Using Antibacterials in Wildlife
(portions borrowed from talks by Drs. Deb Anderson, John Huckabee, and Pat Klein)

General Definitions
- Antibiotic: literally, against life
- Antimicrobial: an agent that causes destruction or inhibition of microorganisms
- Antibacterial: an agent that causes destruction or inhibition of bacteria

Antibacterials work in one or more of the following ways:
- Prevent bacteria from building a good cell wall or disrupt the cell membrane function—becomes weak and easily breaks down
- Alter the structure or synthesis of bacterial RNA or DNA→can't replicate, or die
- Prevent bacteria from synthesizing some type of essential protein

Depending on the mode of action, the **spectrum** is broad (effective against many bacteria), or narrow (selective efficacy)

Bacterial response to Antibacterials:
- **Bactericidal** (they die quickly) or **Bacteriostatic** (they can no longer replicate)

Antibacterial Resistance
- The reproductive cycle of bacteria is very short—many generations can be produced in a short amount of time—allowing genetic mutations that adapt the bacteria to their new, harsher environment (i.e., in the presence of antibacterial drugs); these traits are then passed on to subsequent generations
- Only a few need to survive to recolonize a host with newer, stronger bacteria

Bacteria are divided into two main classes according to their uptake of Gram stain:
(Named after a Danish Physician, Christian Joachim Gram who developed the stain)
Describes the purple dye taken up by bacteria that possess a specific type of cell wall
- **Gram Positive (Gm+) is Purple**
  - The cell wall is thick and usually sensitive to Penicillins
  - All cocci are Gm+: *Staphylococcus, Streptococcus, Enterococcus*
  - Some are rods: *Bacillus, Listeria, Corynebacterium, Clostridium*
  - Some are also Acid Fast: *Mycobacteria, Nocardia*
- **Gram Negative (Gm-) is Pink**
  - The cell wall has an extra coating - that's why they don't pick up purple stain
  - Outer layer has Lipopolysaccarides that are endotoxins in the host
  - Generally more virulent and difficult to deal with bacteria
  - *Aeromonas, Bordetella, Brucella, Pasteurella, Pseudomonas, Enterobacteria*

In-House Gram Stains:
- Supplies needed: Microscope, match or lighter, slides, stain
- Swab an infected area and apply a light coat to slide
- Heat fix by passing the slide over a match or lighter 4 to 5 times
- Follow stain direction on kit
- Let dry and look under microscope on oil immersion

Then bacteria are divided into two sub-classes:

- **Aerobes:**
  - Obligate—need oxygen to live
  - Facultative—can live with or without oxygen (prefer *some* oxygen)
- **Anaerobes:**
  - Will die in presence of oxygen—these are difficult to culture

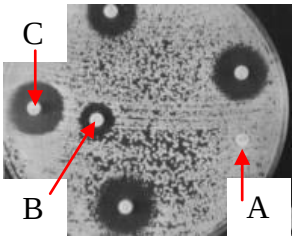
They are further classified as spore-forming or non-spore-forming (the spore state can survive in much harsher environments, so those bacteria tend to be harder to destroy)

It's more expensive and takes longer, but sending out for a culture and sensitivity is actually easier and more precise than in-house diagnostics

- You need a lab acct. and culturette tubes (you can get both from most vet practices)
- Procedure:
  - Open culturette tube and remove swab without touching *anything* but what you intend to culture
  - Swab area in question—touch the cotton tip to the infection
  - Immediately place the swab in the culturette tube
  - Allow to sit at room temp for about 20 minutes
  - Place in fridge and call the lab to pick up (or drop off at vet clinic)

How is antibacterial efficacy determined?

