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Case Reports

Comparison of Two Strategies for Diagnosis and Treatment of Infection in Dogs (*Canis familiaris*) with Long-term Intravascular Catheters

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Exteriorized chronic intravascular catheters (ECICs) are used frequently for repeated substance administration, sampling, and measuring of hemodynamic parameters in biomedical research protocols. ECICs can be a management challenge because they have been associated with catheter occlusion, thrombosis, sepsis, and serious clinical sequela. A monitoring regimen that identified infection early and a treatment protocol that eliminated infection would be of great benefit to animals and to research protocols using ECICs. Using clinical pathology and other parameters, this study compares 2 management strategies in their ability to maintain the physiologic condition of the animals with ECICs. We compared the clinical outcome of treatment initiated in light of an elevated white blood cell count without delay for development of left shift or clinical signs coupled with prolonged duration of treatment (28 d for the first treatment and 42 d for subsequent treatments) with conventional antibiotic treatment initiated after the advent of clinical signs. Significant findings of the study were that the use of fever as an indicator of infection unnecessarily delayed the initiation of treatment by an average of 12 d and that the use of a single clinical pathologic parameter (white blood cell count more than 18,000 cells/ml) as indication for treatment, with or without fever, in addition to prolonged antibiotic treatment (28 d for the first treatment and 42 d for subsequent treatment) initiated as soon as the white blood cell count exceeded 18,000 cells/ml and without delay for development of fever resulted in superior health of the animals with ECICs.

Abbreviations: CBC, complete blood counts; CI, confidence interval; ECIC, exteriorized chronic intravascular catheter; WBC, white blood cell count

Chronic intravascular catheters are frequently required in biomedical research for repeated sampling of blood and systemic delivery of substances.[5,28,32,33] These devices can be exteriorized through the skin or connected to vascular access ports implanted subcutaneously. Performance advantages of vascular access ports over exteriorized chronic intravascular catheters (ECICs) for long-term venous sampling and delivery of substances include decreased incidence of catheter occlusion, thrombosis, and infections.[31] However, vascular access ports are not recommended for monitoring hemodynamic variables.[30,31]

Catheter-related infections most commonly are due to migration of skin organisms at the insertion site (for short-term [less than 7 d]) or contamination of the catheter hub (long-term catheters).[20] Therefore, the density of skin flora at the catheter insertion site and the technique used when handling catheters influences the risk of subsequent catheter infection. For short-term catheters, sterile insertion techniques and aseptic handling techniques are most effective in minimizing infection.

For long-term catheters, the likelihood of infection increases with the time the catheter is in place.[1,25] Maintenance of long-term catheters has involved 1 or more of the following: antimicrobial- or antiseptic-impregnated catheters, antibiotic lock techniques, regular disinfection of the dermal ECIC exit site, and prophylactic antibiotic administration.[10-12,17,23-26] Despite these procedures, the prevalence of bloodstream infection due to ECICs has been reported to be between 3 and 11 per 1000 catheter days.[20]

Even with these improvements, long-term maintenance of ECICs remains clinically challenging. Exit-site infection, reduced catheter patency, bacterial contamination, sepsis, and subsequent clinical sequella are reported as common complications.[1,18] Therefore, long-term studies still have the potential for debilitation and complications associated with septic emboli.[1,25]

Diagnosis of catheter-related infections traditionally has been based on the combination of culture results and the presence of local or systemic clinical symptoms attributable to bloodstream infections in patients bearing ECICs for which no other source of infection is identified.[10,18,19,24,29] However, catheter-related infections without overt clinical manifestations of infection have occurred in 10% to 55% of hemodialysis catheters.[1,19] Therefore, the traditional clinical diagnosis of catheter-related infection, based on clinical signs[18,19,21,24] may be delaying treatment, rendering it less effective.

Once infection is confirmed, removal of the catheter has been recommended.[10,19] Attempts at catheter salvage, without removal of the catheter, typically are unsuccessful in clearing infection.[15,18] Therefore, for peripheral catheters that are easy to remove and replace, removal of infected catheters is generally recommended.[13] However, in the case of surgically implanted catheters, removal should be considered more carefully. In biomedical research, there are additional considerations because removal of the catheter may terminate the protocol, confound

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the interpretation of results, and ultimately result in the use of additional animals to gain the data. There is an imperative to prevent infection of ECICs or, when necessary, detect and treat the infection as soon as possible, with the principal aim of maintaining the animal model in a physiologic state. A specific regimen of ECIC care that could improve both humane animal care and optimize data collection with the use of the fewest number of animals would be a substantial contribution to animal welfare and biomedical research.

