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An antimicrobial targeting toolbox for the swine practitioner

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The absolute best way to evaluate a regimen is by controlled clinical trials. However when we are forced off label, these types of trials rarely exist. Then we must rely on combining pharmacodynamics and pharmacokinetics in a predictive modeling scenario to try and target our regimens.

Pharmacodynamics

Mechanism of action

Take home message on bactericidal vs. bacteriostatic: It is not a hard and fast classification, but based on the relationship of the MIC and MBC. Bacteriostatic compounds can kill microbes at the proper concentration in-vitro, but the question is if this concentration can be practically obtained in-vivo.

Antimicrobial susceptibility testing

There are two primary methods for bacterial susceptibility profile determination in use today.

Kirby-Bauer ("disk diffusion")

A paper disk containing the antimicrobial is placed on an agar plate that has been inoculated with the pathogen. The plate is incubated and the zones of inhibition (absence of any visible bacterial growth) are measured surrounding the disks. The diameter of the zone is correlated back to dilutional concentrations used to set "susceptible", "intermediate", and "resistant" classifications for pathogens. This technique is obviously heavily dependent on quality control. Depth and contents of the agar, and antimicrobial contents of the disks must be closely controlled.

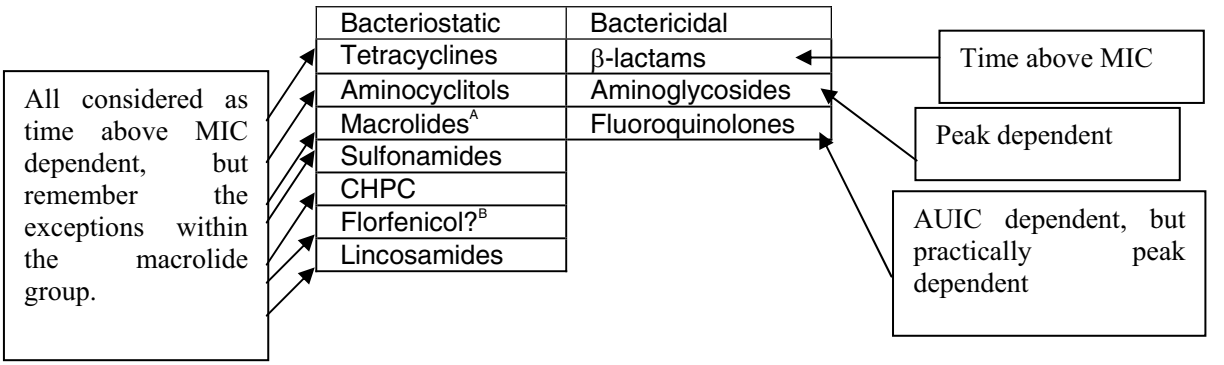
Microwell dilution method

This system uses a plate with wells that contain different concentrations of the selected antimicrobials. Ideally we would have a well for each antimicrobial at 1:2 dilution intervals to accurately evaluate the MIC of the compound for each pathogen. However, cost prohibits this technique, so "breakpoints" are selected based on reported serum/plasma pharmacokinetic properties of antimicrobials in the species of interest. For example, commonly used breakpoints for tetracycline are 4 and 8 mg/ml.

- A pathogen growing in neither of the wells would be considered susceptible
- A pathogen growing only in the 4 mg/ml well would be considered intermediately susceptible
- A pathogen growing in both wells would be considered resistant

The NCCLS/VAST Subcommittee periodically updates guidance publications for veterinary susceptibility test-

Figure 1: Bacteriostatic versus bactericidal



[A]Azithromycin and clarithromycin appear to be peak dependent against some pathogens
[B]Remember that the MIC vs MBC properties of florfenicol (on *Manheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*) appear to be more representative of a bactericidal antimicrobial.

ing. These documents are produced through a consensus process.

