Development of an Antibiotic Policy in a Zoological Medicine Service and Approach to Antibiotic Dosing Using Minimum Inhibitory Concentration Data

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Abstract: Antimicrobial resistance is a major veterinary concern, and yet despite widespread literature and policies advocating appropriate antibiotic stewardship in domesticated veterinary medicine, there appears to have been very little progress in zoological medicine, especially companion exotic practice. An example of an antibiotic policy for a zoological medicine service is described, along with general advice on appropriate antibiotic use, including minimum inhibitory concentration (MIC)-determined drug dosing.

Introduction

Antimicrobial resistance (AMR) is a global veterinary and public health challenge, which has accelerated by the overuse of antibiotics worldwide. Increased antimicrobial resistance is the cause of severe infections, complications, longer hospital stays and increased mortality. Overprescribing of antibiotics is associated with an increased risk of adverse effects, more frequent re-attendance and increased medicalization of self-limiting conditions. Antibiotic overprescribing is a particular problem in primary care, as the vast majority of all antibiotic prescriptions are issued by general practitioners.[1]

In 2015, the American and European Colleges of Veterinary Internal Medicine (ACVIM, ECVIM) published a consensus statement on therapeutic antimicrobial use and AMR.[2] This consensus provided the veterinary profession with up-to-date information on the pathophysiology, diagnosis and treatment of clinically important animal diseases. The information was derived from evidence-based medicine with specialist commentary, prior to peer review, and subsequent publication in the Journal of Veterinary Internal Medicine.

"The epidemic of antimicrobial resistant infections continues to challenge, compromising animal care, complicating food animal production, and posing zoonotic disease risks. While the overall role of therapeutic antimicrobial use in animals in the development of AMR in animal and human pathogens is poorly defined, veterinarians must consider the impacts of antimicrobial use in animals and take steps to optimize antimicrobial use, so as to maximize the health benefits to animals while minimizing the likelihood of AMR and other adverse effects."[2]

Despite recommendations and policies from many veterinary associations (including the American Veterinary Medical Association, British Veterinary Association, European Commission, etc), and many taxa-based veterinary

organizations (encompassing companion dogs, cats, and horses, as well as production poultry, cattle and swine), it seems that zoological medicine, and especially companion exotic animal care, has largely failed to produce appropriate policies. A review of the Association of Avian Veterinarians (AAV), Association of Exotic Mammal Veterinarians (AEMV), and the Association of Reptilian and Amphibian Veterinarians (ARAV) websites failed to demonstrate any policy on antibiotic stewardship. The author hopes that this presentation will energize the zoological companion animal specialty and associations to exhibit greater leadership in this area.

Review of cases referred to the Zoological Medicine Service, Veterinary Teaching Hospital, University of Georgia (ZMS) has indicated that virtually all animals seen by a previous veterinarian were treated with antibiotics. The vast majority of antibiotic drugs were dispensed without attempting to identify whether any bacterial disease was actually present (by Gram stain, culture, PCR, cytology, or histopathology). Furthermore, many cases were treated with multiple antibiotic drugs and/or courses of therapy using advanced antimicrobials (eg, fluoroquinolones, 3rd or 4th generation cephalosporins). Our subsequent case investigations suggest that the majority of antibiotic prescriptions were unnecessary (no bacterial disease present) or inappropriate (inappropriate choice of drug, drug resistance, inappropriate dose and/or duration).

The reasons for such poor therapeutic decisions may stem from client pressure, lack of knowledge, expertise, or confidence on the part of the veterinarian, and/or the client pressure to prescribe something, anything! Whatever the reasons, the reliance on broad spectrum antimicrobials implies a low level of skill and expertise on the part of the veterinarian. Consequently, changes in policy and culture are required, and we exotic animal veterinarians appear to lag well behind our domestic animal peers in this regard, who have already advocated for, and in many cases adopted, appropriate policies with positive results.[3,4] One such policy has been developed and instigated in the ZMS (Table 1), as part of a larger hospital policy on antibiotic use.

Table 1. University of Georgia Zoological Medicine Service Antibiotic Policy.

