

Letters to the Editor

Confounding in study of antivenom

We read with interest the retrospective study “Multicenter evaluation of the administration of crotalid antivenom in cats: 115 cases (2000–2011).”¹ The authors should be commended on contributing to our understanding of the use of antivenom in cats.

However, we were concerned with the authors’ conclusion that “[t]here was no mortality rate difference between cats that did (6.67%) or did not (5.08%) receive antivenom.” Generally, patients less severely envenomated would tend to not receive antivenom, whereas those more severely envenomated would tend to receive antivenom. Without evidence that groups of cats in the study that did and did not receive antivenom were equivalent cohorts, the comparison of mortality rate between groups may not be valid.

Cats in this study received several types of antivenom, but because of differences in antivenom composition, venom-binding properties, and antivenom manufacturing and purification methods, it may not be appropriate to group all cats receiving antivenom together when evaluating responses to antivenom administration. Also, analysis of antivenom reactions is difficult because antivenom is traditionally given to patients with progressive signs of envenomation, making it hard to differentiate antivenom reactions from venom-related morbidities. Reactions (including allergic reactions) seen after antivenom administration may result from the venom, the antivenom, the other drugs administered, or some combination of these. In a previous study² of antivenom administration in dogs, some reactions were classified as antivenom reactions when they were most likely due to progression of envenomation.

Ideally, antivenom safety issues will be evaluated by administering antivenom to animals that have not

been envenomated. In a previous study³ in which healthy dogs were given an Fab2 antivenom, no reactions were observed following IV administration of 3 vials of antivenom and only mild reactions were seen in a small number of dogs following administration of 6 vials.

In conclusion, we commend the authors for their interest in and contribution to the field of clinical veterinary toxinology and look forward to prospective work in the future.

Michael E. Peterson, DVM, MS
Reid Veterinary Hospital
Albany, Ore
VIPER Institute
University of Arizona
Tucson, Ariz

Craig W. Woods, DVM, MS, MBA
Animal Health Consulting LLC
Prescott, Ariz

Karen E. Seibold, DVM, MS, DACVECC
Animal Urgent Care
Escondido, Calif
VIPER Institute
University of Arizona
Tucson, Ariz

Michael Schaer, DVM, DACVECC, DACVIM
University of Florida
College of Veterinary Medicine
Gainesville, Fla

1. Pashmakova MB, Bishop MA, Black DM, et al. Multicenter evaluation of the administration of crotalid antivenom in cats: 115 cases (2000–2011). *J Am Vet Med Assoc* 2013;243:520–525.
2. Peterson ME, Matz M, Seibold K, et al.

A randomized multicenter trial of Crotalidae polyvalent immune F(ab) antivenom for the treatment of rattlesnake envenomation in dogs. *J Vet Emerg Crit Care (San Antonio)* 2011;21:335–345.

3. Woods C, Young D. Clinical safety evaluation of F(ab)² antivenom (*Crotalus durissus-Bothrops asper*) administration in dogs. *J Vet Emerg Crit Care (San Antonio)* 2011;21:565–569.

Methicillin-resistant staphylococci

I read with interest the Reference Point article on methicillin-resistant staphylococci isolated from dogs with pyoderma.¹ The authors are to be congratulated on the article’s completeness and clarity. Because ensuring that initial treatment of pyoderma is as effective as possible is so important to preventing selection of resistant bacteria, the review is particularly timely.

That said, there is a statement in the report that is controversial because we lack veterinary evidence to support it: “Cefovecin and cefpodoxime proxetil are third-generation cephalosporins that... are only recommended as first-line agents in situations where owner compliance is a concern, because they have the potential to select for both methicillin-resistant staphylococci and extended-spectrum β -lactamase-producing organisms.” The reference used to support this statement is from a book chapter making a similar, but unsupported, recommendation.²

Instructions for Writing a Letter to the Editor

Readers are invited to submit letters to the editor. Letters may not exceed 500 words and 6 references. Letters to the Editor must be original and cannot have been published or submitted for publication elsewhere. Not all letters are published; all letters accepted for publication are subject to editing. Those pertaining to anything published in the *JAVMA* should be received within one month of the date of publication. Submission via e-mail (JournalLetters@avma.org) or fax (847-925-9329) is encouraged; authors should give their full contact information, including address, daytime telephone number, fax number, and e-mail address.