Once a catheter-related infection has been diagnosed, the choice of the optimal treatment regimen remains unclear. The in vitro sensitivity of an organism may not correlate well with in vivo activity, because the adherence properties of a particular organism influences pathogenesis in causing catheter-related infections.[20] The growth of bacteria in biofilms affords the bacteria protection from host defenses and increased resistance to antimicrobial agents.[3] Bacteria growing in biofilms are more resistant to antimicrobials, and biofilm infections are more difficult to resolve with antibiotics alone.[2-4] Antibiotic- and antiseptic-coated catheters have been used to reduce bacterial adherence and biofilm formation, yet their usefulness remains controversial due to inconclusive results regarding improvement in clinical outcome.[6,7,9,23] One study assessing the susceptibility of *P. aeruginosa* to tobramycin found that bacteria harvested from day 7 biofilms were extremely resistant to the antibiotic, suggesting that treatment to eradicate the infection would best be done as early as possible.[2,4]

In this study, we compare 2 diagnostic and treatment regimens in their ability to maintain a physiologically stable animal model. Specifically, the study compared the use of standard clinical and hematologic parameters with the use of hematologic parameters alone as a trigger for treatment in dogs with ECIC. In addition, the response to treatment and assessed condition of the animals when the infection is treated with a standard regimen of antibiotic dosage, frequency, and duration versus those after use of a regimen based on recommendations for antibiotic treatment of human catheter infection was compared.[19,24]

Materials and Methods

Animals. Class B random-source mixed-breed adult hound dogs (n = 13, 20 to 25 kg) were entered into the study. Animals were received with proof of vaccination against distemper, hepatitis, leptospirosis, parainfluenza virus, parvovirus, and rabies, and proof of negative heartworm status. Upon arrival at the facility, animals were examined, vaccinated for bordatella (Bronchi-Shield, Fort Dodge Animal Health, Fort Dodge, IA), dewormed (Drontal Plus, Bayer Animal Health, Shawnee, KS), and treated with a single application of flea and tick control medication (Frontline, Merial Animal Health, Duluth, GA). Animals were housed in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and used in an institutional animal care and use committee-approved protocol.

Surgery. All animals underwent left thoracotomy and insertion of catheters (Tygon catheter, Cardiovascular Instrument, Wakefield, MA) into the aorta, left ventricle, and coronary artery. A pneumatic cuff was placed around the inferior vena cava to perform transient occlusion postoperatively. The surgical site was clipped and asepticially prepped for surgery with chlorhexadine scrub and alcohol. All procedures were performed with aseptic technique. Catheters and wires were exteriorized dorsally between the scapulae. The incision was closed in 3 layers. All surgeries were performed by the same surgeon, who had 12 y prior experience with this surgical model. A morphine epidural (0.15 mg/kg epidurally) and fentanyl patch (25 to 50 µg) provided analgesia. Cefazolin (30 mg/kg intravenously) was initiated at the time of surgery. After surgery, animals were housed in cages in the intensive care unit, and physical examinations were performed twice daily.

All animals were allowed 7 d postoperative recovery after implantation before the experimental model was initiated. Coronary embolization and hemodynamic measurements were performed daily over a 2- to 3-wk period. Once the dogs developed chronic heart failure as evidenced by hemodynamic measurements, generally around 4 to 6 wk, either sham or experimental treatment was started. One week later, hemodynamic measurements were taken every other week for an additional 12 wk, for a total of 20 to 22 wk survival postoperatively.

Catheter care. Catheter exit sites were cleaned 2 to 3 times weekly with chlorhexidine (4% solution) or povidone–iodine scrub (10% solution). After a 2-wk postoperative recovery period, experimental manipulations were initiated. Catheters were handled under aseptic conditions, and sterile heparinized saline flush was used before and after infusion or sampling. Before catheters were handled, sterile or clean exam gloves were donned, and the area around the catheter exit site was clipped and cleaned with chlorhexadine or povidone–iodine as described earlier; all equipment was handled by use of sterile technique.[20]

Control and treatment groups. Animals were assigned to 1 of 2 treatment groups. Group A animals (n = 7) underwent surgery in summer 2003 and received the standard antibiotic regimen used in the intensive care unit, which consisted of perioperative cefazolin (30 mg/kg intravenously every 12 h for 24 h)[32] and cephalexin (22 mg/kg orally every 12 h until 10 d postoperative).[14] When infection was diagnosed subsequently (see the section *Diagnosis of catheter-related infection*), antibiotics were administered for 14 d.[19] Choice of antibiotic was left to the discretion of the clinician and was generally either enrofloxacin (5 mg/kg orally twice daily), cephalexin (22 mg/kg orally twice daily), or metronidazole (15 to 30 mg/kg orally twice daily).