Antibiotics are to be prescribed by a veterinarian for two possible reasons, (I) prevention of infection and (II) treatment of bacterial disease
Prevention of Infection Antibiotics should only be dispensed to prevent infections IF the animal is (a) severely compromised (eg, neutrophil/heterophil count <1, or some other severe tissue compromise/exposure, eg, severe burns or other trauma), OR (b) receiving short term IV or IO antibiotics intraoperatively to prevent infection (eg, orthopedics, enterotomy). Tier 1 drugs can be used.
Treatment of Infection Some attempt to identify the bacterial cause (Gram stain, cytology, culture and sensitivity, MIC PCR) is required prior to prescribing any antibiotic for therapeutic purposes. Tier 1, first-line dr can only be used initially while pending culture and sensitivity or MIC results. Tier 2 drugs can only be used with a specific indication by culture and sensitivity or MIC testing that demonstrat poor efficacy or resistance to tier 1 drugs. Tier 3 drugs should not be used unless specifically authorized following the existing hospital protocol on "Restricted Use Antimicrobial Agents fo Multidrug Resistant Infections."

Table 1 Continued.

Tier 1 Antibiotic Drugs (First line options)
Uses (a) prevention of infection in severely compromised animals, (b) intraoperative IO or IV administration to prevent infection (eg, orthopedics), and (c) first line therapeutic antimicrobial treating infections, while awaiting culture and sensitivity or MIC results;
Trimethoprim, sulfonamides or combinations
Tetracyclines (eg oxytetracycline, doxycycline)
Basic/potentiated penicillins (eg ampicillin, penicillin, amoxicillin/clauv)
Metronidazole
Lincosamides (eg, lincomycin, clindamycin)
Aminoglycosides
1st and 2nd generation cephalosporins (incl intraop cefazolin)
1st generation quinolones (eg, oxolinic acid, nalidixic acid)

Tier 2 Antibiotic Drugs (Only if sensitivity/MIC results indicate resistance to tier 1)
Only to be used if culture and sensitivity or MIC testing indicate tier 1 drugs are ineffective;
3rd generation cephalosporins (ceftazidime, ceftiofur)
Penicillinase-resistant penicillins (eg, methicillin)
Advanced penicillins (eg, piperacillin, cerbenicillin, ticarcillin)
2nd generation fluoroquinolones (eg, enrofloxacin, orbifloxacin, ciprofloxacin)
Florfenicol, Chloramphenicol

Tier 3 Antibiotic Drugs (RESTRICTED)
Only to be used in cases of multidrug resistance where specified hospital criteria have been met authorization has been granted for their use.
Glycopeptides (eg, vancomycin)
Carbapenems (eg, imipenem)
Oxazolidonones (eg, linezolid)
4th generation and above cephalosporins (eg, defepine)
Ketolides (eg, telithromycin)
Lipopeptides (eg, daptomycin)
Ansamycins (eg, geldanamycin)
3rd generation and above fluoroquinolones (eg, levofloxacin)

Prevention of Bacterial Infection

Antibiotics can be used prophylactically to prevent infection; however, such use can increase the chances of commensals developing resistance. There is no argument in favor of prophylactic antibiotics because of poor hospital facilities, equipment, patient preparation or surgical technique. Routine sterilizations (castrates and spays) performed appropriately do not warrant antibiotics. Even in cases of corrective surgery (including enterotomy and orthopedics) where there are concerns regarding the development of post-operative infection, short-term pre- or peri-operative antibiotics (usually intravenous) are more effective and less likely to result in resistance, compared to several days of post-operative treatment.[5,6] There appears to be little to no evidence to support the routine use of post-operative antibiotics to prevent infection following clean-contaminated surgeries.

Broad spectrum antibiotic therapy has frequently been recommended in cases of severe integumental (eg, burns) or gastrointestinal (eg, intestinal breach and gut-origin sepsis) compromise; however, a systematic review and meta-analysis in human burn victims concluded that antibiotic prophylaxis is not currently recommended for patients with severe burns other than perioperatively.[7] In addition, strict criteria and recommendations exist for antibiotic use in cases of gut-origin sepsis.[8] Antibiotics are also prescribed in cases of life threatening immunosuppression, typically associated with radiation or chemotherapy. Antibacterial prophylaxis is only generally recommended for patients expected to have neutrophil counts of $< 1 \times 10^9$/L for > 7 days, unless other factors increase risks for complications or mortality.[9]

Therapeutic Treatment of Bacterial Disease

In order to successfully treat a bacterial disease several facets must be confirmed:

1. Does a bacterial disease actually exist?
2. Can a safe and effective antibiotic drug dose be delivered?
3. Can therapy be continued to the point of cure?