Letters containing defamatory, libelous, or malicious statements will not be published, nor will letters representing attacks on or attempts to demean veterinary societies or their committees or agencies. Viewpoints expressed in published letters are those of the letter writers and do not necessarily represent the opinions or policies of the AVMA.

We would all agree that antimicrobial use drives the selection of resistant bacteria. But I can find no specific evidence in the veterinary literature supporting the hypothesis that cefovecin and cefpodoxime are more likely to select for resistance than are other classes of antimicrobials used repeatedly. In fact, the first reported study³ on cephalosporin-induced extended-spectrum β -lactamase-producing *Escherichia coli* studied cephalixin. I believe that the recommendation against the use of third-generation cephalosporins has been lifted directly from human references, in which reducing the use of a subset of these cephalosporins was associated with a reduction in the prevalence of methicillin-resistant *Staphylococcus aureus*. However, this reduction was also associated with reduced use of ciprofloxacin.^{4,5} Intravenous administration of antimicrobials to hospitalized, critically ill human patients is substantially different from oral administration of antimicrobials to dogs with superficial pyoderma. The incriminated antimicrobials in hospitalized human patients include cefuroxime and cefoxitin, often considered second-generation cephalosporins; the third-generation cephalosporins ceftriaxone and cefotaxime; and the antipseudomonal drug ceftazidime. Do these antimicrobials have enough in common with cefovecin and cefpodoxime to be painted with the same brush? The third-generation cephalosporin class is tremendously diverse, with antimicrobials of various structures and activities. They are not equivalent drugs.

Further, there is evidence that cefovecin and cefpodoxime offer advantages over cephalixin, a first-generation cephalosporin. The product insert for a veterinary cephalixin formulation reports a success rate of 70% for susceptible strains of *Staphylococcus pseudintermedius* when administered at a dosage of 22 mg/kg (10 mg/lb), every 12 hours. By contrast, the product insert for a veterinary formulation of cefpodoxime proxetil reports a success rate of 88.4% when administered at a dosage of 5 mg/kg (2.3 mg/lb) every 24 hours.

It seems that modern microbiology is shifting toward the use

of higher dosages of best-in-class antimicrobials for shorter periods. Given that cefpodoxime and cefovecin have better efficacy than cephalixin, should we not advocate for their use, especially given that in a recent systematic analysis,⁶ cefovecin was the only antimicrobial with good evidence to support its use in the treatment of canine pyoderma?

Before we advocate against the use of a particular group of antimicrobials, we should have sufficient veterinary evidence for why they are to be avoided, compared with other classes of antimicrobials.

Valerie A. Fadok, DVM, PhD, DACVD
Houston, Tex

1. Gold RM, Patterson AP, Lawhon SD. Understanding methicillin resistance in staphylococci isolated from dogs with pyoderma. *J Am Vet Med Assoc* 2013;243:817–824.
2. Guardabassi L, Houser GA, Frank LA, et al. Guidelines for antimicrobial use in dogs and cats. In: Guardabassi L, Jensen LB, Kruse H, eds. *Guide to antimicrobial use in animals*. Ames, Iowa: Blackwell Publishing Ltd, 2008;183–206.
3. Damborg P, Gaustad IB, Olsen JE, et al. Selection of CMY-2 producing *Escherichia coli* in the faecal flora of dogs treated with cephalixin. *Vet Microbiol* 2011;151:404–408.
4. Liebowitz LD, Blunt MC. Modification in prescribing practices for third-generation cephalosporins and ciprofloxacin is associated with a reduction in methicillin-resistant *Staphylococcus aureus* bacteraemia rate. *J Hosp Infect* 2008;69:328–336.
5. Dancer SJ, Kirkpatrick P, Corcoran DS, et al. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile*, extended-spectrum β -lactamase-producing coliforms and methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents* 2013;41:137–142.
6. Summers JF, Brodbelt DC, Forsythe PJ, et al. The effectiveness of systemic antimicrobial treatment in canine superficial and deep pyoderma: a systematic review. *Vet Dermatol* 2012;23:305–329.

