An adverse drug reaction (ADR) is an unfavorable and unintended effect that occurs after use of a medicinal product. Although awareness of some potential adverse drug reactions in veterinary medicine is widespread, others may not be promptly recognized by practitioners, either because they are rarely observed, because they are associated with newer pharmaceutical products and have not become entrenched in the literature, or because they mimic the clinical signs of other common diseases in dogs and cats. In human medicine, unrecognized adverse drug reactions may result in unnecessary patient morbidity and healthcare expense, and the term “prescribing cascade” has been coined to describe the situation of an unrecognized or misinterpreted adverse drug reaction resulting in the prescription of additional drugs to address the clinical signs.

Old age, chronic disease, and use of multiple drugs place a patient at risk for adverse drug reactions and a prescribing cascade in human medicine, and polypharmacy among elderly or critically ill hospitalized pets may create a similar scenario. Veterinary practitioners can avoid a prescribing cascade by increasing their awareness of potential adverse drug reactions (e.g., through periodic review of veterinary literature and perusal of package inserts for new products carried in their hospitals), and by considering that the cause of any new clinical sign in a pet receiving other medications could be a consequence of drug treatment. Examples of several veterinary adverse drug reactions that may initially be unrecognized for various reasons (some with the potential to trigger a prescribing cascade) are discussed below.

1. Phenobarbital and bone marrow toxicity
Most veterinarians are familiar with the phenobarbital-associated side effects of polyuria, polydipsia, polyphagia, sedation/ataxia, and potential hepatotoxicity. Hepatotoxicity with phenobarbital is dose- and duration-dependent (more likely to occur when phenobarbital concentrations are >35-40 mcg/mL). A less common adverse effect of phenobarbital in dogs that may be less familiar to practitioners is idiosyncratic bone marrow toxicity. Reversible neutropenia, thrombocytopenia, and anemia have been reported in dogs on chronic phenobarbital therapy and after an acute overdose. If not suspected to be an adverse drug reaction, the presence of pancytopenia in a dog receiving phenobarbital may occur in unnecessary prescription of immunosuppressive medications, which will not correct the problem. A diagnostic workup to rule out other causes is often appropriate, but discontinuation of phenobarbital as soon as possible and initiation of an alternative anticonvulsant is indicated if another cause of bone marrow disease is not identified. Recovery from phenobarbital-induced bone marrow toxicity usually occurs within 1-3 weeks of drug discontinuation.

Phenobarbital has also been associated with dyskinesia (anxiousness and muscle twitching that appeared dose-dependent and resolved when the drug was discontinued), and superficial necrolytic dermatitis or hepatocutaneous syndrome.

2. Potassium bromide and coughing in cats
Potassium bromide shares with phenobarbital the potential to cause polyuria, polydipsia, polyphagia, sedation, and ataxia in pets. However, an additional species-specific reaction to this drug is coughing in cats. Chronic cough occurs in up to 50% of cats receiving potassium bromide and is often associated with a diffuse bronchial pattern on thoracic radiographs. Because of the frequency of this side effect, potassium bromide is not generally recommended as an anticonvulsant in cats. However, it may still be prescribed by some practitioners, with the subsequent prescription of medications for feline lower airway disease (“feline asthma”) when a cough develops. An adverse drug reaction may ultimately be suspected when treatment is unsuccessful, as the cough generally does not resolve until the drug is discontinued.

3. Methimazole and lymphadenomegaly or pyogranulomatous folliculitis
Gastrointestinal upset, facial excoriation, hepatotoxicity, and leukopenia are well-known as potential side effects of methimazole treatment, and some commercial laboratories offer hyperthyroid monitoring profiles specifically directed at detecting clinicopathologic changes associated with the latter two. However, rare cases of generalized lymphadenomegaly with or without concurrent cutaneous lymphoid hyperplasia have been described in both humans and cats receiving methimazole and may mimic lymphoma cytologically. In cats, the lymphadenomegaly resolves within a few days after discontinuation of the drug. Pyogranulomatous mural folliculitis was also diagnosed by skin biopsy in a cat receiving methimazole that developed non-pruritic alopecia with scales, crusts, and erythema.

4. Metoclopramide (or mirtazapine, or metronidazole) and neurologic signs
Hospitalized patients with systemic illness causing inappetence, nausea, or decreased GI motility may be prescribed a combination of promotility agents, antiemetics, anti diarrheals, and appetite stimulants. If neurologic signs appear in these patients, they may be
attributed to other possible disease sequelae (e.g. thrombosis, cerebral edema, electrolyte abnormalities). However, both infusion of metoclopramide and administration of mirtazapine can cause behavior changes and/or tremors, and recent medication history should be examined in patients exhibiting neurologic signs. Metronidazole can also cause vestibular and cerebellar signs in both dogs and cats at high concentrations. Either geriatric vestibular disease or primary neurological disease may be misdiagnosed if this is not realized.

5. Fluoxetine and weight loss
Fluoxetine may be prescribed to dogs and cats for various anxiety-related behavioral disorders. One of the most common side effects reported with a veterinary-labeled fluoxetine product in dogs was inappetence and weight loss (approximately 30% of dogs). This may trigger an extended diagnostic workup if it is not realized that the inappetence may be an adverse drug reaction. This scenario emphasizes the importance of educating oneself, other hospital veterinarians, and veterinary staff regarding potential adverse events associated with products prescribed or dispensed through the hospital. Package inserts are often a valuable source of information.

6. Any medication and adverse drug reactions involving the skin (e.g. erythema multiforme or toxic epidermal necrolysis)
Adverse drug reactions involving the skin are notorious for being attributed to other causes such as infection, allergy, or idiopathic immune-mediated disease. Drugs or classes of drugs that have been associated with cutaneous adverse reactions include antiparasitics (amitraz, metaflumizone, ivermectin), antibiotics (e.g. beta lactams, sulfonamides, tetracyclines), vitamin K, shampoos, contrast agents, NSAIDs, hydralazine, anticonvulsants, chemotherapeutic agents, griseofulvin, allopurinol, corticosteroids, and levotyroxine. A thorough drug history is important in any animal presenting with skin lesions and even drugs that the pet has received for many months should be considered as a potential etiology. More information about specific dermatologic syndromes and methods of diagnosis and treatment can be found in Reference 16.

Conclusion
The above are only a few examples of potential adverse reactions to veterinary drugs, and with the diversity of medications available in the human and veterinary marketplaces, it is not always possible for veterinarians to maintain full awareness of the occurrence of all potential adverse effects of all products used. However, recognition of adverse drug reactions and avoidance of an unneeded prescribing cascade can be facilitated by regular review of drug information (e.g. through regular perusal of package inserts and the veterinary literature, and utilization of product safety updates provided by the FDA and veterinary news sources). Veterinarians should also consider the possibility of an adverse drug reaction whenever new clinical signs appear in a patient receiving multiple medications, particularly geriatric or systemically ill patients. Involvement of the bone marrow, liver, or skin is also common with idiosyncratic adverse drug reactions and an adverse drug reaction should be on the differential list when these organs are affected. Whenever possible, polypharmacy should be avoided and the need for each medication re-assessed on a regular basis.

References
Antibiotic Review:
Things You Wish You Remembered from Vet School, and Things You Might Never have Learned
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When selecting an antibiotic for use in dogs or cats, important considerations include the antibiotic’s spectrum of action (i.e. activity against likely pathogens) and its suitability for treatment of infections in a particular site (which may be affected by drug characteristics such as lipophilicity, degree of protein binding, and route of elimination). Details regarding antimicrobial spectrum and disposition may be easily recalled for frequently used antibiotics, but drug activity against emerging pathogens, or the spectra and pharmacokinetics of recently approved antibiotics, may not be as familiar. The goal of this presentation is to review of the characteristics and spectra of action of different antibiotic classes, together with questions that may arise concerning their use in light of newer options.

Antibiotics effective against gram-positive organisms
Penicillins, first-generation cephalosporins, monobactams, glycopeptides, macrolides, and lincosamides have activity primarily against Gram-positive organisms. For penicillins, these organisms include streptococci, enterococci, some staphylococci (those without beta-lactamases), Arcanobacter, Actinomyces, Listeria, and spirochetes such as Leptospira and Borrelia. The Gram-negative spectrum of penicillins is very limited but includes Pasteurella (the predominant pathogen in cat bite abscesses), and aminopenicillins and first-generation cephalosporins are effective against selected Gram-negative organisms (e.g. E. coli, Proteus mirabilis, Salmonella). Penicillins, aminopenicillins, and lincosamides have good anaerobic coverage except against Bacteroides fragilis.

Among beta lactams, activity against beta-lactamase producing staphylococci requires an antistaphylococcal penicillin (e.g. methicillin), addition of a beta-lactamase inhibitor, or the bulkier side chain of a cephalosporin (excluding carbapenems, which should be reserved for life-threatening resistant infections). Potentiad sulfonamides, tetracyclines, and chloramphenicol also have activity against Gram-positive organisms, including staphylococci.

Q: Amoxicillin-clavulanate is often thought of as “broad-spectrum”. What does it NOT cover?
Amoxicillin-clavulanate is not reliably effective against Bacteroides fragilis, Bordetella bronchiseptica, Enterobacter and Citrobacter spp, Klebsiella, non-mirabilis Proteus spp., Pseudomonas, and Serratia. In addition, it is not effective against organisms (generally Gram negative Enterobacteriaceae) that have acquired beta lactam resistance. Therefore, amoxicillin-clavulanate (or ampicillin-sulbactam) should not be selected as a sole or first choice for potentially life-threatening infections with suspected involvement of Gram-negative organisms.

Q: What about MRSA/MRSP?
Recently, there has been an increase in the incidence of infections involving multi-drug resistant staphylococci (mexitillin-resistant Staphylococcus aureus or pseudintermedius). These pathogens tend to be resistant to all beta lactams and multiple other drug classes, and preferred antibiotics include doxycycline, fluoroquinolones (variably) and aminoglycosides. Rifampin may also be used in combination with other antibiotics.

Q: Earlier generations of cephalosporins tend to have more Gram-positive activity, whereas later generations in general have greater Gram-negative at the expense of Gram-positive activity. How do the spectra of cefpodoxime and cefovecin compare with those of first-generation cephalosporins? Have they lost activity against common Gram-positive veterinary pathogens?
Cefpodoxime, like the first-generation cephalosporins, is effective against streptococci and staphylococci (other than MRSA/MRSP). It also has efficacy against beta-lactamase negative E. coli, Klebsiella, Serratia, Proteus mirabilis and vulgaris, Providencia, and Salmonella. Approximately half of human isolates of beta-lactamase-producing E. coli, Enterobacter spp, Citrobacter spp., and Morganella are susceptible. Therefore, it has slightly expanded Gram-negative coverage compared with first-generation cephalosporins, but maintains some Gram positive activity (e.g. against opportunistic skin flora causing pyoderma in veterinary patients).

Cefovecin is also a third-generation cephalosporin and is more active with lower MICs for many bacteria than first-generation cephalosporins. In studies conducted by the sponsor of a long-acting veterinary formulation, the MIC90 was 0.25 ug/mL for S. intermedius (vs. 2 ug/mL for cephalaxin), and it had an MIC90 of 1 ug/mL (vs. 16 ug/mL for cephalaxin and cefadroxil) for many Gram-negative organisms and very low MICs for feline Pasteurella isolates and Streptococcus canis. However, as noted by the manufacturer, this antibiotic is heavily protein-bound and free concentrations may not be sufficient to reach an appropriate time above MIC for E. coli in the plasma in vivo. Therefore, single administration may be effective only for highly susceptible pathogens (Gram-positive and Pasteurella) and for urinary tract infection (as the drug is eliminated in the urine.) It is labeled for treatment of pyoderma,
bite wounds, and abscesses in the United States, and additionally for E. coli UTI in Europe. It is not effective against Pseudomonas or enterococci.

In both cases, amoxicillin for Pasteurella or susceptible UTI, or amoxicillin-clavulanic acid or cephalexin for pyoderma, would be appropriate choices in lieu of third-generation cephalosporins unless compliance is an obstacle or Gram-negative involvement is suspected.

Antibiotics effective against gram-negative organisms

Aminoglycosides, fluoroquinolones, and parenteral third-generation cephalosporins (cefotaxime, ceftazidime) are generally used primarily for Gram-negative coverage. Aminoglycosides require oxygen-dependent transport into bacteria and are not effective against anaerobes, and among Gram-positive organisms, fluoroquinolones are effective against staphylococci but not streptococci. Fluoroquinolones (particularly enrofloxacin) have variable efficacy against Pseudomonas and antipseudomonal penicillins (e.g. ticarcillin) or selected third-generation cephalosporins (ceftazidime) might be preferable when fluoroquinolone resistance is encountered. Other options for treatment of Gram-negative infection include potentiated sulfonamides, tetracyclines, and chloramphenicol.

Pradofloxacin is a third-generation fluoroquinolone with expanded activity compared to other classes of fluoroquinolones. It is effective against a variety of Gram-positive, Gram-negative, and anaerobic pathogens and is labeled for treatment of dental as well as soft tissue infections in dogs.

Anaerobes

Drugs of choice for anaerobes include penicillins, clindamycin, metronidazole, and third-generation cephalosporins. Carbapenems and chloramphenicol also provide anaerobic coverage. Coverage is variable with tetracyclines.

Q: Is there any rationale for using both a penicillin and metronidazole in animals with suspected anaerobic (e.g. clostridial) infections?

Metronidazole’s coverage is exclusively anaerobic and in contrast to that of penicillins, it includes Bacteroides fragilis. However, the significance of this pathogen in veterinary medicine is questionable, and there is minimal difference in the effectiveness of metronidazole and penicillins against clostridia.
Can I Substitute?
Ensuring Your Patients Get the Right Drugs in the Clinic or at the Human Pharmacy
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Because of the relatively small proportion of pharmaceuticals marketed for dogs and cats and the limited dispensary space in many veterinary hospitals, veterinarians frequently prescribe medications via an outside pharmacy (either human or veterinary). Confusion may arise during multiple steps in this process, e.g. during communication of the prescription (which often occurs via telephone), or during filling of the prescription and delivery of the medication to the client and ultimately to the pet. Veterinarians may also receive inquiries from clients about prescribed medications for which a seemingly comparable human or generic formulation is available.

The problem of prescribing confusion is not unique to veterinary medicine, and in human medicine, the nonprofit Institution for Safe Medical Practices (ISMP) has produced guidelines for hospitals and pharmacies to help reduce the likelihood of patient harm from medication errors. Application of these guidelines to veterinary prescribing can be helpful, as can an understanding of the distinctions between different formulations of human and veterinary drugs.

Accidental substitution during the prescription process: sources of error and measures to prevent them
“Look-alike/sound-alike” drugs
Considering the array of medications available for prescription through human pharmacies, it is not surprising that one drug may be inadvertently substituted for another based on a similar-sounding name, or a name with a similar written appearance. To prevent such a substitution, which can be life-threatening for the patient (e.g. azathioprine for azithromycin in a cat), the following (adapted from ISMP guidelines) are recommended.

1. Educate staff about common “sound-alike” drugs, and consider posting a list in an accessible area where telephone prescribing occurs. A list of “sound-alike” drugs from human medicine is periodically published by the ISMP and this can be reviewed to select those applicable to a particular veterinary practice. The list can be reviewed and renewed at least quarterly by a staff member.