Group B animals (n = 6) underwent surgery in summer 2004 and received intraoperative and perioperative antibiotics for 10 d postoperatively identical to that of Group A. However, diagnosis in group B was based on clinical pathology data (see the section *Diagnosis of catheter-related infection*), and antibiotic treatment was administered for 28 d for the first course of treatment and for 42 d for any subsequent treatments.[8,19] The choice of antibiotic was the same as for group A.

Clinical pathology. Complete blood counts (CBCs) with differential were performed weekly on an automated cell counter (Beckman Coulter, Miami, FL). CBC parameters included hemoglobin, hematocrit, white blood cell count (WBC), red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, and differential count.

Diagnosis of catheter-related infection. For group A, diagnosis of a catheter-related infection[18,19,21,24] was defined as a body temperature in excess of 39.4 °C for 24 h; leukocytosis (more than 18,000 white blood cells/ml) accompanied by left shift (presence of immature white blood cells in peripheral blood); or clinical signs such as inappetance for more than 24 h, weight loss, shifting leg lameness, or evidence of organ infection for which no other source of infection was apparent. For group B, diagnosis of a catheter-related infection was defined as the presence of leukocytosis (more than 18,000 white blood cells/ml) independent of left shift, fever, or other clinical signs, such as inappetance.

Clinical scoring. *CBC data and assessment of condition.*

Table 1. Clinical scoring: CBC–Condition

Animal no.	Reviewer no. 1	2	3	4	Mean	1 standard deviation
Group A						
1	5	4	5	4	4.5	0.57735
2	4	5	2	4	3.75	1.2583
3	4	4	3	3	3.5	0.57735
4	3	4	3	3	3.25	0.5
5	4	4	4	3	3.75	0.5
6	3	4	3	3	3.25	0.5
7	3	3	3	1	2.5	1
		Overall			3.5	0.88191
Group B						
8	3	2	2	2	2.25	0.5
9	2	2	2	1	1.75	0.5
10	2	1	1	1	1.25	0.5
11	1	1	3	1	1.5	1
12	3	3	1	1	2	1.1547
13	3	3	4	1	2.75	1.2583
		Overall			1.92	0.928611

Weekly CBC, body temperature, and blood culture results were reviewed, and a composite score (scale, 1 through 5) was assigned, with 1 indicating only minor clinical issues, 3 indicating moderate or considerable clinical issues, and 5 indicating considerable to severe clinical issues.

Table 2. Clinical scoring: assessment of condition

Animal no.	Reviewer no. 1	2	3	4	Mean	1 standard deviation
Group A						
1	4	5	5	4	4.5	0.57735
2	4	5	5	4	4.5	0.57735
3	5	5	4	4	4.5	0.57735
4	3	4	2	3	3	0.81649
5	4	4	3	3	3.5	0.57735
6	2	3	2	2	2.3	0.5
7	2	5	3	3	3.3	1.2583
		Overall			3.64	1.0615
Group B						
8	3	3	1	3	2.5	1
9	1	2	1	1	1.3	0.5
10	1	3	1	1	1.5	1
11	4	3	4	3	3.5	0.57735
12	2	3	1	2	2	0.81649
13	2	3	1	2	2	0.81649
		Overall			2.13	1.0347

Medical records notes for assessments, diagnoses, and treatments were reviewed, and a composite score was assigned on a scale of 1 through 5 (*see* Table 1).

Weekly CBC results, body temperature, and blood culture results (called "CBC-Condition") for each animal were randomized, blinded via removal of date and individual animal identification, and distributed to 4 veterinarians experienced in laboratory animal medicine. Each veterinarian, blind to the treatment group, independently assessed the severity of clinical issues likely associated with the presented objective clinical data from each animal (1, no or minor clinical issues to 5, severe clinical issues). Data were presented temporally, and a single score was assigned to each animal.

From 5 animals in each group, blood cultures were collected at the time of diagnosis of catheter-related infection, as defined earlier, and at 2 d after the completion of a course of antibiotic treatment selected at the discretion of the clinician. A peripheral vein, either the cephalic or lateral saphenous, was clipped and scrubbed with povidone–iodine scrub (10% solution) and alcohol and allowed to dry. The rubber stopper of the collection bottle (BD BBL Septi-Chek TSB, Becton Dickinson, Sparks, MD) was cleaned with alcohol and allowed to dry. Culture tubes were filled with 1 to 3 ml of blood and transported at room temperature.

