

EXTRALABEL MASTITIS THERAPY: WHAT DOES IT MEAN?

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Summary

Extra-label drug use (ELDU) is needed to provide optimal therapy for ill dairy cattle. Proper ELDU requires cooperation and compliance between the veterinarian and producer to ensure that proper drug withdrawal times are observed.

(Key Words: Regulations, Mastitis, Therapy.)

A Severe Case of Clinical Mastitis

This case is presented as a “real-life” situation in which the suitability and legality of therapy will follow. On August 21, a 6-year-old 1400 lb Holstein cow 109 days in milk is presented with a temperature of 101.8°F, a heart rate of 92, a respiratory rate of 32, adequate rumen contractions, and a noticeably swollen but not hard quarter. She is 7-9% dehydrated, depressed, not eating, and not ketotic. Upon exam of her milk from the affected quarter, there are many clots in the watery secretion. There are no other abnormalities present. The first step in managing this cow would be to assess her severity level, which could easily be severe based on her elevated heart rate and her dehydration. The next step would be to approach the management of this case with FANO (Fluids, Antibiotics, Non-steroidal anti-inflammatory, and Other). The cow is 7-9% dehydrated but still standing and the rumen contractions seem normal. Administer 2 liters of 7% hypertonic saline followed by at least 12 gallons of oral fluids spiked with regular salt and diet salt. Because

around 30% of cows with severe mastitis develop bacteria in the bloodstream, use a good broad-spectrum antibiotic (Naxcel®). Then collect a milk sample for culture and treat intramammary (IMM) based on the results of the culture the following day. Administer 15 ml of an anti-inflammatory drug (Banamine®) intramuscularly (i.m.) and oral and subcutaneous calcium.

The following day *E. coli* grows as a lawn (colonies too numerous to count) on blood agar. The cow is re-evaluated the following morning and her temperature is now 104, pulse 94, respiratory rate 38, her rumen motility is still okay and she does not appear dehydrated. Continue the Naxcel at the labeled dose and repeat the Banamine. Treat her intramammary infusion with 6 ml of ceftiofur HCl (Excenel®) twice daily for 3 days. Fluids were repeated on days 3 and 4. Banamine was repeated on day 3. Intramuscular Naxcel was continued through day 5.

Was My Clinical Mastitis Therapy Legal?

Neither Naxcel nor Excenel have a label claim for treatment of clinical mastitis. Is there any antibiotic approved for clinical mastitis or bacteria in the blood for treatment in lactating dairy cows? No, but how would you find this information?

- Go to the website:
<http://www.fda.gov/cvm/>
- Click on “Greenbook”
- Click on “FDA Approved Animal Drug Products On-Line Database System”

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- Click on “Approved Animal Drug Products (Advanced)”
- Type in the generic name of an antimicrobial and refine the search by adding a descriptor (e.g., amoxicillin and cattle). You could also enter mastitis.
- For this example:

| <u>Field</u> | <u>Search Term</u> | <u>Records</u> |
|--------------|------------------------|----------------|
| All Fields | amoxicillin and cattle | 4 |

- Now click on display records.

The only systemic use antibiotics with label indications for lactating dairy cattle are amoxicillin, ampicillin, ceftiofur, erythromycin, oxytetracycline, penicillin, and sulfadimethoxine. None have label indications for clinical mastitis or bacteremia. Therefore, systemic antimicrobial therapy for treatment of clinical mastitis or bacteremia is extralabel. Was it an acceptable ELDU?

Extralabel Drug Use (ELDU)

- ELDU is not permitted if a drug exists that is labeled for the food animal species and contains the needed ingredient, in the proper dosage form, labeled for the indication, and is clinically effective. Okay here.
- ELDU is permitted only by or under the supervision of a veterinarian. Okay here.
- ELDU is allowed only for FDA approved animal and human drugs. Okay here.
- ELDU is permitted for therapeutic purposes only when an animal’s health is suffering or threatened. Okay here.
- ELDU is not permitted if it results in a violative food residue, or any residue that may present a risk to public health. Okay here.
- ELDU requires scientifically based drug withdrawal times to ensure food safety. Okay here.