2. The person placing a telephone prescription should either spell the name of the drug to the pharmacist for verification, or have the pharmacist spell it to the prescriber. The prescribing individual should also provide an indication for the drug, e.g. “for infection”. A drug indication that does not match the drug name will often trigger closer scrutiny.

3. When submitting a written prescription, be sure handwriting is legible, and, as for telephone prescriptions, be aware of drugs with similar-appearing names and provide an indication as part of the prescription. Do not abbreviate drug names.

4. If you routinely leave prescriptions on a pharmacy’s voicemail, make sure the client has the drug name (and potentially the strength and directions) in writing to verify at pickup.

Dosing errors
Dosing errors can result from incorrect interpretation of two similar-sounding numbers (e.g. “fifty” for “fifteen”), from illegible written prescriptions or incorrect placement of decimal points, from incorrect calculations, or from unfamiliar abbreviations. To avoid dosing errors:

1. When communicating a number over the phone, repeat numbers in digits, e.g. “one five” in addition to “fifteen.”

2. As for drug names, make sure drug dosages are legible, with no ambiguity surrounding numbers or decimal points (do not use trailing zeros, and place zeros before decimal points), and avoid abbreviations (particularly SID, which is not used in human medicine) where possible.

3. Double check all calculated drug doses.

General communication obstacles
For either a spoken or a written prescription, the prescriber should always 1) be willing to clarify the prescription to the pharmacist, and 2) maintain a courteous attitude. In a survey conducted among human healthcare workers by ISMP, 83% of pharmacists said they had encountered a reluctance or refusal to answer questions or return calls by prescribers, and 40% of respondents reported that they assumed a medication order they had concerns about was correct, rather than seeking clarification from the prescriber, if the prescriber was perceived as intimidating. 7% of these individuals also acknowledged that they had been involved in a medication error in which intimidation played a role within the previous year.

Potential sources of error when the prescription is filled
Human pharmacists reviewing veterinary prescriptions may note differences in the veterinary and human indications and dosing regimens for certain drugs. When this information is communicated to the client at pickup, it can cause confusion. For example, mirtazapine is an antidepressant in humans; and clients picking up benazepril for treatment of proteinuria may be told that it is for
blood pressure management. When a medication is prescribed, attention should be given by veterinary staff to educating clients about
the drug’s purpose, directions, side effects, and any notable differences from use of the drug in humans.

Substitutions among human formulations
Clients or pharmacists may ask a prescribing veterinarian whether a substitution of one human drug or formulation for another is
acceptable, or pharmacists may assume it is unless otherwise specified. Generic human drugs may be assumed to be equivalent to
name-brand formulations, but this is not always the case in pets, as bioequivalence has been demonstrated between human name-brand
and generic drugs in human populations, but not in canine and feline populations. If a drug has an easily monitored clinical effect
(e.g. amlodipine), if the consequences of lack of efficacy are not serious or life-threatening, if there is not a body of veterinary data
supporting a specific formulation only, or if the drug is not a biological product such as insulin or levothyroxine, substitution of a
generic for a name-brand human formulation may be acceptable. Hormone-based medications are more difficult to standardize among
patients and clients should be aware that substitution of one brand of insulin or levothyroxine for another may require re-regulation of
the patient’s disease.

Substituting a human drug for a veterinary drug
In some situations, clients may ask if a human drug formulation or human drug from the same class can be substituted for a veterinary
prescription, for cost or convenience reasons. Clients may not be aware that human and veterinary-labeled drugs may differ in
effectiveness despite having the same active ingredient, as other components of the product (excipients, enteric coating) can affect
absorption and bioavailability. The approval requirements for veterinary-labeled drugs require substantial evidence of safety and
efficacy, which generally entails clinical trials in the species of interest documenting appropriate pharmacodynamics (with or without
pharmacokinetic data) and information about the incidence of adverse events with that formulation specifically in that species. The
same is not true of human formulations used in pets.

For several human drugs with veterinary analogues, however, a large body of literature describing efficacy and nature of adverse
events to be expected with the drug exists, and efficacy is not restricted to a specific formulation (e.g. cephalexin, methimazole,
amldipine). Substitution of a human drug for the veterinary version in this case will likely result in similar efficacy, but may result in
the loss of modifications specific to the veterinary product (most often improved palatability or precise dosage forms) and support from
the veterinary sponsor in case of adverse reaction. With regard to drugs from the same class, substitution of ciprofloxacin for
enrofloxacin is often requested by clients for financial reasons, but is not advised considering the wide variation in ciprofloxacin
bioavailability among dogs, which has been demonstrated in multiple studies.

Substituting veterinary generic drugs or compounded drugs for veterinary name-brand formulations
Manufacturers of veterinary generic formulations are required to demonstrate bioequivalence of the generic product to the parent
(name brand) drug. Generally, this means that the two products produced drug exposure (as assessed by maximum plasma
concentration and area under the curve) that was similar enough it would not be expected to result in a clinical difference. Therefore,
generic veterinary products can often be substituted for name-brand products with minimal repercussion, although for hormone-based
formulations, re-regulation may then be necessary, as discussed above.

The same is not true of compounded products, for which no comparison with name-brand or generic products must be made and
which are not subject to outside regulations regarding stability, efficacy, and safety. Although compounded products may be effective
in some circumstances, they should be used only when approved alternatives are not available, and inquiries should be made of the
compounding pharmacy regarding stability data and manufacturing practices for their products. Two recent veterinary studies have
identified stability concerns and inadequate plasma concentrations with compounded doxycycline and itraconazole, respectively, in
dogs, and numerous other examples exist.

Additional notes on prescribing through an in-clinic pharmacy
Several of the guidelines for avoiding communication errors with human pharmacies can be applied to medication orders within a
veterinary hospital. Prescribing veterinarians can help to minimize medication errors by communicating medication orders clearly to
staff, and by being courteous and receptive to questions. Additionally, “look-alike/sound-alike” drugs, especially injectable drugs, can
be labeled as such and placed in different areas of the in-clinic pharmacy.

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Physiology of neonatal (0-2 weeks), infant (2-6 weeks), and pediatric (6-12 weeks) dogs and cats differs from that of adults in several important ways that can impact drug metabolism and disposition. Proportion of total body water is substantially higher in puppies and kittens, leading to a higher volume of distribution and lower than expected plasma concentrations of water-soluble drugs; the reverse is true for fat-soluble drugs. Renal and hepatic function are also immature until at least 3-6 weeks of age. In addition, young animals have slower gastrointestinal transit time and a more permeable blood-brain barrier than adults. Because of the latter and because certain systems are still developing (e.g. physes, tooth buds) younger dogs and cats may be more susceptible than adults to certain adverse drug reactions.

For some drugs (primarily antiparasitics), specific information exists to support safe use in puppies and kittens as young as 4 weeks. Other drugs have been demonstrated to have increased risk of toxicity in young compared with mature animals. However, for most drugs, neither of the above is true. Labels for veterinary products may include statements specifying that the product is approved only for use in animals above a certain age. In some cases, a particular adverse effect was noted during safety assessment. However, because most veterinary pharmaceuticals are not specifically designed for puppies and kittens, safety testing is often performed in “healthy young mature animals” as per FDA guidance. Consequently, the label recommendation to avoid use in animals younger than a certain age may simply mean that its safety in pets below that age has not been evaluated. Approval for younger animals may be sought later if they form a substantial portion of the use class after initial marketing (e.g. maropitant). Only a very few medications are approved for pregnant or lactating animals.

Consequently, recommendations for use of specific drugs in puppies and kittens are often based on an amalgam of information from other species, theoretical support or concerns, and clinical experience. A collection of these recommendations, by drug class, is discussed below.

Antibiotics
B-lactams (penicillins and cephalosporins) are often suggested to be safe in young animals because of their wide therapeutic index, which alleviates concern about a slower elimination rate. However, in neonates, penicillins may be associated with suppression of normal GI flora and colonization by pathogenic organisms. The same does not appear to be true of cephalosporins, several of which are active against common pathogens causing neonatal septicemia. Macrolides are not overtly toxic, but undergo hepatic recirculation and may disrupt GI flora. Trimethoprim-sulfonamide has also been recommended as an initial broad-spectrum choice for puppies and kittens, although it has been associated with immune-mediated drug reactions in adults. Chloramphenicol has caused blood dyscrasias in 8-12 week old puppies at 50 mg/kg twice a day, and causes cardiac depression in neonates of other species (e.g. humans). Aminoglycosides have a narrow therapeutic index and young age has been listed as a risk factor for nephrotoxicity; however, these agents may still be used if adequate hydration is ensured. If metronidazole is used, very young puppies and kittens should be closely monitored for neurotoxicity. Tetracycline-induced tooth staining (which appears less common with doxycycline but has still been reported to occur) and cartilage damage with fluoroquinolones in large-breed puppies up to 18 weeks of age are often cited as reasons not to use these drugs in young animals. However, if life-threatening infection is present, fluoroquinolones may be appropriate as a means of Gram-negative coverage.

Analgesics and sedatives
Based on human literature, short-term opioid use is likely to be safe in pregnant, nursing, and neonatal dogs and cats. NSAID use is to be avoided in pregnant animals based on numerous studies in other species documenting fetal nephrotoxicity (as COX-2 is important for the developing kidney) and teratogenesis. Because most NSAIDs are lipid-soluble and highly protein-bound, they may not be transferred in milk in sufficient concentrations to affect nursing animals; however, this has not been demonstrated in dogs or cats, and meloxicam concentrations in the milk of rats were higher than those in plasma. NSAIDs are not recommended for animals less than 6 weeks of age because of ongoing hepatic and renal maturation.

Benzodiazeepines have a large margin of safety and are often recommended as components of sedative or preanesthetic protocols for young puppies. Opioids alone have a sedating effect in pediatrics (<4 mo). Acepromazine may cause CNS depression in young animals and dose reductions to 0.005-0.025 mg/kg have been recommended. Lidocaine can be used as a local anesthetic at 3-6 mg/kg in kittens (with the lower dose to be used in neonatal animals) and 6-10 mg/kg in dogs. Similarly, some authors recommend bupivacaine at 2 mg/kg in older puppies and kittens and half of this dose for patients <12 weeks.
Anticonvulsants
Both phenobarbital and potassium bromide have been used to manage seizures in young puppies. Potassium bromide does not require hepatic metabolism, which may be advantageous in animals with immature liver function. Phenobarbital use in human children and young rats has been shown to interfere with brain development, and some authors recommend reduction of the initial dose for animal younger than 6 months (e.g. 0.5 mg/kg once a day for animals less than 3 months old, 1 mg/kg twice a day for 3-6 month old animals, and 2 mg/kg twice a day for animals older than 6 months). Gabapentin and levetiracetam have not been evaluated in young dogs and cats.

Antiparasitics
Pyrantel has a wide safety margin and has frequently been used in animals as young as 2 weeks of age. Many other antiparasitics and flea/tick control products have been marketed by veterinary pharmaceutical companies, and age recommendations can be found on the product label.

References
Therapeutic Drug Monitoring: Good for Your Patients, Good for Your Practice These Phenobarbital Levels?
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The relationship between administration of a drug to a patient and appearance of a clinical effect is complex, and is affected by both pharmacokinetic and pharmacodynamic factors. Pharmacokinetic (PK) factors include all processes involved in absorption, distribution, metabolism, and elimination of the drug; although these may be broadly similar within a species for a particular drug, they may also vary enough between individuals (or even within the same individual over time) to influence clinical effect. Likewise, pharmacodynamic (PD) processes such as receptor activation or enzyme inhibition vary among patients and may be responsible for differences in therapeutic response. Therefore, although published drug dose ranges may result in the desired clinical effect in some patients, they may not be ideal for others.

Therapeutic drug monitoring (TDM) refers to measurement of a pharmacologic or physiologic parameter at specific time points during drug treatment, with the goal of optimizing the dosing regimen for an individual patient. Traditionally, the parameter measured has been the plasma drug concentration (PK monitoring); however, TDM based on biomarkers or other indicators of drug effect (PD monitoring) may also be appropriate for some drugs. TDM can be thought of as a way to access otherwise hidden information regarding the chain of events that occurs between drug administration and drug effect. This information can be utilized pre-emptively (to assess the appropriateness of the dosing regimen before clinical signs of toxicity or lack of efficacy become apparent) or diagnostically (to investigate whether lack of efficacy or suspected toxicity are related to PK or PD problems, and to evaluate client compliance).

 Obviously, TDM is not necessary or suitable for every drug that is used in veterinary medicine, as treatment goals can often be accomplished via empirical dose adjustment. TDM contributes to patient management primarily when:

- The drug being used has a narrow therapeutic index or a steep dose-response curve (e.g. animoglycosides)
- Drug PK is highly variable among patients or in the same patient over time (e.g. cyclosporine, anticonvulsants)
- The drug is prone to significant drug-drug or drug-disease interaction (e.g. digoxin).

Even when the above criteria are met, TDM is generally employed only when the endpoint of therapy is difficult to monitor clinically, and the consequences of toxicity or lack of efficacy are serious. A serious consequence could mean actual harm to the patient, or it could mean a significant financial or emotional cost to the client of giving an ineffective therapy for an extended period of time. Limitations of TDM include the fact that plasma drug concentration may not reflect drug concentration at the active site or disease interaction (e.g. digoxin).

Because TDM is a “snapshot” of drug concentration or drug effect on a physiologic parameter at only one or two points in time, those points must be chosen carefully to maximize the information received. In understanding appropriate sample timing, two pharmacokinetic concepts are helpful: accumulation and steady state. When the next dose of a drug is given before the last dose has been completely eliminated from the body, drug accumulation will occur. The degree of accumulation is determined by the ratio of the half-life to the dosing interval; if this ratio is large (the half-life is very long compared to the dosing interval) only a small percentage of drug will be eliminated during each dosing interval and accumulation will be marked. Conversely, when the half-life is very short compared to the dosing interval, almost all the administered dose will be eliminated during the dosing interval and accumulation will be minimal.

Any drug that exhibits accumulation will eventually reach steady-state (in which the mass of drug eliminated from the body during each dosing interval has “caught up with” or become exactly equal to the mass of drug administered with each dose). At steady state, which occurs after 5-7 half-lives, the peak and trough plasma concentrations are very similar across dosing intervals. The difference between the peak and trough concentration within a dosing interval is also determined by the ratio of the half-life to the dosing interval; if this is large, the amount of drug eliminated during each dosing interval will be very small compared to the steady-state plasma drug concentration, and there will be only a small difference between peak and trough. For drugs with a shorter half-life:dosing interval ratio, a larger percentage of drug will be eliminated during each dosing interval and the difference between peak and trough will be larger.
The implications of these principles are that for the first category of drugs (extensive accumulation, e.g. KBr), a single missed dose will have little impact on the steady-state plasma drug concentration, and either peak or trough concentration can be measured for preemptive and diagnostic monitoring. For drugs with a shorter half-life/dosing interval ratio (e.g. phenobarbital), missed doses may impact steady-state concentration (i.e. if a history of recent missed doses is discovered on the day TDM was planned, rescheduling should be considered). Trough (before the next dose) is usually measured for preemptive monitoring or diagnostic monitoring for inefficacy (to avoid the influence of variability associated with absorption on peak concentrations), whereas peak is measured if toxicity is suspected. An exception to the latter is aminoglycosides, in which trough drug concentration correlates with toxicity and peak with efficacy.

