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The Rate and Time Course of Complications in Catheter-Dependent Hemodialysis Patients

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ABSTRACT

Many patients with end-stage renal disease come to rely on catheters as their only means of hemodialysis when other options are no longer viable. These patients have a very poor quality of life due to their chronic illness as well as many long-term complications related to the use of tunneled catheters. Many prior attempts have been made to understand these catheter-related problems. Yet, they continue to be a major cause of morbidity and mortality in chronic catheter-reliant patients. We hope to examine the rate as well as long term time course of these complications such that in future, we may decrease their occurrence. We predict that over time, chronic catheter use decreases the mean indwell time for each catheterization and increases the incidence of complications. To study this, we conducted a retrospective study looking at all patients who had three or more tunneled catheter exchanges between July 2003 and July 2008. We collected information from Yale IDX database on the patient's age and gender, the type of catheter used, the indwell time of the catheter, the vessel used as access, the indication for catheter removal, whether the procedure was performed by a medical doctor (M.D.) or physician's assistant (P.A.) and whether it was a de novo insertion or over-the-wire exchange. We collected a total of 764 data points on 191 patients (89 males and 102 females). They ranged from 8 to 87 years old with a median age of 56 years. Infection was the number one indication for catheter removal at 37%. The rate of infection was 3.34 per 1,000 catheter days. There was no difference in the rate of complications by the side of vessel accessed nor by type of catheter. However, right-sided catheters had a longer indwell time of 117 $\pm$ 159 days compared to left-sided catheters, 87 $\pm$ 124 days ($p = 0.008$). There was no significant difference in the indwell duration of first catheter in comparison to all subsequent placements. There was also no difference in complications whether the catheter was exchanged over the wire or placed de novo.

Nor were complication rates different among M.D. versus P.A. conducted procedures. We conclude that our rates of infection are similar to other institutions and the vessels located on the right-side of the neck are preferable to left-sided vessels to increase catheter longevity. Future research is needed to better assess how rates and incidences of complications change with long standing catheter-reliance.

ACKNOWLEDGEMENTS

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INTRODUCTION

In 2005 there were 500,000 people in the U.S. with end stage renal disease (ESRD) (l). Of these, approximately 75,000 relied on catheters for hemodialysis (2). The National Kidney Foundation Dialysis Outcomes Quality Initiative or DOQI recommends that for all patients requiring hemodialysis, arteriovenous fistulae (AVF) and arteriovenous grafts (AVG) should be considered first-line access options. They recommend that: “Less than 10% of chronic maintenance hemodialysis patients should be maintained on catheters continuously for ≥90 days as their permanent chronic dialysis access” (3). However, we are far from achieving these standards. Currently, 21% of hemodialysis patients in the U.S. rely on tunneled catheters for long-term dialysis (4).

Fistulae and grafts are the preferred methods for dialysis because of lower mortality associated with their use when compared to tunneled catheters. The number one and two causes of death in dialysis patients are cardiovascular disease and infections, respectively (5). Forty-five percent of all deaths in hemodialysis patients are due to cardiac etiologies (6). Patients who use catheters for dialysis have a much greater risk for adverse cardiac events than those using AVF and AVG (6). When deaths attributable to infections are examined, 75% of those deaths result from progression of an infection into sepsis (7). Pastan et al. noted that patients using catheters are at much higher risks for infections compared to patients using permanent accesses such as fistulae and grafts (8). They reported that 15.2% of patients using tunneled catheters had an infectious episode. This contrasted starkly against 7.3% incidence of infection in patients using fistulae and 9.1% in patients using grafts (8). Thus, the DOQI recommends that AVF should be the first options for dialysis patients, followed closely by grafts. Catheters should be used only temporarily as other means of permanent access mature or as last resort in patients with no further options.

Despite the significantly greater risks associated with tunneled catheter use, the distribution of fistulae and grafts is sub-optimal. As mentioned previously, instead of less than 10% chronic catheter use, 21% or more patients rely on catheters for long-term dialysis. Why is there such a discrepancy between the goals and practice? Often, one of the obstacles that prevents a decrease in the prevalence of tunneled catheter use is the late referral of patients with chronic kidney disease to nephrologists (9). Also, high rates of primary failure in new AVF and AVG failure keep the prevalence of catheter use high (9). Of course, some patient refuse surgery for the placement of vascular access or have medical/surgical contraindications that make them catheter-dependent.

Late referrals and high failure rates of fistulae and grafts are not the only barriers that increase the use of dialysis catheters in the U.S. The types of accesses patients use also vary by demographics. Dhingra et al. noted that patients who receive AVF tend to be younger than their counterparts who are dialyzed via grafts and catheters (6). They also noticed that people who receive AVF tend to be male, married, non-diabetics and typically people with high school diplomas. Patients with fistulae are usually healthier than their counterparts with fewer histories of peripheral vascular disease (PVD), coronary artery disease (CAD), congestive heart failure (CHF) and cancer. Overall, their laboratory values are closer to normal ranges with higher amounts of albumin, higher hematocrit, calcium, phosphate and creatinine when compared to lab values of patients with grafts or catheters (6). African Americans and patients with higher body mass indices (BMI) are more likely to receive grafts and catheters.

Despite the differences in demographics, over time many patients who initiated therapy via fistulae and grafts may come to rely on tunneled catheters as the sole means for dialysis as other access options become impossible. When compared to other ESRD patients, these ‘catheter dependent’ patients are much sicker. They have generally had ESRD for a longer duration (8). Their cardiovascular status is much poorer. They also have higher rates of combordities (8). In one study, Lee et al. examined the total percent of patients using catheters at their institution and identified 18.5% who were ‘catheter-dependent’ or 20 patients from total of 108 patients (10). The reasons this subgroup relied on catheters varied. Some had consumed all other major vessel sites as options for the placement of future AVF or AVG. Others had such severe peripheral vascular disease that it precluded placement of other accesses. Others had severe arterial calcification that was impenetrable. Lastly, others had a history of such severe, recurrent access infections that they were no longer candidates for either fistulae or grafts (10).

Typically, catheter-dependent patients are not candidates for peritoneal dialysis or kidney transplantation (11). Most of these patient have been on dialysis for an average of 6.2±1.2 years, with a continuous use of catheter for 1.5 ± 0.3 years (10). They have spent on average 3.9±0.5 years prior to becoming catheter-dependent using fistulae and/or grafts that have failed (10). Thus, by the time that patients become catheter-dependent, they are some of the sickest ESRD patients and must survive via use of a tunneled line.

Catheter-dependent patients spend much of their lives in and out of the hospital. The sequelae of ESRD make them anemic, uremic, immunocompromised, hyperkalemic etc. In addition to these ailments, the presence of a tunneled line makes them even more susceptible to other complications. Complications associated with catheters can generally be categorized as short-term and long-term complications. Many of the short-term complications are rare and depend on the level of expertise and comfort with the individual performing the procedure. These complications include pneumothorax, hemothorax, hemomediastinum, dissection or occlusion of an artery as well as perforation of a central vessel (7). Mechanical errors with the catheters can also occur and are generally grouped into the category of “catheter malfunction”. Other than faulty catheters, other causes of ‘malfunction’ include malpositioning, catheter kinking or poor flow from unidentified causes such as undetected thrombi or stenoses (7).

