Antibiotic selection, use and residue avoidance: Things to consider

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Abstract

This document discusses the importance of connecting pharmacodynamic and pharmacokinetics in considerations when developing feeder and stocker cattle antibiotic treatment protocols. Simple illustrations of the use of the pharmacodynamic and pharmacokinetic link for commonly used FDA-approved antibiotics are explored. Additionally, important residue avoidance points to consider are discussed when using medication in feeder and stocker cattle with special emphasis on extra label drug use is employed.

Key words: antibiotic, judicious, stewardship, pharmacodynamics, pharmacokinetic

Introduction

As responsible prescribers of antibiotic use, it is critical we understand mechanisms of action and resistance development. To avoid lengthy verbiage, I will use numerous tables and graphics in this proceeding paper. The titles of the table and graphics will, in general, provide adequate explanation for the information contained in the table or graphic. For tables and graphics that need additional explanatory information, it will be inserted below the table or graphic title. Information to explain abbreviations contained in the table or graphic will be listed at the bottom of each table or graphic. For tables and graphics for which additional resources can be found, an Internet link to those resources will be included either below the title or in table footnote area.

Antibiotic Mechanisms of Actions and Bacterial Resistance Mechanisms

The 4 antibiotic mechanism actions are: 1) crippling production of the bacterial cell wall that protects the cell from the external environment (CW), 2) interfering with protein synthesis by binding to the machinery that builds proteins, amino acid by amino acid (PS), 3) wreaking havoc with metabolic processes, such as the synthesis of folic acid, that bacteria need to thrive (MP), and 4) blocking genetic replication by interfering with synthesis of DNA and RNA (GR) (Table 1). Examples of antibiotics approved for cattle are listed in Table 2.

Antibiotic Resistance Mechanisms

1) Decrease cell wall uptake and permeability which impact aminoglycosides; 2) efflux of the antibiotic which impacts macrolides, fluoroquinolones and tetracyclines; 3) induction of enzymes which impact aminoglycosides, florfenicol and beta-lactams actions; 4) altering target binding sites: ribosome binding site impacts macrolides, lincosamides; wall protein binding site impacts beta-lactams and glycopeptides; DNA binding site impacts fluoroquinolones; 5) gene resistance: plasmids development include b-lactams, tetracycline, macrolides, lincosamides, fluoroquinolone, sulfas; transposons development include b-lactams and glycopeptides; chromosomal resistance impacts b-lactams, fluoroquinolones (Table 3).

PK/PD Relationships

There is a predictive relationship between the pharmacodynamic of an antibiotic and the antibiotic's pharmacokinetics. In general these include; "Time above Minimum Inhibitory Concentration (MIC)", "Peak Concentration" / "Concentration Maximum (Cmax)", and the relationship between the antibiotic's concentration throughout its absorption and depletion referred to as "Area Under the Curve (AUC)". The specific relationships are outlined in Table 4.

Building Resistance

Figure 1 shows the growth of resistant bacterial pathogens that remain after insufficient antibiotic treatment management. This can happen if treatment management does not maintain a sufficient antibiotic level above the targeted MIC for time-dependent antibiotics or not achieving a sufficient AUC for concentration-dependent antibiotics. The efficacy of time-dependent antibiotics can be improved by increasing the dosing frequency to ensure the drug concentration stays above the targeted MIC (time above MIC, or T>MIC). The efficacy of concentration-dependent antibiotics can be improved by increasing the concentration or level of drug in the animal by either increasing the drug dose or by decreasing dosing interval/cycle to insure AUC is at least 125 times (AUC/MIC = AUMIC >125) the MIC for gram-negative targeted bacteria, and at least 40 times for gram-positive targeted bacteria (AUC/MIC = AUMIC >40). This concept is illustrated in Figure 2. With antibiotic exposure, the population of sensitive bacteria rapidly decrease. If these are targeted pathogens

Table 1. Antibiotic Mechanisms: Conjugation & Mutation

CW*	crippling production of the bacterial cell wall that protects the cell from the external environment
PS*	interfering with protein synthesis by binding to the machinery that builds proteins, amino acid by amino acid
MP*	wreaking havoc with metabolic processes, such as the synthesis of folic acid, that bacteria need to thrive
GR*	blocking genetic replication by interfering with synthesis of DNA and RNA

