SAN DIEGO STATE UNIVERSITY

IACUC Guidelines

Maintenance of Chronic Indwelling Devices

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INTRODUCTION

In a research setting, animals are implanted with chronic indwelling devices for a variety of reasons. The implantation of jugular catheters for the intravenous administration of compounds, intracerebro- or intracerebroventricular cannulae or electrodes for administration of compounds or stimuli into structures of the brain, subcutaneous pumps or pellets for continuous administration of compounds, and telemetry devices for collection of physiological data are just a few examples. The rationale for implanting devices such as those described above is to allow for repeated sampling, compound administration or data collection over time. And although the implantation of the devices may initially involve an invasive surgical procedure, overall the animal is subjected to less invasive manipulations over the course of the study by having the device in place. However, the placement of a chronic indwelling device is not without potential for complications. Devices have the potential to become dislodged, displaced, become nonfunctional, serve as a conduit for or a nidus of infection, cause localized or systemic complications, and ultimately become a source of pain and/or distress to the animal. It is for these reasons that the decision to implant a chronic indwelling device into an animal should be carefully weighed and great care should be taken in the implantation and management of the device to minimize the likelihood of complications.

IMPLANTATION OF THE DEVICE

It is imperative that the surgical implantation of a device be done with strict adherence to aseptic technique. Investigators using rodents must resist the temptation to compensate for inadequate aseptic surgical or device maintenance techniques by increasing animal numbers to achieve statistical significance in their studies (1). However, improper aseptic technique may invalidate a study. Serious adverse consequences and complications regarding the physiology, metabolism, and behavior or rodents with postoperative infections have been well documented (1). Every component of the device must be sterile prior to implantation. Many devices purchased from medical suppliers arrive prepackaged and sterilized. In addition, it may be preferred to utilize devices which are impregnated with antibiotics or made of materials known to be associated with fewer infectious complications such as Teflon or polyurethane. If devices are assembled "in-house" then only medical/surgical grade components which can be sterilized should be selected. If certain components of the device are unable to withstand the autoclaving

process, then an effective alternative sterilization process such as ethylene oxide or hydrogen peroxide (Sterad®) should be used. As chronic indwelling devices often access the vasculature or central nervous system the consequences of contamination at the time of surgical implantation can be profound and may have serious consequences as to the effect on the research data and/or the animal.

The following resources are available which detail performing surgery using aseptic technique:

- SOPs
- Surgery Training Class and Video
- Veterinary Consultation
- DAR Library Reference Materials

MAINTAINING THE DEVICE

Often, the purpose for a chronic indwelling device is to allow for repeated access to a body compartment such as the vasculature or the central nervous system. Each time devices such as catheters or cannulae are accessed there is the potential for complication and the major medical complication associated with the use of implanted devices is infection (2). And with any implanted device, the potential for complications exists for as long as the device is in place. Methods for reducing possible infections include:

- The use of aseptic technique when accessing any device including if applicable surgical preparation of the site, sterile gloves, sterile draping of the site
- The use of sterile equipment such as plugs/stylets, tubing, syringes, needles, adaptors
- The use of sterile medical grade compounds or solutions for administration
- Secure caps/ports/ protectors which effectively close off and protect the access site
- Frequent assessment of the devices and equipment for potential contamination
- Frequent replacement of equipment such as stylets, tubing, syringes, adaptors particularly if sterility cannot be maintained or confirmed

