A guide to antimicrobial options for common small ruminant diseases

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There are few antibiotics approved for use in small ruminant species in the United States. According to the Animal Medicinal Drug Use Clarification Act (AMDUCA), extralabel drug use may only be employed under the direction of a licensed veterinarian in the context of a valid veterinarian-client-patient relationship. However, with the implementation of FDA Guidance for Industry #263, producers will no longer have access to antibiotics which were previously available over the counter and could have been utilized in an extralabel manner without veterinary oversight. The aim of this discussion is to provide veterinarians with a logical approach to selecting appropriate antibiotics for use in small ruminants.

Antibiotics approved for small ruminants

There are 8 different antibiotics available for use in sheep and 3 with label claims for goats.[1] Only ceftiofur sodium is approved for use in lactating animals of either species. While these drugs should be the first options considered in the face of bacterial disease in small ruminants, clinical relevance and efficacy may dictate that their use is not appropriate and other options must be considered for effective treatment.

If an effective treatment option cannot be identified from the list of drugs labeled for small ruminants, expanding your search to drugs approved in a similar species is the ideal next step. In the case of small ruminants, drugs approved for use in other ruminant species – especially cattle – would be the most appropriate alternative.

Restricted and banned drugs

Before beginning your quest to find the perfect extralabel treatment regimen, it is important to remember that some drugs are "off the table" when it comes to food-producing species (even if the intended purpose of the individual animal is a pet). The following antibiotics are banned from extralabel drug use (ELDU) in food animals by the FDA Center for Veterinary Medicine. Because none of these products are labeled for sheep or goats, the reader should interpret this section as "banned for use in small ruminants": chloramphenicol, clenbuterol, diethylstilbestrol (DES), nitroimidazoles (including dimetridazole, ipronidazole and metronidazole), fluoroquinolones (including enrofloxacin and danofloxacin), glycopeptides (including vancomycin), and nitrofurans (including furazolidine and nitrofurazone), and dipyrone (no labeled human or animal products currently on-market).

Also consider that phenylbutazone and sulfonamide-class antibiotics are prohibited for use in female dairy cattle greater than 20 months of age. While this stipulation does not directly include dairy sheep or goats, other options for non-steroidal anti-inflammatory drugs and antibiotics with similar spectrum are available and preferable. Grade A dairy operations are also banned from using, storing, or feeding the following drugs to lactating dairy cattle: non-medical grade dimethylsulfoxide (DMSO) and colloidal silver. Avoidance of these drugs in female dairy-breed small ruminants is strongly encouraged.

A step-wise approach to selecting an extralabel therapy

Stipulations for extralabel drug use

Extralabel drug use (ELDU) refers to any deviation from the instructions on the FDA-approved label including dose, volume per injection site, route of administration, dosing interval or frequency, duration of treatment and purpose for use. Only animal or human drugs may be used in an extralabel manner, pesticides labeled for topical use do not qualify as they are regulated by the Environmental Protection Agency (EPA) and may NOT be used in any way except as described on the label. Feed additives may be used in an extralabel manner for minor species, unlike major species[2] however, this use is restricted to using a drug that is not labeled for the target species, dose and duration of administration may not change, however the recommended withdrawal time will likely be extended. Finally, ELDU may only be utilized for therapeutic purposes and drugs cannot be prescribed to increase production.[3]

Rational decision-making for conditions without any approved drugs

Choosing an appropriate antibiotic regimen for any species should be undertaken in a stepwise manner keeping certain considerations in mind:

1. **What type of drug is most likely to produce a successful outcome for the pathogen(s) in this case?** Table 1 is an adapted version of Dr. Hans Coetzee's table of antimicrobial classes compared to their efficacy against Gram-positive and Gram-negative aerobes and anaerobes.[4] Culture and sensitivity is always appropriate for assistance in directing treatment strategies. It is important to remember that sensitivity data does not directly reflect the sensitivity of pathogens in vivo and should be interpreted with consideration for the Clinical & Laboratory Standards Institute- (CLSI) established breakpoints. There are no established breakpoints in small ruminants so clinicians should understand that culture and sensitivity data for pathogens isolated from these species has been extrapolated from either human or bovine work. Consideration must also be given to route of administration as well as dose, duration and frequency of treatment when using sensitivity data to direct treatment recommendations.
2. **Consider potential adverse effects** – this should include effects on the animal as well as potential for violative drug residues. Of immediate concern regarding violative residues in food products is anaphylaxis, especially regarding penicillins. If the animal is close to market status, then a shorter withdrawal period may be a key factor in choosing between 2 drugs with similar potential efficacy. Antimicrobial resistance is also a concern as residues carry antibacterial properties that can contribute to development of resistance.