* Note: These abbreviations will be used throughout this paper

Table 2. Antimicrobial groups approved for cattle
(See http://www.aavpt.org/ for more information)

Antibiotic Class	Mechanism	Antibiotic Within Class
Aminocoumarins	GR*	Novobiocin/albamycin
Aminocyclitols	PS*	Spectinomycin
Aminoglycosides	PS*	Gentamicin, neomycin, dihydrostreptomycin
Beta-lactams	CW*	Amoxicillin, ampicillin, ceftiofur, cephapirin, cloxicillin, Hetacillin, Penicillin G
Phenicols	PS*	Florfenicol
Fluoroquinolones	GR*	Enrofloxacin, danofloxacin
Lincosamides	PS*	Lincomycin, pirlimycin
Macrolides	PS*	Erythromycin, gamithromycin, tildipirosin, tilmicosin, tulathromycin, tylosin
Sulfonamides	MP*	Sulfachloropyridazine, sulfadimethoxine, sulfamethazine
Streptogramins	PS*	Virginiamycin
Tetracyclines	PS*	Oxytetracycline, chlortetracycline

* Note: the abbreviations will be used throughout this paper

Table 3. Antibiotic Resistance Mechanisms

Decrease cell wall uptake / perm: ▶aminoglycosides
Efflux: ▶macrolides, fluoroquinolones, tetracyclines
Enzymes induced: ▶aminoglycosides, florfenicol, beta-lactams
Altered target binding sites: ▶ribosome …macrolides, lincosamides ▶wall protein … beta-lactams, glycopeptides ▶DNA … fluoroquinolones
Gene resistance: ▶plasmids (b-lact, tetra, macro, linco, fluro, sulfa), ▶transposons (b-lactams, glycopeptides),▶chromosome (b-lactams, FQs)

Table 4. PK/PD Relationships
(See http://www.aavpt.org/ for more information)

PK to PD Predictive Relationships	Antibiotic Class	Examples
T (50%) > MIC*	Beta-lactams	Ampicillin, amoxicillin, ceftiofur, PenG
T (50 to 100%) > MIC*	Macrolides	Erythromycin, lincomycin, tilmicosin?, tylosin
T (100%) > MIC*	Phenol, sulfas, tetracyclines, linco	Florfenicol, lincomycin, oxytetracycline, sulfas
Peak or Cmax (10x) / MIC*	Aminoglycosides	Gentamicin, neomycin
AUC/MIC (>100 x = efficacy) Cmax/MIC (< 4 to 8 x = resistance)	Fluoroquinolones	Danofloxacin, enrofloxacin
AUC/MIC (>100 x)	Macrolides	Tulathromycin, gamithromycin, tildipirosin
No Information Available … PK/PD not predictive	Aminocyclitols	Spectinomycin

* MIC: (Minimum Inhibitory Concentration) … typically reported for 90% of isolates (MIC90)
T (50%): Time above MIC for 50% of the dosing interval
T (100%): Time above MIC for 100%, or entire dosing interval
Cmax: Concentration Maximum (maximum or peak concentration level achieved during dosing interval
AUC: Area Under the Curve (total area under the drug absorption and depletion curve
PK (Pharmacokinetics: the drug absorption, distribution & excretion behavior within the animal)
PD (Pharmacodynamics: the relationship of bacterial sensitivity to the portions of the drug fractions typically reported as MIC(population%) & is generally related to the "unbound" portion of the drug.