An American Veterinary Medical Association (AVMA) ELDU algorithm has been developed to help with these decisions:

<http://www.avma.org/scienact/amduca/amduca1.asp>

One has a diagnosis of severe clinical mastitis made in the presence of a valid veterinary/client/patient relationship. When contemplating extra-label drug use for systemic antimicrobial therapy, one must ask:

1. Are the animals to be treated lactating dairy cows (food animals)? Yes or No.
Yes, this is a food animal.
2. Does a lactating dairy cow (food animal) labeled drug exist that fulfills all of the following? Yes or No.
 - contains the needed ingredient
 - in the proper dosage form
 - labeled for the indication
 - clinically effective
 No, a labeled drug does not exist.
3. Is there a lactating dairy cow (food animal) approved drug which could be used extra-label? Yes or No.
Yes, an approved drug can be used extra-label.
 - Proceed with Extra-label use of food animal drug.
 - Establish extended withdrawal time.
 - Ensure food safety.
 - Maintain required records.
 - Label drug appropriately.

Extralabel antimicrobial therapy must be prescribed only in accordance with the Animal Medicinal Drug Use Clarification Act amendments to the Food, Drug, and Cosmetic Act and its regulations (21 CFR Part 530). No drug can be marketed unless its quality, safety, and efficacy have been demonstrated. Thus, the first choice should be based on the products approved for the species and the indication concerned. When no suitable product is approved for a specific condition or species, or the approved product is considered to be clinically ineffective, the choice of an alternative product should be based, when possible, on the results of valid scientific studies and a proven efficacy for the condition and species concerned (www.fda.gov/cvm/index/fdvet/2000/septvet.htm). Based on ELDU guidelines and the algorithm, antimicrobials not labeled for lactating dairy cattle but still legal for use in cattle would be okay to use. However, it would seem prudent to use products that are approved for lactating dairy cattle as the

meat and milk withdrawal times have been scientifically validated.

When no approved drug is available or when higher-than-approved dosages of approved drugs are needed, veterinarians must use their professional judgment regarding the benefits and risks to sick animals associated with extra-label use of drugs. Extra-label use for analgesic purposes is common because few animal-specific drugs have been approved for the relief of pain and suffering. Was use of Banamine extralabel and if so was its use appropriate? The answers to this are yes and yes. Anti-inflammatory drugs are often used to treat cases of clinical mastitis and none have a label claim specific for mastitis. However, our purpose in administering these drugs is to decrease fever, swelling, inflammation, and combat endotoxin. Based on reasons and listed indications in Table 1, Banamine is an acceptable ELDU.

In the U.S., the only intramammary antibiotic labeled for clinical mastitis is pirlimycin, which that has proven efficacy against staphylococcus and streptococcus species. Indications for some of the other intramammary antibiotics imply clinical mastitis therapy but use words such as acute or chronic mastitis or administer at first signs of inflammation or any alteration in the milk. So was the use of intramammary ceftiofur HCL extralabel? Yes. But the use of intramammary ceftiofur HCL appears to be an appropriate ELDU because no approved and proven effective products for severe clinical coliform mastitis exist. But let's go a step further. Are there other requirements?

One of the provisions the AVMA persuaded the Center for Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA) to include in its regulations allows extralabel use when an approved drug is judged to be clinically ineffective for its intended use. But what about ampicillin (Hetacin K) that has the only approved

intramammary label claim against *E. coli*. I could not find a single study published in a peer-reviewed journal that reported on the efficacy of intramammary ampicillin (as the sole treatment) for clinical mastitis. Ampicillin in combination with other antibiotics has been reported to be inferior to other intramammary preparations. However, when the ampicillin and cloxacillin preparation was compared only to itself with no controls, the results looked a lot better. When the same ampicillin/cloxacillin preparation was compared to either parenteral cefquinome therapy, with or without intramammary cefquinome (cures of 82.6 to 95.2%), against experimentally induced *E. coli*, results indicated that the ampicillin product (cures of 54.5%) was significantly inferior. This study supports the lack of efficacy of ampicillin and cloxacillin in the treatment of clinical coliform mastitis in dairy cows.

