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Bacteriophage K Antimicrobial-Lock Technique for Treatment of *Staphylococcus aureus* Central Venous Catheter–Related Infection: A Leporine Model Efficacy Analysis

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Abstract

Purpose: To determine whether a bacteriophage antimicrobial-lock technique can reduce bacterial colonization and biofilm formation on indwelling central venous catheters in a rabbit model.

Materials and Methods: Cuffed central venous catheters were inserted into the jugular vein of female New Zealand White rabbits under image guidance. Catheters were inoculated for 24 hours with broth culture of methicillin-sensitive *Staphylococcus aureus.* The inoculum was aspirated, and rabbits were randomly assigned to two equal groups for 24 hours: (*i*) untreated controls (heparinized saline lock), (*ii*) bacteriophage antimicrobial-lock (staphylococcal bacteriophage K,

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propagated titer > 10^8/mL). Blood cultures were obtained via peripheral veins, and the catheters were removed for quantitative culture and scanning electron microscopy.

Results: Mean colony-forming units (CFU) per cm^2 of the distal catheter segment, as a measure of biofilm, were significantly decreased in experimental animals compared with controls (control, 1.2×10^5 CFU/cm^2; experimental, 7.6×10^3; P = .016). Scanning electron microscopy demonstrated that biofilms were present on the surface of five of five control catheters but only one of five treated catheters ($P = .048$). Blood culture results were not significantly different between the groups.

Conclusions: In a rabbit model, treatment of infected central venous catheters with a bacteriophage antimicrobial-lock technique significantly reduced bacterial colonization and biofilm presence. Our data represent a preliminary step toward use of bacteriophage therapy for prevention and treatment of central venous catheter–associated infection.

Microorganisms that colonize indwelling catheters have the capability to form biofilms on the catheter surface, which are a microbially derived community of cells embedded in a matrix of extracellular polymeric substances that are irreversibly attached to a living or nonliving substratum. These biofilms form a microenvironment that confers increased antimicrobial resistance to the embedded microorganisms via various mechanisms. Biofilm-associated organisms can also elicit disease processes by detachment of individual cells or aggregates of cells resulting in bloodstream infections, by production of endotoxin, or by providing a niche for the development of antibiotic-resistant organisms (1–3).

Approximately 250,000 cases of intravascular catheter-related bloodstream infections occur in the United States each year, resulting in a mortality of 12%−25% with an estimated cost of treatment *per episode* of approximately $25,000 (4). The standard management of catheter-related infection involves decisions regarding removal of the catheter and the administration of appropriate antibiotics. Catheter removal and eventual replacement raises important practical problems in these patients requiring parenteral nutrition, chemotherapy, and hemodialysis. To avoid catheter removal, strategies for treatment of catheter-related bacteremia with antibiotics administered through the catheter or locked within the catheter lumen have been previously studied (5–7). However, antibiotic catheter salvage protocols, which include systemic antibiotics, are rarely recommended, particularly in the commonly encountered setting of coagulase-positive Staphylococcus species infection owing to a high failure rate of > 30% and the serious risk of contributing to the development of antibiotic-resistant bacteria (6,7). It is widely believed that the high rate of therapy failure is explained in part by the inability of most antibiotics to kill bacteria growing in a biofilm (3,8–15).

Bacteriophages are viruses that infect bacteria and multiply via a lytic cycle in which the phage particle attaches to the host bacterial cell surface, injects its genomic material, and takes over the host metabolic machinery, resulting in intracellular phage multiplication (1,3). Subsequent bacterial cell lysis and liberation of multiple progeny phage complete the phage lytic cycle. Bacteriophages have been used therapeutically for the treatment of infectious diseases in plants, animals, and humans (eg, dysentery, skin infections, lung infections, meningitis, wound infections, osteomyelitis) caused by various organisms, including *Staphylococcus, Streptococcus, Escherichia coli,* and *Pseudomonas aeruginosa* (16).