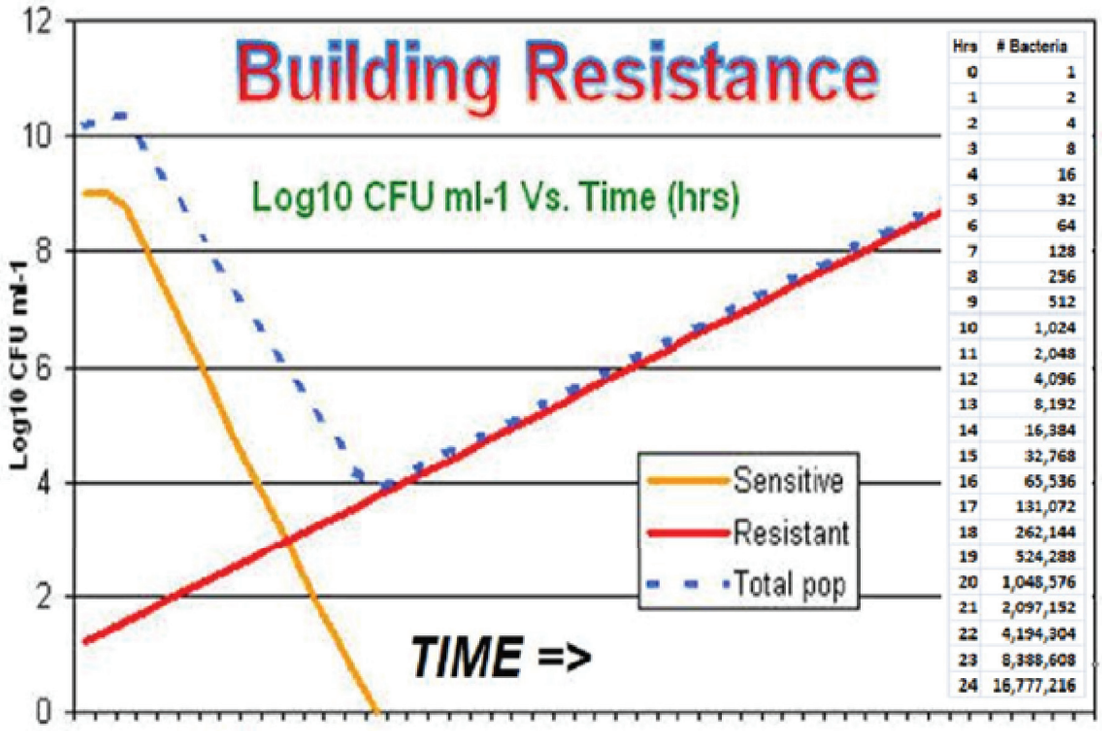

Figure 1. Building Resistance Graphic

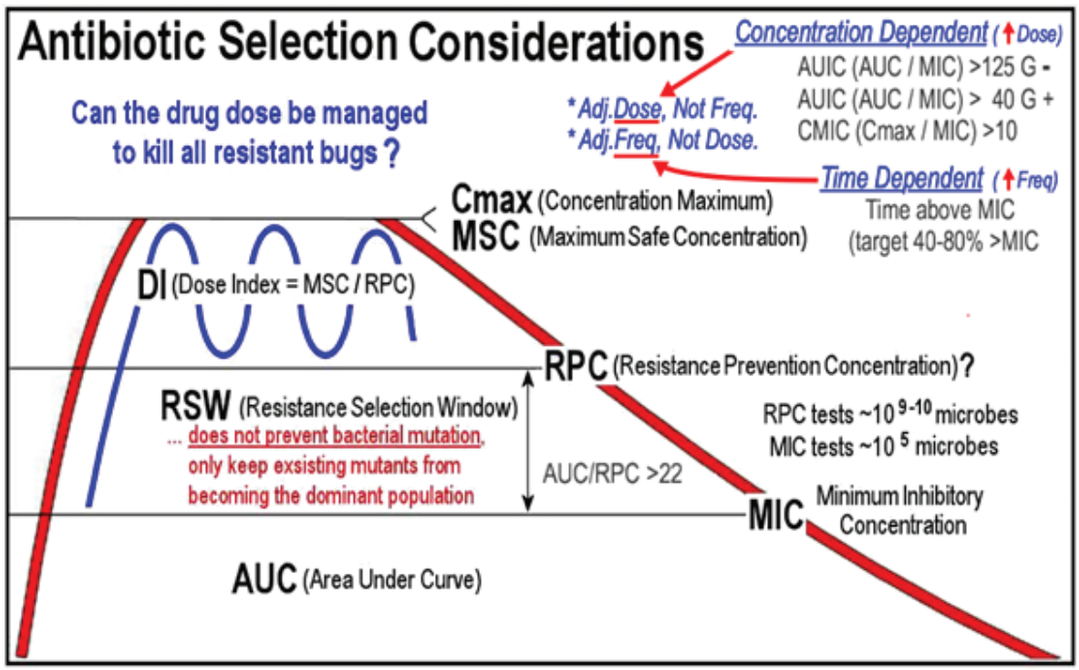

Figure 2. The above Antibiotic Selection graphic is an attempt to summarize information for good treatment/dosing managing practices for both "time-dependent" (T>MIC) and "concentration-dependent" (AUMIC >125 for G- pathogens & >40 for G+ pathogens) antibiotics from the following papers;
Craig W. Pharmacokinetic/pharmacodynamic parameters; rational antibiotic dosing. *Clin Infect Dis* 1998;26:1-12.
Jumbe N. Applications of mathematical model to prevent ab. resist. pop. amp. *J Clin Invest* 2003;112:275-285.
Blondeau J. New concepts in antimicrobial susceptibility testing: the mutant prevention concentration and mutant selection window approach. *Vet Dermatol* 2009;20:383-396.
Blondeau J. Targeted drug delivery and drug resistant pathogens. *Expert Rev Respir Med* 2018;12:161-164.

sensitive to the selected antibiotic, the patient will typically appear to have a favorable treatment response. However, if the dosing management of the antibiotic is not proper for the population of bacterial disease pathogens, resistant bacterial pathogens will remain and, as represented in the right-side population multiplication table of the Building Resistance Graphic (Figure 1), within a short time the patient may relapse due to the massive increase/invasion of resistant bacteria. As demonstrated in the table, $16x10^7$ bacteria can populate an area from a single bacteria multiplying once an hour. This far exceeds the 10^4 to 10^6 pathogenic bacteria generally considered an "infective pathogen dose".

Antibiotic Selection Consideration

Figure 2 contains an abundance of information! The point of the graphic is to help you think through how or if an antibiotic therapy can be managed to "control" (kill, weaken or slow their growth) the bacterial pathogens sufficiently to allow the animal to recover. It is important for each of us to remember that disease recovery involves