Long-term complications of catheter placement are the real problems catheter-dependent patients must overcome. These interfere with the longevity and functioning of catheters, thus increasing the morbidity and mortality associated with catheter use (11). The major long-term complications related to catheter use include infections or catheter-related bacteremia (CRB), thrombi and fibrin sheath formation and central venous stenosis (12).

Infections are one of the most common and most serious complications associated with the use of tunneled catheters (13). Fifty percent of the infections that develop in hemodialysis patients, including those with fistulae and grafts, are due to the presence of the vascular access itself (14). As mentioned previously, patients with catheters are at highest risks for infections related to vascular access (14). Catheters allow bacteria to enter systemic circulation in one of two ways. Bacteria can either track down the catheter subcutaneously or can colonize the internal surface of the catheter and then embolize into the bloodstream during dialysis (14). The former method of invasion can be diminished by using antimicrobial ointments when the catheter is initially placed into the vessel (7). The type of infections that result when bacteria track down subcutaneously occur from external sources of contamination such as the patient's skin or the hands of medical staff participating in the procedure (15). These external sources of infection typically occur within the first 30 days of insertion (15).

"Biofilm" is the term given to a matrix that forms in the lumens of indwelling catheters. It is thought to facilitate the introduction of bacteria into the bloodstream once the bacteria migrate from external sources into the blood (15). When foreign surfaces such as catheters remain in the blood stream, bacterial colonies can secrete molecules such as extracellular polysaccharides to form a complex, multi-layered structure referred to as a "biofilm" (16). The presence of a biofilm complicates the treatment of infection. Since there are several layers in a biofilm it precludes treatment of catheter infection by systemic antibiotics alone since these antiobiotics cannot penetrate all the layers. Hence, the layers add virulence to the bacteria (15). In order to treat such infections, the infected catheter must be either replaced with over the guidewire exchange alongside systemic antibiotics or be removed and delay placement of a new catheter until infection resolves on systemic antibiotics (17, 18). A third option, which is still under clinical investigation is the addition of an antibiotic-lock solution into the catheter lumen. Since this option has a potential risk of causing metastatic infection, it is not currently recommended and needs to be explored further (2).

The control of infection is an important goal in the management of hemodialysis patients because of their immunocompromised status secondary to renal disease. Hemodialysis patients are more susceptible to serious complications from such bacteremia not only due to the breach in their skin barrier and insertion of a foreign object, but also due to three major factors: 1)impaired host immunity, 2) high bacterial virulence and 3) the hazards associated with dialysis (7). Chronic kidney disease impairs several elements involved in host immunity leading to abnormal neutrophil, T-cell and B-cell functions. Synthesis of cytokines is also impaired (7). Individual host factors can further increase the risk of infection. These include the presence of diabetes mellitus, longer duration of catheterization, frequent manipulation of the catheters, poor dressing technique for catheter insertion and hosts with prior colonization of bacteria such as *Staphylococcus aureus* in their nares or other regions (8, 19). History of prior CRB also increases the risk for future episodes of bactermia. Of course, this may originate from host susceptibility factors such as iron overload, bacterial colonization, presence of biofilm or fibrin sheath etc. (20).

Once peripheral bactermia ensues, it can progress to more serious complications such as endocarditis, osteomyelitis, septic arthritis and septic shock (2). In a study that examined four outpatient hemodialysis centers, 22% of the patients who developed CRB progressed onto more severe outcomes including osteomyelitis, septic arthritis, infective endocarditis and death (20). The actual incidence of infection in catheter dependent patients is estimated as ranging from 2.2/1,000 to 5.5/1,000 catheter days across various studies in literature with the most commonly accepted range between 3.0-4.0episodes per catheter days (11,13, 18, 20-21). Roughly, this translates to 0.26-2.0 cases of infection per patient year.

Lee et al. found an incidence of 4.6 episodes of catheter-related bacteremia per 1000 days (10). They extended this to study the likelihood of CRB up to 9 months duration and found that the likelihood of CRB was 35% at 3 months and 48% at 6 months with a linear increase up until 9 months (10). Marr et al calculated that 40% of the catheter dependent patients developed at least one episode of CRB within a 9 month period (20). Coupled with the mortality that each incident of CRB carries about 9% risk of death, morbidity and mortality associated with CRB is a very serious concern (8, 17). Thus, with such a high mortality and ineffectiveness of systemic antibiotics alone for infection, it is easy to see why infection is such a dire complication of hemodialysis catheters.

Thrombosis is another common complication encountered in patients who are dependent on catheters for hemodialysis. Dialysis patients are hypercoaguable due to platelet and plasma abnormalities. Smits et al. noted that part of this hypercoagulable state may be due to abnormal expression of platelet membrane proteins (22). The counts of platelets are also higher in these patients due to the trauma associated with being attached to the dialyzer and the shear stress of the dialysis treatments. Hyperfibrinogenemia in the setting of decreased levels of antithrombin III, protein C and increased homocysteine may also explain why catheter dependent patients are at high risk for forming thrombi (15, 22).

Thrombi that form in the setting of tunneled catheters are classified as either extrinsic or intrinsic. Forms of extrinsic thrombi include mural, central vein and atrial thrombi. Typical intrinsic form of thrombi include the thrombus that forms at the catheter tip and the fibrin sheath (19). An extrinsic thrombus, as the name suggests, forms outside the catheter. A mural thrombus is one such form of extrinsic thrombus that is seen in almost 33% of patients who have an indwelling catheter for one month or longer (23). Of these 33% patients with mural thrombi, however, only 5% will have symptoms ranging from mild pain/tenderness at the entry site to obstruction leading to severe ipsilateral extremity, neck or facial swelling (24). Mural thrombi form secondary to injury at the entry site or at the catheter tip (7). With movement, catheter irritates the area it contacts. This can lead to catheter malfunction, but the more dreaded complication is the risk of embolism with removal of the catheter (19).

Central vein thrombosis is also another common form of an extrinsic thrombus. This type of thrombus is cited as having a frequency ranging from 2 to 64% in literature (25). Similar to mural thrombi, if symptomatic, it may result in pain/tenderness or more severe symptoms such as ipsilateral swelling. However, it is generally asymptomatic. An atrial thrombus is a very rare, but potentially life threatening clot that can lead to pulmonary emboli or cardiac arrest (26). Some consider atrial thrombi as a variant of a mural thrombus. These thrombi are generally diagnosed when an incidental large mass is seen within the right atrium during an echocardiogram or angiography (19).

Intrinsic thrombi are more common causes of complications in patients with tunneled catheters than extrinsic thrombi. These form within the lumen of the catheter due to inadequate amount of heparin solution within the lumen, the loss of heparin with repeat dialysis treatments or if blood enters the lumen (19). A catheter tip thrombus is a common type and forms due to inadequate access to heparin at the distal tip of the catheter. Many catheters have side holes in their arterial branch. The portion of the catheter that is distal to these holes does not get exposed to the heparin that contacts the portion of catheter proximal to the side holes. Thus, the distal tip is at an increased risk for clot formation (19).