Identifying antimicrobial resistance

I am writing on behalf of the Veterinary Antimicrobial Susceptibility Testing subcommittee of the Clinical and Laboratory Standards Institute (CLSI) regarding the recent study by Hamilton et al¹ on antimicrobial resistance among bacteria isolated from dogs and cats

admitted to a veterinary teaching hospital.

In assessing antimicrobial resistance, Hamilton et al used breakpoints published in a 2007 CLSI standard for testing bacterial isolates from humans. This standard is now outdated and has been replaced by a new standard.² In fact, there have been several versions of the CLSI standard since the 2007 publication.

More importantly, antimicrobial susceptibility of veterinary isolates should be determined on the basis of interpretive criteria developed for bacteria isolated from animals. The most recent edition of the CLSI standard for testing veterinary isolates was published in July 2013 by the Veterinary Antimicrobial Susceptibility Testing subcommittee of the CLSI.³ It contains many new and updated breakpoints for bacterial isolates from animals. Several of these breakpoints differ considerably from values published in the current² and previous standards for testing of human isolates. Thus, it is possible that resistance reported for some bacteria-drug combinations in the study by Hamilton et al¹ would have been different if appropriate veterinary-specific criteria had been used. Because only numbers and percentages of isolates were reported, rather than minimum inhibitory concentrations, it is not possible to determine which values would have changed if appropriate breakpoints had been used or to what extent.

We commend these authors for performing valuable work to assess antimicrobial resistance in bacterial isolates from hospitalized dogs and cats. However, whenever possible, veterinary investigators should use current CLSI interpretive criteria specific for veterinary organisms and antimicrobial agents when assessing antimicrobial resistance in bacterial isolates from animals.

Mark G. Papich, DVM, MS
Raleigh, NC

1. Hamilton E, Kruger JM, Schall W. Acquisition and persistence of antimicrobial-resistant bacteria isolated from dogs and cats admitted to a veterinary teaching hospital. *J Am Vet Med Assoc* 2013;243:990–1000.
2. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing*. 23rd

- informational supplement; document M100-S23. Wayne, Pa: Clinical and Laboratory Standards Institute, 2013.
- Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals*. Approved standard. 4th edition. Document VET01-A4. Wayne, Pa: Clinical and Laboratory Standards Institute, 2013.

The authors respond:

We greatly appreciate the comments from Dr. Papich concerning the use of Clinical and Laboratory Standards Institute (CLSI) breakpoints in our recent publication.¹ The opportunity to explain our methods and continue the discussion of antimicrobial resistance in bacteria isolated from dogs and cats will further efforts in this area.

Dr. Papich mentions that several versions of the CLSI standard have been published since the 2007 standard, which was used in our research. The research reported in this manuscript was generated as a part of a larger study that took place from 2007 to 2009. We are aware that there were versions of the CLSI standard published between 2007 and 2009, but we decided to use the 2007 version throughout this longitudinal study so that we could compare results over the three-year study period. Our intent was to preserve the integrity of our larger study by consistently analyzing resistance.

Additionally, we recognize that there are different breakpoints for assessing resistance based on origin of the isolates. The overall study that resulted in our manuscript aimed to assess resistance among human, animal, and environmental isolates. At the time of our analysis, breakpoints for those antimicrobials used in our study for which standards were listed for both human and animal isolates were identical; thus, we felt confident in using the human standards for isolates from all three sources.

In closing, we are pleased to have this opportunity to clarify these details of our research.

Elizabeth Hamilton, MPH, PhD
John B. Kaneene, DVM, MPH, PhD
Center for Comparative Epidemiology
College of Veterinary Medicine
Michigan State University
East Lansing, Mich

- Hamilton E, Kruger JM, Schall W. Acquisition and persistence of antimicrobial-resistant bacteria isolated from dogs and cats admitted to a veterinary teaching hospital. *J Am Vet Med Assoc* 2013;243:990-1000.

Spaying and neutering controversy

I just read the recent *JAVMA* News article¹ on the controversy regarding elective gonadectomy in dogs and can't remember a time when a single article has caused so many veterinarians to question their current recommendations and practices. I have to wonder how many have actually read the University of California study² discussed in the news article on possible connections between neutering and various joint disorders and cancers in Golden Retrievers. A quick read might suggest that elective gonadectomy was associated with increases in the incidence of all of the conditions examined; a closer read would call that conclusion into question.