For calculation of half-life, two samples (generally peak and trough) are necessary; for drugs expected to have half-lives substantially shorter than the dosing interval, “trough” samples should be taken two half-lives after the peak to avoid undetectable drug concentrations prior to the next dose.

A summary of monitoring recommendations for selected drugs in dogs is as follows

**Phenobarbital**
- Half-life: 32-75h
- Preemptive monitoring
- Trough for consistency (peak vs trough not important in 90% of patients)
- Post-load
- 2 weeks (steady-state)
- 3-6 months after starting (due to enzyme auto induction)
- Every 6-12 months (clinical judgment)
- Diagnostic monitoring
- Peak (4-5 h) if suspect toxicity
- Trough (before next dose) if suspect lack of efficacy
- Peak and trough if suspect short half-life

**Potassium bromide**
- Half-life: 14-21 days
- Preemptive monitoring
- Any time within dosing interval (i.e. peak, trough, or in between)
- Post-load
- 3 weeks (one half-life) after load – if concentration has declined from post-load, maintenance dose may need to be increased
- 3 months (steady-state)
- Every 6-12 months (clinical judgment)
- Salt content of diet must be kept constant
- Diagnostic monitoring
- Any time within dosing interval

**Levetiracetam**
- Half-life: 2-3.6 h
- Preemptive monitoring
- Peak (2 h) and “trough” (two half-lives, or 4-6h, after peak) when beginning therapy
- Goal: determine half-life and customize dosing regimen
- Diagnostic monitoring
- Peak if suspect toxicity (rare)
- Trough (+/- peak for half-life) if suspect lack of efficacy

**Zonisamide**
- Half-life 16-65 h
- Preemptive monitoring
- Peak (2 h) and trough (before next dose) when beginning therapy
- Steady-state 10 d
- Diagnostic monitoring
- Peak if suspect toxicity
- Trough if suspect lack of efficacy
Aminoglycosides
- Half-life
  - 0.9-1.3 h (gentamicin)
  - 1-3 h (amikacin)
- Preemptive monitoring
  - Peak (0.75-1 hour) and “trough” 2 half-lives (4-6 h) after peak (to determine half-life in patient)
- Diagnostic monitoring
- Trough if suspect toxicity

Cyclosporine
- Half-life: 3-8 h
- Preemptive monitoring
- Trough
  - 1-2 days (steady state) after starting
- Peak (2h) concentrations correlate best with total drug exposure in humans; PD monitoring (calcineurin inhibition) may be alternative to PK monitoring
- Diagnostic monitoring
- Peak if suspect toxicity
- Trough if suspect lack of efficacy
- Therapeutic range not well defined
- Trend in patient may be more important
- Trough <50 ng/mL associated with lack of efficacy

When interpreting the results of pre-emptive monitoring for drugs such as phenobarbital, the need for further investigation and/or dose adjustment can be determined based on 1) whether or not the plasma concentration is as expected from the administered dose, and 2) how the results of TDM fit the clinical picture. With regard to the first point, it is helpful to consider that drug dosage and plasma drug concentration should vary in a proportional manner for drugs with linear pharmacokinetics (most drugs utilized in veterinary medicine). Therefore:

\[
\text{Old dose} = \text{New dose} \\
\text{Old } C_p = \text{New } C_p
\]

where \( C_p \) = plasma drug concentration.

If a higher plasma drug concentration is desired, the new dose required to achieve that concentration can be calculated using this equation. Additionally, when plasma drug concentration is measured after a dose change, the new concentration expected can be calculated and compared with the actual results. A large discrepancy may indicate difficulties with owner compliance or changes in drug absorption or elimination, and these issues can be further investigated.

Information regarding practice management aspects of TDM will also be covered by a co-presenter.

References
Antiepileptic drug snafu

An 8 yo Fs field spaniel presented for tonic clonic seizures and was started on phenobarbital, but seizures were poorly controlled and the dog was PU/PD/PP. The dog was referred to our Neurology service within a month, and MRI imaging and CSF analyses were negative for structural or inflammatory disease. Levetiracetam (Keppra XR, 500 mg (25 mg/kg q 12h) was added, but seizures were still poorly controlled, so zonisamide (10 mg/kg q 12h) was added 2 months after the onset of seizures.

One month later, the dog developed lethargy, anorexia, and jaundice. ALT was 1939, ALP was 2093, bilirubin was 3.9, and albumin was 1.7. HCT was normal at 43%. She was hospitalized for IV fluids (rehydration with isotonic fluids, with maintenance rates on Normosol-M). N-acetylcysteine (140 mg/kg IV diluted to 5% in saline, given by short infusion over 20 minutes, then 70 mg/kg IV q6h for 48 hours) was given as a hepatoprotectant (glutathione precursor). Phenobarbital and zonisamide were discontinued. Abdominal ultrasound was negative for biliary obstruction; the liver was enlarged and hyperechoic with subtle hypoechoic nodules, but no evidence of ascites. The dog had 3 break-through seizures in the hospital that were managed with IV midazolam. When she was eating, oral KBr (loading dose of 400 mg/kg divided in doses of 50 mg/kg q12h over 4 days) and gabapentin were started, along with a higher dosage of oral levetiracetam.

The dog was discharged from hospital after one week of supportive care, on high dose maintenance KBr, gabapentin (20 mg/kg q8h), levetiracetam (Keppra XR, 750 mg (37 mg/kg q12h)), Denamarin, and ursodiol. At discharge, ALT was 724, ALP was 1839, bilirubin was 1.9, and albumin was 1.7. These parameters normalized slowly over 10 weeks, although ALP remained mildly (2-fold) increased. Her serum bromide level is high therapeutic at 2.6 mg/ml (target without phenobarbital, 2.0-3.0 mg/ml), and she has had only 4 seizures over 5 months (3 in the first few weeks after discharge and one 4 months later).

Case assessment

This episode of acute liver failure was very likely an idiosyncratic drug reaction to zonisamide, based on two recent case reports with a similar clinical presentation. In one dog, clinical signs of liver toxicity began three weeks after starting zonisamide, with a mixed biochemical pattern (Schwartz 2011). Abnormalities resolved with drug discontinuation. In a second dog, marked increases in ALT and hyperbilirubinemia were noted 10 days after zonisamide was started (Miller 2011). This dog was euthanized due to hepatic failure, and histopathology showed massive panlobular hepatic necrosis with marked periportal microvesicular steatosis. Further clinical experience is needed before the incidence of zonisamide hepatotoxicity is clear; however, dog owners should be informed of this potential adverse drug reaction when zonisamide is prescribed. Clients should be alerted to watch for acute signs of illness; if noted, liver enzymes and bilirubin should be evaluated.

More recently, zonisamide has been associated with erythema multiforme, to include erosions, crusting and ulceration of the ventrum, beginning about 6 weeks after starting the drug (Ackermann 2015). Ulceration of the hard palate was also noted; all lesions resolved within 2 weeks of stopping zonisamide. Although zonisamide is a “sulfonamide” anticonvulsant, it lacks the reactive arylamine group that leads to hypersensitivity to sulfonamide antibiotics. However, it is very likely that zonisamide reactions are triggered at least in part by a reactive metabolite.

Because phenobarbital can also cause hepatotoxicity, it was discontinued at the same time as zonisamide. However, it is unlikely that phenobarbital was the proximate cause. Phenobarbital hepatotoxicity is typically seen after prolonged administration (> one year), and is accompanied by nodular regeneration or even cirrhosis. Using combination antiepileptic drugs to minimize the dosage of phenobarbital needed, and monitoring a biochemical panel and bile acids every 6 months during phenobarbital treatment can minimize risk.

More is not better

A 1½ yo Mn Maltipoo presented for coughing and gagging of one week’s duration. On physical exam, the dog was lethargic but responsive, 5% dehydrated, and mildly febrile at 102.8. The respiratory rate of 50 breaths/min with harsh bronchovesicular sounds bilaterally. Abdominal palpation was negative for pain or organomegaly. Chest radiographs showed a mild to moderate alveolar/interstitial pattern in the right middle lung lobe, consistent with aspiration pneumonia. Esophagram by fluoroscopy revealed proximal esophageal dysfunction. Resting cortisol was 4.2 ug/dl, ruling out hypoadrenocorticism. Serum for an acetylcholine receptor antibody test was submitted. Tracheal wash cytology showed suppurative inflammation and a positive culture for E. coli, sensitive to enrofloxacin. Following rehydration with IV fluids, the dog was discharged with enrofloxacin, along with omeprazole and sucralfate for possible reflux.
The fever, lethargy, and cough improved over the next 48 hours. The dog then became progressively more lethargic and weak, with an increased respiratory effort, and re-presented to the emergency service one week after discharge. The owners described attempts to eat, but trouble swallowing. At re-presentation, the dog was depressed, weak, and febrile at 103.9. The dog was stabilized with oxygen and IV fluids. Repeat chest radiographs showed worsened pneumonia, and a repeat tracheal wash revealed an E. coli, now resistant to enrofloxacin. The dog’s drug history was reviewed, and a drug interaction between enrofloxacin and sucralfate was suspected, since sucralfate impairs the absorption of fluoroquinolones in humans. Meropenem (12 mg/kg SC q. 8 h) was instituted based on sensitivity results. The dog’s pneumonia improved, but he still appeared weak and had trouble prehending food.

The acetylcholine receptor antibody test returned as positive (2.56 nmol/L), indicating acquired myasthenia gravis as a cause for the weakness, dysphagia, and proximal esophageal dysmotility. The dog was given an oral dose of pyridostigmine (1.75 mg/kg) but had trouble swallowing the tablet. When the next dose was due 8 hours later, he was instead given neostigmine (0.05 mg/kg SC). Within 15 minutes of neostigmine administration, the dog defecated, began salivating profusely, and became bradycardic (60 bpm) with second degree AV block. His chest excursions weakened and he went into respiratory arrest. The dog was treated with atropine and supported with assisted ventilation for 16 hours until he could breathe on his own. No further treatment with cholinesterase inhibitors was attempted (!). Glucocorticoids were not initiated for the myasthenia because of active aspiration pneumonia. The dog’s dysphagia improved over the next few days without additional treatment, and the acetylcholine receptor antibody titer became negative (< 0.6 nmol/L) over the next 8 months.

**Case assessment**

Injectable neostigmine can be used for initial management of myasthenia gravis, followed by pyridostigmine for oral maintenance. These acetylcholinesterase inhibitors increase acetylcholine at the neuromuscular junction, so that more neurotransmitter is available to interact with a decreased number of functional acetylcholine receptors. However, dose titration can be difficult, and too much acetylcholinesterase activity can lead to a cholineric crisis. This likely happened in this dog. In retrospect, the low end of the dosing range (0.5 mg/kg) should have been chosen for the first dose of pyridostigmine, with hourly monitoring of the dog’s heart rate and character of respirations.

We initially suspected a drug interaction between sucralfate and enrofloxacin as the cause of relapsed, antibiotic-resistant pneumonia. Sucralfate can form complexes with many other drugs in the GI tract, including several fluoroquinolones in humans. Although it was recommended that the sucralfate be given 2 hours after the enrofloxacin, this can be difficult for clients to comply with. I prefer not to send patients home on sucralfate when they are being given any other oral drugs for which absorption is decreased by sucralfate (drugs.com, Drug Interactions Checker) because of the burden on clients to separate dosing appropriately.

However, since this case was managed, a recent study found that although sucralfate does impair the absorption of ciprofloxacin and doxycycline in dogs, it did not decrease the absorption of enrofloxacin in a small study in 5 healthy Greyhound dogs (Kukanich 2016). Given this recent study, it is possible that the dog’s recurrent, resistant pneumonia may have been due to re-aspiration rather than an interaction between sucralfate and enrofloxacin.

**Nothing but trouble**

A 5 yo Mn mixed breed dog (28 kg) presented with inappetence and occasional vomiting. Serum ALT ranged from the 315 to 875 IU/L, with a modestly decrease albumin but a normal bilirubin, BUN, and cholesterol. A wedge liver biopsy was obtained, which showed chronic hepatitis with bridging fibrosis. Copper was not quantitated but staining was negative. Bile acids were normal at 18 umol/L pre and 24 umol/L post. The dog was treated with SAMe, ursodiol, famotidine, and l/d diet ©, which brought some clinical improvement, but serum ALT activities continued to climb. Prednisone was instituted, but led to unacceptable polyuria and polydipsia.

Budesonide was substituted; however, dosages of budesonide (1 mg daily) that led to reductions in serum ALT activities were associated with progressive muscle atrophy. Cyclosporine was added at 5 mg/kg BID to allow dosage reductions in budesonide to every other day; this combination was associated with near normalization of ALT, although appetite was somewhat subdued. Appetite improved when the dosage of cyclosporine was reduced to 3 mg/kg BID, and the dog was finally doing well.

Several months after starting cyclosporine, the dog developed SC masses on the nasal planum. Excisional biopsy revealed pyogranulomatous inflammation with fungal hyphae. Fluconazole was started (5 mg/kg BID), and the dog was monitored for recurrence. A dosage reduction or discontinuation of cyclosporine was discussed, but the owners were reluctant to immediately change the regimen that had brought optimal clinical control of the dog’s chronic hepatitis. Two weeks later, the dog developed inappetence. Serum ALT was 1295 IU/L, the highest ever. Since no changes had been made except for the addition of fluconazole, dose-dependent azole antifungal hepatotoxicity was suspected. Fluconazole was discontinued; itraconazole was not substituted because it also carries a risk of hepatotoxicity. Without antifungal prophylaxis, continued immunosuppression with cyclosporine could not be recommended, so cyclosporine was also discontinued. The dog’s appetite normalized with these two changes, and serum ALT fell to previous moderate elevations (391 IU/L). The dog continued to be clinically stable (6 years after diagnosis) on budesonide, SAMe, ursodiol, and famotidine, although progressive muscle atrophy and carpal laxity from the budesonide was considerable.
**Case assessment**

These owners were very dedicated and patient throughout various therapeutic misadventures. This dog developed dose-dependent side effects that were an extension of drug pharmacologic effects (PU/PD from prednisone, muscle atrophy from budesonide, secondary fungal infection on cyclosporine), and dose-dependent effects that were independent of the drug’s intended effects (anappetence from cyclosporine and hepatotoxicity from fluconazole). Fluconazole reportedly has a lower risk of hepatotoxicity than itraconazole in both humans and in rodent models, which is why it was chosen in this dog with underlying liver disease. However, we have since observed several dogs with blastomycosis that have developed reversible moderate to marked increases in serum ALT activities on fluconazole treatment. In a retrospective study of dogs with blastomycosis (Mazepa et al, 2011), we documented a 17% incidence of increased serum ALT in dogs on fluconazole (most were quite mild), compared to a 26% incidence for itraconazole; however, this difference did not reach statistical significance, and the population numbers were relatively small.