Quotations and adaptations from tables included here are reproduced with permission from NCCLS publication M31-A2 - *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated form Animals; Approved Standard - Second Edition* (ISBN 1-56238-461-9). Copies of the current edition may be obtained from NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA. The NCCLS office may be reached at 610-688-0100, (fax) 610-699-0700, or on the web at Exoffice@nccls.org. In this proceedings article, quotations from M31-A2 are presented indented.

Some definitions from M31-A2

> **2.8.2 Susceptible:** This category implies that there is a high likelihood of a favorable clinical outcome when the drug is administered at label dosage, because of adequate pharmacodynamic parameters relative to the MIC of the causative organism.
>
> **2.8.3 Intermediate:** This category provides a "buffer zone". This buffer zone should prevent small, uncontrolled technical factors from causing discrepancies in interpretations (e.g., a resistant organism being categorized as susceptible [termed a *very major error*], or a susceptible organism being categorized as resistant [termed a *major error*], especially for drugs with narrow pharmacotoxicity margins.
>
> This category includes strains with MICs that approach or can exceed usually attainable blood or tissue levels (but do not have flexible labeling); and for which response rates can be lower than for strains in the "susceptible" category. These strains can be inhibited by attainable concentrations of certain antimicrobial agents:
>
> - In body sites, such as the urinary tracts, where drugs are physiologically concentrated (e.g., quinolones, b-lactams); and
> - Provided the drug has a wide pharmacotoxicity margin and is administered at maximal dosage (e.g., B-lactams).
>
> If the organism is not susceptible to alternative clinically feasible drugs, if the site of infection is not one where the drug is concentrated, or if the high dose cannot be used, the test should be repeated.
>
> **2.8.5 Resistant:** This category implies that there will not be a favorable outcome, because the achievable systemic concentrations of the agent will be lower than the MIC of the causative organism with normal dosage schedules and/or fall in the range or where specific microbial resistance mechanisms are likely (e.g., B-lactamases), and clinical efficacy has not been reliable in treatment studies.

Practitioners commonly receive susceptibility information from both standard dilution tests and disk diffusion tests. How do MICs and zone diameters relate?

> **3.1 Equivalent MIC Breakpoints**: Disk diffusion zone diameters correlate inversely with MICs from standard dilution tests, usually broth microdilution. Table 2 *[not reproduced here]* lists the zone diameters and MIC breakpoints used for the interpretive guidelines. Zone diameters and MIC breakpoints are correlated based upon zone-diameter versus MIC regression, population distributions, pharmacokinetics, and clinical efficacy studies. However, the zone diameters may not correspond precisely to the listed MIC breakpoints due to differences in the methodologies and the original databases. Thus, the information provided in Table 2 cannot be used to convert zone diameters to absolute MIC values. See also Section 1.3

What about susceptibility testing where NCCLS veterinary-specific interpretive criteria are not available? A distinct distinction between veterinary-specific interpretive criteria and criteria adapted from human medicine is made in M31-A2.

> **2.8.1 MIC and Zone-Size Interpretive Criteria**: Table 2 shows interpretive criteria for the sizes of the zones of inhibition for use with agar disk diffusion susceptibility tests and MIC breakpoints for use with dilution susceptibility tests. For those agents for which veterinary-specific interpretive criteria are not available, the use of these values in relation to veterinary bacterial isolates must be done with caution for three reasons. First, the value listed in the gray shaded areas listed in Table 2 were developed in human medicine by comparing zone diameters to MICs in broth or agar dilution tests and from population distributions of zones and/or MICs of known susceptible and resistant strains. Second, the MICs and correlated zone-size distributions were analyzed in relation to the clinical pharmacokinetics of the drug from normal dose-range schedules in humans. Third, the in vitro and pharmacologic data have been analyzed in relation to studies of clinical outcome of treatment of specific human pathogens.
>
> Additionally, caution should be exercised in using the interpretive criteria listed in Table 2. These criteria apply to particular uses of the antimicrobial drugs in specific animal species. Extension of these data to other disease indications or other animal species may lead to an incorrect prediction of clinical outcome. Antimicrobial concentrations differ across regions of the body depending on the specific drug, route of administration , drug formulation, and the animal's metabolism, and these differences can profoundly affect clinical performance of the drug. Therefore, the subcommittee has listed only approved animal species and pathogens in Table 2 to define those conditions where interpretive criteria are known to be applicable...