Interestingly, none of the sexually intact male and female dogs in that study² reportedly developed cranial cruciate ligament rupture and none of the sexually intact females developed mast cell tumors. But, certainly, we cannot conclude from these findings that sexually intact dogs will never develop these conditions. And, we should not discount the potential benefits of neutering. None of the male dogs in the study neutered after 1 year of age developed lymphosarcoma and none of the female dogs neutered after 1 year of age developed mast cell tumors, although, again, we should not conclude that dogs in these groups will never develop these conditions.

There is a lot that we do not know about the long-term effects of gonadectomy and much yet to be learned. Additional research will eventually confirm or negate the conclusions of the study by Torres de la Riva et al,² but until and unless there is confirmation that these conclusions can be extrapolated to dogs in general, it is not prudent to have a knee-jerk response.

In a study by Hoffman et al³ involving 40,000 neutered and

sexually intact dogs, neutering was strongly associated with an increase in life span. Similarly, the Banfield State of Pet Health 2013 report⁴ found that neutered dogs and cats, on average, had substantially longer life spans than did sexually intact animals. Both of these studies drew their conclusions from much larger and more diverse populations of dogs and cats than did the study by Torres de la Riva et al,² but their findings are discussed less frequently and with less emotion.

Neither the Hoffman et al³ study nor the Banfield report⁴ identified why neutered dogs and cats live longer, so again there is much yet to be learned. It may take years or even decades to collect enough data to completely understand the gamut of changes associated with spaying and castration. As additional studies are published, gradual shifts in our recommendations will occur.

For now, let's keep things in perspective. Spaying and castration is still a valid choice for many dogs and cats. Every patient should be evaluated individually and every owner should be educated so that an informed decision can be made together with the veterinarian. Remember to keep it all in balance.

Boyd Harrell, DVM
Lakeland, Fla

- Nolen RS. Study shines spotlight on neutering. *J Am Vet Med Assoc* 2013;243:1218-1223.
- Torres de la Riva G, Hart BL, Farver TB, et al. Neutering dogs: effects on joint disorders and cancers in Golden Retrievers. *PLoS One* [serial online] 2013;8(2):e55937. Available at: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0055937. Accessed Oct 22, 2013.
- Hoffman JM, Creevy KE, Promislow DE. Reproductive capability is associated with lifespan and cause of death in companion dogs. *PLoS One* [serial online] 2013;8:e61082. Available at: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0061082. Accessed Oct 22, 2013.
- Banfield Pet Hospital. State of pet health 2013 report. Available at: www.stateofpethealth.com/Content/pdf/Banfield-State-of-Pet-Health-Report_2013.pdf. Accessed Oct 22, 2013.

The *JAVMA* News article "Study shines spotlight on neutering"¹ was an interesting and

informative discussion of neutering. However, I wish that mention had been made of options to prevent animals from reproducing that do not involve removing the gonads. The Parsemus Foundation, for example, discusses what it calls the ovary-sparing spay,² which involves removing the uterus while leaving the ovaries intact. The surgery is no more difficult than a conventional ovariohysterectomy, except that extra care must be taken to ensure that the uterus and cervix

are entirely removed to prevent possible stump pyometra.

Similarly, for male dogs, vasectomy is a potential alternative to removal of the testes. Again, extra care is required to identify the ductus deferentes (vasa deferentia) prior to ligation, but the surgery is not particularly difficult. With proper training and handling, behavior problems are generally not a major concern in sexually intact or vasectomized males.

Ovary-sparing spay and vasectomy are valuable tools to prevent

unwanted pregnancies and still allow dogs to retain the beneficial effects of their gonads. It would be a service for the AVMA to open a dialogue about the use of these options.

*Sara Fox Chapman, DVM
Upper Marlboro, Md*

-
1. Nolen RS. Study shines spotlight on neutering. *J Am Vet Med Assoc* 2013;243:1218–1223.
 2. Parsemus Foundation. Ovary-sparing spay. Available at: www.parsemus-foundation.org/ovary-sparing-spay/. Accessed Oct 28, 2013.