# Spring 2015 Antimicrobial Notes
## Pharmacology II

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Simplified spectrums for antimicrobials

First, some major points to understand about simplifying these spectrums. 1) Pathogens don’t read these notes and specific pathogens in individual cases may or may not adhere to our prediction of their susceptibility. That is why we learn about interpreting susceptibility testing. 2) The purpose of this section of the course is not to turn you into a specialized infectious disease therapy expert, but to get you headed in the right direction with antimicrobial therapy and to avoid some huge mistakes. So, with that in mind, these notes provide “generalized spectrums” of the major antimicrobial groups on which we are focusing.

Notes on interpretation. I have selected three options for a quadrant for use in this class:

++ = inconsistent activity in the quadrant. This may mean both a minimal proportion of the pathogens in this quadrant are susceptible to the drug and there is a wide range of susceptibility among pathogen groups within the “spectrum” in that quadrant.

+++++ = consistent activity in the quadrant. This indicates the drug would be a reasonable choice for empiric therapy in that quadrant. We can still run into resistant isolates, especially for the enterobacteriaceae, Staph, and Pseudomonas.

A blacked-out quadrant = minimal or nonexistent coverage in a quadrant. We would not consider this drug for empiric treatment of a pathogen located in this quadrant for this drug. However, as for the ++ category, as you go through the medicine courses, clinics, and then practice you will likely run into some exceptions in these quadrants.

++ (as compared to a ++++) in the Gram negative aerobic quadrant typically means we have no, or very variable activity against enterobacteriaceae and/or Pseudomonas.

++ in a quadrant, as opposed to a ++++ does not indicate there is no therapeutic application in that quadrant. Rather, it indicates you need to look specifically at a disease with a pathogen in that quadrant to see if that pathogen is reasonably in the spectrum. It also suggests a greater need for susceptibility testing when using the antimicrobial in that quadrant as opposed to a ++++ quadrant.

Quadrant Key

<table>
<thead>
<tr>
<th>Aerobic</th>
<th>Anaerobic</th>
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<tbody>
<tr>
<td>Gram (+)</td>
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<tr>
<td>Gram (-)</td>
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</table>

An isolate of a pathogen which is in the “spectrum” of an antimicrobial may still be clinically resistant due to possessing a resistance gene, or due to the location of the infection.
THE AMINOGLYCOSIDES

MEMBERS OF THE AMINOGLYCOSIDE GROUP

Mycin aminoglycosides are derived from *Micromonospora spp.*
Mycin aminoglycosides are derived from *Streptomyces spp.*

Parent compounds (Year discovered or developed) and derivatives

**Streptomycin** (1944)
The “neomycin family” – 4,5 disubstituted deoxystreptamines
  **Neomycin** (1949) [VL Biosol] – Paromomycin
The “kanamycin family” – 4,6 disubstituted deoxystreptamines
  **Kanamycin** (1957) - Tobramycin (1967), Amikacin (1972) [VLs Amiglyde V, Amikacin Sulfate Injection, AmiMax™ E Solution]
The “gentamicin family” – also 4,6 disubstituted deoxystreptamines
  **Gentamicin** (1963) [VL Gentocin®, Garasol® and generics] – Isepamicin (derivative of gentamicin B)
  Sisomicin (1967) - Netlimicin (1973)
Others marketed outside the U.S. – isepamicin, dibekacin (sisomicin also)

In the KSU CVM Pharmacy:

- Gentamicin injectable solution
- Amikacin injectable solution
- See list of possible products in the “route of administration” section below

**Commonly stocked in practices:** Neomycin oral solution, many others on the “route of administration” list below.

**DRUGS SOMETIMES CONFUSED WITH AMINOGLYCOSIDES** (ending with an “in” doesn’t make it an aminoglycoside)

**Spectinomycin** (An aminocyclitol without the aminoglycosidic groups, a product of *Streptomyces spectabilis*)
**Apramycin** (Technically an aminocyclitol, a product of *Streptomyces tenebrans*, no longer available)
**Polymyxin B** (A Polymyxin, a product of *Bacillus polymyxa*)
Lincosamides: Lincomycin and Clindamycin (Lincomycin, the parent compound, is a product of *Streptomyces lincolnensis*)
A little history:

“Pen/Strep”—a fixed combination of procaine penicillin G and dihydrostreptomycin, no longer marketed. By the time the penicillin was dosed appropriately, the dihydrostreptomycin was significantly overdosed. At the label dose, the penicillin G was under-dosed.

“Azimycin”—a fixed combination of procaine penicillin G, Dihydrostreptomycin, “Azium” (a brand name for dexamethasone), and an antihistamine. No longer marketed. Same relative dose problem as for pen/strep above. Plus, steroids and antihistamines are not routinely indicated along with an antibiotic.

STRUCTURAL CHARACTERISTICS

The aminoglycosides consist of an aminocyclitol nucleus (a six-membered ring that contains amino groups) that is linked to at least two sugar groups. Streptomycin has a streptidine aminocyclitol nucleus while the other aminoglycosides have a 2-deoxystreptadine nucleus. Spectinomycin, an aminocyclitol, also has an aminocyclitol nucleus but lacks the sugar groups. Therefore, the correct full name for the aminoglycosides is the aminoglycosidic aminocyclitols.

PHYSIOCHEMICAL PROPERTIES

- Highly polar polycations, organic bases, \( \text{pK}_a \) values range from 7.2 to 8.8
- Highly hydrophyllic, lipid insoluble
- Optimal antibacterial activity at a pH of 7.5-8.0
- Aminoglycosides can be inactivated by \( \beta \)-Lactams \textit{in-vitro}, gentamicin is the most susceptible
- Storing drinking water solutions in rusty containers (swine) will lead to inactivation of gentamicin
- Aminoglycosides are minimally absorbed from the gut (3-5% for most)
- Minimally bound to plasma protein, but readily bind to cellular debris

MECHANISM OF DRUG ACTION

- Protein synthesis inhibition
  - Individual aminoglycosides do one or more of the following:
    (1) Bind to 30S ribosomal subunit (one or more sites) to cause RNA codon misreading
    (2) Ribosome / mRNA initiation process is blocked
    (3) tRNA binding to ribosome is stabilized, preventing translocation
    (4) There is also possibly some cell surface labilizing properties (steps 1-3 alone do not account for the bactericidal activity of the aminoglycosides)

Gentamicin, kanamycin, and neomycin groups: 1 and 3
Streptomycin group: 1 and 2
In contrast, spectinomycin, a bacteriostatic aminocyclitol, only inhibits translocation (3)

Unique situation! A protein synthesis inhibitor that is bactericidal.
The hydrophillic nature of aminoglycosides gives poor penetration into bacteria. Penetration into bacteria is dependent on the following processes.

1. Water filled channels in the polysaccharide outer layer, "porins", allow penetration of the aminoglycoside through the cytoplasmic membrane.

2. **Energy dependent phase I** - Oxygen dependent, active uptake occurs at the cytoplasmic membrane. This process is dependent on electron transport to establish a membrane potential (negative on inside) to "pull in" the aminoglycoside. This process is blocked by hyperosmolality, low pH, and anaerobic conditions.

3. **Energy dependent phase II** is thought to involve disruption of the cytoplasmic membrane, ion leakage is noted before cell death. This helps explain the bactericidal action of the aminoglycosides.

Relate these mechanisms of action to the generalized group spectrum below!

**SPECTRUM**

Primarily includes aerobic, gram (-) bacilli and gram (+) cocci. Aminoglycosides are especially noted for their gram (-) aerobic spectrum. They have minimal activity against anaerobes or facultative bacteria in anaerobic conditions.

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<td>++++</td>
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</table>

Gram (+) aerobe specifics:
Variable Streptococcus efficacy with many resistant

Gram (-) aerobe specifics:
Enterobacteriaceae – yes
Pseudomonas - yes

Anaerobe specifics:
Just nothing there (remember oxygen-dependant uptake into bacteria)
Generalized 4-quadrant classification of aminoglycosides: Keep in mind that different dosing regimens may be necessary for the different pathogens included in a drug’s “spectrum”. Also, the spectrum of different members of the aminoglycoside group differ.

<table>
<thead>
<tr>
<th>Aerobic</th>
<th>Anaerobic</th>
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<tbody>
<tr>
<td><strong>Gram (+)</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staph</em> spp.</td>
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<tr>
<td>Some <em>Strep.</em></td>
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<tr>
<td><strong>Gram (-)</strong></td>
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<tr>
<td><em>E. coli</em></td>
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<tr>
<td><em>Klebsiella</em></td>
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<tr>
<td><em>Proteus</em></td>
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<tr>
<td><em>Pseudomonas</em></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em></td>
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<tr>
<td><em>Enterobacter</em></td>
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<tr>
<td><em>Shigella</em></td>
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<tr>
<td><em>Mannheimia hemolytica</em></td>
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<tr>
<td><em>Pasteurella</em></td>
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<tr>
<td><em>Haemophilus</em></td>
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<tr>
<td><em>Serpulina hyodysenteria</em>, an oxygen-tolerant anaerobe, and <em>Mycoplasma</em> spp. may also be susceptible.</td>
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</tbody>
</table>

Many *Pseudomonas* isolates are resistant, also *E. coli* and *Klebsiella* (Amikacin may be effective where gentamicin is not.) Gram (+) activity is limited. *Streptococcus* spp. may be highly resistant, gentamicin is sometimes added to *Strep.* cultures to reduce contaminants. Resistant species of *Staph.* may emerge rapidly during therapy with gentamicin.

**Bacteria that the literature lists as “susceptible”:**

<table>
<thead>
<tr>
<th><em>E. coli</em></th>
<th><em>Salmonella</em></th>
<th><em>Mycoplasma</em></th>
<th><em>Shigella</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Klebsiella</em></td>
<td><em>Enterobacter</em></td>
<td><em>Staphylococcus</em></td>
<td><em>Serattia</em></td>
</tr>
<tr>
<td><em>Proteus</em></td>
<td><em>Pseudomonas</em></td>
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</tbody>
</table>

Common uses for the aminoglycosides include *Salmonella, Pseudomonas aeruginosa* and *E. coli*.

**Streptomycin** has the most activity against *M. tuberculosis*.

**Tobramycin** is noted for the best in-vitro potency against *Pseudomonas aeruginosa* of the aminoglycosides. Practically, you will have more ready access to amikacin in a veterinary clinic and will likely go with that as your best aminoglycoside choice. Amikacin will also be the one you can ask for in an expanded susceptibility test.

**Amikacin** is more resistant to enzymes produced by enterobacteiraceae, so it may be effective when resistance is found for gentamicin and tobramycin. It is considered to have the broadest spectrum of the aminoglycosides.

**Paromomycin** is primarily noted for amoebicidal and antihelmintic uses in human medicine.
There is a high degree of **cross-resistance** between gentamicin and other aminoglycosides (except for amikacin and tobramycin).

**RESISTANCE DEVELOPMENT**

Resistance of primary clinical importance is due to plasmid-controlled enzymes in the periplasmic space of gram-negative bacteria. Several of these enzymes are known, with varying specificity across the aminoglycoside antimicrobials. Other mechanisms of resistance include decreased uptake into the cell, and modification of the ribosome. Chromosomal mutation may also play a role. This is most important for streptomycin.

The important concept about these plasmid-associated resistance genes is that the plasmid may also carry resistance genes for multiple other antimicrobials. We often encounter E. coli isolates that are multi-drug resistant (3 or more antimicrobials test as resistant), or pan resistant, where almost all antimicrobials tested result in “resistant”.

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

**IV, IM, or SC** for systemic effects. Oral use is relegated to situations where activity only in the gastrointestinal tract is needed. In human medicine, the IV dose is often given in an infusion over 30-60 minutes. In veterinary medicine, the IV dose is commonly given as a bolus.

As of 2014, “Animal Drugs @ FDA” lists 46 veterinary products for gentamicin, 68 veterinary products for neomycin, and 3 veterinary products for amikacin. Not all of these may be currently marketed. Many are generic equivalents of others. Here is a partial list to demonstrate the diversity of products.

**Amikacin solution**, 50 or 250 mg/ml (dogs, horses)

**Gentamicin Intrauterine in mares**
**Gentamicin ophthalmic ointment and solution**
**Gentamicin topical spray for dermal infections** in dogs
**Gentamicin otic solution** (gentamicin, mometasone Furoate, Clotrimazole)
**Gentamicin otic ointment** (with betamethasone)

**Neomycin/aminopropazine tablets** (diarrhea in dogs)
**Neomycin/tetracaine/hydrocortisone ointment** (dogs and cats)
**Neomycin/prednisolone ophthalmic ointment** (dogs and cats)
**Neomycin/flumethasone/polymyxin B ophthalmic solution** (dogs and cats)
**Neomycin injectable solution** (dogs and cats, would be very infrequently used)
**Neomycin/fluocinolone** (dermal cream for dogs and cats)
**Neomycin/triamcinolone/nystatin/thiostreptin ointment or cream** (Panalog®, dogs and cats)
Neomycin/bacitracin/polymyxin B/hydrocortisone ophthalmic ointment (dogs and cats)

Food animal applications:

Gentamicin oral solution for swine (for enteric infections, *E. coli*)
Gentamicin soluble oral powder for swine (for enteric infections, *E. coli*)
Gentamicin egg dipping solution for turkey eggs (breeding only, not for human consumption)
Gentamicin topical Ophthalmic spray for Infectious Bovine Keratoconjunctivitis

Neomycin soluble powder (cattle, goats, sheep, swine, turkeys)
Neomycin/oxytetracycline feed additive (cattle, chickens, turkeys, sheep, swine)
Neomycin medicated feed premix or milk replacer (cattle, goats, sheep, swine)
Neomycin liquid (Biosol®, undiluted orally or in water, cattle, goats, sheep, swine)

PHARMACOKINETICS

The aminoglycosides are poorly lipid soluble (remember they are highly polar). They have limited capability to penetrate cellular membranes, resulting in minimal absorption after oral administration, a low **volume of distribution** (usually in the 0.2 - 0.4 L/kg range, which approximates extracellular fluid volume), and minimal distribution to the CNS. Volumes of distribution are expected to be higher in neonates due to the higher amount of ECF.

Their highest **tissue concentrations** are in the renal cortex and cochlear tissue. These tissues have the highest concentrations of phospholipids in their cellular matrix. The anionic nature of these phospholipids attract the cationic aminoglycoside. For this reason, these phospholipids (phosphatidylinositol especially) are sometimes referred to as “aminoglycoside receptors.”

**Relate these tissue concentrating characteristics to the key toxicities**

**Plasma protein** binding is usually less than 20-25%, but there is significant binding to cellular debris.

**Elimination half-times** are short, typically 1-3 hours. But, they have been documented to increase to as long as 24 hours in humans with end-stage renal failure. **The primary route of excretion** is through the kidneys for the parent compound. Urine concentrations may be 100 times serum concentrations.

The aminoglycosides will back diffuse into plasma from intramammary administration in cattle in concentrations sufficient to produce prolonged renal residues.

When the aminoglycosides are **dosed** on a weight basis, larger animals require a lower dose on a mg/kg basis. This is because GFR decreases on a per KG basis in larger animals. In contrast, doses are fairly constant across species if based on body surface area or basal metabolic rate.
PHARMACODYNAMICS

The aminoglycosides are considered to be “peak dependent”, bactericidal compounds. While it is a generalization, current therapies typically aim for a peak serum concentration that is 8-10 times the MIC of the target pathogen. This peak is achieved once a day. You will see some references that still list doses as often as Q6H. These should not be used. Combining the total daily dose into a Q24H dosing regimen not only increases the peak, but also allows a low trough concentration prior to the next dose that appears to allow the concentrations in renal and otic tissue to decline, thereby decreasing toxicity as compared to a more frequent dosing regimen.

For some bacteria, aminoglycosides have demonstrated a concentration-dependant post-antimicrobial effect which causes the bacteria to be “crippled” for a period after the concentration falls below the minimal inhibitory concentration (MIC).

DO NOT ADMINISTER AMINOGLYCOSIDES BY CONSTANT INTRAVENOUS INFUSION!

In human medicine they may administer the dose over 30-60 minutes through an IV infusion pump. This still results in a short duration peak while achieving a sufficient plasma concentration trough prior to the next dose.

SUSCEPTIBILITY TESTING

Aminoglycoside breakpoints adapted from CLSI VET01-S2 (2013). Only the “generic” breakpoints (unshaded) have been specifically approved for use in veterinary medicine based on pharmacokinetic and pharmacodynamic data.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>16</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>“Generic” breakpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin – dogs – Enterobacteriaceae, <em>Pseudomonas aeruginosa</em></td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

“Generic” gentamicin breakpoints – Derived from microbiological, pharmacokinetic (using accepted clinical doses), and pharmacodynamic data. For dogs, the dose of gentamicin modeled was 10 mg/kg q24h, IM. For horses, the dose modeled was 6.6 mg/kg q24h, IM.
ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Renal toxicity - Neomycin is the most severe and is not appropriate for systemic use. Gentamicin also has extensive potential. Amikacin is considered less toxic than neomycin or gentamicin, but also has significant renal toxicity potential. Concurrent use with loop diuretics or osmotic diuretics may increase nephrotoxic potential of the aminoglycosides. Nephrotoxicity is best avoided by allowing the serum concentration to fall below a critical “trough” concentration prior to the following dose. In humans, this concentration for gentamicin is reported as approximately 2 µg/ml, and 6 µg/ml for amikacin.

Nephrotoxicity will typically be bimodal, with an initial nonazotemic phase followed by a clinical, azotemic phase. Once you enter the azotemic phase, cessation of aminoglycoside therapy will most likely not stop the azotemia where it is, instead you may expect increasing severity of the situation. One study showed that the urine GGT:creatinine ratio was a much earlier indicator of renal toxicity as compared to urine protein:creatinine ratios, urine SG, or serum creatinine. If therapeutic monitoring is available, an increase in the elimination half-life of gentamicin is a very sensitive indicator. Urine protein may be monitored in practices, with development of proteinuria being an indication of renal toxicity; although by the time this is detected there has already been significant renal damage.

Ototoxicity - Auditory or vestibular symptoms: Auditory symptoms are most frequent with amikacin, neomycin, kanamycin. Vestibular symptoms are most frequent with streptomycin, gentamicin, tobramycin. Cats are very susceptible to the vestibular effects of the aminoglycosides, while dogs tend to present with auditory symptoms. You may expect that renal toxicity will occur prior to significant ototoxicity. Think about this in working dogs before taking off with a regimen of aminoglycosides!!

A predisposition to aminoglycoside auditory toxicity has been linked to mutations in ribosomal RNA. Animal models have also demonstrated that reactive oxygen species play a major role in auditory toxicity. This research has suggested that concurrently administered antioxidants or iron chelators may decrease ototoxicity due to aminoglycosides. Bates, DE. Aminoglycoside ototoxicity. Drugs of Today, 39(4): 277-285, 2003.

Neuromuscular blockade - Use concurrently with general anesthetics or neuromuscular blocking agents may potentiate neuromuscular blockade.

Excessive withdrawals for extra-label use in food animals - FARAD is suggesting an 18 month withdrawal for injecting gentamicin in cattle. For neomycin, less than 240 days in cattle, after an extralabel intramuscular or subcutaneous injection, will get you in trouble.
NOTES ON THE USE OF AMINOGLYCOSIDES IN FOOD ANIMALS

FACTS

The only food animal injectable label for gentamicin is for IM injection in pigs up to 3 days old for the treatment of colibacillosis. All other labels are for oral or topical use. The only beef cattle label for gentamicin is a pinkeye spray. No serum concentrations are detectable after use of this spray, therefore there is no tolerance for gentamicin in bovine tissues. Neomycin is labeled in beef-cattle for oral use only.

The therapeutic index is extremely narrow in animals with normal hydration status. We must assume it is even narrower in dehydrated animals (pneumonia in cattle?). There is the fact (not possibility) of extended tissue residues to deal with. This creates a problem when gentamicin is used on stocker or background cattle that are then sold to a finishing lot with no treatment records. It is possible that residues will be present at slaughter, or in realizers, in these situations. These occurrences have been documented. FARAD (Food Animal Residue Avoidance and Depletion program 1-888 USFARAD) has established a slaughter withdrawal of 18 months (540 days), in cattle. A minimal withdrawal of 240 days is necessary for the parenteral use of neomycin. This is confirmed by documented residue violations.

OPINION

The parenteral use of gentamicin or neomycin for the treatment of pneumonia in cattle does not make sense. (1) The extended slaughter withdrawal creates a significant chance of slaughter residues. This is particularly irresponsible when we consider that this residue may be passed to another owner without their knowledge. (2) There is absolutely no published clinical trial data to support the efficacy of these drugs in bovine pneumonia. (3) Neomycin has an extreme potential for nephrotoxicity, with the therapeutic index being even narrower in dehydrated animals. (4) Cost is not a valid reason for extra-label drug use. (5) If you use gentamicin or neomycin in this manner, you are on your own. You may expect no company support for residue violations or loss of cattle due to toxicity. The benefit flow is one-way to the company.

Detriments

- Extended withdrawal
- Toxicity potential
- No company backing
- Veterinarian liability

Benefits

- Veterinarian???
- Producer???

The following position statements or resolutions have been adopted.

The Academy of Veterinary Consultants has adopted the following position statement.

“The systemic use of aminoglycoside antibiotics presents a potential conflict to the stated objectives of the AVC Standards of Practice because scientific justification for such use is limited, and because it is known that identifiable residues in kidney tissue can result for an undetermined extended period of time.
Therefore, the AVC hereby resolves that until further scientific information becomes available alleviating safety and efficacy concerns, aminoglycoside antibiotics should not be used in cattle, except as specifically approved by the FDA.”

**The American Association of Bovine Practitioners adopted the following statement by a vote of its members.** “The American Association of Bovine Practitioners, being cognizant of food safety issues and concerns, encourages its members to refrain from the intramuscular, subcutaneous intravenous or intramammary extra-label use of the aminoglycoside class of antibiotics in bovines.”

**The National Cattlemen’s Beef Association has adopted the following resolution.**

“When, the Academy of Veterinary Consultants (AVC) is developing standards of veterinary practice and drug use; and Whereas, the National Cattlemen’s Beef Association’s ongoing efforts to establish and implement a Beef Quality Assurance program requires the cooperation of veterinarians, nutritionists and the pharmaceutical industry.

Therefore be it resolved, that NCBA recognizes and endorses the efforts of AVC and encourages other organizations and individuals to join in these efforts.

Be it further resolved, the NCBA endorses the AVC recommendation that until scientific information becomes available alleviating safety and efficacy concerns, aminoglycoside antibiotics should not be used in cattle except as specifically approved by the FDA.”

**AVMA Position on Aminoglycoside Antibiotics, Approved by AVMA House of Delegates, 1998**

“Until further scientific information becomes available, aminoglycoside antibiotics should not be used in cattle, except as specifically approved by the FDA.”
THE AMINOCYCLITOLS

MEMBERS OF THE GROUP

**Spectinomycin**

Veterinary labels - Spectinomycin HCL injectable (Spectam®), water soluble powder (Spectam® water soluble), water soluble powder form in combination with lincomycin (LS-50®), oral solution (Spectam® Scour-Halt™)

Spectinomycin sulfate injectable (Adspec®) - No longer available, this formulation was approved for treatment of bovine respiratory disease with daily injections.

**Apramycin** – As of 2003, no longer available

**PHYSIOCHEMICAL PROPERTIES**

Water soluble, poorly lipid soluble

**MECHANISM OF DRUG ACTION**

Spectinomycin binds to the 30S ribosomal subunit, inhibiting protein synthesis.

Usually considered bacteriostatic, some reports indicate bactericidal activity at approximately 4 times the MIC

Spectinomycin is not very potent on a weight basis, with “susceptible” bacteria having MICs in the 20 - 30 µg/mL range.

**SPECTRUM**

<table>
<thead>
<tr>
<th></th>
<th>Aerobic</th>
<th>Anaerobic</th>
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<tbody>
<tr>
<td>Gram (+)</td>
<td>Strep.</td>
<td></td>
</tr>
<tr>
<td>Gram (-)</td>
<td><em>Mannheimia hemolytica</em></td>
<td></td>
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<tr>
<td></td>
<td><em>Pasteurella multocida</em></td>
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<td></td>
<td><em>Histophilis somni</em></td>
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<td></td>
<td><em>Salmonella</em></td>
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<td></td>
<td><em>E. coli</em></td>
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<td></td>
<td><em>Enterobacter</em></td>
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<td></td>
<td><em>Klebsiella</em></td>
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<td></td>
<td><em>Proteus</em></td>
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</table>

Also Mycoplasma

Spectinomycin is most commonly used in veterinary medicine in poultry, cattle, and swine. Adspec (Pfizer) was labeled for bovine respiratory disease but the company ceased marketing the product in the United States in 2007.
Therapeutic targets in food animals include *Mannheimia haemolytica* in cattle and *Actinobacillus pleuropneumonia* in swine, although susceptibility summaries indicate mounting resistance. Efficacy against Gram-negative rods is unpredictable. *Pseudomonas* and anaerobic bacteria are considered resistant. *Mycoplasma* spp. are considered within the spectrum, but not to the extent of the tetracyclines and macrolides.

**RESISTANCE DEVELOPMENT**

The major mechanism of importance is chromosomally mediated. Resistance may develop very quickly. Cross-resistance with aminoglycosides has not been reported.

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

**IV, IM, or SC** for significant systemic effects. Systemic bioavailability following oral administration is very low. Activity after **oral** administration should be considered as being limited to the gastrointestinal tract. There are oral products available as powders for inclusion in water systems or as oral solutions.

**PHARMACOKINETICS**

Spectinomycin pharmacokinetics are very similar to the aminoglycosides, with short elimination half-times, low volumes of distribution, and limited distribution beyond the extracellular fluid in veterinary species.

**ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES**

The aminocyclitolos do not display the toxicity profile of the aminoglycosides. However, the aminocyclitolos may cause neuromuscular blockade as do the aminoglycosides.
### BETA - LACTAMS: THE PENICILLINS
(6-aminopenicillanic acid derivatives)

| Penicillin G (benzyl penicillin) | - Isolated from *Penicillium notatum* by Alexander Fleming in 1929.  
|                                 | - Provided in several forms, injectable only  
| **Na and K pen G:**             | Used for IV injection, very rapidly absorbed from IM or SC injection sites. Very rapidly eliminated, would require Q6h administration.  
| **Procaine Pen G:**             | Multiple veterinary labels, procaine molecule increases absorption time from injection site (flip-flop kinetics) thereby increasing apparent elimination half-time. Not for IV use (a suspension).  
| **Benzathine penicillin G:**    | Multiple veterinary labels, “long acting penicillin” typically a 50:50 mix with procaine pen G in commercial products. A very large molecule (benzathine bridge between 2 pen G molecules) which displays more pronounced flip-flop kinetics. |

| Penicillin V (Phenoxymethyl penicillin) | - Active against gram (+) cocci, but readily hydrolyzed by penicillinase  
|                                         | - Penicillin V is acid-stable, and may be given orally |

**Penicillinase-resistant penicillins**, effective against penicillinase resistant *Staph. aureus*, but less potent against other organisms sensitive to penicillin G.

- **Methicillin** (no longer available, but often referred to as the class prototype)  
- **Isoxazolyl penicillins** - Oxacillin, Cloxacillin (VL intramammary products), Dicloxacillin (VL Dicloxin capsules, intramammary products), Flucloxacillin  
- Nafcillin

**Aminobenzylpenicillins**, activity extended on the gram (-) side, such as *Haemophilus, E. coli,* and *Proteus*. The aminopenicillins are readily hydrolyzed by broad-spectrum beta-lactamases found in some gram (-) isolates

- **Ampicillin** [VL Polyflex injectable suspension] (Potassium metacillin is hydrolyzed to ampicillin, both are active, VL Hetacin® K).  
- **Amoxicillin** [VL Amoxitabs, Amoxidrops]  
- **Bacampicillin** (Spectrobid®, human label) – a prodrug rapidly transformed to ampicillin

**Antipseudomonal (extended spectrum) penicillins**, activity extended to include *Pseudomonas, Enterobacter,* and *Proteus*.