The Table 2 discussed in the M31-A2 quotation contains serial dilution and zone diffusion interpretive criteria for antimicrobials used in food animal medicine.

Extended dilution summaries from the ISU Diagnostic Laboratory, Diagnostic Bacteriology Section

Selected swine and bovine susceptibility testing summaries are presented in the Appendix below. Be sure to read the section of the Appendix that summarizes rules for interpretation of these data.

Practical pharmacokinetics

Terms describing or making inferences about concentrations

$\mathbf{C_{max}}$ is the highest concentration reached in the plasma or a specific tissue.

The **volume of distribution (Vd)** may be used as an indication of the relationship between vascular and extravascular concentrations for a drug. The apparent volume of distribution is the volume of fluid (expressed as l/kg of body weight) necessary to contain the total amount of drug in the body if it were uniformly distributed and the concentration in this hypothetical fluid were equal to the plasma concentration. Drugs that tend to stay in the plasma have a Vd much less than 1, drugs that have wide distribution have a Vd near 1, and drugs with very wide distribution have a Vd much greater than 1.

Area under the curve (AUC) refers to the total area under the plasma concentration curve. The AUC following an IV injection of a drug essentially represents "all of the drug". Comparing this AUC to the AUC following IM, SC, or oral administration allows the calculation of bioavailability. Bioavailability is the percent of a drug available after administration by a specified route (other than IV) compared to IV administration of the same amount.

Terms describing rates

$\mathbf{T_{max}}$ describes time to peak concentration in the plasma, this may also be described for a tissue. In the plasma, it is at the time of injection for an IV bolus, and reflects the rate of absorption from an IM injection.

$\mathbf{T_{1/2\_}}$ is the time required for the plasma concentration to decrease by 1/2 during the distribution phase of the plasma concentration curve (distribution half-time), and estimates the rate of distribution to the tissues. This phase consists primarily of distribution to the tissues, but also includes some elimination processes. It is greatly confounded by absorption following an IM injection.

Table 1: Extended range dilution testing at Iowa State University.

Antimicrobial	Food animal (μg/ml)	Mastitis (μg/ml)
Ampicillin	0.25-16	0.12-8
Apramycin	4-32	
Ceftiofur	0.5-8	0.5-4
Cephalothin		2-16
Chlortetracycline	0.5-8	
Clindamycin	0.25-2	
Enrofloxacin	0.12-2	
Erythromycin	0.25-4	0.25-4
Florfenicol	0.25-8	
Gentamicin	1-8	
Neomycin	4-32	
Oxacillin		2-4
Oxytetracycline	0.25-8	
Penicillin	0.12-8	0.12-8
Penicillin/Novobiocin		1-8
Pirlimycin		0.5-4
Spectinomycin	8-64	
Sulfachlorpyridazine	32-256	
Sulfadimethoxine	32-256	32-256
Sulfathiazole	32-256	
Tetracycline		1-8
Tiamulin	4-32	
Tilmicosin	4-32	
Trimethoprim/Sulphamethoxazole	0.5-2	
Tylosin tartrate	2.5-20	

$T_{1/2\_}$ is the time required for the plasma concentration to decrease by 1/2 during the elimination phase of the plasma concentration curve (elimination half-time). Elimination from the plasma and tissues predominates in this phase. Although the plasma $T_{1/2\_}$ may give an indication of the tissue $T_{1/2\_}$, they are not necessarily equal.