A fibrin sheath thrombus is the most difficult form of thrombus to treat. Although some people classify it as a separate entity, it is a subtype of intrinsic thrombi. The sleeve forms around the catheter where it enters the vein. It is hypothesized that most, if not all central venous catheters form fibrin sheaths within a few days after insertion (27). Its presence has been confirmed in many catheters at autopsy (28). Some newer studies suggest that the fibrin sheath probably represents a progression of biofilm (15). Like other thrombi, the presence of a fibrin sleeve is not necessarily symptomatic. Literature cites that dysfunction due to fibrin sheaths probably occurs in 13-57% of the cases and often occurs weeks or months after the sheath develops and grows distally (29). It becomes problematic when the sleeve covers the tip of the catheter and creates a flap valve mechanism that allows the injection of fluids into the catheter but prevents the withdrawal (7). The formation of a fibrin sheath may be unavoidable.

Overall, the incidence of thrombotic events varies in literature. Develter et al. found an incidence of 1.94 thrombotic events/1,000 catheter days and discovered that many catheters experienced more than one thrombotic episode (13). A typical catheter had an average of 0.5 thrombotic events over the course of its lifetime (13). The risk of thrombotic events was also affected by the site of catheter insertion. For instance, the prevalence of internal jugular vein thrombosis is reported to be around 26% (30).

Thrombotic events are problematic. They are estimated to result in the loss of about 12% of catheters when they do not respond to treatment with either a local injection of heparin or a thrombolytic agent such as alteplase or urokinase (13). As previously mentioned, thrombi place patients at risk for embolic events (26). They also diminish flow across the catheters during dialysis and interfere with adequate dialysis treatment. Studies have examined the role of anticoagulation systemic therapy in preventing thrombi formation. Mokrzycki et al. randomized patients and administered either 1 mg of warfarin or aspirin to reduce the incidence of clot formation. However, they found no difference in the risk of thrombosis when compared to the placebo group (31). Increasing the INR has not shown to prevent thrombi and in fact, can lead to further complications associated with higher INR values (32).

Once a thrombus forms instead of catheter removal, catheter salvage can be attempted with infusion of tissue plasminogen activator (tPA) or another thrombolytic agent. However, since most catheters are at risk for multiple episodes of thrombus formation, thrombi can become refractory to interventions. Some studies have shown that after tPA is used two or more times, a thrombus or fibrin sleeve will stop responding to conservative thrombolytic management (33). More aggressive interventions such as fibrin sheath stripping, catheter exchange or using a balloon dilatation and disruption of sheath become necessary (34). Some studies suggest that catheter exchange may be superior to sheath stripping while others have found no difference. For instance, Merport et al. found that catheter exchange is more effective than fibrin sheath stripping (35). They found that initially, both stripping and exchange resolve problems with dialysis flow. However, when the two were compared in longevity, exchange had a longer patency. The mean catheter patency for the fibrin sleeve group that underwent stripping was 24.5 $\pm$ 29.3 days while the exchange group had a patency of 52.2 $\pm$ 43.0 days (35).

In data published by d'Othee et al., all three of the major interventional methods of removing fibrin sheaths had similar outcomes (36). Currently, the DOQI recommends exchange of the catheter followed by disruption of the fibrin sheath by balloon angioplasty as treatment (37). Regardless, of what types of interventions are undertaken to treat thrombi, once a thrombus forms, the patency of the catheter is compromised and there is a high risk that the catheter patency and vessel may be lost to future access despite aggressive interventions (34, 38). In addition, the formation of a thrombus increases future risk for infection. The presence of a thrombus, including fibrin sheaths provide medium for bacterial growth and colonization. Thus, thrombi increase the incidence of catheter-related bacteremia (34,39). When thrombi and infection coexist, the morbidity is also greatly increased.

The last major complication associated with long-term tunneled catheter use is stenosis. Like thrombus formation, the presence of stenosis may be clinically silent initially due to compensation through extensive venous collaterals. However, once the stenosis is established it will eventually lead to loss of the access site (30). The risk of stenosis depends greatly on which vessel is used as the access site. Most clinicians avoid the subclavian vessel because of the high incidence of central vessel stenosis associated with its use (40-41). Central venous stenosis includes narrowing of the superior vena cava, brachiocepahlic and/or subclavian vessels. It is estimated that 40-50% of subclavian catheters develop central stenoses (40). This is in severe contrast to the estimated 10% of patients who have internal jugular catheters and develop brachiocephalic vein stenosis (42). The femoral vein is also notorious for high stenotic rates. Up to 30% of the patients with femoral access for greater than 4 weeks will develop either a femoral or external iliac vein stenosis (43).

Thus, the DOQI recommends the right internal jugular vein should be the initial site for tunneled catheter access (37). The site has the lowest risk for stenosis and has a relatively direct pathway to the SVC/right atrium (19). Even the left internal jugular (LIJ) vein use is dissuaded because the LIJ must traverse both the junction of internal jugular vein with the subclavian and bend at the union of left and right innominate vein. Areas of bend are high risk for venous irritation and resulting stenoses (44). Schon and Whittman found that the incidence of stenosis of the right IJ was 27% while that of LIJ vein inserted catheters was 40% (12). Thus, the right internal jugular vein should be the first site for catheter placement.

Once the RIJ is no longer a viable option, the preferred sites for insertion of a tunneled catheter include the right external jugular vein, LIJ, and left external sites. The subclavian vessels should be used only after these sites are no longer viable (45). Frequently in chronic hemodialysis patients, all of the jugular veins thrombose. In these instances, sites such as the brachiocephalic, translumbar, transrenal, transhepatic and femoral veins can also be used (45). All of the aforementioned sites are known to have high rates of infection and other catheter dysfunctions. For instance, femoral vein catheters have 25% frequency of lower extremity deep vein thrombosis

(46). Thus, once the internal jugular veins stenose, the incidence of complications associated with other vessel access dramatically increases and causes many problems with dialysis access in catheter dependent patients.

Once a vessel is stenosed, it can be treated via percutaneous transluminal angioplasty (PTA). However, the treatment is considered temporary as there is a high incidence of re-stenosis (47-49). Stenting of central venous stensosis can improve residual stenosis when PTA alone does not work, but has not shown to increase the patency nor longevity of hemodialysis access site function compared to PTA alone (50). Thus, once a vessel is stenosed , it is only a matter of time until that vessel is no longer a viable option for dialysis access. Catheter dependent patients eventually can lose all their major vessels sites and have to rely on such poor options as femoral veins and translumbar options. It is understandable why these patients spend much of their lives in and out of the hospital, battling the problems that accompany such access options.