Infections now thought to be associated with biofilms, including otitis media, urinary tract infections, periodontitis, and burn infections, have been effectively treated with phage therapy (16–18). Phage therapy could be targeted against multidrug-resistant bacteria with the potential to limit the use of antimicrobial drugs and the spread of antimicrobial resistance (9,15,17–21). Few studies have concentrated on phage application to biofilm control and treatment (19). In vitro investigations suggest that the application of bacteriophages to indwelling medical devices, such as intravascular catheters, could provide a strategy for the reduction in biofilm formation by clinically relevant bacteria such as *Staphylococcus* (20,21).

The purpose of this study was to evaluate bacteriophage antimicrobial therapy for treatment of *Staphylococcus aureus* central venous catheter–related infections in a leporine model. A secondary objective was to investigate whether bacteriophage antimicrobial therapy could reduce catheter-related bloodstream infections in a leporine model.

MATERIALS AND METHODS

Animal Model and Catheter Insertion Technique

This study was approved by the Duke University institutional animal care and use committee. Intramuscular anesthesia with ketamine (70 mg/kg body weight) and xylazine (7 mg/kg body weight) was administered to 10 female New Zealand White rabbits weighing 3–4 kg. General anesthesia was maintained with isoflurane via an endotracheal tube. After the surgical sites were shaven and prepared in usual sterile fashion, a surgical cutdown was performed over the right internal jugular vein. The vein was accessed with a 22-gauge needle under direct visualization. An 0.018-inch guide wire was inserted through the needle, which was exchanged for a micropuncture sheath (Cook, Inc, Bloomington, Indiana). A 5-F peel-away sheath (Bard Access Systems, Salt Lake City, Utah) was inserted over a 0.025-inch guide wire. The exit site was created in an intrascapular location, and a single-lumen 4.2-F Broviac catheter with polyethylene cuff (Bard Access Systems) was tunneled to the access site and inserted via the peel-away sheath (Figs 1, 2). The catheter tip was positioned in the right atrium using fluoroscopic guidance.

Microorganisms and Culture Conditions

S. aureus 46106, a methicillin-susceptible isolate from an abdominal wound that was negative for toxic shock syndrome toxin and Panton-Valentine leucocidin, was obtained from the U.S. Centers for Disease Control and Prevention Clinical and Environmental Laboratory Branch culture collection. This strain was used for growing biofilms in the rabbit catheter model. Cultures were stored at —71 °C and subcultured on trypticase soy agar containing 5% sheep's blood (blood agar) (BD Diagnostics, Franklin Lakes, New Jersey) overnight. Viable cultures were grown in Brain Heart Infusion Broth (BD Diagnostics) at 37°C with shaking to obtain a cell suspension equivalent to a 0.5 MacFarland standard (10^8 colony-forming units [CFU]/mL) on the day of use. *S. aureus* Phage K and its host strain *S. aureus* (ATCC 19685) were obtained from ATCC (Manassas, Virginia). Phage K was propagated using the soft agar overlay technique (22). Crude high-titer phage broth cultures were prepared according to Adams (23) using Brain Heart Infusion Broth supplemented

with 3 mmol/L magnesium chloride and 4 mmol/L calcium chloride (added as $MgCl_2 \cdot 6H_2O$ and $CaCl_2 \cdot 2H_2O$). Phage broth cultures were diluted in heparinized saline (1:10 dilution) and filter sterilized (0.2 μm) before use.

Catheter Inoculation

After placement, catheters were filled with 0.3 mL of a 10^8 CFU/mL log phase culture of *S. aureus* 46106. The inoculum was locked in the lumen of the indwelling catheter and remained in place for 24 hours. After 24 hours, the inoculum was carefully withdrawn from all catheters by aspiration. Experimental design was based on prior work with bacteriophage K and clinical *S. aureus* strain (19,21).