Caveat

You should have reservations any time a hard number is given for a pharmacokinetic (PK) parameter. C_{max}, T_{max}, and $T_{1/2\_}$ will vary between animals within a species, and even between different administrations in the same animal, and that's in healthy animals! Almost all of the pharmacokinetic parameters reported for animal and human drugs are determined in healthy subjects.

Always view PK parameters reported as a single value as middle values in a range. For example, a study determining the elimination half-time of IV oxytetracycline in cattle found a mean of 9.04 hours, with a range of 6.97 to 10.98 hours. The introduction of disease variation would be expected to make the range even wider.

Take home point

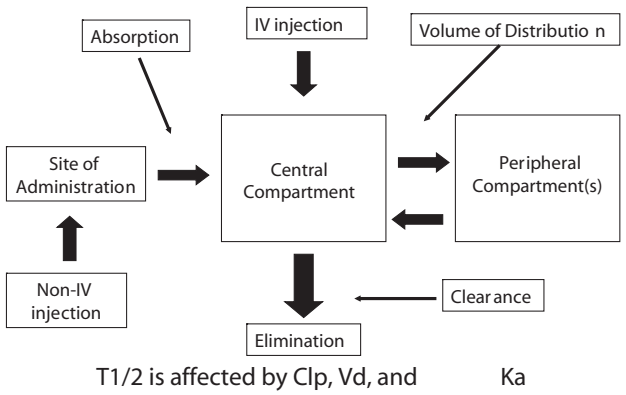
Published PK parameters may be used as a rough starting point for the animal(s) you are working on. We should not consider published PK values as an accurate indication for individual cases when used in conjunction with pathogen susceptibility data. These PK values may be used as a base for ruling out drugs which are way out of a reasonable efficacy range for your case. Published PK data and pathogen MIC data are suitable for determining a rough starting point for individual cases.

Pharmacokinetics of selected antimicrobials in swine

Injectable gentamicin

Six female piglets weighing 6.6 ± 0.8 kg and six finishing gilts weighing 83.2 ± 7.9 kg were given a single intramuscular injection of gentamicin sulfate (5% solution) at 5 mg/kg. C_{max} was reported as a mean of 15.1 mg/ml (range 11.3 - 19.8) and 24.3 mg/ml (range 22.9 - 26.6) in piglets and adults respectively. Elimination half lives were reported as means of 3.8 hours in piglets and 2.7 hours in the gilts.[1]

Figure 2: Compartmental modeling.



Ceftiofur

Ceftiofur is rapidly metabolized to the metabolite desfuroylceftiofur in cattle and swine (See **Table 2**). The parent compound and metabolite are essentially equipotent except for *Staph*, where the MIC90 reported for ceftiofur is 1.0 mg/ml and for desfuroylceftiofur is 4.0-8.0 mg/ml (4.0 mg/ml for *Staph hyicus*. 8.0 mg/ml for *Staph aureus* and *Staph* spp).1 There was also some difference on strep, but at very low dilutions. For *Strep dysgalactiae* and *Strep zooepidemicus* the MIC90 reported for ceftiofur was < 0.0019 mg/ml and for desfuroylceftiofur it was 0.03 mg/ml. For *Strep uberis*, their relationship was 0.03 mg/ml for ceftiofur and 0.5 mg/ml for desfuroylceftiofur, which appears to have more of a chance of being clinically significant. Equal MIC90s were reported for *Actinobacillus pleuropneumoniae*, *Pasteurella* spp., *Haemophilus somnus*, *Salmonella* spp., and *E. coli*.[2]

Table 2: Excenel label information. Comparative bioavailability of sodium and hydrochloride salts of ceftiofur in swine.[A]

