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How Much Evidence is there for the Most Effective Treatments for Common Calf Diseases?

The dairy industry economy has been bad like the world economy recently. However, 96% of the US population, a proportion that has held steady for many years, says they consume meat and other animal derived food. There is some evidence that only about 2% of people in the US really do not consume meat at all. That means the dairy industry is not only a relatively steady business, but is performing a vital service for just about all of us – feeding us. At least it does not appear that the industry will seriously crash and have a major drop in demand for our major products, milk and meat. Over time, just about everyone wants and needs them on a regular basis.

A dairy producer told me years ago that two of the best things for a dairy farm are to have a lot of pregnant heifers and a lot of healthy heifer calves. Certainly the birth of any calf represents the start of a new lactation curve and the creation of new wealth (sometimes we wish the amount of wealth was higher). Raising a heifer calf to have at least one calf of her own and complete at least one lactation is critically important to at least maintain herd size - of course we want more than that, but it points out how important the loss of any heifer calf is. We not only lose her, we lose the lactations and the other replacements she might have produced. Calf mortality remains high in the US, averaging 9.6% of heifer calves alive at 48 hours old, but not surviving to have a calf. 11.1% of 48 hour old heifer calves die in herds milking 100-500 cows, a number that has held true for years. In my experience, many dairy producers do not know the percentage of calves that die in their herd per year. However, they often have sufficient records to calculate it. If you review your clients' records of how many heifer calves were born in the last year, in another place you can usually find the number that died, calculate the percent mortality, and it can often reveal more problems with calf death than they have perceived.

We know that husbandry, sanitation and prevention are critical to control of calf disease, but this article does not address that. The scope here will be treatment of clinical signs of dairy calf disease.

Most dairy farms still raise all of their own heifer calves

88% of dairy heifers, on 97% of dairy farms, are raised on the operation where they are born and will be milked, according to the NAHMS Dairy 2007 report. Almost all of our dairy clients are raising their heifer calves as well as running a lactating and dry cow facility, and often raising a lot of feed crops.

How common is a specific diagnosis of what killed a dairy calf?

92% of dairy farms in the US do not perform any necropsies to determine cause of death of heifer calves, again according to NAHMS 2007. On the 8% of farms doing any necropsies, 96% of their individual heifer calf deaths are not necropsied. This does not mean that no other diagnostic testing was done, such as fecal sample testing. I could find no data on the percentage of calf deaths having diagnostic testing in some way, but it seems quite clear that most farms are not doing any laboratory testing of what kills heifer calves, and the vast majority of all heifer calf deaths are not tested for specific cause. Most commonly, people on the dairy farm deal with calf disease on the basis of either managing or treating common clinical signs, diarrhea and/or respiratory disease. This is no surprise to anyone who has had much to do with the raising of dairy calves.

What percentage of dairy calves have diarrhea, respiratory disease, or other diseases?

According to the NAHMS Dairy 2007 report, the percentage of all dairy calves with the following clinical signs of disease were:

Diarrhea/digestive problem   24%
Respiratory disease   12%
Navel infection   2%
(No other category was very common)

When dairy calves contract the above diseases, what percentage of them die?

I calculated this, using the estimates of what fraction of all heifer calves died from each clinical complex, and dividing by the fraction of all heifer calves that contracted each one:

Diarrhea/digestive problem   23% of those affected die
Respiratory disease   18% of those affected die
Navel infection   8% of those affected die

Therefore, as we might suspect, there are two major disease complexes that not only cause most calf disease, they kill the highest proportion of calves that contract them: diarrhea and respiratory disease, respectively.

What are the most common antibiotic treatments for dairy calf diseases?