If the answer to any of these questions is no, then antibiotic therapy is unlikely to be successful and should not be pursued.

Confirmation of bacterial disease

Any oral swab from a snake is likely to reveal *Pseudomonas*, but that merely indicates the presence of bacteria, not that stomatitis is present. This is especially critical when dealing with commensal organisms. To demonstrate bacterial disease, it is generally necessary to demonstrate a host pathologic response (ie, cytology, histopathology) as well as the bacterial cause (ie, Gram, culture, PCR).

Antimicrobials should not be prescribed until some attempt has been made to identify a bacterial disease. In most cases this entails cytology and culture (but PCR may be used concurrently especially if antibiotics have been recently given and bacteria are no longer viable for culture). Such laboratory confirmation can take up to several days, and therefore in-house Gram stains should be routinely employed to help direct initial antibiotic drug selection. Indeed, in those cases where clients baulk at the costs of professional cytology and microbiologic culture, in-house Gram stain and cytology can be performed at lower costs to external labs; however, confirming the presence of a bacterial disease should be considered an integral, critical requirement prior to prescribing antibiotics (just like analgesia is considered an integral, non-optional component of anesthesia and surgery).

Initial drug selection and dose

Antibiotic therapy should be delayed until the animal is normothermic, and hydrated. If disease has been confirmed, then initial Gram stains, site of infection and likely organism involved should be used to help direct initial drug selection from a list of first-tier drugs (see Tables 1 and 2). For example, gram-positive infections should be treated using a basic penicillin, 1st and 2nd generation cephalosporin, or a potentiated sulphonamide. The opinion that the more modern drugs (eg, carbenicillin, ceftazidime) are more efficacious against susceptible bacteria than older products is simply untrue. If the patient is severely compromised then bacteriostatic drugs may be less favored (eg, tetracyclines, macrolides, lincosamides) over bactericidal options. Aminoglycosides

and fluoroquinolones are not indicated and typically less effective against gram-positives. Conversely, first-tier drugs against gram-negative infections would include potentiated sulphonamides or aminoglycosides, while metronidazole is indicated for suspect anaerobes. More advanced or modern drugs (Table 1 tier 2) should not be used as first line options, and their use is best restricted to cases where culture and sensitivity dictate their necessity. Furthermore, those drugs that play a critical role in the treatment of multidrug resistant diseases should be restricted and their use not permitted without permission from hospital authorities (Table 1, tier 3).

Regarding dose, many published formularies are available, but a majority of doses are anecdotal and not pharmacokinetically derived; however, where such data exists in the species of interest (or a closely-related species) it is often the most reliable source for dose determination. A quick search through Google Scholar can often be most rewarding for indicating pharmacokinetic research. Extrapolation from one species or taxa to another, or allometric scaling may be unavoidable but the increased risks of inappropriate dosing has to considered.

Table 2. Standard bacterial sensitivities to various classes of antibiotics.

Penicillins	
Penicillin G	Bactericidal, inhibit mucopeptide synthesis in the cell wall. Active against most spirochetes and gram-positive and gram-negative aerobic cocci, but not penicillinase producing strains. Effective against some aerobic and anaerobic gram-positive bacilli such as *Bacillus anthracis*, *Clostridium* sp. (not *C. difficile*), *Listeria*, *Fusobacterium*, *Actinomyces*, *Corynebacterium*. Inactive against most gram-negative aerobic and anaerobic bacilli, mycobacteria, and mycoplasmas.
Ampicillin Amoxicillin	Increased activity against many strains of gram-negative aerobes not covered by penicillin G, including some *E. coli*, *Klebsiella*, *Salmonella*, *Shigella*, and *Haemophilus*. Some anaerobic activity against Clostridia. Generally ineffective against *Pseudomonas aeruginosa*, *Serratia*, indole-positive *Proteus* (*Proteus mirabilis* is susceptible), *Enterobacter*, *Citrobacter*, *Acinetobacter*, *Mycobacterium*, and *Mycoplasma*. Clavulanate (B-lactamase inhibitors) improves activity against B-lactamase staphylococci, *H. influenzae*, *Neisseria*, *Moraxella catarrhalis*, *Bacteroides*, and *Klebsiella*.
Cloxacillin Methicillin	The penicillinase-resistant penicillins are active against staphylococci and streptococci (including pneumococci) but not against enterococci. Their primary use is for infections caused by penicillinase-producing staphylococci.
Carbenicillin Piperacillin Ticarcillin	Broad-spectrum, with similar activity to ampicillin but are also active against *Enterobacter*, *Serratia*, and *P. aeruginosa*. Piperacillin is also active against many strains of *Klebsiella*. The addition of clavulanate to ticarcillin and of tazobactam to piperacillin adds activity against *Klebsiella*, *Serratia*, and *Bacteroides* and against B-lactamase-producing strains of staphylococci, *H. influenzae*, and *N. gonorrhoeae*.
Cephalosporins	
1st generation cephalothin cefazolin cephapirin cephradine cephalexin cefadroxil	Bactericidal, inhibit mucopeptide synthesis in the cell wall. Excellent coverage against most gram-positives, *Streptococcus* (except *Enterococcus*), *Staphylococcus*, *Proteus mirabilis* and some *E. coli*, *Klebsiella*, *Actinobacillus*, *Pasturella*, *Haemophilus*, *Shigella* and *Salmonella*. Most anaerobes are very susceptible, except *Bacteroides fragilis*. Most species of *Corynebacteria* are susceptible. Group D streptococci/enterococci (*S. faecalis*, *S. faecium*), Methicillin-resistant *Staphylococcus*, indole-positive *Proteus* sp., *Pseudomonas* sp., *Enterobacter* sp., *Serratia* sp. and *Citrobacter* sp. are generally resistant.
2nd generation cefaclor cefamandole cefonicid ceforanide cefuroxime	Similar gram-positive coverage as 1st generation, but also good activity against *Bacteroides* fragilis. Gram-negative spectrum variable.