CHRONIC INDWELLING VASCULAR CATHETERS

Chronic indwelling vascular catheters are commonly used in research animals for procedures including chronic drug self-administration, intermittent blood sampling, and pressure monitoring (3). Complications arising from intravascular catheters can be grouped into three general categories: mechanical, infectious and thrombotic (4). In humans, intravascular catheters are one of the most common causes of hospital-acquired blood stream infections (5) and are a substantial cause of morbidity and death in hospitalized patients (6). Much of the two- to three-fold increase in nosocomial bloodstream infections observed beginning in the 1980's has been attributed to catheter infection (7). The common sources of infection are from the microbes that colonize the skin at the insertion site and the catheter hub (8,9). The mechanisms include: infection of the skin surrounding the catheter exit site, followed by migration of microbes along the external catheter surface; contamination of the catheter hub followed by intralumenal catheter colonization; and hematogenous seeding of the catheter (4). Various institutions,

including the Centers for Disease Control (10), have developed guidelines and training programs for the insertion and maintenance of catheters to help reduce the incidence of catheter-associated infections (6,10,11). Maximal sterile barrier precautions including a large sterile drape, sterile gown, sterile gloves, cap and mask have been recommended for the insertion of chronic indwelling central catheters due to the substantially higher risk for infection (6,10,12).

CATHETER CONSTRUCTION

Foreign bodies are well known to predispose to infection (5) and catheter material may promote thrombogenesis and adherence of organisms (12). The construction of the catheter is an important factor. Catheters with surface irregularities or those made of polyethelene or polyvinyl chloride are more likely to become infected (5). Flexible silicone and polyurethane catheters have been demonstrated to be less thrombogenic (10,12). Catheters may also be coated or impregnated with various anti-thrombotic, antiseptic or antibacterial agents which may reduce the incidence of thrombosis and infection at the catheter site (1,13,14). The use of antimicrobial impregnated or thrombo-resistant coated catheters should be considered (1,4). Advantages and disadvantages of two of the more commonly employed antimicrobial impregnated catheters are described in table 1.

Table 1. Advantages and disadvantages of antimicrobial impregnated catheters for the prevention of catheter-related infection.

Type of Impregnated Catheter	Advantages	Disadvantages
Chlorhexidine and silver sulfadiazine	Several studies support efficacy Cost-effective Agents not used therapeutically	Coated only on the external surface Antimicrobial durability of less than 1 week Anaphylactic reactions have been described
Minocycline and rifampin	Coated on both external and internal surface Antimicrobial durability of more than two weeks More efficacious than the chlorhexidine and silver sulfadiazine impregnated catheter in large randomized trial No hypersensitivity reactions have been reported	Greater risk of resistance More expensive than the chlorhexidine and silver sulfadiazine impregnated catheter

From Carratala (15).

CATHETER SURGERY

Aseptic surgical technique is critical during catheter placement. Nonsterile rat catheterization techniques contradict the basic surgical principle that implantation of a contaminated foreign body leads to almost certain infection and to subsequent death if the foreign body is allowed to remain in contact with the blood stream (3). A study by Popp

et al., compared rats subjected to a sterile superior vena cava (SVC) catheterization, a conventional clean but nonsterile SVC catheterization or sham operation. Three of six nonsterile conventionally catheterized animals died and 5/6 had infected catheters. All sterilely catheterized animals survived the 25d study period and none had catheter infection (3).

Central venous catheters (CVCs) carry a substantially greater risk for infection. The level of barrier precautions needed to prevent infection during insertion of CVCs should be more stringent. Maximal sterile barrier precautions (e.g. cap, mask, sterile gown, sterile gloves and large sterile drape) during insertion of CVCs substantially reduce the incidence of catheter related bacterial systemic infections (10).

CHRONIC CATHETER CARE

Table 2. Risk and protective factors associated with catheter related infection.

Risk Factors	Protective Factors
Prolonged catheterization	Insertion/Maintenance of catheter by infusion therapy team
Frequent manipulations	
Improper aseptic techniques*	Use of topical disinfectants and antibiotics
Catheter material	Use of silver-impregnated cuff
Number of catheter lumens	Coating catheters with antimicrobial agents
Location of catheter	

*During insertion or maintenance.
Adapted from Raad et al. (12).

