Access Preservation Catheter Introductory Notes

Introduction

Each year, about 12–15,000 hemodialysis (HD) patients worldwide die because they exhaust mechanisms to connect to a dialysis machine, about 60,000 more require uncomfortable and infection-prone long-term femoral access, and about 240,000 receive a less durable and riskier-to-place left jugular HD catheter. Access Preservation Catheters (APCs) address this unmet need.

Background

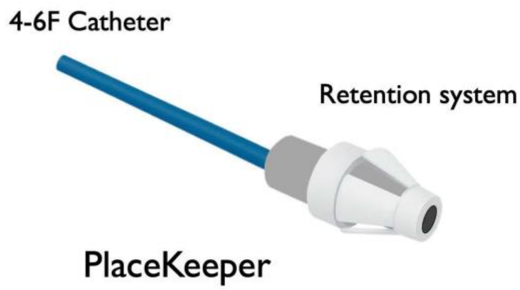
About 80% of patients receive a catheter when HD is initiated. A catheter can be implanted quickly and used immediately. As soon as possible, however, a fistula or graft is established in an arm, and the catheter is removed. This is because (1) fistulas and grafts have a several-fold lower risk of infection and death than catheters, (2) HD catheters comprise bulky external portions that limit patient comfort and activities, and (3) HD catheters have a large diameter, which increases the risk of injury to the veins that they enter and cross.

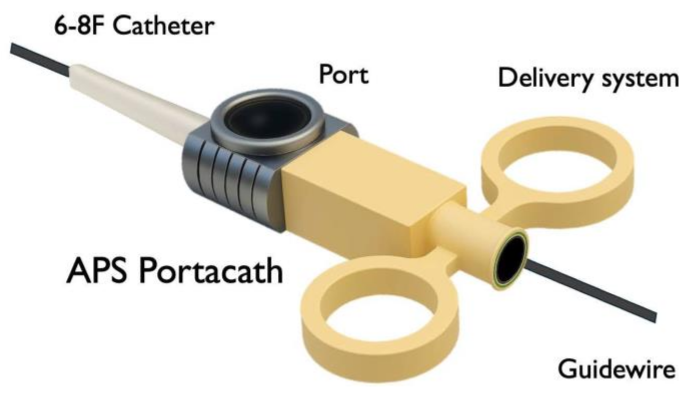
Over time, fistulas and grafts can become unrepairable and require replacement. When this occurs, a catheter is re-implanted in the chest for a few weeks or months while a new fistula or graft is established in an arm.

Over their dialysis lifetime, HD patients often require multiple catheter placements. As the number and total dwell time of catheters increase, catheter placement can become increasingly difficult. Each time a catheter is implanted, there can be further injury to the venous pathway. Sometimes the injuries can be fixed, but sometimes the injuries lead to irreversible occlusion once the catheter is removed.

The best entry point for catheter access is the right internal jugular vein. This approach has the lowest infection rate, the lowest implantation complication rate, and the greatest durability. In about 10% of patients, however, providers are forced to switch to less desirable access veins because the right jugular approach is no longer usable. There can be a cascade of switching initially to a left jugular vein, then femoral veins in the groin or to other riskier and less comfortable locations. In a small but not insignificant number of HD patients, which we estimate at roughly 2-3% of the total HD population, access loss becomes a critical issue associated with significant morbidity and mortality. This is a fatal stage that may be referred to as access exhaustion or End-stage Vascular Access Failure (ES-VAF). Access Preservation Catheters would at least slow and potentially prevent this cascade of progressive access loss.

Easy-to-place, Low-profile, Fully Internal Access Preservation Catheters (APCs)