Parameter	Ceftiofur HCL	Ceftiofur Na
C_{max} (μg/ml)	26.1 ± 5.02	29.2 ± 5.01
T_{max} (hrs)	0.66 - 2.0 (range)	0.33 - 2.0 (range)
$T_{1/2\beta}$ (hrs)	16.2 ± 1.55	14.0 ± 1.23
T>0.2 μg/ml (hrs)	93.8 ± 7.98	85.0 ± 7.71
C24h (μg/ml)	3.45 ± 0.431	3.53 ± 0.791
C72h (μg/ml)	0.518 ± 0.126	0.407 ± 0.0675
AUC0-LOQ (μg•h/ml)	321 ± 50.2	314 ± 55.1

A5.0 mg/kg IM, concentrations represent ceftiofur and desfuroylceftiofur metabolites. Total lung ceftiofur concentrations at 12 hours after the last of 3 daily injections (24 hour intervals were 3.66 and 5.63 mg/g at 5.0 and 7.5 mg/kg BW respectively

Lincomycin pharmacokinetics in swine after administration in feed

Eighteen pigs averaging 29.5 kg were fed either 110 or 220 mg/kg of feed for 23 days prior to sampling. See **Tables 3** and **4**.[3]

Penicillin G

See **Tables 5**[4] and **6**[5].

Oxytetracycline pharmacokinetics in feed

Peak plasma concentration of near 0.4 mg/ml was detected at the 48 hour sample after administration of approximately 500 g/ton oxytetracycline in a commercial-type ration fed to approximately 70 pound pigs. Only three pigs were used. The oxytetracycline form was oxytetracycline hydrochloride from Sigma Chemical.[6] In a second study, thirty pigs (30 kg mean weight) with blood samples drawn 6 days after the start of medicated feed, just before and 3 hours after the 13th feeding of medicated feed (**Table 7**).[7] In a third study, three 10 week-old pigs were fed a pelleted feed containing oxytetracycline hydrochloride powder ad-libitum. Steady-state plasma concentrations of approximately 0.20 mg/ml on the third day of administration of 400 ppm (363 g/ton) to 32-38 pound pigs in a commercial, pelleted ration.[8]

Chlortetracycline pharmacokinetics in feed

Eighteen, 35-44 kg pigs were fed 100, 400, or 1000 mg CTC/kg of feed (91, 363, and 908 g/ton respectively). Plasma plateaus were reached at the 24 hr sample time. Mean concentrations for days 1-6 were 0.14 ± 0.06, 0.36 ± 0.12, and 0.75 ± 0.19 mg/ml for 100, 400, and 1000 mg CTC/kg of feed respectively.[9] In a second study, pigs weighing 21 kg at the start of the study were given 100 g/ton of CTC in a commercial ration for the first 28 days with varying calcium levels in the feed. They were then switched to a uniform calcium level at 200 g/ton for the next 13 days. Serum concentrations were determined at days 28 and 42 (**Table 8**).[10]

Comparative feed pharmacokinetics of chlortetracycline and oxytetracycline

Steady-state average plasma concentrations of chlortetracycline and oxytetracycline resulting from a medicated feed regimen of 22 mg/kg per day were reported as 0.80 ± 0.10 and 0.20 ± 0.07 respectively.[11]

Injectable oxytetracycline

In a French paper utilizing "Terramycine Long Action" from Pfizer, a long-acting, 200 mg/ml product was administered at 20 mg/kg intramuscularly to pigs weighing 37 to 53 kg. C_{max} was 4.40 ± 0.92 at a T_{max} of 4.0 ± 2.7 hours. Mean plasma concentrations at 48, 72 and 84 hours were 0.50 ± 0.12, 0.27 ± 0.10, and 0.26 ± 0.09 µg/ml respectively.[12]

Florfenicol

See **Table 9**.[13]

Amoxicillin in water

In this Danish study, a herd of 201 Landrace x Yorkshire pigs were administered amoxicillin trihydrate "soluble" powder (Clamoxyl vet, a SmithKline Beecham product in the UK) through a nipple water system. The pigs ranged in weight from 27 to 123 kg. Twice daily (7:30 am and 4:30 pm), water consumption was monitored and blood samples were collected from 10 randomly selected pigs.[14]

A proportioner was used to supply the amoxicillin. Water samples were collected from the nipple drinkers on days 2, 3, and 4 after initiation of dosing. The amoxicillin concentration was calculated to 92.7 mg/L at the start and adjusted to 182 mg/L after 2 days of dosing. Water concentration at the nipples was measured at 192, 219, and 192 mg/L on days 2, 3, and 4 respectively.