Compared to arteriovenous fistulae and arteriovenous grafts, tunneled catheters pose a series of problems for the hemodialysis patients. Once an ESRD patient is catheter-dependent, the quality of dialysis treatments is suboptimal due to decreased blood flow through the catheter. More importantly, the overall morbidity and mortality of the patient increases greatly due to the higher rates of complications such as infection, thrombi and stenoses associated with the use of tunneled catheters. Classifying and understanding these complications and well as investigating methods that may potentially reduce their occurrences not only decreases the cost of medical care, but greatly improves the quality of life of 75,000 patients who rely on tunneled catheters (2).

STATEMENT OF PURPOSE

Catheter-dependent patients are a unique set of patients with long-standing, severe end stage renal disease (ESRD). Due to the long duration of their chronic illness and the presence of a tunneled catheter, they are prone to complications associated with chronic catheter use. Understanding and classifying these complications is a colossal task. Prior studies have examined catheter-related morbidities and estimated varying incidences and rates of such complications at their institutions. We hope to examine our patient population and study the rate and incidences of the catheter-related complications at our institution and also examine whether complications increase in frequency and incidence in those patients with long-standing catheter-dependence. We hope to be better able to predict when such complications will occur so that instead of waiting for the complication to arise, we can prevent their onset. Preventing catheter-related complications not only improves the morbidity and mortality of catheter-reliant patients, but also improves their quality of life with fewer hospitalizations. Fewer complications also increase the longevity of the access site survival and preserve other vessels for future catheterizations. We hypothesize that patients have longer indwell catheter times for their first catheterization, but with each subsequent catheterization, the indwell times shorten. We also hypothesize that the incidence of complications increases the longer these patients are catheter dependent. We predict that the rates of infection, thrombus and fibrin sheath formation are similar at our institution to other institutions where such studies have been previously conducted. We will look at the effect of side of vessel that catheter was placed into and the risk of complications. We predict that the rates of complications will be lower for right-sided vessels. When comparing de novo catheter insertions to over-the-wire exchanges, we predict the rates of complications will be similar. Also, we will compare the success of catheterizations performed by physician’s assistants (P.A.) at Yale New Haven Hospital (YNHH) to those performed by the M.D.s in the Yale interventional suite. We predict, there will be no differences in the rate of complications among those two groups. Specifically, we will answer the following questions:

1. Does the rate of developing complications vary by gender?

2. Do the types of complications that develop vary by gender?
3. Does the rate of developing complications vary by age?
4. What is the rate of infection over 1,000 catheter days?
5. What is the rate of fibrin sheath formation over 1,000 catheter days?
6. What is the rate of thrombus formation over 1,000 catheter days?
7. Is there a difference in the rate of developing a complication based on whether the catheter was inserted into a right- or left-sided vessel?
8. Are there differences in the type of complications that develop depending on whether it the catheter insertion site was a right- or left-sided vessel?
9. Is there a difference in the indwell time when the catheter was first inserted compared to the indwell times for the second, third, fourth and subsequent exchanges? What does the graph of this timeline look like?
10. Does the rate of complications vary by the type of catheter that was used?
11. Does the rate of complications vary depending on whether the catheter was inserted by a medical doctor (MD) or a physician's assistant (PA)?
12. Does the rate of complications vary by whether the catheter was exchanged over-the-wire versus if it was removed and re-tunneled?

METHODS

Patients

The study was approved by Human Investigation Committee at Yale University School of Medicine. It looked at all hemodialysis patients at Yale New Haven Hospital (YNHH) who underwent a catheter placement in the interventional radiology department from July 2003 to July 2008. The data was collected by searching for specific codes indicating catheter insertion in the Yale Diagnostic radiology IDX database. Of the several hundred data points collected, 'catheter-dependent' patients were identified as those who came underwent at least three or more separate catheter placements for chronic hemodialysis access.

Demographic data, including the age and gender of the patient, person performing the procedure, type of catheter used, site of insertion, whether the procedure was an exchange or removal and new insertion, dwell time and indication for removal was all collected from the IDX database and Synapse imaging reports.

Evaluation and Definitions of Imaging outcomes

Ultrasound was used to investigate the patency of the vessel prior to catheter insertion as per guidelines. The insertions were conducted by either an M.D. or a P.A. assigned to the case. All procedures were conducted in the interventional suites. Poor flow was defined as flow rates < 300 mL/min as recommended by the DOQI guidelines and required intervention (37). Infection was clinically defined. The patients with infections were started on systemic antibiotics and brought to the IR suite for either an over the guidewire catheter exchange or catheter removal and then insertion of a temporary catheter until the infection cleared and a new tunneled line could be inserted. Whether catheters were removed or exchanged was randomized and depended on attending preference.

Data on the presence or absence of a 'thrombus', 'fibrin sleeve' or 'stenosis' was collected from imaging reports in synapse. The patients with thrombi were generally treated with a thrombolytic. Patients with fibrin sleeves underwent exchanges or insertion of catheters into other vessels, if the sleeves were causing poor flow. Stenotic vessels either underwent angioplasty or a new catheter was inserted into a different vessel.

We grouped the reasons for catheter removal into seven general categories: (1) infection, (2) presence of fibrin sleeve, (3) presence of thrombus/clot, (4) stenosis of vessel, (5) 'malfunction' (which we defined as poor flow of otherwise unidentified etiology, catheter malposition or catheter mechanical malfunction), (6)no longer needed, (7) Unstated reasons for removal in imaging reports or other reasons for removal.

Statistical analysis

Lawrence Staib conducted the statistical analyses. All of the statistical analyses were performed using software (Minitab 15, State College, Pennsylvania). 95% confidence limits were computed for proportions and Fisher's exact test was used to compare proportions. Two sample t tests were used to compare means. For all statistical tests, differences were considered to be significant if the P values were less than 0.05.

Data End points

Rates of occurrence of all complications were computed by dividing the number of catheters that were removed for each particular complication by the total indwelling time of all catheters. The results were expressed in units of “per 1,000 catheter days”.

Catheter types

Angiodynamic, Palindrome, Palindrome with heparin, and Ashsplit catheters (all are tunneled lines)

RESULTS

There were a total of 191 patients enrolled in the study. Of these, 89 were males and 102 females. The patients ranged in ages from 8 to 87 years old with median age of 56 years. There were a total of 764 catheter data points for these 191 patients. The mean number of catheters for all patients was 4.4 $\pm$3.71. The most common reason for catheter removal was infection (278 catheters, 37%) followed by malfunction (267 catheters, 35%), presence of fibrin sleeve (83 catheters, 11%), stenosis (27 catheters, 4%), and thrombus (7 catheters, <1%). Ninety-three catheters (12%) were taken out because they were no longer needed and 16 catheters (2%) that were taken out for either reasons not clearly stated in the imaging reports or for other complications. Two of these “other” complications were intractable bleeding from the insertion site. In total, there were 771 reasons for removal because seven catheters had multiple indications for removal. Two catheters were removed because they both had malfunctions and fibrin sheaths. Another two were removed for both infection and stenosis. One was removed for both fibrin sheath and stenosis. Another catheter was removed for co-infection and malfunction and lastly, one catheter removed for co-existing fibrin sheath and thrombus. “Malfunction” as defined earlier included mechanical malfunction of the catheter, catheter malposition as well as poor flow that otherwise could not be attributed to other etiologies.