- **Carboxypenicillins**: Carbenicillin (discontinued in the U.S.), Ticarcillin (VL Ticillin), Temocillin – a modified ticarcillin has increased enterobacteriaceae activity at the expense of other activity  
- **Acylaminopenicillins (ureidopenicillins)**: Azlocillin, Mezlocillin, Piperacillin (all discontinued in the U.S., except for potentiated piperacillin as below)

**Potentiated penicillins**

- **Amoxicillin-Potassium clavulanate** [VL Clavamox®, HL Augmentin®]  
- **Ticarcillin-Potassium clavulanate** [HL Timentin®]  
- **Ampicillin-sulbactam** [HL Unasyn®]  
- **Piperacillin-Tazobactam** [Zosyn®]
In the KSU CVM Pharmacy:

- Procaine penicillin G injectable
- Penicillin G sodium injectable
- Penicillin G potassium injectable

- Amoxicillin tablets
- Amoxicillin oral suspension
- Amoxicillin/clavulanate oral suspension
- Amoxicillin/clavulanate tablets

- Ampicillin sodium injectable
- Ampicillin trihydrate injectable
- Ampicillin/sulbactam injectable
- Ampicillin capsules

**PHYSIOCHEMICAL PROPERTIES**

The penicillins are water soluble, organic acids with very poor lipid solubility.

One mg of Sodium Pen G = 1667 International units (IU), 1 mg of Potassium Pen G = 1595 IU, 1 mg of procaine penicillin G = 1000 IU.

Several natural penicillins can be produced, Penicillin G is the only one used clinically. The penicillin nucleus (containing the β-lactam ring) is necessary for antibacterial activity; any change in this molecule causes loss of all antibacterial activity.

The basic penicillin molecule: an acyl side chain, a beta-lactam ring, and a thiazolidone ring.

Depleting cultures of *Penicillium chrysogenum* of side-chain precursors yields 6-aminopenicillanic acid. Synthetically adding different sidechains alters spectrum and β-lactamase resistance. This is the basis for the synthetic penicillins.

Sodium and potassium salts of penicillin G and amoxicillin are water soluble and may be injected IV. Benzathine penicillin G and the procaine salt of penicillin G are not water soluble, so are available in suspensions. IV administration of the procaine salt may result in procaine toxicity due to rapid dissociation of the procaine molecule from the penicillin G molecule. The procaine also dissociates after IM or SC administration, but the release is slow enough to prevent toxicity.
MECHANISM OF DRUG ACTION

**Penicillins work by inhibiting bacterial cell wall synthesis.** Cross linking of the peptidoglycan chain is inhibited. It is thought that penicillins bind to penicillin binding proteins (PBPs) in the bacterial cell wall. PBPs are enzymes that are essential in the final transpeptidation (crosslinking) step of cell wall synthesis. The beta-lactam ring acts as a structural analogue of acyl-D-alanyl-D-alanine, the substrate for the enzymes leading to the formation of the peptide chain crosslinks. The enzymes are used up on the “fake” substrate, limiting their activity on the true substrate. Cell wall crosslinking is now defective, decreasing the ability of the bacterial cell to withstand osmotic pressure.

**Main point!! Penicillins are most active against bacteria which are growing and dividing!!**

Bacterial cell wall (surface view):

![Peptidoglycan: Long Polysaccharide chains consisting of N-acetyl muramic acid and N-acetyl glucosamine](image)

![Peptide chain crosslinks](image)

Binding to PBPs 1A, 1B, 2, and 3 are lethal (bactericidal), but binding to PBPs 4, 5, and 6 do not typically result in cell death. Types of PBPs vary between Gram (-) and Gram (+) bacteria. Penicillins also differ in affinity for the different PBPs. Penicillins and cephalosporins with more affinity for PBP 3 may be more likely to cause extensive release of endotoxin in Gram (-) septicemia therapy. Some of the literature suggests that aminoglycosides are less likely to cause this endotoxin release. One paper suggests combining amikacin with ampicillin, imipenem, or ceftiofur to decrease this endotoxin release by the beta-lactams. In human medicine, ceftazidime has been suggested as a third generation cephalosporin with potential for increased endotoxin release. The jury is still out on the clinical significance of these findings.

Penicillins may also induce bacterial autolysis by inhibition of compounds responsible for inhibiting murein hydrolases. When cell wall synthesis occurs, the murein hydrolases are responsible for cleaving the cell wall to make way for new peptidoglycan structures. Penicillins may “turn them loose”, resulting in cell autolysis. It has been demonstrated that some species of staphylococci and streptococci either do not have these enzymes or have them in very low amounts. The penicillins will inhibit, but not kill these variants.
SPECTRUM

For interpretation of ++, +++++, and blacked-out quadrants see the key immediately following the index for these notes.

Penicillin G

<table>
<thead>
<tr>
<th>++</th>
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<td>+++</td>
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</table>

Gram (+) aerobe specifics:
- Staph may be initially susceptible but may rapidly become resistant due to inducible penicillinase enzymes. A potential drug for *Streptococcus*, *Erysipelothrix rhusiopathiae*, *Bacillus anthracis*, *Listeria monocytogenes*, *Truperella pyogenes*.

Gram (-) aerobe specifics:
- It would not be a drug of choice for Gram (-) aerobe infections
- Enterobacteriaceae – no
- Pseudomonas – no
- Pasteurella multocida on the label for bovine respiratory disease, but ???

Anaerobe specifics: Consider it an excellent anaerobic antimicrobial
- Inactive against *Rickettsia*, mycobacteria, fungi, *Mycoplasma* (why not Mycoplasma?)

Aminopenicillins (amoxicillin, ampicillin)

<table>
<thead>
<tr>
<th>++</th>
<th>++</th>
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</thead>
<tbody>
<tr>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

Gram (+) aerobe specifics:
- We are emphasizing a decreased spectrum in this quadrant as compared to Pen G. There can still be significant activity against Staph and Strep. You will use oral amoxicillin a lot in small animal practice aimed at this quadrant since it is able to be given orally as opposed to penicillin G.

Gram (-) aerobe specifics:
- We have gone to +++++ to emphasize a dramatically increased spectrum in this quadrant as compared to Pen G, but it is not equal to an aminoglycoside, or a fluoroquinolone.
- Enterobacteriaceae – no (technically in the spectrum, but extensive resistance. However we may still address these pathogens in urinary tract infections due to huge concentrations in the urine) ⚠️
- Pseudomonas – no
- Plasmid-mediated, acquired resistance is common in gram (-) organisms such as *E. coli* and *Salmonella*
Anaerobe specifics:
These still have significant anaerobic potential, but less as compared to Pen G. There may be times it is combined with a drug such as a fluoroquinolone for 4-quadrant outpatient therapy, where amoxicillin or potentiated amoxicillin is looked to for picking up the Streptococci and anaerobic slack for the fluoroquinolone. Amoxicillin is picked instead of penicillin G because amoxicillin can be administered orally with good bioavailability.

“Others”
Also includes spirochetes (Borrelia, Leptospira)

Antipseudomonal (extended spectrum) penicillins (ticarcillin, piperacillin)

Gram (+) aerobe specifics:
We are emphasizing a decreased spectrum in this quadrant as compared to Pen G and the aminopenicillins.

Gram (-) aerobe specifics:
The best of the penicillins for this quadrant
Enterobacteriaceae – yes
Pseudomonas – yes (frequently reported resistance out there, but the best of the penicillins)

Anaerobe specifics:
Probably a little harsh saying no activity, but for this course we want to emphasize that it would definitely not be the penicillin group of choice for anaerobes. For example, Bacteroides fragilis is considered to be in the spectrum.

Don’t confuse “extended spectrum” with “penicillinase resistant”, this group may still be inactivated by some penicillinases.

Penicillinase resistant penicillins (oxacillin, cloxacillin)

For this course, consider for Staph only
There may be activity against other pathogens, but other penicillins would be better choices for these pathogens
Resistance to this class of penicillins is termed “methicillin resistance” even though methicillin is no longer available for clinical use. Oxacillin may be tested in its place.

“Methicillin-resistant” strains of Staph. are here and are common!! By convention, methicillin resistance in a Staph isolate is considered to indicate resistance to all β-lactams. This was a rule
developed in relation to intravenous therapy of MRSA in humans. We don’t know how this applies to examples in veterinary medicine such as MRSA in canine dermatology.

**Potentiated penicillins**

Significant improvement against beta-lactamase producing pathogens (penicillinase in this case). The potentiation does not expand the spectrum beyond the original spectrum of “susceptible” organisms, but rather regains activity against beta-lactamase producing pathogens due to the potentiating compound binding with significant amounts of the beta-lactamase and taking it out of play, allowing the penicillin group antimicrobial to reach the site of activity in an active form.

**RESISTANCE DEVELOPMENT**

Bacterial resistance to penicillins is mediated by:

- Degradation by bacterial enzymes (over 400 β-lactamases now identified)
- Reduced penetration
- Penicillin binding site alteration

Gram-positive bacteria: Inducible, plasmid mediated extracellular enzymes are released which destroy the beta-lactam ring. *Staphylococcus aureus* is particularly noted for this property. Example: *mecA* gene encoding for methicillin resistance in *Staph. aureus*.

Gram-negative bacteria: Inherent (present prior to exposure) resistance is due to lack of penicillin binding proteins, low permeability to the beta-lactams, and beta-lactamase enzymes. Extended-spectrum beta-lactamases (ESBLs) are becoming a problem with *Enterobacter*, *Klebsiella*, and *E. coli*.

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

**Na and K pen G: IV, IM, or SC.** The Pen G for IV use! K pen G more common than Na pen G due to cost.

**Procaine pen G: IM or SC.** An aqueous suspension with a significant amount of procaine, both of which spell trouble for IV administration.

**Penicillin G/ Novobiocin combination.** Lactating and dry cow intramammary products

**Benzathine penicillin G: IM or SC.** Make sure you realize the long concentration curve tail with the SC and the potential for extended residues in food animals with both IM and SC routes.

**Penicillin V: Oral.** The ONLY acid stable version of penicillin G suitable for oral administration.

**Oxacillin** – all human products, Oral: oxacillin sodium capsules, powder for oral solution, IV, IM (SC?): oxacillin sodium

**Cloxacillin** – available in dry cow (benzathine) and lactating cow (sodium) intramammary formulations.
**Ampicillin** – IV as sodium salt, **IM or SC** as trihydrate salt, **oral** as capsules (trihydrate or anhydrous forms)

**Ampicillin sodium/sulbactam sodium** – IV, IM, (SC?) (human label) reconstituted powder for injection

**Hetacillin** – intramammary preparation for cattle (dry cow and lactating cow), quickly metabolized to ampicillin, also capsules, tables, oral liquid (dogs and cats)

**Amoxicillin** – IV as sodium salt, **oral** as tablets and suspensions, suspension for IM or SC administration, **intramammary** formulation

**Amoxicillin/clavulanate** – **Oral**: tablets and powder for oral suspension

**Ticarcillin** – IV or IM (SC?): (Human labeled) Ticarcillin disodium powder for injection, VL is ticarcillin sterile powder for equine uterine infusion.

**Ticarcillin/clavulanate potassium** – IV or IM (SC?): (human labeled) ticarcillin disodium/clavulanate posassium powder for injection

**Piperacillin/tazobactam** – IV (IM or SC?) (human label)

**PHARMACOKINETICS**

A pKa of approximately 2.7 for the penicillins causes these acidic compounds to be primarily ionized in the plasma. Their distribution is predominantly confined to the extracellular fluid space, although inflammation of the meninges or other membranes may enhance penetration. This limited distribution is reflected in a small volume of distribution, usually in the 0.2 - 0.4 L/kg range. Elimination half-times are very short (0.5 - 2.0 hours). Intramuscular administration of procaine salts or benzathine forms of penicillin, or the trihydrate form of ampicillin, contribute to significantly longer elimination half-times.

The penicillins are excreted primarily through the kidney in the active form, both through filtration and active secretion.

**Amoxicillin is more orally bioavailable than ampicillin after oral administration.** (75-90% vs. 30-50% for humans, approximately 60% vs. 30% in dogs)

**PHARMACODYNAMICS**

Beta-lactams are classified as bactericidal. The efficacy of beta-lactams is most closely linked to the time the serum concentration remains above the MIC of the pathogen. For Gram (+) pathogens, the regimen should provide for the serum concentration remaining above the pathogen MIC for at least 50% of the dosing interval. For Gram (-) pathogens, the time>MIC is debated, but should probably be at least 50% of the dosing interval with some arguments made for close to 100% of the dosing interval.

The beta-lactams exhibit significant post-antibiotic effects (PAE) against most Gram (+) cocci, but little PAE is expected against Gram (-) bacteria.
SUSCEPTIBILITY TESTING: Penicillin group breakpoints adapted from CLSI VET01-S2 (2013). Ampicillin, amoxicillin-claculanic acid, and penicillin “generic” breakpoints are approved by CLSI utilizing veterinary data. The penicillin-novobiocin mastitis breakpoint is a full CLSI-approved breakpoint, meaning that it was brought to the committee by a sponsor and included clinical data. Ampicillin is the class representative for the aminopenicillins and is considered equipotent to amoxicillin in-vitro. Potentiated penicillin breakpoints are listed in the next section. The CLSI has also adapted human breakpoints for penicillin, ampicillin, oxacillin, and ticarcillin. When there is not a veterinary breakpoing available, laboratories may used these instead of the CLSI-approved breakpoints. For example, at this time, there are no veterinary-approved oxacillin or ticarcillin breakpoints, therefore the human breakpoints would be used for susceptibility testing.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ μg/ml)</th>
<th>Intermediate (μg/ml)</th>
<th>Resistant (≥ μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillin G / Novobiocin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine mastitis – <em>Staph. Aureus, Strep agalactiae, Strep. dysgalactiae, Strep. uberis.</em></td>
<td>1/2</td>
<td>2/4</td>
<td>4/8</td>
</tr>
<tr>
<td><strong>Ampicillin CLSI “generic” breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs – skin and soft tissue (<em>Staph. Pseudintermedius</em>)</td>
<td>0.25</td>
<td>---</td>
<td>0.5</td>
</tr>
<tr>
<td>Dogs – skin and soft tissue (<em>Streptococcus canis, Group G, α-hemolytic</em>)</td>
<td>0.25</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Dogs - skin and soft tissue (E. coli) (see note immediately below)</td>
<td>0.25</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>A susceptible breakpoint of ≤ 8 should be used for urinary tract infections. This breakpoint was derived from published literature in which orally administered ampicillin 25.6 mg/kg, and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for five consecutive doses and produced urine concentrations in dogs &gt;300 μg/mL.</td>
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</tr>
<tr>
<td>Horses – respiratory disease <em>Streptococcus equi</em> subsp. <em>zoopneumonieus</em> and subsp. <em>equi</em></td>
<td>0.25</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Swine - respiratory disease <em>Actinobacillus pleuropneumoniae, P. multocida, Strep. suis, B. bronchiseptica</em></td>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Penicillin G CLSI “generic” breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horses – Respiratory, soft tissue <em>Staphylococcus spp., Streptococcus spp.</em></td>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cattle – Respiratory disease <em>Mannheimia haemolytica, Pasteurella multocida, Histophilus somni</em></td>
<td>0.25</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Penicillin G / Novobiocin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine mastitis – <em>Staph. Aureus, Strep agalactiae, Strep. dysgalactiae, Strep. uberis.</em></td>
<td>1/2</td>
<td>2/4</td>
<td>4/8</td>
</tr>
</tbody>
</table>

*Doses modeled for generic breakpoints were*
- Amoxicillin 22 mg/kg P.O. Q12H for canine skin and soft tissue, 11 mg/kg PO, Q8H for canine UTI, 15 mg/kg IM Q24H for swine respiratory disease
- Ampicillin 22 mg/kg IM Q12H for equine resp. disease
- Procaine Penicillin G 22,000 IU/kg IM Q24H for equine respiratory disease and soft tissue, 22,000 IU/kg IM Q24H for bovine respiratory disease
ADVERSE REACTIONS/CONTRAINdications/toxICITIES ★☆☆

The penicillins are very safe, even at very high doses, unless acute anaphylaxis is encountered. Mild reactions such as fever and urticaria are more common. Cross-sensitivity between penicillins should be expected.

Procaine penicillin G may cause violative procaine residues in race horses. Some recommend discontinuation of therapy at least 30 days prior to racing.

The "k pen squirts" may occur in horses after IV injection of potassium penicillin G. This occurs within a few minutes after administration and is typically short lived. It is most likely due to the sudden effect of the potassium as opposed to the penicillin G.

Cases of abortion in sows following procaine penicillin G administration have been reported in the literature.

Penicillin G may be fatal to guinea pigs. Ampicillin may cause clostridial colitis in small rodents and rabbits. Caution should be used in non-ruminant herbivores. We very commonly use K Pen G and Procaine Pen G in horses. **Do not interpret the caution in non-ruminant herbivores as precluding the injectable use of K Pen G and Procaine Pen G in horses.**

Be aware of possible endotoxin release due to rapid bactericidal activity against some Gram (-) organisms. See discussion of relative potential of various beta-lactams under mechanism of action.

Rapid administration of potassium penicillin G may lead to cardiac arrest due to release of potassium. Sodium penicillin G is safer for intravenous use. Procaine penicillin G should never be given by the intravenous route. Even if given IM, extremely high doses of procaine penicillin G may lead to excitement and even death, especially in horses. This is why you pull back on the plunger to make sure that you aren’t in a vessel when injecting procaine pen G IM in horses.

High doses of ticarcillin have been associated with bleeding in humans; use caution in animals with bleeding disorders or those receiving heparin or oral anticoagulants.

Penicillin G has been linked with cases of Coombs-positive hemolytic anemia in horses.
BETA-LACTAMS: BETA-LACTAMASE INHIBITORS

MEMBERS OF THE GROUP

Clavulanic acid
Sulbactam
Tazobactam

Aztreonam may be considered in this group, but has significant antimicrobial properties of its own and a much more limited beta-lactamase binding spectrum. (see monobactams below)

PHYSIOCHEMICAL PROPERTIES

Clavulanic acid is synthetic. The structure is similar to penicillin. It is very sensitive to inactivation by moisture. Sulbactam is a synthetic derivative of 6-aminopenicillanic acid

MECHANISM OF ACTION

Clavulanic acid and sulbactam have very little antimicrobial activity of their own. They both bind with all chromosomally mediated penicillinases and most of the plasmid mediated penicillinases. Sulbactam affinity for beta-lactamases is less than that of clavulanic acid; this difference may be accommodated by dose. Neither has much activity against chromosomally-mediated cephalosporinases.

SPECTRUM

Clavulanic acid - amoxicillin: The therapeutic range is extended to resemble that of “second-generation” cephalosporins. The Enterobacteriaceae and anaerobic spectra are significantly improved over amoxicillin. Activity against Staph. is dramatically improved.

Clavulanic acid - ticarcillin: Activity of ticarcillin against the Enterobacteriaceae and Pseudomonas is improved.

Sulbactam - ampicillin: The spectrum is very similar to clavulanic acid - amoxicillin.

RESISTANCE DEVELOPMENT

Resistance development to the beta-lactamase inhibitors has been minimal. Inducible beta-lactamases may occur in some species, including Enterobacter.

PHARMACOKINETICS

Sulbactam and clavulanic acid pharmacokinetics are very similar to the beta-lactams they are combined with. Sulbactam is only minimally absorbed orally. The oral human product, sultamicillin, is a pro-drug which releases ampicillin and sulbactam in the intestinal wall after absorption.
ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Amoxicillin/clavulanic acid may cause gastrointestinal upset. In cats, stop administration when the cat stops eating. Continuing administration may drive the cat into hepatic lipidosis due to inappetance.

Nausea, vomiting, and diarrhea may occur in human patients after oral administration of clavulanic acid. This is thought to be due to a direct effect on GIT motility.

Neither clavulanic acid or sulbactam should be used in non-ruminant herbivores.

**B-Lactam /β-lactamase inhibitor breakpoints adapted from VET01-S2 (2013).** The amoxicillin-clavulanic acid generic breakpoints were developed using pharmacokinetic and pharmacodynamics data along with MIC distributions of the listed veterinary pathogens. The shaded cells are human breakpoints which have been adapted for veterinary use.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin-clavulanic acid CLSI “Generic” breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs - skin and soft tissue (<em>Staphylococcus</em> spp., <em>Escherichia coli</em>) (see note immediately below)</td>
<td>0.25/0.12</td>
<td>0.5/0.25</td>
<td>1/0.5</td>
</tr>
<tr>
<td>A susceptible breakpoint of ≤ 8 should be used for urinary tract infections. This breakpoint was derived from published literature in which orally administered ampicillin 25.6 mg/kg, and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for five consecutive doses and produced urine concentrations in dogs &gt;300 µg/mL.</td>
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</tr>
<tr>
<td>Cats – skin, soft tissue, UTI (<em>Staphylococcus</em> spp., <em>Streptococcus</em> spp., <em>Escherichia coli</em>, <em>pasteurella multocida</em>)</td>
<td>0.25/0.12</td>
<td>0.5/0.25</td>
<td>1/0.5</td>
</tr>
<tr>
<td><strong>Amoxicillin-clavulanic acid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td>4/2</td>
<td></td>
<td>8/4</td>
</tr>
<tr>
<td>Other organisms</td>
<td>8/4</td>
<td>16/8</td>
<td>32/16</td>
</tr>
<tr>
<td><strong>Ticarcillin-clavulanic acid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em>, Enterobacteriaceae</td>
<td>16/2</td>
<td>32/2 – 64/2</td>
<td>128/2</td>
</tr>
</tbody>
</table>

Doses modeled for generic breakpoints
- Amoxicillin 11 mg/kg orally Q12H for feline skin and soft tissue
- Amoxicillin 11 mg/kg orally Q12H for canine skin and soft tissue
- Amoxicillin 11 mg/kg orally Q8H for canine urinary tract infections
BETA-LACTAMS: THE CEPHALOSPORINS

MEMBERS OF THE GROUP/SPECTRUM

The classic cephalosporin classification system has relied on “generations”. Some authors feel this system fails to address the diversity of more recent cephalosporins. Cephalosporins are modifications of the 7-aminocephalosporanic acid molecule produced by *Cephalosporium acremonium*; those discovered before 1975 are spelled with a “ph” and those 1975 or later are spelled with a “f”. Cephamycins (cefotetan, cefoxitin) are based off of a molecule produced by *Streptomyces* spp., or are a synthetic alterations produced by substituting oxygen for sulfur (latamoxef). They are considered along with the cephalosporins due to almost identical chemical structures and the same pharmacokinetic, pharmacodynamic, and spectrum characteristics.

Classifying cephalosporins by chemical structure is useless since structure and activity are not consistently related; therefore they are classified by activity. Classification systems and information on class characteristics are adapted from the following.


### Traditional cephalosporin classification (“Generations”) table:

<table>
<thead>
<tr>
<th>Generation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First</strong></td>
<td>Oral: cephradine, [<strong>cefdroxil</strong> [VL Cefa-tabs®, Cefa-drops®] cephalexin [HL Keflex®], cephaloglycin&lt;br&gt;Parenteral: cefacetrile, [<strong>cefapirin</strong> [VL (intramammary tubes) Today®, Cefa-Lak®], <strong>cefazolin</strong> [HL Kefzol®, Ancef®], cephalothin [HL Keflin®]]</td>
</tr>
<tr>
<td><strong>Second</strong></td>
<td>Oral: cefachlor [HL Ceclor®], cefuroxime axetil, cefprozil, loracarbef&lt;br&gt;Parenteral: cefamandole, cefonicid, ceforanide, the cephamycins: cefoxitin, cefotetan, cefmetazole</td>
</tr>
<tr>
<td><strong>Third</strong></td>
<td>Oral: [<strong>cefixime</strong> [HL Suprax®, good PK data for dogs], <strong>cefpodoxime proxetil</strong> [human label: Vantin®, VL Simplice™”, generics including a veterinary labeled generic], ceftibuten (HL Cedax), cefdinir (HL Omnicef), cefditoren pivoxil (HL Spectracef)&lt;br&gt;Parenteral: cefmenoxime, cefoperazone, [<strong>cefotaxime, ceftazidime</strong>]&lt;br&gt;ceftizoxime, [<strong>ceftiraxone</strong> [HL Rocephin®], latamoxef (moxalactam), <strong>ceftiofur Na, hydrochloride, and crystalline free acid</strong> (VL Naxcel®, Excenel®, Excede™ respectively), cefsulodin , <strong>cefovecin</strong> (VL Convenia®)]</td>
</tr>
<tr>
<td>“Fourth”</td>
<td>Parenteral: <strong>cefepine</strong>, cefpirome, cefpiramide, cequinome</td>
</tr>
<tr>
<td>“Fifth”</td>
<td>ceftobiprole, ceftaroline, ceftolozane (with tazobactam)</td>
</tr>
</tbody>
</table>

*Also known as “surgicef” or “orthocef”, slang terms for common use as a prophylactic antimicrobial in soft-tissue and orthopedic surgery.*
The first generation cephalosporins are considered to be heavy on gram (+) activity and light on gram (-) activity. Gram (-) activity increases with the generation. In order to address variances within generations, a different system has been adapted by some authors (see revised system below).

**Second generation:** This generation contains cephalosporins and the cephamycins. The Gram (+) activity is considered similar to the 1st generation, with more extensive activity against Gram (-). The cephamycins have less activity against Staph. and Strep., but are much more active against some enterobacteriaceae.

**Third generation:** Much more Gram (-) activity as compared to 1st and 2nd generations. Cefotaxime was the first of the third-generation cephalosporins (it has the best activity against anaerobes out of this generation). Only ceftazidime, cefoperazone and cefsulodin have significant activity against *Pseudomonas* out of this group (ceftazidime is the best). Ceftriaxone represents a molecular modification to lengthen the elimination half-life.

**Fourth generation:** The fourth generation cephalosporins represent an attempt to overcome resistance problems encountered by other generations, notably against *Pseudomonas* and enterobacteriaceae. Cefepime has broad activity against *Strep.*, *Staph.*, *Haemophilus*, and *enterobacteriaceae*. Cefepime, cefpirome, and cefquinome are examples of C-3, quaternary ammonium cephalosporins.

**Fifth generation:** Ceftobiprole has significant coverage of *Pseudomonas aeruginosa*, *Streptococcus pneumonia*, methicillin-resistant *Staph. aureus* (MRSA), and vancomycin-resistant enterococci (VRE). Ceftaroline has efficacy against MRSA as well as broad spectrum activity against both Gram (+) and Gram (-) bacteria.

<table>
<thead>
<tr>
<th>Revised (contemporary) cephalosporin classification.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-quadrant generalized spectrum for groups 1-3 (1st and 2nd generations)</td>
</tr>
<tr>
<td>+++++</td>
</tr>
<tr>
<td>++</td>
</tr>
</tbody>
</table>

Cefazolin has the best Gram (-) activity of the first generation

Essentially very similar to Pen G. There are some differences between first and second generation cephalosporins, with the second generation cephalosporins being similar to the aminopenicillins. We have lumped them together for simplicity in this course. Isolates commonly found to be resistant: *E. coli, Klebsiella, Proteus, Salmonella, Bacteroides fragilis, Bordetella bronchiseptica, Campylobacter, Citrobacter, Enterobacter, Nocardia, Enterococcus faecalis (enterococci), Pseudomonas aeruginosa, Rhodococcus equi, Serratia, Yersinia.*
Four-quadrant generalized spectrum for groups 4-6 (3rd generation): Enhanced activity against Gram (-) aerobes as compared to Groups 1-3.

<table>
<thead>
<tr>
<th></th>
<th>++</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

Cefotaxime is the best choice from this group for anaerobic infections

Ceftazidime is the most active against Pseudomonas

This group is a little dangerous to generalize in this manner due to some large variations within the group. However, we will use the above 4-quadrant presentation for this class, recognizing some individual 3rd generation cephalosporins as being responsible for much of the activity in some of the quadrants.

