Maintaining vascular access: the management of hemodialysis arteriovenous grafts

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ABSTRACT
For the nephrologist and surgeon, maintaining vascular access is a significant challenge in hemodialysis (HD), because the portal is vulnerable to infection, stenosis, and thrombus. Vascular access options for HD include the placement of arteriovenous (AV) fistulas, AV grafts, and double-lumen, cuffed central vein catheters. Catheter use is generally associated with higher rates of infection and could compromise the adequacy of HD. Primary AV fistulas, which are generally recommended and provide excellent HD access, are not always the ideal choice for certain patients, such as the elderly or patients with diabetes mellitus. AV grafts allow for a large surface area available for cannulation, and thrombosed grafts have longer patency rates after revision than do revised fistulas. Although both AV fistulas and AV grafts are vulnerable to thrombosis and/or stenosis, surveillance and techniques such as Doppler ultrasound and intravascular ultrasound can minimize such complications. In addition, pharmacotherapeutic options are being studied to determine whether these complications can be prevented. Studies using a variety of pharmacologic agents have been conducted to determine whether stenosis and graft thrombosis can be prevented and have produced varying results. The use of warfarin can result in significant bleeding, but agents such as fish oil and angiotensin-converting enzyme inhibitors have shown some effect in increasing the patency in AV grafts and fistulas. Additional randomized trials with at least 1 or 2 yrs of follow-up are necessary to assess the long-term use of these pharmacotherapies.

Key words: Hemodialysis, Vascular access, Arteriovenous graft, Arteriovenous fistula, Central vein catheter

INTRODUCTION
In the United States, approximately 300,000 patients with end-stage renal disease (ESRD) currently undergo hemodialysis (HD) (1). Although operational vascular access is vital in providing efficient dialysis therapy, it remains a weak link in HD, vulnerable to complications such as stenosis, infection, thrombus, and bleeding. Thus, optimizing vascular access is a persistent challenge for the surgeon and nephrologist.

Since the introduction of the Schrier shunt in 1960, creating a gateway for HD has emerged as one of the most commonly performed surgeries in the United States, with approximately 500,000 vascular access procedures performed annually (2). Optimizing the vascular access necessary for HD consumes ~8% of the money spent by Medicare on ESRD (roughly $1.8 billion per year) (3). In 2006, the cost of ESRD rose to $23 billion, or 6.4% of the total Medicare budget of $355 billion.

In most patients, the primary goal of HD vascular access is to keep the patient alive until a transplant is available. Some patients do not qualify for a transplant because of age and/or comorbid medical conditions. Thus, HD can be enduring, with the recurrent threat of vascular access complications. Approximately 1 in 5 patients starting HD will die within the first year of dialysis, typically from cardiovascular or diabetes complications. In addition, an estimated 25% of all patients starting HD will die because of inadequate vascular access or complications related to vascular access (4, 5).

ARTERIOVENOUS FISTULAS VERSUS ARTERIOVENOUS GRAFTS
Vascular access options for HD currently include the placement of arteriovenous (AV) fistulas, AV grafts, and double-lumen, cuffed central vein catheters. Catheter use is generally associated with higher rates of infection and could compromise the adequacy of HD (6, 7). Other risk factors linked to catheter use include increased luminal thrombosis, unreliable blood flows, central venous stenosis, and patient cosmetic concern (7).

AV FISTULAS
Is either an AV fistula or an AV graft superior to the other? Primary AV fistulas provide excellent HD access and are generally recommended (8). However, they are not always the ideal choice for certain subsets of patients. For example, late referral of patients to nephrologists and surgeons limits their use. In addition, patients who are elderly or have diabetes mellitus may have a limited
number of suitable sites for the formation of primary AV fistulas, which restricts their use (4). A significant number of AV fistulas (30-50%) never mature to support dialysis (9). One study of 374 patients with AV fistulas revealed an overall failure rate of 31% (10). The inability of AV fistulas to mature occurs in higher rates among women than among men (41% vs. 27%); the most rational explanation for this difference is the smaller size of vessels in women. Moreover, women within the study population often had diabetes mellitus or hypertension or were classified as “early postmenopausal”, all of which are conditions that may produce a form of atherosclerosis that accelerates more rapidly than that in men. Other risk factors, including positive HIV status, hypertension, and diabetes mellitus, demonstrated relatively minimal failure differences (33%, 31%, and 36%, respectively) (10).