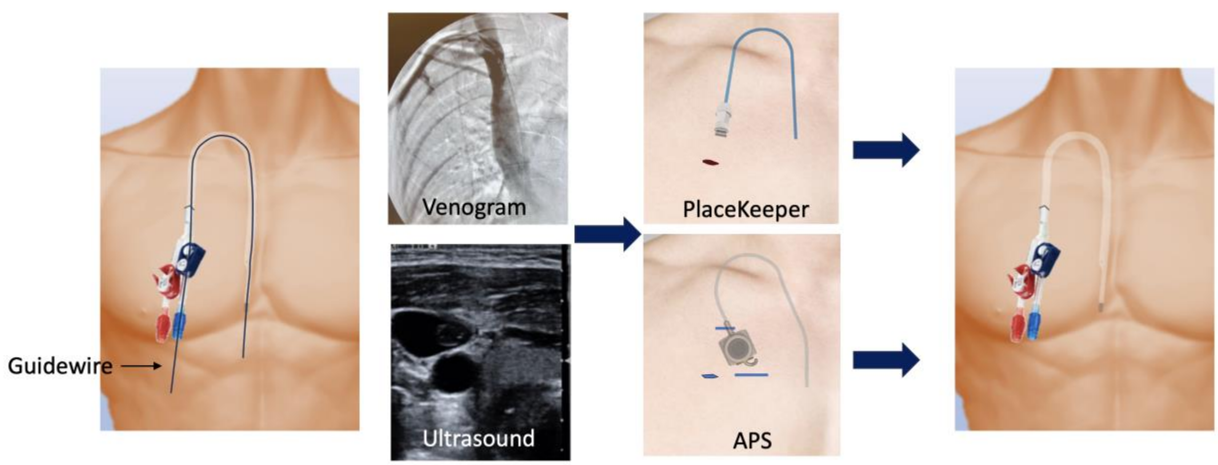


The PlaceKeeper is a simple low-profile, fully internal catheter, which functions only to preserve the access pathway. On the other hand, the Alexander Preservation System (APS) is a low-profile, fully internal over-the-wire portacath. Since it is a portacath, in addition to preserving the access pathway, it would also provide venous access for blood draws and infusions while implanted. The patient would receive fewer IV's, fewer peripherally inserted central catheters (PICCs), and fewer de novo central venous catheters.

How the Method and Devices Work

At a time when an arm graft or fistula becomes functional, rather than the current practice of just removing the HD catheter, the operator instead performs a venogram and duplex to determine whether the vein pathway is at risk of occlusion. If so, and if the patient has a reasonable life expectancy, the operator replaces the bulky internal/external HD catheter with an APC. For the next weeks, months, or years, the patient receives dialysis via the arm graft or fistula, and the APC remains implanted in the chest.

The next time the patient needs a catheter, rather than a de novo placement, the operator makes an incision to free the APC, advances a wire through it, removes the device over the wire, and then advances the new HD catheter over the same wire. This process of exchanges is maintained for as long as the patient requires dialysis.



What are the Clinical Benefits of the APC System?

1. At a time when the patient needs a new HD catheter, there would be no new central venous needle stick, which is the highest risk portion of catheter placement.
2. Successful passage of the new HD catheter is nearly guaranteed.
3. The patient will rarely if ever need a femoral long-term catheter.
4. The patient will rarely if ever experience access exhaustion.
5. If the APS is implanted, the patient will require fewer IVs or PICCs, which helps maintain graft and fistula surgical options.

HD Patients Who Would Benefit:

- We estimate that 2-3% of patients die primarily because of access loss issues, including exhaustion/End-stage Vascular Access Failure (ES-VAF). There is no registry that provides an exact percentage, but multiple sources support an exhaustion percentage in the low single digits.

- About 4% of patients need femoral access long-term, roughly 3% tunneled catheters and an additional 1% femoral grafts, because upper body pathways are exhausted.
- About 10% of patients need left jugular access because the right jugular pathway is exhausted. These patients typically require more catheters over time, so the frequency of left jugular catheter insertions is about 15%.

For perspective, there are roughly 500-550,000 chronic hemodialysis patients in the US and roughly 3 million worldwide. Greater than 90% will use a tunneled catheter at some point. Roughly 70% in the US (350,000) and worldwide (2.1M) will need more than 1 HD catheter over their dialysis lifetime.

There are 2 mechanisms by which a tunneled HD catheter could be exchanged for an APC.

In the case of a PlaceKeeper device, a simple 1-minute over- the-wire exchange could be performed. To limit the risk of infection, the tunnel must be long enough that, after exchange, the PlaceKeeper back-end cuff can be positioned at least 3 cm above the chest wound. Generally, HD catheter tracts are only significantly colonized by bacteria over the 2-3 cm adjacent to the chest wound, with the retention cuff acting as a partial barrier. An over-the-wire exchange for a PlaceKeeper is analogous to a tunneled HD catheter exchange, which is a commonly performed procedure that only rarely results in infection.

In the case of an APS portacath, or as an alternative approach for the PlaceKeeper, placement would take about 15 minutes. A cut-down would be performed between the chest wound and venotomy, followed by the creation of a new small separate incision and tunnel.