Ceftiofur has demonstrated clinical efficacy against *Fusobacterium necrophorum* in bovine infectious pododermatitis (foot rot), but otherwise is not considered as having extensive anaerobic activity. Remember, count ceftiofur out for staph!

Both Ceftiofur and cefpodoxime are considered to have poor activity against *Pseudomonas* as compared to other 3rd generation options. Also, recall that cefovecin does not reach MIC90 for E. coli or Pseudomonas

Gram (+) aerobe specifics:
  - We are losing Staph activity but a lot of Strep activity is maintained.

Gram (-) aerobe specifics:
  - Just like other beta-lactams with activity against enterobacteriaceae, be aware that there are a significant number of resistant isolates out there.

Four-quadrant generalized spectrum for group 7 (4th generation): Refractive to extended-spectrum β-lactamases.

<table>
<thead>
<tr>
<th></th>
<th>++++</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We have a ++++ for the Gram (+) category since this would be the one exception to saying that a Staph resistant to methicillin (or oxacillin) would be considered resistant to all other beta-lactams regardless of susceptibility results.

But, the main, HUGE, point for this group is that we get activity back against enterobacteriaceae isolates with extended-spectrum beta lactamases (ESBLs)! Cefepime is an injectable 4th generation that may step in and save a case with an extremely resistant enterobacteriaceae pathogen. Pseudomonas activity is probably not that much improved over the 3rd generation, but may catch some of the isolates resistant to ceftazidime. It depends on the isolate. Pseudomonas isn’t simple.
<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Characteristics and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. First generation, parenteral</td>
<td>Cephacetrile, Cephapirin, Cephaloridine, <strong>Cefazolin</strong>, Cephradine, <strong>Cephalothin</strong></td>
<td>Cephalothin is used as the class representative for 1st generation cephalosporin susceptibility testing, although it is no longer commercially available in the U.S. Cefazolin is considered to have the greatest Gram (-) activity among the 1st generation group. Very effective against Gram (+) pathogens except for enterococci, including β-lactamase producing Staph spp. However, Methicillin-Resistant Staph. Aureus (MRSA) should also be considered resistant to all β-lactams, including the cephalosporins. Acquired resistance is common in Gram (-) pathogens. Consider this group as having no activity against <em>Pseudomonas aeruginosa, Enterobacter</em>, or <em>Serratia</em> spp. However, Gram (-) activity is greater than penicillin G.</td>
</tr>
<tr>
<td>2. First generation, oral</td>
<td>Cefadroxil, Cephadine, <strong>Cephalexin</strong>, Cephaloglycin</td>
<td>As for group 1 with the exception of possibly being more susceptible to the β-lactamases of the Enterobacteriaceae.</td>
</tr>
<tr>
<td>3. Second generation, parenteral and oral</td>
<td>Cefachlor, Cefotetan, Cefoxitin, Cefuroxime, Cefamandole</td>
<td>The published contemporary classification systems include cefachlor and cefuroxime axetil in a general parenteral 2nd generation group. However, they are referenced as effective orally in human references. The Gram (+) activity is considered equal to groups 1 and 2. Gram (-) activity is increased, but resistance is encountered among many Gram (-) genera. Cefoxitin and cefotetan are considered as active against Gram (-) anaerobes.</td>
</tr>
<tr>
<td>4. Third generation, parenteral</td>
<td><strong>Cefotaxime</strong>, <strong>Ceftiofur</strong>, <strong>Cefovecin</strong>, <strong>Ceftriaxone</strong>, Cefmenoxime, Ceftizoxime, Latamoxef</td>
<td>Activity against Streptococci is retained but activity against <em>Staphylococci</em> is reduced as compared to groups 1-3. Gram (-) activity is excellent, with good activity against most Enterobacteriaceae, except for <em>Enterobacter</em> and <em>Serratia</em> spp. Cefotaxime would be the choice out of this group for anaerobic infections.</td>
</tr>
<tr>
<td>5. Third generation, oral</td>
<td>Cefetamet, Cefixime, <strong>Cefpodoxime</strong></td>
<td>As for group 4.</td>
</tr>
<tr>
<td>6. Third generation, parenteral</td>
<td>Cefoperazone, Cefsulodin, <strong>Ceftazidime</strong></td>
<td>This group is very similar to group 4, with the exception of much greater activity against <em>Pseudomonas aeruginosa</em>. (Ceftazidime is considered the most active). Cefsulodin activity is considered narrow other than for <em>P. aeruginosa</em>.</td>
</tr>
<tr>
<td>7. Fourth generation</td>
<td><strong>Cefepime</strong>, Cefpirome, <strong>Cefquinome</strong></td>
<td>Gram (+) activity is back with enhanced activity against <em>Staphylococci</em> spp. Efficacy is also demonstrated against MRSA and <em>Streptococcus</em> spp. High activity against Gram (-) bacteria, especially the Enterobacteriaceae, including those resistant to group 6. Cefepime is especially noted for activity against <em>E. coli</em> and <em>Klebsiella</em> resistant to other cephalosporins and even the fluoroquinolones.</td>
</tr>
</tbody>
</table>
In the KSU CVM Pharmacy:

Injectables
Cefazolin
Cefoxitin
Ceftiofur sodium
Ceftiofur hydrochloride
Ceftiofur crystalline free acid
Cefovec
Cefotaxime
Ceftazidime

Oral
Cephalexin capsules
Cephalexin oral suspension
Cefpodoxime proxetil tablets

CEPHALOSPORIN AND CEPHAMYCIN PHYSIOCHEMICAL PROPERTIES

Like the penicillins, the cephalosporins are acids that are extremely water soluble but poorly lipid soluble.

True cephalosporins are derived from *Cephalosporium acremonium*, based on modifications of the 7-aminocephalosporanic acid nucleus with the addition of synthetic sideshains. The cephalosporins are therefore semisynthetic compounds.

Cephamycins are derived from *Streptomyces* spp., except for latamoxef, which is a synthetic derivative. This group differs from the cephalosporins in having a methoxy group at position 7 of the β-lactam ring of the 7-aminocephalosporanic acid nucleus.

The cephim nucleus: a beta-lactam ring and a dihydrothiazine ring.

R1 modifies spectrum
R2 modifies pharmacokinetic properties, although some spectrum changes may result
R3 modifications for increased beta-lactamase resistance
MECHANISM OF ACTION / PHARMACODYNAMICS

The cephalosporin mechanism of action is the same as for the penicillins. Cephalosporin efficacy is considered to be most closely related to time above the MIC of the pathogen, as for the penicillins. They are bactericidal. See the mechanism of action section under penicillins for a discussion of differential binding to penicillin binding proteins and the effect on endotoxin release.

FOCUS ON VETERINARY CEPHALOSPORINS

Cefovecin (Convenia®)

Cefovecin is an injectable third-generation cephalosporin (Convenia®, Pfizer Animal Health) indicated for the treatment of skin infections associated with *Staphylococcus intermedius* and *Streptococcus canis* (Group G) in dogs and *Pasteurella multocida* in cats.

It has the unique characteristic of mean T1/2 values of 133 hrs (5.5 days) in dogs and 166 hrs (6.9 days) in cats. The extended duration of activity is primarily attributed to extremely high protein binding (98.5% in dogs and 99.8% in cats). Drug bound to plasma proteins is not available for renal elimination and therefore apparent plasma cefovecin clearance is slow.

It is noteworthy that therapeutic free drug concentrations following a single administration in the dog are maintained for 7 days against *Staphylococcus intermedius* and *Pasteurella multocida* but 14 days against *Streptococcus canis* (Group G).

Cefovecin has been shown to increase free concentrations of carprofen, furosemide, doxycycline and ketoconazole due to competitive protein binding, so care should be taken when administering these drugs concurrently. The most common side effect associated with cefovecin administration is allergic reaction or anaphylaxis. Since 65 days are required to eliminate 97% of the administered dose, adverse reactions may require prolonged treatment.

Other adverse events that have been reported include false positive urine glucose tests, neutropenia, anemia, thrombocytopenia, prolonged prothrombin time and transient increases in BUN and creatinine. In a target animal safety study animals receiving 1.5X to 7.5X the label dose exhibited vomiting, diarrhea and swelling at the injection site.

Cefovecin does not reach the MIC90 for *E. coli, Pseudomonas* spp. or enterococci.

Ceftiofur sodium label indications taken directly from the label.

**Indications:** For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine, sheep, goats and horses. For subcutaneous injection in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep and goats.

**Cattle:** NAXCEL® Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Pasteurella haemolytica*, *Pasteurella multocida* and *Haemophilus somnus*. NAXCEL® Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

**Swine:** NAXCEL® Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2.

**Sheep:** NAXCEL® Sterile Powder is indicated for treatment of sheep respiratory disease (sheep bacterial pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*.

**Goats:** NAXCEL® Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*.

**Horses:** NAXCEL® Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*.

**Dogs:** NAXCEL® Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis*.

**Day-Old Chickens:** NAXCEL® Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

**Day-Old Turkey Poults:** NAXCEL® Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old turkey poults.”

Effect of route on pharmacokinetics

**Bovine Pharmacokinetic values for desfuroylceftiofur (1 mg/kg) Note similarities between IV and IM injection.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IM</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>4.14 ± 0.84</td>
<td>7.09 ± 1.59</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>0.75 ± 0.27</td>
<td>0.30 ± 0.59</td>
</tr>
<tr>
<td>AUC 0-∞ (µg•hr/ml)</td>
<td>34.28 ± 6.29</td>
<td>35.89 ± 11.65</td>
</tr>
<tr>
<td>T½β (hrs)</td>
<td>9.65 ± 1.97</td>
<td>8.63 ± 1.28</td>
</tr>
</tbody>
</table>

Adapted from: Product Information Manual. Ceftiofur Sodium Sterile Powder For Use in Cattle. Pharmacia and Upjohn. Only Cmax was significantly different between routes (P < 0.01)
Ceftiofur-specific spectrum information (taken directly from ceftiofur sodium label):

<table>
<thead>
<tr>
<th>Animal</th>
<th>Organism</th>
<th>n</th>
<th>MIC Range (µg/mL)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>Date tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine*</td>
<td>Pasteurella haemolytica (Mannheimia spp.)</td>
<td>461</td>
<td>≤0.03-0.13</td>
<td>0.06</td>
<td>1988-1992</td>
</tr>
<tr>
<td></td>
<td>Pasteurella multocida</td>
<td>318</td>
<td>≤0.03-0.25</td>
<td>0.06</td>
<td>1988-1992</td>
</tr>
<tr>
<td></td>
<td>Haemophilus somnus</td>
<td>109</td>
<td>≤0.03-0.13</td>
<td>0.06</td>
<td>1988-1992</td>
</tr>
<tr>
<td></td>
<td>Fusobacterium necrophorum</td>
<td>17</td>
<td>≤0.06</td>
<td>≤0.06</td>
<td>1994</td>
</tr>
<tr>
<td>**</td>
<td>Salmonella spp.</td>
<td>28</td>
<td>0.06-2.0</td>
<td>1.0</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Bacteroides fragilis group</td>
<td>29</td>
<td>≤0.06-16.0</td>
<td>16.0</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Bacteroides spp., non-fragilis group</td>
<td>12</td>
<td>0.13-16.0</td>
<td>16.0</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Peptostreptococcus anaerobius</td>
<td>12</td>
<td>0.13-2.0</td>
<td>2.0</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Moraxella bovis</td>
<td>100</td>
<td>0.03-0.5</td>
<td>0.25</td>
<td>1998</td>
</tr>
<tr>
<td>Swine**</td>
<td>Actinobacillus pleuropn.</td>
<td>83</td>
<td>≤0.03-0.06</td>
<td>≤0.03</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Pasteurella multocida</td>
<td>74</td>
<td>≤0.03-0.06</td>
<td>≤0.03</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Streptococcus suis</td>
<td>94</td>
<td>≤0.03-1.0</td>
<td>0.25</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Salmonella choleraesuis</td>
<td>50</td>
<td>1.0-2.0</td>
<td>1.0</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>84</td>
<td>0.25-4.0</td>
<td>1.0</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Salmonella typhimurim</td>
<td>98</td>
<td>1.0-2.0</td>
<td>2.0</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus hyicus</td>
<td>100</td>
<td>0.13-1.0</td>
<td>1.0</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>beta-hemolytic Streptococcus spp.</td>
<td>24</td>
<td>≤0.03-0.06</td>
<td>≤0.03</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>Actinobacillus suis</td>
<td>77</td>
<td>0.0019-0.0078</td>
<td>0.0078</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Haemophilus parasuis</td>
<td>76</td>
<td>0.0039-0.25</td>
<td>0.06</td>
<td>1998</td>
</tr>
<tr>
<td>Sheep*</td>
<td>Pasteurella haemolytica</td>
<td>39</td>
<td>≤0.03-0.13</td>
<td>0.13</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>Pasteurella multocida</td>
<td>23</td>
<td>≤0.03</td>
<td>≤0.03</td>
<td>1992</td>
</tr>
<tr>
<td>Horses**</td>
<td>Streptococcus equi subsp. equi</td>
<td>12</td>
<td>≤0.0019</td>
<td>≤0.0019</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Streptococcus zooepidemicis</td>
<td>48</td>
<td>≤0.0019</td>
<td>≤0.0019</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Rhodococcus equi</td>
<td>67</td>
<td>≤0.03-2.0</td>
<td>8.0</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Bacteroides fragilis group</td>
<td>32</td>
<td>0.13-16.0</td>
<td>&gt;16.0</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Bacteroides spp., non-fragilis group</td>
<td>12</td>
<td>0.25-4.0</td>
<td>4.0</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Fusobacterium necrophorum</td>
<td>16</td>
<td>≤0.06</td>
<td>≤0.06</td>
<td>1995</td>
</tr>
<tr>
<td>Canine*</td>
<td>Escherichia coli</td>
<td>44</td>
<td>0.06-64.0</td>
<td>4.0</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>18</td>
<td>0.013-0.5</td>
<td>0.25</td>
<td>1990</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
<td>17</td>
<td>≤0.06-5.5</td>
<td>≤0.06</td>
<td>1990</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
<td>23</td>
<td>≤0.06-4.0</td>
<td>1.0</td>
<td>1992</td>
</tr>
</tbody>
</table>

* Clinical isolates supported by clinical data and indications for use.
** Clinical isolates not supported by clinical data, the clinical significance of these data is not known.
MIC<sub>90</sub> Minimum inhibitory concentration for 90% of the isolates.
MIC<sub>50</sub> Minimum inhibitory concentration for 50% of the isolates.
n = Number of isolates.
Unlike ceftiofur sodium, ceftiofur hydrochloride comes ready to use (RTU) in a cottonseed oil carrier.

Ceftiofur hydrochloride label indications taken directly from the label.

“Swine: … indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus* (Haemophilus) pleuropneumoniae, *Pasteurella multocida*, *Salmonella choleraesuis* and *Streptococcus suis* type 2.

*Cattle*: …indicated for treatment of the following bacterial diseases:
- Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia* spp. (*Pasteurella haemolytica*), *Pasteurella multocida* and *Haemophilus somnus*.
- Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.
- Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.”

**This table is taken directly from the Excenel® label:** Table 2. Cattle plasma concentrations and related parameters of ceftiofur and desfuroylceftiofur metabolites after EXCENEL® RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) administered intramuscularly or subcutaneously at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW and Naxcel® Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) administered intramuscularly at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW.

<table>
<thead>
<tr>
<th></th>
<th>Ceftiofur hydrochloride</th>
<th>Ceftiofur sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM</td>
<td>SC</td>
</tr>
<tr>
<td>Cₘₐₓ (µg/mL)</td>
<td>11.0 ± 1.69</td>
<td>8.56 ± 1.89</td>
</tr>
<tr>
<td>tₘₐₓ (h)</td>
<td>1 - 4 (range)</td>
<td>1 - 5 (range)</td>
</tr>
<tr>
<td>t&gt;0.2 (h)</td>
<td>60.5 ± 6.27</td>
<td>51.0 ± 6.53</td>
</tr>
<tr>
<td>AUC₀₋LOQ (µg*h/mL)</td>
<td>160 ± 30.7</td>
<td>95.4 ± 17.8</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>12.0 ± 2.63</td>
<td>11.5 ± 2.57</td>
</tr>
<tr>
<td>C₂₄h (µg/mL)</td>
<td>1.47 ± 0.380</td>
<td>0.926 ± 0.257</td>
</tr>
<tr>
<td>C₄₈h (µg/mL)</td>
<td>0.340 ± 0.110</td>
<td>0.271 ± 0.086</td>
</tr>
</tbody>
</table>

Note the similarities between IM and SC administration of ceftiofur HCl and IM ceftiofur Na (IM anda SC ceftiofur Na are essentially equivalent). The takehome is that there is no reason to use either formulation IM.

Definitions:
- t₀ₓ₀.₂ - the time (in hours) plasma concentrations remain above 0.2 µg/mL
- AUC₀₋LOQ - the area under the plasma drug concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL)
- t₁/₂ - the drug half life in plasma expressed in hours
- C₂₄h - the plasma drug concentration 24 h after administration
- C₄₈h - the plasma drug concentration 48 h after administration

¹ Values represent the separate means from each study.
CCFA is the crystalline free acid form of ceftiofur in a miglyol® and cottonseed oil based suspension. In cattle, it is labeled only for injection under the skin of the ear and at the base of the ear. You must be trained in this method of administration as injecting into an artery in the ear may lead to retrograde movement into the carotid artery and a fatal cerebral embolism of the product. Injection of CCFA SC in the neck results in a drastically extended slaughter withdrawal time.

Indications from bovine label (the bovine product is 200 mg/ml, 6.6 mg/kg once in base of ear or posterior aspect of the ear): “…indicated for treatment of BRD (shipping ever, pneumonia) associated with Mannheimia haemolytica, P. multocida and H. somnus. …is also indicated for the control of respiratory disease in cattle which are at high risk of developing BRD associated with Mannheimia haemolytica, P. multocida and H. somnus.”

Indications from swine label (the swine product is 100 mg/ml, 5 mg/kg once in neck): “…indicated for the treatment of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, and Streptococcus suis.”

Indications for equine label (same product as for cattle, 200 mg/ml, but dose is 6.6 mg/kg IM, 2 doses 4 days apart): “For the treatment of lower respiratory tract infections in horses caused by susceptible strains of Streptococcus equi ssp. zooepidemicus.”

Table with bovine pharmacokinetic parameters after a single SC injection of Excede at 6.6 mg/kg BW in the posterior ear of cattle. (Source: Excede bovine label)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu$g/mL)</td>
<td>6.9 ± 2.68</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>12.0 ± 6.2</td>
</tr>
<tr>
<td>$t_{\geq 0.2 \mu$g/ml in plasma (h)}</td>
<td>183 ± 40.8</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>62.3 ± 13.5</td>
</tr>
</tbody>
</table>

Table with swine pharmacokinetic parameters after a single IM injection of Excede™ For Swine at 5 mg/kg BW in the neck. (Source: Excede swine label)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu$g/mL)</td>
<td>4.17 ± 0.92</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>22.0 ± 12.2</td>
</tr>
<tr>
<td>AUC$_{0-\text{LOQ}}$ ($\mu$g•h/mL)</td>
<td>373.0 ± 56.1</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>49.6 ± 11.8</td>
</tr>
</tbody>
</table>

Ceftiofur Slaughter Withdrawal Times

<table>
<thead>
<tr>
<th>Product</th>
<th>Bovine - Meat</th>
<th>Bovine - Milk</th>
<th>Swine – Meat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftiofur sodium</td>
<td>4 days</td>
<td>0</td>
<td>4 days</td>
</tr>
<tr>
<td>Ceftiofur hydrochloride</td>
<td>4 days</td>
<td>0</td>
<td>4 days</td>
</tr>
<tr>
<td>Excede</td>
<td>13 days</td>
<td>0</td>
<td>14 days</td>
</tr>
</tbody>
</table>
Cefpodoxime proxetil (Simplicef™)

Generic tablets approved in 2012

Cefpodoxime is a third generation cephalosporin in the traditional classification system. Cefpodoxime proxetil is a prodrug that is rapidly metabolized to cefpodoxime. It is available as 100mg and 200 mg tablets.

Indications from label: “…indicated for the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius*, *Staphylococcus aureus*, *Streptococcus canis* (Group G, β hemolytic), *Escherichia coli*, *Pasteurella multocida*, and *Proteus mirabilis*.”

Cefpodoxime minimum inhibitory concentration values from a 2002 field study evaluating skin infections (wounds and abscesses) of canines in the United States. Simplicef Product Monograph, Pfizer Animal Health

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of isolates</th>
<th>MIC$_{50}$ (µg/ml)</th>
<th>MIC$_{90}$ (µg/ml)</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staph. intermedius</em></td>
<td>118</td>
<td>0.12</td>
<td>0.50</td>
<td>0.12 to &gt;32.0</td>
</tr>
<tr>
<td><em>Strep. canis</em> (group G), β- hemolytic</td>
<td>33</td>
<td>≤0.03</td>
<td>≤0.03</td>
<td>All isolates equal</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>41</td>
<td>0.25</td>
<td>0.50</td>
<td>0.12 to &gt;32.0</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>32</td>
<td>≤0.03</td>
<td>≤0.03</td>
<td>≤0.03 to 0.12</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>14</td>
<td>≤0.03</td>
<td>0.06</td>
<td>≤0.03 to 0.06</td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
<td>19</td>
<td>2.0</td>
<td>2.0</td>
<td>0.12 to 2.0</td>
</tr>
</tbody>
</table>

Don’t expect clinical activity against *Pseudomonas aeruginosa*.

Cefpodoxime pharmacokinetics in dogs. Simplicef Product Monograph, Pfizer Animal Health

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single dose of 5 mg/kg</th>
<th>Single dose of 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_{max}$ (µg/mL)</td>
<td>8.2</td>
<td>16.40 ± 11.8</td>
</tr>
<tr>
<td>t$_{max}$ (h)</td>
<td>Same as higher dose</td>
<td>2.21 ± 0.54</td>
</tr>
<tr>
<td>T$_{1/2}$ (h)</td>
<td>Same as higher dose</td>
<td>5.61 ± 1.15</td>
</tr>
<tr>
<td>AUC0-LOQ (µg•h/mL)</td>
<td>71.0</td>
<td>142.0 ± 77.5</td>
</tr>
</tbody>
</table>

RESISTANCE DEVELOPMENT

Resistance mechanisms for the cephalosporins are as for the penicillins. Beta-lactamases in the periplasmic space may contribute to constitutive resistance. Rapid emergence of resistance (during therapy in individual patients) has been noted for *Citrobacter*, *Enterobacter*, *Pseudomonas*, and *Serratia* spp. This resistance is due to stable derepression of inducible, chromosomally mediated beta-lactamases in the periplasmic space. These organisms are then resistant to all cephalosporins, monobactams, penicillins, and cephamycins.
This is serious! *Salmonella Heidelberg* in poultry, *Salmonella Newport* and *Salmonella Typhimurium* in dairy cattle are displaying significant cephalosporin resistance.

**PHARMACOKINETICS**

Some cephalosporins reaching therapeutic levels in the CNS in human patients are cefuroxime, ceftazidime, ceftriaxone, cefpime, and cefotaxime.

Elimination half-times and volumes of distribution are similar to the penicillins. One exception is ceftiofur sodium, which has significantly longer elimination half-times in veterinary species.

Cefoperazone is predominantly eliminated in the bile in humans.

**SUSCEPTIBILITY TESTING:** Cephalosporin breakpoints adapted from CLSI VET01-S2 (2013). Only ceftiofur and cefpodoxime have CLSI approved breakpoints derived from veterinary data. Generic breakpoints are available for cephalothin (Dogs) and cefazolin (Horses, Dogs). Shaded breakpoints are adapted human breakpoints in CLSI Table 2B.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftiofur</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle (BRD) - <em>P. haemolytica, P. multocida, H. somnis</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle (mastitis) – <em>S. aureus, Strep. agalactiae, Strep. dysgalactiae, Strep. uberis, E. coli</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swine (resp disease) - <em>A. pleuropneumoniae, P. multocida, S. choleraesuis, Strep. suis</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equine (respiratory disease) - <em>Strep equi subsp. zooepidemicus</em></td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefpodoxime</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs (wounds and abscesses) – <em>S. aureus, S. intermedies, Strep. Canis</em> (Group G, β hemolytic), <em>E. coli, P. multocida, Proteus mirabilis</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cephalothin CLSI “Generic” Breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs (skin and soft tissue) – <em>S. aureus, Staph pseudIntermedius, Streptococi –β-hemolytic group, E. coli</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefazolin CLSI “Generic” Breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs (skins and soft tissue, respiratory, urinary/genital) – <em>S. aureus, Staph. pseudintermedius, P. multocida, Streptococi –β-hemolytic group, E. coli</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horses (respiratory, genital tract) – <em>Streptococi –β-hemolytic group, E. coli</em></td>
<td>2 4 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cephalothin</strong></td>
<td>8 16 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefazolin</strong></td>
<td>8 16 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefoxitin</strong></td>
<td>8 16 32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dosing regimens modeled for “generic” breakpoints are…
• Cephalexin - 25 mg/kg Q12H orally in dogs
• Cefazolin – 25 mg/kg Q6H IV for both horses and dogs

Ceftiofur is rapidly metabolized to the metabolite desfuroylceftiofur. The parent compound and metabolite are essentially equipotent except for Staph, where the MIC90 reported for ceftiofur is 1.0 µg/ml and for desfuroylceftiofur is 4.0-8.0 µg/ml (4.0 µg/ml for Staph hyicus, 8.0 µg/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 µg/ml and for desfuroylceftiofur it was 0.03 µg/ml. For Strep uberis, their relationship was 0.03 µg/ml for ceftiofur and 0.5 µg/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. (1Salmon SA, Watts JL, Yancey RL Jr. In vitro activity of ceftiofur and its primary metabolite, desfuroylceftiofur, against organisms of veterinary importance, J Vet Diag Invest, 8:332:336,1996.)

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES ★ ★

Anaphylactic and allergic reactions are possible as for the penicillins. Cross-sensitivity between penicillins and cephalosporins in veterinary species (anaphylactic and allergic reactions) is unknown, but is estimated at 15% in humans.

Cephalothin has been demonstrated to have nephrotoxic potential in human patients, although rational clinical use in patients with normal renal function is considered to have minimal risk. Some clinicians recommend that cephalosporins not be used concurrently with aminoglycosides due to possible nephrotoxicity, but this view is not universally held. An adverse reaction to concurrent use in this manner has only been documented for cephalexin which is no longer marketed.

Very high doses or very prolonged use may lead to complications with an immune component such as hepatitis, agranulocytosis, and thrombocytopenia.

Anorexia, vomiting, and diarrhea may occur with oral administration of cephalosporins.

May be regional problems with equine diarrhea following ceftiofur, especially if given IV (Ceftiofur sodium is labeled for IM administration in horses). There appears to be a greater prevalence of Clostridium difficile enterocolitis in racehorses with ceftiofur as opposed to other horses.

Cephalexin has a reported side effect in humans of occasional seizures. This has been reported in dogs being given cephalexin which were well titrated on phenobarbital for seizures.
FDA Issues Order Prohibiting Extralabel Use of Cephalosporin Antimicrobial Drugs in Food-Producing Animals

On July 3, 2008, the U.S. Food and Drug Administration (FDA) published a final rule that prohibits the extralabel use of cephalosporin antimicrobial drugs in food-producing animals, including, but not limited to cattle, swine, chickens, and turkeys. Comments were received, the rule was revoked, and in January, 2012, the rule was reissued in a much less intrusive form. The basics of the prohibition rule are…

- Extralabel use for off-label indications in cattle, swine, and poultry only if all other label directions are observed (dose, route, duration, frequency, species).
- No extralabel use for prevention, but you can for control (still not clear on the difference, nor does the FDA/CVM have definitions for these uses)
- No extralabel use of human cephalosporins in food animals
- Cephapirin extralabel use is OK
- Extralabel use as described under AMDUCA is allowed in minor food animal species (e.g., sheep, goats)
BETA-LACTAMS: THE CARBAPENEMS

MEMBERS OF THE GROUP (“The Thienamycins”): All are human labels, no veterinary-labeled antimicrobials in this group

**Thienamycin** from *Streptomyces cattleya* is the parent compound for:

**Imipenem** [HL Primaxin®], an N-formimidoyl derivative

Imipenem undergoes extensive metabolism by renal dehydropeptidase 1 (DHP-1) in the brush border of proximal renal tubular cells. This metabolite is nephrotoxic, as well as limiting activity in the urine. Therefore, imipenem is combined with a synthetic DHP-1 inhibitor, cilistatin, in the commercial preparation, available in the U.S. since 1986.