In years past, most candidates for HD were men who were relatively young (<65 yrs of age) and did not have diabetes mellitus, and the majority did not have cardiovascular comorbidities (11). Thus, construction of AV fistulas in the wrist could be expected to mature adequately and remain patent and functional for years with scant intervention. Currently, the HD population is older, diabetic, and more balanced between the sexes, with higher comorbidities, including atherosclerotic disease; many of these patients have extensive vessel damage that hinders the construction of native fistulas. These factors had resulted in the increased use of AV grafts and a tendency away from AV fistulas. Currently, only 2 in 3 patients who receive HD in the United States have an AV fistula (12).

AV Grafts

Dialysis AV grafts have some distinct advantages, as presented in Table I. However, synthetic vascular grafts also have some drawbacks. Nevertheless, AV grafts have been found to be comparable to AV fistulas within a number of parameters. For example, a recent study that reviewed 1,700 consecutive access procedures demonstrated that AV grafts are equivalent to AV fistulas in long-term patency (2). Median patency time was 10 months, with no significant difference between groups. There was no significant difference in patency life when comparing upper arm (70%), lower arm (25%) and thigh (~5%) sites. Graft infection rate was 10% and fistula infection rate was 1% (p<0.001); overall infection rate for the life of the AV graft or AV fistula was 4.5%, and decreased patency significantly (4 months vs. 11 months). Thrombosis occurred in 25% of grafts and 9% of fistulas. Thrombosed grafts had better salvage rates than did fistulas (8 months for grafts vs. 4 months for fistulas; p<0.001). The incidence of thrombosis observed in 91% of the accesses was significantly increased among patients with hypertension (p=0.003). However, the data showed that diabetes mellitus, hypertension, or HIV had no overall impact on patency of either access type. Therefore, when an AV fistula cannot be created, an AV graft is a better alternative than a catheter. Although grafts have a higher incidence of thrombosis, post-revision grafts have a significantly longer patency than do revised fistulas.

Reducing graft thrombosis

Access surveillance is based on the following assumptions: (a) most episodes of access failure are preceded by the development of stenosis at or near the venous anastomosis, and (b) the development of stenosis in the graft access that is predictive of thrombosis can be detected by monitoring techniques. The incidence of AV graft thrombosis can be prevented in several ways. Here, we discuss surveillance issues, as well as pharmacologic interventions.

Surveillance

Monthly surveillance of grafts via flow measurements is a part of the dialysis outcome quality initiative (DOQI) guidelines of the National Kidney Foundation (8). Until additional studies are performed to determine the optimal frequency, the DOQI guidelines recommend against taking measurements less frequently. One study suggested that, because flow and change in flow are inaccurate predictors of thrombosis, adequate assessment of risk should consider many measurements obtained over time (13). Logistic regression analysis was used to compute the risk of thrombosis and receiver operating characteristic (ROC) curves were employed to assess the accuracy in predicting thrombosis within 1 month. The results showed that

TABLE I - ADVANTAGES OF ARTERIOVENOUS GRAFTS

- Large surface area available for cannulation
- Technically easy to cannulate
- Short lag-time from insertion to maturation (early cannulation: 24-72 hr)
- Late cannulation - after 2 weeks, no difference in patency, thrombosis, or wound infection rates
- Multiple insertion sites available
- Variety of shapes and configurations available to facilitate placement
- Easy for the surgeon to handle, implant, and construct the vascular anastomoses
- Thrombosed grafts have longer patency rates after revision than do revised fistulas

newer grafts were most likely to thrombose, whereas older grafts were unlikely to thrombose even during low flows or large decreases in flow. More than half the thromboses lacked a change in flow measurement, usually because thrombosis occurred before a change could be measured. Thus, the effective predictive accuracy of change in flow was much less than the ROC curves indicated because the curves do not consider missing measurements. Many thromboses are not predicted, and intervention based on surveillance likely yields many needless procedures. Therefore, this study does not support routine application of surveillance to avert thrombosis.

