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See related article, "Reduced Ciliary Polycystin-2 in Induced Pluripotent Stem Cells from Polycystic Kidney Disease Patients with *PKD1* Mutations," on pages 1571–1586.

The Upfront Risks of Vascular Access Complications

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Both infectious and noninfectious complications related to vascular access are common and are associated with increased morbidity, mortality, costs, and a reduced patient quality of life.[1–3] Complications such as thrombosis and infections account for nearly 30% of hospital admissions in hemodialysis patients and consume a significant proportion of outpatient resources, including vascular access monitoring and diagnostic radiology.[4] The substantial burden of vascular access on health and health care costs demands a critical review and intensified prevention efforts to minimize the frequency of these serious health care associated complications.

In this issue of *JASN*, Ravani *et al.*[5] undertook an important analysis, using data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to study the temporal risk of infectious (access infections or sepsis from any cause) and noninfectious (dysfunction leading to access interventions) complications over the life of the vascular access. Among incident patients, for all types of accesses, the hazard rate for complications was 5–10 times greater in the first 3–6 months than in later follow-up after access creation. The hazard rate for observing a complication event declined over time, with the greatest decline observed among patients using a fistula compared with those using a graft or catheter.

There are other important results to highlight. Surprisingly, the majority of patients (65%) started dialysis with a temporary catheter. Additionally, with a median follow-up of 14 months, 37% and 15% of surviving patients required a second and third access creation, respectively. The rate of noninfectious complications was 10 times higher than that of infectious complications and was primarily related to thrombosis (10,452 noninfectious events and 1131 infectious events in 112,085 patient-months). Complication rates per 1000 access-days, in the first month, were highest for catheters (22 noninfectious events and 2.7 infections), than in grafts (13.4 non- infectious events and 1.8 infections) and fistulas (0.32 noninfectious events and 0.03 infectious). After 3 months, the infectious rates were significantly lower and tended to be less than 0.6, 0.3, and 0.2 per 1000 access-days for catheters, grafts, and fistulas, respectively. Notably, noninfectious complications recurred in almost 50% of the patients using the same access, with a similar pattern being observed for those with infectious complications. Finally, second and subsequent accesses had a substantial increase in the risk of complications compared with the initial access: 35%–58% for noninfectious risk and 51%–85% for infectious risk.

The outcomes of this study are difficult to compare with the existing literature because of the use of nonstandardized definitions. Ravani and colleagues reported infectious complications were evenly divided between access infection and all-cause sepsis. In the U.S. Renal Data System (USRDS) data, the rate of sepsis is higher than the infection rate for all access types; the catheter sepsis rate is 1.6 times greater than catheter infectious rates.[6] Similarly, incident patients in the USRDS using a catheter were 3.8 times more likely to have a catheter-related infection than to have a graft or fistula.[7]

Upon examining the control group from a randomized controlled trial comparing catheter locking solutions, the rate of catheter-related bacteremia was only a third less than that of catheter malfunction, with bacteremic rates of 1.37 per 1000 access-days with follow-up between 3 and 6 months.[8] A recent observational study reported access events at 1 year with bacteremic rates per 1000 access-days of 1.27 for catheters, 0.37 for fistulas, and 0.39 for grafts.[9] Of note, the risk of bacteremia did not appear higher in the first 3 months, as per the Kaplan-Meir curve, with the median time to bacteremia of 85 days for catheters, 111 days for fistulas, and 116 days for grafts.