Again citing NAHMS 2007, The most commonly used antibiotics used for the clinical signs are:

Diarrhea/digestive problem (% of farms observing the disease using the treatment)
Tetracycline   **20%**
Beta-lactam/penicillin   **11%**
Sulfonamide   11%
Cephalosporin   8%
Aminoglycoside   5%
Florfenicol   5%
Aminoglycitol   3%
Macrolide   3%
No antibiotic   21% (this could include other treatments, but not antibiotics)

Respiratory disease (% of farms observing the disease using the treatment)

Florfenicol	27%
Macrolide	23%
Beta-lactam/penicillin	**18%**
Tetracycline	**13%**
Cephalosporin	13%
Sulfonamide	3%
Aminoglycoside	1%
No antibiotic	2% (this could include other treatments, but not antibiotics)

Navel infection (% of farms observing the disease using the treatment)

Beta-lactam/penicillin	**64%**
Cephalosporin	7%
Tetracycline	**4%**
Florfenicol	3%
Sulfonamide	3%
Macrolide	2%
No antibiotic	8% (this could include other treatments, but not antibiotics)

(The percentage of actual sick heifer calves treated with each antibiotic [rather than percent of farms using it] is similar; that data is on page 130 of the NAHMS Dairy 2007 report, Part III).

It can be seen from the results that despite much published evidence (and stated opinions by veterinarians in lecture notes, online courses, etc.) that antibiotics often do not work well in cases of calf diarrhea, the majority of cases of calf diarrhea and nearly all cases with signs of respiratory disease are treated with antibiotics. Except for florfenicol and macrolides used against respiratory disease, beta-lactams and tetracyclines remain very commonly used antibiotics, and even in respiratory cases they are among the most commonly used antibiotics. What is the evidence, as far as clinical or other definitions, of "cure rates" for different antibiotics against calf diseases?

Efficacy of treatments for neonatal calf diarrhea

Much of the recent literature on calf diarrhea focuses on genetics of the agents or development of antimicrobial resistance. Recent data on cure rates against calf pathogens is not easy to find. A June, 2008 paper by J. Kaneene et al., J Clin Microbiol, reports on fecal samples from both healthy and sick preweaned dairy heifer calves on 8 farms. The percentage of the following fecal pathogens susceptible to tetracycline as defined by MIC testing were: *E. coli* 1.7%, *Salmonella* 21.4%, *Campylobacter* 0%; i.e. most of these calf fecal isolates (including calves with diarrhea as well as healthy calves) were resistant to tetracycline. Treatment efficacy was not studied, however.

In J Vet Med B Infect Dis Vet Public Health, June, 2000, J. Orden et al. reported from Spain. 195 *strains* of *Escherichia coli* isolated from neonatal diarrhea cases in dairy calves were tested for antimicrobial susceptibility. The authors defined resistance to each antibiotic as: very high (above 65% of *E. coli* strains) - streptomycin, tylosin and tetracycline, or high (23 - 50% of strains) - ampicillin, neomycin, kanamycin, spectinomycin, sulphadimethoxine and trimethoprim. Alternatively, some *E. coli* strains were very susceptible (89-95% of strains susceptible) - apramycin, or highly susceptible (99-100% of strains) - polymyxin B, florfenicol and nitrofurazone. 68% of the *E. coli* strains were resistant to at least four antibiotics. Interestingly, an article published at the same time, by D. White et al. in J Clin Microbiol, December, 2000 suggested that diarrheal *E. coli* resistance to florfenicol in the US as opposed to Spain had already increased dramatically by 2000. 48 *E. coli* strains from diarrhea cases of calves less than 2 weeks old were tested. The proportion found

<u>resistant to antibiotics included: florfenicol 92%, ampicillin 88%, amoxicillin-clavulanic acid 69%, cephalothin 77%, ceftiofur 69%, tetracycline 100%, kanamycin 92%, streptomycin 100%, sulfamethoxazole 100%, trimethoprim-sulfamethoxazole 69%.</u>

The most recent information I found regarding ampicillin and calf diarrhea clinical response was from the August 22, 1987 Vet Record, by W. Grimshaw et al. In studies on more than 300 dairy calves 3 – 10 days old, mortality from diarrhea was 14.0% in cases treated with ampicillin 6.6 mg/kg IM s.i.d. compared with 26.4% in untreated controls.