Table 1: Common bacterial classifications and antimicrobial classes acceptable for use in small ruminant species with high likelihood of susceptibility.[4]

	Aerobic	Anaerobic
Gram (+)	Penicillin G Potentiated penicillins Some cephalosporins Macrolides Phenicols Potentiated sulfonamides	Penicillin G Some cephalosporins Macrolides Phenicols Metronidazole Potentiated sulfonamides
Gram (-)	Aminoglycosides Some cephalosporins Fluoroquinolones Potentiated sulfonamides	Penicillin G Some cephalosporins Macrolides Phenicols Potentiated sulfonamides

3. **Is the dosing regimen feasible?** Changing the route of administration, dose or frequency can impact the validity of CLSI breakpoint data and therefore should alter the practitioner's expectations of clinical outcomes.
4. **What is the cost?** This should include cost of the drug and may also encompass lost income due to dumped milk, additional cost of milk- or colostrum replacer for dam-reared young, and increased feed costs due to delays in bringing animals to market.

Drug residue avoidance

Once an appropriate drug has been selected based on the microbiological context of the condition, an appropriate withdrawal period must be determined. The Food Animal Residue Avoidance Databank (FARAD) should be consulted for withdrawal recommendations each time an extralabel prescription is dispensed as new research may alter previous recommendations. FARAD responders can provide guidance for interpreting culture and sensitivity data as well as selecting a dose, route and frequency of administration. Withdrawal recommendations for on-farm protocols should be revisited routinely to ensure that clients are abiding by the most current recommendations. The USDA has a zero-tolerance policy for extralabel drug residues if there is no established tolerance in the species. This means that there must be no detectable drug in the target tissues at the time of processing. This stipulation necessitates extended estimations of withdrawal times as compared to animals with label approval and established tolerances. The moral of the story is: ELDU requires an extended withdrawal time compared to on-label use.

Lactating animals whose milk is being used for human or animal consumption should be separated from the regular milking herd and milk should be disposed of until the recommended withdrawal period has passed. Before re-entering the milking string, on-farm antibiotic residue testing can be utilized to ensure residue avoidance. The DSM Delvotest® P 5 system[a] is validated for detection ampicillin, amoxicillin, cephapirin and procaine penicillin G[5] in pasteurized and raw goat's milk.[6] This test requires 2 hours for sample incubation before results are available which may be problematic for some producers. Charm SL Beta-lactam[b] antibiotic test is approved to detect amoxicillin, ampicillin, ceftiofur, cephapirin and penicillin G in raw, commingled sheep's milk.[7]

Example cases

Case #1

Four Boer does present for respiratory disease after returning home from county fair. What drug do you reach for? Many veterinarians believe that ceftiofur sodium must be utilized to treat all respiratory disease in goats because it is the only drug with a label claim in these species. However, this drug is approved for treatment of respiratory disease caused by *Mannheimia haemolytica* and *Pasteurella multocida* and while these 2 pathogens are commonly associated with caprine respiratory disease complex, *Mycoplasma spp.* is also commonly implicated in this syndrome, especially in mature animals,[8] and likely contributes equal or greater pathogenicity than either of the other causes. Ceftiofur is not effective for treating *Mycoplasma* so utilizing the product with a label claim may not be appropriate in cases of respiratory disease in mature goats. A macrolide (such as tulathromycin) or a phenicol (such as florfenicol) may be a more appropriate treatment. Enrofloxacin or danofloxacin would not be an acceptable choice as extralabel use of fluoroquinolones is prohibited in food animals. Tilmicosin would not be inappropriate from a regulatory standpoint, but it would be a poor choice clinically as it has been known (anecdotally) to cause acute death in goats.