Table 3 Summarizes Recommendations from the Centers for Disease Control (CDC) and other publications regarding Inserting/Maintaining Catheters

1.Standardization of aseptic care decreases the risk for infection and insertion and maintenance of intravascular catheters by inexperienced staff may increase the risk for catheter colonization and catheter related bacterial systemic infections (8,10).
2. Skin antisepsis – povidone iodine is widely used for cleaning insertion sites. However, 2% aqueous chlorhexidine gluconate lowered infection rates when compared with 10% povidone iodine or 70% alcohol (8,10).
3. In-line filters reduce the incidence of infusion related phlebitis.
4. Catheters and cuffs impregnated with antimicrobial or antiseptic agents can decrease the risk of infection (4,10).
5. Antibiotic/antiseptic ointments. Use of povidone iodine ointment at the catheter insertion site may be more effective in reducing exit-site infections than triple antibiotic ointment (bacitracin, neomycin, polymyxin (8,10). To avoid compromising the integrity of the catheter, the ointment and catheter manufacturers' recommendations regarding compatibility should be checked. (10).
6. Prophylactic antibiotic therapy. No clear evidence to support the use of oral or parenteral antibacterial or antifungal drugs to reduce the incidence of infection.
7. Intralumenal antibiotic locks may be useful however antibiotic resistant bacterial infection is of concern (10)
8. Anticoagulant flush solutions are widely used to prevent catheter thrombosis. Thrombi and fibrin deposits may serve as a nidus for microbial colonization of intravascular catheters, therefore anticoagulants may have a role in the prevention of catheter related systemic bacterial infections (10).
9. Hub maintenance/replacement. Excessive manipulation of central venous catheters increases the risk for catheter related bloodstream infection (8). This is probably due to the greater risk for a breach in aseptic technique with multiple manipulations (8). Catheter hubs and sampling ports should be disinfected before they are accessed. Alcohol, povidone-iodine and chlorhexidine are effective to physically remove most pathogens from the catheter hub (8). During prolonged catheterization, catheter hubs are accessed multiple times, increasing the likelihood that catheter related bloodstream infection emanates from colonized hubs rather than the insertion site (5,8). More frequent hub changes may be required to

lower the rate of catheter related bloodstream infections (4)
10. Catheter replacement remains controversial (12). The exchange of a central venous catheter over a guidewire carried with it a high risk of reinfecting the new central venous catheter (5,12). Replacement of catheters in the presence of bacteremia is not an acceptable replacement strategy (10). The more frequently a catheter is replaced with a new catheter at a new site, the more likely the patient will have a mechanical complication during insertion (4).
11. Replace IV administration sets every 72-96 hours (10).
12. Remove catheters as soon as possible after their intended use (8,10).

CATHETER ACCESS

Catheter access may be accomplished by externalizing the proximal end of the catheter or by surgically implanting vascular access ports to allow percutaneous catheter access. Externalized catheters have the disadvantage of possible local or systemic infections because they disrupt the epidermal integrity. Externalized catheters may also elicit local inflammatory reactions such as fibrous tracts or granulomas. Elimination of these infections and inflammatory reactions usually involves removal of the catheter and rigorous antimicrobial therapy. Subcutaneous access ports may help avoid catheter tract infections, however, careful attention to aseptic procedure is of utmost importance when accessing the port. (1).

CATHETER MAINTENANCE

Sepsis and thrombosis are the primary catheter-related complications. The incidence of these complications depends largely on how long the catheter is in place and how the catheter is maintained. Various solutions containing antimicrobials, anticoagulants or combinations of both have been used to flush and/or lock catheters. The antibiotic lock technique consists of filling and closing the catheter lumen with an antibiotic solution and allowing it to dwell for a period of time (15). The method is designed to allow delivery of a high concentration of an antimicrobial to the catheter lumen. While the technique may be effective at reducing bacterial colonization, the emergence of resistant bacteria is of great concern (15). Table 4 compares some catheter lock solutions.

Table 4. Comparison of activity, advantages and disadvantages of catheter lock solutions.