Experimental Approach

The 10 rabbits were randomly assigned to treatment or control arms. After 24 hours of bacterial inoculation, five control-arm animal catheters were locked with 0.3 mL of heparinized saline, and five experimental-arm catheters were locked with 0.3 mL of a 10^8 plaque-forming units/mL solution of bacteriophage K, prepared as described earlier, for 24 hours. After 24 hours of lock treatment, blood cultures were obtained from each treated and control animal via peripheral ear veins and analyzed using the BACTEC 9000 System (BD Diagnostics) reporting presence of bacteremia, species, and antibiotic sensitivity profile. All rabbits were euthanized by intravenous injection of sodium thiopental (Euthasol euthanasia solution; Virbac, Fort Worth, Texas). Catheters were removed for microbiologic evaluation using aseptic technique, clamped on each end to prevent dehydration of biofilms in the catheter lumen, and processed to recover microorganisms from the luminal surfaces using a previously published method (21). Briefly, the outer surface of the catheters was disinfected with 0.525% sodium hypochlorite, rinsed in sodium thiosulfate, and air dried in a biologic safety cabinet. A 1-cm section was cut from the distal end of the catheter, rinsed gently in sterile phosphate-buffered saline, and bisected lengthwise using a sterile scalpel. Each half of the catheter section was placed into a tube containing 10 mL of phosphate-buffered saline and subjected to three alternating 30-second cycles of water bath sonication (45 kHz, Branson Sonicator; Branson Ultrasonics Corporation, Danbury, Connecticut) and vortexing. The resulting biofilm suspension was diluted in Butterfield Phosphate Buffer (Hardy Diagnostics, Santa Maria, California), and the dilution plated on blood agar, incubated for 48 hours at 37°C, and counted using standard microbiology technique.

Scanning Electron Microscopy of Catheter Segments

Adjacent catheter segments were also collected for examination using scanning electron microscopy (SEM). Catheter segments were opened to expose the lumen, fixed in 2% glutaraldehyde, and dehydrated for SEM. The fixed and dehydrated catheter segments were sputter coated with gold-palladium (60/40) and viewed under a Philips XL30 scanning electron microscope (FEI Company, Hillsboro, Oregon). Subjective assessment of biofilm burden was based on nonquantitative evaluation of SEM images from each of the catheter segments by a pathologist blinded to the experimental design. Images were graded as either positive for biofilm (presence of biofilm cells on the catheter surface) or negative (absence of biofilm cells on the catheter surface).

Statistical Analysis

All statistical tests were performed using SPSS version 19 (IBM, Armonk, New York). Mean plate counts (as $\log_{10}$ CFU per cm^2) for treated and untreated catheter sections were compared using the Mann-Whitney *U* test. Results from blood cultures and qualitative SEM biofilm analyses were compared between the groups with the Fisher exact test (two-tailed). A *P* value < 0.05 was considered statistically significant.

RESULTS

All 10 rabbits survived the catheter insertion, inoculation, and treatment protocol. After intraluminal inoculation with *S. aureus* and a subsequent catheter lock solution consisting of heparinized saline for 24 hours, analysis of catheter tips from these control animals revealed a mean of 1.2×10^5 CFU/cm^2 (range, 2.7×10^4—3.6×10^5 CFUcm^2; SE, 6.3×10^4 CFU/cm^2). In comparison, catheter tips from catheters that were treated with a catheter lock solution consisting of bacteriophage K for 24 hours had a mean of 7.6×10^3 CFU/cm^2 (range, 0–3.46×10^4 CFU/cm^2; SE, 6.7×10^3 CFU/cm^2); this was significantly lower than the control group (*P* = .016) (Fig 3).

SEM analysis of the catheter segments demonstrated qualitative reduction of biofilm in treated catheter segments compared with untreated controls (five of five controls with biofilm present, one of five experimental catheter segments with biofilm present, *P* — .048) (Fig 4a–d). Blood culture results were not significantly different between the control and experimental groups (three of five positive vs four of five positive, *P* — 1.0). Positive blood cultures in all instances confirmed the presence of methicillin-sensitive *S. aureus*.