Monitoring of serum ALT appears to be important during fluconazole therapy in dogs, as it is for other azole antifungals. Liver enzyme increases have been shown to be dose-dependent for azole antifungals, and do not necessarily require drug discontinuation. Some dogs can be managed with dose reductions (e.g. by 50%), with or without glutathione precursors such as SAM-e. Since this dog was already on SAM-e when he developed apparent drug toxicity, and already had underlying liver disease, we did not attempt to treat him with a lower dose of fluconazole.

In retrospect, several things might have led to better management in this case. Copper quantitation should have been performed, to see whether a copper restricted diet such as l/d was actually indicated. The dog had never shown signs of encephalopathy, so the protein restriction in Hill’s l/d (or other liver formulated diets) was probably not necessary. Even in human patients with cirrhosis, protein restriction is no longer routinely recommended, since it can lead to protein-calorie malnutrition and muscle catabolism (Abdelhayed 2015). If this dog had high copper levels but no encephalopathy, a better option might have been to supplement the commercial copper- and protein-restricted diet with dairy or soy source proteins.

Second, it is questionable whether cyclosporine was the best add-on drug for management of hepatic inflammation in this dog. We have since published a case series of 8 dogs treated with both prednisone and cyclosporine (including this dog) that developed cutaneous and/or serious systemic fungal infections (Dowling 2016). In humans, autoimmune hepatitis is treated with prednisone followed by azathioprine (Liberal 2016), which may lead to less profound immunosuppression than cyclosporine. In retrospect, a modest dose of azathioprine may have been a preferable add-on to budesonide in this dog. However, azathioprine does have some hepatotoxic potential, and moderate increases in ALT occur in about 15% of dogs within the first 3 weeks of azathioprine treatment (Wallisch & Trepanier 2015), so increased monitoring in this time frame is indicated.
Drug Dose Adjustment for Disease
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There is considerable evidence to support the adjustment of drug dosages in human patients with heart failure, hepatic failure, or renal insufficiency. In contrast, similar studies are mostly lacking in dogs and cats. This presentation will discuss veterinary situations in which drug dose adjustments may be warranted.

Considerations in heart failure
Decreased cardiac output in heart failure can lead to prerenal azotemia, which may necessitate lower doses of renally cleared drugs such as enalapril, furosemide, or digoxin. In contrast, benazepril, which can also undergo hepatic clearance, should not require a dose reduction in dogs and cats with mild to moderate azotemia. In overt heart failure, blood is preferentially shunted to the brain and heart. For drugs like digoxin, this may enhance both cardiac toxicity (arrhythmias) and CNS toxicity (central nausea and GI upset).

The presence of gastrointestinal edema in right heart failure may lead to erratic oral absorption of some drugs, including oral furosemide (Ogawa 2014). In addition, in fulminant failure, blood flow to the subcutaneous tissues is poor because of peripheral vasoconstriction. Therefore, intravenous or intramuscular drug administration is preferred over oral or SC routes in these patients to assure adequate drug delivery.

Cardiac drugs have many potential drug interactions, caused by additive drug effects, opposing drug actions, or competition for drug elimination. For example, diltiazem and atenolol in combination may lead to AV block and bradycardia. Furosemide can lead to hypokalemia, which increases the risk of digoxin toxicity and can diminish the effectiveness of lidocaine.

In humans, dosing of digoxin and other drugs is based on nomograms that incorporate ideal body weight and creatinine clearance. In addition, cardiac drug dosages are titrated to achieve target reductions in BNP or NT-pro-BNP (De Vecchis 2014), and this leads to better outcomes than following clinical signs alone. Similar evidence-based practices are lacking in veterinary medicine.

Key points
- Parenteral dosing (esp. IV) preferred in acute heart failure
- Polypharmacy common in heart disease – always consider possible drug interactions
- Frequent monitoring of appetite, hydration, body weight, electrolytes, kidney function is important

Hepatic insufficiency
In humans with inflammatory liver disease without cirrhosis, hepatic drug metabolism is fairly well conserved. With cirrhosis or severe hepatic dysfunction, however, drugs that are normally extensively metabolized are not cleared as readily. Based on human data, dosages of some drugs may need to be reduced in our patients with severe liver disease (for example, fulminant hepatic lipodisosis, acute hepatic necrosis, or cirrhosis). Drugs that merit dose reductions in humans with liver failure include propranolol, chloramphenicol, benzodiazepines, and metronidazole. In humans, dosing at 25-50% of the standard dosages are recommended.

Alternatively, if metronidazole toxicity is a concern in liver failure, lactulose can be substituted when treating hepatic encephalopathy, and amoxicillin/clavulanate or ampicillin/sulbactam can be used instead if systemic anaerobic coverage is needed.

Hypoalbuminemia is a common complication of hepatic insufficiency, and could theoretically lead to increased adverse effects from highly protein drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and benzodiazepines. However, this had not actually been documented. Ascites is uncommon in cats with liver disease, but can be seen in dogs with portal hypertension from hepatic fibrosis or cirrhosis. Lipid soluble drugs will not distribute to ascites fluid. The normal body weight (minus estimated ascites fluid weight) should be used to calculate dosages of lipid soluble drugs such as propofol, fentanyl, and vitamin K. Water soluble (polar) drugs will distribute to ascites fluid unless they are highly protein bound. For polar drugs such as aminoglycosides, the total body weight (including ascites fluid) should be used to calculate drug dosage.

Patients with hepatic insufficiency or shunts have increased sensitivity to central nervous system (CNS) depressants. Therefore, benzodiazepines, barbiturates, and acepromazine should be avoided or used at reduced dosages. Opioids should also be used at reduced dosages, and reversible agents are preferable. For encephalopathic seizures, consider using diazepam or midazolam at 20-30% of standard doses and titrating upwards to effect.

Some therapies can worsen hepatic encephalopathy and should be avoided. Avoid stored whole blood and stored packed red blood cell transfusions in patients with significant liver dysfunction, since stored blood can have high ammonia concentrations. Instead, use an in-house blood donor or a unit with a distant expiration date. Avoid NSAIDs in dogs and cats with significant liver disease, because of the risk of gastrointestinal bleeding. GI bleeding is a protein load on the gut, and can worsen hyperammonemia. Furosemide can also worsen hepatic encephalopathy by leading to hypokalemia, dehydration, azotemia, and alkalosis. Spironolactone/hydrochlorothiazide is better tolerated than furosemide when treating ascites.
As for fluid therapy, avoid 0.9% saline IV in patients with liver disease, since this high sodium fluid can lead to volume overload. Instead consider 1/2 strength saline with 2.5% dextrose, and added potassium, for liver patients. Finally, avoid glucocorticoids in patients with liver disease until signs of hepatic encephalopathy are controlled. Glucocorticoids are catabolic, and will enhance muscle breakdown, deamination of proteins, and release of NH₃.

**Key points**
- No need to dose adjust drugs in patients with liver disease unless liver failure or shunting are present
- Caution with sedating drugs – typically need lower dosages in liver failure
- Avoids drugs that cause hypokalemia, GI bleeding, or sodium retention in patients with liver disease

**Renal failure**
Renal failure leads to decreased filtration of renally eliminated drugs and active metabolites, as well as decreased tubular secretion of some drugs, such as cimetidine, trimethoprim, and digoxin. Renal failure is also associated with less obvious effects on drug disposition, such as decreased renal P450 and Phase II drug metabolism, impaired binding of some drugs to albumin, and reduced tissue binding of other drugs (e.g. digoxin).

Given these complexities, it is unfortunate that there are very few studies on dosage adjustments in dogs or cats with renal failure. Creatinine clearance is used to make rational dosage adjustments in azotemic humans, but this measurement is typically not available for veterinary patients. Dosage reductions in humans are typically made when creatinine clearance values are less than approximately 0.7 to 1.2 mL/min/kg (depending on the drug); this corresponds to a serum creatinine of greater than approximately 2.5 to 3.5 mg/dL (220-310 umol/L). Dosage reductions can be made by giving less drug at the same intervals, the same dose at less frequent intervals, or a combination of the two.

Drugs that require dosage reductions in renal failure include those with a relatively narrow margin of safety that are primarily eliminated by the kidneys (or have an active metabolite that is eliminated by the kidneys). Penicillins are renally excreted, but toxicity is unlikely. However, dose reduction would be appropriate and would decrease the cost of more expensive penicillins and related drugs (such as ticarcillin or meropenem) in patients with azotemia. Cephalosporins such as cephalothin and cefazolin can be nephrotoxic at very high doses in some animal models, so dose reduction of these two drugs may be indicated in dogs and cats with renal failure.

Most fluoroquinolones are renally cleared. Given the risk of retinal toxicity with enrofloxacin in cats, the dosage should be routinely adjusted in cats with renal insufficiency. Although the optimal method is not established, consider extending the dosing interval, which will still preserve peak plasma concentrations for this concentration-dependent antibiotic class. However, less retinotoxic fluoroquinolones, such as pradofloxacin, marbofloxacin, or orbifloxacin, appear to be much safer choices in cats with renal insufficiency.

Aminoglycosides are dose-dependent nephrotoxins. Aminoglycosides should be avoided whenever possible in azotemic patients, and other drugs with a good Gram negative spectrum should be chosen (e.g. marbofloxacin or orbifloxacin, ticarcillin, or cefotetan), with dosage adjustment. When aminoglycosides are necessary, always rehydrate first, and use concurrent fluid therapy (IV or SC). Consider the use of amikacin (15 mg/kg SC q. 24h), which is possibly less nephrotoxic than gentamicin in cats (Christenson 1977). Monitor for tubular damage by examining daily fresh urine sediments for granular casts. Do not use aminoglycosides in patients with urinary obstruction, and do not use furosemide or NSAID’s concurrently. Finally, limit aminoglycoside therapy to 5 days or less whenever possible.

Although oxytetracyclines can cause nephrotoxicity (reported in dogs), doxycycline does not carry the same risk. However, all tetracyclines can increase blood urea nitrogen (BUN), independent of any renal damage, due to protein catabolism. This increase in BUN is reversible and is not an indication to stop the antibiotic. Outdated tetracyclines should never be administered to patients, as the breakdown products are nephrotoxic, leading to proximal tubular damage.

Chloramphenicol is sometimes indicated for infections that are resistant to more commonly used antibiotics. In cats, 25% or more of chloramphenicol is excreted unchanged in the urine; therefore, its use should be avoided in cats with renal insufficiency, or at minimum, a CBC should be monitored weekly for dose-dependent leukopenia. Potentiated sulfonamides should also be used with caution in azotemic patients, due to decreased renal clearance and decreased protein binding. If they are used in renal failure, it is important to reduce the dosage, especially for sulfadiazine (found in Tribriessen), which is the least soluble sulfonamide, especially in acid urine. In dehydrated human patients, sulfadiazine can precipitate as drug crystals in the renal tubules and lead to hematuria and even tubular obstruction. When using sulfonamides, always rehydrate first, dose accurately, and avoid concurrent use of urinary acidifiers.

Furosemide must be dosed conservatively in azotemic dogs and cats (and only with good rationale, i.e. fulminant congestive heart failure). Patients treated with furosemide should be monitored closely for dehydration, hypokalemia, and worsened azotemia (skin turgor, body weight, PCV/TP, potassium, BUN, and creatinine at each recheck).
H₂ blockers such as cimetidine, ranitidine, and famotidine are cleared by the kidneys, and lead to CNS disturbances (mania, confusion) in elderly humans with decreased GFR. Therefore, the dosage of these drugs should probably be decreased if they are used in dogs and cats with renal failure. Metoclopramide is also renally cleared. Standard continuous rate infusion (CRI) dosages (1-2 mg/kg/day) can cause tremor and ataxia in azotemic patients, and lower doses (e.g. 0.5 mg/kg/day as a CRI) appear to be better tolerated.

Mirtazapine is an effective appetite stimulant in cats, and has also been shown to decrease vomiting in cats with chronic kidney disease (Quimby 2011). However, mirtazapine shows modestly delayed clearance in cats with renal failure (Quimby 2011). The suggested dosing is 1.88 mg every 48 hours in cats with azotemia; further dose reductions are indicated if excessive sedation or hypotension is noted.

Benazepril is preferred over enalapril in overtly azotemic dogs and cats, since benazepril does not depend solely on the kidneys for elimination, and does not require dose adjustment in mildly to moderately azotemic animals. However, any ACE inhibitor can adversely affect GFR if systemic hypotension is produced. It is important to monitor blood pressure, BUN, creatinine, and electrolytes in all patients on ACE inhibitors (initially after one week, then every one to 3 months depending on clinical status).

The selective β-1 blocker atenolol is also cleared by the kidneys. The atenolol dosage is reduced in humans with moderate to severe renal insufficiency. Consider similar dosage adjustments in azotemic dogs or cats, with monitoring of heart rate and blood pressure.

NSAID’s can have adverse effects on GFR, and also show decreased renal clearance and decreased protein binding in renal failure. If patients with renal failure require analgesia, buprenorphine or tramadol are probably better choices. If an anti-inflammatory effect is needed, use conservative NSAID dosages, and monitor carefully for dehydration, inappetence, and increases in BUN and creatinine. Coxibs have the same potential adverse renal effects as do non-selective NSAIDs (COX-2 is important for renal blood flow), and are not safer in renal insufficiency. Other options for arthritis management in renal failure include diets supplemented with omega-3 fatty acids, physical therapy, and acupuncture.