**Meropenem** [HL Merrem®] is also a derivative of thienamycin.

It is much more DHP-1 stable and does not need to be administered with a DHP-1 inhibitor.

**Biapenem** Approved in several countries around the world for human use, including Japan, but not in the U.S.

**Panipenem** is currently approved in Japan

**Ertapenem** (Invanz®, 2002) - narrower spectrum than imipenem or meropenem.

**Doripenem** (Doribax®, 2007) - 1-β-methylcarbapenems, 4-substituted thiazol-2-y1thio moiety at the C-2 side chain, activity similar to imipenem and meropenem. Some earlier indications of doripenem having superior activity against *Pseudomonas aeruginosa* are not thought to translate into a clinical advantage over other carbapenems.

**PHYSICOCHEMICAL PROPERTIES**

The carbapenem structure differs from the penem penicillins by a CH₂ group replacing the sulfur in the 5 membered ring attached to the beta-lactam ring. Hence, the Carbapenems. This change creates a class of compounds which are arguably the most broadspectrum of any class.

**MECHANISM OF ACTION**

Covalent binding to penicillin binding proteins in the bacterial cell wall is responsible for bactericidal activity.

**SPECTRUM**

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  +++++  +++++
  +++++  +++++
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Imipenem is probably one of the widest spectrum antimicrobials available, definitely among the β-lactams. Gram-positive and negative, aerobic and anaerobic rods and cocci. The carbapenems have been considered to be the most active of the beta-lactams against Gram-negative organisms, including *Pseudomonas aeruginosa* and enterobacteriaceae. This may change due to some of the new fourth-generation cephalosporins. Resistance has been demonstrated by some
**Pseudomonas, Enterococcus faecium,** and methicillin-resistant Staph. The carbapenems are considered resistant to many of the beta-lactamases which affect the 3rd and 4th generation cephalosporins.

Among the carbapenems, meropenem and ertapenem have the best activity against the *Enterobacteriaceae.* Ertapenem has very little activity against *Pseudomonas aeruginosa,* with meropenem thought to be superior to imipenem against this organism. Imipenem is considered superior to ertapenem in Gram (+) activity.

1beta-methyl carbapenems (doripenem) have in-vitro activity superior to imipenem against *Klebsiella pneumoniae,* *E. coli,* and *proteus* spp. This group demonstrated in-vitro activity against *Enterococcus faecium* that is equal to or superior to quinupristin-dalfopristin and linezolid. Efficacy of the 1beta-methyl carbapenems was equivalent to vancomycin and linezolid in methicillin-resistant *Staph. Aureus* (MRSA) mouse infection models.

**RESISTANCE DEVELOPMENT**

Resistance has been reported in *Pseudomonas* due to changes in outer membrane proteins and a beta-lactamase. *Pseudomonas* resistance may rapidly develop during treatment; leading to some to suggest that therapy of Pseudomonas with a carbapenem should be in conjunctin with an aminoglycoside, although proof that this will suppress resistance development is lacking. The carbapenems are considered to generally be resistant to hydrolysis by betalactamases including plasmid mediated and chromosomal, inducible betalactamases. This resistance is thought to also include extended spectrum beta lactamases such as some of those produced by *Pseudomonas* and *Enterobacteriaceae.*

A recently emerging issue of shared resistance between human and animal pathogens is that of carbapenemase-producing enterobacteriaceae (CRE). Human cases of CRE have been in the news lately where multidrug resistant pathogens have displayed resistance to this class of antimicrobials previously considered to be omnipotent. And, once again, the situation in veterinary medicine is mirroring the antimicrobial resistance challenges in human medicine. Carbapenemase-producing isolates of *Klebsiella pneumoniae* and *E. coli* have been identified in dogs from a single hospital in Germany, with the clonal nature of the isolates suggesting nosocomial spread.3 Carbapenemase producing *E. coli* have also been confirmed in clinical isolates derived from dogs and cats in the United States.4 An analysis of the literature related to potential sources of these organisms cites detection in dairy cows (France), horses (Belgium), a wild raptor (Germany), poultry and swine (China), dogs and cats (Germany and USA), and multiple instances in water and sewage throughout the world.5 The pattern reasonably supports a hypothesis of spread to multiple veterinary species through environmental dissemination of human sources; this is further supported by no labeled carbapenems for food animals, a cost structure which makes extralabel use in food animals highly unlikely, and limited use in

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companion animals. While certainly not yet ubiquitous in occurrence, confirmation of these isolates in veterinary species strongly supports the need for continued evaluation of our use of carbapenems in veterinary species, and the potential for the occurrence of these organisms in clinical practice.

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

- **Oral administration** is not possible due to poor absorption. **IV** administration is usually done over 15-30 minutes. **IM** and **SC** administration of a commercial imipenem/cilastatin suspension is possible, although it is usually reconstituted with 1% lidocaine to control pain. **SC** meropenem pharmacokinetics appear favorable in dogs.

**PHARMACOKINETICS**

Imipenem elimination half-time is approximately 1-3 hours in humans. Imipenem is eliminated through the kidneys where it is metabolized to an inactive form in the tubules. Approximately 25% may be eliminated by nonrenal mechanisms. Cilastatin inhibits renal metabolism, so that active drug is eliminated in the urine, and nephrotoxicity potential is decreased. Cilastatin does not affect the systemic pharmacokinetics of imipenem. Imipenem is used in human medicine in a 1:1 ratio with cilastatin.

Imipenem pharmacokinetics in dogs have been reported as T1/2 of 0.8 ± 0.23 hrs, 0.92 ± 0.33 hrs, and 1.54 ± 1.02 hrs after IV, IM, and SC administration respectively. Tmax was 0.5 ± 0.16 and 0.83 ± 0.13 hrs after IM and SC injection respectively. Cmax after IM injection was 13.2 ± 4.06 µg/ml and after SC administration was 8.8 ± 1.7 µg/ml. 6 (Reported MICs for E. coli range from 0.06 to 0.25 µg/ml.)

In dogs, meropenem has been reported to have an elimination half-time of 0.67 ± 0.07 hrs, and a volume of distribution of 0.05 L/kg. Plasma T1/2 after SC administration was 0.98 ± 0.21 hrs. 7

Penetration into the CNS is considered poor for this group, even in the presence of inflamed meninges. Oral bioavailability of the current carbapenems is very poor.

**ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES**

- GIT disturbances are the most common side-effect
- CNS toxicity has been observed in dogs and cats due to imipenem. Caution should be used in patients with head trauma or seizure disorders. For imipenem, human seizure rate (which is

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often associated with underlying neurological conditions, very high doses, and/or renal dysfunction) is about 0.5%.

**USE IN VETERINARY MEDICINE**

Imipenem has been used in refractive cases in dogs and cats. It is relatively insoluble, so a dose must be dissolved in a large volume of water (100 ml) and given IV over 20-30 minutes. Alternately, this volume has been injected subcutaneously with clinical results apparently being similar. The intramuscular suspension is very painful, and stability is low. Therefore, a lot of the IM suspension tends to be wasted when it is mixed up in low dosage situations.

Meropenem has been shown to have almost complete absorption from subcutaneous injection in dogs without the pain displayed with imipenem injection. Meropenem is more soluble than imipenem, so the injection volume is much lower. The reconstituted solution is also much more stable.

**SUSCEPTIBILITY TESTING:** Carbapenem breakpoints adapted from CLSI VET01-S2. These are human breakpoints adapted for veterinary use.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ μg/ml)</th>
<th>Intermediate (μg/ml)</th>
<th>Resistant (≥ μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>
BETA-LACTAMS: THE MONOBACTAMS

MEMBERS OF THE GROUP

Aztreonam, tigemonam (oral administration possible), carumonam

PHYSIOCHEMICAL PROPERTIES

Monobactams possess the beta-lactam ring but not the thiazolidine ring of the penicillins, cephalosporins, and carbapenems. Aztreonam is a synthetic analogue of a naturally produced antibiotic.

MECHANISM OF ACTION

Bactericidal activity is by binding to penicillin binding proteins in the cell wall as for other β-lactam antimicrobials.

SPECTRUM

Activity is limited to gram-negative aerobic bacteria. Aztreonam has been used in human medicine to replace the more toxic aminoglycosides in combination therapy with a macrolide, lincosamide, or metronidazole. Aztreonam is usually beta-lactamase stable.

RESISTANCE DEVELOPMENT

Resistance may occur due to plasmid-mediated beta-lactamases which are also active against some cephalosporins. For some organisms, such as Pseudomonas, resistance is due to impermeability of the cell membrane. Aztreonam does not induce betalactamases and is also considered a poor substrate for most of these enzymes.

PHARMACOKINETICS

Aztreonam is generally administered IV, although good absorption occurs from IM administration. Excretion is primarily renal with elimination half-times in the 1 - 2 hour range in humans. Distribution is confined primarily to the extracellular fluid with significant penetration into cerebrospinal fluid in the presence of meningitis.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Toxicity follows that of other beta-lactams with relative safety at usual clinical doses.
THE FLUOROQUINOLONES

MEMBERS OF THE GROUP

**First generation**, activity limited to the Enterobacteriaceae

* Nalidixic acid, a bicyclic 4-quinolone, the parent molecule from which the fluoroquinolones are derived through molecular alterations
* Flumequine, no longer marketed, was not marketed in the U.S.

**Second generation**, extended spectrum to include Gram (+) and additional Gram (-)

* **Enrofloxacin**: Baytril®, dogs, cats (1988), (injectable, oral, and otic solution), a generic is now available as a version of taste tabs for dogs and cat, a version of the conventional tablets, and of the 2.27% injectable. Baytril 100® (injectable) for treatment and control of bovine and swine respiratory disease (injectable), as of late 2013 a generic is now available labeled only for daily treatment of bovine respiratory disease (not single injection).
* **Difloxacin**: Dicural®, dogs (tablets only in US, injectable in EU)
* **Orbifloxacin**: Orbax®, dogs and cats (tablets and oral suspension)
* **Marbofloxacin**: Zeniquin™, dogs, cats (tablets only)
* **Danofloxacin**: Advocin®, previously A-180®, labeled for treatment of bovine respiratory disease (injectable)
* **Ibafloxicin**: small animal oral formulation marketed in Europe

**Human label examples of second generation fluoroquinolones:**

There are many more than these examples
* **Norfloxacin** (first second generation, patented in 1979, first marketed in 1986, but had poor oral absorption), **Enoxacin, pefloxacin** (1979),
* **Ofloxacin** (1981), these three FQ’s had similar activity to norfloxacin but much better oral absorption
* **Ciprofloxacin** (1981, marketed in U.S. in 1987), added good efficacy against *Pseudomonas*

**Third generation, enhanced spectrum** with improved *Streptococcus* and anaerobic activity.

* **Pradofloxacin** – Veraflox® (2013), cats, a moxifloxacin derivative

**Human label examples of Third generation fluoroquinolones:**

* **Trovanofloxacin, gatifloxacin, moxifloxacin**

**Note:** The extralabel use of fluoroquinolones in food animals is illegal! Danofloxacin is labeled only for bovine respiratory disease in cattle not intended for dairy production and not intended to be processed for veal. Enrofloxacin is labeled for swine respiratory disease and bovine respiratory disease (treatment and control) including dairy heifers less than 20 months of age, but not in dairy cattle 20 months of age or older (same as a lactating dairy cow) and not in veal calves. In 2015, an addition to the enrofloxacin label was approved including control of colibacillosis.
Previous veterinary labels:
   Sarafloxacin (Saraflox WSP®, poultry) – label withdrawn in 2000
   Enrofloxacin (Baytril®, Poultry) - label for poultry use removed by FDA/CVM in 2005

Human fluoroquinolones withdrawn after approval due to rare adverse reactions detected during post-approval monitoring. These are included to demonstrate that the multiple alterations of the original bicyclic 4-quinolone molecule have resulted in varied combinations of efficacy and toxicity.

   Temafloxacin due to immune hemolytic anemia
   Trovafloxacin due to hepatotoxicity
   Grepafloxacin due to cardiotoxicity
   Clinifloxacin due to phototoxicity

IN THE KSU PHARMACY

   Ciprofloxacin tablets
   Orbifloxacin oral suspension
   Enrofloxacin injection (Baytril® 100 for food animals, Baytril® 2.27% for dogs)
   Enrofloxacin 22.7, 68, and 136 mg tablets
   Pradofloxacin oral suspension
   Ofloxacin and ciprofloxacin ophthalmic drops

In other clinics:
   Enrofloxacin “taste tabs”
   Danofloxacin injectable
   Diflouxacin tablets
   Marbofloxacin tablets
   Enrofloxacin otic solution

PHYSIOCHEMICAL PROPERTIES

The fluoroquinolones are completely synthetic, making them an antimicrobial rather than an antibiotic. This is an issue of semantics, as antibiotics are also included in the definition of antimicrobials.

The fluoroquinolones under development and in use today are drastically different from nalidixic acid, the first 4-quinolone developed in 1962. It had a narrow gram (-) spectrum and suffered from rapid development of resistance as well as significant toxicity. The addition of two chemical groups to the 4-quinolone nucleus was the primary advance resulting in the fluoroquinolones. A piperazine ring attached to carbon 7 extended the spectrum to include *Pseudomonas*. A fluorine molecule at carbon 6 extended the spectrum to many gram (+) bacteria. The fluoroquinolones also possess improved toxicity and pharmacokinetic profiles as compared to nalidixic acid.

Enrofloxacin is one of the fluoroquinolones with alkyl chains on the para position and a nitrogen molecule at position one of the piperazine ring. These additions have the effect of increasing
l lipid solubility and volume of distribution. Fluoroquinolones generally have poor lipid solubility except in the pH range of 6.0-8.0, which gives them excellent lipid solubility when used clinically. They are also amphoteric molecules due to an acidic carboxylic group and a basic tertiary amine group. Although structural alterations have resulted in notable differences in pharmacokinetics and bacterial spectrum among the fluoroquinolones, all possess the same basic mechanism of action.

MECHANISM OF ACTION

Fluoroquinolones are rapidly bactericidal (susceptible organisms usually lose viability in 20-30 minutes).

Topoisomerase Inhibition: Two enzyme targets have been identified in bacteria, both of which are classified as a topoisomerase. (1) DNA gyrase (topoisomerase II) is responsible for inducing negative supercoiling in the DNA molecule to allow replication. Binding of a Fluoroquinolone to this enzyme stabilizes the DNA-DNA gyrase complex, blocking movement of the replication fork. (2) Topoisomerase IV is responsible for decatenation of the original chromosomes and replicates (separation) so that they can be segregated into daughter cells.

Both of these mechanisms, when altered by Fluoroquinolone binding, lead to DNA strand breaks and eventually cell death. DNA gyrase is thought to be the primary target in Gram (-) bacteria, topoisomerase IV is considered the primary target in Gram (+) bacteria. Mammalian topoisomerases are not affected by fluoroquinolones.

SPECTRUM of Veterinary Fluoroquinolones (The spectra of the fluoroquinolones used in veterinary medicine are very similar to the aminoglycosides. In relation to this similarity, the fluoroquinolones have been called the “oral aminoglycosides”, although toxicity, pharmacokinetics, and pharmacodynamics are quite different)

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An exception to this for veterinary fluoroquinolones is pradofloxacin. This fluoroquinolone has a spectrum extended to include Streptococci, Enterococci and some obligate anaerobes, including Clostridium spp., Bacteroides spp., Fusobacterium spp., Prevotella spp. I have ++ rather than ++++ in the anaerobic quadrants below because of uncertainty of the extent of activity in obligate anaerobes as compared to other antimicrobials with anaerobic potential.

<table>
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Second generation spectrum inclusions:

<table>
<thead>
<tr>
<th></th>
<th>Aerobic</th>
<th>Anaerobic</th>
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</thead>
<tbody>
<tr>
<td>Gram (+)</td>
<td><em>Staph aureus</em>&lt;br&gt;<em>Strep. (very variable)</em>&lt;br&gt;<em>Rhodococcus equi</em></td>
<td></td>
</tr>
<tr>
<td>Gram (-)</td>
<td><em>Enterobacteriaceae</em>&lt;br&gt;<em>E. coli</em>&lt;br&gt;<em>Klebsiella</em>&lt;br&gt;<em>Salmonella</em>&lt;br&gt;<em>Mannheimia haemolytica</em>&lt;br&gt;<em>Actinobacillus</em>&lt;br&gt;<em>Brucella</em>&lt;br&gt;<em>Haemophilus</em>&lt;br&gt;<em>Histophilus</em>&lt;br&gt;<em>Moraxella</em>&lt;br&gt;<em>Pasteurella</em>&lt;br&gt;<em>Coxiella burnetii</em>&lt;br&gt;<em>Pseudomonas (variable)</em></td>
<td><em>Activity against E. coli in an anaerobic environment has been demonstrated.</em></td>
</tr>
</tbody>
</table>

Also *Mycoplasma, Ehrlichia, Rickettsia, Campylobacter, Lepto, Ureaplasma*

**RESISTANCE DEVELOPMENT**

Two mechanisms of resistance have been identified. These are alteration of the target enzymes (DNA gyrase and topoisomerase IV), and decreased drug permeation into bacterial cells by altered outer membrane porins and/or active efflux pumps.

Resistance is thought to start with mutations in DNA gyrase, resulting in 2-4 fold increases in MIC values. Then, alterations in Topoisomerase IV lead to higher level resistance. For example, in Gram (-) organisms, the initial mutation in DNA gyrase (Topoisomerase II) may move the MIC distribution of an isolate from the “wild type” of around 0.03 µg/ml to 0.25 – 0.5 µg/ml (low level resistance). The addition of a Topoisomerase IV mutation would then move the MIC to ≥ 4 µg/ml (high level resistance). Campylobacter does not have Topoisomerase IV, so the first mutation takes this organism to high level FQ resistance (≥ 32 µg/ml).

Decreases in porin influx is thought to generally result in low level resistance.

Efflux pumps may extrude antimicrobials from multiple classes, for example, some pumps that extrude fluoroquinolones may also affect other antimicrobials groups, such as the cephalosporins, tetracyclines, and carbapenems.
For many years, lack of plasmid-mediated resistance was considered a characteristic of fluoroquinolones. However, plasmid-mediated resistance was first reported in 1998 in a Klebsiella Pneumoniae isolate and was also reported in E. coli isolates from China in 2003. This qnr gene encodes for resistance in DNA gyrase but not for Topoisomerase IV, therefore resulting in 2-4 fold MIC differences which are thought to be of minimal clinical significance.

Single-step mutations resulting in resistance to the new fluoroquinolones have been documented in Staph. aureus and Pseudomonas aeruginosa. Fluoroquinolone resistance has also been extensively studied in E. coli. These mutants have rarely displayed resistance at fluoroquinolone concentrations greater than 1 μg/ml. Selection for more resistant isolates requires growing the bacteria in multiple serial passes containing the fluoroquinolone or using fluoroquinolone-containing media. Cross resistance among the newer fluoroquinolones has been a characteristic of these mutants. Some mutants have displayed resistance to other antimicrobial groups.

Emergence of resistance in animal models has been limited, and usually results from situations in which the Cmax (maximal serum concentration) to MIC (minimal inhibitory concentration of the pathogen) ratio did not achieve 8:1. This suggests that resistance is of concern primarily in isolates with MICs exceeding 1 μg/ml. Single-step mutations usually have resulted in 4-8 fold increases in MICs for the resistant organism. It is estimated that using fluoroquinolones at concentrations ranging from the MIC to 10 times the MIC result in low-level resistance occurring at the rate of approximately 10^-9 to 10^-10. This has been termed a mutant selection window, a concept recognized as in-vitro data so far related to only limited bacterial species. Also, a new type of pharmacodynamic relationship, the mutant prevention concentration (MPC) has been proposed. It is defined as the concentration above which two concurrent mutations for resistance must occur for an organism to grow. The MPC varies dramatically for different fluoroquinolone/bacteria combinations.

Changes in susceptibility of bacteria to some fluoroquinolones may result from environmental influences. Increased magnesium concentration, acidic pH, and urine (combination of magnesium concentration and pH?) may decrease fluoroquinolone activity. Any effect of urine on fluoroquinolone efficacy in the bladder is likely more than offset by the high concentrations attained there. Inoculum size has little effect on fluoroquinolone activity, except in anaerobic bacteria. This could contribute to the minimal effect of fluoroquinolones on gram (-) enteric flora during therapeutic use.

There is evidence that nalidixic acid resistance precedes fluoroquinolone resistance in some bacteria.

PHARMACOKINETICS

The fluoroquinolones generally exhibit very high bioavailability from oral, intramuscular, or subcutaneous administration (typically greater than 80%). The high monogastric oral

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bioavailability combined with high potency has enabled oral treatment of diseases previously relegated to parenteral therapy. Peak plasma concentrations after oral dosing in the dog are reached in 30-60 minutes. Peak plasma concentrations from injectable formulations (not given IV) usually occur within 1-2 hours in most species regardless of route.

**Fluoroquinolones, as a group, have a very high volume of distribution (VD).** A high VD indicates the drug tends to aggressively move outside of the vascular system. This attribute is partially due to the high lipid solubility displayed by the fluoroquinolones at plasma pH. Another contributor to the high VD is the low plasma protein binding, which has the effect of making more drug available to the diffusional pool within the vasculature. Plasma protein binding may vary significantly between fluoroquinolones.

The fluoroquinolones typically reach tissue concentrations equal to or greater than plasma concentrations. Because these tissue concentrations are determined by whole-tissue homogenates, the exact location in the tissues has not been confirmed. However, there are data showing that one location of tissue concentration for the fluoroquinolones is leukocytes. The brain and prostate are two tissues usually presenting a diffusional barrier to antimicrobials. The fluoroquinolones typically reach therapeutic concentrations in these tissues.

The primary route of fluoroquinolone excretion is the kidney. Renal elimination is due to both renal tubular excretion and glomerular filtration. Concentrations in the urine may reach 100-300 times that of the plasma. Crystals may form in acidic urine. The liver acts as a secondary route of elimination. A de-ethylation reaction in the liver biotransforms enrofloxacin to ciprofloxacin. The extent of this reaction varies between veterinary species. Biliary excretion is also important for some fluoroquinolones (difloxacin is 80% excreted in the feces).

Generic ciprofloxacin is used by some veterinarians in place of enrofloxacin due to cost. However, the bioavailability is approximately 50% and appears to also be much more variable. The takehome is that giving the same dose of ciprofloxacin and enrofloxacin is NOT equivalent.

**PHARMACODYNAMICS**

The efficacy of fluoroquinolones is closely associated with both peak concentration and the ratio of the area under the serum concentration curve to the pathogen MIC (termed the AUIC). The peak concentration to pathogen MIC ratio target is 8 – 10 (serum or plasma Cmax is 8-10 times the pathogen MIC). This target is based on exceeding the mutant prevention concentration and preventing proliferation of first step resistant mutants. The target for AUC to the pathogen MIC ratio (also termed the AUIC) is a minimum of 125. This means that you should be able to divide the 24 hour AUC by the pathogen MIC and come up with a number of 125 or greater for maximum efficacy.

**ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES**

**Articular cartilage damage** - In the rapid growth phase of puppies (enrofloxacin) at high doses for extended periods. (No lesions observed in 8-10 week old cats @ 25 mg/kg/day for 2 weeks). So how does “high doses for extended periods” relate to label doses? The label dose is 5-20 mg/kg per day for dogs (5 mg/kg per day for cats).
From the label: “Oral treatment of 15 to 28 week old growing puppies with daily dosage rates of 25 mg/kg has induced abnormal carriage of the carpal joint and weakness in the hindquarters. Significant improvement of clinical signs is observed following drug withdrawal. Microscopic studies have identified lesions of the articular cartilage following 30 day treatments at either 5, 15, or 25 mg/kg in this age group. Clinical signs of difficult ambulation or associated cartilage lesions have not been observed in 28 to 34 week old puppies following daily treatments of 25 mg/kg for 30 consecutive days nor in 2 week old puppies with the same treatment schedule.”

Ciprofloxacin did not induce cartilage lesions in juvenile Beagles at 10 mg/kg per day for 14 days, but did at 30 and 90 mg/kg. The lesions induced at the higher doses persisted during further growth of the dogs.  

Foals are also susceptible to cartilage damage due to enrofloxacin therapy.

In 2 calf studies, no articular cartilage damage @ 5, 10, or 15 mg/kg for 15 consecutive days.

Retinal degeneration in cats ★★★ (Because this adverse effect very nicely demonstrates the complexity of drug toxicity and how you can become better informed)

– Enrofloxacin has the potential to cause acute and diffuse retinal degeneration in cats. Enrofloxacin should not be used in cats at doses exceeding the manufacturers recommendation. A study of 17 cats displaying enrofloxacin-related retinal degeneration indicated that possible predisposing factors include large doses or high plasma concentrations, rapid IV administration, prolonged courses of therapy, and age. Since phototoxicity is thought to be involved, exposure to sunlight during therapy may play a role.  

A study in cats using 10x the label dose (essentially a huge overdose) of enrofloxacin demonstrated generalized degenerative changes in the retina after 3 doses. Also, concurrent therapy of fluoroquinolones with furosemide or cimetidine may increase fluoroquinolone plasma concentrations, thereby increasing the potential toxicity.

Orbifloxacin was administered to 6 month old cats at doses of 0, 15, 45, and 75 mg/kg per day for 30 days (label dose range is 2.5 – 7.5 mg/kg Q24H). The cats getting 45 and 75 mg/kg Q24H developed tapetal hyperreflectivity along with minimal photoreceptor degeneration.  

The same paper reports on the Marbofloxacin package insert study where 8 month-old cats were treated orally with 0, 5.5, 16.5, or 27.5 mg/kg per day for 6 weeks. No ocular lesions were reported. We should view the absence of lesions in the unaffected groups with caution as these were healthy cats, aged 6 and 8 months. We are left wondering what the effects would have been in old cats with deficiencies in fluoroquinolone elimination due to renal and possibly hepatic insufficiency.


13 Wiebe V. Fluoroquinolone-induced retinal degeneration in cats. JAVMA. 221(11), 1568-1571, 2002.
Pradofloxacin, administered at 6-10 times label dose to cats caused no change in rod or cone function as demonstrated through electroretinography, however the toxicity of enrofloxacin at a toxic dose of 30 mg/kg per day was confirmed in the same study.14

A bit of history: (note to start with, Adverse Drug Event reporting consists of reports where suspected adverse events were seen in animals associated with administration of a drug. In many cases, there are also other possible factors which could contribute to the proposed adverse event.) In 2004, the FDA Center for Veterinary Medicine published a special report on adverse drug event reports, including the monitoring of reported enrofloxacin adverse reactions related to cats.15 One complaint was received in 1992, 1 in 1995, and 2 in 1997. Then, in 1998 the CVM received 14 complaints of blindness in cats after administration of enrofloxacin, increasing to a total of 52 complaints by April, 2000. These reports were from owners, industry, veterinary practitioners and diplomates of the American College of Veterinary Ophthalmologists. At the time, the approved label dose was 5 to 20 mg/kg/day. This label dose had been changed from 2.5 mg/kg every 12 hours in July, 1997. Of 42 cats with enrofloxacin-associated blindness, prior to 2000, for which a reported dose was reported, 2 cats were administered a dose of < 5 mg/kg per day. Thirty-seven of the cats ranged from 5.1 to 20 mg/kg per day, and the other 5 received variable off-label doses or > 20 mg/kg per day overdoses. In July 2000, the manufacturer sent a “Dear Dr.” letter advising that cats receive no more than 5 mg/kg per day. In March 2001, another letter was sent confirming the relationship between high-dose enrofloxacin and visual disturbances and emphasizing a new label dose of ≤ 5 mg/kg per day.