Solution	Activity	Advantages	Disadvantages
Vancomycin/Heparin	Antimicrobial/ Anticoagulant	Decreased frequency of catheter related bacteremia attributed to luminal colonization	Emergence and spread of vancomycin resistance
Minocycline/EDTA	Antimicrobial/ Anticoagulant	Work synergistically no toxicities reported	
Minocycline-Rifampin	Antimicrobial	More effective in combination than when used individually	
Ciprofloxacin-Rifampin	Antimicrobial	More effective in combination than when used individually	
Vancomycin-Rifampin	Antimicrobial		Vacomycin antagonistic to Rifampin Vancomycin resistance
Taurolidine (2%)-polyvinylpyrolidine (5%)	Antimicrobial	Novel method of action makes resistance less likely Has anticoagulant activity	Dose-related reversible thrombocytopenia and neutropenia at high doses.
Ethanol	Antimicrobial	Activity based on denaturization	Side effects – fatigue, headache,

		Has anticoagulant activity	dizziness, nausea, light-headedness

From Carratala (15) and Sherertz et al (16).

DEVICE-RELATED INFECTIONS

The spectrum of systemic infections may range from a clinically inapparent infection to fulminant sepsis (5). Symptoms and signs of infection in patients with central venous catheters without another confirmed source should raise the concern of catheter infection (4). However, it is important to realize that in the majority of cases of central vein catheter associated bacteremia there will be little or no evidence of sepsis at the insertion site (5). Thrombotic complications are common in long-term catheterized veins and are often associated with catheter sepsis (17).

Table 5. Possible clinical signs/observations associated with device related infections.

Device	Complication	Clinical Signs
Catheter Subcutaneous Implant	Local Infection	-swelling -erythema -tenderness -warmth -discharge (purulent, serous, sanguinous)
Catheter	Tunnel or Intracutaneous Infection (5)	-swelling, erythema, and cellulitis along the subcutaneous tract -"milking" the vein after catheter removal and demonstrating the presence of pus
Any Implanted Device	Blood Stream Infection/ Septicemia	-weight loss -inappetance -inactivity -abnormal posture -fever -palor -signs of other systemic illness (respiratory difficulty, oculonasal discharge) -diarrhea -hypothermia
Catheter	Thrombosis/ Emboli	-acute death -respiratory distress -cyanosis -edema -ascites
Intracerebral/ Intracerebro-ventricular Implant	Meningitis	-weight loss -inappetance -inactivity -abnormal posture -fever -painfulness -neurological signs (head tilt, ataxia)
	Osteomyelitis	-weight loss -inappetance -inactivity -abnormal posture

		-fever -painfulness

PATHOGENESIS OF INFECTION

The major medical complication with the use of implanted devices is infection (2). The impact of such infections is profound because they often result in tissue destruction, serious dysfunction of the implanted device, and systemic dissemination of the pathogen (2). It is widely accepted that these infections are difficult to cure with antimicrobials and often necessitate removal of the device (1,2,18,19). In general, once significant infection of the CSF has occurred, most studies indicate the need for need for removal of the infected apparatus and the administration of appropriate systemic antibiotics (18). Endocarditis or septic thrombophlebitis may be suspected if bacteremia persists for more than 48h after removal of the infected device and initiation of antibiotic therapy (12). Catheter removal is recommended for tunnel infections and/or septicemia (5,12). The most effective approach to foreign body infections is prevention. In most cases, introduction of microorganisms associated with permanently implanted devices are introduced with the device at the time of surgery(18).

The presence of a foreign body may compromise host defenses by a variety of mechanisms. Many devices transect the cutaneous barrier and provide a direct route of invasion for bacteria and fungi (2). In some instances bacteria may only produce infections in the presence of a foreign body. The foreign body may interfere with the host's ability to clear these normally avirulent organisms (20). The body reacts to foreign implants by coating them with a film which contains various proteins such as fibronectin, fibrin, collagen and immunoglobulins. This coating may play a role in bacterial adherence as well (2). The properties of colonizing bacteria may also be a factor in the pathogenesis of device infection. Bacterial slime production is important in bacterial adherence and colonization of smooth surfaces such as catheters (20,21).