Table 2 Continued.

3rd generation cefotaxime moxalactam cefoperazone ceftizoxime ceftazidime ceftriaxone ceftiofur cefixime	Similar gram-positive activity of 1st and 2nd generations, plus expanded, but variable, Gram-negative activity. Ceftazidime and cefoperazone are active against most strains of *Pseudomonas aeruginosa*.
Aminoglycosides	
Amikacin Gentamicin Kanamycin Neomycin Streptomycin Tobramycin	Bactericidal, bind to the 30S ribosome and inhibit bacterial protein synthesis. Only effective against aerobic gram-negative bacilli and staphylococci. Activity against streptococci and anaerobes is poor. Aminoglycosides may be used in combination with a penicillin in staphylococcal and streptococcal infections. Streptomycin, neomycin, and kanamycin lack activity against *Pseudomonas aeruginosa*, whereas gentamicin, tobramycin, and amikacin have good activity. An aminoglycoside should always be added to a B-lactam antibiotic when treating serious *Pseudomonas* infections. Amikacin has the same spectrum of activity as gentamicin and tobramycin but is less susceptible to enzymatic inactivation. Therefore, amikacin may be useful in treating gentacin or tobramycin resistant infections.
Macrolides and lincosamides	
Azithromycin Clarithromycin Clindamycin Erythromycin Lincomycin Tilmicosin	Primarily bacteriostatic and bind to the 50S subunit of the ribosome and inhibit bacterial protein synthesis. Active against aerobic and anaerobic gram-positive cocci, and against gram-negative anaerobes. Erythromycin is active against most gram-positive cocci (including anaerobes), but many human *Staphylococcus aureus* strains are now resistant. Erythromycin is also active against *Mycoplasma*, *Chlamydophila*, *Bordetella*, *Corynebacterium*, *Campylobacter*, and *Treponema*. Although it has activity against anaerobic gram-negative bacilli, its activity is much less than that of clindamycin. Clarithromycin and azithromycin have enhanced activity against *Haemophilus influenzae* and activity against *Mycobacterium avium*-intracellulare.Clindamycin has poor activity against *Mycoplasma* but much greater activity against anaerobic bacteria, especially *Bacteroides* sp. CNS penetration into the brain and CSF is poor.
Tetracyclines	
Doxycycline Oxytetracycline Tetracycline	Bacteriostatic, bind to 30S subunit of ribosome and inhibit bacterial protein synthesis. Effective against many B-hemolytic streptococci, nonhemolytic streptococci, gram-negative bacilli, rickettsiae, spirochetes, *Mycoplasma*, and *Chlamydophila*. Bacterial resistance to one tetracycline indicates likely resistance to the others. Used primarily for urinary tract infections, rickettsial, chlamydial, *Mycoplasma*, *Shigella*, *Brucella*, and *Vibrio* infections. Considered an alternative to penicillin treatment for syphilis in humans and maybe useful for rabbits.
Fluoroquinolones	
Ciprofloxacin Enrofloxacin	Bactericidal and inhibit the activity of DNA gyrase. Activity against Enterobacteriaceae and staphylococci, *P. aeruginosa*, *Mycoplasma*, *Chlamydia*, and some streptococci, but not reliably active against anaerobes. Resistance has been noted, particularly with *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus*. Resistance to one fluoroquinolone generally means resistance to all.
Potentiated sulphonamides	
Trimethoprim-sulfa combinations	Bacteriostatic, both drugs block the folic acid metabolism cycle of bacteria and are synergistic together. Sulfonamides are competitive inhibitors of the incorporation of p-aminobenzoic acid. TMP prevents reduction of dihydrofolate to tetrahydrofolate. Trimethoprim-sulfa is active against most gram-positive and gram-negative organisms but is inactive against anaerobes. *Pseudomonas aeruginosa* is usually resistant.