**Key points**
- Dose adjust renally cleared drugs with narrow safety margins in patients with CKD.
- Use extrapolated human guidelines for dose adjustment until better veterinary data are available.
- Find substitutes for drugs with adverse effects on GFR (NSAIDs, diuretics, aminoglycosides)

**Table 1: Empirical recommendations for drug dosage adjustment in renal failure**
(based on human studies and reviews (Munar 2007; Goodman and Gilman’s textbook), a few veterinary studies, and adapted from expert opinion.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard dosage</th>
<th>Method for adjustment</th>
<th>IRIS Stage 2 renal disease (cr 1.6-2.8 mg/dl in cats)</th>
<th>IRIS Stage 3 renal disease (cr 2.9-5.0 mg/dl in cats)</th>
<th>IRIS Stage 4 renal disease (creatinine &gt; 5.0 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>15 mg/kg q. 24h</td>
<td>Interval</td>
<td>q. 24-48h</td>
<td>q. 48h</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Avoid if possible</td>
<td>*Adjust interval for trough concs. &lt; 2 ug/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>1 mg/kg IV three times weekly</td>
<td>Use liposomal formulation only</td>
<td>Use liposomal formulation only</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.25-10 mg/kg q. 12h</td>
<td>Dose/Interval</td>
<td>0.19 mg/kg q. 12-24 h</td>
<td>0.125 mg/kg q. 12-24 h</td>
<td>0.06 mg/kg q. 24h</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>5-10 mg/kg q. 24h</td>
<td>-</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Benazepril</td>
<td>0.5 mg/kg q. 12h</td>
<td>Dose</td>
<td>No adjustment</td>
<td>0.25 mg/kg q. 12h</td>
<td>0.125 mg/kg q. 12h</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>30 mg/kg SC q.12h</td>
<td>Interval</td>
<td>No adjustment</td>
<td>30 mg/kg SC q.24h</td>
<td>30 mg/kg SC q.24-48h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>25 mg/kg PO q.24h</td>
<td>Dose or Interval</td>
<td>No adjustment (dogs; safety unclear in cats)</td>
<td>12-25 mg/kg q. 24h</td>
<td>12 mg/kg q.24h</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>5 mg/kg q. 12h</td>
<td>-</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Enalapril</td>
<td>0.5 mg/kg q. 12h</td>
<td>Dose</td>
<td>0.375-0.5 mg/kg q. 12h</td>
<td>0.25-0.375 mg/kg q. 12h</td>
<td>0.25 mg/kg q. 24h</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>5 mg/kg q. 24h</td>
<td>Interval</td>
<td>5 mg/kg q. 24-48 h</td>
<td>5 mg/kg q. 48h (not recommended in cats)</td>
<td>5 mg/kg q. 48-72h (not recommended in cats)</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose/Interval</td>
<td>Dose/Interval</td>
<td>Interval</td>
<td>Dose/Interval</td>
<td>Dose/Interval</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Famotidine</td>
<td>1 mg/kg q. 12h</td>
<td>No adjustment</td>
<td>1 mg/kg q. 24 h</td>
<td>0.5 mg/kg q. 24 h</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>5 mg/kg q. 12h</td>
<td>5 mg/kg q. 12-24h</td>
<td>5 mg/kg q. 24-48 h</td>
<td>5 mg/kg q. 48-72 h</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>6-8 mg/kg SC or IV q. 24h</td>
<td>q. 24-48h *Avoid if possible *Adjust interval for trough concs. &lt; 2 ug/ml</td>
<td>q. 48h *Avoid if possible *Adjust interval for trough concs. &lt; 2 ug/ml</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>10 mg/kg po q. 12h</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td></td>
</tr>
<tr>
<td>Maropitant</td>
<td>1 mg/kg SC q. 24h</td>
<td>Negligible renal clearance (Benchaoui 2007)</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>8 mg/kg SC q. 12h</td>
<td>Dose</td>
<td>4-8 mg/kg q. 12h</td>
<td>4 mg/kg q. 24h</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>1-2 mg/kg/day CRI</td>
<td>1.0 mg/kg/day CRI</td>
<td>0.5 mg/kg/day CRI; monitor for tremors</td>
<td>0.25 mg/kg/day CRI; monitor for tremors</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>7.5-15 mg/kg q. 12h</td>
<td>Dose</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1.88 mg per cat q 24h (Quimby 2011)</td>
<td>Interval</td>
<td>1.88 mg per 24-48h</td>
<td>1.88 mg every 48h (Quimby 2011)</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.1-0.2 mg/kg q. 6-12h</td>
<td>Dose</td>
<td>No adjustment</td>
<td>0.05-0.1 mg/kg q.6-12h</td>
<td></td>
</tr>
<tr>
<td>Potentiated sulfonamides</td>
<td>15 mg/kg po q.12h</td>
<td>Interval</td>
<td>q. 12h</td>
<td>q. 12-24h</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.1-0.2 mg/kg q.8h</td>
<td>Dose</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1.0 mg/kg q. 12h</td>
<td>Dose/Interval</td>
<td>0.5-1.0 mg/kg q.24h</td>
<td>0.25 mg/kg q.24h</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>1-4 mg/kg q.8-12h</td>
<td>Dose/Interval</td>
<td>0.5-2 mg/kg q. 12h</td>
<td>0.5-1 mg/kg q. 12h</td>
<td>0.5-1 mg/kg q. 24h</td>
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</tbody>
</table>
Empirical Antibiotic Choices
Lauren Trepanier, DVM, PhD, DACVIM, DACVCP
University of Wisconsin
Madison, WI

This session will cover practical indications for empirical antibiotics, what to choose for specific clinical presentations, when cultures are strongly recommended, and common errors in over-prescribing antibiotics in dogs and cats. There are several very real drawbacks to the overuse of antimicrobials: additional cost of the visit without contributing to a diagnosis; vomiting, diarrhea, or decreased appetite that can obscure the underlying problem; adverse reactions and drug interactions; and importantly, the selection of resistant bacteria, both in your patient, in your hospital, and globally.

The first step before empirical antibiotics
The first step before empirical antimicrobial therapy is to first critically ask whether there is good evidence of a bacterial infection. Cases such as superficial pyoderma, tooth root abscess, traumatic wounds, cat bite abscess, or uncomplicated cystitis (in a dog) are straightforward indications for empirical antibiotics. However, antimicrobials are prescribed too often for vague clinical signs, without a presumptive diagnosis.

Fever alone is an inadequate criterion for prescribing an empirical antimicrobial, since viral fevers are common in cats and immune-mediated fevers are common in dogs. If fever is due to a systemic bacterial infection, such as pneumonia, bacterial cholangitis, pyelonephritis, pyothorax, or peritonitis, you should be able to detect clinical signs to localize the source, such as increased respiratory rate or abdominal pain. Fever from a systemic bacterial infection is serious and requires additional diagnostics to choose the right antibiotic.

If you can localize the likely source of infection based on physical exam or additional diagnostics, then you can narrow down the likely organism(s) based on what is typically isolated from infections at that site (Tables 1 and 2).

| Table 1: Common isolates from bacterial infections in dogs |
|----------------------------------|-----------------|----------------------------------|
| **Indication** | **Most common organisms** | **Empirical antimicrobial** |
| Bacterial cystitis | E. coli (51%) | Amoxicillin/clavulanate (female) Fluoroquinolone (male; assume prostatic involvement) |
| Bite wound (from another dog) | Pasteurella, Strep (Meyers 2008) | Amoxicillin/clavulanate or cephalexin |
| Endocarditis | Gram positives (51%; esp. Strep canis); Gram negatives (22%); Bartonella (20%) | Cephalexin plus fluoroquinolone, awaiting cultures and Bartonella testing. |
| Hepatobiliary infection | 72% negative cultures (bile) E. coli, gram positives, anaerobes | Amoxicillin/clavulanate plus fluoroquinolone |
| Joint sepsis | Staph. sp. | Cephalexin |
| Osteomyelitis | Staph. and Strep | Cephalexin |
| Pneumonia | Young dogs: Bordetella, other gram negatives | Doxycycline (apparently low risk of enamel discoloration) |
| Prostatitis | E. coli | Fluoroquinolone |
| Pyometra | E. coli | Fluoroquinolone |
| Superficial pyoderma | Staph pseudintermedius | Cephalexin |

| Table 2: Common isolates from bacterial infections in cats |
|----------------------------------|-----------------|----------------------------------|
| **Indication** | **Most common organisms** | **Empirical antimicrobial** |
| Cat bite abscess | Pasteurella, anaerobes | Amoxicillin (95% efficacy) |
| Documented bacterial cystitis | E. coli, Staph, Strep, and Enterococcus (Dorsch 2016) | Amoxicillin/clavulanate or trimethoprim/sulfamethoxazole |
| Hepatobiliary | 64% negative cultures (bile) Mixed gram positives, negatives, and anaerobes | Amoxicillin/clavulanate plus fluoroquinolone |
| Otitis | Staph, Pasteurella (Harharan 2006) | Amoxicillin/clavulanate |
| Pyelonephritis | E.coli, Enterococcus | Base on urine sediment |
| Pyothorax | Anaerobes, Pasteurella | Penicillin (awaiting culture) |
| Sepsis | Gram negative enterics, Staph, Strep, anaerobes (Greiner 2007) | Ampicillin/sulbactam plus fluoroquinolone (awaiting culture) |

Based on the likely organism(s), choose the narrowest spectrum drug for the suspected organism. For example, choose amoxicillin, instead of amoxicillin-clavulanate, for a cat bite abscess, and doxycycline, rather than a fluoroquinolone, for suspected...
When making antibiotic choices, consider tissue penetration. In male dogs with urinary tract infections, antimicrobials with good prostatic penetration, such as fluoroquinolones, doxycycline, chloramphenicol, or potentiated sulfonamides, should be chosen. For bronchitis without pneumonia, drugs that achieve high concentrations in bronchial secretions should be prescribed, to include fluoroquinolones, doxycycline, azithromycin, or potentiated sulfonamides. Beta lactams and aminoglycosides, which are relatively polar, have poor penetration into protected sites such as the prostate, eye, testes, brain, or bronchial secretions.

Finally, treat for the shortest effective period possible. There is good evidence to support the use of shorter courses of antimicrobials in human patients, with equivalent efficacy compared to longer regimens. Acute sinusitis, pneumonia, and uncomplicated urinary tract infections are treated effectively with 3 to 7-day courses of antibiotics in humans. Pediatric bacterial otitis can be treated with a single dose of azithromycin, which is as effective as 7 days of dosing. Antibiotics for community-acquired pneumonia are continued for only 2-3 days beyond resolution of fever. In veterinary medicine, there is little evidence to support the longer antibiotic courses that are recommended in textbooks. Consider using these shorter antibiotic regimens, with follow-up evaluation one week after discontinuation. Shorter treatment regimens are less expensive for clients (allowing more resources for diagnostics and follow-up), are associated with better compliance, and lead to less bacterial resistance.

When to pull the trigger on cultures
Cultures are important for any second line antimicrobial treatment, to include lack of response to empirical treatment, relapse after treatment discontinuation, or waxing and waning signs. Avoid antibiotic roulette in these cases! With recurrent urinary tract infections, serial cultures can be helpful, as repeated culture of the same organism suggests inadequate clearance (immunosuppression, poor compliance, uroliths, or prostatitis with inadequate drug penetration), while different organisms suggest ascending infections (urethral incompetence, vulvar fold pyoderma, poor perineal hygiene, or ectopic ureters).

Table 3: Typically effective antimicrobials for different bacterial infections

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
<th>Betalactamase-producing gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Staph., Strep., Enterococcus)</td>
<td>(Staph, Strep., Enterococcus)</td>
</tr>
<tr>
<td><strong>Commonly effective</strong></td>
<td><strong>Commonly effective</strong></td>
</tr>
<tr>
<td>Penicillin</td>
<td>Amoxicillin/clavulanate</td>
</tr>
<tr>
<td>Amoxicillin, ampicillin</td>
<td>Cephalexin</td>
</tr>
<tr>
<td>Clindamycin (except Enterococcus)</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Cephalexin (except Enterococcus)</td>
<td>Fluoroquinolones (Staph &gt; Strep)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Potentiated sulfonamides</td>
</tr>
<tr>
<td><strong>Typically ineffective</strong></td>
<td><strong>Typically ineffective</strong></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Penicillin, amoxicillin, ampicillin</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram negative aerobes</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E. coli, Klebsiella, Proteus)</td>
<td><strong>(Bacteroides, Clostridium, oral flora)</strong></td>
</tr>
<tr>
<td><strong>Commonly effective</strong></td>
<td><strong>Commonly effective</strong></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Amoxicillin/clavulanate</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate (urine)</td>
<td>Cephalexin</td>
</tr>
<tr>
<td>Cephalexin (urine)</td>
<td>Clindamycin, azithromycin</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Potentiated sulfonamides</td>
<td><strong>Typically ineffective</strong></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone (except pradofloxacin for oral flora)</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Cephalexin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaerobes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typically ineffective</strong></td>
<td></td>
</tr>
<tr>
<td>Clindamycin, azithromycin</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
</tr>
</tbody>
</table>

When to pull the trigger on cultures
Cultures are important for any second line antimicrobial treatment, to include lack of response to empirical treatment, relapse after treatment discontinuation, or waxing and waning signs. Avoid antibiotic roulette in these cases! With recurrent urinary tract infections, serial cultures can be helpful, as repeated culture of the same organism suggests inadequate clearance (immunosuppression, poor compliance, uroliths, or prostatitis with inadequate drug penetration), while different organisms suggest ascending infections (urethral incompetence, vulvar fold pyoderma, poor perineal hygiene, or ectopic ureters).
Cultures are also important for serious or life-threatening infections, to include pyothorax, endocarditis, osteomyelitis, joint infection, pyelonephritis with acute renal failure, or sepsis. Cultures are also recommended for suspected hospital-acquired infections (those developing > 72 hours after admission), since nosocomial bacteria may have multi-drug resistance patterns.

**Effective culture techniques**

Ideally, urine culture should be set up within 15 to 30 minutes of collection, but this is often impractical. Alternatively, a sterile syringe containing urine can be capped and refrigerated immediately, for up to 12 hours prior to culture. While some fastidious bacteria may not survive storage > one hour, this approach is adequate in most situations, and allows quantitative cultures (CFU/ml).

For urine and other fluids, submitting whole fluid instead of a swab is preferable to avoid false negative results. Body fluids for culture should be placed in a sterile red top tube or transport media; do not use heparin or EDTA tubes, which can inhibit bacterial growth in vitro. Our microbiologist recommends the transport media in A.C.T.II agar tubes (Remel), to which you can add fluid (or swabs if necessary); organisms are stable for 24 hours for both aerobic and anaerobic culture set up. Anaerobic cultures should be included for bile, pleural or abdominal fluid, and pus. Mycoplasma cultures should be included in tracheal wash samples. For very small fluid volumes where a swab is necessary, our microbiologist recommends BBL CultureSwab Plus (Amies gel formulation included for bile, urines. Bacteria with pyuria in a urine sediment, along with clinical signs, provides a strong indication for antimicrobials if a source cannot be identified or owners are not cooperative.

Once you get a culture result, “step down” to a narrower spectrum antibiotic if possible, or discontinue if the culture is negative.

**Clinical presentations where antibiotics are over-used**

**Leukocytosis.** Leukocytosis alone can result from stress, inflammation, or glucocorticoids, as well as from an infection. If a left shift and toxic change are also present, then a source of infection (bacterial, fungal, or otherwise) or significant inflammation should be pursued. Severe neutropenia, however, is an established indication for empirical antimicrobials in humans. Meta-analyses of studies in humans suggest that the benefit of antibacterials in neutropenic patients (< 1000/ul) even prior to fever, outweighs the negative effects of selecting for bacterial resistance. A beta lactam and fluoroquinolone combination is recommended in humans, which provides coverage against gut flora to include anaerobes and Enterococcus (beta lactam) and gram negatives (fluoroquinolone).

**Cats with lower urinary tract signs.** There is a < 5% incidence of positive urine cultures in cats with lower urinary tract disease overall. Clients’ money is better spent on a urinalysis and bladder imaging for stones. Cats at higher risk for symptomatic bacterial urinary tract infections are those with diabetes mellitus, perineal urethrostomies, chronic renal failure, or in older cats with dilute urine. Bacteria with pyuria in a urine sediment, along with clinical signs, provides a strong indication for antimicrobials in a dog or cat, although bacteriuria can be overdiagnosed. If cocci are frequently diagnosed in your in-house urine sediments, be suspicious; stain precipitates can mimic cocci.

As for cats with upper respiratory signs, there are no published placebo-controlled studies to support antibiotic use. This is astonishing given the resources devoted to treating these cats with antibiotics in shelters and in primary care practices. Herpes virus is the most common pathogen isolated from cats with acute upper respiratory disease. Although Mycoplasma is commonly isolated from pharyngeal swabs in these cats, it is unclear what contribution Mycoplasma has to active clinical signs. When Mycoplasma or Chlamydia infection is documented or suspected, doxycycline, not amoxicillin, is the drug of choice. Doxycycline suspension is preferable to capsules, to decrease the risk of esophagitis.