A thorough review of calf diarrhea antimicrobial therapy was written by P. Constable in J Vet Intern Med, Jan-Feb 2004. He states that despite preventative measures, "improved treatment protocols for calf diarrhea are required". This article is excellent reading for a concise, interesting review of pathogenesis of calf diarrhea. Of particular interest is that studies dating from 1924 to 1987, which are no longer well publicized, show that calves with diarrhea have 5-10,000 fold increases in *E. coli* in the abomasum, duodenum, jejunum, and ileum. He thinks the key to clinical improvement and saving the life of diarrheal calves may be control of this upper GI *E. coli* invasion. The paper also says, "Unfortunately, the majority of the valuable information - - by pharmaceutical companies to support their label claim of treating calf diarrhea has not been published and is therefore unavailable for independent evaluation". In his chronological summary of studies on oral antibiotics vs. calf diarrhea, only one paper was more recent than 1977, and that was a 1998 study on two drugs not available in the US.

The review article notes that most drugs have no label claims for parenteral treatment of calf diarrhea. Nevertheless, studies on parenteral treatment were also evaluated chronologically. A 1980 study by B. Buntain et al. found that fluid therapy combined with trimethoprim-sulfa treatment did not reduce mortality from diarrhea compared with untreated controls. The only other recent study was the 1987 Grimshaw study mentioned above.

Evaluation of cryptosporidial treatments

In my experience, a major calf diarrhea that can cause common chronic problems and death of calves is cryptosporidiosis; published findings agree that it is a common cause of calf diarrhea. It has characteristic appearance and smell in many cases, and often producers and calf raisers become good at diagnosing it clinically. There is no specific antidiarrheal treatment that always seems to work, but antibiotics make it worse. A drug approved since 2002 for human cryptosporidiosis is nitazoxanide (NTZ). A new preliminary study by M. Schnyder et al., in Vet Parasitol, November, 2008 reports on its use in calves. They inoculated 9 calves 1-3 days old with *Cryptosporidium parvum*: 3 untreated controls, 3 given NTZ from 1 day before to 8 days after challenge, and 3 given NTZ for 10 days after diarrhea was seen. The use of NTZ was not associated with clinical benefit. In fact, cryptosporidial diarrhea lasted longer and feces were softer in the group treated after diarrhea appeared. In 5 of the 6 treated calves, oocyst shedding stopped only after treatment was ceased. The authors conclude that "use of NTZ in calves did not show - - positive effect on the course of *Cryptosporidium*-infection - - ".

A paper by B. Jarvie et al., in J Dy Sci, May, 2005 described halofuginone lactate (HL), a medication said to have an unknown mechanism of action, as a treatment against cryptosporidial diarrhea in 31 Holstein bull calves. The HL treated calves (10 ml P.O. for first 7 days of life) shed less *C. parvum*, and had delay in onset of diarrhea compared with controls. However, overall incidence of diarrhea during the first 4 weeks of life, necessity for sulfamethazine treatment of calves for diarrhea of any kind, and weight gain did not differ compared with control calves.

Efficacy of treatments for calf respiratory disease

Several recent studies on respiratory treatment for calves involve florfenicol. V. Aslan et al. in Vet Quarterly, February, 2002 reported on 27 calves aged 1 – 16 months old with respiratory infections in Turkey. Florfenicol 20 mg/kg IM twice 48 hr apart was given. Broncho-alveolar lavage and culture were performed. One calf died, 3 showed no healing, and 23 were healed. Florfenicol was considered effective against the most common respiratory disease causing bacteria isolated. B. Catry et al., J Vet Pharmacol Therap, October, 2008 reported on respiratory disease in 84 Holstein bull and heifer calves 14 to 90 days old. Florfenicol 40 mg/kg SQ, tilmicosin 12.5 mg/kg p.o. b.i.d. 5 days, doxycycline 12.5 mg/kg p.o. b.i.d. 5 days, or saline control SQ were each administered to randomized groups of 13-15 calves each. Nasopharyngeal swabs on all calves and lung lavages on 18 calves were tested. While not statistically significant, 11/16 treatment failures were in the florfenicol group and only 2 were in the saline control group; none of the doxycycline treated calves had treatment failure. There are several recent publications demonstrating that florfenicol resistance genes are appearing in bovine respiratory pathogens. Even a few years ago, there were no florfenicol resistance genes found in agents of bovine respiratory disease.