- Bacteria are grown on a petri dish
- One pure colony is selected and grown in a liquid medium
- It's poured on a new petri dish in an even and homogenous layer
- Antibacterial discs of known concentration are placed on top
- If there is a clear zone around the disc, this means the bacteria are sensitive to it and have died.
  - The larger the zone the more sensitive
  - e.g., A. the bacteria is resistant to this drug (no clearing)
    B. the bacteria is sensitive to this drug (clear zone)
    C. the bacteria is more sensitive to this drug



Keep in mind that the drug in the body is not evenly distributed in all tissues

- Some drugs may accumulate in certain organs (usually liver, kidney and fat)
- Some drugs are excluded from certain areas (e.g., CSF and brain)
- The medical status of the host may alter drug concentrations
- If kidneys don't function, the drug may reach toxic levels
- If infections are walled off, the drug may not reach it

Questions to ask when deciding to treat:

- **Is this even treatable with antibacterials?**
  - Evidence of draining pus in mammals, or cheesy exudates in birds and reptiles
  - Fever in mammals (often, but not always bacterial)
  - Open contaminated wounds; known cat bites
  - Gram stain or culture shows bacteria of one predominate type

- **Where is the infection located?**
  - Does the antibacterial get into that organ/tissue type?
  - Does the infection appear to be walled off?
- **What pathogen is most likely involved?**
  - Based on species of animal and Type & cause of injury
    e.g., rabbit abscesses are often Staph spp; bone infections are often Gm+
  - Do a Gram stain to check if unsure
- **What is the best drug to use given the situation?**
  - Some species are overly sensitive to certain drugs
    - e.g., penicillin can destroy normal bacteria in hind-gut fermenters
  - Debilitated animals may not be able to tolerate a commonly used drug
  - Large amounts of dead tissue and pus may inactivate a drug
- **Which dose and route is best?**
  - Little information is available about the absorption & metabolism in wildlife
  - May need to choose drug on basis of minimal handling of patient
- **How long should drug be given?**
  - Stopping before all bacteria are killed will hasten their resistance to the drug
  - Consider minimum of 7 days or ***at least 2 days*** after clinical signs are normal.

CLASSES OF ANTIBACTERIALS

Penicillins*—Bactericidal→Prevent synthesis of bacterial cell wall

Contain β-Lactam, which is broken down by bacteria that produce β-Lactamase

Types in this class:

- Narrow-spectrum
  - Gm+, a few Gm-, but not Staph aureus
  - Penicillin G Procaine and Pen G Procaine/Pen G Benzathine
- Broad-spectrum β-Lactamase sensitive
  - Gm+ and Gm-, many anaerobes
  - Ampicillin and Amoxicillin
- Broad-spectrum β-Lactamase sensitive with extended spectra
  - Gm+ and Gm-; *Proteus, Acinetobacter, Enterobacteriacea, Pseudomonas*
  - Carbenicillin, Piperacillin, and Ticarcillin
- Broad-spectrum β-Lactamase resistant (potentiated)
  - Clavamox

Body location:

- Liver, kidney, lung, intestine, lymph, bile, semen, and urine; pleural, pericardial, synovial and ascitic fluids

Excretion:

- Urinary mostly, newer drugs have GI excretion

Side effects:

- Destroys flora of hind-gut fermenters (any antibacterial with a Gm+ spectrum)
- Rodents, Birds, Snakes and Turtles particularly sensitive to Procaine Pen G

Interactions:

- Action is lessened with given with Aspirin, Phenylbutazone, Sulfonamides
- Ampicillin inactivated with food
- Carbenicillin and Ticarcillin can be given with Aminoglycosides

Cephalosporins[&*]—Bactericidal→Inhibit cell wall synthesis

Cross resistance probable, short half-life
Range is similar to Penicillins

Types in this class:

- 1st Generation
  - Strong Gm+ and anaerobes; slight Gm-
  - Cefazolin, Cephalexin, Cefadroxil
- 2nd Generation
  - Gm+ and Gm-
  - Cefuroxime
- 3rd Generation
  - Gm+, Gm- including *Pseudomonas, Proteus, Enterobacter, Citrobacter*
  - Ceftiofur, Cefotaxime, Ceftazidime
- Long-acting 3rd Generation
  - Ceftiofur CFA, Cefovecin

Body location:

- Extracellular fluids: inflamed synovial, pleural, peritoneal, pericardial
  - Only 3rd generation cephalosporins reach the CSF
- Good oral absorption; IV is preferred as other parenteral routes are painful
- Metabolized and excreted by kidneys

Side effects:

- May cause vomiting, diarrhea, or anorexia in some individuals

Tetracyclines*—Bacteriostatic→Inhibit protein synthesis

- Host must have functional immune system
- Gm+, Gm-, PLUS: *Mycoplasma, Rickettsia, Ehrlichia, Chlamydia* and some protozoa (broad spectrum)
- Most *E.coli, Klebsiella* and *Pseudomonas* are resistant

Types in this class:

- Short-acting
  - Tetracycline and Oxytetracycline
- Longer-acting
  - Doxycyline
  - Also good against *Nocardia,* anaerobes and *Staph*

Body location:

- Liver, gall bladder, kidney, bone, lungs, urine, bile
- Lower concentrations in synovial fluid and eye
- Doxycycline reaches CSF

Side effects:

- IM injection can cause tissue necrosis, IV injection can cause heart arrhythmias
- GI upset-especially in ruminants, can cause rumen stasis
- Causes photosensitivity—keep patient out of sun during therapy
- **Don't use if expired--become toxic--can cause kidney damage**

Interactions:

- Bind to Ca^{+} and Mg^{+}, so are inactivated by milk antacids, kaolin and iron in diet
- Bind irreversibly in tooth and bone, causing permanent staining

***Excretion**:*

- Mostly in urine and some in milk
- Doxycylcine excreted in feces (good for kidney patients)

Aminoglycosides[&*]—Bactericidal→Inhibit protein synthesis

- Gm- , some Gm+ aerobes, mycoplasma [primarily used for Gm-] (narrow)
- Spectinomycin has most narrow spectrum; and Amikacin, Gentamicin and Tobramycin are a little broader
- Poor oral absorption; give IM or SQ
- Amikacin has the least amount of resistance…..for now; resistance is increasing
- Poorly absorbed orally—must be injected to go systemic

Body location:

- Fluids: synovial, pleural, pericardial, abscesses; also bone, lung & kidneys

Side Effects:

- Excreted by kidneys and can cause damage in some patients or at too high or too frequent dosing, and can be lethal to patients with pre-existing kidney damage
- Ototoxic—can cause vestibular (balance) disease and deafness; especially rabbits
- Potentially cardiotoxic

Interactions:

- Neurotoxic if interacts with some anesthetics
- Synergistic with Piperacillin and the β-Lactam antibacterials
- Inactivated by Ticarcillin and Carbenicillin

Choramphenicol[&%]—Bacteriostatic→Inhibit protein synthesis

- Gm+, Gm-, *Rickettsia, Coxiella, Chlamydiophila*
- Pseudomonas is resistant

Body location:

- Liver, kidney, gall bladder, muscle, lungs, heart, CSF, eye, pleural, synovial, milk
- Metabolized in liver
- Excreted in urine

Side Effects:

- Bone marrow suppression—aplastic anemia; potentially toxic to humans
- Vomiting and diarrhea
- Delayed wound healing
- Occasional severe reactions in neonates

Interactions:

- May prolong action of other drugs
- Inhibited by bactericidal antibacterials

Macrolides[&*]—bacteriostatic→Inhibit protein synthesis

- Gm+ and anaerobes; a few Gm- *Neisseria, Hemophilus, Mycoplasma*
- Azithromycin, Tylosin
- Most effective at high pH, inactive in acid environments (abscesses)
- Coated tabs to protect from stomach acid (don't split tabs!) suspension form is chemically stabilized; don't give with food (slows absorption)

Body location:

- Milk and other secretions, lungs, wounds, osteomyelitis, abscesses
- Doesn't reach CSF very well

Excretion:

- Urine and feces (metabolized in liver)

Side effects:

- Mild GIT signs–DON'T USE in horses, ruminants, rabbits, hamsters, guinea pigs!