more than the bacterial pathogen's antibiotic sensitivity. It is also important to remember that many, perhaps all, antibiotics are potentially toxic to animals being treated. Renal and hepatic function not only impact antibiotic excretion, but are prime organs that if damaged by a treatment drug increases the likelihood of prolonged recovery or death of the animal. Examples are sulfas causing renal crystallization or IV tetracyclines not properly diluted being associated with renal tubular nephrosis or hepatic injury. Under the best of circumstances, MIC can be an inadequate predictor of an animal's response to antibiotic therapy. In the graphic, the AUC line has been removed from the top of the curve to illustrate that a dose can be so high as to be lethal. The dosing index (DI) must be kept below a toxic drug level, but above a level that can lead to bacterial pathogen resistance development.

Most MIC testing is done with approximately 10^5 bacteria, whereas "resistance" or "mutant" prevention concentrations (RPC/MPC) require much higher ($10^{9\text{-}10}$) bacterial populations for testing. The bacteria required for testing generally delay test results for approximately an additional day, and automated systems for type testing are not widely available outside a research setting. The RPC/MPC does not prevent bacterial mutation, but helps keep existing antibiotic-resistant bacteria from becoming the dominant bacterial pathogen population.

Antibiotic Movement Between Cellular Spaces

As demonstrated in Figure 3, it is the "unbound" portion of an antibiotic that moves between cellular spaces. Understanding this can aid a practitioner's antibiotic choice to select an antibiotic that will have the maximal impact on a bacterial pathogen residing in a particular tissue compartment. For example, ceftiofur is highly bound (80 to 90%) which can be extremely useful to keep the maximal amount of the drug in the plasma or interstitial spaces in cases of septicemia. Drugs