A review of enrofloxacin ADE reports from April 30, 2001 to March 22, 2002, found 39 complaints of vision abnormalities in cats, primarily mydriasis and blindness with retinal lesions. Eighteen of these cats received only tablets (5.6 to 34 mg/kg per day). Some of the other cats received either IV or a combination of IV and oral dosing. Nine cats had vision abnormalities at oral doses ≤ 5 mg/kg per day. Six of these has other possible etiologies (e.g., anesthesia, west nile virus infection, hypertension with retinal detachment, suspected toxoploasmosis, or diabetes mellitus). Two of the 3 cats receiving 5 mg/kg per day orally regained their vision within days after withdrawal of the enrofloxacin; the other cats (12 years old, 3 mg/kg per day) still had poor vision 1 month after cessation of dosing.

Adverse Drug Reports for enrofloxacin in cats related to the eye 01/01/1987 through 01/31/2012:16 These lack information on dose, duration, confounding events/treatments, and date. We are also lacking a denominator against which to put these occurrences (number of total cats treated with enrofloxacin during this time period), so interpretation as to rate in the population is not possible.

**Oral administration** - Mydriasis (188), Blindness (140), Retinal abnormalities (118), Pupil(s) areflexia (52), Blindness (partial) (50), vision disorder (24), these are 6 out of the top 7 reports

**Parenteral administration** - Mydriasis (90), Blindness (74), Retinal abnormalities (48), Pupil(s) areflexia (25), Blindness (partial) (21), vision disorder (15), these are 7 out of the top 9 reports

In contrast, Marbofloxacin for the same period has one report of an ocular adverse event (uveitis).

**Suspected retinal degeneration due to a 14 day course of enrofloxacin in a guanaco** has been reported (2.4 mg/kg IM SID).\(^\text{17}\)

**Neural effects** - Headaches, hallucinations, and seizures have been reported in humans taking ciprofloxacin or norfloxacin. Increased seizure frequency in dogs taking enrofloxacin while being treated with phenobarbital for epilepsy. No problems encountered in routine therapeutic situations. However, rapid IV administration of high doses in horses can lead to tremors, excitability, and seizure-like activity. These effects are usually transient. (How many do we have so far that could cause problems with an epileptic dog on phenobarbital?) Don’t use enrofloxacin on yourself (it gains higher CNS concentrations than ciprofloxacin and leads to hallucinations)!!

**Bone marrow suppression**: The pradofloxacin label carries the warning “DO NOT USE IN DOGS. Pradofloxacin has been shown to cause bone marrow suppression in dogs. Dogs may be particularly sensitive to this effect, potentially resulting in severe thrombocytopenia and neutropenia.” It is interesting to note that the safety data for dogs which was considered too great a risk in the United States was considered acceptable in the European Union, where pradofloxacin is labeled for dogs.

**Drug interactions** – (1) Fluoroquinolones form chelates with divalent cations. Aluminum and magnesium have particular affinity, with iron, calcium zinc also will bind fluoroquinolones. Decreases in bioavailability of as much as 85% may occur when FQs are administered at the same time as antacids or sucralfate. (2) Some fluoroquinolones have strong affinity for the cytochrome P-450 isozyme IA-2 (enoxacin the strongest affinity, grepafloxacin, ciprofloxacin, and pefloxacin have more moderate affinity). Enoxacin is capable of doubling theophylline levels. Ciprofloxacin can raise serum theophylline levels in humans by 2-5 µg/ml. Fluoroquinolones can also double the elimination half-life of caffeine.

**Irritation** - Enrofloxacin (Baytril 100®) has been infused into the uterus of horses. It has been demonstrated to be very irritating in this application and is not advised.

Ciprofloxacin in humans carries a black box warning about potential tendon rupture. This has not been a problem with veterinary labeled fluoroquinolones, but you may hear about this in humans.

**SUSCEPTIBILITY TESTING:** Fluoroquinolone breakpoints adapted from CLSI VET01-S2 (2013). All breakpoints are veterinary derived.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
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<tbody>
<tr>
<td><strong>Danofloxacin – Cattle (respiratory disease)</strong>&lt;br/&gt;<em>Mannheimia haemolytica</em>&lt;br/&gt;<em>Pasteurella multocida</em></td>
<td>0.25</td>
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</tr>
<tr>
<td><strong>Difloxacin – Dogs (dermal, UTI)</strong>&lt;br/&gt;Enterobacteriaceae&lt;br/&gt;<em>Staphylococcus</em> spp.</td>
<td>0.5</td>
<td>1-2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Enrofloxacin - Cats (dermal)</strong> &amp; <strong>Dogs (dermal, respiratory, UTI)</strong>&lt;br/&gt;Canine organisms: Enterobacteriaceae&lt;br/&gt;<em>Staphylococcus</em> spp.</td>
<td>0.5</td>
<td>1 - 2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Enrofloxacin - Cattle (respiratory disease)</strong>&lt;br/&gt;<em>Mannheimia haemolytica</em>&lt;br/&gt;<em>Pasteurella multocida</em>&lt;br/&gt;<em>Histophilus somni</em></td>
<td>0.25</td>
<td>0.5 - 1</td>
<td>2</td>
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<tr>
<td><strong>Enrofloxacin – Swine (respiratory disease)</strong>&lt;br/&gt;<em>Pasteurella multocida</em>&lt;br/&gt;<em>Actinobacillus pleuropneumoniae</em></td>
<td>0.25</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Enrofloxacin – Swine (respiratory disease)</strong>&lt;br/&gt;<em>Streptococcus suis</em></td>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Marbofloxacin - Cats (dermal)</strong> &amp; <strong>Dogs (dermal, UTI)</strong>&lt;br/&gt;Canine organisms: Enterobacteriaceae&lt;br/&gt;<em>Staphylococcus</em> spp.</td>
<td>1</td>
<td>2</td>
<td>4</td>
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<tr>
<td><strong>Orbifloxacin - Cats (dermal)</strong> &amp; <strong>Dogs (dermal, UTI)</strong>&lt;br/&gt;Canine organisms: Enterobacteriaceae&lt;br/&gt;<em>Staphylococcus</em> spp.</td>
<td>1</td>
<td>2-4</td>
<td>8</td>
</tr>
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</table>

Fluoroquinolone breakpoint summary table

<table>
<thead>
<tr>
<th>Cattle</th>
<th>Swine</th>
<th>Cats</th>
<th>Dogs</th>
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<tr>
<td><strong>Respiratory disease</strong></td>
<td><strong>Respiratory disease</strong></td>
<td><strong>Dermal</strong></td>
<td><strong>Dermal</strong></td>
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<tr>
<td>Danofloxacin</td>
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<td>Difloxacin</td>
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<td>Enrofloxacin</td>
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<td>Orbifloxacin</td>
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Macrolides, Ketolides, Azalides, and Triamalides

Macrolide means “large Lactone”, named after the large lactone rings which are the basis for these antimicrobials

14 member ring macrolides

**Erythromycin** (1952), **Oleandomycin**

Newer 14 member semisynthetics

**Roxithromycin**: a substituted derivative of erythromycin, it is acid stable, no longer available in the U.S.

**Clarithromycin** [HL Biaxin®]: a substituted derivative of erythromycin, about twice as potent on a weight basis as compared to erythromycin, and also twice the elimination T1/2

**Dirithromycin**: a derivative of erythromycylamine

The ketolides: **Telithromycin** [HL Ketek®], A 3-keto substitution on the 14 membered ring in place of the L-cladinose moiety. Non-inducers of MLSB cross-resistance in *Staph.* and *Strep.*

15 member ring macrolides

The azalides: 

**Azithromycin** [HL Zithromax®]: Nitrogen insertion into the 14 member macrolide ring produces the 15 member ring, giving enhanced stability in acid and activity against Gram negative organisms.

**Gamithromycin** (VL, Zactran®): approved for treatment and control of bovine respiratory disease

The triamilides: semi-synthetic, 15-membered ring macrolides containing three polar amine groups.

**Tulathromycin** [VL Draxxin®], is approved for bovine and swine respiratory disease, and also control of bovine respiratory disease. About 90% of the mixture is the 15 member ring compound, and 10% of the mixture is a 13 member ring compound.

16 member rings

**Human medicine**: Spiramycin, Josamycin, Midecamycin, Rikamycin

Not used in human medicine:

**Tylosin** [VL Tylan® and generic labels, feed additive for cattle, swine, chickens, injectable for cattle and swine]

**Tildipirosin** [VL Zuprevo®] A tylosin derivative with substantial molecular
alterations, approved for treatment and control of bovine respiratory disease. **Tylvalosin** (VL Alvlosin®) – a derivative of tylosin, water soluble granules for swine, approved in U.S. in 2012 for treatment of porcine proliferative enteritis. It is rapidly metabolized to 3-O-acetytylosin, which is equal in efficacy to tylosin.


**IN THE KSU PHARMACY**

Azithromycin tablets and oral suspension
Clarithromycin tablets and oral suspension
Erythromycin ethylsuccinate oral suspension

Tilmicosin injection
Tulathromycin injection

**What you will find in many clinics in addition to these**

Gamithromycin
Tildipirosin

**If you work in food a food animal practice, you will deal with**

Tylosin in the feed for cattle and swine
Tylvalosin in the water for swine
Tilmicosin in the feed for cattle and swine (will need to become familiar with VFDs)

**PHYSIOCHEMICAL PROPERTIES**

*All are basic compounds.* Erythromycin pKa = 8.8, Tylosin pKa = 7.1, Tilmicosin pKa = 7.4, 8.6

Highly lipid soluble, alcohol soluble, poorly water soluble (some salts may be water soluble), unstable in acidic media (pH < 4.0)

**MECHANISM OF ACTION**

Generally considered bacteriostatic for the majority of pathogens at therapeutically reachable concentrations. **Newer human and veterinary macrolides have demonstrated bactericidal activity against some pathogens.**

**Inhibition of protein synthesis** by interference with the translocation step. The macrolides bind to the 50S ribosomal subunit, specifically to the 23S ribosomal RNA molecule, inhibiting transfer RNA from binding to the donor site. Sixteen-member ring compounds are thought to inhibit the peptidyl transferase reaction while 14-member compounds interfere with translocation of...
peptidyl-tRNA. Short polypeptides may still be formed, but long chain proteins are prevented. The mechanism of other macrolides is similar. This binding is not permanent, and may reverse with drug removal. The binding of 14 and 16-member compounds to the 50S subunit is at the 23S RNA molecule. The macrolides may also interfere with the formation of the 50S ribosomal subunit.

The binding sites are thought to be the same as for the lincosamides, streptogramins, and oxazolidinones. However, the binding site for chloramphenicol is different.

**SPECTRUM**

**Veterinary macrolides** (erythromycin, tylosin, tilmicosin, tulathromycin, of these only erythromycin is used in humans)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Gram (-) aerobes are marked down due to very poor coverage of the enterobacteriaceae and many other Gram (-) pathogens. These drugs do, however, adequately address Gram (-) respiratory pathogens in cattle and swine. Erythromycin and tylosin have significant resistance against these respiratory pathogens and some resistance is developing to tilmicosin and the newer bovine respiratory disease macrolides (tulathromycin, tildipirosin, gamithromycin)

“Others” – Lepto (although not one of the main ones), *Rhodococcus equi* (resistance mounting to erythromycin, so clarithromycin and azithromycin now used), *Mycoplasma bovis* (tylosin and tulathromycin, other *Mycoplasma* spp. for all of the macrolides)

**Human macrolides** (clarithromycin, azithromycin, and telithromycin). Improved Gram (-) spectrum, but you would still not select a macrolide for empirical therapy of an enterobacteriaceae.
**Erythromycin**: good susceptibility with MICs ≤ 0.5 µg/ml, **moderate susceptibility** (1-4 µg/ml) in bold type

<table>
<thead>
<tr>
<th>Gram (+)</th>
<th>Aerobic</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus</td>
<td>Arcanobacterium</td>
<td>Actinomyces (facultative)</td>
</tr>
<tr>
<td>E. rhusiopathiae</td>
<td>Listeria</td>
<td>Clostridium</td>
</tr>
<tr>
<td>Staph.</td>
<td>Strep.</td>
<td></td>
</tr>
<tr>
<td>Rhodococcus equi</td>
<td>Enterococci</td>
<td></td>
</tr>
<tr>
<td>Bordetella</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram (-)</th>
<th>Aerobic</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinobacillus</td>
<td>Brucella</td>
<td>Bacteroides (except B. fragilis)</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Haemophilus</td>
<td>Fusobacterium</td>
</tr>
<tr>
<td>Ehrlichia</td>
<td>Pasteurella</td>
<td></td>
</tr>
<tr>
<td>Mannheimia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Also *Leptospira*

Resistant organisms (≥ 8 µg/ml): *Enterobacteriaceae, Pseudomonas, Nocardia, Chlamydia psittaci, Mycobacterium* (except possibly *M. Kansasi*)

**Tylosin**: Similar spectrum to erythromycin, more active against *Mycoplasma*.

**Azithromycin** and clarithromycin have been evaluated for use in *Rhodococcus equi* infections in foals. The combination of clarithromycin-rifampin was found to be more effective than azithromycin-rifampin or erythromycin-rifampin for the treatment of foal pneumonia caused by *R. equi* referral population.¹⁸

**Tulathromycin susceptibility data** (from the label)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>MIC 90 (µg/ml)</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mannheimia haemolytica</em></td>
<td>642</td>
<td>2</td>
<td>0.5 to 64.5</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>221</td>
<td>1</td>
<td>0.25 to 64.0</td>
</tr>
<tr>
<td><em>Histophilus somni</em></td>
<td>36</td>
<td>4</td>
<td>1.0 to 4.0</td>
</tr>
<tr>
<td><em>Mycoplasma bovis</em></td>
<td>35</td>
<td>1</td>
<td>≤0.063 to 2.0</td>
</tr>
</tbody>
</table>

Tilmicosin MICs:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasteurella haemolytica</td>
<td>3.12</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>6.25</td>
</tr>
<tr>
<td>Haemophilus somnus</td>
<td>6.25</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.78</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>3.12</td>
</tr>
<tr>
<td>Arcanobacterium pyogenes</td>
<td>0.024</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>3.12</td>
</tr>
<tr>
<td>Clostridium sordelli</td>
<td>3.12</td>
</tr>
<tr>
<td>Fusobacterium necrophorum</td>
<td>3.12</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>50</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
<td>50</td>
</tr>
<tr>
<td>Mycoplasma dispar</td>
<td>0.097</td>
</tr>
<tr>
<td>Mycoplasma bovirhinis</td>
<td>0.024</td>
</tr>
<tr>
<td>Mycoplasma bovoculi</td>
<td>0.048</td>
</tr>
</tbody>
</table>


a 98.2% at 12.5 µg/mL, b Clinical isolates with an MIC > 50 µg/mL have been found.

**OTHER EFFECTS BESIDES ANTIMICROBIAL ACTIVITY**

Some macrolides are noted for anti-inflammatory effects. In some human inflammatory pulmonary diseases, some macrolides (erythromycin, azithromycin, clarithromycin, and roxithromycin) inhibit mucus secretion by inhibiting infiltration of neutrophils into the airways. Part of the effect is thought to be due to inhibition of formation of cytokines such as the interleukins, and also some leukotrienes. Some macrolides may also have effects on adaptive immunity.

Fourteen- and 16-member ring macrolides have been demonstrated to have prokinetic effects on the intestinal tract due to agonistic activity on motilin receptors. Erythromycin in horses, and erythromycin, tylosin, and tilmicosin in cattle have demonstrated this effect.

**RESISTANCE DEVELOPMENT**

Chromosomal mutations to resistance are selected for during use and may rapidly predominate during therapy for some macrolides. Cross-resistance to other macrolides and the lincosamides is common. Alteration of the 23S rRNA by methylation of adenine confers cross-resistance to all macrolides, lincosamides, and spectinomycin group B antimicrobials. This resistance is encoded for by the *erm* class of genes. These genes may be either chromosomal or plasmid mediated, and either constitutive or inducible. Other resistance mechanisms include other mutations of the 23S rRNA, macrolide inactivating enzymes, changes in drug permeability, and active drug efflux mechanisms.
The ketolides have not been characterized as exhibiting MLSB cross resistance.

**From tulathromycin Guidance 152 submission to the CVM (2002):** Expression (production) of *erm* genes (MLSB phenotype) in gram-positive organisms is under either inducible or constitutive control. Some macrolides serve to stimulate inducible resistance genes, while other macrolides do not. For example, 14-membered ring macrolides such as erythromycin stimulate expression of the inducible MLSB genes, while the 16-membered macrolides such as tilmicosin and tylosin do not. Thus bacterial strains carrying inducible MLSB are susceptible to 16-membered ring macrolides but are resistant to 14-membered ring macrolides. Bacteria carrying inducible MLSB genes, however, have elevated MICs (i.e., resistance) to 16-membered ring macrolides when the expression of these genes is already induced by 14-membered ring macrolides at sub-MIC concentrations.

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

**Erythromycin** is available in numerous salt forms (acetate, base, estolate, ethylsuccinate, lactobionate, glucoside) for oral, intravenous, and parenteral administration. The acetate salt is water soluble.

**Tilmicosin** is available for SC administration ONLY in cattle. IV administration is fatal, IM is extremely irritating. Tilmicosin is available for oral administration in the feed for swine and cattle. Systemic injection in swine is FATAL.

**Tylosin** is labeled for IM administration in cattle. IV and SC uses have occurred. Tylosin is also used as a feed additive in cattle and swine (the tartrate salt is much better absorbed after oral administration than the phosphate salt). A water-soluble formulation is available for use in the water for chickens, turkeys, and swine.

**Tulathromycin** is labeled for SC use in cattle and IM use in swine.

**Tildipirosin** and gamithromycin are for SC use in cattle.

**Azithromycin** is available in human formulations as tablets and powder for oral suspension. There is also a powder for injection. Reactions around IV injection sites have been reported.

**Clarithromycin** is available in human formulations as tablets and granules for an oral suspension.

**Telithromycin** is available as a human oral tablet formulation.

**PHARMACOKINETICS**

The macrolides “concentrate” in tissues to a great extent, with tissue concentrations typically many times serum concentrations. Some of the macrolides have been shown to reach extremely
high concentrations in leukocytes. This ability for intracellular penetration and concentration likely accounts for the high tissue concentrations. In spite of high lipid-solubility, CSF concentrations of erythromycin and tylosin are reported as poor.

Volumes of distribution are typically ≥ 1 L/kg, reflecting the highly lipid-soluble nature of the macrolides. Oral bioavailability is usually very good, although gastrointestinal irritation must be anticipated at high doses. Erythromycin bioavailability is only approximately 40% and 65% after SC and IM injection respectively in cattle.

Erythromycin base is about 70-80% bound to serum proteins, with the stearate salt being bound ≥ 95%. Passage into the milk is at least 50% of serum concentrations for erythromycin and 20% for tylosin.

Elimination is primarily through the bile with only minimal renal contribution. For example, only 3-5% of a dose of erythromycin is eliminated in the urine. Elimination half-times for erythromycin in dogs, cats, and horses are in the 1-2 hour range with approximately 3 hours being typical in cattle. Tilmicosin phosphate has significantly longer elimination half-times in cattle due to the effect of the carrier at the SC injection site. Significant lung concentrations are maintained for 72 hours post-administration. Reported elimination half-times for tylosin are shorter than for erythromycin, around 1 hour for small animals and 1-2 hours in cattle.

Tulathromycin Plasma Pharmacokinetics in cattle after IV and SC administration of 2.5 mg/kg BW.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV (Mean)</th>
<th>SC (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>0.414</td>
<td></td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>AUC 0–∞ (ng•hr/ml)</td>
<td>13,800</td>
<td>12,600</td>
</tr>
<tr>
<td>T½β (hrs)</td>
<td>65</td>
<td>92</td>
</tr>
<tr>
<td>Vss (L/kg)</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td></td>
<td>91.3</td>
</tr>
</tbody>
</table>

Tildipirosin pharmacokinetics in cattle 4 mg/kg SC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>0.71</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>23</td>
</tr>
<tr>
<td>T½β (hrs)</td>
<td>210</td>
</tr>
<tr>
<td>Vss (L/kg)</td>
<td>11.0</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>79</td>
</tr>
<tr>
<td>Plasma protein binding (%)</td>
<td>30</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>50</td>
</tr>
</tbody>
</table>

The serum elimination half-life of azithromycin in cats and dogs is approximately 30 and 29 hrs respectively. Volume of distribution in the dog is reported as 12 L/kg. Oral bioavailability in the cat is approximately 60% with close to 100% reported in the dog.

Hunter RP, et al. Pharmacokinetics, oral bioavailability and tissue distribution of azithromycin in cats. J Vet Pharmacol Ther. 18(1): 38-46, 1995. 5 mg/kg orally (p.o.) and 5 mg/kg IV. After oral administration, 58%
bioavailability (higher than humans but lower than dogs), tmax of 0.85 +/- 0.72 h and a Cmax of 0.97 +/- 0.65 μg/mL. After IV administration, t1/2 was 35 h.

**Jacks S**, et al. **Disposition of oral clarithromycin in foals.** J Vet Pharmacol Ther. 25(5): 359-62, 2002. Clarithromycin administered intragastrically to foals at 10 mg/kg BW. All foals had detectable serum concentrations by 20 minutes post administration. Tmax was reported as 1.5 hours and Cmax was 0.92 +/- 0.17 μg/ml. At 24 hours, mean serum concentrations had decreased to 0.03 μg/ml. An oral dose 7.5 mg/kg Q12H was suggested for treatment of *R. equi* infections in foals.

**Other veterinary pharmacokinetic studies of human macrolides**


**PHARMACODYNAMICS**

Macrolides as a class are considered to be bacteriostatic (but we can also have bactericidal activity against some pathogens) with efficacy most closely correlated with the time that the concentration is above the MIC (time > MIC) of the target organism. Just where this concentration is measured is an interesting discussion for some of the macrolides.

Recent work on azithromycin and clarithromycin indicate their efficacy is most closely linked to peak concentration.

The ketolides (e.g., telithromycin), have been characterized as concentration dependent with significant post-antimicrobial effects demonstrated for some pathogens.

An approximately 9 hour PAE has been demonstrated against Gram (+) cocci for erythromycin and roxithromycin.

For respiratory infections, the current focus is on the relationship between Pulmonary Epithelial Lavage Fluid (PELF) and the MIC of the target pathogen.
SUSCEPTIBILITY TESTING

Macrolide breakpoints adapted from CLSI VET01-S2 (2013). Only tilmicosin and tulathromycin have CLSI validated breakpoints from veterinary data.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp., <em>Staphylococcus</em> spp.</td>
<td>0.5</td>
<td>1 - 4</td>
<td>8</td>
</tr>
<tr>
<td>Streptococci</td>
<td>0.25</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle respiratory disease (BRD) <em>P. hemolytica</em></td>
<td>8</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Swine respiratory disease <em>Actinobacillus pleuropneumoniae, Pasteurella multocida</em></td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Tulathromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle respiratory disease <em>Mannheimia haemolytica</em> Pasturella multocida Histophilus somni</td>
<td>16</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Swine respiratory disease <em>B. bronchiseptica</em> P. multocida</td>
<td>16</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Swine respiratory disease <em>Actinobacillus pleuropneumoniae</em></td>
<td>64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional breakpoints for Gamithromycin and Tildipirosin were approved at the January, 2014 meeting of the CLSI and will be released in the next supplement to VET01.

DRUG INTERACTIONS

Some macrolides (erythromycin) interact with the P450 enzyme system, causing increased accumulation (and therefore higher systemic concentrations) of drugs which are dependent upon CYP3A metabolism for elimination, such as theophylline, midazolam, carbamazepoine, omepraxole and ranitidine. Clarithromycin has lower affinity for the P450 system, and azithromycin does not interact with the P450 system.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Gastrointestinal effects - Not advisable for use in rabbits or horses. Watch for GIT upset in dogs and cats given erythromycin orally (“what color is your carpet, Mrs. Smith?”). Rectal edema and partial anal prolapse have been associated with erythromycin and tylosin in swine. GIT motility stimulation by erythromycin at low doses has been used by some clinicians for therapeutic applications in horses. Erythromycin has caused deaths in horses due to *Clostridium difficile*. Illness due to *C. diff* has also been reported in mares with foals treated for *Rhodococcus equi* with erythromycin.
Death due to GIT upset has occurred in rabbits receiving a ration with traces of tylosin due to improper flushing techniques at the feed mill.

**Injection site concerns in food animals** - Intramuscular injection of tylosin and erythromycin may cause prolonged and extensive tissue blemishes. Tilmicosin and tulathromycin are labeled for subcutaneous use only. Disregard of this labeling by injecting intramuscularly may also result in prolonged and extensive tissue blemishes.

**Temperature regulation** - Erythromycin has been associated with hyperthermia in 2-4 month foals.

⭐️ **Tilmicosin**: ⭐️

IV tilmicosin has been fatal to cattle at 5 mg/Kg. No adverse systemic effects at doses up to 150 mg/Kg SC. Three times the label dose has been given 3 times, 3 days apart, with no adverse effects.

Tilmicosin has been fatal in goats and should be used with great caution in camels. It is labeled for respiratory disease in sheep.

Pigs die at 20 mg/Kg IM. (Oral use at the proper dose is clinically effective, marketed as Pulmotil by Elanco Animal Health for feed additive use in swine.)

Swelling at injection site is due to osmotic pull of the drug, usually regresses by 10-14 days.

**DO NOT USE IN DAIRY COWS (15-29 day milk residues).**

Do not use in automatic powered syringes or any system capable of injecting a large dose accidentally.

The tilmicosin (Micotil, Elanco Animal Health) label carries warnings relating to accidental injection of humans, which may be fatal. Elanco has received reports of 1462 accidental human exposures for the 4 year, 5 month period from May 1992 to December 1996. No serious sequelae were reported after follow up for these exposures, which included 718 exposures by puncture or scratch, 214 by injection of less than 1 ml, 209 dermal contacts, 201 exposures by ingestion, and 120 cases of exposure by a combination of skin, eye, and ingestion contact. These data should not be interpreted as advocating reduced caution in the handling of tilmicosin. It is important that tilmicosin be used in accordance with label directions. **Two deaths due to accidental injection of tilmicosin have been reported as of 2004.** Within 5 hours of accidental injection of less than half of a filled 12 ml syringe, a 28-year-old man with no prior history of heart disease developed severe chest pain, inverted T waves, and intraventricular conduction delay on EKG and mild elevation of cardiac enzymes. An uneventful recovery was made.19

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From the Micotil® label: Note to the Physician: The cardiovascular system is the target of toxicity and should be monitored closely. **Cardiovascular toxicity may be due to calcium channel blockade.** In dogs, administration of intravenous calcium offset Micotil-induced tachycardia and negative inotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. β-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs. Epinephrine potentiated lethality of Micotil in pigs. This antibiotic persists in tissues for several days.
THE LINCOSAMIDES

MEMBERS OF THE GROUP

**Lincomycin** [VL Lincoxin®], **tablets and capsules.** For swine and poultry there are **injectable, feed- and water-soluble products**

**Clindamycin** [VL Antirobe®] Antirobe® **capsules** are labeled for dogs, Antirobe **aquadrops®** are labeled for dogs and cats., [HL Cleocin®] **capsules, granules, injectable solution**

**Pirlimycin** [VL Pirsue®] (bovine intramammary preparation)

IN THE KSU PHARMACY

Lincomycin injectable  
Clindamycin hydrochloride capsules (Antirobe®)  
Clintabs hydrochloride tablets 25 mg  
Clindamycin hydrochloride liquid (25 mg/ml)

**In other clinics**

Pirlimycin for bovine mastits

If you are in a food animal practice
You will deal with lincomycin feed and water-soluble for swine

PHYSIOCHEMICAL PROPERTIES

The lincosamides are basic compounds (pK ≈ 7.6) which are very lipid soluble. The lincosamides are considered “related” to the macrolides because of similar pharmacokinetics and spectrum properties. However, the structures of the macrolides and lincosamides are very different.