DISCUSSION

The broad objective of this research was to investigate further an alternative antimicrobial therapy for salvage treatment of long-term central venous catheter–related infection using bacteriophage. We demonstrated in an animal model a significant decrease in *S. aureus* biofilm formation on the intraluminal surface of indwelling central venous catheters treated with a bacteriophage lock compared with untreated controls. Prior studies by Curtin and Donlan (21) and Fu et al (20) demonstrated in in vitro models 99.9%–99.99% reductions of bacteria on catheters pretreated with bacteriophage; later, Lungren et al (19) demonstrated > 99% reduction of biofilm on treated catheter surface material using bacteriophage in vitro. However, the clinical significance of this prior *in vitro* work is unclear. Phage therapy involves the targeted application of bacteriophages that, on encounter with specific pathogenic bacteria, can infect and kill them. To be successful, phage therapy must deliver sufficient phage density in the vicinity of the target bacteria to achieve bacterial clearance (24,25). For this reason, the antimicrobial “lock” strategy used in the present study as a treatment for indwelling central venous catheter infections has a high likelihood of delivering satisfactorily high concentrations of phage to the target in vivo. In view of the more challenging environment in the animal model, the 94% reduction in biofilm formation in the present study is noteworthy. Examination by SEM also confirmed qualitative reduction of biofilm in treated catheter segments.

Bacteriophage K, used in the present study, is a polyvalent *Staphylococcus* phage and is capable of lysing 10 different *Staphylococcus epidermidis* strains and 9 different *Staphylococcus* species including a vancomycin-resistant *S. aureus* strain and several methicillin-resistant *S. aureus* strains (26–29). Our study used bacteriophage K titers in a bacteriophage lock in the lumen of colonized catheters with concentrations of $> 10^8$ plaque-forming units/mL. We are unaware of other studies that have investigated the use of bacteriophage K in an animal model, and it is currently unknown whether varying phage concentrations would lead to a more or less effective therapeutic response. Further work is needed to delineate an ideal dwell time, concentration, and systemic response to therapy. At the present time, it is virtually unknown how phage will interact when exposed to the intravenous environment in humans, and research is needed to understand what is likely to be a complex biologic interaction.

Catheter-related infection can occur via numerous routes, including intraluminal contamination from infusates and handling, extraluminal tracking of microorganisms along the outer surface of the catheter into the bloodstream, and hematogenous seeding from a distant source (30). Our in vivo experiment employed a model of intraluminal colonization with bacteriophage lock therapy 24 hours after initial inoculation. The effective use of bacteriophage therapy relies on employing a bacteriophage specific for the bacterial strain being targeted. Although the specific bacteriophage can be generated or obtained when the responsible bacterial strain has been identified, a more practical approach may involve the use of a “cocktail” of a variety of bacteriophages against the most common, or perhaps the most virulent, organisms. Although this strategy could potentially treat the catheter lumen, it does not address the outer surface of the catheter and the bloodstream, both of which are frequently involved in catheter-related infection. With our experimental model, bloodstream seeding likely occurs during or very soon after catheter lumen inoculation. It is not surprising that we did not find a reduction in bacteremia with the bacteriophage lock therapy considering that the quantity and technique chosen for bacteriophage treatment was designed solely for treatment of the catheter lumen. This study is a preliminary step toward the development of a new strategy for treating central venous catheter infections because bacteriophage therapy has never been reported, to our knowledge, for an intravascular surface.

This study has additional limitations. The small sample size may limit a broad generalization of the findings, although statistical significance was achieved. The biofilm in this work was artificially composed entirely of a single strain of *S. aureus*. However, we chose bacteriophage K because it has a broad spectrum of lytic activity, particularly against the organisms most commonly found in device-associated infections. Further work is needed to investigate effectiveness of phage therapy on polymicrobial biofilms. With this study design, there is the potential for sampling error because only 1 cm of distal intravenous catheter was sampled for analysis, and it is possible that alternative catheter segment sampling strategies would yield different results. Nonetheless, this protocol was in keeping with standard of care for the management and speciation of indwelling central line infections. We did not compare varying phage lock catheter dwell times, concentration of phage, or, more importantly, the rabbit antibody response after exposure to phage therapy. Based on prior literature, it is possible that phage lock therapy may lead to decreased effectiveness over time secondary to

the immune response and subsequent clearance (26–29). Further work is needed to investigate this and other important aspects of this therapeutic strategy.