**Acute diarrheas** in dogs and cats are usually not caused by pathogenic bacteria. For example, the prevalence of Salmonellosis (2%), Campylobacter (5%), and Clostridium difficile toxin (10%) is low in dogs with acute diarrhea. Empirical antimicrobials such as amoxicillin or fluoroquinolones are not indicated for mild to moderate acute diarrheas without evidence of neutropenia or bacterial translocation. A more conservative approach in these cases includes a short-term diet change, probiotics, fiber, or bismuth/subsalicylate (in dogs).

Finally, **pancreatitis** is usually sterile in dogs and cats. Antimicrobials are not indicated unless peritonitis, pancreatic abscess, or loss of intestinal mucosal integrity (bloody diarrhea with mucosal sloughing) develops, and these complications are uncommon. In humans, antimicrobials in necrotizing pancreatitis do not affect clinical outcomes, including mortality.

**Key points**

- Fever alone is not an adequate justification for empirical antimicrobials. A fever from a systemic bacterial infection is serious and needs a diagnosis.
- Once you have localized an infection source, choose an antibiotic with the narrowest possible spectrum, and make sure your choice will have adequate tissue penetration if a “protected site” is involved.
- Consider shorter courses of antibiotic treatment, as are supported by human meta-analyses.
- Additional work-up or cultures are indicated if there is no response to a first line empirical regimen.
- Change the prescribing culture of your clinic regarding the use of antibiotics where there is no evidence of a benefit.
Vomiting is a common problem in veterinary patients, and can lead to dehydration, hypokalemia, reflux esophagitis, and weight loss. There are several clinically effective veterinary anti-emetic drugs. Choosing among these options depends on the likely cause of the vomiting and the mechanisms of action and side effects of each drug.

The first step before considering an antiemetic in a dog or cat is a reasonable work-up to rule out serious underlying disease. Every acutely vomiting animal that is brought to a veterinary clinic deserves two view abdominal radiographs to rule out obstruction. Using antiemetics empirically in animals with unrecognized GI obstruction can delay the diagnosis and worsen the prognosis. If vomiting is severe or persistent, a CBC, biochemical panel, and pancreatic lipase test are indicated.

**Anti-Emetics**

**Maropitant (Cerenia™)**

Neurokinin-1 receptor antagonist.

- Inhibits substance P binding to NK-1 receptors in emetic center, chemoreceptor trigger zone (CRTZ), and enteric plexus of gut.
- Very effective antiemetic.
- May not prevent nausea after some stimuli (for example, after doxorubicin, hydromorphone, and morphine; Rau 2010, Claude 2014, Koh 2014)

**Indications**

- Vomiting due to uremia, gastroenteritis, or pancreatitis
- Prevention of vomiting due to motion sickness in dogs and cats
- Prevention of vomiting prior to cisplatin, doxorubicin, morphine, or hydromorphone
- Potent enough to prevent xylazine-induced emesis in cats (Hickman, 2008).
- Has anesthetic-sparing effect during spays in dogs (Boscan, 2011)
  - 1 mg/kg IV, followed by 30 ug/kg/hr CRI
  - Comparable or better than morphine as a pre-medicant in the control of post-operative pain at extubation during spays in dogs (!) (Mansfield 2015)

**Dosing**

- Dogs: 1 mg/kg IV or SC; 2 mg/kg PO
  - 8 weeks of age and older
  - Dosing limited to 5 days in a row for puppies 2 to 7 months old
  - Longer treatment now label-approved for dogs older than 7 months
- Dogs for motion sickness: 8 mg/kg PO once daily for maximum of 2 days
- Cats: 1 mg/kg IV, SC, or PO once daily
  - 16 weeks of age and older

**Drug interactions/Contraindications/Side effects**

- Well tolerated and effective treatment for various causes of vomiting.
- Pain on injection can be decreased by refrigerating vial (Narishetty 2009)
- Maropitant may not alleviate nausea without actual vomiting. Therefore, consider other approaches for inappetent patients that are not vomiting.

**Metoclopramide**

Increases release of acetylcholine in GI smooth muscle, leading to increased gastric emptying and net "downstream" intestinal motility, without ileus.

- Antagonizes the actions of dopamine on the chemoreceptor trigger zone in dogs (central antiemetic action in dogs).
- As effective as maropitant in blocking apomorphine-induced emesis in dogs (Selacek 2008)
- Traditionally thought to increase tone in the lower esophageal sphincter (reducing reflux), but actually has little effect on LES pressure (at least after a single dose). Cisapride is much more effective (Kempf 2014)

**Metoclopramide in cats:**

- Metoclopramide does not appear to be effective as a central D2 antagonist antiemetic in cats. Emesis in cats appears to be mediated though receptors other than D2, particularly alpha-2 receptors.
  - This is consistent with the finding that cats are also very insensitive to vomiting induced by apomorphine (a dopaminergic agonist), but are sensitive to emesis from xylazine (an alpha-2 agonist).
Further, metoclopramide can decrease xylazine-induced vomiting in cats (Kolahian 2010)

**Metoclopramide does appear clinically to decrease vomiting in cats,** either due to its prokinetic effects or through indirect effects not involving D2 receptors.

**Indications**
- Delayed gastric emptying
- Nausea associated with ileus
- Central antiemetic in dogs, especially when ileus is also suspected (e.g. renal failure, infiltrative GI disease, pancreatitis)
- Prevention of GI upset during cyclosporine treatment (anecdotal success)
- Prevention of nausea due to overdistended stomach during esophagostomy tube feedings

**Dosing**
- 0.2-0.4 mg/kg q. 6 hours SC or PO.
- May be most effective when given by continuous rate IV infusion (1-2 mg/kg/day).
- Cover infusion set with foil (light sensitive)
- Reduce the dosage in renal failure.

**Drug interactions/Contraindications**
- Rule out intestinal obstruction first
- Enhances acetaminophen and ethanol absorption in humans (therefore, should be avoided for treatment of vomiting due to intoxications; may enhance delivery of toxin to small intestine)

**Side effects**
- Tremor, hyperactivity, and anxiety after high doses (Parkinson's-like; stop the drug and treat with diazepam)
- Decrease dosage in renal failure (decreased metoclopramide clearance may lead to tremor).

**Ondansetron (Zofran®)**
Antiemetic that antagonizes serotonin (5-HT3) receptors in both the CNS and GI tract. Particularly effective for vomiting due to peripheral stimulation (Sedlacek 2008)

**Indications**
- Refractory vomiting in patients with diagnosed visceral disease (e.g. pancreatitis, GI neoplasia, hepatic disease).
- Prophylaxis of vomiting associated with chemotherapy.
- Prophylaxis of vomiting from dexmedetomidine in cats (0.22 mg/kg of ondansetron in same syringe as dexmedetomidine, given IM) (Santos 2011)
- May be more effective for nausea (without vomiting) than maropitant (Kretzing 2011)

**Formulations/Dose/Route**
- 2 mg/ml injectable; 4 mg tablet; oral solution 4 mg per 5ml.
- Best estimated dosage: 1.0 mg/kg SC q. 12 hours. (Quimby 2014)
  - Marked variability in pharmacokinetics in dogs (Baek 2015)
  - Prior recommended dosage of 0.5 mg/kg PO q 12h may be sub-therapeutic in cats (Quimby 2014)
  - SC route in cats may provide longer duration of action than PO or IV (Quimby 2014)

**Drug interactions/Contraindications/Side effects**
- Headache or dizziness in humans
- Increases in ALT reported in humans.
- Ondansetron is a p-glycoprotein substrate in humans but has not been evaluated in dogs—potential for adverse effects in Collies and other dogs with MDR1 mutations [http://www.vetmed.wsu.edu/depts-VCPL/drugs.aspx](http://www.vetmed.wsu.edu/depts-VCPL/drugs.aspx)

**Dolasetron (Anzemet)**
Another 5-HT3 receptor antagonist in both the CNS and GI tract.
- Less frequent dosing than ondansetron in humans.

**Indications**
- As for ondansetron
- Also available as injectable
- May allow once daily dosing (?)

**Formulations/Dose/Route**
- 0.6 – 1.0 mg/kg IV once daily(?)
  - Elimination half-life of active metabolite is only 4 hours in dogs (Dow 1996).
- Oral tablets (50 and 100 mg) too large for use without reformulation.

**Drug interactions/Contraindications/Side effects**
- Headache or dizziness in humans
- Associated with prolongation of QT interval in humans (hypokalemia is a risk factor).
Prochlorperazine (Compazine®), Chlorpromazine (Thorazine®)

Central antiemetics with multiple mechanisms of action: dopamine antagonist, H1 antagonist, alpha-adrenergic antagonist, and anticholinergic. Inhibit vomiting at chemoreceptor trigger zone anddirectly at emetic center (therefore, potent antiemetic). Less effective for peripheral triggers of vomiting (Sedlacek 2008)

**Indications**
- Not recommended for empirical outpatient use because of potential for hypotension and sedation (undesirable in a sick patient).
- Prochlorperazine or chlorpromazine may be useful for refractory vomiting in patients with diagnosed underlying disease and a central cause for vomiting (e.g. chemotherapy, uremia), for which IV fluid support can be provided.
- Additional effect of sedation may be beneficial in anxious dogs or fractious cats.
- Inexpensive
- Note: acepromazine (0.05 mg/kg IM) is also effective as an adjunct treatment to prevent nausea in dogs, for example prior to morphine pre-medication (Koh 2014)

**Dosage**
- 0.1-0.5 mg/kg SC q. 8 hours.

**Drug interactions/Contraindications/Side effects**
- Can cause hypotension (alpha-blockade) or tremors (dopaminergic antagonism).
- Can cause sedation and potentiate effects of sedatives, anesthetics, and organophosphates.
- Do not use this drug in dehydrated patients or in those without a diagnosis.
- Do not use formulations that contain anticholinergics such as isopropamide.
- Do not use in combination with metoclopramide (additive antidopaminergic effects).

Mirtazapine

Antidepressant with appetite-stimulating and anti-emetic properties. Complex mechanisms of action! Central antagonist at presynaptic alpha-adrenergic receptors. Increases central serotonergic (5-HT) and noradrenergic activity, but inhibits other serotonin receptors (5-HT2 and 5-HT3) and histamine (H1) receptors. Weaker inhibition of alpha-1 and muscarinic receptors.

- Effective as an appetite stimulant
- Anti-emetic and anti-nausea effects in humans (likely via 5-HT3 blockade)
- Increases gastric emptying in dogs (Yin 2014)

**Indications**
- Decreased appetite or anorexia unresponsive to treatment of the underlying disease
  - Effective in cats with CKD (Quimby 2013) and in dogs (anecdotal)
- Reduced vomiting in cats with CKD (Quimby 2013), along with increased appetite and weight gain

**Formulations/Dosage: 15 mg tablets**
- 1.88 to 3.75 mg (1/8 to 1/4 tab) every 24 to 48 hours in cats with normal renal function - start with the lower dose
- 1.88 mg (1/8 tab) every 48 hours in cats with CKD (Quimby 2011)

**Drug interactions/Contraindications**
- Contraindicated with monoamine oxidase inhibitors, tricyclic antidepressants, and serotonin reuptake inhibitors because of risk of serotonin syndrome in humans (tremor, rigidity, myoclonus)
  - Do not combine mirtazapine with drugs that directly or indirectly increase serotonergic activity, to include tramadol, buspirone, amitriptyline, clomipramine, amitraz (in Certifex®), dextromethorphan (in Robitussin), and even the antibiotic linezolid
- Because of many drug interactions, use the Interactions Checker on [www.drugs.com](http://www.drugs.com) prior to adding mirtazapine to other medications
- Contraindicated in patients with glaucoma

**Side effects**
- Sedation, mydriasis common
- Idiosyncratic neutropenia in humans
- Overdose leads to vocalization, agitation, ataxia, tremors, hypersalivation (Ferguson 2015)
  - Do not dispense full 15 mg tablets to owners

**Adjunctive drugs for vomiting patients**

Famotidine (Pepcid®)

Famotidine is not an antiemetic, and is overused in vomiting animals, since hyperacidity is probably a relatively uncommon cause of vomiting in dogs and cats.
**Indications**

- Persistent vomiting where secondary reflux and esophagitis are a concern
- Vomiting due to hyperacidity (mast cell disease).
- No direct antiemetic effects.
- Note: gastric ulceration is actually **uncommon** in dogs and especially cats with renal disease; gastric fibrosis and mineralization are seen instead (Peters 2005; McLeland 2014); therefore, antacids are of questionable benefit in CKD, despite widespread use

**Omeprazole (Prilosec®; Gastrogard®)**

H+/K+ ATPase pump inhibitor. Blocks the final step in gastric acid secretion. **Not an antiemetic!**

**Indications**

- Clinically proven gastroduodenal ulceration
- Erosive esophagitis
- NSAID overdose
- Portal hypertension
- Prevention of NSAID-induced ulcers (humans)
- (Gastrinomas - uncommon)
- 1.5-2.6 mg/kg once daily (Tolbert 2011)

**Side effects**

- Chronic administration of omeprazole is associated with gastric polyps in humans.
- Safety for long-term administration (months to years) not established in dogs/cats.
- Omeprazole does lead to gastric mucosal hypertrophy in dogs at high doses given chronically.
- Can increase risk of bacterial pneumonia in patients that aspirate

**Sucralfate (Carafate®)**

Disaccharide complexed to aluminum hydroxide; at acid pH in stomach, acquires negative charge and adheres to positively charged matrix elements exposed in ulcer beds.

- Also binds pepsin and bile salts (which can otherwise contribute to ulcer formation)
- May enhance production by gastric mucosa of cytoprotective prostaglandins (increased blood flow and cell turnover lead to faster ulcer healing).

**Indications**

- Gastric ulceration
- Esophagitis
  - Note: sucralfate has been shown to prevent acid-induced esophagitis experimentally in cats; may be useful prior to surgery when reflux is anticipated (recent meal; megaesophagus; esophageal or gastric foreign body).
- Gastric or duodenal neoplasia with ulceration
- Post-endoscopic retrieval of gastric or esophageal foreign bodies
- (Disappointing topical efficacy for radiation mucositis in humans)
- Not indicated for non-specific vomiting, and can lead to drug interactions!

**Empirical dosage**

- 1/4 to 1 gram PO q. 6 to 8 hours.
- May be crushed and suspended in water; stable for 14 days in the refrigerator as a 200 mg/ml suspension.

**Drug interactions**

- Very important! Sucralfate binds other drugs and impairs their absorption (tetracycline, digoxin, some fluoroquinolones)
- Important to give most other drugs at least 2 hours before sucralfate (not vice versa). This is difficult for many clients to achieve.
- Exception: sucralfate can be given concomitantly with H₂ blockers without affecting their overall absorption (Albin, 1986; Mullersman, 1986); therefore, no separation of dosing times is necessary.