Lincomycin is a product of *Streptomyces lincolnensis* var. *lincolnensis*. The molecular structure consists of a side chain which resembles an amino acid attached to monoglycoside nucleus.

Clindamycin is a derivative of lincomycin (7-chloro-7-deoxylincomycin).

MECHANISM OF ACTION

The lincosamides bind to the 50S ribosome where they inhibit protein synthesis (inhibition of the peptidyltransferase enzyme). They are considered bacteriostatic.

The toxin production-inhibiting effect of clindamycin is thought to be one of the reasons clindamycin has worked well against dermal Staphylococcus infections. Clindamycin, as of 2012, is being widely used in the therapy of MRSA in humans.
### SPECTRUM

**Generalized spectrum:**

<table>
<thead>
<tr>
<th>Gram (+)</th>
<th><strong>Aerobic</strong></th>
<th><strong>Anaerobic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus</td>
<td><em>Actinomyces</em> (facultative)</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium</td>
<td><em>Clostridium perfringens</em></td>
<td></td>
</tr>
<tr>
<td>E. <em>rhusiopathiae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staph.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram (-)</td>
<td><strong>Campylobacter</strong></td>
<td><strong>Bacteroides</strong></td>
</tr>
<tr>
<td></td>
<td>Fusobacterium</td>
<td></td>
</tr>
</tbody>
</table>

Also *Serpulina hyodysenteria, Toxoplasma* (clindamycin)

* not all Clostridial species

Activity against *Mycoplasma* is similar to that of erythromycin.

Consider clindamycin to be more active than lincomycin against Staph. and anaerobes.

*The lincosamides are less active against gram-negative bacteria than the macrolides.*

### RESISTANCE DEVELOPMENT

Most gram-negative bacteria are resistant because of impermeable cell membranes and incompatible binding sites.

Step-wise chromosomal resistance and plasmid-mediated resistance are common. Plasmid-mediated resistance is by methylation of the RNA of the 50S ribosomal subunit, which prevents binding of the lincosamide.

There is complete cross-resistance between the lincosamides. There is often cross-resistance with the macrolides and Virginiamycin (a streptogramin antibiotic). Some of this “MLS” cross-resistance is constitutive, where the other antimicrobials will not work at the start of therapy. Some of the “MLS” resistance is inducible; for example, bacteria with existing erythromycin resistance may rapidly develop lincosamide resistance during lincosamide therapy.

### PHARMACOKINETICS

**Lincomycin** may be protein bound 55-75% depending on concentration. *Food will decrease rate of absorption and bioavailability.* CSF concentrations may achieve 40% of serum concentrations in the presence of inflamed meninges (as for clindamycin).

**Clindamycin** is 90-95% plasma protein bound in humans. Canine elimination half-times are around 3-5 hours and 10-13 hours after oral and SC administration respectively. *Oral bioavailability in humans is high (about 90%). Food will slow the rate of absorption but does not effect the bioavailability.*

Elimination is primarily through hepatic metabolism with excretion of the parent compound and metabolites through the urine and also the bile into the feces.
PHARMACODYNAMICS

The lincosamides are considered bacteriostatic with efficacy dependent on time above MIC. However, the data supporting this conclusion are limited.

DOSING

Cats are on the liquid label but not the capsules. You may get the first liquid dose into cats with minimal challenge, but due to the taste the next doses will be very difficult, often with perfuse salivation.

To counteract this dosing challenge, some veterinarians have used the clindamycin capsules in cats. Similar to issues with doxycycline, when cats get the capsule only partially swallowed and then hide and refrain from drinking water for an extended period, there have been problems with esophageal damage with the capsules in cats.

SUSCEPTIBILITY TESTING

Lincosamide breakpoints adapted from CLSI M31-A4. All are CLSI approved utilizing veterinary data. Clindamycin is used as the class representative to test for lincomycin susceptibility. Clindamycin is more active than lincomycin against most staphylococcal strains.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (&lt;= μg/ml)</th>
<th>Intermediate (μg/ml)</th>
<th>Resistant (&gt;= μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin - Dog (skin and soft tissue infections) <em>Staphylococcus</em> spp.</td>
<td>0.5</td>
<td>1 - 2</td>
<td>4</td>
</tr>
</tbody>
</table>
| Pirlimycin - cattle mastitis *Staphylococcus aureus*  
*Streptococcus agalactiae*  
*Streptococcus dysgalactiae*  
*Streptococcus uberus* | 2 | 4 |

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

The lincosamides are not recommended for administration to horses, rabbits, hamsters, guinea pigs and ruminants. Administration to nonruminant herbivores may be fatal.

LS-50 (lincomycin and spectinomycin), a water-soluble product marketed for poultry, has been commonly compounded and administered to cattle in the U.S. for mastitis and respiratory disease. Anecdotal reports of diarrhea and decreased feed intake have been presented. Lincomycin is labeled for beef cattle in Europe.

Nursing puppies and kittens may develop diarrhea if the bitch or queen is administered a lincosamide due to significant concentrations (equal to plasma) in the milk.
Clindamycin has been used to treat cats with toxoplasmosis. Adverse reactions should be watched for, especially in cats with pulmonic toxoplasmosis. A research study indicated a high fatality rate in cats with pulmonic toxoplasmosis that were treated with clindamycin.
NITROIMIDAZOLES

MEMBERS OF THE GROUP

Metronidazole (HL, Flagyl®)
Dimetridazole (Emtryl®)
Ipronidazole (Ipropan®)
Ronidazole
Tinidazole

All members of the nitroimidazoles are banned from use in food animals in the U.S.

PHYSIOCHEMICAL PROPERTIES

The nitroimidazoles have some structural similarities to the nitrofurans. They are based on a 5-membered nucleus.

MECHANISM OF ACTION

A reduction of the nitro group in anaerobic bacteria produces unstable metabolites, some of which break DNA strands and inhibit repair enzymes. Bacteria in aerobic conditions possess the necessary reduction system, and are resistant. The nitroimidazoles may function against aerobic bacteria in anaerobic conditions.

SPECTRUM

+++

The nitroimidazoles are active only against anaerobic bacteria or possibly facultative anaerobes in an anaerobic environment.

<table>
<thead>
<tr>
<th></th>
<th>Aerobic</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram (+)</td>
<td></td>
<td><em>Clostridium</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Eubacterium</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Peptococcus</em></td>
</tr>
<tr>
<td>Gram (-)</td>
<td></td>
<td><em>Bacteroides</em></td>
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<td></td>
<td></td>
<td><em>Bacillus</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Fusobacterium</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(Extensive coverage of all Gram (-) anaerobes)</em></td>
</tr>
</tbody>
</table>

Actinomyces show significant resistance

Activity against *Entamoeba histolytica*, *Giardia*, *Balantidium coli*, and *Trichomonas* has also been demonstrated.
RESISTANCE DEVELOPMENT

Resistance is rare, but may result from decreased intracellular reduction to form toxic intermediates. Cross-resistance between nitroimidazoles is complete and may also occur with the nitrofurans.

PHARMACOKINETICS

Metronidazole is well absorbed after oral administration, but high variability in dogs has been reported (50-100% oral bioavailability). Oral bioavailability in the horse has approximately the same range, with a mean around 80%. Metronidazole is only approximately 20% bound to plasma proteins in humans.

Elimination is primarily by hepatic metabolism, but substantial amounts (up to 2/3) may be eliminated in the urine, much of which is in the active form. Elimination half-times range from 6-10 hours in humans to 3-5 hours in the dog and horse.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

A carcinogenic effect observed in lab animals for metronidazole may or may not have clinical relevance but accounts for the ban on use in food animals. Metronidazole has been used in women for vaginal trichomoniasis with no increase in cancer morbidity.

Nausea is a common side effect in humans. Inappetence may be noted in horses. Nausea and vomiting have been reported in dogs.

Acute central nervous system toxicosis has been reported in dogs and cats with high doses.
“PHENICOLS”

MEMBERS OF THE GROUP

Chloramphenicol: (often abbreviated CHPC): Veterinary labels - Amphicol® tablets, Duricol® capsules, Viceton®, Human label – Chloromycetin®
Thiamphenicol

Florfenicol: Nuflor® for cattle (injectable) and swine (concentrate for oral use in water, generic water soluble concentrate for swine available in 2013 “Florvio”), Aquaflor® for fish (feed additive, along with tilmicosin for swine and cattle, the two antimicrobials with VFD status)

Nuflor Gold® is the same concentration of florfenicol but with an improved formulation. Resflor Gold® is florfenicol in a fixed combination with flunixin meglumine (Banamine®).

IN THE KSU PHARMACY

Chloramphenicol 250, 500, 1 gram tablets
Florfenicol injectable

PHYSIOCHEMICAL PROPERTIES

These drugs are very lipid soluble with high volumes of distribution (> 1 L/kg).

Florfenicol is a structural analogue of chloramphenicol.

Chloramphenicol is the parent of Thiamphenicol which is the parent of Florfenicol

Thiamphenicol is formed by substituting the nitro group of chloramphenicol with a sulfonylmethyl group.

Florfenicol, which also lacks the nitro group, is a fluorinated derivative of thiamphenicol.

One of the major mechanisms of chloramphenicol inactivation is the acetylation of hydroxyl groups. The enzyme responsible is referred to as chloramphenicol acetyltransferase. Florfenicol has one possible site for acetylation compared to two for chloramphenicol and thiamphenicol. This may be responsible for florfenicol activity against some chloramphenicol and thiamphenicol resistant organisms.

MECHANISM OF ACTION

Protein Synthesis Inhibition; chloramphenicol and florfenicol bind to the 50S subunit of bacterial ribosomes. Amino acids are not able to transfer to growing polypeptides due to prevention of the binding of aminoacyl tRNA to the ribosome. This binding is reversible.

These drugs have been considered bacteriostatic for the majority of pathogens except at extremely high concentrations or for extremely susceptible isolates, where they may be
bactericidal. However, florfenicol displays bactericidal activity against *Mannheimia haemolytica* and *Pasteurella multocida* (MICs and MBCs are only one dilution apart for these 2 organisms.)

Chloramphenicol also inhibits protein synthesis in the bone marrow of mammals. This aplastic anemia is usually reversible in humans and veterinary species and is regimen related (dose and duration). In humans, it is thought that a hereditary predisposition leads to fatal aplastic anemia in 1 of every 25,000 to 60,000 patients treated with chloramphenicol. This form of aplastic anemia is not dose related. Almost all of the aplastic anemia cases reported in humans have been due to therapy rather than contact. However, veterinarians should be careful in handling this drug and advise clients of the risk. In today's legal climate, it would be advisable to dispense exam gloves for use while dosing.

The typical dosage regimens in companion animals do not lead to bonemarrow suppression. However, problems may occur if the animal has depressed hepatic microsomal enzyme activity or severely impaired renal function.

The possible irreversible, aplastic anemia in humans is why **CHLORAMPHENICOL IS BANNED FOR USE IN FOOD ANIMALS!**