Table 6. Preventive measures that have been advocated to decrease the incidence of infection of permanently implanted devices.

- The use of a laminar air flow and high volume air filtration in the operating theater.
- Preoperative skin preparation with aseptic soap.
- Administration of prophylactic antibiotics.
- Minimizing operative time and tissue trauma.
- Use of prosthetic materials that have lower affinities for pathogens, antimicrobial properties and/or enhanced biocompatibility with the tissue environment into which the device is placed.

Dickinson (13)

DIAGNOSTIC TECHNIQUES – CULTURE

Various quantitative and semi-quantitative culture methods may be acceptable. Table 7 excerpted from article by Siegman-Igra et al compares the various techniques.
In a review of methods for diagnosing catheter related infections, Siegman-Igra et al., concluded that quantitative culture was the most accurate method for catheter segment culture and unpaired quantitative catheter blood culture was the most cost-effective test, especially for long-term catheters (7).

Table 7. Summary of various techniques for diagnosing catheter related infection.

Material Employed	Technique	Criterion for Positive Result reported from various sources	Catheter in situ	Rapid
Catheter segment	Quantitative culture	>=10^3 CFU per segment	No	No
	Qualitative culture	Any growth	No	No
	Gram stain	>=1 organism per 20 oil immersion fields	No	Yes
Blood from catheter	Quantitative culture paired with blood from peripheral vein	Catheter counts>vein counts	Yes	Yes
	Quantitative on pour plate or agar	Any growth to >=25 CFU per ml	No	No
Skin swab at insertion site	Nonquantitative	Any growth	Yes	No
	Gram stain (if purulent)	Not reported	Yes	Yes

Adapted from Siegman-Igra et al (7)

RECOMMENDED INTERVENTIONS FOR CATHETER ASSOCIATED INFECTIONS

Table 8 describes potential complications associated with chronic indwelling devices and the recommended interventions for therapy and/or maintaining the device. Any therapeutic intervention, whether medical or surgical, must be done under veterinary direction. Inappropriate or indiscriminate therapeutic intervention may further compromise the animal or confound further efforts to treat the animal. Consultation with the veterinary staff is encouraged with regard to the animal's clinical status, experimental status, and therapeutic options. Research personnel are encouraged to contact the veterinary staff if they suspect a health related problem based on such things as observation of the animal, changes in the experimental performance of the animal, changes in weight and/or changes in food/water consumption. A positive outcome is more likely if therapy is initiated earlier in a disease process rather than in the later stages. In some cases, a lack of response to therapy or progression of signs can be determined sooner in the disease course so the animal can be euthanized prior to becoming critically ill or moribund. Animals with severe clinical signs are unlikely to respond to therapeutic intervention. In addition, as removal of the device is often a necessary component of therapy, these animals are unlikely to survive a surgical procedure particularly if the animal is in a weakened condition or has cardiovascular or respiratory compromise. Some conditions require aggressive therapy (e.g. meningitis)

with antibiotics, analgesics, steroids, fluids which may not be practical or possible within the constraints of the experiment. For these animals it is imperative that a decision be made regarding euthanasia rather than adopting a “wait and see” approach which would only prolong the animal’s pain and distress.

Table 8. Potential complications of chronic indwelling devices and recommended interventions.