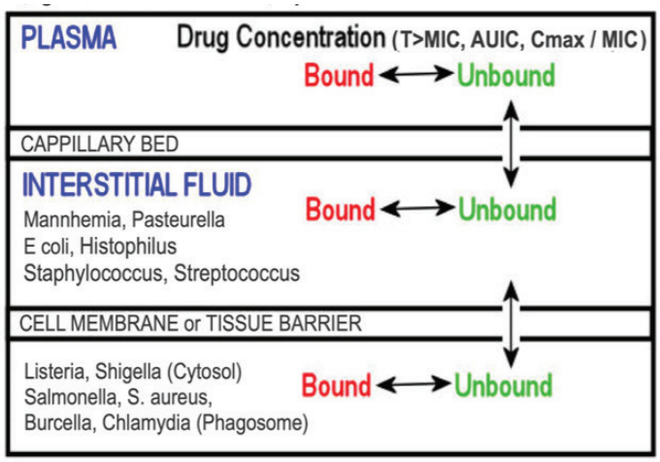

Figure 3. Drug movement between compartments.

that are highly unbound may, if the sensitivity is appropriate, have maximal impact for bacterial pathogens such as *Histophilus somni* or *Salmonella* sp during an intracellular phase.

Understanding the "unbound" portion (percentage) is a critical piece of information in calculating the appropriate dose and adjusting the dosing index. In the ceftiofur example (80 to 90% bound), Excede (information from the package insert) has a Cmax for ~ 6.4 ug/mL and has T1/2 (time for excretion of half the drug level) of ~ 50 hours in an adult cow. The unbound drug (drug available to control (kill, weaken, slow the growth, etc.)) would be ~ 10% to 20% of the measurable drug level. For this reason, the manufacturer has very ethically included a "therapeutic threshold" (tt) level for the practitioner to consider. If the MIC of *Pasteurella multocida* is listed as 0.03 ug/mL, the tt would need to be 2.0 ug/mL to ensure adequate unbound drug was available to control the infection.

The "Key Cattle Antibiotic Pharmacodynamic and Pharmacokinetic Parameters" (Table 5) contains approximate PK & PD information for the majority of antibiotics reported to be considered for cattle bacterial pathogens.

Griffin's Hits to avoid Violative Residues: Antibiotic Residue Avoidance Strategy

1. Identify all animals treated.
2. Record all treatments:
   i. Date; animal's ID; dose given;
   ii. Administration route;
   iii. Person treating; withdrawal time.
3. Strictly follow label directions for use.
4. Use newer-technology antibiotics when possible.
5. Select antibiotics with short WD when equivalent.
6. Never give more than 10 mL per IM injection site.
7. Avoid extra label drug use (ELDU) of antibiotics.
8. Avoid using multiple antibiotics at the same time.
9. Don't mix antibiotics in the same syringe.

Table 5. Key cattle antibiotic pharmacokinetic parameters & common BRD pharmacodynamics.

Generic Name	NADA#	PK/PD	TM	CM	AUC	T½	Dose	PB %	MIC90 Mh	MIC90 Pm	MIC90 Hs
Ampicillin (Polyflex)	055-030	T>MIC	*	10	*	1.2	10	< 10	32	0.25	0.25
Ceftiofur Na (Naxcel)	140-338	T>MIC	1.2	14	115	10	1	80-90	0.03 (0.2)[tt]	0.03 (0.2)[tt]	0.03 (0.2)[tt]
Ceftiofur HCl (Excenel)	140-890	T>MIC	2.5	11	160	12	1	80-90	0.03 (0.2)[tt]	0.03 (0.2)[tt]	0.03 (0.2)[tt]
Ceftiofur cryst acid (Excede)	141-209	T>MIC	19	6.4	376	50	3	80-90	0.03 (0.2)[tt]	0.03 (0.2)[tt]	0.03 (0.2)[tt]
Chlortetracycline CTC	048-761	T>MIC	10.2	0.4+	4.3	15.7	10	47-54	4	4	2
Danofloxacin ** (Advocin)	141-207	A^{UC}/M^{IC}	3.2	1.3	9	4.5	2.7	40-50	0.06	0.02	0.06
Enrofloxacin ** (Baytril)	141-068	A^{UC}/M^{IC}	5.8	1.8	19	6.4	5.7	54-61	0.06	0.03	0.03
Florfenicol (Nuflor/Gold)	141-063	T>MIC	5.3	5.4	71	18.3	18	15-20	1	1	0.5
Gamithromycin (Zactran)	141-328	A^{UC}/M^{IC}	1	~0.5 18	9.25 1607	50.8 90.4	2.7	26	1	1	0.5
Gentamicin ** Don'tInject	101-862	C^{Max}/M^{IC}	*	<8	*	2	1	~30?	8	4	16
Neomycin ** Do Not Inject	200-113	C^{Max}/M^{IC}	*	10	*	2.5	2	~45	64	64	64
Oxytetracycline (LA)***	Many	T>MIC	1.8	3.6	72	21	9	18-22	8	8	8
Oxytetracycline (feed)	008-804	T>MIC	2	0.16	4	9	10	18-22	8	8	8
Pen G, Benzathine	Many	T>MIC	*	1.7	*	60	10k	28	16	8	16
Pen G, Procaine	Many	T>MIC	*	3.4	*	5.2	10k	~28?	16	8	16
Sulfa-dimethoxine (IV)	041-245	T>MIC	*	64	*	13.1	25	75-85	350	350	350
Sulfa-dimethoxine (oral)	093-107	T>MIC	*	8.9	*	13.1	62.5	75-85	350	350	350
Sulfa-methazine	140-270	T>MIC	*	16	*	12.9	200	75-85	350	350	350
Tildipirosin (Zuprevo)	141-334	T>MIC	1.8	4 L24	0.7 L3.5	21 to 33	210	25%	2	1	4
Tilmicosin (Lung CM) Pulmotil / Micotil	140-929	T>MIC	1.4	1(9) x2	8	~24	4.5x2	~17?	16	32	8
Tulathromycin (Draxxin)	141-244	A^{UC}/M^{IC}	0.25 L24	3.8 +/-.4	16.7 L1.2k	90 L185	1.1	40	2	1	4
Tylosin (Tylan 200)	012-965	T>MIC	1.3	4.7	29	24	8	33-44	32	32	16

