administering tilmicosin phosphate (**Micotil**®, Elanco Animal Health) at the

auction barn and at feedlot arrival.[viii] A second cited study found that administration at arrival significantly reduced respiratory morbidity compared to administration at the auction barn.[ix] Performance was not different between treatment groups in either of these studies. McClary and Vogel's study found that administration on arrival significantly reduced respiratory morbidity as compared to administration at the point of origin and negative controls. (Respiratory morbidity for negative controls, metaphylaxis at the point of origin, and metaphylaxis upon arrival was 54%, 29%, and 15% respectively.) Metaphylaxis at the point of origin was also significantly different from the negative controls. These studies would suggest that metaphylaxis prior to shipment to the feeding facility gives no advantage at best, and more likely decreases the benefit of metaphylaxis. The difference would likely vary depending on how advanced the calves were in respiratory disease incubation at the time of shipment.

What about not applying metaphylaxis immediately upon arrival? Klemesrud, et al examined administering tilmicosin on arrival vs. 6 days after arrival.[x] In the group of cattle in the study, the on-arrival and day 6 treatments resulted in essentially identical improvements in morbidity as compared to negative controls. While these results may vary with group of cattle, the paper does support the approach that metaphylaxis may be applied later in the feeding period with good results, especially if the start of a respiratory disease outbreak would indicate the need for metaphylaxis in the first few weeks. Maybe you can wait on some borderline groups and catch them later if they need it.

Oxytetracycline or chlortetracycline in the feed at 10 mg/lb per day may appear as an attractive and economical shortcut to administering a control drug by injection. Keep in mind that concentrations of oxytetracycline and chlortetracycline in the serum after feed administration at this dose are approximately 1/6 to 1/8 that of administering a label dose of a 200 mg/ml long-acting oxytetracycline product. These low concentrations may be effective at suppressing the growth of pathogens in cattle that are incubating respiratory disease. However, cattle already in advanced stages of disease, severely compromised due to stress, or with a large/combined disease challenge may not be able to provide enough immune system help for the drug to be successful. Veterinarians and stocker operators have to work together to decide if and when to go to feed vs. injectable control strategies.

Initial respiratory disease therapy

Somewhere, somehow, it got started that we must use 2 or even 3 antibiotics together to achieve acceptable results. This concept is located in the same chapter of the farm book of knowledge as the following gems.

> When you castrate a horse, throw the testicles over his head to make him fast and behind him if you want him to be a nice, slow kid’s horse.

A snake or turtle on the road means it is going to rain.

There are no studies to support the use of multiple antibiotics vs. one antibiotic in bovine respiratory disease. Searches for synergistic combinations in the laboratory have shown that the antimicrobial interactions vary by genus, species, and even individual isolate of the pathogen. One thing we most certainly achieve with an antibiotic combination is increased cost.

The concept of antibiotic combinations probably originated from the same situations that lead to stories of how one antibiotic is worthless and another is liquid gold. When you receive high-risk or stale cattle, many of the cattle are already in advanced stages of respiratory disease incubation or are clinically ill. The case-fatality rate (number that die divided by number treated) on these calves will be higher than ones that incubate the disease at your facility and are detected early in the process. So, the drug you start out with is working against some really tough cases. Once death loss and poor treatment response is detected (usually 4-5 days into the outbreak), a new drug is selected out of frustration. The new drug is used on cattle that are essentially an entirely new population of animals. They are in the early stages of disease, so results get much better. This same flawed comparison happens when we compare the response of different drugs on different groups of cattle.

The drug chosen for initial therapy may vary depending on the facilities available for treatment. There are now antibiotics that have from 24 hours to 10-14 days of therapeutic duration. A veterinarian should be involved in a decision involving efficacy, cost, and the ability to follow up on cattle after each regimen. It is important that you are able to identify the animals at the end of the initial treatment regimen in order to make the success/failure decision. One of the tragedies in BRD therapy is to look at treatment histories of mortalities and see a gap between the first and second treatments. The animal entered the “lost calf” cycle and was lost during the time when continuing the therapy in a timely manner could have made a difference.