Both implantation techniques may be used if the operator stages the procedure. At the time of HD catheter removal, the operator may perform a speedy and simple PlaceKeeper over-the-wire exchange. The patient may then be brought back days or weeks later, when there is more time on the schedule and when the original chest wound has healed, to convert the PlaceKeeper into an APS portacath using a separate small incision.

How Does the APS Portacath Differ from Current Portacaths?

Unlike existing portacaths, the APS has a closeable aperture at the back end of the port. This permits the attached port and catheter to be advanced as a unit over a wire. The APS also comprises rounded sides, which stabilizes the port and facilitates insertion through a small incision. Because of this rounded design, the APS can be inserted using dilators, rather than blunt dissection, to create a subcutaneous pocket. This makes a portacath implantation and exchange faster and easier, more like a tunneled catheter implantation and exchange. These and other features are covered by 2 pending US patents.

How Is the APS Better Than Existing Portacaths for Preserving Access in the ESRD Population?

In addition to being faster and easier than existing portacaths to implant, APCs are better for the management of infections, which are 3-4 times more common in the ESRD population. If the device is infected or the patient is septic, management would consist of antibiotics and simple over-the-wire exchanges. There could also be an intermediate internal/external catheter specifically designed to act as a bridge while the patient receives antibiotics.

Strategies for APC Implantation

1. **Protect the left jugular pathway after the right jugular pathway has occluded.**

   In 10% of patients, the right IJ is lost over the course of a dialysis lifetime. To avoid femoral access or exhaustion death, the APC would be used to preserve left jugular catheter access. Patients would receive a routine yearly exchange, and some number would also receive exchanges due to infections. APC catheter prevalence in this setting is 10%.

2. **Screen the RJ at the time of catheter removal. Implant an APC if the screening is positive for a high risk of pathway occlusion after removal.**

   Reason 1. In general, any patient with a reasonable life expectancy can be managed more reliably over the long-term if the right IJ pathway is always available. This approach stops the access loss cascade at the earliest point.

   Reason 2. The patient could avoid a riskier-to-place and less durable left jugular catheter, which is often preceded by a failed attempt to place a right jugular catheter. The failed right attempt can be time-consuming, involving contrast injection, multiple approaches with various catheters and wires, dressing the right chest and neck after failure, prepping the left chest and neck, and then eventually placing the less favorable left jugular catheter.

   Since screening is imperfect, and since it is better to err on the side of sensitivity, APC prevalence in this setting would be approximately 15%. This would occur if 10% of RJ removals result in APC implantation.

The best strategy may be some combination of 1 and 2. The screening process for RJ APC implantation would be designed for very high sensitivity to access loss risk but also reasonably high specificity to exclude patients at lower risk. Patients who eventually lose the RJ because of high specificity screening would receive an APC at the time of left jugular catheter removal, so that upper body access is preserved.

Recent Example of Avoidable Access Loss

This is a 28-year-old woman dialyzed for 2 years via a right jugular catheter. She had required multiple attempts to establish arm access. A right upper arm graft functioned for a year before thrombosing. Here is the initial central venogram at the time of thrombectomy. The right brachiocephalic vein occlusion could not be crossed.

At the time of catheter removal last year, had the operator performed venography (because of the long catheter dwell time), there would have been a significant stenosis of the right brachiocephalic vein (BCV). Had the operator placed an APC at the time of catheter removal, the right BCV could have been crossed and repaired during the thrombectomy.

Why Not Provide Access Preservation for Every HD Patient?

There are 2 liabilities of an APC: (1) a risk of infection with associated mortality and (2) a need for simple maintenance procedures. Maintenance for either device would include yearly catheter exchanges. The APS would also require heparin flushes by a nurse every 3 months between exchanges. As material science improves, maintenance may be stretched over longer intervals.

If there is not significant RJ pathway disease at the time of RJ dialysis catheter removal, then there is no reason to expose the patient to the infection risk or additional cost of maintenance of an APC.

For the 10% Cohort of Patients Who Lose the Right Jugular Pathway, APCs Decrease Exhaustion Mortality Much More Than They Increase Infection Mortality

HD catheters have a very high infection rate. However, HD catheters comprise external portions and are accessed multiple times per week. On the other hand, the APS is fully internal and may be accessed only sporadically. Based on this, the APC infection rate should be much lower than the HD catheter rate. For initial modeling, we assume that the APC infection rate is approximately that of a CIED in the ESRD population.