**Access blood flow**

Static venous pressure (SVP), dynamic venous pressure (DVP), and access blood flow (ABF) have been used in predicting subsequent graft thrombosis and/or failure. One study found that a falling level of access flow, as opposed to the absolute level, is the most potent predictor of graft thrombosis (14). The purpose of that study was to compare prospectively the predictive accuracy of SVP, DVP, and ABF in determining subsequent graft thrombosis and/or failure in 43 patients with functional AV grafts. Neither SVP nor DVP showed acceptable sensitivity or specificity for graft thrombosis. Ten (23%) patients either began with or developed an ABF <600 mL/min during the 3 months of measurements, but only five (12%) of those cases clotted. A change in ABF of >20% provided the best combination of sensitivity (86%) and specificity (90%) for graft thrombosis. Among AV grafts that have an ABF <600 mL/min, those grafts with falling ABF appear most likely to clot in the short term.

Despite surveillance, some grafts clot. A significant percentage (40%) of graft thromboses that do occur despite ABF surveillance arise in grafts with preserved ABF (>600 mL/min) (15). More than 70% can be successfully thrombectomized or angioplastied, resulting in ~35% long-term (6 months) survival.

**Doppler techniques**

Doppler techniques appear valuable in detecting stenoses in grafts. Percutaneous transluminal angioplasty performed under color Doppler ultrasonography guidance is useful in maintaining and improving graft patency (16). Percutaneous transluminal angioplasty with color Doppler ultrasonography guidance allows patients to avoid surgical intervention, hospitalization, and adverse reactions to contrast media and exposure to ionizing radiation, with reduced cost and with better graft survival.

One study that used Doppler ultrasonography did demonstrate superior graft survival in two groups of patients who participated in stenosis surveillance (17). In group 1, ultrasound examinations performed every 3 months were added to traditional screening (ie regular access examination at HD, monitoring of venous pressure and access flow); group 2 was screened only traditionally (without ultrasound). Group 1 was found to have significantly longer access patency (p<0.001). Another study showed that the presence of what is deemed “a significant stenosis” does not necessarily correlate with measured vascular access flow and may not be associated with early thrombosis needing immediate intervention (18).

**Intravascular ultrasonography**

Intravascular ultrasonography is a relatively new technique capable of detecting subtle vascular abnormalities. Intravascular ultrasonography can give a 3-dimensional, 360º visualization of the vessel and can detect more vascular abnormalities than can angiography. In one study, angiography assessed 32% of vessel segments to be normal, vs. 17% of segments assessed as normal using intravascular ultrasonography (p<0.001) (19). In addition, intravascular ultrasonography detected lesions in 32% more segments than did angiography (p<0.001). Thrombi were detected in 59% of vessel segments by intravascular ultrasonography, but in only 2% of segments by angiography (p<0.001).

**Preemptive angioplasty**

It is debatable whether stenosis surveillance coupled with preemptive angioplasty can favorably impact graft outcomes. Studies have been done to assess the impact of stenosis surveillance on preemptive angioplasty and graft outcome. A number of studies show that angioplasty frequency is higher in the surveillance groups, meaning that stenoses are being identified in a large number of patients. The techniques used in these studies to recognize stenoses include Doppler ultrasonography (17, 20, 21), access flow (20, 22), and static DVP (23). However, most studies do not show a correlation between surveillance and thrombosis-free survival/graft survival (20-23).

Prophylactic intervention (angioplasty or surgery) can delay thrombosis. But, one problem with angioplasty is that the interventionist may perform it repeatedly. It is this author’s opinion that after three angioplasties, the patient should be referred to a surgeon. Further studies are needed to elucidate the best surveillance protocol and the role of preemptive intervention in significant stenosis.

**Pharmacologic interventions**

Whether stenosis and graft thrombosis can be prevented with pharmacologic agents has been studied using a variety of agents and has produced varying results. In addition to the studies mentioned below, Table II presents a summary of other pharmacotherapy studies.
Fish oil

Novel strategies to prevent dialysis access thrombosis are needed to reduce the cost and morbidity of maintenance HD. Diets enriched with $\omega-3$ fatty acids, derived from fish oil, may offer such an opportunity. Such diets may favorably impact the vascular perturbations that could contribute to synthetic graft thrombosis. In a double-blind, prospective trial that assessed the ability of fish oil to prevent HD graft thrombosis, 24 patients were randomized to receive 4 g of fish oil or 4 g of control oil for 12 months. The primary patency rates at 1 yr were 15% for the control group and 76% for the group that received fish oil; survival analysis revealed a significant difference between patients who received fish oil and patients who did not ($p<0.03$). In addition, an analysis of covariables, including age $\geq$ 50 yrs, sex, race, body weight, presence of diabetes mellitus, bleeding times, and lipid profiles, indicated that this effect occurred predominantly as a result of fish oil administration. Notably, fish oil therapy also decreased venous outflow resistance and systemic blood pressure, compared with control values.