Full clinical history and assessment of condition. Once the CBC-Condition assessments were returned, the full clinical history (animal medical record notes, assessment of condition and treatment), presented in the same weekly format, was reviewed by the same veterinarians (called "Assessment of Condition") and scored as described earlier.

Body temperature. Body temperature was recorded each day at the time the CBC was collected, between 0800 and 1000.

Left shift. CBC differentials were assessed for left shift, or the presence of immature neutrophils, and quantified.

Completion of the study. The number of animals that completed the study, which was defined as reaching the intended experimental endpoint, was quantified and compared between the 2 groups. A body-weight decrease to less than 15% of the baseline weight or clinical symptoms of infection (as defined earlier) that did not respond to therapy within 48 h of treatment were defined as humane endpoints, prompting early removal from the study.

Statistical analysis. ***Clinical scoring: CBC data (CBC-Condition) and full clinical history (Assessment of Condition).*** The scores from each reviewing veterinarian were averaged for each animal. These mean scores then were averaged for each respective groups, and results were compared by using 2-sample *t* tests.

Body temperature. Because initial body temperatures among animals varied from 37.8 to 39.2 °C, differences between baseline body temperatures were normalized by subtracting the initial body temperature from subsequent body temperature values. The temperatures then were aligned temporally, and means for both individual animals and groups were compared.

For group A, the number of days from the first WBC count that exceeded 18,000 cells/ml until the initiation of treatment according to criteria described earlier was recorded.

Left shift. A left shift was defined as the presence of immature neutrophils in the bloodstream. The weekly CBCs were examined, and the number of animals in each group with a left shift was compared by use of Fisher Exact tests.

Completion of study. The number of animals removed from the study before the intended experimental endpoint was compared between the 2 groups by use of Fisher Exact tests (StataCorp, Stata Statistical Software: Release 8.0, College Station, TX).

Results

Clinical scoring. CBC and Assessment of Condition data are presented in Tables 1 and 2, respectively. Group B dogs had significantly ($P < 0.001$) lower mean CBC-Condition scores than did Group A animals (Group A: $U = 3.5$; 95% CI, 2.93 to 4.07; Group B: $U = 1.92$; 95% CI, 1.35 to 2.48), indicating that group B dogs were in better condition. In addition, group B dogs had significantly ($P = 0.008$) lower mean scores according to the full medical history (Group A: $U = 3.64$; 95% CI, 2.82 to 4.46; Group B: $U = 2.13$; 95% CI, 1.28 to 2.97).

All 7 of the animals in treatment group A grew *Pseudomonas aeruginosa* on blood culture. The condition of 2 dogs resolved