**Cisapride**

Prokinetic drug in the same family as metoclopramide; increases release of acetylcholine from myenteric plexus (via effects on serotonin receptors) in smooth muscle of esophagus, stomach, small intestine, and colon; increases lower esophageal sphincter pressure, gastric emptying, small intestinal motility, and colonic motility

- More potent than metoclopramide and no antidopaminergic effects
- Appears to be more effective than metoclopramide at increasing tone in the lower esophageal sphincter (Kempf 2014)

**Indications**

- Constipation, feline megacolon
- Gastroesophageal reflux
- Recurrent bloating due to gastroparesis
- Gastroparesis associated with inflammatory bowel disease

**Formulations/Dosage**

10 mg tablets. Empirical dose: 0.5 mg/kg PO q. 8 hours (for cats, 2.5 mg q. 8 hours to start); use with lactulose if megacolon present; food enhances absorption in humans

**Drug interactions/Contraindications**

- Rule out GI or pelvic obstruction
  - Contraindicated for mechanical obstructions or for colonic strictures.
- Caution with ketoconazole or itraconazole: these antifungals inhibit cisapride metabolism in humans and can lead to cardiac arrhythmias.
- No direct efficacy as an antiemetic.

**Side effects**

- Diarrhea, cramping in some humans
- Unlike metoclopramide, no CNS side effects
- In cats, cisapride can also lead to QT prolongation, but at dosages 20 times higher than those used clinically.
  - These same ECG changes (QT prolongation) have been reported for dolasetron. Until more is known, the combination of cisapride and dolasetron may best be avoided.
Therapeutic Decisions in Internal Medicine: 
Case Discussions
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Playing catch up 
An 8 yo Fs Yorkie presented for vomiting, inappetence, and small bowel diarrhea progressive over 3 weeks. She had developed abdominal distension over several days. On presentation, she weighed 2 kg with a BCS of 3/9, and was tachypneic with shallow breathing. There was no murmur but heart sounds were difficult to auscult ventrally, and there was palpable abdominal fluid. Limbs were normal on palpation with no peripheral edema. Blood work showed severe panhypoproteinemia (albumin 0.9 g/dl, globulin 1.2 g/dl), hypocalcemia (4.7 mg/dl) and hypocholesterolemia (66 mg/dl). Chest radiographs revealed a normal cardiac silhouette on VD view, with pleural effusion that was a transudate on cytology. Abdominal ultrasound showed marked free fluid (also a transudate) with no evidence of liver nodules or changes in echogenicity, normal mesenteric lymph nodes, and no evidence of intestinal thickening or striations.

Ionized calcium was markedly decreased at 0.82 mmol/L (normal, 1.25-1.45) and serum vitamin D levels were submitted. A GI panel showed low normal serum cobalamin at 302 ng/l (251-908). Thromboelastography was not available, but a serum antithrombin was decreased at 57%.

A presumptive diagnosis of protein-losing enteropathy (lymphangiectasia) of Yorkies was made. The dog was treated in hospital with therapeutic thoracocentesis, Hetastarch CRI, and low dose aspirin (in suspension). Intestinal biopsies were not attempted given the dog’s bicavitary effusion and severe hypoalbuminemia. Oral prednisolone and calcium carbonate (Tums) were started, along with SC cobalamin injections and a low fat diet. Diarrhea resolved over several days and appetite improved.

One week later, the dog re-presented for weakness and tremors. Total calcium was 3.6 mg/dl (!) and ionized calcium had fallen to 0.50 mmol/L. Magnesium was also low at 0.7 mg/dl. Serum vitamin D (25OH D3) levels from initial work-up were returned as low (reference 60-215 nmol/L). The dog was treated with an IV calcium gluconate CRI (in Hetastarch) and oral calcitriol (10 ng/kg q 12h), which should increase both calcium and magnesium absorption. After 4 days in CCU, the dog was still hypocalcemic and hypomagnesemic. Oral malabsorption of medications was a concern, so treatment was switched to SC dexamethasone (at 1/7 of the prednisone dosage) and SC calcitriol (at the same dosage). The dog’s strength returned and she was weaned off IV calcium and discharged after another 3 days (total calcium was still only 5.9 mmol/L). Modified cyclosporine (5 mg/kg Po q 12h) was added to further decrease presumptive intestinal inflammation and lymphatic rupture. Calcium normalized slowly over 2 months, and the dog did well over the following 2 years on tapering dosages of dexamethasone and cyclosporine, with continued calcitriol, Tums, low dose aspirin, and a low fat diet.

Case assessment 
This dog had a classic presentation for lymphangiectasia, and was a predisposed breed (Simmerson 2014). Hypocalcemia based on total calcium is common in animals with hypoalbuminemia, but ionized calcium should also be checked. This is particularly important in severe presentations of PLE/lymphangiectasia, in which vitamin D malabsorption can lead to clinically significant ionized hypocalcemia, to include tremors and seizures (Whitehead 2015). This was further worsened in this dog by starting glucocorticoids without starting concurrent calcitriol supplementation, since glucocorticoids will increase urinary loss of calcium.

In retrospect, we should also have supplemented this dog with IV magnesium sulfate in addition to calcium gluconate during hospitalization. Low magnesium blunts responses to PTH in dogs (Freitag 1979), and likely exacerbated this dog’s hypocalcemia. Recovery would likely have been faster in the hospital with magnesium supplementation.

An important feature of managing PLE/ lymphangiectasia is to test for, or presume, hypercoagulability. Dogs with PLE can lose the anticoagulant protein antithrombin, and can also develop platelet hyperaggregability. (Goodwin 2011) Treatment with low dose aspirin or clopidogrel is indicated, since a common cause of death in these dogs is acute thromboembolism.

A short list 
A 12 yo Fs DSH cat presented for progressive weight loss with a good appetite over the past year, and small bowel (liquid) diarrhea over the past few days. Fecal presentation was negative, and she was treated with a 5-day course of fenbendazole.

Several weeks later, there was no improvement in the diarrhea. Appetite was still good with no vomiting or PU/PD. Physical exam showed a BARH but thin cat (2.76 kg, BCS 3/9), T=100.8, with a normal heart rate (180 bpm on exam), no murmur or gallop, no palpable goiter, “ropy” intestines, and a normal hind limb gait. CBC was normal, with no evidence of anemia, changes in RBC indices, leukocytosis, left shift, or toxic change. Biochemical testing showed a blood glucose of 98 mg/dl, ALT of 313 IU/L, ALP of 59 IU/L (normal), albumin of 2.9 g/dl, and a slightly increased bilirubin at 0.5 mg/dl. UA showed a USG of 1.037 with no glucosuria and an inactive sediment. Serum T4 was normal at 2.6 ug/dl.
Abdominal ultrasound was performed. The muscularis layer of the jejunum was thickened, equal to or greater than the mucosa in width, with one rounded enlarged right colic lymph node seen. Other regional lymph nodes were of normal shape and echogenicity. The gall bladder contained gravitationally dependent hyperechoic material extending into the cystic duct. The common bile duct (5.2 mm) and the pancreatic duct (1.9 mm) were dilated. Peri-pancreatic fat was hyperechoic. A GI panel was submitted, and the cat was started on cobalamin (250 ug SC weekly) and prescribed a hydrolyzed hypoallergenic diet (z/d). The GI panel returned with an increased fPLI of 4.4 ug/L (normal < 3.5), a markedly increased TLI of 294 ug/L (12-82), and low serum cobalamin at < 150 ng/L (290-1499).

The overall clinical picture was consistent with infiltrative small bowel disease unresponsive to hydrolyzed diet, pancreatitis, and partial pancreatic and bile duct obstruction or stasis. One week after cobalamin and diet change, the cat remained BAR and had a small increase in body weight (2.84 kg), but the small bowel diarrhea had not improved and appetite for z/d was subdued. Serum bilirubin was stable at 0.4 mg/dl, and on recheck single organ ultrasound, the bile duct (5.4 mm) and the pancreatic duct (1.9 mm) were dilated but still static.

Exploratory laparotomy was discussed to evaluate the biliary tree and to obtain bile cultures and full thickness duodenal, jejunal and ileal biopsies. The owner, a vet student, could not undertake the cost of the surgery. The pancreatic duct dilation along with high TLI, polyphagia, small bowel diarrhea, and continued weight loss raised the possibility of secondary EPI caused by stricture or obstruction of the pancreatic duct. Before empirical prednisolone was instituted for infiltrative intestinal disease, a trial of pancreazyme (1/8 tsp per meal) was prescribed. Ursodiol (30 mg once daily) was also started to address cholestasis, with careful clinical monitoring and a recheck scheduled in one week. Weekly cobalamin was prescribed for 6 weeks, and the cat was allowed to transition back to her previous diet.

At recheck 8 days later, the cat was bright and stools were becoming less liquid and more formed. She had gained weight to 2.98 kg. Bilirubin had fallen further to 0.2 mg/dl with no evidence of abdominal pain or lethargy, so the ursodiol was refilled. Pancreazyme was continued with instructions to recheck body weight and diarrhea status in another week to confirm a response to (and need for chronic administration of) Pancreazyme. Predisolone was dispensed (5 mg once daily) to begin in one week.

Case assessment

The differential list for weight loss with a good appetite in cats is a short one: diabetes mellitus, hyperthyroidism, or intestinal malabsorption (endoparasites, IBD, or small cell GI lymphoma). Maldigestion (EPI) is another differential, but is relatively rare in cats. In this case, screening diagnostics ruled out diabetes and hyperthyroidism. Abdominal ultrasound, fPLI and even TLI were suggestive of chronic pancreatitis. However, pancreatitis alone could not explain weight loss in the face of a strong appetite. The intestinal thickening (both palpable and on ultrasound) suggested infiltrative small intestinal disease. In particular, a thickened muscularis layer (greater than half the thickness of the mucosa), as found in this cat, has been reported to increase the likelihood of small cell (diffuse T cell) lymphoma in cats (Zwingenberger 2010). However, a follow-up study reported that a thickened muscularis might indicate either IBD or small cell lymphoma. Unfortunately, a long duration of signs (> one year as seen in this cat) cannot be used to rule out GI lymphoma in cats (Evans 2006). Hypoallergenic diet trials are indicated in any adult dog or cat with chronic GI signs for which IBD is a remaining differential. Approximately 50% of cats with chronic enteropathies will respond to a hypoallergenic diet, and responses are seen within 2-3 days (Guilford 2001). Previously recommended 6-to-8-week diet trials do not appear to be necessary.

Low serum cobalamin concentrations have been associated with pancreatitis, IBD, and small cell lymphoma in cats, with very low concentrations common in small cell lymphoma (Simpson 2011). Macrocytosis is present in about 25% of cats with low serum cobalamin, and can be a clue to measure cobalamin levels (Simpson 2011). Treatment with cobalamin alone can lead to weight gain in cats with chronic enteropathies, and may have contributed to initial weight gain in this cat.

The dilated common bile duct in this cat suggested obstruction, but in combination with a stable to falling bilirubin (without evidence of gall bladder rupture on ultrasound) this finding was more consistent with partial obstruction or marked cholestasis. As a choleretic, ursodiol is contraindicated in complete biliary obstruction. In this cat, a trial of ursodiol was prescribed, with careful monitoring, to address sludging material extending into the cystic and bile ducts.

Finally, given that both IBD and small cell lymphoma respond to prednisolone, this drug was indicated in this cat, particularly if biopsies were not going to be obtained. However, we also suspected acquired EPI, and wanted to confirm a response to pancreatic enzymes before adding prednisone, since acquired EPI would dictate long-term treatment with pancreatic enzymes and cobalamin supplementation (Steiner 2012).

I’m crushed

Lexie, a 10 yo Fs Shepherd mix, presented for PU/PD and polyphagia. The dog was drinking her water bowl dry, waking the owners to go outside and urinate overnight, and counter-surfing for food. On physical exam, she was BARH and in adequate body condition (25 kg, BCS 6/9), but with muscle wasting of the hind limbs. Her abdomen was moderately distended with palpable hepatomegaly. Hair coat was thin ventrally. CBC showed a stress leukogram with thrombocytosis (584,000). ALP was 1100 IU/L and ALT was 214
IU/L, with a cholesterol of 398 mg/dl and a normal serum bilirubin. USG was 1.019 with an inactive sediment and 2+ protein. UPC was 2.1 and urine culture was negative. Systolic BP was 168 mmHg.

Given the high index of suspicion for hyperadrenocorticism, an abdominal ultrasound and ACTH stim were performed. The liver was hyperechoic on ultrasound, with bilateral adrenomegaly and dystrophic mineralization of some vessels. Cortisol was 14 ug/dl pre and 38 ug/dl post ACTH stimulation. Treatment of hyperadrenocorticism with either trilostane or mitotane was discussed with the owner. Because of the owner’s schedule and the need for consistent timing of ACTH stimulation tests after trilostane dosing, treatment with mitotane was initiated. A daily loading dose of 40 mg/kg/day (1000 mg/day) was prescribed, along with prednisone (5 mg tablets) to be given if needed.

One week later, the dog was rechecked. PU/PD was unchanged. Recheck BP was 162 mmHg (nervous dog, HR 140), and the ACTH stim was 12 ug/dl pre and 27 ug/dl post, indicating inadequate control. The loading dose was continued for another 10 days, but clinical signs were still unchanged and the ACTH stim was still abnormal (11 ug/dl pre and 18 ug/dl post). Options for changing the treatment regimen were discussed, and it was decided to simply crush the mitotane tablets (in a Ziploc bag to avoid aerosolization) and mix them into canned food. This has been shown to substantially increase mitotane bioavailability in dogs (Watson 1987). The owner monitored the dog’s clinical signs carefully, and PU/PD was diminished over 3 days. On the fourth day, an ACTH stim was 4 ug/dl pre and 5 ug/dl post, indicating good control. Blood pressure was improved at 141 mmHg but UPC was still increased mildly at 1.9. Enalapril was started and the dog was switched to maintenance mitotane (250 mg four times per week, crushed into canned food). The dog did fairly well on this regimen over the next 5 years, with gradual increases in the dose of mitotane as needed, and rechecks for management of progressive hypertension.

Case assessment

Hyperadrenocorticism is a relatively common endocrinopathy in older dogs. However, successful treatment requires a motivated and observant owner. If these two factors are not present, treatment should be initially targeted at controlling complications of disease (proteinuria, hypertension, pyoderma). Screening tests should only be performed in animals with clinical, biochemical, and/or imaging findings that suggest hyperadrenocorticism, to include several of the following:

- Clinical signs of PU/PD, PP, or panting
- PE signs of pot belly, thin skin, ventral alopecia, hyperpigmentation (calcinosis cutis in severe cases)
- CBC – stress leukogram and thrombocytosis
- Chem panel – moderate to marked increase in ALP, modest increase in ALT, increased cholesterol
- UA - USG < 1.030 with proteinuria
- UPC – about half of dogs having UPCs in the range of 1 to 4 (Hurley 1998)
- BP – modest hypertension (155-180 mmHg)
- Abdominal ultrasound – hyperechoic liver and unilateral or bilateral adrenomegaly.

Hyperadrenocorticism can be confirmed with either an ACTH stim (takes less time, may be more specific) or a LDDST (cheaper, may be more sensitive). The standard dose of 5 ug/kg IV of ACTH (Cosyntropin) is still recommended to diagnose hyperadrenocorticism by ACTH stim, which can be expensive. However, a recent study has validated the use of a lower dose of ACTH (Cosyntropin 1 ug/kg IV) to monitor response to mitotane or trilostane in dogs (Aldridge 2016), which can save money during follow-up. Both drugs require frequent monitoring, including ACTH stims every 3 months (or sooner if not doing well), serial blood pressure and UPC measurements, and periodic electrolyte measurements (especially in patients that do not feel well).