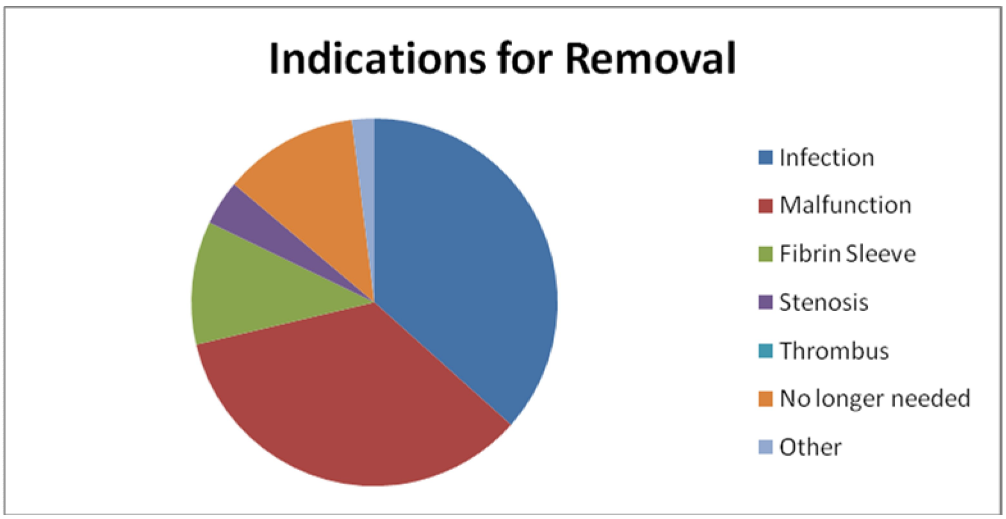

Chart A. Indications for Removal. “Malfunction” included mechanical malfunction of the catheter, catheter malposition as well as poor flow due to unknown etiologies. “Other” included catheters that were taken out for a complication that was not explicitly defined in imaging reports or for complications that did not fit into our other categories. Of these 2 were taken out for bleeding.

Altogether, out of 164 patients with multiple catheter points (the remaining of original 191 had incomplete data that yielded only 1 catheter exchange point), 75.9% (or 113 patients) developed infections, 78.7% (or 118 patients) had complications related to poor flow, 38.1% (or 50 patients) has fibrin sheaths, 16.1% (or 17 patients) had stenoses, 8.6% (or 7 patients) developed thrombi and 15.4% (or 16 patients) had some other form of complications. Of the patients who developed infections, 57.5% developed further episodes of infection (65 out the 113). The patients who were prone to infection had a mean of 2.34 infectious episodes.

When we compared complications by gender, the mean indwell time for males was 94 $\pm$ 109 days and the mean rate of complications for females was 97$\pm$ 117 days. This difference was not statistically significant (p =0.73). We also wanted to know whether males and females developed different types of complications. The results showed that there was no difference among the rates of no complications between males and females. The males had a rate of 0.13, 46 episodes of no complications over 349 total exchanges, while females had a rate of 0.11 where 47 of the total 415 catheter exchanges had no complications (p=0.44). The rate of infections was also not significantly different between the genders (p=0.13). The rate of infection for males was 0.39, where 137 of the total 349 catheter exchanges were removed for infection, while 141 of the total 415 exchanges were infection-related removals for females. Lastly, the rate of catheter-specific malfunction (with was defined as poor flow, fibrin sheath, stenosis or thrombus presence) was 0.46 or 161 catheter exchanges of total 349 exchanges for males and 0.52 or 216 out of 415 total exchanges for females. There was no significant difference in the rate of catheter-specific malfunction between the two genders (p=0.11).

When we looked at whether there was a difference in who developed complications by age, we found that the mean age of the patients of patients who did not develop complications was 55.0 $\pm$ 15.0 years old and the mean for those who developed complications was 55.2 $\pm$ 15.9 years old. There was no significant difference between the patients ages for those who developed complications and those who did not (p =0.93).

Since a variety of tunneled catheters were used for hemodialysis, we compared the rate of complications by the type of catheter. Overall, the rate of no complications for all catheters was near 14%. There were a total of 483 (63%) Angiodynamic catheters, 150 (20%) Palindrome, 80 (10%) Ashsplit, 11(1%) Palindrome with heparin and 40 (5%) that were unknown. Of all the Angiodynamic catheters placed, 35% were removed due to infections, 49% had a catheter-specific malfunction, 13% were no longer needed and were removed and 2% were removed for unknown/other reasons. For the Palindrome catheters, 42% were removed due to infection, 47% due to catheter-specific malfunction, 10% were no longer needed and 1% removed for unknown/other reasons. In the Ashsplit catheter 33% had to removed due to infection, 57% removed due to catheter-specific malfunction, 9% were no longer needed and 1% removed for unknown/other reasons. The palindrome catheter with heparin was underrepresented in our experiment comprising one percent of all the catheters exchange data points. Of the eleven palindrome catheters with heparin, 36% were removed due to infection and 64% due to catheter-specific malfunction. Of the 40 unknown catheters, 43% removed for infection, 38% for catheter-specific malfunction, 18% were no longer needed and 3% removed for unknown reasons.

Table B. Indications for Catheter removals. Indications were simplified into 4 general categories. Catheters were removed for (1) infection, (2) catheter-related specific malfunction such as poor flow, fibrin sheath, stenosis or thrombus formation, (3) no longer required or (4) imaging report did not state reason for removal.

Type Catheter	Total No. of catheters	Removed for Infection	Removed for catheter-specific malfunction (poor flow, fibrin sheath, stenosis or thrombus	Removed b/c no longer needed	Removed for unknown reasons

			formation)		
Angiodynamic	483 (63%)	35%	49%	13%	2%
Palindrome	150 (20%)	42%	47%	10%	1%
Ashsplit	80 (10%)	33%	57%	9%	1%
Palindrome with heparin	11 (1%)	36%	64%	0%	0%
Unknown	40 (5%)	43%	38%	18%	3%

When we examined rate of complications by the number of catheter days we found that the rate of infection was 3.34 per 1000 catheter days. The rate of fibrin sheath formation was 0.99 per 1000 catheter days and lastly, the rate of thrombus formation was 0.082 per 1000 catheter days.

At Yale both medical doctors (M.D.s) and physician's assistants (P.A.s) participate in hemodialysis catheter insertions and exchanges. We examined whether the rate of no complications varied by whether the person performing the procedure was an M.D. or P.A. For a total of 285 cases performed by the P.A. service, 43 (15.1%) had no complications. For a total of 479 cases completed by M.D., 50 (10.4%) had no complications. The difference was not significantly difference (p=0.067).

Once complications occurred, tunneled catheters could either be removed and replaced with temporary catheters until de novo insertions or be exchanged over a guidewire. We looked at whether there was a difference in the occurrence of no complications depending on whether the catheter was removed and replaced de novo or exchanged. Out of the 398 total catheters that were replaced de novo, 47 (or 12%) had no complications. For 366 total over the wire exchanges, 46 (or 13%) had no complications. There was no significant difference in the percent of no complications between de novo catheter insertions or over the wire exchanges (p=0.83).