The first large, multicenter, randomized, controlled trial of a natural supplement in preventing HD access thrombosis involved 232 patients receiving chronic HD who required a new graft access. Patients were divided into ACE inhibitor and non-ACE inhibitor groups based on the use of ACE inhibitors during access patency. No distinction was made on the brand or dosage of ACE inhibitor. The results showed that ACE inhibitor use was associated with greater access patency duration (672 days in the ACE inhibitor group vs. 460 days in the non-ACE inhibitor group; $p=0.012$). Compared with the non-ACE inhibitor group, the ACE inhibitor group had fewer clotting events (55% vs. 71%; $p=0.042$). ACE inhibitor use had little effect on primary patency of the fistula; however, male sex increased time to fistula failure ($p=0.002$). Fistula patency is impacted by patient sex, with longer patency noted among men. This evaluation suggests that ACE inhibitor use in patients with polytetrafluoroethylene grafts may prolong and maintain patency. Further prospective studies are necessary to validate the function of ACE inhibitors in maintaining vascular access patency.

Angiotensin-converting enzyme inhibitors

Endothelial injury via angiotensin II may mediate a hyperplastic and prothrombotic response. Therefore, reducing angiotensin II with angiotensin-converting enzyme (ACE) inhibitors may prolong vascular access patency. In a retrospective study 266 accesses from four dialysis centers were analyzed. Patients were divided into ACE inhibitor and non-ACE inhibitor groups based on the use of ACE inhibitors during access patency. No distinction was made on the brand or dosage of ACE inhibitor. The results showed that ACE inhibitor use was associated with greater access patency duration (672 days in the ACE inhibitor group vs. 460 days in the non-ACE inhibitor group; $p=0.012$). Compared with the non-ACE inhibitor group, the ACE inhibitor group had fewer clotting events (55% vs. 71%; $p=0.042$). ACE inhibitor use had little effect on primary patency of the fistula; however, male sex increased time to fistula failure ($p=0.002$). Fistula patency is impacted by patient sex, with longer patency noted among men. This evaluation suggests that ACE inhibitor use in patients with polytetrafluoroethylene grafts may prolong and maintain patency. Further prospective studies are necessary to validate the function of ACE inhibitors in maintaining vascular access patency.

Anticoagulation therapy

Many American patients receiving HD use a polytetrafluoroethylene graft as their primary blood access. The most common complication of vascular access is thrombosis. To reduce the risk of thrombotic failure, many nephrologists prescribe anticoagulants. However, research,

<table>
<thead>
<tr>
<th>Treatment(s)</th>
<th>Results</th>
<th>Statistical Significance</th>
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<tr>
<td>Aspirin vs. placebo (43-45)</td>
<td>Favored active treatment over placebo</td>
<td>OR, 0.42, 95% CI, 0.20-0.86; $p=0.02$</td>
</tr>
<tr>
<td>Dipyridamole vs. placebo and dipyridamole/ aspirin vs. placebo (45)</td>
<td>Favored active treatment over placebo</td>
<td>OR, 0.57, 95% CI, 0.13-2.51; OR, 0.77, 95% CI, 0.19-3.19, respectively</td>
</tr>
<tr>
<td>Fish oil vs. placebo (24)</td>
<td>Favored active treatment over placebo</td>
<td>OR, 0.07, 95% CI, 0.01-0.49</td>
</tr>
<tr>
<td>Low-dose warfarin vs. placebo (28)</td>
<td>Trial terminated because of increased bleeding events in the treatment group; favored placebo over active treatment</td>
<td>OR, 1.76, 95% CI, 0.78-3.99</td>
</tr>
<tr>
<td>Clopidogrel vs. placebo (33)</td>
<td>Favored active treatment over placebo in early thrombosis prevention but no difference was seen in proportion of fistulas that become suitable for dialysis</td>
<td>OR, 0.01, 95% CI, 0.00-0.15</td>
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Abbreviations: AV: arteriovenous, CI: confidence interval, ESRD: end-stage renal disease, OR: odds ratio
albeit limited, has documented some problems with this approach. A multicenter, randomized, double-blind, placebo-controlled clinical trial was performed to determine whether or not low-intensity, monitored-dose warfarin therapy reduced the risk of failure of polytetrafluoroethylene dialysis grafts (28). The trial was prematurely terminated after 37 weeks because of a significant increase in major hemorrhage seen in the treatment group. The overall result favored placebo (odds ratio, 1.76). This study demonstrates that warfarin administered to achieve an international normalized ratio of 1.4 to 1.9 is ineffective and potentially dangerous when it is used for the prevention of polytetrafluoroethylene dialysis access graft failure, particularly in combination with aspirin, a drug for which many patients who receive chronic dialysis have an accepted indication.