Several factors could contribute to an early access-related infection among incident hemodialysis patients. The access creation itself introduces infectious risk, but one needs to consider the host (patient) and the environment. The highest rate of death is within the first 3 months of dialysis initiation, with infection being the second most common cause of death.[6] These patients tend to be older and have higher comorbidity scores, so it is not surprising to see this early infectious risk. In addition, there has been a recent interest in the population of microbes (microbiome) in the intestine among patients with ESRD, possibly contributing to the increased risks of infections.[10] One could hypothesize that patients with an altered microbiome may be at a higher risk of infections and that treatment with antibiotics may further increase the risk, which may explain the recurrence rate among patients with a previous infection.[11] Lastly, one is left questioning whether the decline in complication rate is just due to a change in the population at risk, with the patients at higher risks of complications dying early, leaving a healthier population with a lower risk of complications. As nephrologists, we often question whether the sophisticated statistical analysis really accounts for these differences. Perhaps a pragmatic approach is to compare the population demographics at the start and at 3–6 months to ensure that the compared population is truly the same.

Noninfectious complications (80% were thrombotic events) are perhaps easier to compare and interpret, although Ravani *et al.* do not report the use and type of access surveillance or the type of intervention. The authors report a decline from 0.27 per month after placement to 0.06 noninfectious event per month at 3 months in fistulas, presumably reflecting the known high rate of primary failure.[12] The median time to a noninfectious complication was 1.8 months for catheters, 3.8 months for grafts, and 8.7 months for fistulas. Surprisingly, this model did not change when the authors considered the first use date instead of the access placement date, considering the well documented decrease in primary patency rate when primary failures are included in the calculation.[12] Grafts have a lower early failure rate, but the rate of access thrombosis is higher in the early portion of the graft life compared with later in the access life.[12] Ravani *et al.* also observed higher noninfectious complications after access intervention. This may not be a surprise because in grafts and fistulas, angioplasty is a common intervention and is considered a controlled injury to the vessel wall, contributing to accelerated stenosis and need for repeat intervention at increasing frequency rate.[13] The increased rates of early noninfectious catheter complications have also been described.[14] Xue *et al.* reported use of tissue plasminogen activator and rate of catheter replacement use of 6.38 and 1.05, respectively, per 1000 access-days over 1 year, with a higher rate of intervention in the first 90 days.[9]

Strengths of this investigation include the ascertainment of longitudinal data and a large cohort (n=7140) of randomly selected incident patients starting hemodialysis for the first time from the DOPPS. Moreover, during the follow-up, the authors had updated information on treatments, which allowed them to use sophisticated statistical techniques using time-varying (updated) covariates. In their adjusted analyses, the authors appropriately considered multiple accesses per patient and repeated access complications. Furthermore, Ravani and colleagues also used frailty models to adjust for shared (but unmeasured) variables that may have affected the risk of developing the outcome of interest. The use of sophisticated statistical techniques and consistent results in sensitivity analyses lends confidence that the reported results are accurate and less likely to be affected by bias.

However, DOPPS has all the inherent bias associated with observational studies, including confounding by indication (sicker patients use catheters and have more complications) and measurement bias (hospital-related infections may be documented more readily than complications not requiring hospitalization).[6] Additionally, the report lacks detail on the type of access infectious complications (*e.g.*, exit site infection, catheter-related bacteremia, sepsis from another site) and noninfectious complications (*e.g.*, thrombosis, steal, aneurysm, hemorrhage), and all complications cannot be considered equal, particularly those resulting in death. In addition, this observational study reports association without the ability to provide further insights into underlying pathophysiologic mechanisms that may increase or decrease the risk of vascular access complications.

These limitations notwithstanding, this study provides a step forward to understanding the epidemiology of vascular access complications. Use of preventive strategies, such as prophylactic tissue plasminogen activator,[8] antibiotic catheter locking solutions, application of topical antibiotic, and dutiful monitoring of the vascular access in the first 3–6 months, may have an important role in reducing access-related complications and the burden these complications have on the health care system.[15] In addition, economists and those developing vascular access "bundled" payments will have to consider the time-varying costs in association with the higher early access-related complications in future analysis of vascular access cost comparisons.

DISCLOSURES

None.

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See related article, "Temporal Risk Profile for Infectious and Noninfectious Complications of Hemodialysis Access," on pages 1668–1677.