Table 2 Continued.

Polypeptides	
Polymyxin B	The polypeptides are bactericidal antibiotics with activity against gram-negative aerobic bacilli including *Pseudomonas aeruginosa*. Polymyxin B is not active against *Proteus* sp. or gram-positive organisms.
Bacitracin	Bacitracin is a bactericidal, inhibits cell wall synthesis. Active only against gram-positive organisms and very few gram-negatives. Used topically and may be effective orally in the treatment of *Clostridium difficile*.
Miscellaneous	
Chloramphenicol Florfenicol Thiamphenicol	Primarily bacteriostatic, binds to the 50S subunit of the ribosome and inhibits bacterial protein synthesis. Wide spectrum of activity against gram-positive and gram-negative cocci and bacilli (including anaerobes), *Rickettsia*, *Mycoplasma*, and *Chlamydophila*. Primary uses in serious *Salmonella* infections, *Haemophilus*, and *Pasteurella*, but also effective against *Mycoplasma*. Ineffective in meningitis caused by *E. coli* and other Enterobacteriaceae.
Metronidazole	Bactericidal, disrupts bacterial DNA and nucleic acid synthesis. Activity against most obligate anaerobes including *Bacteroides* sp. (including *B. fragilis*), *Fusobacterium*, *Veillonella*, *Clostridium* sp., *Peptococcus*, and *Peptostreptococcus*. *Actinomyces* is frequently resistant to metronidazole.
Rifampin	Bactericidal or bacteriostatic dependent upon bacterial susceptibility and drug concentration, inhibits DNA-dependent RNA polymerase. *Mycobacterium*, *Staphylococcus aureus*, *Neisseria*, *Haemophilus*, and *Rhodococcus*.

Modification of drug selection

Disc sensitivity testing provides a subjective in vitro assessment of antibacterial sensitivity (sensitive, intermediate, resistant), and although it provides a useful guide there are often times when in vivo results do not concur with disc sensitivity. Minimum inhibitory concentration (MIC) is much more reliable and provides a more objective, quantifiable sensitivity. MIC data are useful, not only for determining which drug should be selected from a group of efficacious options, but also for calculating the patient's required dose from pharmacokinetic data (Vd, Cmax).

Clinical application of MIC data using therapeutic factor

As a rule of thumb, clinical response correlates best for:

1. systemic infections if the attainable peak serum/plasma level is 2-4X MIC;
2. urinary tract infections, if attainable bladder level is 10X MIC (µg/ml);
3. biofilm in lumens 1000–1500X MIC.

In order to use MIC data to direct patient therapy by calculating a preferred drug dose (PDC), the following must be known, approximated, or calculated:

1. The cultured bacteria's MIC to specific antibacterial drug(s).
2. The hosts MIC breakpoint. A breakpoint is a chosen concentration of antibiotic which defines whether a species of bacteria is susceptible or resistant. If the MIC is less than or equal to the susceptibility break-point the bacteria is considered susceptible to the antibiotic. The closer the MIC is to the breakpoint the greater the chance that the antibiotic may not be clinically effective.

3. The drug's volume of distribution (Vd) in the host species.

4. Therapeutic factor (TF). MIC values are multiplied by a therapeutic factor, often between 4 and 10, in order to compensate for differences between the culture MIC and the patient's condition (eg, organism virulence, immune status of the patient, seriousness of the infection, difficulty for the drug to penetrate to the site of infection, etc).