In conclusion, treatment of central venous catheter *S. aureus* infection with a bacteriophage antimicrobial-lock technique significantly reduced bacterial colonization and biofilm presence in a leporine model. Although evidence supporting the use of phages for the treatment of device-associated biofilms in humans is lacking, this and other recent studies involving the interaction of phage and biofilms have shown phages to have promise as an alternative therapy for biofilm-associated infection. Further investigation is warranted.

Acknowledgments

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ABBREVIATIONS

CFU	colony-forming unit
SEM	scanning electron microscopy

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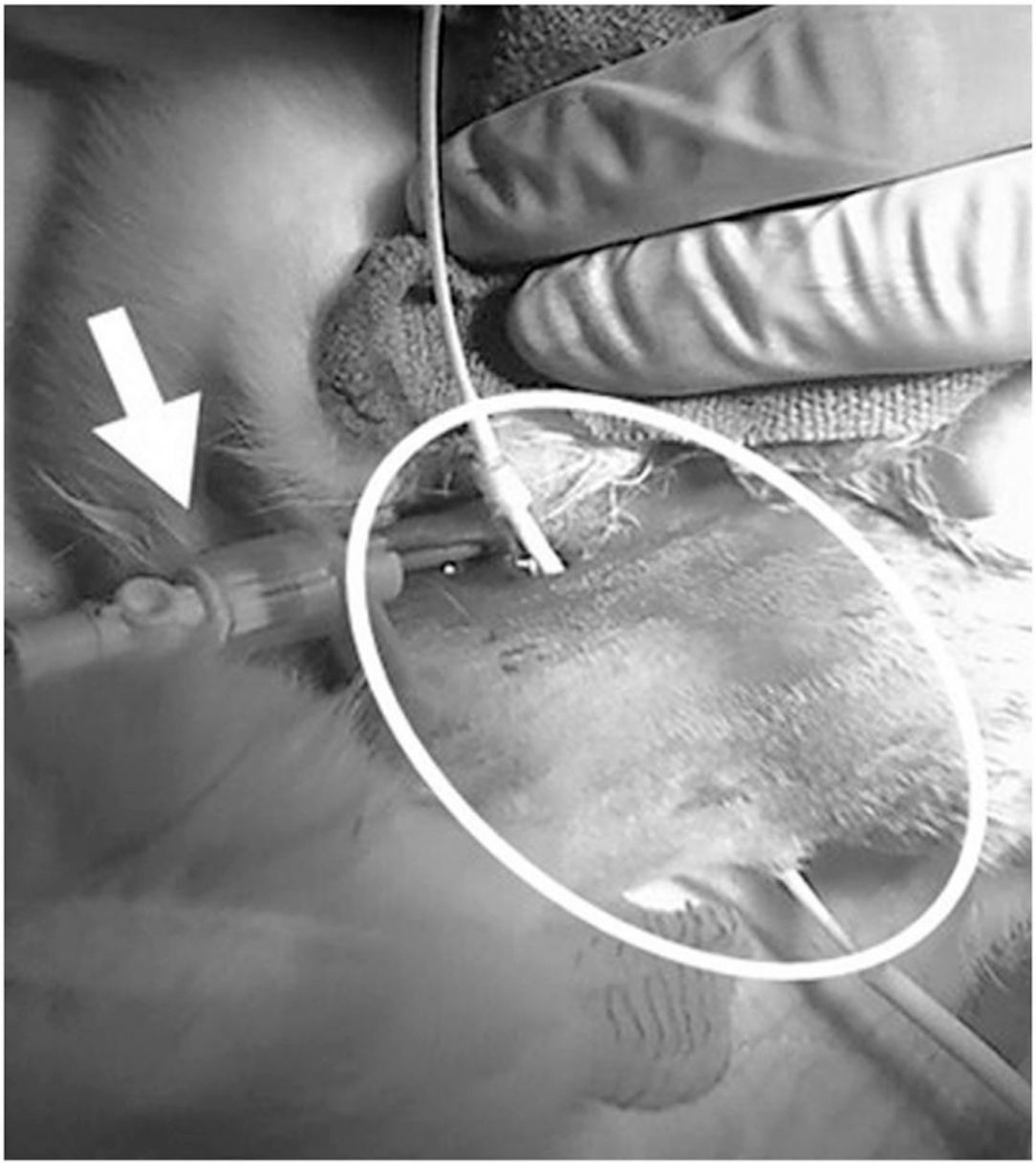