* No available data ** Not AMDUCA approved ELDU or BQA *** LA = long acting formulations designed for >72 hrs PTI
Dose: refers to typical dose (mg/lb body weight) and is listed as the maximum label approval
TM: TMAX- Time corresponding to concentration maximum CM: Cmax=Peak ppm concentrations (ppm=ug/Ml)
AUC: Area Under the Curve (mcg x hr / ml) T: Time, T½ Life: Half-life in hours (T½)

MIC listings are all for concentrations greater than the values listed as MIC 90% http:// www.vads.org [tt] therapeutic threshold
Ref: Dx lab data, Iowa State University 2000-2003 for 90% of isolates, FDA NADA FOI, & Shryock *J Vet Diag Invest* 8:337 (96)

NOTE: Use the PHARMACOKINETICS, PHARMACODYNAMICS, & MIC information only as a starting guide.
Therapeutic regimen management requires response monitoring through accurate case definition, protocol adherence, record examination and outcome follow-up. Additional Info from http://www.AAVPT.ORG

10. Check ALL medication/treatment records before marketing

- All WD times should be figured from the last day of treatment and for the longest WD of the list of products used.
- If multiple doses of a product designed for a single-dose usage are given, the WD time should be the "sum of the WD days" for each administration. Example: consider an antibiotic intended for a single application that has a 13-day WD. If a 2nd dose is given 6 days after the 1st dose, the WD would be (13 - 6) + (13) = 20 days from the last injection. This WD estimate is very conservative and draws the ire of the associated pharmaceutical company, but the medication in question has been 1 of the 3 leading violative residue violations for over a decade. I have never had a residue violation when following the "sum of WD days" technique.
- Never give greater than 10 mL per IM site. Large IM doses can depot the drug and increase the potential for a violative residue.
- ELDU (off label use) of non-feed medications (OTC or Rx) requires a veterinary prescription and the withdrawal to be extended, and must not have a violative residue.
- ELDU of FDA-approved feed antibiotics is never acceptable and must never be practiced by veterinarians, nutritionists, or producers. Forbidden are the use of feed antibiotic additives that are used for a condition/disease that is not listed for "approved prevention, control or treatment" or using a dose not listed on the feed antibiotic label or using a frequency of the feed antibiotic not listed on the label.

Please contact me at **dgriffin@tamu.edu** if you have questions or would like an electronic copy of the materials, including a wallet card summarizing Figure 2 and the PD/PK information from Table 5 of antibiotics commonly used in feeder and stocker cattle.