In the general population, CIED infections occur in roughly 1% over a period of several years. Infections are more common in the ESRD population, with reported rates of 2-5%. Based on these data, we estimate the APC infection rate will be comparable to the higher end of reported CIED infections, 5%/year.

Regarding mortality of CRBSIs in an ESRD population, there is wide variation in reported series. Optimized settings have reported a CRBSI mortality as low as 1%, whereas single-center CRBSI cohorts have demonstrated a 6-10% mortality. In resource-limited populations, or in the case of S. aureus or gram-negative bacteremia, mortality is much higher. For this document, we assume an overall 10% risk of mortality per CRBSI episode.

Based on the above assumptions, the mortality due to CRBSI of an APC implantation would be about 0.05 x 0.1 = 0.5%/year.

What percentage of lives are saved by implanting the APC? We estimate the risk of death primarily due to access loss to be about 2-3% for the entire ESRD population. However, we propose to treat only patients who have lost or are at a high risk of losing the RJ, which is roughly 10% of the ESRD population. Since all patients with access exhaustion have lost the RJ, the risk of access exhaustion in the RJ-occluded cohort is 20-30%, as opposed to the 2-3% in the total population.

If we assume that the average ESRD patient with a severely diseased RJ lives for 4 additional years, then the annualized risk of dying from access exhaustion that the APC prevents is 5-7%/year.

How Much Will APCs Decrease RJ-lost Cohort Mortality?

In the 10% of the ESRD population with severe RJ disease, assume a 20% baseline rate of death/year from all events that are not directly related to access loss, such as heart disease, cancer, and so on. When access loss events are included in the mortality rate, patients receiving APCs would have a 20.5% annual mortality. On the other hand, patients not receiving APCs would have a 25-27% annual mortality.

How Much Will APCs Decrease RJ-lost Major Adverse Events, Including Femoral Access and Death?

In the total ESRD population, assume a 5-7% risk of either access exhaustion death or femoral access in a dialysis lifetime. Since all patients in this category will have lost the RJ, among the RJ-lost cohort about 50-70% will experience a major adverse event.

If we assume that the average ESRD patient with a severely diseased RJ lives for 4 additional years, then the annualized risk of major adverse event related to access exhaustion that the APC prevents is 12-18%/year.

In the 10% of the ESRD population with severe RJ disease, assume a 20% baseline rate of death/year from all events that are not directly related to access loss, such as heart disease, cancer, and so on. When access loss events are included in the major adverse event rate, patients receiving APCs would have a 20.5% annual major adverse event rate. On the other hand, patients not receiving APCs would have a 32-38% annual major adverse event rate.

US Patent Protection

1. Device and Method to Extend the Lifetime of a Venous Pathway for Catheter Access (published)
2. Portacatheters With Improved Stability that Utilize Small Incisions and are Easy to Implant (published)

Path to FDA Approval

The APS should receive FDA approval based on a 510(k) submission, with a standard portacath as the predicate device. This is because the APS would have a primary indication of long-term venous access, which is the indication for any portacath. Here is possible language:

> *The subject device is a subcutaneous, implantable port system substantially equivalent in design, materials, and intended use to the predicate device. The primary technological difference is the inclusion of a closeable posterior aperture to allow over-the-wire insertion or exchange via standard guidewire techniques. This feature is intended to facilitate easier placement and allow device exchange in the event of infection or malfunction, reducing the need for repeated new central access site creation. Once placed and sealed, the device functions identically to traditional portacaths.*

On the other hand, the PlaceKeeper would probably not be eligible for a 510(k) as a stand- alone device, since the PlaceKeeper clinical indication could only be access preservation, and there would be no predicate device. However, an FDA approval mechanism for the PlaceKeeper could be a De Novo submission or to make a PlaceKeeper a component of the APS system.

Summary

Access Preservation Catheters represent a low-risk, moderate-cost program that would nearly ensure an indefinite ability to perform hemodialysis. A typical patient may experience several years of catheter exchanges, and some catheters will become infected. However, in a selected cohort of 300,000 patients who have lost or are at risk of losing the right jugular pathway, APC placement will provide significant benefit: 12-15,000 patients can be saved from fatal advanced access loss, 60,000 more can avoid lifestyle-limiting, high-risk femoral access, and 240,000 more can maintain a right jugular catheter rather than a less durable and riskier left jugular catheter.