Table 3. WBC ($\times 10^3$/ml) and band counts over time

Dog no.	Week postoperative																					
Group A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1[a]	20.6 0	20.8 0	16.9 0	18.8 0	22.8 0	30.5 0	23.9 0	25.7 0	24.6 0	20.3 0	24.9 0	25 0	15.8 0	16.4 0	15.4 0	19 0	18.5 0	13.3 0	17.2 0	16.9 0	13.9 0	ND
2[a]	18.9 0	16.7 0	18.4 0	27.6 0	23.9 0	26.4 0	28.4 284	40.5 0	20.2 0	29.6 0	26.5 189.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
3[a]	16.1 0	21.7 0	17.2 0	19.5 0	22.6 0	20.6 0	9.2 0	22.3 0	25.7 771	26.5 0	20 0	26.9 269	27.3 304	28.6 571	17.2 0	20.4 0	21.8 124.5	20.4 0	24.1 0	ND	ND	ND
4	19.5 0	17.4 0	15.5 0	24.6 0	24.6 0	23.5 0	23.7 0	11.5 115	28.8 864	23.8 0	24.8 0	28.2 0	22.7 0	18.9 0	16.6 0	27.4 0	23.5 283	21.6 0	21.1 0	23.4 0	20.6 0	ND
5	17.9 0	ND	32.7 0	28.5 0	ND	21.1 0	27.6 276	20.5 0	39.7 0	23.1 0	29.5 1180	21.9 0	20.3 0	18.5 0	3.5 35	21.1 0	22.1 0	21.6 0	26.5 0	ND	ND	ND
6[a]	17.4 0	15.4 0	23.5 470	24.1 0	24.1 0	ND	24.6 492	26.9 0	39.2 1568	45.9 1377	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
7	21.3 0	14. 0	14.8 0	19.4 0	23.4 0	18.9 0	17 0	16.5 0	17.2 0	18.2 0	20.9 0	26.5 530	18.9 0	18.2 0	16.5 0	24.1 284	17.7 0	15.5 0	18.0 0	24.3 0	ND	ND
Group B																						
8	ND	13.9 0	13.1 0	29.1 0	27.6 0	16.1 0	13.3 0	13.2 0	15.5 0	16.3 0	15.2 0	20.1 0	16.1 0	15.1 0	12.5 0	13.9 0	12.1 0	16.7 0	ND	18.7 0	24 0	19 0
9[b]	15.8 0	10.2 0	9.9 0	9 0	11.8 0	11.4 0	19.2 0	24.6 0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
10[b]	12.2 0	12.6 0	24.3 0	18.9 0	21.3 0	17.8 0	23.5 0	22.7 0	21.9 0	24.6 0	16.3 0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
11	12.8 0	11.6 0	9.9 0	13.2 0	16.3 0	17.5 0	15.3 0	22.8 0	11.7 0	ND	11.5 0	14.9 0	15.6 0	14.1 0	14.6 0	17.5 0	15.9 0	14.9 0	15.4 0	18.8 0	ND	ND
12	13.3 0	11.3 0	21.1 0	15.2 0	14.8 0	12 0	12.4 0	12 0	13.6 0	15 0	15.4 0	19.4 0	24.2 0	15.6 0	13.3 0	13.1 0	11.1 0	22.6 0	27 0	14.2 0	12 0	15 0
13[a]	12.4 0	10.9 0	11.5 0	12.4 0	13 0	8.9 0	12.8 0	10.8 0	15.2 0	15.1 0	15.5 0	18.1 0	23.7 0	14.7 0	10.3 0	17.8 0	9.8 0	11.9 0	13.3 0	ND	ND	ND

ND, no data.
[a]Dogs were euthanized before the study's intended experimental endpoint in light of humane considerations.
[b]Dogs were euthanized before the study's intended experimental endpoint due to equipment failure.

such that there was no growth on blood culture subsequent to treatment, but 1 of these 2 dogs later had a recurrent positive *P. aeruginosa* blood culture. In treatment group B, all 6 animals had blood cultures that were positive for either *Staphylococcus intermedius*, *S. aureus*, or *Alcaligenes xylosoxidnes* on initial culture but had no growth on posttreatment cultures.

Body temperature. No significant difference was observed between the 2 groups with respect to baseline or normalized body temperature during the postoperative period.

Treatment. All 13 dogs required treatment with antibiotics at some point during the study. For group A, the number of days from the first WBC count in excess of 18,000 cells/ml until the initiation of antibiotic treatment is reported in Table 3. The average number of days by which treatment was delayed if group A dogs had been treated according to the same criteria as group B was 12 d.

Left shift. Comparison between the 2 groups indicated significantly ($P = 0.005$, Fisher's Exact test) fewer animals in group B experienced a left shift than did those in group A.

Completion of study. Of the 7 animals in group A, 4 did not complete the intended study timeline and were euthanized based on humane endpoints due to their clinical condition. Animals 1 and 3 developed anterior uveitis and secondary glaucoma that became refractory to treatment over time. Animals 2 and 6 developed recurrent shifting leg lameness that over time could not be controlled with antibiotic and analgesic therapy. In group B, only 1 of the 6 dogs did not complete the study because of humane endpoints: animal 13 developed a spontaneous pneumothorax during postoperative week 19.

Discussion

ECICs are associated with considerable morbidity in animals used in research.[32] The goals of this study were to minimize ECIC-associated infection and its adverse effects, thus improving the condition of animals in these studies. The stimulus for this study was dissatisfaction with the outcome of previous studies using generally recommended criteria to diagnose and treat ECIC-related infections. However, the basis for these putative regimens appears to be based largely on procedures used in general veterinary practice, where there is seldom a requirement for ECICs to be maintained for the lengthy durations often required in research. Therefore it is unsurprising that the combination of early recognition of clinical signs consistent with ECIC infection with aggressive and prolonged antibiotic

treatment yielded superior results in this study. Contributing factors likely include intervention with bacterial colonization (biofilm) at an earlier stage and increased antibiotic penetration due to prolonged treatment. Early intervention was possible because neither an elevated temperature nor a WBC with a left shift was required for treatment of infection.

