Reasonable Expectations of Antimicrobial Efficacy in Cattle Expressed as Number Needed to Treat (NNT)

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Use of the Number Needed to Treat (NNT) statistic allows for evaluation and communication of reasonable treatment outcome expectations in populations. The NNT value for a treatment estimates the number of animals which need to be treated in order to make an outcome difference in one animal. Evaluation of negative control studies for bovine respiratory disease suggests that the NNT values in high-risk calves for creating a treatment success, prevention of a mortality, and prevention of a clinical case through treatment for control of BRD are 2, 7, and 5, respectively. These values will obviously vary significantly in different clinical situations, but give reasonable expectations for the use of multiple antimicrobials in different groups of cattle over time. NNT values are also presented for digital dermatitis (1-2), infectious pododermatitis (2), infectious keratoconjunctivitis (3), and mastitis (5). These values may vary dramatically based on case parameters and treatment regimen, and should also be interpreted in light of the case definitions.

Introduction

The pinnacle of the evidence scale is the randomized, masked, negative control, naturally occurring disease trial conducted in an environment with external validity for feedlot practice. The inclusion of a negative control allows separation of the true drug effect, as opposed to just reviewing clinical response data. The reason is that with few exceptions, the trials meeting these requirements I have reviewed contain animals that (1) respond without treatment in the control group, (2) display disease resolution in the treated group beyond what was displayed in the control group, and (3) animals that do not display disease resolution in the treated group. Therefore, we have some disease resolution in the untreated control group, and some failure to resolve the disease in the treated group.

Granted, these studies do not take into account the potential improved production performance of the successful cases in the treated group as opposed to the successful cases in the control group, but some type of clinical response is the basis for your clinical experience as far as drug effect, correct? In feedlot practice it is typical to treatment outcomes and to use these data to constantly monitor therapeutic efficacy. How much of the monitored clinical outcomes are actually due to the drug?

A good statistic for evaluating drug effects in a population is the Number Needed to Treat (NNT). This is the number of animals which need to be treated with the drug to make a clinical outcome difference in one animal. It is calculated using the Attributable Reduction in Risk (ARR). For example, in a trial where 25% of the untreated controls were classified as treatment successes, and 75% of the treated group was classified as
treatment successes, the ARR is 50% (75% – 25%). If the only two outcome options are success or failure it doesn’t matter how you subtract, the difference is the same whether for the difference in successes or the difference in failures. Figure 1 illustrates this concept.

Figure 1: ARR and NNT calculation

![ARR and NNT](image)

The NNT in this example would be 100%/50%, or 2, indicating that you need to treat 2 animals to make a difference in 1. Another way of looking at the example is that in every 4 treated animals there would be one response regardless of treatment (the 25% of untreated controls which are successes), one failure regardless of the treatment (the 25% of treated animals which were treatment failures), and 2 successes in the treated group which would have been failures in the control group (the ARR). Therefore, we made a difference in 2 out of 4, or 1 out or 2. We have to treat 2 to make a difference in 1, an NNT of 2.

NNT Analysis for Therapy and Control of Bovine Respiratory Disease

Clinical success rates in the therapy of cattle with BRD: Thirty bovine respiratory disease (BRD) therapeutic trials involving negative controls were evaluated to determine the NNT for treatment success in each study. Twenty-eight of the studies were from pivotal approval studies published in freedom of information summaries (FOIs) available from the FDA Center for Veterinary Medicine (FDA/CVM). All of the BRD references are cited in a 2013 AABP proceedings article. Additional analysis of these data have also been published in the Veterinary Clinics of North America.

Cattle in these studies were primarily high risk calves which had to meet the inclusion criteria for the studies, then were treated for BRD, followed by success/failure evaluation at the end of the post-treatment interval. The clinical success rate in the treated calves ranged from 51.0% to 92.0%. In the negative controls, the success rate ranged from 0% to 57%. Interestingly, the 0% success rate in the negative controls was in the same study as the 92% success rate in the treated animals. The NNT in the studies ranged from 1 to 8, with a median of 2; for every 2 animals treated for BRD in the overall population, one animal became a treatment success. Figure 2 displays the difference in treatment success between the negative controls and the treated cattle. It is not possible to compare one drug to another in this chart based on the difference in treatment outcome because they are separate studies with only one drug per study.

Figure 2: Treatment success rate for negative controls (bottom bar for each study) and treated cattle (top bar for each study)

In Figure 3, the difference in the clinical success rate (classified as a success and never treated again) between the successes and failures is illustrated by the center bar (green if printed in color. The left side of the center bar is set on the success rate for the negative controls, and the top of the center bar is set at the success rate for the treated cattle. This
center bar is the Attributable Reduction in Risk (ARR). It is apparent that the ARR varies in magnitude, and also where the left side is located based on spontaneous cures (or perhaps erroneous classification as diseased?) in the negative control cases.

Figure 3: BRD therapy % success with ARR bar included

Case fatality rates in the therapy of cattle with BRD: Figure 4 illustrates the comparative mortality in untreated controls and treated cattle in a subset of 24 of these 30 trials where mortality was reported.

Figure 4: Bovine respiratory disease case fatality rates in untreated controls (bottom bar for each study) and treated animals (top bar in each study).
These percent mortality rates are equivalent to case fatality rates. If you ever wondered what the case fatality rate would be in high risk calves without treatment, here it is. The mortality rates in the untreated controls ranged from 0% to 48%. The mortality rates in the treated calves ranged from 0% to 23%. The NNT ranged from 2 to 40, with a median of 7.