**SPECTRUM**

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+-----+-----
|+++++|+++++|
|++   |+++++|
```

CHPC has activity in all 4 quadrants, but the lack of consistent enterobacteriaceae and *Pseudomonas* activity (due to resistance) causes us to downgrade the activity in the Gram (-) aerobe quadrant. The lack of enterobacteriaceae activity is not because of constitutive resistance (i.e., the drug never did work on the bacteria because of bacterial binding site structure, lack of target enzyme or some other reason) but rather because resistance has developed in many of these isolates.

Florfenicol is broad spectrum like chloramphenicol, with greater *in vitro* potency against most pathogenic organisms. Florfenicol also has activity against some chloramphenicol resistant strains of *Salmonella typhimurium*, and *Staph. aureus*. Consider activity against *E. coli* and *Salmonella* to be variable.

Florfenicol is clinically active against the Gram (-) bovine respiratory disease pathogens *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*.  

__________________________
Antimicrobial Notes, Pharm II, Apley, Kansas State University, 2015, Page 73
Chloramphenicol: generalized spectrum

<table>
<thead>
<tr>
<th>Aerobic</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram (+)</strong></td>
<td><strong>Broad coverage</strong></td>
</tr>
<tr>
<td>A. pyogenes</td>
<td></td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium</td>
<td></td>
</tr>
<tr>
<td>E. rhusiopathiae</td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
</tr>
<tr>
<td>Staph. Strep.</td>
<td></td>
</tr>
<tr>
<td>Rhodococcus equi</td>
<td></td>
</tr>
<tr>
<td><strong>Gram (-)</strong></td>
<td><strong>Broad coverage</strong></td>
</tr>
<tr>
<td>Actinobacillus</td>
<td></td>
</tr>
<tr>
<td>Bordetella bronchiseptica</td>
<td></td>
</tr>
<tr>
<td>Brucella canis</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae*</td>
<td></td>
</tr>
<tr>
<td>Haemophilus</td>
<td></td>
</tr>
<tr>
<td>Pasteurella</td>
<td></td>
</tr>
</tbody>
</table>

Also *Leptospira*

*Resistant organisms: Mycobacterium, Nocardia, possible acquired resistance with Enterobacteriaceae

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

**Chloramphenicol:** Oral tablets approved for dogs only, human label CHPC capsules, powder for injection, CHPC palmitate oral suspension, otic and ophthalmic preparations.

**Florfenicol:** Injectable (IM or SC) for cattle, oral solution for use in water systems for swine, feed additive for fish

**PHARMACOKINETICS**

Chloramphenicol elimination half-times vary among veterinary species, from approximately 1 hour in horses to 6 hours in cats. Elimination is primarily through hepatic conjugation with glucuronic acid. Only very small amounts (10-20%) are excreted unchanged through the kidney.

**The fetus and neonate are deficient in glucuronyl transferase activity, and so elimination of chloramphenicol is much slower.** For example, the elimination half-time in one day old calves was reported as 14 hours in comparison with 8.2 hours at 3 days and 4.2 hours in adults. In contrast, the glucuronyl transferase activity in foals appears to reach adult levels in one week.
Chloramphenicol reduces the activity of glucuronide conjugation and oxidative pathways in the liver. It may dramatically prolong the activity of barbiturates. The classic example is administration of chloramphenicol to a dog on phenobarbital for control of seizures. The dog will lapse into a phenobarbital induced comatose state until the drug can be eliminated. OOPS!!

How many antimicrobials do we have now that will cause problems with a dog on phenobarbital for epilepsy?

PHARMACODYNAMICS

Chloramphenicol is considered bacteriostatic with efficacy dependent on time above MIC. Florfenicol shows evidence of being bactericidal against target pathogens.

SUSCEPTIBILITY TESTING

"Phenicol" breakpoints adapted from CLSI VET01-S2. Florfenicol breakpoints are CLSI approved utilizing veterinary data. CHPC breakpoints (shaded) are human derived.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
<th>Extended Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organisms other than Streptococci</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Streptococci (not S. pneumoniae)</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Streptococci (S. pneumoniae)</td>
<td>4</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Florfenicol – bovine respiratory disease</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>0.25-8</td>
</tr>
<tr>
<td>Florfenicol – swine respiratory disease* (all label organisms except Salmonella cholerasuis)</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>0.25-8</td>
</tr>
<tr>
<td>Florfenicol – swine respiratory disease* (Salmonella cholerasuis)</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>0.25-8</td>
</tr>
</tbody>
</table>

*Swine respiratory disease breakpoints are for the using the water premix product only, and not for extralabel use of the bovine florfenicol injectable product in pigs.

ADVERSE REACTIONS/CONTRAINICATIONS/TOXICITIES

Chloramphenicol

Human safety concern - Aplastic anemia reported in humans, a human exposure concern when CHPC is dispensed.

Dose-related bone marrow suppression - Encountered in all veterinary species with prolonged therapy, is usually reversible.

Patients with impaired renal and/or hepatic function - Extensive CHPC accumulation is probable.

“Gray-baby syndrome” in humans - Circulatory collapse most likely due to the inability to conjugate or excrete the conjugate effectively. Raises question about the use of CHPC in veterinary neonates. Caution is recommended when using CHPC in kittens. Found in human
milk at approximately 50% of serum levels, so we may assume that high levels are getting to nursing veterinary species when administered to the bitch, queen or mare.

Concerns of chloramphenicol-related immune suppression have been published in the literature but subsequent trials have demonstrated no effect on the ability of animals (dog in one study) to respond to vaccinations while undergoing chloramphenicol therapy. Chloramphenicol was demonstrated to have no effect on response to distemper vaccine in beagle pups; this was confirmed by disease challenge. Chloramphenicol has, however, been demonstrated to decrease phagocytosis of Staph. Aureus by bovine mammary PMNs in an in-vitro study. Not sure how this relates to in-vivo, but…

Florfenicol

Slaughter withdrawal for florfenicol is 28 days or 38 days depending on regimen. Residue warnings from the product label include:

- Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues.

- Do not use in veal calves, calves under one (1) month of age, or calves being fed an all-milk diet. Use in these classes of calves may cause violative tissue residues to remain beyond the withdrawal time.

These two statements from the Nuflor® label indicate a lack of data submitted to the FDA/CVM regarding residue characteristics of this drug for these two production classes of cattle. They are not statements of absolute prohibition, as in the prohibition of extralabel use of fluoroquinolones in food animals. Veterinarians may still use florfenicol in adult (≥20 months of age) dairy cattle and in veal calves, but only under the AMDUCA regulations which require that sufficient data be available to establish a withdrawal time for the extralabel use. Your source for this information is the Food Animal Residue Avoidance and Depletion service (FARAD, 1-888-USFARAD, www.farad.org). If they can’t provide you with an extralabel regimen withdrawal time, don’t use the drug in that manner.

Florfenicol has been commonly used in an extralabel manner in dairy cattle. Previously, the beef cattle tolerance for liver was applied to a cull dairy cow. However, now the Food Safety and Inspection Service (FSIS) along with the FDA/Center for Veterinary Medicine have determined that since a lactating dairy cow (or a veal calf) are not on the label, that this tolerance does not apply. Therefore, the tolerance in the tissues of a veal calf or a cull dairy cow is zero. This has resulted in a FARAD-recommended slaughter withdrawal time in a cull dairy cow of 90 days compared to 38 days in beef cattle for the label regimen of a single dose of 6 ml/100 lbs (40 mg/kg). Any florfenicol detected in milk would be violative.

The product label lists inappetence, decreased water consumption, and diarrhea as adverse effects that may occur transiently following treatment. A 43 day controlled study was conducted in healthy cattle to evaluate the effects of Nuflor administered at the recommended dose on feed consumption. A transient decrease in feed consumption was observed. There was no long term effect on body weight, rate of gain, or feed consumption. The label also reports slight decreases in feed and water consumption when the recommended dose was administered for 3X the label duration (6 administrations). Additional effects were noted for higher doses administered for the same period.

Florfenicol has the potential to cause serious gastrointestinal disturbance in horses. Reports vary from mild softening of the feces to diarrhea. Significant alteration of the intestinal flora has also been reported.

Could florfenicol impede immune response as was once proposed for chloramphenicol (see above)? Sales representatives of competitive products to florfenicol were making these assertions. In response, a study was done where cattle were vaccinated with a modified-live Infectious Bovine Rhinotracheitis (IBR) vaccine, half were treated with florfenicol, and then all were challenged with IBR. No effect of florfenicol on the immune response was demonstrated. In trout, florfenicol administration at the time of vaccination for Aeromonas salmonicida and Vibrio anguillarum had no effect on antibody production or circulating leukocyte levels. However, there was a depression in phagocytic cell response 5-6 weeks after vaccination in the florfenicol group. Survival challenge was slightly depressed in the florfenicol group (88%) vs 98% in the untreated group. Another study reported decreases in lymphocyte blastogenesis, chemotaxis, phagocytic activity and antibody titers in Egyptian Buffalo calves vaccinated with Strain 19 Brucella abortus. As for CHPC above, there is no clear guidance on how this relates to daily use of florfenicol in practice.

SULFONAMIDES AND DIAMINOPYRIMIDINES

MEMBERS OF THE GROUP

Sulfanilamide (the first one, derived from the azo dye, prontosil)

“Short-acting”
- Sulfathiazole
- Sulfamethazole
- Sulfisoxazole

“Intermediate-acting”
- Sulfadimethoxine [VL Albon®, Di-Trim®, generic labels for water solubles, solutions]
- Sulfamethoxazole
- Sulfapyridine
- Sulfachloropyridazine [VL Vetisulid®]
- Sulfamethazine [Sustain III®, numerous other labels for boluses and water solubles]
- Sulfadiazine

“Long-acting”
- Sulfadimethoxine and sulfamethazine also listed in this category by some
- Sulfabromomethazine
- Sulfaethoxypyridazine

“Enteric sulfas”
- Sulfaguanadine
- Sulfaquinoxaline
- Sulfasalazine – [HL, Azulfidine® - a molecule of sulfasalazine linked to a molecule of a salt of salicylic acid] - Be careful in cats!

Diaminopyrimidines:
- Trimethoprim
- Pyrimethamine – noted for high activity against protozoa
  Ormetoprim, aditoprim - closely related, diaminobenzylpyrimidines

Combinations:
- Trimethoprim/sulfadiazine [VL Tribrissen®]
- Ormetoprim/sulfadimethoxine [VL Primor®]
- Trimethoprim/sulfamethoxazole [HL - Bactrim®, Septra®, Cotrim®, generics] ⭐
- Pyrimethamine/sulfadoxine (HL) – Used to treat malaria

The use of sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine and sulfaethoxypyridazine) is prohibited in the U.S.!
**PHYSIOCHEMICAL PROPERTIES**

The sulfas are derivatives of sulfanilamide. Different sulfas vary in pharmacokinetic parameters and potency. Each sulfa exhibits independent solubility in a solution.

Sulfas are weak acids, and are not water soluble in the acid form. $P_k_a$ values range from 5.0 for sulfasoxazole to 10.4 for sulfanilamide.

Treating with a strong base will form a soluble, sodium salt. These solutions are very basic, with pHs of 9 to 11. An exception is sulfacetamide, which is nearly neutral in solution and is used in ophthalmic solutions.

Trimethoprim is a weak base with a $pK_a$ of $\approx 7.6$. It is very lipid soluble and only minimally soluble in water. Trimethoprim is approximately 60% plasma protein bound.

**MECHANISM OF ACTION**

Sulfas compete with Para Amino Benzoic Acid (PABA) for incorporation into the scheme for folic acid synthesis. Folic acid is used for purine synthesis. This biological antagonism leads to decreased RNA, inhibiting protein synthesis.

There is no effect on mammalian cells because folic acid is obtained through the diet, and is not synthesized. Sulfas lose activity in the presence of cellular debris (pus, etc.) because folic acid and purines are readily available from the bacterial environment. This effect, plus a bacterial-inoculum effect, make it very difficult to extrapolate from laboratory susceptibility testing to clinical efficacy.

Sulfas are considered bacteriostatic, but may be bactericidal when combined with trimethoprim.

The diaminopyrimidines interfere with the function of dihydrofolate reductase which catalyzes the conversion of dihydrofolate to tetrahydrofolic acid. Dihydrofolate reductase is also involved in mammalian folic acid pathways, but diaminopyrimidine affinity for the mammalian enzyme is much less than for the bacterial enzyme.

Combining a diaminopyrimidine with a sulfa results in a synergistic combination acting in a bactericidal manner against susceptible microbes.
SPECTRUM

Sulfas

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</table>

“others” – **coccida for sulfadimethoxine, sulfaquinoxaline.** Chlamydia in general

Potentiated sulfas

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<td>++++++</td>
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<td>++++++</td>
<td>++++++</td>
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</tbody>
</table>

Sulfonamide generalized spectrum: good susceptibility, **moderate susceptibility** organisms in bold type

<table>
<thead>
<tr>
<th>Aerobic</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram (+)</strong></td>
<td><strong>Bacillus</strong>&lt;br/&gt;<strong>E. rhusiopathiae</strong>&lt;br/&gt;<strong>L. monocytogenes</strong>&lt;br/&gt;<strong>Strep</strong>&lt;br/&gt;<strong>Nocardia</strong>&lt;br/&gt;<strong>Staph.</strong>&lt;br/&gt;<strong>Enterococci</strong></td>
</tr>
<tr>
<td><strong>Gram (-)</strong></td>
<td><strong>Brucella</strong>&lt;br/&gt;<strong>Enterobacteriaceae</strong>&lt;br/&gt;<strong>Actinobacillus</strong>&lt;br/&gt;<strong>Haemophilus</strong>&lt;br/&gt;<strong>Pasteurella</strong></td>
</tr>
</tbody>
</table>

-Also: Coccidia (maybe!!), pneumocystis, Cryptosporidium (not effective clinically), **Chlamydia**

* All other Clostridia considered resistant
-Resistant: **Mycobacterium, Mycoplasma, Rickettsia, Pseudomonas, Spirochetes**
Potentiated sulfonamide generalized spectrum: The spectrum doesn’t expand that much, but efficacy against members of the spectrum expands.

<table>
<thead>
<tr>
<th>Gram (+)</th>
<th>Aerobic</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>E. rhusiopathiae</em></td>
<td><em>Actinomyces</em> (facultative)</td>
</tr>
<tr>
<td></td>
<td><em>L. monocytogenes</em></td>
<td><em>Clostridium</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Strep</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staph.</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Actinomyces</em> spp.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Arcanobacterium</em></td>
<td></td>
</tr>
<tr>
<td>Gram (-)</td>
<td><em>Brucella</em></td>
<td><em>Bacteroides</em></td>
</tr>
<tr>
<td></td>
<td><em>Bordetella</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacteriaceae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Actinobacillus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pasteurella</em></td>
<td></td>
</tr>
</tbody>
</table>

- Also: *Chlamydia*

- May gain efficacy against *Mycobacterium* spp. and *Nocardia* spp.

Trimethoprim, ormetoprim, and aditoprim are generally bacteriostatic when used alone, acting on a broad-spectrum which includes both gram-negative and gram-positive bacteria. Pyrimethamine is used with sulfadiazine for treatment of toxoplasmosis in humans. Prior to ponazuril (Marquis®, Bayer Animal Health), pyrimethamine was used in conjunction with TMP/sulfa or a sulfonamide for treatment of Equine Protozoal Myeloencephalitis (EPM).

**RESISTANCE DEVELOPMENT**

Resistance to sulfas is common in veterinary medicine due to over 50 years of use. Plasmid mediated resistance is more common than chromosomal resistance. The sulfas are considered to exhibit complete cross-resistance. Mechanisms of resistance are as follows.

<table>
<thead>
<tr>
<th>Resistance Mechanism</th>
<th>Chromosomal Resistance</th>
<th>Plasmid-mediated Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered cell permeability</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Refractive dihydropteroate enzymes</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>PABA hyperproduction</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

Resistance R-factors against potentiated sulfonamides have been identified in *enterotoxigenic E. coli* and in *Salmonella typhimurium* (veterinary species isolates).

**ROUTES OF ADMINISTRATION:** Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route. Focus on **TMP/sulfamethoxazole (TMP/sulfadiazine) and sulfadimethoxine as the ones to know** for this class.
**Sulfadimethoxine (Albon®):** IV administration in dogs, cats, horses, cattle with 40% injection (extremely irritating IM or SC), oral boluses in cattle, 12.5% concentrated solution for oral administration in drinking water to cattle, chickens, and turkeys, tablets and oral suspension for dogs and cats, soluble powder for addition to drinking water of cattle, broiler and replacement chickens, and meat producing turkeys.

**Sulfadimethoxine/ormetoprim:** Primor® tablets for dogs, under other brands: medicated premix for chickens, turkeys, ducks, chukar partridges, slamonids, and catfish.

**Trimethoprim/sulfadiazine:** VL Tribrissen® 48% injection (IV) and oral paste for horses, VLS Tucoprim® and Uniprim® powder for horses, oral tablets for use in dogs.

**Trimethoprim/sulfamethoxazole:** Human label (Cotrim®, Bactrim®, Septra®, generics) tablets, oral suspension, injection.

**Sulfamethazine:** oral boluses for cattle, granular feed additive for swine and cattle and soluble powder for swine (used in cattle also).

**Sulfachlorpyridazine:** Vetisulid® injection (IV) or calves, soluble powder for calves and swine.

**Sulfasalazine:** human label, Azulfidine® and generic oral tablets and enteric-coated tablets.

**PHARMACOKINETICS**

Most sulfas are absorbed well from oral or parenteral administration. There are big differences between sulfas, and between species for each sulfa, in degree of protein binding, apparent volume of distribution, and elimination half-life. Examples of differences in the bovine are shown in the following table.

**Comparison of the pharmacokinetics of sulfonamides in cows** (reproduced from Antimicrobial Therapy in Veterinary Medicine, Prescott JF, Baggot JD, ed. ISU press, Ames. 1993, page 233.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK_a</th>
<th>% Nonionized in plasma</th>
<th>T_1/2 (min.)</th>
<th>Apparent Vd (L/kg)</th>
<th>% protein bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfanilamide</td>
<td>10.4</td>
<td>100</td>
<td>370</td>
<td>1.08</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Sulfamethazine</strong></td>
<td>7.4</td>
<td>50</td>
<td>680</td>
<td>0.44</td>
<td>70</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>6.4</td>
<td>9</td>
<td>150</td>
<td>0.75</td>
<td>14</td>
</tr>
<tr>
<td>Sulfadoxine</td>
<td>6.1</td>
<td>4.8</td>
<td>650</td>
<td>0.37</td>
<td>48-66</td>
</tr>
<tr>
<td><strong>Sulfamethoxazole</strong></td>
<td>6.0</td>
<td>3.8</td>
<td>140</td>
<td>0.30</td>
<td>62</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>6.0</td>
<td>3.8</td>
<td>750</td>
<td>0.31</td>
<td>80-85</td>
</tr>
</tbody>
</table>
Note that the elimination half-time for sulfachlorpyridazine in cattle has been reported as 1.2 hours.

In dogs, the elimination half-time for sulfadiazine has been reported as 8.95 ± 2.3 hours after IV administration of 25 mg/kg and 9.9 hours after 30 mg/kg orally.\textsuperscript{24,25} An estimate of elimination half-time for sulfamethoxazole in dogs was reported as 7.5 hours after 30 mg/kg IM.\textsuperscript{26}

It is common to give a “loading dose” of the sulfas as the first dose and then follow with a “maintenance dose” for continued therapy.

**Excretion is by:**

- **Renal excretion** - Alkalinizing the urine increases the solubility of sulfas in the urine as well as increasing the proportion excreted through the urine.
- **Biotransformation**
  1) Acetylation (main one for most sulfas, except in dogs which don’t have this pathway)
  2) Aromatic hydroxylation
  3) Conjugation with glucuronic acid

The acetylation pathway produces a metabolite which is relatively insoluble and poses more of a possibility of crystalluria, whereas the product of glucuronic conjugation is very soluble and safely excreted by the kidneys.

Trimethoprim is primarily excreted by hepatic metabolism. Subcutaneous administration of trimethoprim in cattle results in minimal (if detectable) plasma concentrations because trimethoprim given by this route is eliminated as fast as it is absorbed. Elimination half-times in adult cattle are extremely short (< 1 hour).

Aditoprim is considered to distribute to tissues better than trimethoprim, as evidenced by a higher volume of distribution. Aditoprim also has a longer elimination half-time. Concentrations of trimethoprim in prostatic fluid may reach 10x serum.

A diaminopyrimidine is usually combined with a sulfa in a 1:5 ratio. The ratio is not critical for synergistic activity. The ratio achieved *in vivo* will vary widely among veterinary species.

**PHARMACODYNAMICS**

Sulfas are considered to be bacteriostatic with efficacy dependent on time above MIC. The combination of a sulfa with a diaminopyrimidine is considered to result in a bactericidal effect.

SUSCEPTIBILITY TESTING

Sulfa breakpoints adapted from CLSI VET01-S2. All are human derived breakpoints.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ μg/ml)</th>
<th>Intermediate (μg/ml)</th>
<th>Resistant (≥ μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole – Sulfonamide class representative</td>
<td>256</td>
<td></td>
<td>512</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus spp.</em> Enterobacteriaceae</td>
<td>2/38</td>
<td></td>
<td>4/76</td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td>0.5/9.5</td>
<td>1/19 - 2/38</td>
<td>4/76</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From VET01-S2 – “The results of trimethoprim-sulfamethoxazole can be used to predict the susceptibility of potentiated sulfonamides containing trimethoprim. There are no data on the ability of trimethoprim-sulfamethoxazole results to predict susceptibility to ormetoprim combinations. A breakpoint of ≤ 2/38 should be used for isolates from urinary tract infections. For systemic disease, isolates for which the MICs are ≤ 0.5/9.5 should be considered susceptible.”

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

These adverse reactions are why some veterinarians do not use potentiated sulfas (the primary ones used) in dogs except as a last resort.

**Keratoconjunctivitis sicca** - Dogs, this condition may be irreversible after long-term therapy with sulfasalazine or sulfadiazine.

**Other adverse effects reported in dogs** - bone marrow depression, hypersensitivity reactions (skin), focal retinitis, fever, vomiting, nonseptic polyarthritis (many of the reported cases are in Dobermans), hepatic necrosis, immune-mediated thrombocytopenia

**Neutropenia** - Trimethoprim-sulfamethoxazole has been shown to significantly decrease neutrophil counts in dogs in the 3rd week of approximately 25-30 mg/kg PO, BID (by about 50%). Neutrophil counts returned to normal approximately one week after discontinuation of therapy.27

**Possible crystalluria** in acidic urine, depending on the sulfa.

**Enteric flora alteration** - Long-term oral administration

**Injection site concerns in food animals** - Intramuscular injection of commercial solutions labeled for intravenous administration will cause prolonged and extensive tissue blemishes.

Sulfaquinoxaline is thought to have an antagonistic effect on vitamin K. Hemorrhagic diathesis has been reported. Treatment of puppies with sulfaquinoxaline for coccidiosis has resulted in hemorrhage due to hypothrombinemia.

T₃ and T₄ serum concentrations - Some sulfonamides have induced mild thyroid dysfunction in humans and severe dysfunction in rats. Trimethoprim-sulfadiazine had no significant effect on T₃ and T₄ in dogs when given at 15 mg/kg PO Q12h for 4 weeks. However, trimethoprim-sulfamethoxazole at 30 mg/kg PO Q12H for 6 weeks in dogs significantly decreased T₃ and T₄. You should consider the possibility of inducing clinical hypothyroidism in dogs with long term sulfonamide therapy. The condition will resolve slowly (1 - 12 weeks) with cessation of the drug. This information is from a review article that also covers the effects of other drugs (NSAIDs, glucocorticosteroids, phenobarbital, potassium bromide, furosemide, and others) on the thyroid.²⁸

Important note on adverse reactions of sulfas: There are several potential adverse reactions in dogs as discussed above. Some clinicians have therefore concluded that TMP/sulfa should not be used in dogs. The alternative view is to consider that TMP/sulfa and sulfas may be used in dogs when you rule out cases where an adverse reaction is more likely (e.g., history of KCS, liver disease, thyroid therapy, Dobermans) and monitor for problems that may develop.

Pyrimethamine is teratogenic in animals and resulted in renal hypoplasia, epithelial dysplasia, and lymphoid, myeloid, and erythroid hypoplasia in foals born to mares being treated for EPM.

THE TETRACYCLINES

MEMBERS OF THE GROUP

1st generation (used as produced by an organism)

- **Chlortetracycline** (The first one, discovered in 1948.)
- **Oxytetracycline** (1950)
- **Tetracycline** (1953 through catalytic dehalogenation of CTC)

Note: There is a first generation tetracycline used only for its anti-inflammatory properties – Incyclinide.

2nd generation (semi-synthetic)

- **Doxycycline** (1967)
- **Minocycline** (1972)
- **Demeclocycline**

3rd generation (semi-synthetic or fully synthetic) – these new classes of tetracyclines address resistance mechanisms such as efflux pumps and ribosomal-protection.

- **Glycylcyclines** – New, recently synthesized derivatives to combat resistance to earlier tetracyclines. They are prepared by altering the 9 position of chlortetracycline, minocycline, or doxycycline. **Tigecycline** (1993) has been reported as having increased activity against glycopeptide-resistant enterococci and staphylococci with decreased glycopeptide susceptibility.

- **Aminomethylcyclines** - Omadacycline (2003), a synthetic derivative of minocycline.

- **Fluorocyclines** - Eravacycline (2010)

PHYSIOCHEMICAL PROPERTIES

Lipid soluble, amphoteric molecules. At physiological pH they form a mix of cations, anions, and zwitterions (you will recall that a zwitterion is an ion with both a positive and negative charge). So they are always ionized. At pH values between 4 and 7, the neutrally charged zwitterion predominates, which helps the tetracyclines have reasonable tissue distribution.

MECHANISM OF ACTION

**Protein Synthesis Inhibition**: Tetracyclines bind to the 30S ribosomal subunit, preventing access of transfer RNA to the ribosome-messenger RNA complex. This prevents addition of amino acids to a growing peptide chain. The majority of this binding is reversible. Removing tetracyclines allows reversal of the inhibitory effects.
Bacterial penetration mechanisms

Gram (-) - Two processes appear to be required:

(1) Passive diffusion through hydrophilic channels in outer membrane. The tetracyclines must complex with magnesium to cross through these porins.

(2) Energy dependent active transport through inner cytoplasmic membrane.

Gram (+) - Less well understood, also requires an energy dependent system.

**SPECTRUM**

This is a tough group to get a handle on. Many of the pathogens listed as “in the spectrum” have developed significant resistance. Also, there are differences in clinical efficacy among the group, a large portion of which may be due primarily to differences in absorption, distribution, and elimination, although in-vitro differences between oxytetracycline and chlortetracycline have been demonstrated.

**1st generation - Tetracycline, chlortetracycline, oxytetracycline**

<table>
<thead>
<tr>
<th></th>
<th>++</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Significant acquired resistance floating around for *Staph*, *Strep*, enterobacteriaceae, *Clostridium*, *Bacteroides* (so basically in all 4 quadrants).

**2nd generation - Doxycycline, minocycline**

<table>
<thead>
<tr>
<th>++++</th>
<th>++++</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

Basically you get increased potency and less acquired resistance present in the pathogen populations in each quadrant.
3rd generation – Tigecycline

Due to being less susceptible to efflux pumps and ribosomal protection proteins, efficacy is regained against many 1st and 2nd generation tetracycline-resistant organisms. However, the 3rd generation tetracyclines are still susceptible to enzymatic degradation. Do not consider tigecycline to be effective against *Pseudomonas*.

RESISTANCE DEVELOPMENT

Resistance may be plasmid mediated. Cross-resistance within the group is common. Tetracycline concentrations within the bacterial cell may be decreased by reduced penetration of the drug (changes in the outer membrane pores) or by energy dependent, active efflux of the drug. Genes identified as encoding for active efflux mechanisms in Gram (-) organisms include tetA through tetG, and tetK, tetL in Gram (+) organisms.

There may also be alterations to the ribosome which prevent binding. A slightly different mechanism is the production of proteins in the bacterial cytoplasm that prevent binding of the tetracycline to the ribosome. This is called the "ribosomal protection" strategy and is encoded by the genes tetM, tetO, or tetQ.

Enzymatic degradation of the tetracycline by bacteria has also been documented. The *tetX* gene encodes for oxidation of tetracycline in aerobic bacteria.

ROUTES OF ADMINISTRATION: Some of these routes may be extralabel routes, although they may be appropriate for some uses. When you use an extralabel route of administration you are responsible for knowing and interpreting the pharmacokinetic differences that accompany the change in route.

**Tetracycline:** Tetracycline oral suspension (Aquadrops®) for dogs and cats, oral boluses for calves, water soluble powders for swine and cattle. Human labels – tablets, capsules, oral suspension. Delta Albaplex® tablets contain tetracycline HCL, novobiocin sodium and prednisolone, for dogs.

**Chlortetracycline:** Soluble powders and granular feed additives for cattle, swine, sheep, turkeys, ducks, chickens.

**Oxytetracycline:** Terramycin® ophthalmic ointment contains OTC and polymyxin B. Oral boluses for calves, 100, 200, and 300 mg/ml injectable solutions for cattle and swine. Feed additives for chickens, turkeys, cattle, sheep, swine, soluble powders for swine, cattle, sheep, chickens, turkeys. Human label – capsules and injection.

**Doxycycline:** Doxirobe® gel for periodontal use in dogs. Human label – tablets, capsules, powder for oral suspension, oral syrup, powder for injection.

**Minocycline:** Human label – oral capsules and suspension, powder for injection.

**Tigecycline** [HL Tigecyl]– Powder for reconstitution for injection
PHARMACOKINETICS

The tetracyclines are well absorbed from oral, IM, and SC administration. Volumes of distribution are approximately 0.8 to 1.0 L/kg. Plasma protein binding varies from 65% for chlortetracycline to 20-25% for oxytetracycline and tetracycline.

Elimination half-times are in the 6-10 hour range, except for long-acting injectable products, where elimination half-times are in the 25-30 hour range. The oral bioavailability of chlortetracycline, oxytetracycline, and tetracycline is adversely affected by the presence of food in the stomach (over 60% decrease in bioavailability for tetracycline) but this effect is minimal for doxycycline. Divalent cations such as Mg, Ca, and Fe chelate the tetracyclines and decrease absorption.

The tetracyclines distribute well to most tissues. Distribution to the CNS is variable, with minocycline expected to have superior concentrations due to extensive lipid solubility.

Tetracycline, chlortetracycline, and oxytetracycline are excreted primarily in the urine as the unchanged, original compound. They also exhibit extensive enterohepatic recirculation, which has the effect of prolonging their apparent elimination half-times.

Doxycycline and minocycline are more lipophilic than the other tetracyclines. Minocycline is thought to undergo significant metabolism. Doxycycline is primarily eliminated through the bile and diffusion into the intestinal tract. The renal component of doxycycline elimination is minimal, making it the tetracycline of choice for patients with renal impairment. Doxycycline is approximately 90% protein bound in dogs and approximately 99% protein bound in cats, both of which will limit distribution to tissues by decreasing the diffusion gradient based on free drug in the plasma. Doxycycline concentrations in the prostate are approximately 15% that of plasma.

Doxycycline is much less bioavailable in horses than in dogs. Dogs receiving 5 mg/kg for several days will achieve peak plasma concentrations of around 3.5 µg/ml, while horses receiving 10 mg/kg orally for several days will top out around 0.5 µg/ml in the plasma.

PHARMACODYNAMICS

The efficacy of the tetracyclines has typically been considered to be most closely linked to the time the serum concentration remains above the MIC of the target pathogen. However, the literature would indicate that the ratio of the area under the serum concentration curve (AUC) to the pathogen MIC is the best predictor of clinical efficacy for some tetracyclines. They are classified as bacteriostatic. However, most of this work has been done on the newest generation tetracyclines, with little data generated for the earliest tetracyclines (OTC, CTC, TC)

OTHER THERAPEUTIC APPLICATIONS OF TETRACYCLINES:

High-dose, IV oxytetracycline has been advocated for use in flexor tendon contraction deformities in neonatal foals. Oxytetracycline administration reportedly results in relaxing of the tendons, allowing a more normal joint angle. Reports in the literature have confirmed that the
angle of the metacarpophalangeal joint may be increased with single injections of oxytetracycline.\textsuperscript{29,30} In vitro work has shown that collagen gel contraction by equine myofibroblasts was inhibited by oxytetracycline in vitro.\textsuperscript{31} Be careful, because these very high doses could be associated with renal toxicity.

**Extensive effects of tetracyclines on inflammation have been established,** many of which have been utilized in human dermatology.\textsuperscript{32} These include suppression of neutrophil chemotaxis, inhibition of T-lymphocyte activation and phospholipase A2, and inhibition of mitogen-induced human lymphocytic proliferation. While the use of tetracyclines for acne was initially thought to be based on inhibition of *Propionibacterium acnes*, it is now believed that much of the therapeutic benefit is actually due to the inhibition of *P. acnes* lipase, neutrophil chemotaxis, and proinflammatory cytokines and metalloproteinases.

**SUSCEPTIBILITY TESTING**

**Tetracycline breakpoints adapted from CLSI VET01-S2.** The “generic” breakpoints have been derived utilizing veterinary pharmacokinetic data combined with pharmacodynamic data derived from other bacterial species and without supporting clinical data.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible (≤ µg/ml)</th>
<th>Intermediate (µg/ml)</th>
<th>Resistant (≥ µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetracycline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organisms other than streptococci</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Streptococci</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>“Generic” oxytetracycline breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle respiratory disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mannheimia haemolytica</em></td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Histophilus somni</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swine respiratory disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Actinobacillus pleuropneumoniae</em></td>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus suis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From VET01-S2 regarding the “generic” breakpoints: “Breakpoint derived from the pharmacokinetic data of oxytetracycline at 20 mg/kg IM, once, and pharmacodynamic data.


These interpretive criteria are applicable only for the injectable formulations. Tetracycline is the class representative.”

Although not mentioned in the document, the PK data were from the 200 mg/ml products.

**ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES**

**Nephrotoxicity** - Oxytetracycline at elevated doses (2x-3x label), consider this in dehydrated patients or those with renal disease. High doses of the tetracyclines may also create an anti-anabolic effect, which can contribute to elevated BUN in patients with renal failure. Outdated tetracyclines with extensive degradation products can lead to Fanconi’s syndrome, which is damage to the renal tubules.

Renal examples in cattle:

Toxicity is minimal at recommended doses. There may be some toxicity at extremely high doses. Thirty-three mg/Kg (15 mg/lb) of oxytetracycline IV daily for 3 days induced a rise in BUN and renal casts in the urine of normal heifers. Griffin DD, Morter RL. *Experimental oxytetracycline toxicity in feedlot heifers*. Bov Pract 14:37-40, 1979.

Calves given 44 mg/Kg (20 mg/lb) LA-200 as mass treatment on arrival, and then treated for respiratory disease with either LA-200 44 mg/Kg (20 mg/lb) IV or conventional OTC 22 mg/Kg (10 mg/lb) IV followed by 4 days of conventional OTC at 22 mg/Kg (10 mg/lb) IM did not improve clinically and had a 48% death loss. BUN values averaged 218 mg/dL. All calves had subacute bronchopneumonia and moderate to severe renal cortical tubular nephrosis confirmed histopathologically at necropsy. Lairmore MD, Alexander, AF, et al. *Oxytetracycline-associated nephrotoxicosis in feedlot calves*. J Am Vet Med Assoc 185:7930795, 1984.


Rapid IV injection of the 100 mg/mL products may cause a shock-like reaction in which the animal collapses. Injection of a propylene glycol based oxytetracycline preparation produced cardiac asystole and systemic hypotension in instrumented calves. The dose required to produce this response was 11 mg/Kg (5 mg/lb) in 2 calves, 22 mg/Kg (10 mg/lb) in two calves, and 55 mg/Kg (25 mg/lb) in one calf. Propylene glycol alone also produced these effects. Injection of an aqueous oxytetracycline preparation at the same dose and the same volume in each calf produced no effect on the cardiovascular system. Gross DR, Kitzman JV, et al. *Cardiovascular effects of intravenous administration of propylene glycol and of oxytetracycline in propylene glycol in calves*. Am J Vet Res 40:783-791, 1979.