Figure 1.
Intraoperative photograph of a female New Zealand White rabbit after insertion of the peel-away sheath (arrow) into the right internal jugular vein and interscapular subcutaneous tunneling of the 4.2-F catheter from the venotomy to the skin exit site (circle).

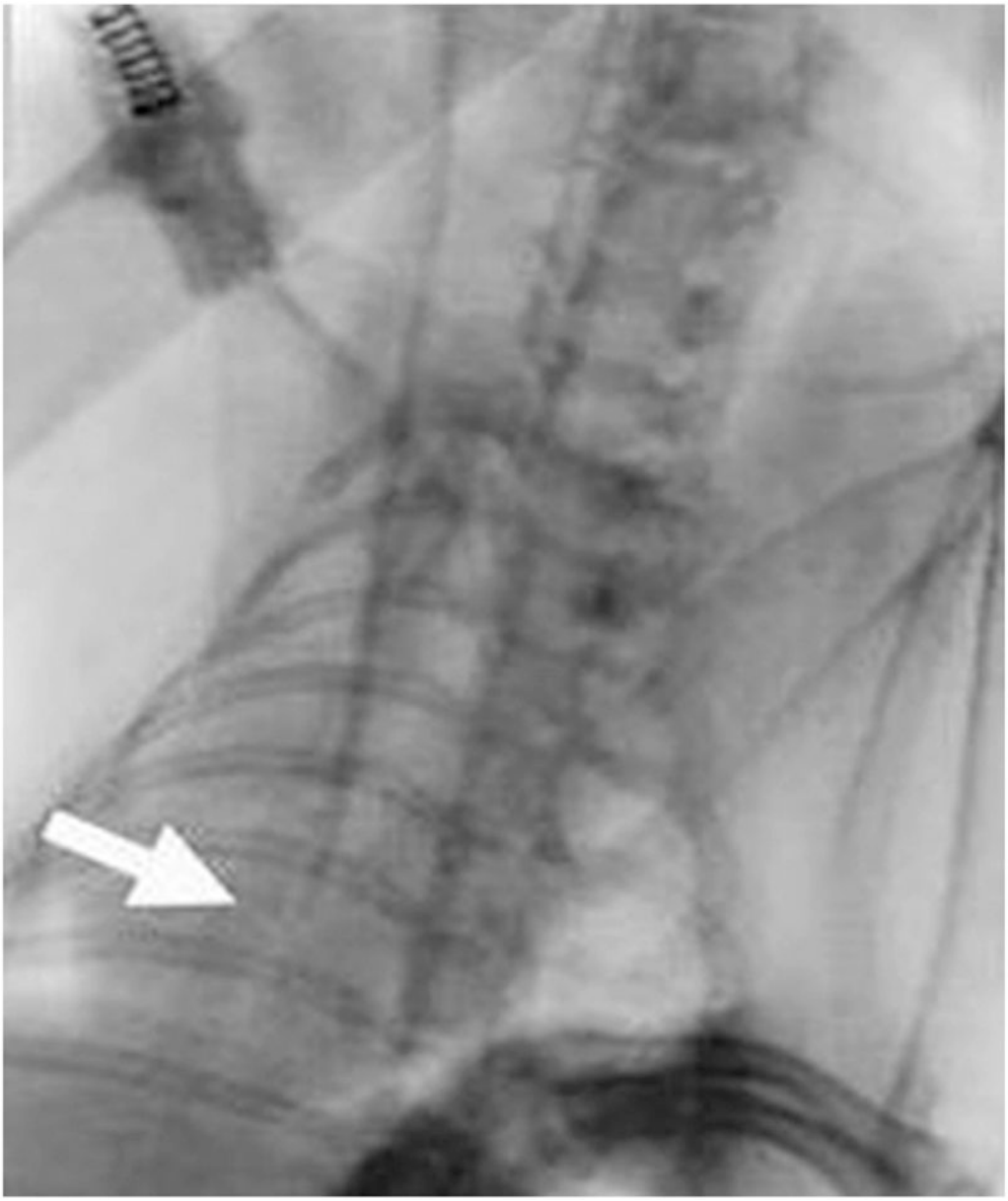

Figure 2.
