Evaluating the Effects of Drugs Using Number Needed to Treat (NNT)

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Part1. Understanding Number Needed to Treat

How do we determine the real effects of treatments on disease outcomes? We undertake drug therapy to treat disease because we have the idea that the drug treatment will improve the outcome of the disease process in some, most, or all of the patients we treat. Oftentimes, this is true; the patient has a better outcome with drug therapy than they would have had without it. However, often some patients would have recovered without drug treatment. We can determine how many cases were truly affected by drug treatment, relative to the number that would have recovered anyway, using the concept of "Number Needed to Treat" (NNT).

NNT is usually calculated using the outcomes of randomized controlled clinical trials of naturally occurring diseases. The number need to treat is the number of patients that must be given a particular treatment in order to prevent one additional bad outcome. The NNT is related to the Absolute Risk Reduction, or how much the treatment reduces the risk of a bad outcome. So, let's say that we have an amazing disease treatment; with treatment, 90% of patients get better, while without treatment, only 10% recover. The Absolute Risk Reduction is 90%-10% = 80% or .80. (If there are only 2 outcomes under consideration, the calculated difference between good outcome rate and bad outcome rate will be the same.) The NNT is the inverse of the ARR: 1/ARR = NNT. In this example of an extremely effective drug, the NNT is 1/.80 = 1.25. So for every 1.25 people treated, 1 person would improve when they would not have improved without treatment. We can increase this to whole numbers and say that with the drug, you need to treat 5 people in order to cause 4 of them to improve *because of the treatment* (they otherwise would not have improved). Another way to look at it is this: if we treat 10 patients with this drug, 1 will do poorly regardless of treatment (the 10% treatment failures) one will do well but would have done so anyway (the 10% good outcomes in untreated controls), and 8 will get better with treatment when they would not have got better without it. That is an effective drug! To recap our calculations:

NNT = 1/ARR ARR = Absolute Risk Reduction

ARR = CER-EER CER =Control Event Rate, EER= Experimental Event Rate

Event Rate = percentage that had a particular outcome of interest.

The You Tube video "How to Calculate the Number Needed to Treat" by Terry Shaneyfelt provides a clear step-by-step explanation of this calculation.

Part 2. Bovine Respiratory Disease in Feedlots

Now let's talk about some real veterinary examples using NNT. In 2013, Apley and DeDonder published a review of NNT values for drugs used to treat Bovine Respiratory Disease (BRD) in feedlot cattle. They reviewed randomized controlled clinical trials of antibiotic drug treatment of naturally occurring BRD in feedlots, in which the control group was not treated. Among 30 trials of 8 different drugs, the NNT to produce one additional "treatment success" (good clinical outcome) ranged from 1 to 8, with a median value of 2. In 24 of the trials, mortality rate was also reported, and the NNT to prevent an additional case mortality ranged from 2 to 40, with a median value of 7. For the prevention of BRD in 12 clinical trials, the median NNT to treat was 5, meaning that for every 5 calves treated with preventive antibiotic drugs, 1 case of BRD was prevented. One might question whether this practice constitutes good antimicrobial stewardship, when 4 of the 5 calves would not have developed BRD regardless. In this review article, the caveat is provided that many of these clinical trials were done on high-risk calves, so the clinical success rate might be lower in these studies than would be expected in calves at lower risk.

Part 3. Mastitis

In 2021, Dr. Pamela Ruegg authored a review of antibiotic treatment of mastitis in dairy cows. In that article, she makes a statement directly related to the concept of NNT: "Use of antimicrobial therapy is most beneficial for cases that are caused by pathogens that have a low rate of spontaneous cure but high rate of therapeutic cure". This defines a combination of pathogen, clinical disease and antibiotic drug that would have a low NNT; the ratio of the number animals treated to the number of good outcomes due to treatment would be low. It also defines good antimicrobial drug stewardship, retaining antibiotic drugs for use in cases in which they are most likely to affect the outcome. Clinical trials of mastitis therapy with untreated controls are uncommon; Ruegg reports only 6 in her review, compared to 20 positively-controlled studies. Among the 6 negatively-controlled studies, in 2 the treatment is enrofloxacin, with is prohibited for extralabel use in lactating dairy cows in the US.