Lincosamides*—Bacteriostatic→Inhibit protein synthesis

- Gm+ cocci, anaerobic cocci and bacilli, mycoplama (inactive against Gm-)
- Lincomycin and Clindamycin

Body location:

- Bone, peritoneal fluid, pericardial fluid, placenta; low concentration in CSF

Excretion:

- Urine, bile, milk

Side effects:

- Minimal, but don't use in horses, ruminants, rabbits, hamsters, guinea pigs!
- May see neuromuscular effects if given with anesthesia

Interactions:

- Bactericidal drugs interfere

Nitroimidazoles[&]—Bactericidal→Disrupt DNA synthesis

- Metronidazole
- Anaerobes: *Clostridium, Bacteroides, Fusobacterium*
- Flagellates (*Giardia, Trichomonas*) & Amoeba: *Entamoeba, Balantidium*

Body location:

- Most tissues and fluids: reach bone, abscesses & CSF

Excretion:

- Urine and feces (metabolized in liver)

Sulfonamides*—Most are bacteriostatic→PABA inhibitors; resistance is common except for TMS (bactericidal)→ inhibit enzymes in folic acid

- Gm+, Gm-, *Nocardia* and coccidia (broad spectrum)
- Most absorbed orally, but food slows absorption; also given IV
- Best used early on in an infection.
- Standard-use sulfonamides
  - Sulfathiazole, sulfamethazine, sulfadiazine, sulfadimethoxine
- Highly soluble
  - Sulfasoxazole–goes straight to the urine unchanged- good for UTI
- Poorly soluble-
  - Sulfasalazine–stays in the GI tract-good for enteric infections
- **Potentiated-Trimethoprim-sulfa**
  - Broad spectrum AND kills protozoa like coccidia & toxoplasmosis

Body location:

- Good distribution throughout all tissues, including ocular, skin , CSF
- Poor penetration in pus and necrotic debris

Excretion:
- Metabolized in kidneys; excreted in urine

Side effects:
- Photosensitization, dry eye (KCS—irreversible), arthritis, urine crystal formation to the point of obstruction and kidney damage

Interactions:
- NSAIDS, antacids and mineral oil

Fluoroquinolones[&]—Bactericidal→Inhibit DNA gyrase→prevents DNA replication
(Growing number of resistant bacteria: *E. coli, Pseudomonas*, Methicillin-resistant *Staph*)
- Fluoroquinolones: Gm-, Gm+, *Chlamydiophila, Mycoplasma, Mycobacteria* (broad)
  - Ciprofloxacin—developed for humans
    - Has better activity against *Pseudomonas*
  - Enrofloxacin—made for animals, cheaper than Cipro; not safe in humans
    - Absorbed 3-4 times better than Cipro
    - 10% is metabolized to Cipro (why some animals get better despite the C&S saying it's resistant)
    - Some strains of *Pasteurella* are now resistant
  - Marbofloxacin
    - Good skin penetration, good against *Staph*
  - Lomefloxacin
    - Great tortoise *Mycoplasma* and rabbit *Pasteurella* treatment

Body location:
- Good distribution to genitourinary, GI, respiratory tract and skin

Side effects:
- May cause bone marrow suppression or cartilage abnormalities in young
- Injections are painful and may cause muscle necrosis; dilute with LRS or NaCl

Interactions:
- Synergistic with doxycycline for *Mycoplasma*
- Bacteriostatic drugs interfere with function

Antibacterial Classification:

Bactericidal (CAMPS-TF):
Cephalosporins
Aminoglycosides
Metronidazole
Penicillins
Sulfonamides with Trimethoprim
Flourouinolones

Bacteriostatic: (SLCT)
Sulfonamides
Lincosamides
Chloramphenicol
Teteracylines

Lincosamides and Macrolides can actually be –static or –cidal, depending on the dose

Symbols appearing next to the Antibiotic Class:
& = Do not use in animals that may be eaten/hunted
* = Can be used in animals that may be eaten/hunted, but must not release until withdrawal period is over. Recommended withdrawal times for cattle used as a guide.
% = Caution with handling or disposal (e.g., chloramphenicol)