The macrolide antibiotic tulathromycin is a relatively new treatment for respiratory disease in calves. K. Godinho et al., Vet Therapeut, Summer, 2005 report on a study of cattle of various ages on commercial farms in Europe. Of 128 tulathromycin treated respiratory cases, 83.3% had clinical improvement 14 days later; for 125 florfenicol treated cases, 81.0% were improved 14 days later, not significantly different. The same authors, in the same journal issue had another paper studying induced *M. bovis* respiratory infections in 145 young dairy calves. Tulathromycin 2.5 mg/kg SQ was significantly more effective than saline control treatment in reducing rectal temperatures and post mortem lung lesion scores. However, I could not find published data on tulathromycin treatment of naturally occurring respiratory disease specifically in young dairy calves.

D. Francoz et al., Vet Microbiol January, 2005, reported on antimicrobial sensitivities of *Mycoplasma bovis* isolates from 51 dairy and 4 beef cattle; age was not specified.   Of 18 lung isolates, resistance to antibiotics was found in: spectinomycin 39%, tetracycline 17%, erythromycin 100%, clindamycin 22%. From 14 tracheo-bronchial isolates, resistance was: spectinomycin 50%, tetracycline 0%, erythromycin 100%, clindamycin 36%.

Conclusions

The major conclusion is that more published efficacy data is needed, especially recent data on older more established treatments for dairy calf disease. Increasing microbial resistance to antibiotics and decreased clinical efficacy over time seems apparent, but in many cases treatments have not been studied for clinical effectiveness in many years, or at least that has resulted in published information.

Most dairy farms raise their own heifer calves, more than one-third of them contract diarrhea or respiratory disease, and more than one-fifth of those die. Treatment is almost entirely based on observed clinical signs, and relies heavily on antibiotic therapy. Therefore we need more information regarding antibiotic effectiveness against calf disease.

Much of the recent data on older treatments is antimicrobial sensitivity/resistance data. Based on that, the common use of tetracyclines to treat calf diarrhea does not seem to be strongly indicated. This still leaves the major question, considering the lack of data, what treatments "should be used"? Many dairy farms today are large enough to do their own clinical trials, and some do. Veterinarians and their clients should consider randomizing calves into treatment groups, for example every third calf with diarrhea gets one of three treatments being considered. I would be glad to discuss this further with anyone interested. Outcome measures such as survival, stool firmness, days until clinically normal, etc. can be evaluated. Based upon their own farm's data, producers together with their veterinarian can make informed decisions. In my experience, this

data often contradicts perceptions people on the farm have of which treatments seem to work better. Unfortunately, the newest treatments evaluated for treatment of cryptosporidia do not appear to work well in dairy calves.

The common use of florfenicol to treat calf respiratory disease seems justified by the published data. However, resistance genes in the pathogens are increasing. The "macrolide" antibiotic category in relatively common use may reflect the macrolide tulathromycin, which many producers and veterinarians tell me they feel is effective against calf respiratory disease. The published data on tulathromycin is favorable. However, we need published data on survival and other clinical outcomes following tulathromycin treatment of young dairy calves.

Based strictly on antimicrobial sensitivity/resistance data, erythromycin and possibly spectinomycin use against calf respiratory disease may not be strongly indicated. Just as for calf diarrhea, clinical trials using randomized assignment of animals to different respiratory treatments can be conducted on dairy farms to evaluate what treatments work best on that particular farm. There is no substitute for the vet-client-patient relationship.

This article is not intended to specifically recommend or not recommend any particular commercial product/trade name for treatment of calf disease, but only to summarize the published literature on this subject.

As always, I like to hear from our readers, including suggestions for future topics. I can be reached at (435) 797-1899 M-W, (435) 797-7120 Th-F or David.Wilson@usu.edu.

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