Anteroposterior and lateral intraoperative fluoroscopic images of a New Zealand White rabbit after percutaneous intrascapular tunneled line insertion. Catheter tip (arrow) projects over the right atrium.

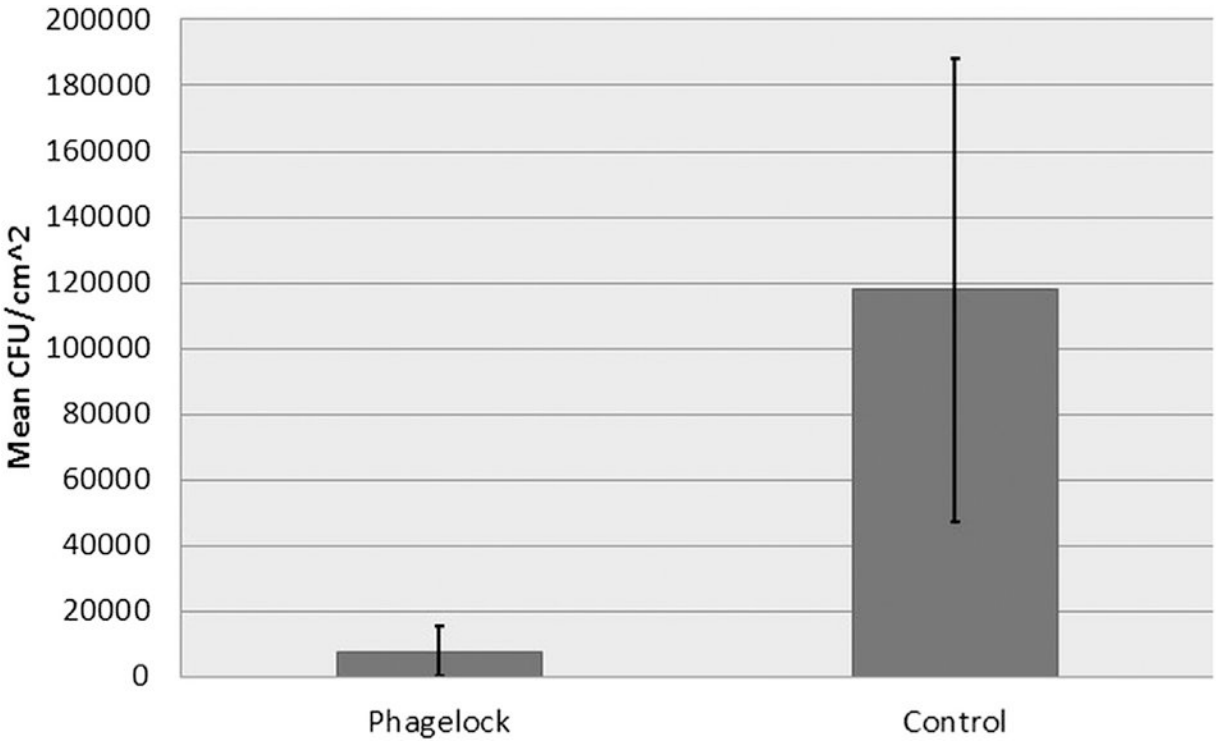

Figure 3.
Mean CFU/cm^2 of experimental bacteriophage-treated and control groups (n = 5 per group; P = .016).