Figure 5 includes the ARR bars for difference in mortality rates between untreated controls and treated calves. To emphasize differences, the x axis scale is 0-60% rather than 0-100%.

**Figure 5: BRD therapy % case fatality with ARR bar included**

![BRD Therapy % Mortality](image)

Reduction in morbidity due to treatment for control of BRD at feedlot arrival: Figure 6 illustrates the reduction in clinical cases in high risk calves due to treatment for control of BRD at feedlot arrival. The antimicrobials in the 7 studies were:

- Ceftiofur crystalline free acid: 2003 FOI
- Florfenicol: 1998 FOI
- Tulathromycin: 2005 FOI
- Oxytetracycline 300 mg/ml: 2006 FOI
- Tilmicosin: 1996 FOI
- Gamithromycin: 2011 FOI
- Tildipirosin: 2012 FOI

Morbidity in the calves treated for control of BRD ranged from 3.0% to 67.0%. Morbidity in the untreated control calves ranged from 9.0% to 81.0%. The NNT in the studies ranged from 4 to 30, with a median of 5.
Figure 6: Bovine respiratory disease % morbidity in high-risk calves treated for control of bovine respiratory disease on arrival at a feedlot, as compared to negative controls.

With few exceptions, these studies are pivotal dose finding and clinical efficacy approval studies conducted under good clinical practices (GCP) guidelines and accepted in the approval process by the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM). These studies would predominantly represent high-risk calves. In my experience, the success/failure criteria used by the FDA/CVM result in a lower apparent clinical success rate than would be observed in typical feedlot practice. The mortalities have a fairly constant definition. The extrapolation of these results to low risk cattle would likely overestimate the effect of the antimicrobials due to an expected higher response rate in the untreated controls.

Ranking the efficacy of these antimicrobials based strictly on the lowest number needed to treat is inappropriate. I have concerns about comparing drugs based on separate negative-controlled clinical trials due to the potential for different factors influencing the negative control group’s success rate in each trial, and these factors having different influences on the ability of the drug to respond. These factors could include age and weight of the cattle, clinical scoring criteria and interpretation, success/failure criteria, nutritional background, pathogens (susceptibility of bacterial pathogens and involvement of viral pathogens), and weather.

We should expect that resistant pathogens would result in the treatment success, mortality, and morbidity rates displayed by the untreated control groups in these studies.
NNT Analysis for Individual Animal Therapy of Digital Dermatitis and Infectious Pododermatitis

A chapter by this author in the Veterinary Clinics of North America Food Animal Practice addressed evidence for individual animal therapy of infectious pododermatitis and digital dermatitis. The reader is directed to this publication for in-depth discussion of the references with citations.iii For infectious pododermatitis, initial cure in the studies seldom had follow up regarding the common issue of recurrence of lesions. This recurrence rate is very dependent on the time of intervention in relation to stage of disease. Figure 7 illustrates the success rate for treatment of digital dermatitis with the indicated drug. Response varied as to inclusion of lesion score, pain, or both. The NNT for treatments with a significant effect ranged from 1 to 2.

Figure 7: Treatment response for treated and untreated control dairy cows with digital dermatitis. The top bars indicate the cure rate (lesion scores and/or pain) for treated cattle; the bottom bars indicate the cure rate for untreated controls.

Figure 8: Treatment response infectious pododermatitis in untreated controls (bottom bar for each study) and treated animals (top bar in each study).
The NNT for treatment of infectious pododermatitis ranged from 1 to 3, with a median of 2. Details of treatment regimens are available in the cited reference. References include both pivotal approval studies from FOIs and data from published studies.

NNT Analysis for Individual Animal Therapy of Infectious Keratoconjunctivitis

For a detailed discussion of evidence related to treatment of bovine infectious keratoconjunctivitis, the reader is referred to a recent article by Angelos in the Veterinary Clinics of North America. The summary presented in Figure 9 relates to 9 studies concerning the drugs listed in the figure. There are two available studies for procaine penicillin G which are not included in the illustration due to the results being in days to ulcer healing for each treatment rather than defining a success or failure (usually ulcer resolution) at approximately days 10-16. Neither of these studies demonstrated an effect for subpalpebral procaine penicillin G, but the addition of dexamethasone to the injection did numerically extend the time to ulcer healing.

Figure 9: Treatment response for treatment of infectious keratoconjunctivitis in untreated controls (bottom bar for each study) and treated animals (top bar in each study).

The treatment success rate in the untreated controls and treated cattle ranged from 20% to 100%, and 82.6% to 100%, respectively. The NNT ranged from 2 to 8, with a median of 3.

NNT Analysis for Therapy of Bovine Mastitis

An analysis of efficacy of antimicrobial therapy for bovine mastitis has recently been published in the Veterinary Clinics of North America by Royster and Wagner. The reader is referred to this article for discussion of the references for this chart in the
context of the chapter. A summary of treatment results for 12 studies is presented in Figure 10.

**Figure 10: Treatment response for treatment of infectious mastitis in untreated controls (bottom bar for each study) and treated animals (top bar in each study).**

The NNT values ranged from 1 to 10, with a median of 5. As for all of these data, the reader is directed to the original references for details on treatment protocols, isolated pathogens, and case definitions for both inclusion in the study and success or failure.

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