Catheters could also either be placed into right-sided or left-sided neck vessels. The rate of complications for catheters placed on the right side was 469 out of 538 total right sided catheter insertions (or 87%) and 215 out of 238 for catheters placed in the left sided vessels (or 90%). There was no significant difference in the percent of complications based on whether the catheter was placed into a right-sided or left-sided vessel (p=0.23). Broken down by the type of complications (infection, poor flow, fibrin sheath, stenosis and thrombus as well as catheters that were no longer needed), there was no significant difference in whether the catheter was placed on the left or right side. The result for rate of infection was almost significantly different when comparing right and left sided catheters. Of 534 right-sided catheters, 185 had infections, while of the 237 left-sided catheters, 99 had infections (p=0.061), suggesting greater risk of infection for left sided catheters.

Table C. Comparing the type and incidence of complications seen in catheters placed in right-sided vessels versus left-sided vessels. None of the complications had any significant difference between the two sides.

Percent of Catheters with following complications	Right-sided vessels	Left sided vessels
Infection	35%	42%
Poor flow	36%	33%
Fibrin Sheath	11%	9%
Stenosis	3%	4%
Thrombus	1%	0%
Unknown/Other	2%	2%
No longer needed	13%	10%

However, when we compared indwell times by the side of vessel accessed, there was a difference in catheter survival. Catheters placed in right-sided vessels lasted longer, at 117 $\pm$ 159 days when compared to left-sided catheters that last for 87 $\pm$ 124 days. The difference was statistically significant (p =0.008).

Since this study spanned the course of several years, we compared the indwell time for the first catheter data point on a patient to subsequent catheter data points. Across all patients with multiple data points, the indwell time for the 'first' catheterization was 105 $\pm$ 126 days. All subsequent insertions had a mean indwell time of 92 $\pm$ 109 days. The difference in catheter survival for the first catheterization in comparison to subsequent catheterizations was not statistically different due to large standard deviations (p=0.22).

We were also interested in comparing mean indwell time for sequential catheter placements to each other. Was there a difference in the indwell time for the first catheter, the second, the third etc. and difference in the percent of complications? Our data showed no difference among indwell times or survival of individual catheterizations depending on their relative order of placement. We also did not find a difference in the percent of catheters that were removed for complications compared to those removed without complications depending on what number of catheterization occurred.

Graph D: Comparing the mean indwell times for each consecutive catheterization data points with standard deviations shown as marked. The Y-axis shows the mean number of days plus-or-minus one standard deviation for the indwell catheter survival. The x-axis shows the relative number of catheter data points. Due to the large standard deviations, the difference in the indwell times were not significant.

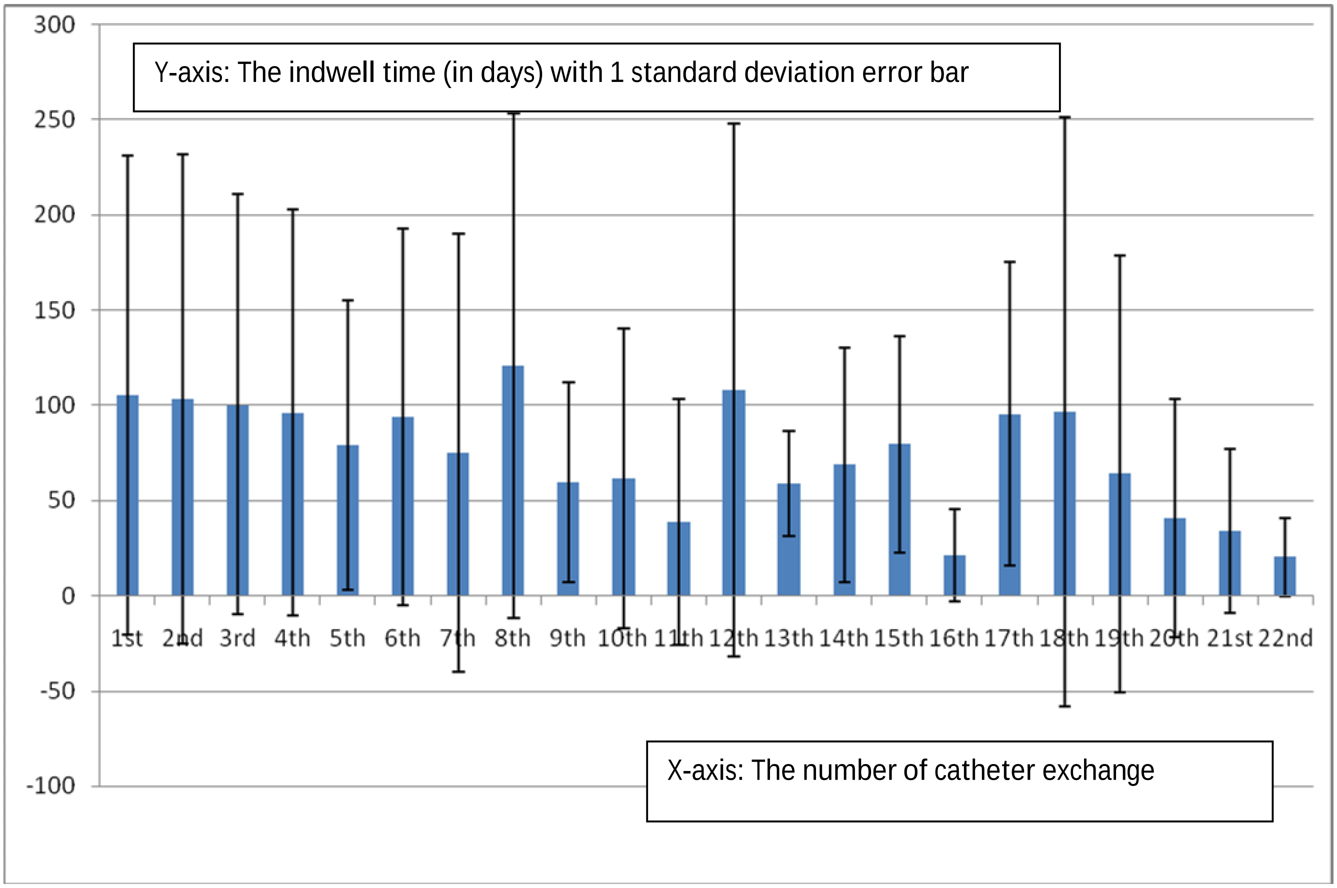

Table E: Shows a numerical summarization of the data plotted in Graph D. The mean indwell time is shown in days with one standard deviation in the column next to it. Also, the percent of catheters that were removed for complications are shown for each relative catheter data point.