**Adverse fetal and juvenile effects** - Teeth staining is possible
Gastrointestinal effects - Cats have frequent problems with oral tetracyclines (colic, hair loss, fever, depression). Interference with digestion in ruminants and nonruminant-herbivores is a possibility. Work looking at inclusion in feed for calves utilizing 10 mg/lb per day of chlortetracycline showed no adverse effects on gain or feed intake.

Tetracyclines should be administered with caution to horses, intravenous oxytetracycline is used, but oral administration in feed is definitely not advisable. Watch for adverse GIT effects in stressed horses.

One study of oral doxycycline pharmacokinetics in the horse reported no toxicity at 20 mg/kg, orally. The authors report the oral formulation is well tolerated in horses and cite a recommendation of 10 mg/kg Q12H. However, intravenous doxycycline has been reported as being fatal in horses due to cardiovascular dysfunction. Oral doxycycline is commonly used in horses and is relatively economical. (depending on production shortages, as occurred in 2013)

Injection site concerns in food animals - Intramuscular injection of some products may cause prolonged and extensive tissue blemishes. We have subcutaneous labels for 200 mg/ml and 300 mg/ml food animal products in cattle and they should not be used IM. Conventional, 100 mg/mL products cause the most severe reactions in food animals.

Photosensitivity reactions - Sometimes associated

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Gram (+) Thumpers: Antimicrobials focused on tough Gram (+) infections

Spectrum (Takehome: These have activity against Staphylococci, Streptococci, Enterococci, MRSA, and VRE)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Route</th>
<th>Staph</th>
<th>Strep</th>
<th>Enterococci</th>
<th>MRSA</th>
<th>VRE</th>
<th>Clostridium</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic Lipopeptides</td>
<td>IV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>IV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Oral</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptogramins</td>
<td>IV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Broad anaerobic</td>
<td>Leptospira Mycoplasma Toxoplasma</td>
</tr>
<tr>
<td>Polypeptides (Bacitracin)</td>
<td>Topical</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mupirocin</td>
<td>Topical</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>*</td>
</tr>
</tbody>
</table>

*Be aware of resistance issues in these applications
- Combination therapy is often used against MRSA and VRE targets

In the KSU pharmacy you will find Vancomycin injectable. Topical mupirocin and bacitracin are also used. The cyclic lipopeptides, oxazolidinones, and streptogramins are going to be rarely used in veterinary medicine, except for the streptogramin virginiamycin, which is labeled as a growth promoter in cattle, swine, and poultry; this use will be gone by 2017-2018. Concentrate on the 3 commonly used in veterinary medicine and recognize the others as Gram (+) thumpers.
**CYCLIC LIPOPEPTIDES**

**MEMBERS OF THE GROUP**

*Daptomycin* (Cubicin®), 2003

**SPECTRUM**

Daptomycin is *approved in human medicine* for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subspecies *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible strains only).

In-vitro activity has been demonstrated against vancomycin-resistant *Enterococcus faecium* (VRE) and oxacillin-resistant *Staphylococcus aureus*.34,35

An interesting lesson in drug development for linezolid. The pharmacokinetics/pharmacodynamics of the drug suggested efficacy against Gram positive pneumonia. However, the actual human clinical trials on pneumonia cases showed poor efficacy. The reason? daptomycin is highly bound to surfactant and therefore becomes largely unavailable for interaction with the pathogen in the airways. Therefore, skin structure infection indications are on the label, and not pneumonia. Your takehome is that this drug is a very poor choice for extralabel treatment of a Gram (+) pneumonia in a dog (also very expensive).

**MECHANISM OF ACTION**

Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential, resulting in inability to synthesize proteins, DNA, or RNA.

In-vitro synergism with aminoglycosides, β-lactams, and rifampin have been observed against some *Staph.* and *Enterococci*, including some methicillin resistant *Staph. aureus* (MRSA) and vancomycin resistant enterococci (VRE).

**PHARMACOKINETICS/PHARMACODYNAMICS**

In humans, administered once daily by IV administration. Human protein binding is 90 – 93% with a Vd of 0.1 L/kg. Excretion is primarily by the kidney.

Rapid, bactericidal activity with activity best related to concentration.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Mild to moderate intensity adverse reactions reported in human studies include gastrointestinal disorders, injection site reactions, fever, headache, insomnia, dizziness, and rash. Elevations in creatine phosphokinase (CPK) were reported in human trials, some with clinical symptoms of muscle pain.
GLYCOPEPTIDES

MEMBERS OF THE GROUP

**Vancomycin** (human label) – a tricyclic glycopeptide, produced by Streptococcus orientalis, an organism isolated in 1953 from a soil sample collected by a missionary in the Jungles of Borneo.

Teicoplanin (human label) – Produced by another organism, *Actinoplanes teichomyetius*, and is available in Europe

Avoparcin (a feed-additive not available in the U.S., now banned in the E.U. and many other countries)

The lipoglycopeptide semisynthetic derivatives

Dalbavancin is a lipoglycopeptide with a prolonged plasma half-life in humans, allowing for once-weekly intravenous dosing. Human approval in May of 2014 for treatment of acute bacterial skin and skin-structure infections in humans to include MRSA and *Strep. Pyogenes*. It is the first new antimicrobial approved under the accelerated Generate Antimicrobial Incentives Now (GAIN) program of the FDA.

Oritavancin – an IV single-dose lipoglycopeptide in humans (August, 2014). It has activity against *Staph aureus*, *MRSA*, *Enterococci*, *Streptococci*, and *Clostridium difficile*.

Telavancin

The Mannopeptimycins – a new class of glycopeptides not related to vancomycin

*The use of glycopeptides in food animals is banned in the U.S. due to concerns over resistance development!*

PHYSIOCHEMICAL PROPERTIES

Vancomycin is a product of *Streptomyces orientalis*. It has a very high molecular weight and is very water soluble in the hydrochloride salt form in which it is available. Teicoplanin is composed of 5 closely related antibiotics.

MECHANISM OF ACTION

*The glycopeptides are bactericidal by inhibiting cell-wall peptidoglycan synthesis.* Vancomycin binds to the D-Alanine - D-Alanine cross linking site. This binding site for inhibition of peptidoglycan cross-linking is different than that for the penicillins and cephalosporins.
Oritavancin efficacy has been demonstrated to be most closely related to Cmax as opposed to time > MIC or AUC for \textit{Staph. aureus} in a mouse thigh infection model.\textsuperscript{36} Vancomycin efficacy against \textit{Staph. aureus} and MRSA has been most closely associated with the AUC:MIC ratio, but a suggested trough concentration of 4-5 times the MIC has also been suggested.\textsuperscript{37}

\textbf{SPECTRUM}

Glycopeptide activity is primarily against Gram-positive, aerobic, cocc \\ and bacilli. Most Gram-negative bacteria are resistant due to poor penetration. Vancomycin is considered active against \textit{Neisseria} spp. and \textit{Clostridium} spp. Vancomycin is a first line of defense against MRSA. Vancomycin and rifampin are considered synergistic against \textit{Staph. aureus}. Teicoplanin is only additive or indifferent with rifampin but is considered synergistic with imipenem against gram-positive cocci. Teicoplanin has greater activity against \textit{Streptococcus}, and may also bind endotoxin.

\textbf{RESISTANCE DEVELOPMENT}

The glycopeptides were considered as “immune” to resistance development for some time. However, vancomycin resistant \textit{Enteroccci} (VRE) are becoming more common and the first strain of vancomycin-resistant \textit{Staph aureus} (VRSA) was reported in the United States in 2002.

Vancomycin resistance requires a complicated combination of genes encoding for changes in peptidoglycan cross-linking in the cell wall. Three enzymes are necessary for resistance.

1. \textit{vanA} or \textit{vanB} encode for a D-Alanine - D-Lactate crosslink to replace the D-Alanine - D-Alanine crosslink to which vancomycin binds.

2. \textit{vanH} is necessary to encode for production of lactate for this new crosslink from pyruvate.

3. \textit{vanX} encodes for an enzyme that lyses the D-Alanine - D-Alanine crosslinks but not the D-Alanine - D-Lactate crosslink. In the absence of \textit{vanX}, the continued presence of the D-Alanine - D-Alanine crosslinks still makes the bacteria susceptible to vancomycin.

\textbf{PHARMACOKINETICS}

\textit{Vancomycin} is poorly absorbed after oral administration and is only administered IV. It must be administered over a period of about 30 minutes in humans, after which it exhibits an elimination half-time of about 6 hours. A 2 hour elimination half-time has been reported in dogs. IM administration results in severe irritation. Almost all of the drug is eliminated renally although a small amount may be excreted in the bile.

\textsuperscript{36} Boylan, CJ; Campanale, K; Iversen, PW; Phillips, DL; Zeckel, ML; Parr, TR. Pharmacodynamics of oritavancin (LY333328) in a neutropenic-mouse thigh model of \textit{Staphylococcus aureus} infection. Antimicrobial agents and chemotherapy, 47 (5): 1700-1706, 2003.

Teicoplanin differs in having a 45-70 hours elimination half-time in humans. It may be given as a rapid IV bolus, and also may be given IM.

**ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES**

Vancomycin may cause ototoxicity in humans. It must be administered slowly to avoid “Redman Syndrome”, which is the release of large quantities of histamine. The highly irritant nature of vancomycin hydrochloride must always be considered. It is very tough on veins and is administered diluted in saline.

Teicoplanin and vancomycin are thought to be synergistic with the aminoglycosides against gram-positive cocci. However, extreme care should be taken to avoid ototoxicity, especially if renal insufficiency is present.

Emesis is likely after administration of vancomycin to dogs. Nephrotoxicity is of primary concern in dogs.
**OXAZOLIDINONES**

**Linezolid** [HL - Zyvox®, generic became available in 2013
Eperzolid
Tidezolid phosphate – (Sivextro®) approved in June, 2014 to treat human patients with acute bacterial skin and skin structure infections (ABSSSI) caused by certain susceptible bacteria, including Staphylococcus aureus (including methicillin-resistant strains (MRSA) and methicillin-susceptible strains), various Streptococcus species, and Enterococcus faecalis.

PHYSIOCHEMICAL PROPERTIES

The oxazolidinones are synthetic compounds.

MECHANISM OF ACTION / PHARMACODYNAMICS

The oxazolidinones bind to the 50S ribosomal subunit and inhibit the formation of the initiator complex, thereby inhibiting protein synthesis. They are considered dependant on AUC/MIC for efficacy.

SPECTRUM

Primarily Gram (+) aerobes and anaerobes with some Gram (-) aerobes. Linezolid is labeled in human medicine for treatment of methicillin-resistant staphylococcal and vancomycin-resistant enterococcal infections. In-vitro anaerobic activity includes *Clostridial* and *Fusobacterium* species. One study demonstrated similar anaerobic activity of linezolid and clindamycin.

RESISTANCE DEVELOPMENT

The mechanism of action of the oxazolidinones has not been reported for other drugs, making cross-resistance unlikely. Some examples of resistance developing during therapy have been reported in humans although *in vitro* studies have not demonstrated the rapid development of resistance.

PHARMAKOCINETICS/PHARMACODYNAMICS

Linezolid has almost complete oral bioavailability in humans. Volumes of distribution in humans approximated total body water. Human tissue:serum ratios ranged from 20% in the CNS and bone to 70% in muscle, heart, and lung. Human products include tablets, oral suspension, and a 2 mg/ml injection.

In humans, approximately 35% of linezolid is excreted unchanged in the urine while 50% appears as one of two metabolites.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Gastrointestinal effects (diarrhea, nausea, vomiting) are the most commonly reported adverse reaction in human clinical trials. Others include myelosuppression (reversible thrombocytopenia, anemia, neutropenia), skin eruptions, tongue discoloration and elevated liver enzymes. It is recommended that complete blood counts be monitored in patients receiving linezolid for 14 days or more.\textsuperscript{39}

Superficial dental enamel discoloration has been reported after prolonged therapy, which was reversible with cleaning.\textsuperscript{40}

Clostridium difficile overgrowth in the gastrointestinal tract has been reported, but is uncommon.

\textsuperscript{40} Matson, KL; Miller, SE. Tooth discoloration after treatment with linezolid. Pharmacotherapy, 23 (5): 682-685, 2003
**STREPTOGRAMINS**

Each streptogramin is a mixture of two structurally unrelated molecules:

- **Group (type) A** – macrolactones
- **Group (type) B** – cyclic hexadepsipeptides

**Virginiamycin (Stafac®)** – virginiamycin M (group A)/virginiamycin S (group B)

Produced by *Streptomyces virginiae*

This growth promotion label for cattle, swine, and poultry will likely be gone by 2017-2018.

**Synercid (RP 59500)** – dalfopristin (group A)/quinupristin (group B) in a 70:30 ratio

Produced by *Streptomyces pristinaespiralis*

**PHYSIOCHEMICAL PROPERTIES**

Synercid is water soluble

**MECHANISM OF ACTION**

The streptogramins are members of the “MLS” group of antibiotics (Macrolides-Lincosamides-Streptogramins). Although lumped together, there are important differences between the macrolides and the streptogramins.

Bacterial protein synthesis is carried out in ribosomes (70 S) with two subunits (50S and 30S). The 30S subunit binds messenger RNA and starts the protein synthesis cycle. The 50S subunit controls elongation by binding to transfer RNA. Peptide bond formation is the key activity leading to elongation of the protein chain. The MLS antibiotics and chloramphenicol inhibit activity at the 50S subunit.

Macrolides and group B streptogramins compete for the same binding site.

**MLS$_B$** antibiotics cause the elongating peptide chain to detach prior to completion

Group A streptogramins block the substrate site of the peptidyl transferase center on the 50S subunit

Chloramphenicol interferes with the catalytic portion of the peptidyl transferase center on the 50S subunit.
Group A and B streptogramins are considered bacteriostatic alone, but are synergistic and bactericidal when used together. Group A streptogramins increase the affinity of the ribosome for Group B streptogramins, which promotes synergism even against bacteria resistant to the MLSB group.

**PHARMACOKINETICS/PHARMACODYNAMICS**

**Systemic bioavailability from oral administration is effectively zero.** Groups A and B exhibit very similar serum pharmacokinetics; both penetrate and accumulate in macrophages.

Quinupristin-dalfopristin significantly inhibits the cytochrome P450-3A4 enzyme system

In a mouse thigh infection model, Synercid was demonstrated as have efficacy most closely related to AUC:MIC. Synercid also demonstrated a prolonged PAE (approx. 10 hrs). In-vitro cultures showed a dose-dependant bactericidal activity.41

**SPECTRUM**

For virginiamycin, the main spectrum includes gram-positive and anaerobic bacteria. *Leptospira, Haemophilus, and Serpulina hyodysenteriae* are considered sensitive. Many *Mycoplasma* as well as *Toxoplasma* spp. may be within the spectrum also.

**Applications for synercid:**

Enterococci resistant to vancomycin/teicoplanin and/or macrolides/lincosamides

*Streptococcus pneumoniae* (Pneumococcus) resistant to beta-lactams and macrolides

Methicillin-resistant *Staph. aureus* – activity has been demonstrated as equal to vancomycin

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RESISTANCE DEVELOPMENT

Group B streptogramins exhibit a high level of cross-resistance with macrolides and lincosamides. Group A streptogramins do not. The combination of groups A and B usually does not display cross-resistance with the macrolides.

Neither group of streptogramins is considered a good inducer of the methylase enzyme, which is responsible for mediating resistance to the MLSB group of antibiotics.

The MLSB “phenotype” is usually due to post-transcriptional methylation of an adenine residue on the 23S ribosomal RNA. Other methods (impermeability, efflux, or drug inactivation) have been suggested by work in *E. coli* and *Staph. spp* where resistance was induced to 14-member ring macrolides (erythromycin, oleandomycin) but not to 16-member ring macrolides (spiramycin) or lincosamides. A streptogramin acetyltransferase enzyme has been identified in *Staph. and Enterococci*, encoded by *vat* and *sat* genes.
POLYPEPTIDES - Bacitracin

PHYSIOCHEMICAL PROPERTIES

Bacitracin is a polypeptide antibiotic produced by *Bacillus subtilis*. It was discovered in a *Bacillus subtilis* contaminated wound in 1948 and consists of 5-10 different entities.

MECHANISM OF ACTION

Peptidoglycan formation in the bacterial cell-wall is inhibited. Bacitracin binds to the pyrophosphate carrier, and prevents the dephosphorylation reaction required for regeneration of this carrier. It is bactericidal to susceptible bacteria.

SPECTRUM

Bacitracin activity is limited to gram-positive bacteria. It is combined with aminoglycosides and/or polymyxin B for topical use. Bacitracin is labeled for feed efficiency, rate of gain, and some diseases in chickens, turkeys, pheasants, quail, and swine. The diseases in chickens include necrotic enteritis, coccidiosis, chronic respiratory disease, and bluecomb (non-specific infectious enteritis). It is labeled for swine dysentery.

RESISTANCE DEVELOPMENT

Little resistance has been reported.

PHARMACOKINETICS

Bacitracin is highly nephrotoxic, so use is limited to topical or oral use, from which it is poorly absorbed. Any absorbed drug is eliminated primarily through the kidneys.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Bacitracin is extremely nephrotoxic if administered systemically.
**MUPIROCIN** (pseudomonic acid A) - Bactroban®

**PHYSIOCHEMICAL PROPERTIES**

Produced by *Pseudomonas fluorescens*. It has increased activity at lower pH but is inactivated by fluids such as pus and mucus secretions.

**MECHANISM OF ACTION**

Mupirocin is a bactericidal, protein synthesis inhibitor. Inhibition of isoleucyl transfer RNA synthetase prevents isoleucine being incorporated into bacterial proteins.

**SPECTRUM**

Mupirocin is primarily used topically to treat dermal infections involving *Staphylococcus* or *Streptococcus*.

Activity against other bacteria is limited.

**RESISTANCE DEVELOPMENT**

Plasmid-mediated resistance in *Staphylococci* has been reported. Cross-resistance with other antimicrobials is unlikely.

Mupirocin has been used to clear nasal carriage of MRSA in humans, but mupirocin-resistant methicillin-resistant Staph aureus (MS-MSRA) is becoming more prevalent.42

**PHARMACOKINETICS**

Mupirocin is available only for topical use due to rapid metabolism after systemic administration.

**ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES**

A case of toxic epidermal necrolysis has been reported after intranasal application of mupirocin in a human patient.43

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Also referred to as the moenomycins, flavomycin or flavophospholipol. They are composed of 4 different components in a complex, with the A and C components predominating. They are produced by *Streptomyces* spp. with synthetic alteration.

**Tradenames:**

- **Flavomycin®**: increased rate of gain and improved feed efficiency in broiler chickens, growing finishing swine and growing turkeys
- **Gainpro®-10**: increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter. For increased rate of weight gain in pasture cattle (slaughter, stocker and feeder cattle, and dairy and beef replacement heifers)...

**Spectrum:** Primarily Gram (+). However, the MIC’s of *Clostridium Perfringens* have been reported in the range of 16-34 µg/ml in one study and ≥64 µg/ml for 96 isolates in another paper.44,45

Even though the MIC values for *E. coli* and *Salmonella* spp. are also very high, animals fed bambermycins have been demonstrated to have decreased shedding of *E. coli* and *Salmonella* as well as a decreased level of resistance.46,47,48 There is also evidence that plasmid transfer among potential pathogens, such as resistance in the gut environment may be decreased by the bambermycins.49,50

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44 Martel A;DeVriese LA;Cautwerts K;De Gussem K;Decostere A;Haesebrouck F; Susceptibility of Clostridium perfringens strains from broiler chickens to antibiotics and anticoccidials. 2004 Feb Avian Pathology 33 (1) : 3 - 7
45 DeVriese LA;Daube G;Hommez J;Haesebrouck F; In vitro susceptibility of Clostridium perfringens isolated from farm animals to growth-enhancing antibiotics. 1993 Jul Journal of Applied Bacteriology 75 (1) : 55 - 57
46 Dealy J;Moeller MW; Effect of bambermycins on Escherichia coli and antibiotic resistance in calves. 1977 Apr Journal of Animal Science 45 (6) : 1239 - 1242
47 Dealy J;Moeller MW; Influence of bambermycins on Salmonella infection and antibiotic resistance in calves. 1977 Apr Journal of Animal Science 44 (5) : 734 - 738
48 Dealy J;Moeller MW; Influence of bambermycins on Salmonella infection and antibiotic resistance in swine. 1976 Apr Journal of Animal Science 42 (5) : 1331 - 1336
**FOSFOMYCIN**

A phosphoenolpuuvate analogue, fosfomycin was developed in the U.S. but was not marketed here. It is used for urinary tract infections in humans in Europe, Japan, and Latin America. It has also been used in the therapy of urinary tract infections in small animal medicine.

**MECHANISM OF ACTION**

Fosfomycin acts as an analogue of phosphoenolpyruvate, permanently inhibiting enolpyruvate transferase. This enzyme catalyzises the formation of N-acetylmuramic acid, which is essential in the initial step in peptidoglycan biosynthesis.

**SPECTRUM**

Fosfomycin has good activity against many of the Enterobacteriaceae; activity against *E. coli* has been noted, but *Pseudomonas* spp. are considered resistant. Activity against vancomycin resistant *Enterococcus* spp., including *faecium* and *faecalis*, has been demonstrated.  

**PHARMACOKINETICS**

It is available as a parenteral and as an oral formulation. The elimination half-life in humans is approximately 5.75 hrs. It is reported to concentrate in the kidneys and bladder.

**TOXICITY**

The principal organ for toxicity is the kidney.

Notes on clinical use: Rarely used here at KSU. GI upset is common and it is contraindicated in dogs with metabolic acidosis. Not tolerated well in cats. There are no safety or efficacy studies available in veterinary species.

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IONOPHORES

MEMBERS OF THE GROUP

Monensin (Rumensin®)
Lasalocid (Bovatec®)
Maduromycin, Narasin, Salinomycin, Tetronasin

The ionophores had reported sales in the U.S. of 3,821,138 kg in 2010. This is out of 13,457,582 kg total 2010 veterinary reported sales of antimicrobials (28.3%).

PHYSIOCHEMICAL PROPERTIES

The ionophores are polyether, carboxylic antibiotics. Monensin is derived from Streptomyces cinnamonensis.

MECHANISM OF ACTION

Complexes are formed with cell-wall sodium, causing export of potassium and import of hydrogen into the bacterial cell. The resulting drop in intracellular pH is lethal.

The mechanism of action for growth promotion in ruminants is the elimination of some of the gram-positive population of the rumen, which shifts volatile fatty acid production away from lactic acid towards proprionic acid. This shift results in more efficient glucose formation.

The ionophores also decrease the formation of 3-methylindole from tryptophan, reducing the occurrence of “fog-fever” if fed far enough in advance. Methane production in the rumen is also decreased.

SPECTRUM

The ionophores are very specific for gram-positive bacteria. Other parts of the spectrum include Campylobacter spp, Serpulina hydysenteriae, Toxoplasma, and coccidia.

Anti-coccidial activity is a major reason for use in food animals.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Disruption of cell membranes leads to muscular toxicity, especially skeletal and cardiac muscle. The primary muscle affected in cattle and horses is cardiac, while sheep seem to be most affected in skeletal muscle.

Horses are extremely susceptible to the toxic effects of monensin, with a reported LD50 of 2-3 mg/kg. Toxicity is also possible in ruminants with very high doses.
The inclusion of tiamulin in the feed at the same time as an ionophore will decrease ionophore excretion and potentiate toxic effects. Any drug which decreases hepatic metabolism, such as chloramphenicol or possibly the macrolides, will potentiate ionophore toxicity. Tylosin is fed concurrently with monensin in cattle with no toxicity, but there has been a reported case where macrolide contamination of distillers grains (a byproduct of ethanol production) were correlated with monensin toxicity in cattle at normal monensin doses. Cause and effect?
ISONIAZID

PHYSIOCHEMICAL PROPERTIES

Isoniazid is a water-soluble derivative of isonicotinic acid. It has a low molecular weight.

MECHANISM OF ACTION

The mechanism is interference with bacterial intermediary metabolism.

SPECTRUM

Isoniazid is one of the most potent antitubercular drugs in human medicine. Mycobacterium tuberculosis, Mycobacterium bovis, and many Mycobacterium kansasii are considered susceptible. The drug has been used in veterinary medicine for therapy of Actinomyces bovis with questionable efficacy.

RESISTANCE DEVELOPMENT

Isoniazid is not used alone due to resistance development estimated at 1 in 1 x 10^6 against Mycobacterium tuberculosis. Mutation rate by other pathogens will vary.

PHARMACOKINETICS

Bioavailability after oral administration is good and distribution includes significant levels in the CNS.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Hypersensitivity, hepatitis, and convulsions have been reported in humans.
METHENAMINE

PHYSICOCHEMICAL PROPERTIES

Also called hexamine, methenamine is a water soluble compound which decomposes in acidic environments to release formaldehyde.

MECHANISM OF ACTION

Formaldehyde acts as a urinary antiseptic

PHARMACOKINETICS

Methenamine is well absorbed after oral administration and is excreted unchanged in the urine. Acidic urine results in the release of formaldehyde.

This drug has been used for long-term maintenance of refractive urinary tract infections in dogs.

Clinical note from Dr. Kate KuKanich (2014): They rarely try methenamine for controlling complicated UTIs. While it can be effective, they do see GI upset with it and believe it is contraindicated in dogs with metabolic acidosis. It is not tolerated well in cats. There are no safety studies in dogs or cats, another reason to be cautious.
NITROFURANS

MEMBERS OF THE GROUP

Furazolidone (Topazone®)
Nitrofurantoin (HL, Furadantin®, Macrodantin®, tablets, capsules, suspension)
Nitrofurazone (Furacin®)
Nifuratel
Nifuroquine

The use of nitrofurans is prohibited in food animals in the U.S.! Approved topical uses were previously permitted, but these labels have been withdrawn due to documented residues from these uses.

PHYSIOCHEMICAL PROPERTIES

The nitrofurans are synthetic derivatives of 5-nitrofuraldehyde (1930). Most of them (too numerous to list) are slightly water soluble. Nitrofurantoin is a weak acid with a pKₐ of 7.2.

MECHANISM OF ACTION

The nitrofurans are reduced in bacteria to reduction products characteristic of the individual nitrofuran. These products lead to breakage of the bacterial DNA strands.

SPECTRUM

The nitrofurans are relatively broad spectrum with the greatest activity under anaerobic conditions. The “spectrum” usually includes Staph., Strep., Corynebacterium, E. coli, Salmonella, Klebsiella. Pseudomonas is not considered susceptible. Other therapeutic applications have included Giardia, coccidia, and Trichomonas vaginalis and foetus.

Furazolidone is considered the most active, then nitrofurazone and nitrofurantoin.

RESISTANCE DEVELOPMENT

Resistance is rare, and is most likely chromosomally mediated. There is often cross-resistance with the nitroimidazoles.

PHARMACOKINETICS

Nitrofurantoin is suitable only for urinary tract infections. Even though it is well absorbed orally, it is so rapidly eliminated through the kidneys that effective concentrations are not achieved systemically. The elimination half-time reported for humans is 20 minutes, with approximately 50% of the drug excreted unchanged.

Oral administration of furazolidone and nitrofurazone result in almost 0% bioavailability.
ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Nitrofurantoin and furazolidone may result in CNS effects after high oral doses. Lower doses have caused thrombocytopenia and prolonged bleeding times in calves and dogs.

Other dose related effects include inappetence, convulsions, neurotoxicity, and in poultry, cardiotoxicity.

The nitrofurans are mutagenic and procarcinogenic, resulting in the ban of extralabel use in food animals in the U.S.
NOVOBIOCIN

Novobiocin - Biodry® mastitis tube
Novobiocin/penicillin G – Albadry Plus® mastitis tube
Novobiocin/prednisolone/tetracycline – Delta albaplex®
Novobiocin/ tetracycline – Albaplex®

PHYSIOCHEMICAL PROPERTIES

Novobiocin is an acidic drug available as a calcium salt (minimal water solubility) and as a monosodium salt (improved water solubility).

MECHANISM OF ACTION

Novobiocin inhibits DNA supercoiling by inactivating DNA gyrase.

SPECTRUM

The most clinically important activity is against Staphylococcus aureus. Less potent activity is present against Streptococci, Haemophilus, Brucella, and even more limited activity against Enterobacteriaceae. Most gram-negative bacteria are considered resistant. Some Mycoplasma spp. may demonstrate moderate susceptibility.

RESISTANCE DEVELOPMENT

Novobiocin is typically not used alone.

PHARMACOKINETICS

Novobiocin is well absorbed after oral administration. It is about 90% protein bound and primarily excreted through the bile and feces. Only about 3% is excreted in the urine.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

The occurrence of hypersensitivity reactions, blood dyscrasias, and hepatotoxicity have limited the use of novobiocin in humans.
PLEUROMUTILINS (DITERPINES)

MEMBERS OF THE GROUP

**Tiamulin** (Denagard®, swine, available in water soluble or feed additive forms)

**Feed administration:** Tiamulin (35 g/ton of complete feed) is labeled for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* and swine dysentery associated with *Brachyspira hyodysenteriae*. At 200 g/ton of complete feed it is labeled for treatment of swine dysentery.

**Drinking water administration:** At 3.5 mg/lb body weight per day, tiamulin is labeled for treatment of swine dysentery. At 10.5 mg/lb body weight per day, tiamulin is labeled for treatment of swine pneumonia due to *Actinobacillus pleuropneumoniae*.

PHYSIOCHEMICAL PROPERTIES

Tiamulin is a semisynthetic compound. It is derived from pleuromutilin, which is a diterpine-class antibiotic.

MECHANISM OF ACTION

Tiamulin binds to the 50S ribosomal subunit where it inhibits protein synthesis. It is typically bacteriostatic.

SPECTRUM

The spectrum of tiamulin is similar to the macrolides with the exception of better Gram-negative anaerobic and *Mycoplasma* activity. The spectrum also includes *Actinomyces pleuropneumoniae* and *Brachyspira (Serpulina) hyodysenteriae*. There is almost no activity against Gram-negative aerobes, although *Haemophilus* and some *E. coli* may be exceptions.

RESISTANCE DEVELOPMENT

Chromosomal mutation occurs as for the macrolides. *Mycoplasma* resistant to tiamulin will probably be resistant to tylosin. Emergence of resistance is reportedly slower than with tylosin.

PHARMACOKINETICS

Tiamulin exhibits approximately 85% oral bioavailability in swine after oral administration with a T<sub>max</sub> of around 2-4 hours after a single oral dose.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

- Tiamulin fed concurrently with ionophores may lead to fatal, toxic reactions.
- Do not administer to horses or non-ruminant herbivores.
POLYMYXINS

MEMBERS OF THE GROUP

Numerous compounds - Polymyxin A, B, C, D, E

Polymyxin B (HL, Aerosporin®, also in many topical preparations, otic, ocular, ophthalmic)

Polymyxin E (HL, Colistin®): Even though very nephrotoxic, this drug is being used systemically as a last-resort drug in some human cases due to pathogens resistant to every other option.

PHYSIOCHEMICAL PROPERTIES

The polymyxins are water soluble products of Bacillus polymyxa. They are basic, cyclic decapeptides.

MECHANISM OF ACTION

A detergent-like action is responsible for disrupting gram-negative cell membranes. The cationic polymyxins interact with the anionic phospholipids (endotoxin) in the Gram-negative cell wall, disrupting cell wall integrity.

Polymyxin B is used at low, carefully controlled doses to bind endotoxin. Equine colic is an example of such a use. Accurate dosing is essential!!

SPECTRUM

Initial interest was for therapy of Pseudomonas. Gram-negative organisms in the spectrum also include Salmonella and E. coli. Gram-positive bacteria are usually considered resistant.

RESISTANCE DEVELOPMENT

Pseudomonas may develop resistance through altered permeability.

PHARMACOKINETICS

Oral bioavailability is very poor. The polymyxins display poor distribution in the body, where binding to mammalian cell membranes contributes to significant accumulation during long therapeutic regimens. Elimination is by glomerular filtration of the parent compound.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Parenteral administration may lead to nephrotoxicity, neuromuscular blockade, and CNS toxicity. These toxicities appear to be dose dependent. Therapy with a polymyxin requires strict adherence to dose guidelines.
QUINOXALINE DERIVATIVES

MEMBERS OF THE GROUP

**Carbadox** – Mecadox® (Phibro). Labeled for control of swine dysentery and bacterical swine enteritis due to *Salmonella* when fed at 50 ppm in the feed. Labeled for increased weight gain and improved feed efficiency in swine when fed at 27.5 ppm in the feed.

Olaquindox
Cyadox

MECHANISM OF ACTION

Bacterial DNA synthesis inhibition as well as denaturing existing DNA. The effect on the DNA is thought to be due to an unstable reduction product.

SPECTRUM

The spectrum would be considered primarily Gram (+). Clostridia and *Serpulina hyodysenteriae* (swine dysentery) are primary targets. Carbadox is more active under anaerobic conditions, including against aerobes in anaerobic environments. Protozoa and Chlamydia may also be susceptible to carbadox.

RESISTANCE DEVELOPMENT

Plasmid mediated resistance has been reported in E. Coli.

TOXICITY

Feeding at concentrations greater than 100 ppm in the feed may result in some pigs displaying signs of hypoaldosteronism. Carbadox has been demonstrated to suppress aldosterone production at this feed inclusion rate, leading to increased plasma potassium and decreased plasma sodium. Morphological alterations in the zona glomerulosa of the adrenal cortex have been demonstrated. A feed concentration of 50 ppm is the maximum concentration on the label, and therefore the maximum feed concentration that may be fed.

It was banned in Canada in 2004 and has also been banned in the European Union.

Carbadox has been demonstrated to be a carcinogen in laboratory animals. It may be used in swine as a feed additive due to the slaughter withdrawal time being based on a metabolite. When this metabolite is below a specified level in the liver, it has been established that the carcinogenic parent compound is no longer detectable in the animal. The slaughter withdrawal time is 42 days.
RIFAMYCINS

MEMBERS OF THE GROUP

Rifampin – this section focuses on rifampin, but of some interest…

Ansamycins – derivatives of 3-piperazine rifamycin. Some ansamycins have hypolipidemic activity in both non-primates and primates. Others have demonstrated anti-tumor activity. Rifampicin and rifabutin have demonstrated synergistic or additive activity with fluoroquinolones against *Mycobacterium leprae*. Immunosuppressive activity has also been attributed to some of the ansamycins.

PHYSIOCHEMICAL PROPERTIES

Rifampin is slightly soluble in water and alcohol. It is very lipophilic, giving good distribution in the body.

MECHANISM OF ACTION

Rifampin inhibits RNA polymerase, which is necessary to catalyze the transcription of DNA to RNA. It is considered to be bactericidal.

SPECTRUM

Rifampin is used for the treatment of tuberculosis in humans. In veterinary medicine, it is used together with erythromycin or another macrolide to treat *Rhodococcus equi* infections. The general spectrum is Gram-positive and anaerobic bacteria and *Mycobacterium tuberculosis*. Rifampin is especially noted for activity against *Staph. aureus* and *Chlamydia*. Gram-negative bacteria are usually resistant, although some, such as *Brucella* are susceptible (strain 19 is susceptible, RB51 is not).

Antiviral activity (at high concentrations) is reported against poxviruses and adenoviruses. Antifungal activity is displayed when combined with other antifungal drugs.

RESISTANCE DEVELOPMENT

Resistance develops rapidly during therapy of *Mycobacterium tuberculosis*. For this reason, it is recommended that rifampin never be used as a single antimicrobial. The resistance is chromosomal and stable once developed.

PHARMACOKINETICS

There is information in the literature regarding a variety of veterinary species. The dog has significantly greater bioavailability after oral administration than do horses or ruminants. Oral bioavailability is good in all species with elimination half-times varying from 3 hours in sheep to 8 hours in dogs. Extensive metabolism may take place in the liver. The active metabolite and parent compound are excreted primarily in the bile with some renal component.
Rifampin is a potent microsomal enzyme inducer. It creates clinically significant increases in the excretion of steroid drugs, ketoconazole, barbiturates, digitoxin, and oral anticoagulants.

The lipophilic nature of rifampin is reflected in a volume of distribution near 1 L/kg in most veterinary species. It is 70-90% bound to plasma proteins.

ADVERSE REACTIONS/CONTRAINDICATIONS/TOXICITIES

Clinical hepatitis may occur with prolonged therapy in dogs. Rifampin may function as a hapten, and has caused immune-complex disease in humans with prolonged, intermittent therapy.

Rifampin may cause an orange-red discoloration of body fluids such as tears, urine, sweat, and saliva.