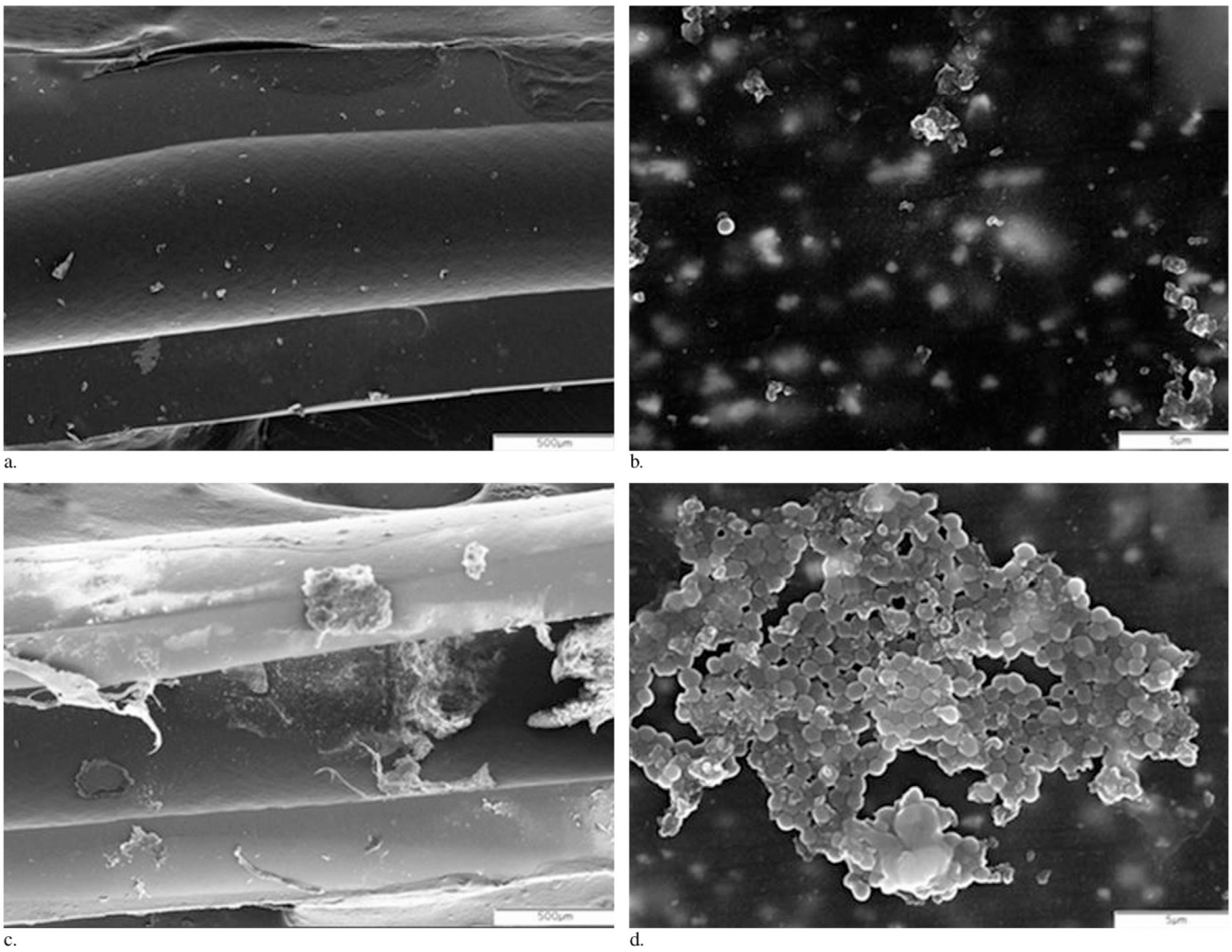

Figure 4.

Representative SEM images of distal catheter segments. Experimental catheter segment is shown under 40× **(a)** and 4,000× **(b)** and demonstrates no visible bacterial cells or biofilm matrix. Control catheter segment image reveals biofilm-coated catheter segment at both 40× **(c)** and 4,000× **(d)**.