Table 3: Concentration of lincomycin measured in fluid or tissue (µg/ml) by concentration in feed.[3]

Dose	Carpal joint fluid	Stifle joint fluid	Pericardial fluid	Serum	Lung tissue	Duodenum tissue	Jejunum tissue	Ileum tissue	Colon tissue
110 mg/kg of feed	0.10	0.12± 0.02	0.11± 0.01	0.16± 0.04	0.66± 0.37	---	---	---	---
220 mg/kg of feed	0.10	0.11	0.15± 0.02	0.14± 0.02	1.13± 0.50	1.36± 0.94	1.26± 1.11	1.33± 0.72	0.73± 0.05

Table 4: Concentration of lincomycin measured in contents (µg/ml) by concentration in feed.[3]

Dose	Stomach	Duodenum	Jejunum	Ileum	Colon
110 mg/kg of feed	5.15± 4.95	5.90± 4.97	13.71± 9.90	47.82± 21.20	34.51± 15.28
220 mg/kg of feed	9.86± 6.85	7.18± 6.40	14.48± 9.36	25.05± 10.97	101.01± 24.64

Table 5: Penicllin G concentrations in plasma of piglets (approximately 3-4 kg, 7-10 days old) after injection of benzathine/procaine penicillin G (150,000 IU/ml each) or procaine penicillin G (300,000 IU/ml).[4]

Formulation	Dose	Route	C_{max} (µg/ml)	C_{max} SEM	$T_{1/2}$ (hrs)	$T_{1/2}$ SEM
Benzathine/ Procaine	33,000 IU/kg[A]	IM	2.14	0.19	30.48	11.04
Benzathine/ Procaine	33,000 IU/kg	SC	1.42	0.11	33.84	5.76
Benzathine/ Procaine	100,000 IU/kg[B]	IM	7.29	1.06	41.52	9.12
Benzathine/ Procaine	100,000 IU/kg	SC	3.94	0.63	38.88	5.04
Procaine	100,000 IU/kg	IM	12.38	0.90	2.88	0.48
Procaine	100,000 IU/kg	SC	16.97	7.22	5.04	0.72

[A]33,000 IU/kg (15,000 IU/lb) equals 1 ml/20 lbs of a 300,000 IU/ml solution
[B]100,000 IU/kg (45,454 IU/lb) equals 1 ml/6.6 lbs of a 300,000 IU/ml solution

Table 6: Procaine penicillin G (300,000 IU/ml) IM in approximately 4 month old Duroc-Yorkshire barrows and gilts.[A,5]

	IU/ml			µg/ml		
Hours post-dosing	Mean	Lower end	Upper end	Mean	Lower end	Upper end
0	0			0		
1	7.8	3.4	12.8	4.9	2.1	8.0
2	7.65	4.6	9.2	4.8	2.9	5.8
3	6.17	3.1	8	3.9	1.9	5.0
5	2.84	1.6	3.7	1.8	1.0	2.3
7	1.49	0.99	2.2	0.9	0.6	1.4
10	0.74	0.4	1.8	0.5	0.3	1.1
24	0.05	0	0.18	0.0	0.0	0.1

Dose= 600 IU/lb (21,120 IU/kg) IM, approximately 1 ml/30 lbs of 300,000 IU/ml suspension; $T_{1/2}$ calculated at 4.25 hours

Table 7: Thirty pig sample (30 kg mean weight) with blood drawn 6 days after the start of medicated feed, just before and 3 hours after the 13th feeding of medicated feed.[7]

OTC mg/kg in feed	Mean body weight (kg)	Drug dose mg/kg•day	Plasma µg/ml (HPLC)
400	66.0	12.1	0.13 - 0.22
800	60.5	26.4	0.19 - 0.50

Table 8: Pharmacokinetics of varying doses of chlortetracycline administered in feed.