A systematic review of mainly observational studies of full-intensity anticoagulation and a randomized, controlled trial of low-intensity anticoagulation revealed major bleeding episode rates ranging from 0.1 to 0.5 events/patient-year of warfarin exposure (29). These rates are approximately twice as high as those of patients receiving HD who receive either no warfarin or subcutaneous heparin.

However, patients have considerable difficulties adhering to warfarin regimens, and this poor adherence has a significant effect on anticoagulation control. One study that assessed patient adherence to warfarin showed that participants who missed their warfarin dose 1 to 2 days per week had more than a 2-fold increase in the odds of undercoagulation (odds ratio, 2.10) (30), thereby potentially jeopardizing the patency of their HD graft.

Antiplatelet therapy

Clopidogrel plus aspirin

In the HD population, therapy with daily aspirin (325 mg) and clopidogrel (75 mg) has been associated with a significantly increased risk of bleeding and would likely not result in a reduced frequency of graft thrombosis (31). In this 2-yr study, the cumulative incidence of bleeding events was significantly greater for patients who received aspirin/clopidogrel, compared with patients who received placebo (p=0.007). Of patients in the placebo group, 24% experienced a bleeding event, compared with 42% of participants in the active treatment group (p=0.006). No significant benefit of active treatment in the prevention of thrombosis was observed (p=0.45).

Clopidogrel

In a related study designed to determine whether clopidogrel reduces early failure of HD fistulas, clopidogrel reduced the frequency of early thrombosis of new AV fistulas, but did not increase the proportion of fistulas that become suitable for dialysis (32, 33). Fistula thrombosis occurred in 12% of participants assigned to receive clopidogrel, compared with 20% of participants assigned to receive placebo (p=0.018); failure to attain suitability for dialysis did not differ significantly between the clopidogrel and placebo groups (62% vs. 60%, respectively; p=0.4).

Dipyridamole plus aspirin

Dipyridamole, a non-nitrate coronary vasodilator, inhibits platelet activation in two ways: (1) by blocking the adenosine transporter, which results in an increased adenosine extracellular concentration and leads to a subsequent increase in intracellular cyclic adenosine monophosphate levels, and (2) by inhibiting the cyclic guanosine monophosphate-specific phosphodiesterase type V, thereby increasing cyclic guanosine monophosphate. Dipyridamole is also a potent antioxidant and has anti-inflammatory mechanisms and antiproliferative properties that may be of relevance in vascular graft patency. The Effect of Extended-Release Dipyridamole Plus Aspirin (ERDP/ASA) on Hemodialysis Arteriovenous Graft Patency Trial with 649 randomized participants is the largest controlled trial of AV graft patency to date (34). Patients in the active arm of the trial received ERDP 200 mg BID and aspirin 25 mg BID and participated in a 6-month follow-up. The study investigated whether ERDP/ASA can reduce stenosis and prolong primary unassisted graft patency, as measured by the time from access surgery to first thrombosis or to employment of a procedure required to maintain or restore patency.