5. Target PDC (plasma drug concentration) = MIC x TF, should be < breakpoint of the antibiotic organism combination.

6. Patient dose = PDC x Vd.

Examples of calculated dosages for *Salmonella* hepatitis in a slider are provided in Table 3.

Table 3. Hepatic biopsy reveals *Salmonella* hepatitis in a slider (*Trachemys scripta*), calculated drug doses.

Drug	Disc sensitivity	MIC (µg/ml)	Vd (L/kg)	Calculated dose[a] (mg/kg)
Carbenicillin	Sensitive	16	0.24	31 mg/kg[b]
Enrofloxacin	Sensitive	1	2.48	20 mg/kg[c]
Metronidazole	Resistant	128	0.74	758 mg/kg[d]

[a]Calculated drug doses from MIC calculated as follows: MIC (µg/ml = mg/L) x Vd (L/kg) x treatment factor (often 4-10, using 8 in this example).
[b]The calculated dose (31 mg/kg) is well below the pharmacokinetically evaluated, published dose (200 mg/kg). Therefore, use of the published dose would easily achieve high tissue levels and greater likelihood of treatment success, despite the *intermediate* disc sensitivity.
[c]The calculated dose (20 mg/kg) is greater than the pharmacokinetically evaluated, published dose (10 mg/kg). Therefore, use of the published dose would fail to achieve adequate tissue levels and result in treatment failure, despite the *sensitive* disc sensitivity. The high calculated dose may achieve adequate tissue levels at the expense of causing drug toxicity.
[d]The calculated dose (758 mg/kg) is far greater than the pharmacokinetically evaluated, published dose (20 mg/kg). Therefore, use of the published dose would fail to achieve adequate tissue levels and result in treatment failure, and is consistent with the *resistant* disc sensitivity. It would likely be impossible to achieve such high tissue levels, and attempts to do so would cause drug toxicity.

Evaluation of therapy

There are many reasons why even pharmacokinetically derived drug doses may result in inappropriate drug levels, even in the same species. The author has been surprised by how measured drug levels often deviate significantly from those of published pharmacokinetic studies, resulting in the need to adjust doses by up to 50%. Therefore, measuring drug levels in chronic cases requiring prolonged therapy is recommended.

Most, if not all, pharmacokinetic studies use healthy experimental animals. Hydration, concurrent disease, temperature, nutrition, age, gender, season and reproductive state, etc, can influence drug absorption, distribution and elimination. In addition, most pharmacokinetic investigations operate over a short time period, often a single dose, and therefore the longer term effects of accumulation or induced metabolism are seldom appreciated. Finally, compounded drugs may not act in the same way as manufactured products. For example, although not an antibiotic, compounded itraconazole consistently failed to achieve any detectable plasma levels in tortoises, whereas the commercial product produced high levels (unpublished observations). Manufactured oral cipro-

floxacin contains microcapsules (hence its high cost) and therefore compounding tablets to obtain a cheaper oral suspension may result in less reliable pharmacokinetics. Compounding metronidazole to improve palatability may also risk changing absorption characteristics.

References

1. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf.* 2014;5:229-241.

2. Weese JS, Giguère S, Guardabassi L, et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. *J Vet Intern Med.* 2015;29:487-498.

3. Weese JS. Investigation of antimicrobial use and the impact of antimicrobial use guidelines in a small animal veterinary teaching hospital: 1995-2004. *J Am Vet Med Assoc.* 2006;228:553-558.

4. American Veterinary Medical Association. Policy statement: judicious therapeutic use of antimicrobials. Available at https://www.avma.org/KB/Policies/Pages/Judicious-Therapeutic-Use-of-Antimicrobials.aspx Accessed June 30, 2017.

5. Stone HH, Haney BB, Kolb LD, et al. Prophylactic and preventive antibiotic therapy: timing, duration and economics. *Ann Surg.* 1979;189:691-698.

6. Mathur P, Trikha V, Farooque K, et al. Implementation of a short course of prophylactic antibiotic treatment for prevention of postoperative infections in clean orthopaedic surgeries. *The Indian J Med Res.* 2013;137:111-116.

7. Avni T, Levcovich A, Ad-El DD, et al. Prophylactic antibiotics for burns patients: systematic review and meta-analysis. *BMJ.* 2010;340:c241.

8. Offenbartl K, Bengmark S. Intraabdominal infections and gut origin sepsis. *World J Surg.* 1990;14:191-195.

9. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013;31:794-810.