Study Days	Group	CTC in feed	Calcium in Feed	CTC Serum Concentration
0-28	1	100 g/ton	0.3 %	0.482 µg/ml[A]
0-28	2	100 g/ton	0.7 %	0.360 µg/ml[A]
0-28	3	100 g/ton	1.1 %	0.263 µg/ml[A]
29-42	1	200 g/ton	0.3 %	0.695 µg/ml[B]
29-42	2	200 g/ton	0.3 %	0.662 µg/ml[B]
29-42	3	200 g/ton	0.3 %	0.560 µg/ml[B]

[A]Concentrations with this superscript are significantly different at $P < 0.01$.
[B]0.560 is significantly different from 0.695 and 0.662 at $P < 0.01$.

Table 9: Single administration pharmacokinetics of florfenicol.

Parameter	15 mg/kg intramuscularly	15 mg/kg orally
AUC0-24hr (μg•hr/ml)	74.8 ± 34.3	100.5 ± 16.5
AUC0-∞ (μg•hr/ml)	110.6 ± 31.5	103.4 ± 17.8
$T_{1/2\beta}$ (hr)	14.6 ± 7.2	5.5 ± 4.2
C_{max} (μg/ml)	7.3 ± 6.0	14.8 ± 2.6
T_{max} (hrs)	2.3 ± 1.2	3.0 ± 1.9

Based on water consumption and concentration calculations, the pigs were estimated to receive doses of 17.6 – 18.8 mg/kg during the period 7:30 am to 4:30 pm and doses of 8.2 – 8.4 mg/kg during the rest of the 24 hour period. These figures are based on study period with a 182 mg/L proportioner setting.

Three days after starting amoxicillin administration in the water, the serum concentrations stabilized (keep in mind the proportioner was adjusted on day 2) with a low concentration of approximately 0.5 mg/ml in plasma for morning samples and 1.3 mg/ml for afternoon samples.

Appendix: 2002 ISU Diagnostic Laboratory susceptibility results for swine isolates

Some rules for interpreting the grids and data

Lightly shaded areas in the grids indicate the dilutions tested for each drug.

The darkest shaded cell in each row indicate the concentration at which the drug would be reported as "susceptible" at ISU. You should check with your laboratory to see if the same breakpoints are being used. Breakpoints validated for applications in swine are included in the table below. Other breakpoints require interpretation in light of pharmacokinetics/pharmacodynamics and/or clinical trial results linked to regimens and pathogen susceptibility. Validation for a disease is only for specific pathogens. See **Table App 1**.

The value in the lowest dilution tested should be interpreted as less than or equal to that dilution because the actual MIC could be lower than the lowest value tested.

When the highest dilution tested did not inhibit growth of the organism, the result was reported as the next higher dilution. This would be the next dilution tested if the range was extended higher and could be interpreted as being greater than or equal to that dilution. The actual MIC could be any value higher than the actual range tested.

A reported MIC indicates that the actual inhibitory value is somewhere between the reported value and the next lowest dilution.

Lower MICs for one drug compared to another drug does not necessarily equate to superior efficacy for the drug with the lower MICs.

It is very important that these susceptibility results be interpreted in light of presence or absence of a validated breakpoint and the pharmacokinetics/pharmacodynamics of the antimicrobial.

Table App 1: The National Committee for Clinical Laboratory Standards (NCCLS) Veterinary Antimicrobial Susceptibility Testing (VAST) Subcommittee has approved these veterinary specific breakpoints.