At 1 yr, ERDP/ASA showed a 28% incidence of primary unassisted patency compared to only a 23% with placebo (p=0.03) and showed a median patency duration of 5.8 months. However, over the course of the 4.5-yr trial, a total of 80% of patients in the ERDP/ASA group vs. 84% in the placebo group reached the primary endpoint of overall failure of primary patency (35). An 18% relative risk reduction in the failure rate of primary unassisted patency for new AV grafts (p=0.034) and a 28% relative risk reduction in clinically significant stenosis was seen with treatment of ERDP/ASA (p=0.005). Yet, no increase in bleeding or adverse events, including death, was observed in the active treatment group.

A recent meta-analysis that reviewed randomized, controlled trials of active drug vs. placebo in patients with ESRD undergoing HD via an AV fistula or prosthetic interposition AV graft concluded that no trials with follow-up periods longer than 36 months demonstrated a beneficial effect of antithrombotic or antiplatelet treatment to increase patency of AV fistulas and grafts; therefore, their long-term effect remains unclear (36). Additional randomized trials with at least 1 or 2 yrs of follow-up study are necessary to assess the long-term use of such pharmacotherapies.
DISCUSSION

Do preoperative work beforehand. Preoperative physical evaluation and vein mapping are pivotal in establishing which access type will suit a particular patient. For example, preoperative ultrasound mapping prior to HD access placement can result in superior surgical management, with an improved probability of selecting the most-functional vessels. Preoperative ultrasound mapping resulted in a change in the planned surgical procedure in 31% of patients in a prospective study that assessed the effect of preoperative ultrasound mapping on surgical selection, placement of AV fistulas and grafts, and negative surgical exploration rates (37). The incidence of unsuccessful surgical explorations decreased from 11% to 0%.

Work together. Nephrologists and surgeons should work jointly to pinpoint appropriate timing of access and to allow adequate time for either fistula maturation or graft placement. Physicians who do >50 AV fistulas or grafts per year should refer patients to a center of excellence. Late referral of patients to nephrologists and surgeons limits the use of AV fistulas.

Be flexible. Schild et al performed a study at the University of Miami Leonard M. Miller School of Medicine, where autogenous AV fistulas are used whenever possible, to document maturation and failure rates in a large, homogeneous series of AV fistulas (10). The data from that study imply that an AV graft should be used for patients in whom such a fistula does not mature and is not functional. In addition, although grafts tend to have higher rates of infection and thrombus, techniques are available to manage these complications. For instance, if an autogenous wrist radiocephalic AV fistula cannot be created, the next choice for chronic HD access may be a prosthetic forearm looped AV graft or a native upper-arm AV fistula, which has a lower incidence of complications and non-elective reinterventions (38). To maximize the benefits of upper-arm AV fistulas; however, early surgical referral is required.

Skip the catheter. Everyone should now agree that when a primary AV fistula is not possible, then an early cannulation graft is the superior option to a catheter for vascular access. Central venous catheters have many harmful complications, including bacteremia and death, and can limit the future availability of access sites because of the development of central venous stenosis (39, 40). Moreover, there is a risk of central vein stenosis, even 2 weeks after catheter placement, and an impaired venous outflow precludes the creation of any vascular access and sometimes inhibits the placement of a kidney transplant in the iliac fossa for years (40). In addition, research shows that switching from a central venous catheter to either an AV fistula or graft reduces the risk for mortality (41).

For best results ... Whether vascular access achieves long-term patency depends on the ability to prevent and correct thrombosis and stenosis. An optimal outcome is likely when there is:
• a multidisciplinary team approach to vascular access;
• consensus regarding the goals of vascular access among all involved, ie nephrologists, surgeons, radiologists, dialysis nurses, and patients. Ideally, a medical coordinator, such as a nurse or a physician, will also be involved;
• early referral for placement of vascular access;
• restriction of vascular access procedures to surgeons with demonstrable interest and experience;
• routine, preoperative mapping of the patient’s arteries and veins;
• close, ongoing communication among the involved parties;
• prospective tracking of outcomes, with continual quality assessment.

Great improvements have been made in minimally invasive vascular interventions as well as graft technology. Today’s grafts can be cannulated within the first 72 hr, and many have self-sealing properties that curb hematomas and seromas despite being repeatedly cannulated in the same region. Although AV fistulas are recommended as the first choice for HD vascular access (8), when a fistula cannot be created, an early cannulation AV graft is a better alternative compared with a double-lumen, cuffed catheter.

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