Two of the mastitis treatment studies reported by Ruegg in her review reflect investigation into practices that may decrease the overall use of antibiotic drugs in dairy cows, with the hope that wellness and welfare will be preserved. Fuenzalida and Ruegg (2019b) investigated the use of intramammary ceftiofur (2-day and 8-day treatment regimens) compared to not treating cows with mild or moderate clinical mastitis caused by gram-negative pathogens. Fifty-six cows were enrolled in each treatment group. Clinical status was followed for 90 days after treatment, or until the end of lactation, and repeat milk cultures were performed weekly for 28 days after diagnosis ± treatment. The risk of recurrence of clinical mastitis in cows with gram-negative pathogens was the same for the 3 three treatment groups (32% for untreated and 8-day treatment, 34% for 2-day treatment). The bacterial cure rate was the same in all groups for cows with mastitis due to *E. coli*. For cows with mastitis due to *Klebsiella*, bacterial cure rate was 18% in the untreated group and 74% in drug-treated cows

(combined 2-day and 8-day groups). For cows with mild or moderate mastitis caused by *E. coli*, the NNT to improve clinical and bacterial outcomes, according to the outcomes of this study, is basically infinite, since treatment and no treatment had the same rate of clinical and bacterial cure. For cows with mild or moderate mastitis due to *Klebsiella*, the NNT to achieve an additional bacterial cure was 1/(74%-18%) = 2 (1.78). Based on the results of this study, the benefit of antibiotic drug treatment in cows with mild to moderate mastitis due to *E.coli* is inapparent, while the treatment of 2 cows with the same clinical condition due to *Klebsiella* will affect one additional bacterial cure. Unfortunately, differentiation of the two pathogens using on-farm culture is not yet reliable.

The same pair of investigators also compared a 5-day course of intramammary ceftiofur and no treatment for cows with mild or moderate mastitis and a negative bacterial culture in 121 quarters (Fuenzalida and Ruegg, 2019b). The cows were observed for clinical status for 90 days or until the end of lactation, and milk cultures of the affected quarter were performed 14 and 28 days after the initial diagnosis. They calculated that 8 mastitic quarters that were negative on initial culture would require intramammary drug treatment to prevent 1 case of intramammary infection on a subsequent culture, and that 20 culture-negative mastitic quarters would require intramammary drug treatment to prevent 1 treatment failure (need for an additional drug treatment). In that study, cows in the drug treatment group were more likely to have a recurrence of clinical mastitis than were cows in the untreated control group.

Part 4. Lameness

NNT can also be applied to therapies other than antimicrobial drugs. For example, a randomized controlled clinical trial was performed to evaluate various treatments for claw horn disruption lesions (sole ulcer, sole hemorrhage, white line disease) in lame dairy cows (Thomas et al, 2015). A cure was defined as normal locomotion 35 days after treatment. Among cows that were treated only with therapeutic trimming, the cure rate was 24.4%, while in cows treated with therapeutic trimming plus a block to elevate the affected claw plus administration of a 3-day course of the non-steroidal anti-inflammatory drug ketoprofen, the cure rate was 56.1%. In this case, the NNT can be calculated for the addition of the block and drug to the therapeutic trim as 1/(56.1-24.4%) = 3.15. For every 3 cows that are treated with a block and an NSAID drug in addition to a therapeutic trim, there will be one additional cure.

Part 5. Summary

Number needed to treat is easy to calculate and provides a different and intuitive way to understand the efficacy of therapies for disease. This value can be useful for making decisions about strategies for the reduction of antimicrobial drug use in the interest of good

stewardship. It can also be a useful tool for making and recommending (or not recommending) treatment protocols in a production setting, based on disease-related and financial criteria.

Note: For FDA approved veterinary drugs, Freedom of Information Act summaries of the drug approval process often contain the information necessary to calculate NNT for the drug. These summaries can be found by searching the FDA "Green Book" using the trade or generic name of the drug, here: https://animaldrugsatfda.fda.gov/adafda/views/#/search (Accessed June 9, 2021)

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