The selection of a WBC count of more than 18,000 cells/ml as a trigger for antibiotic treatment provided an early warning sign of infection. In our experience, using this trigger for treatment and initiating treatment without waiting for the development of additional clinical signs (like fever, inappetance, or evidence of other organ infection) or left shift lead to a more physiologically stable model with respect to CBC parameters and animals that clinically fared better in regards to medical condition as recorded in the medical records. Because the stimulus for a neutrophilia that increases the WBC count is primarily purulent inflammation,[16] an increase in WBCs would be more specific for an infectious cause than clinical symptoms such as fever alone. In our opinion, although the initial WBC count might have been indicative of infection and an appropriate trigger for treatment, subsequent WBC counts did not necessarily reflect the clinical condition of the animal and thus were not used as an outcome measure in this study.

Left shift, or the release of band neutrophils into the bloodstream, is indicative of purulent inflammation in which the increased tissue demand for neutrophils exceeds the marginated storage pool.[16] Therefore, left shift is generally the hallmark of infection or severe purulent inflammation. The polymorphonuclear leukocyte count reflects the number of neutrophils in the circulating pool, and an almost equal number of polymorphonuclear leukocytes are held in a marginating pool which is not reflected in the CBC count. In severe inflammation, such as an intravascular infection, a release of polymorphonuclear leukocytes from the marginating pool is reflected as an increase in circulating pool, which is reflected in the WBC. Because left shifting in dogs is considered indicative of severe infection and because the marginating pool in dogs contributes a pool of neutrophils as large as the circulating pool before the band neutrophils are recruited,[16] we considered any band count greater than 0 in our comparison of the 2 groups. We interpret the lack of left shift in group B as alleviating the infectious stimulus while the marginating pool of neutrophils is still being recruited and before it is depleted, necessitating the recruitment of the more immature band neutrophils into circulation. Therefore, responding to the elevated WBC count without waiting for left shift results in initiation of treatment 2 to 3 d earlier,[16] decreasing the level of bacterial colonization and reducing the likelihood of development of resistance due to biofilm formation. This effect decreases the occurrence of catheter-related bacteremia, which has been associated with osteomyelitis, septic arthritis, endocarditis, and pyelonephritis.[18,27] Early and prolonged treatment, in agreement with the findings of this study, has been shown to improve clinical outcomes.[8,19,27]

Blood culture data were supportive of the increased physiologic stability of treatment group B. Although the development of increasingly resistant bacterial organisms due to long-term antibiotic treatment is a concern, these results suggest that the converse may be true. Further studies, including more frequent testing and larger numbers of animals, are warranted.

Body temperature generally is considered to be a sign of infection or inflammation. Interestingly, there was no significant difference in this parameter between the groups, suggesting that body temperature is not a useful parameter to identify animals that have potential for substantial clinical pathology or clinical conditions that would be consistent with catheter infection and require treatment. This finding is noteworthy, because body temperature monitoring and indications for either treatment or a humane endpoint frequently are used in monitoring animals in research protocols with a potential for catheter-related infections. One study indicated that 71% of catheters from patients with suspected catheter-related infections according to the presence of fever and mild to moderate disease were sterile.[19] Therefore, diagnosis of catheter-related infection due to clinical signs including fever may be erroneous, lead to premature or unnecessary removal of the catheter, and increase the number of study subjects needed to achieve statistical significance.

Clinical condition is a complex and difficult assessment to quantify. However, maintaining the highest standard of animal welfare through the refinement of research protocols is a tenant of our profession. The ability to maintain a complex animal model with the most physiologic stability speaks to both concerns about humaneness in animal research and the generation of refined research data. Within the limits of sample size, our findings imply that the Group B treatment regimen produced a more physiologically stable model, which would represent both refinement in reducing potential experimental variables and a reduction in the total number of animals to complete the study objectives. Further studies with larger numbers of animals are warranted to substantiate this hypothesis.

In this study, dogs bearing ECICs that underwent prolonged antibiotic treatment that was initiated early in light of an elevation in the WBC count remained in better health than did conventionally treated animals. Specifically our findings suggest that:

1. a WBC count that exceeds 18,000 cells/ml is sufficient evidence to initiate treatment,
2. a prolonged course of antibiotic treatment leads to improved health outcome,
3. body temperature alone is not a sufficient predictor of infection, and
4. dogs bearing ECICs that are treated in the described manner are more likely to maintain a physiologic condition (based on humane endpoints) that allows them to complete the study.

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