Case #2

You have a client with an outbreak of abortions in his breeding ewes. He has a month left before his lambing window is set to begin and wants to feed chlortetracycline for the next 30 days. This is a grey area. If the abortive agent was diagnosed as *Campylobacter* or leptospirosis, only the labeled dose can be used, however many clinicians see better efficacy with higher than labeled dosages. Finally, this treatment plan may not be microbiologically appropriate as *Campylobacter* associated with ovine abortion has largely been identified as resistant to tetracyclines but is generally susceptible to tilmicosin, florfenicol, tulathromycin, enrofloxacin and tylosin.[9]

Case #3

A client calls you to examine a ram that was attacked by dogs last night. He has extensive superficial cuts and scrapes with a deeper bite wound on the hind leg. Procaine penicillin G, ampicillin, oxytetracycline, or florfenicol would be appropriate choices in this case as they tend to have good activity against Gram-positive anaerobes like *Clostridium tetani*. From a judicious use perspective, penicillin or ampicillin would be the most prudent choices while saving the "big guns" for secondary treatment.

Closing thoughts: You are not alone

Selecting an appropriate antibiotic in small ruminants is challenging given that there are no established breakpoints and very few studies evaluating antimicrobial susceptibility in these species. Combining these challenges with the complexities of ELDU can leave a veterinarian's head spinning. When questions arise about selecting appropriate treatments and withdrawal times, FARAD is an excellent resource as is your friendly local clinical pharmacologist. Requesting help before initiating treatment is always the best approach for ensuring animal health and safety of the food products that they will provide.

Endnotes

[a] Nelson-Jameson, Inc, Marshfield, WI

[b] Charm Sciences, Inc. Lawrence, MA

References

1. Food Animal Residue Avoidance Databank – VetGRAM. (2023). Minor species. FARAD. **http://www.farad.org/vetgram/min_species.html**

2. CPG Sec 615.115 Extralabel Use of Medicated Feeds for Minor Species. (2016). **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-615115-extralabel-use-medicated-feeds-minor-species#:~:text=The%20CPG%20is%20intended%20to,medicated%20feeds%20in%20minor%20species**

3. Martin KL, Clapham MO, Davis JL, Baynes RE, Lin Z. (2018, Oct 15). Extralabel drug use in small ruminants. *J Am Vet Med Assoc* 253(8). **https://doi.org/10.2460/javma.253.8.1001**

4. Coetzee, J. Personal communication, 14 September 2023.

5. Beta Lactam and Other Test Methods For Use Under Appendix N And Section 6 Of The Grade "A" Pasteurized Milk Ordinance (PMO). (2018). **https://www.in.gov/boah/files/M_a_85_Beta_Lactam_Revision_16.pdf**

6. Nelson-Jameson, Inc. (n.d.). Delvotest Antibiotic Residue Tests. Retrieved from Nelson-Jameson, Inc. **https://nelsonjameson.com/content/pages/specialties/dsm-food-specialties/delvotest-antibiotic-residue-tests/**

7. CHARM Sciences, Inc. (n.d.). ROSA Lateral Flow. Retrieved from CHARM Sciences, Inc. **https://www.charm.com/products/test-and-kits/antibiotic-tests/rosa-lateral-flow/**

8. MacKay E. (2022, September). Overview of Respiratory Diseases of Sheep and Goats. Retrieved from *Merck Veterinary Manual*. **https://www.merckvetmanual.com/respiratory-system/respiratory-diseases-of-sheep-and-goats/overview-of-respiratory-diseases-of-sheep-and-goats**

9. Sahin O, Plummer PJ, Jordan DM, Sulaj K, Pereira S, Robbe-Austerman S, . . . Zhang Q. (2008). Emergence of a Tetracycline-Resistant Campylobacter jejuni Clone Associated with Outbreaks of Ovine Abortion in the United States. *J Clin Microbiol, 46*(5), 1663-1671. **http://doi:https://doi.org/10.1128/jcm.00031-08**