Drug	Taxa:disease/pathogen
Ceftiofur	cattle and swine: respiratory disease
Tilmicosin	cattle: bovine respiratory disease
Tilmicosin	swine: respiratory disease
Enrofloxacin	chickens and turkeys: (P. multocida, E. coli)
Enrofloxacin	cattle: bovine respiratory disease
Enrofloxacin	canine and feline: dermal, URI, UTI
Orbifloxacin	canine and feline: dermal, UTI
Penicillin/novobiocin	cattle: mastitis
Florfenicol	cattle: bovine respiratory disease
Spectinomycin sulfate	cattle: bovine respiratory disease
Pirlimycin	cattle: mastitis
Clindamycin	canine sin and soft tissue infections
Orbifloxacin	canine dermal and UTI
Tiamulin	swine respiratory disease

References

1. Fink-Gremmels J, Pijpers A, Verheijden JHM (1992), Age-dependent pharmacokinetics of Gentamicin after intramuscular injection in pigs, *Proceedings 13th International Pig Veterinary Society World Congress* 650-651
2. Salmon SA, Watts JL, Yancey RL Jr. In vitro activity of ceftiofur and its primary metaboite, desfuroylceftiofur, against organisms of veterinary importance, *J Vet Diag Invest*, 8:332:336,1996.
3. DeGeeter MJ, et al. Concentrations of lincomycin in body tissues and fluids of swine fed diets fortified with the antibiotic, *Proceedings of the 6th International Pig Veterinary Society World Congress 6*: 283, 1980.
4. Ranheim B, et al. Benzathine penicillin G and procaine penicillin G in piglets: comparison of intramuscular and subcutaneous injection. *Veterinary Research Communications* 26(6):459-465, 2002.
5. Mercer HD, et al. Serum concentrations of penicillin and dihydrostreptomycin after their parenteral administration to swine. *J.A.V.M.A*. 159(1):61-68, 1971.
6. Hall WF, Kniffen TS, Bane DP, et al. Plasma concentrations of oxytetracycline in swine after administration of the drug intramuscularly and orally in feed. *J Am Vet Med Assoc* 194;1265-1268, 1989.
7. Pijpers A, Schoevers EJ, Haagsma N. Plasma levels of oxytetracycline, doxycycline, and minocycline in pigs after oral administration in feed. *J Anim Sci* 69:4512-4522, 1991.
8. Mevius DJ, Vellenga L, Breukink HJ, et al. Pharmacokinetics and renal clearance of oxytetracycline in piglets following intravenous and oral administration. *The Veterinary Quarterly* 8:274-284, 1986.
9. Kilroy CR, Hall WF, Bane DP, et al. Chlortetracycline in swine: bioavailability and pharmacokinetics in fasted and fed pigs. *J Vet Pharmacol Therap* 13:49-58, 1990.
10. Wahlstrom RC, Ballos J, Libal G. Dietary calcium's effect on chlortetracycline absorption in growing swine examined. *Feedstuffs*, March 3, 1980, pp. 32-33.
11. del Castillo JRE, Martineau GP, Hannon MR, Besner JG. Comparative pharmacokinetics and efficacy of Aureomycin chlortetracycline granular premix and an oxytetracycline premix against experimental pleuropneumonia in pigs. *Proceedings of the 31st Annual Meeting of the American Association of Swine Practitioners* 31, 89-94. 2000.
12. Archimbault P, Navetat H, Vidal R, et al. Plasma bioavailability of 2 long-acting oxytetracycline formulations in the pig. *Vet Res* 25:299-404,1994.
13. Voorspoels J, et al. Pharmacokinetics of florfenicol after treatment of pigs with single oral or intramuscular doses or with medicated feed for three days. *Vet Rec* 145:397-399, 1999.
14. Agerso H, et al. Water medication of a swine herd with amoxicillin. *J Vet Pharmacol Therap* 21:199-202, 1998.