Device	Complication	Intervention/Management of Device
Catheter	Local Infection at Port	topical povidone-iodine ointment therapy daily for 7-10 days -if no resolution with topical therapy, suspect tunnel infection.
	Tunnel Infection	-removal of catheter -parenteral antibiotic therapy -topical povidone-iodine ointment at former exit site.
	Systemic Infection	discontinue use of animal in study for 2 week period -intravenous antibiotic therapy for 10-14 days -if no response to therapy, or if positive catheter blood culture after 72 hrs then suspect septic thrombus or endocarditis. -if no response to therapy or positive culture at 72hr, euthanasia is indicated.
	Thrombosis/ non-patent catheter	-catheter is not patent upon routine flushing. -if any clinical signs or evidence of systemic infection catheter removed and cultured, if positive culture systemic antibiotic therapy for 2-3 weeks before any recatheterization. if no clinical signs or evidence of systemic infection consider recatheterization.
	Seroma	-preventative measures decrease amount of subcutaneous tissue undermined during the surgical procedure use subcutaneous simple interrupted tacking sutures to decrease subcutaneous pocket created during surgery. -therapeutic measures – removal of serous fluid using aseptic technique shave area over seroma surgical scrub don sterile gloves use sterile needle/syringe to withdraw fluid -surgical measures – lance, drain and repair
	Abscess	Typically a walled off subcutaneous infection. Can occur at any point post-operatively if bacteria gain entry to port site area or if bacteria introduced into seroma during drainage of fluid. Removal of device, discontinue animal in study for minimum of 2 weeks, systemic antibiotic therapy surgical measures – lance, drain and repair
	Port site dislodged, exposed, displaced	If due to incision dehiscence in the immediate post-operative period (<24hrs) and port/incision otherwise uncomplicated perform aseptic repair of incision site. Flush area with antiseptic solution (betadine) thoroughly, close incision with appropriate material (wound clips, synthetic non-absorbable suture material, tissue glue) continue post-operative medications (analgesia, antibiotics). Extend antibiotic therapy to 10-14days If port site exposed (mesh, tubing) in the non-immediate postoperative period catheter may need to be removed/spliced. Removal indicated if evidence of systemic infection, catheter non-patent or if clinical presentation of animal does not support repair/replacement of existing catheter. Culture catheter segment, initiate systemic antibiotic therapy, remove animal from study while under therapy. If the port site is minimally compromised (i.e. no evidence of systemic/local infection) then splicing in a new sterile port can be considered. Antibiotics initiated several days before procedure and continued for 10-14 days.

Table 8 Cont'd. Potential complications of chronic indwelling devices and recommended interventions.

Device	Complication	Intervention
ICV/IC Cannula(e) Electrodes	Local Infection at Exit Site	topical povidone-iodine ointment therapy daily for 7-10 days -if no resolution with topical therapy, suspect more severe infection.
	Osteomyelitis	-removal of device -parenteral antibiotic therapy -topical povidone-iodine ointment at former exit site.
	Systemic Infection	discontinue use of animal in study for 2 week period -intravenous antibiotic therapy for 10-14 days -if no response to therapy, or if positive blood culture after 72 hrs then suspect additional complications such as meningitis, endocarditis. -if no response to therapy or positive culture at 72hr, euthanasia is indicated.
	Meningitis/ Encephalitis	-removal of device Aggressive therapy with intravenous fluids, intravenous antibiotics, steroids, analgesia Removal of animal from study for prolonged period
	Device dislodged, displaced	Any animal for which the cranial implant has been dislodged to expose underlying cranium must be euthanized within 72hrs as probability of infection very high. Any animal which has clinical signs as well must be euthanized within 24hrs.
Subcutaneous pump, telemetry, pellet	Seroma	-preventative measures decrease amount of subcutaneous tissue undermined during the surgical procedure use subcutaneous simple interrupted tacking sutures to decrease subcutaneous pocket created during surgery. -therapeutic measures – removal of serous fluid using aseptic technique shave area over seroma surgical scrub don sterile gloves use sterile needle/syringe to withdraw fluid -surgical measures – lance, drain and repair
	Abscess	Typically a walled off subcutaneous infection. Can occur at any point post-operatively if bacteria gain entry to device site area or if bacteria introduced into seroma during drainage of fluid. Removal of device, discontinue animal in study for minimum of 2 weeks, systemic antibiotic therapy surgical measures – lance, drain and repair
	Device dislodged, displaced	If due to incision dehiscence in the immediate post-operative period (<24hrs) and device/incision otherwise uncomplicated perform aseptic repair of incision site. Flush area with antiseptic solution (betadine) thoroughly, close incision with appropriate material (wound clips, synthetic non-absorbable suture material, tissue glue) continue post-operative medications (analgesia, antibiotics). Extend antibiotic therapy to 10-14days If device exposed or dislodged in the non-immediate postoperative period the device may need to be removed/replaced. Removal indicated if evidence of systemic infection, device nonfunctional or if clinical presentation of animal does not support repair/replacement of existing device. Initiate systemic antibiotic therapy, remove animal from study while under therapy. Animal must be free of clinical signs and previous site healed prior to implantation of new device. New device should be implanted in an alternate location such as the opposite side of the animal.