So what criteria must a practitioner use to justify extralabel use in a situation where the [approved] drug is ineffective? There is nothing in the regulations to guide veterinarians in making this assessment. FDA recognizes that it is the professional judgment of a veterinarian to make that determination. Veterinarians aren't required to state their criteria as to why they thought the drug was ineffective but economics should not be used as justification of ELDU. So is the extralabel intramammary use of ceftiofur effective for severe clinical *E. coli* mastitis? Yes, it is. Figure 1 indicates the daily colony forming units (cfu) for the case presented. The first two data points were prior to any intramammary ceftiofur. The third data point was after the first treatment and although it appears there was no effect on the cfu, cfu decreased. The cow was treated once on day 2, twice on day 3, twice on day 4 and once more on day 5. Only the case cow is presented here but this figure represents a typical cfu response of cows with coliform mastitis treated with intramammary ceftiofur.

Table 1. Anti-Inflammatory Drugs*

| Drug | Approved Lactating | Indication | Milk Withdraw | Meat Withdraw |
|--------------------|--------------------------|--|---------------|---------------|
| Aspirin | No official FDA approval | Fever reduction | 1 d suggested | 1 d suggested |
| Dexamethasone | Yes | Ketosis, inflammation | 0 | 0 |
| Predef 2X | Yes | Ketosis, inflammation | 0 | 7 d |
| Flunixin meglumine | No | Pyrexia, endotoxemia, inflammation | 4 d | 4 d |
| Phenylbutazone | No | Inflammation of the musculoskeleton | 5 d | 45? d |
| Dipyrrone | No | Prohibited | | |
| Ketoprofen | No | Inflammation and pain of the musculoskeleton | 1 d | 7 d |

*A selected reference for extralabel use of nonsteroidal anti-inflammatory drugs can be found in JAVMA 1997 Vol. 211, No. 7, pgs 860-861.

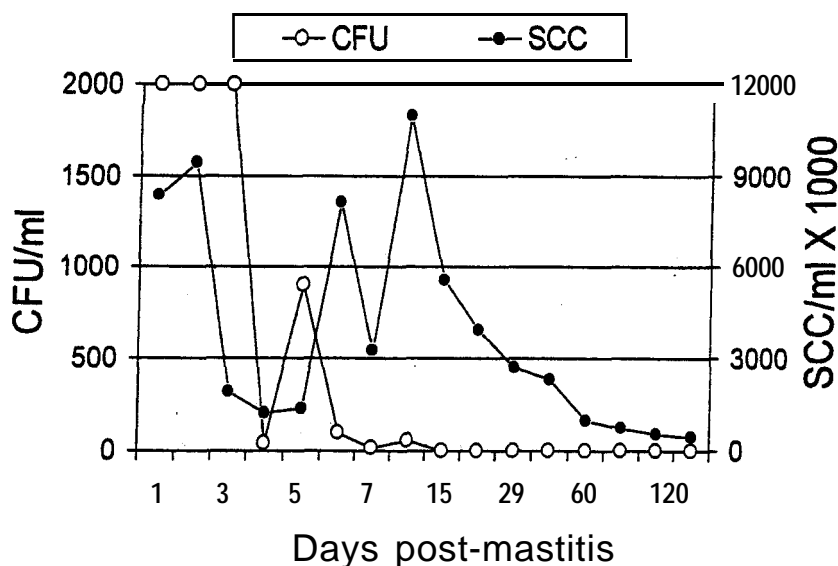


Figure 1. Colony-Forming Units and Somatic Cell Count by Days Post-Mastitis for a Case of Severe Clinical *E. coli* Mastitis.