Therapy of animals that have not responded to initial respiratory disease therapy

Should you switch to a new drug for continued therapy? This really isn’t necessary if you are getting satisfactory response in the majority of cases with the drug currently being used. If this is the case, the few that are not responding (15-25% of those initially treated for respiratory disease) are likely to need additional duration of therapy instead of different therapy. Don’t hesitate to retreat with the same drug in these situations. To make this decision, it is necessary to have a good understanding of actual treatment response. This requires time invested in keeping and interpreting records.

If initial response to therapy is poor, factors to evaluate include progression of disease at the time of detection, accuracy of diagnosis, drug selection, and selection and application of preventive strategies. Too often we focus on drug selection and ignore the other components of treatment success. If all you do in response to wrecks is change antibiotics, then you are doomed to be like Sisyphus, forever rolling a rock up the mountain only to have it roll to the bottom where you start uphill again.

There are some basic truths relating to BRD therapy

- An initial case definition describing exactly how you will select animals for treatment is necessary.
- The treatment regimens must be thoroughly described (dose, route, duration, frequency, slaughter withdrawal, injection site, and volume per site).
- A case definition for success or failure must be defined.
- Second and third treatment regimens must be described in a similar manner.
- You must keep the treatment regimens consistent enough to evaluate them.

Salmonella

Salmonella species will likely be our first untreatable bacterial infection in cattle since the beginning of the antimicrobial age for agriculture in the late 1940s. An example is *Salmonella newport*, which in diagnostic lab isolates displays a susceptibility profile indicating potential therapeutic response for only 3 antimicrobials. One of these is illegal for extralabel use in food animals (and is not labeled for Salmonella), one will result in kidney residues up to 18 months, and one is banned for extralabel use in lactating dairy cows. In the United States, we do not have a form of the latter drug, a potentiated sulfa, which allows practical use in feedlot cattle. *Salmonella typhimurium* often has more optimistic susceptibility testing results, but not by much.

Prevention of Salmonella in a hutch or feedlot setting centers on reasonable biosecurity practices. Transmission of Salmonella by oral instruments has been confirmed, including the growth of Salmonella on oral instruments (speculums, balling guns) kept in a bucket of dilute chlorhexidine solution. Therefore, anything going in the mouth of calves must be thoroughly cleaned and preferably sterilized between animals. This author remains to be convinced of the necessity for inclusion of any orally administered drugs in a feedlot hospital protocol.

One thing that makes no sense at all is the administration of an oral tetracycline or sulfa in feed or milk replacer in the face of an outbreak of *Salmonella* or *E. coli* species that are resistant to these antibiotics. All that is being accomplished is

the suppression of bacteria that might compete with, and therefore hamper the proliferation of the pathogen. It is important that a veterinarian be involved early in a suspected Salmonella outbreak, that necropsies are performed, and that appropriate samples are submitted for culture and susceptibility testing. The susceptibility results are not well correlated to the potential for clinical response, but antibiotics to which the drug displays very high minimal inhibitory concentrations (MICs) should not be used in attempted therapy and should be removed from uses that result in routine exposure of the normal flora of the animal to the antibiotic.

The main points in a checklist for prevention and therapy of Salmonella in feeding situations include the following.

- In an environment with significant Salmonella infectious pressure, don't utilize antimicrobials for routine prevention or for therapy to which the Salmonella has demonstrated resistance.
- Utilize culture and susceptibility testing to routinely characterize the pathogen and adjust attempts at therapy accordingly.
- Work with your veterinarian to evaluate preventive measures, including biosecurity and vaccination options.
- If you use antibiotics as a routine Salmonella prevention measure, be prepared to not have that option in the future due to resistance development. Perhaps is would be best to try other methods of prevention and reserve effective treatment options for affected animals.

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