Catheter number	Mean indwell time (days)	Std dev. (days)	Percent removed for complications
1st	105.3	125.83	88%
2nd	103.4	128.43	86%
3rd	100.3	110.35	80%
4th	96.0	106.75	89%
5th	79.0	76.08	91%
6th	93.9	98.66	97%

7th	75.0	114.86	92%
8th	120.6	132.55	89%
9th	59.6	52.23	75%
10th	61.5	78.61	91%
11th	38.6	64.36	100%
12th	108.3	139.92	90%
13th	58.9	27.32	100%
14th	68.7	61.44	86%
15th	79.6	56.84	100%
16th	21.3	24.28	100%
17th	95.5	79.81	100%
18th	96.5	154.97	100%
19th	64.0	114.76	100%
20th	40.7	62.74	100%
21st	34.3	43.04	100%
22nd	20.5	20.51	100%

DISCUSSION

Although tunneled catheters are considered last resort for hemodialysis, many patients lose all other means of vascular access and come to rely on tunneled catheters for survival. These patients commonly suffer from complications that decrease the functioning and longevity of catheter use. We wanted to focus on this group of patients who become catheter-dependent and look at their rates of catheter-related complications as well as factors that may influence the risk of these problems. We were also interested in comparing the indwell time from the first data point to the subsequent data points to assess for changes in catheter longevity based on number of catheter exchanges.

Of the 764 catheter exchanges and insertions that took place at our institution during the course of this study, the number one cause of complication was infection. Roughly one-third or 278 catheters out of a total 764 (37%) were removed due to infection. Roughly another one-third, 267 catheters (35%) were due to ‘malfunction’. We broadly categorized malfunction as catheter malposition, mechanical problems with the catheter and poor flow of unidentified origin. The remaining third of our data showed that reasons for removal/exchanges were due to the presence of fibrin sheaths, stenosis, thrombus, or other reasons. Twelve percent of the catheters were removed because they were no longer needed. These results are consistent with prior studies that have examined the outcomes of using dialysis catheters where roughly one-third were removed for infection, one-third for poor functioning and one-third because they were no longer needed (20, 51).

Infection remains as one of the leading causes for catheter exchange at our institution. Overall, our rate of infection was 3.34 episodes per 1,000 catheter days. This rate falls well within the range that is usually cited in literature of 2.2-5.5 infectious events per 1,000 days (18). The rate of fibrin sheath formation at our institution was 0.99 per 1,000 catheter days. Considering that fibrin sheaths form sheaths can form as early as 24 hours after the insertion of a catheter (27, 28), and are seen in anywhere from 42-82% of central venous catheters (34), our rate probably represents an underestimation of the prevalence. We suspect that many more patients had a fibrin sheath, but either did not have these findings stated in the imaging report or were not visualized during the procedure. Of course, since only 13-57% of the fibrin sleeves result in dysfunction and the rest are asymptomatic, the rate of 0.99 per 1,000 catheter days may only represent those sleeves that caused symptoms in our patients (29).

Another idea supporting that the rates of fibrin sheath formation are underreported in our study is the incidence of infection in our patients. Although still under debate, studies indicate that fibrin sheaths may represent the progression of biofilms into larger thrombotic structures

(15). Since biofilms harbor infection, we would expect that more fibrin sheaths were prevalent in our data than were detected or reported, since our rates of infection were not as scant as the rates of fibrin sheath formation would suggest. Altogether, of all the patients with multiple catheter data points who had infection, 57.5% had another repeat infectious episode. The mean number of infections for a patient who had at least one prior episode of catheter-related bacteremia (CRB) was 2.34. This supports prior studies where patients who develop one episode of CRB are at risk for future episodes (20). It also supports the existence of a biofilm or fibrin sleeve in such patients that adds virulence to bacteria and increases the risks of future infections.

We separated the rate of thrombus formation from the rate of fibrin sheath formation in our study because the two are seen and commented on separately in imaging reports. Also, prior literature in interventional radiology tends to describe the two related phenomena as separate entities. Thus, we adhered to the same principles for the sake of comparison. At our institution, the rate of thrombus formation was 0.082 per 1,000 catheter days. Previous studies have reported higher rates of 1.94 per 1,000 catheter days (13). Again, similar to the scenario with fibrin sleeves, the most plausible explanation for this rate is underestimation. Likely, such defects were underreported in the imaging notes either because of negligence in writing these reports or because they were under-detected. The 35% of ‘malfunctions’ that included poor flow may represent some of the undetected, symptomatic thrombi.

Although the rate of infection falls within the range previously reported in literature, some studies have found that the type of catheter used may decrease the rate of complications. Spector et al. found that the use of Tal Palindrome catheter reduced the rate of infections and catheter malfunctions at their institution (52). Their rate of infection was 1.3 infections per 1,000 catheter days, which is much lower than ours and the typical 2.2-5.5 given in prior studies (18, 52). In fact when Kakkos et al. conducted a comparison trial between two tunneled catheters: the HemoSplitt TCC with BioBloc to the Tal Palindrome Ruby TCC, they found that the Palindrome catheter was associated with significantly lower rates of thrombosis and required less re-interventions than the HemoSplitt (11). Thus, in the case of infection and thrombosis, the Palindrome catheter appears to have fewer incidences of complications.

Unfortunately, our study was not able to mimic such results based on the types of catheter used. Largely, this is due to the skew in the variety of catheters that were used. Sixty-three percent of the catheters used in our study were Angiodynamics. Only 21% were Palindromes (20% Palindrome, 1% Palindrome with heparin) and 10% were Ashsplit. Five percent were unknown. In order to truly assess whether catheter types influence the rate of complications, we need to not only identify all of the catheters that are placed in patients from imaging reports, but also choose more evenly among the various catheters. Due to the bias towards Angiodynamics, we cannot support or reject the hypothesis that catheter types affect complication rates.

Our study does show that one factor, sidedness, may affect rate of complications. We saw that 35% of the right-sided catheters had infectious episodes while 42% of the left-sided catheters had episodes, with $p=0.06$. Although the results are not significantly different, 568 catheters were inserted into right-sided vessels while only 238 catheters into the left. Expanding our data to look at great number of left-sided catheters may reveal that there is a difference in the rate of infections that we our study lacked the power to detect. The possibility that there are greater infections among catheters placed into left-sided neck veins has been supported in prior literature. For instance, the risk of stenosis and thrombosis is much greater in left-sided vessels (14, 30). Since the presence of a thrombus increases the risk of infection, left-sided catheters are probably more likely to have higher rates of infection. In order to truly validate our results on sidedness, we would need to conduct a future experiment commenting on the difference not only between left and right sided vessels, but look specifically at what type of vessel (such as internal jugular, external jugular, subclavian etc.) is being used (37).

Although we did not find any difference in the rate of complications by the sidedness of the vessel, there was a significant difference in indwell time of a catheter based on whether it was right-sided or left-sided. Consistent with the DOQI recommendations that the right internal jugular vein should be the first option for catheter placement, we found that right sided catheters lasted 117 $\pm$ 159 days compared to the mean left sided catheter indwell time of 87 $\pm$ 124 days (p =0.008). This suggests that left sided catheters had poorer flow at earlier instances than their right sided counterparts. These results support many prior studies showing the left-sided catheterizations have shorter catheter longevity compared to vessels accessed on the right side (12, 44).