The choice between mitotane and trilostane is still patient-dependent. Both drugs are associated with the same costs and similar survival times (Arenas 2014). Trilostane is approved for dogs, may cause less GI upset, and is usually more rapidly reversible. However, the careful timing needed for ACTH stims is cumbersome, with different results obtained for stim tests started even at 2 or 4 hours after the morning dose (Bonadio 2014). Mitotane is not approved in dogs and can cause GI upset even without hypocortisolemia. Mitotane is preferred in dogs with adrenal carcinomas that are invasive or metastatic, since it is cytotoxic to adrenocortical tumors (Keiser 1999). In dogs that are refractory to mitotane, or if a lower dose is desired in a very large dog to reduce cost, mitotane tablets can be crushed into canned food to increase bioavailability. This needs to be done without contaminating the kitchen workspace. Having the owner crush the tablet in a sealed Ziploc-style plastic bag, and then mix a small amount of canned food into the bag, works well.
Top 10 Potential Drug Interactions
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In humans, the risk of adverse drug interactions multiplies as the number of administered drugs increases. Interactions can occur during IV drug administration, during oral absorption, at the target site, or during hepatic or renal elimination. Drug interactions may lead to loss of efficacy or increased toxicity. Although most of our knowledge of drug interactions comes from data in humans, many of these interactions are likely to occur in dogs and cats as well.

Sucralfate
Aluminum-containing drugs such as sucralfate can form complexes with many other drugs in the GI tract, markedly decreasing drug absorption. In humans, sucralfate impairs the bioavailability of several fluoroquinolones, theophylline, aminophylline, digoxin, and azithromycin. In dogs, sucralfate has been shown to decrease the bioavailability of ciprofloxacin, doxycycline and minocycline (Kukanich 2014, 2015, 2016). Sucralfate co-administration may decrease the efficacy of these antibiotics. These interactions can be minimized or avoided by giving the antibiotic two hours before the sucralfate. The opposite regimen is not recommended (i.e. giving the sucralfate first, followed two hours later by the antibiotic) because of the persistence of sucralfate in the stomach. However, because of the difficulty in coordinating dosing at home, sucralfate should be prescribed only with careful thought when other oral drugs are being given.

Sucralfate delays, but does not decrease the extent of, the absorption of H2 blockers, and there are no reports of adverse interactions between omeprazole and sucralfate. Therefore, staggered dosing does not appear to be necessary for sucralfate and these antacids.

Ketoconazole
Ketoconazole and itraconazole are best absorbed at acidic pH; therefore, these drugs should not be prescribed at the same time as omeprazole, H2 blockers, or other antacids. Interestingly, antacids do not affect the absorption of fluconazole.

Ketoconazole inhibits cytochrome P450 CYP3A enzymes, which have a wide substrate range and high potential for drug-drug interactions. Ketoconazole is also an inhibitor of p-glycoprotein, an important drug efflux transporter in the intestine, kidney, and biliary tree, and a component of the blood-brain barrier. Ketoconazole can therefore decrease the bioavailability and/or clearance of many drugs, such as ivermectin (also shown in dogs), cyclosporine (also shown in dogs and cats), digoxin, amitriptyline, midazolam, and warfarin. In addition, a case of colchicine toxicity due to a suspected interaction with ketoconazole was recently reported in a dog (McAlister 2014). Like ketoconazole, itraconazole also inhibits the metabolism of some drugs in humans.

The effects of ketoconazole to inhibit the clearance of cyclosporine can be exploited to allow lower doses of cyclosporine. Ketoconazole dosages as low as 2.5 mg/kg/day are effective (Myre 1991, Gray 2013). Monitoring of ALT is recommended during ketoconazole therapy. Trough whole blood cyclosporine can be measured at steady state (by one week), just prior to the next dose. Target levels for immunosuppression in humans are 400-600 ng/ml, although lower concentrations may be associated with clinical responses in dogs and cats.

Cyclosporine
As a substrate for both p-glycoprotein and CYP3A, cyclosporine has the potential for numerous drug interactions. Compounds that inhibit CYP3A, including diltiazem and even grapefruit juice, lead to increased cyclosporine blood concentrations and the potential for toxicity. Both cimetidine and metoclopramide have been reported to decrease cyclosporine clearance in humans; however, these drugs do not significantly impact cyclosporine concentrations in dogs, perhaps due to a species difference in enzyme-substrate specificity (Daigle 2001, Radwanski 2011) The nutraceutical St. John’s Wort induces CYP3A in humans and accelerates elimination of cyclosporine, decreasing drug concentrations (Durr 2000); this has also been shown in dogs (Fukunaga 2012). Supplements containing St. John’s Wort should be avoided in dogs being treated with cyclosporine.

In addition to the use of ketoconazole to increase cyclosporine concentrations, both fluconazole and clarithromycin have cyclosporine-sparing effects in dogs (Katayama 2014, Katayama 2008). In fact, fluconazole at 5 mg/kg/day decreased the total daily dose of cyclosporine necessary to maintain therapeutic concentrations in dogs by 39% (Katayama 2010).

Phenobarbital
Phenobarbital is a potent inducer of several P450 enzymes in humans and dogs. Phenobarbital speeds the metabolism of many drugs in humans, including glucocorticoids, mitotane, theophylline, ketoconazole, clomipramine, lidocaine, digoxin, and others. Phenobarbital also induces glucuronidation pathways, and can reportedly speed the clearance of carprofen in dogs (Saski 2015).
Phenobarbital has clinically significant drug interactions with other anticonvulsants. Phenobarbital increases the clearance of zonisamide in dogs, possibly due to induction of CYP3A (Orito 2008). Phenobarbital also increases levetiracetam clearance in dogs, and can lead to a 50% shortening of levetiracetam half-life (Moore 2011) by a P450-independent mechanism (Munana 2015). Phenobarbital lowers the target therapeutic concentrations of bromide needed to maintain seizure control in dogs, although this interaction is likely pharmacodynamic rather than pharmacokinetic (Trepanier 1998). Finally, phenobarbital undergoes autoinduction of its own metabolism, necessitating phenobarbital dosage escalations in some dogs on long-term therapy (Abramson 1998).

Conversely, the clearance of phenobarbital is inhibited by chloramphenicol. This can lead to sedation and ataxia in dogs being treated with both phenobarbital and chloramphenicol (Houston 1989), and this combination should be avoided.

As for cats, phenobarbital causes minimal cytochrome P450 enzyme induction, and therefore P450-mediated enhanced clearance is unlikely in felines.

Fluoroquinolones
The oral absorption of some fluoroquinolones, such as ciprofloxacin, is impaired by drugs that contain divalent or trivalent cations, to include aluminum, zinc, and iron. In contrast, no interaction was seen between enrofloxacin and aluminum-containing sucralfate in a small number of Greyhounds (Kukanich 2016). However, this requires further evaluation before these two drugs can be recommended in combination.

Fluoroquinolone antibiotics inhibit the clearance of theophylline in both humans and dogs, due to inhibition of the cytochrome P450 enzyme CYP1A2. This has led to theophylline toxicosis in humans. In dogs, enrofloxacin leads to higher plasma theophylline concentrations by about 30-50%, and marbofloxacin increases theophylline concentrations by a lesser extent (~25%). The combination of enrofloxacin and theophylline could potentially lead to theophylline side effects in some dogs, particularly dogs with concurrent renal insufficiency when enrofloxacin concentrations might increase.

Other fluoroquinolone drug interactions occur independently of cytochrome P450 effects. Enrofloxacin delays elimination of flunixin meglumine (Banamine), possibly by competitive inhibition of renal tubular transporters, leading to higher flunixin blood concentrations in dogs (Ogino 2005). Ciprofloxacin decreases blood concentrations of the immunosuppressive drug mycophenolate in humans, by impaired enterohepatic recycling of its glucuronidated metabolite (this recycling requires deconjugation by a brush border glucuronidase, which is inhibited by ciprofloxacin (Kodawara 2014)).

Metoclopramide
Metoclopramide, a dopaminergic (D2) antagonist and prokinetic agent, has several important drug interactions in humans. Metoclopramide enhances the absorption of acetaminophen, aspirin, and alcohol overdoses via increased gastric emptying. Metoclopramide can theoretically lead to enhanced extrapyramidal side effects (tremor) in combination with phenothiazines (e.g. chlorpromazine, acepromazine), or with selective serotonin reuptake inhibitors (e.g. fluoxetine). Tremors are also seen at standard metoclopramide dosages in dogs with renal insufficiency without dose adjustment. Interestingly, metoclopramide reduces pain on injection of propofol in humans, as well as the amount of propofol needed for anesthetic induction (by 20-25%), although the mechanisms are not clear. Although metoclopramide is a dopamine antagonist, it has no effect on the use of dopamine for hypotension; this is mediated by D1 receptors.

Furosemide
Furosemide can lead to dehydration and pre-renal azotemia, which will decrease the renal clearance of some drugs, including digoxin. Furosemide can also cause hypokalemia and hypomagnesemia, both of which exacerbate the cardiac toxicity of digoxin. These interactions can lead to digoxin toxicity unless serum digoxin levels are monitored.

In addition, furosemide enhances the nephrotoxicity of amikacin and gentamicin; because of this, mannitol may be preferred over furosemide for treatment of acute renal failure caused by aminoglycosides. When high dosages of furosemide are combined with ACE inhibitors, this can cause hemodynamic changes that can lead to acute renal failure. Initial doses of ACE inhibitors should be conservative when furosemide is also instituted, and clinical status and renal function should be monitored over the first 1-2 weeks.

Other furosemide-drug combinations can affect efficacy. Hypokalemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine. Serum potassium should be evaluated in patients with ventricular arrhythmias, and potassium supplementation should be considered if patients do not respond to lidocaine. Furosemide administration will also increase the renal loss of bromide, and can lower serum bromide concentrations and lead to seizure breakthrough.

Cimetidine
Cimetidine is a potent inhibitor of several families of cytochrome P450s in humans (CYP2D6, CYP3A4 and others), and also inhibits a specific renal drug transporter (OCT2). Because of this, cimetidine decreases the clearance of many drugs in humans, to include chloramphenicol, lidocaine, theophylline, diazepam, midazolam, and others. Cimetidine may lead to toxicity of any of these drugs. Cimetidine appears to be a much weaker inhibitor of P450s in dogs, but effects on renal transporters have not been well studied. Only
a few cimetidine drug interactions have been studied in dogs, with modestly decreased clearance of theophylline (Gascon 1994) and delayed absorption of cyclosporine (Daigle 2001).

Other H₂ blockers such as ranitidine, famotidine, or nizatidine are not P450 inhibitors at therapeutic concentrations. Ranitidine and nizatidine have the theoretical advantage of prokinetic effects. However, oral ranitidine had no effect on GI transit time in one study in dogs (Lidbury 2012).

**Omeprazole**
The pump blocker antacid omeprazole is an inhibitor of some cytochrome P450’s in humans (mostly CYP2C19), and may inhibit the clearance, and possibly increase the toxicity, of diazepam, midazolam, and warfarin (Wedemeyer 2014). Omeprazole can also inhibit p-glycoprotein, and may enhance the absorption of digoxin in humans. Omeprazole inhibits the conversion of clopidogrel to its active metabolite, leading to decreased efficacy in humans. However, a recent study in dogs showed that omeprazole at a dosage of 1 mg/kg q 24h did not significantly reduce the antiplatelet effects of clopidogrel (Thames 2016). This has not yet been evaluated in cats.

As inhibitors of gastric acid secretion, omeprazole and pantoprazole can also decrease the absorption of iron supplements, ketoconazole, and itraconazole. It is wise to discontinue antacids when oral ketoconazole and itraconazole are being given. Alternatively, if antacids cannot be stopped, fluconazole can be considered. Omeprazole also decreases the bioavailability of mycophenolate mofetil in humans, due to poor dissolution of this drug at a pH above 4.5 (Kees 2012). This combination should be avoided in dogs and cats.

**Clomipramine**
Clomipramine is a tricyclic antidepressant that inhibits norepinephrine reuptake. Clomipramine can have serious pharmacologic interactions with monoamine oxidase (MAO) inhibitors, which decrease the breakdown of norepinephrine and serotonin. This can lead to “serotonin syndrome” (twitching, tremor, tachycardia, myoclonic movements, hyperthermia) in humans, which can be fatal. This is a well established interaction in humans. Examples of veterinary MAO inhibitors include selegiline (L-deprenyl) and amitraz. The potential for an interaction between clomipramine and these drugs has not been directly evaluated in dogs, but the Clomicalm® label recommends against clomipramine being given within 14 days of either L-deprenyl or amitraz.

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, also inhibit neuronal reuptake of serotonin leading increased concentrations in the synapse. However, the risk for serotonin syndrome in combination with clomipramine appears to be lower than with MAOIs, at least in humans (Figueroa 1998). Other drugs that inhibit serotonin reuptake, to include tramadol, have the potential for a drug interaction with clomipramine, but the risk appears to be even lower than with MAOIs or SSRIs.

In addition to these target site interactions, clomipramine is a fairly potent inhibitor of canine CYP2D15 (Aidasani 2008), which could lead to interactions with drugs such as dextromethorphan (in Robitussin®) which are metabolized by this pathway in dogs (Shou, 2013). Finally, the metabolism of clomipramine can also be impaired by ketoconazole or itraconazole in humans, and clomipramine should probably not be combined with theseazole antifungals without careful monitoring.

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**Summary table: Drug interactions in humans that may also affect dogs and cats**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>May increase the toxicity of:</th>
<th>May decrease the efficacy of:</th>
<th>Toxicity may be increased by:</th>
<th>Efficacy may be decreased by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucralfate</td>
<td></td>
<td>Ciprofloxacin, doxycycline, erthyromycin, theophylline, digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Cyclosporine, warfarin, digoxin, amitriptyline, midazolam, cisapride, clomipramine, colchicine</td>
<td></td>
<td>Ketoconazole, fluconazole, diltiazem, clarithromycin, powdered grapefruit</td>
<td>Antacids, H₂ blockers, omeprazole, St. John’s wort</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Glucocorticoids, clomipramine, lidocaine, theophylline, digoxin, mitotane, levetiracetam, zonisamide, carprofen?</td>
<td></td>
<td>Chloramphenicol</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Theophylline, flunixin</td>
<td>Mycophenolate mofetil</td>
<td></td>
<td>Sucralfate,</td>
</tr>
<tr>
<td>Drug</td>
<td>Interactions</td>
<td>Effects</td>
<td>Interactions</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Mecloridramide</td>
<td>Ethanol, aspirin, or acetaminophen overdoses; propofol?</td>
<td>Probably <em>does not</em> counteract the renal effects of dopamine</td>
<td>Aceprozamine, fluoxetine (tremor)</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>ACE inhibitors, digoxin, aminoglycosides</td>
<td>Bromide, lidocaine (via hypokalemia)</td>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Lidocaine, theophylline, dexamethasone, propranolol</td>
<td>Ketoconazole, itraconazole, iron supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Diazepam, midazolam, warfarin, digoxin</td>
<td>Ketoconazole, itraconazole, iron supplements, mycophenolate mofetil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Dextromethorphan?</td>
<td>L-deprenyl, amitraz, ketoconazole, itraconazole, fluoxetine, tramadol?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>