INDICATIONS FOR EUTHANASIA

Chronic indwelling devices have the potential to cause serious complications which may lead to pain, distress, debilitation and death of the animal. The prognosis is poor for any animal that develops serious complications related to a chronic indwelling device. It is for these reasons that endpoints must be clearly defined. Table 9 lists endpoints for animals with chronic indwelling devices.

Table 9. Endpoints for animals with chronic indwelling devices.

- Any animal with severe clinical signs including pain, respiratory distress, neurological signs.
- Any animal that does not respond (no improvement or worsening upon clinical re-assessment) to antibiotic therapy within 72 hours.
- Any animal with a positive blood culture within 72hrs of removal of device and initiation of antibiotic therapy.
- Any animal with a non-patent catheter and a positive catheter segment culture.
- Any animal that has lost a cranial implant.
- Any animal that is not experimentally valuable either due to loss of function of a device, clinical disease, or loss to study due to therapeutic intervention.
- Any animal that despite initiation of therapy significantly worsens.
- Any animal that does not eat/drink for more than 48 hours.

CONDITIONS FOR RE-CATHETERIZATION

In some limited instances animals may have a new catheter inserted if there is loss of function of the existing catheter. At minimum the animal must have completed 75% of the study and have no clinical signs noted on physical examination that would preclude the animal from undergoing the surgical procedure. Re-catheterization is only permitted if included within an IACUC approved animal protocol. The process of notification, examination of the animal, diagnostic measures, surgical procedure, therapy, monitoring and time until animal returned to study must be well described within the protocol. The investigator should provide an estimated number of animals which might undergo the procedure based on known or anticipated device fail rates. The following procedures are to be completed for animals undergoing re-catheterization surgery:

- Submission of a re-catheterization request and notification of veterinary staff and vivarium lead
- Physical examination by veterinary staff
- Catheter segment culture at the time of catheter removal – a simple qualitative assessment on an agar plate or gram stain of impression smear of segment
- If segment culture positive submit for sensitivity testing, extend antibiotic therapy and removal from study to minimum of 2 weeks

The following are conditions for which a re-catheterization surgery is not indicated:

- Any animal which has a positive catheter segment or blood culture
- Any animal which has overt clinical signs of an underlying infectious process
- Any animal which is currently under therapy for any type of catheter related complication
- any animal which has already undergone a re-catheterization

ASSURANCES

The principle investigator is responsible to ensure that the above guidelines are followed by all laboratory personnel and that individuals are appropriately trained in the performance of the procedures described. All efforts must be made to ensure that animals are monitored and maintained in a manner consistent with these guidelines and with careful attention to the welfare of the animals.

GOALS

Ultimately, the goals are to promote good science, maximize the data, promote animal well-being and minimize the potential for animal suffering (22). Careful monitoring, use of appropriate analgesics and supportive care, and well defined end-points can help to reduce potential loss of data. Animals that have developed severe physiologic derangements that may be exacerbated by pain, inadequate intake, dehydration, or disease may yield unusable or misleading data, tissues may be lost for accurate post-mortem evaluation if animals are not preemptively euthanized, and animal losses may compromise statistical power if the endpoints are poorly defined.

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