Left-sided catheters are thought to irritate vessels more than their right-sided counterparts due to the bends and kinks that occur as they traverse into the right atrium (44). Other than the risk of thrombus and stenotic complications, left-sided catheters may also be more likely to result in poor flow secondary to malpositioning. Since these catheters needed to be inserted longer distances, there is a greater risk for dislodging with movement. Again, future studies should look at the specific left- and right-sided vessels in order to better understand the relationships between indwell time and vessel use.

One of the hopes of our longitudinal design was to look at the first catheter data point for a particular patient and compare it to subsequent data points for the same patient in hopes of comparing the indwell times for consecutive placements. We found that there was no significant difference in the indwell time for the first catheter insertion compared to all subsequent insertions. When we looked as sequential catheter placements, there was no difference in the indwell time for first, second, third, etc. and up to the 22nd catheterizations. Although our graph (see Graph D) suggested a general decrease in mean indwell time, due to the large standard deviations, the trend was not significant. We also saw a trend in the percent of catheters that were removed for complications increase from the first to 22nd catheterization (from 88% to 100%).

Again this trend was not significant. However, these results do suggest a potential for decrease in catheter longevity with subsequent catheterizations. They may also suggest that while early catheters may be removed as they are no longer needed, most late catheters are only exchanged because complications occur.

Unfortunately our temporal data on first, second, third and subsequent data points lacks generalizability. The ‘first’ data point was not necessarily the absolute first catheter data point collected for that particular catheter-dependent patient. It could represent any number of catherizations from first to a hundredth depending on when that patient entered our data system and whether we had full data on that particular catheterization. Patients at YNHH often use many other outside institutions. If a catheter placed at YNHH was removed at an outside hospital, we would not have been able to include this information in our data. Many of our patients were lost to follow-up and consistently visited various hospitals within the vicinity of YNHH for care. Thus, the ‘first’ data point in our data represent the first *relative* information on a particular patient. Despite being catheter dependent with evidence for several catheter exchanges, some patients only had one complete data point, because information about other catheter removals/exchanges was incomplete in reports. For particular patients we had data for up to 22 catheter exchanges. Likely, these patients solely relied on YNHH for care and represented patients with many comorbidities. However, without being able to follow all catheter dependent patients from their first tunneled line placement to their last, it is impossible to compare catheter survival data in term so first, second, third and all subsequent relative catheterizations. In future studies, either patients will need to agree to attend only one hospital for their care or the studies should examine a more general comparison of indwell times for newly catheter-dependent patients compared to those patients with long-standing catheter-reliance.

Ideally, a study like this should be re-designed and conducted because no prior study has tried to characterize the changes in catheter survival, frequency and incidence of complications in catheter dependent patients. This should begin by enrolling patients who newly become reliant on catheters and then follow them through the course of their chronic disease. Perhaps by inserting bar codes or other forms of tracking devices, we would be better able to follow the survival and time line of each catheter insertion. Until then, the frequent hospitalizations and complications these patients face, as well as poor means of standardizing imaging reports for vital data such as the presence of thrombi, fibrin sheaths and stenosis makes such a task very challenging.

We also compared the rate of complications for over the guidewire exchange to removal and insertion of de novo catheters. The benefits of over the wire exchange are that in catheter dependent patients it preserves the use of other vessels for future central venous access. However, over the wire exchange is not readily accepted by all because some challenge that a simple exchange may not be as effective in eradicating the source of complication. In our study, 47 out of 398 catheters that were inserted de novo (or 12%) had no complications. The rate of no complications for de novo insertions did not differ significantly from over the wire exchange where 46 out of 366 catheters (13%) had no complications. Although we did not look at infection specifically, Duszak et al. have shown that catheter exchange does not increase the rate of infections and had similar long-term patency when compared to de novo catheter placement (53). In a smaller study, d'Othee et al. showed that when exchange is used as the treatment for fibrin sleeves, it is just as effective as de novo catheter insertion or stripping (36). Our results support that over the wire exchange is a safe alternative to de novo placement without compromising the rate of complications. In fact, further research looking at specific types of complication s and the effectiveness of over the wire exchange for each type of complication may preserve future vessel access sites in catheter-reliant patients.

In our study, there were 191 patients of which 53% (102 patients) were female and 47% (89) were males. In general our gender distribution is consistent with the United States Renal

Data System (USRDS) data that reports of that of all patients on catheters for long-term hemodialysis, 60% are females and 40% males (1). We found no difference in the rate of complications by gender which has been replicated and shown in many prior studies (6,8). There was also no difference in the mean indwell time for catheters between males and females. The age of our patients did not affect the complications outcomes. Prior studies have shown that in terms of demographics, neither age nor gender influence the rate of complications. Other factors, which were excluded from our study such as diabetes, however, do change the rate of complications (1, 6). Unfortunately, because of the retrospective nature of this study we were not able to assess other demographic factors for the relative contributions to the rates of catheter-related complications in our patient population.

Prior studies have compared the differences in effectiveness of insertion of central venous catheters by interventional radiologists , surgeons, anesthesiologists, and internal medicine doctors, but none to date have compared the catheters inserted by interventional radiologists to those inserted by physician's assistants (54-56). Since there is a robust P.A. service at Yale that routinely participates in catheter exchanges, we compared the rate of no complications in the M.D. and P.A. service. Our results showed that the rate of no complications was 15.1% when a P.A. performed the procedure and 10.4% when an M.D. performed the procedure. Although the difference was not significantly different (p=0.067), there may well be a difference with lower rates of complications among P.A. Partly, this can be explained by the on-call system as YNHH where the emergent cases are covered by the M.D. Thus, these patient tend to be sicker and are more likely to suffer complications. Regardless of whether P.A. have fewer rates of complications than M.D., our data shows that the P.A. service is just as effective as the M.D. portion of interventional suite in catheter exchanges.

Overall, we hope our study will inspire future studies on the unique group of catheter-dependent patients. We hope that instead of dealing with the complications related to tunneled catheter use, future experiments will work towards the prevention rather than treatment of such problems. As we previously mentioned, the design of this study relied on imaging reports for data gathering and relative definitions of ‘first’, ‘second’ and all subsequent catheterizations. Such methods of data gathering are far from ideal. We cannot look at temporal patterns of complications without properly identifying early and late catheterizations in catheter-dependent patients. Complications such as fibrin sheath and thrombus formation are also underrepresented in our data, which likely represent underreporting in imaging studies. Although, we hypothesized that catheter-dependent patients have shorter indwell times and higher incidence of complications the longer they are maintained on dialysis via catheters, our data was too diffuse to support or negate such a hypothesis. At this time we can only ascertain that there is no difference in the indwell times among first and subsequent catheterizations.

The rates of infection as well as decreased survival of catheters placed in left-sided vessels support much of what has been reported in literature. Future studies should look at specific vessels and specific types of catheter. Also, studies should be designed to follow newly dependent catheter patients and track their catheters more definitely.

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