15 Nephrology in the United States of America

Samaya J. Anumudu and Stephen Z. Fadem

Area	9.834 million km^2
Population	327.2 million (2018)
Capital	Washington, DC
Three most populated cities[1]	1. New York (8,398,748) 2. Los Angeles (3,990,456) 3. Chicago (2,705,994)
Official language	English
Gross domestic product (GDP)[2]	19.39 trillion USD
GDP per capita[2]	59,531.66 USD
Human Development Index (HDI)[3]	0.920
Official currency	US dollar (USD)
Total number of nephrologists[4]	10,883
National society of nephrology	American Society of Nephrology (ASN) www.asn-online.org
Incidence of end-stage renal disease	2016 – 373.4 pmp 2017 – 380.5 pmp
Prevalence of end-stage renal disease[5]	2016 – 2160.7 pmp 2017 – 2282 pmp
Total number of patients on dialysis (all modalities)	2016 – 511,270 2017 – 520,769
Number of patients on hemodialysis	2016 – 457,957 2017 – 468,139
Number of patients on peritoneal dialysis	2016 – 51,005 2017 – 52,630
Number of kidney transplants per year[6]	2017 – 21,167
Prevalence of transplant patients[5]	2016 – 215,061 2017 – 222,848

Table references:
1. US Census Bureau
2. World Bank
3. United Nations
4. ASN
5. USRDS ADR 2019
6. UNOS

Introduction

The specialty of nephrology includes the management of patients with acute and chronic kidney injury, the deciphering of complex acid-base disorders, or the identification and management of patients with glomerular diseases. For many nephrologists, the specialty centers around the diagnosis and treatment of patients who have various stages of kidney disease. What was once a disease that was 100% lethal can now be treated and well managed. Challenges exist, but the field is far more gratifying given this population of patients can enjoy a decent quality of life and be active members of society. This chapter will examine the beginnings of the field and how United States (US) nephrologists are approaching modalities of care as well as various specific issues such as hospitalization rates, arteriovenous access barriers, hospitalizations, volume and cardiovascular disease, the mineral and bone disorder, potassium, and transplantation. It will discuss various opportunities for young physicians and conclude with what lies in the future for nephrologists and, more importantly, for patients.

About the USA

The United States of America (USA) evolved between the 1600s and 1700s to become first British colonies and then to win freedom. In 1789, after a bitter revolutionary war with Great Britain, it created a constitution that set up an infrastructure that would "secure the blessings of liberty to ourselves and our posterity." The US Constitution created three branches of government, a legislative, an executive, and a judicial branch, each designed with checks and balances. The legislative branch is composed of two individuals from each state elected to the senate and a varying number of representatives elected from census determined congressional districts to the house of representatives. There is a president, elected by representatives from each state for a 4-year term who presides over an executive branch that

S. J. Anumudu · S. Z. Fadem (✉)
Baylor College of Medicine, Houston, TX, USA
e-mail: samaya.qureshi@bcm.edu; fadem@bcm.edu

J. A. Moura-Neto et al. (eds.), *Nephrology Worldwide*, https://doi.org/10.1007/978-3-030-56890-0_15

includes among its administrative bureaus the Department of Health and Human Services headed by a secretary of HHS and the Department of Justice headed by an attorney general. The state department is under the executive branch and presides over international affairs, and the secretary of defense heads the vast Defense Department that oversees the military. And a third branch, the judicial branch, is composed of nine Supreme Court justices who are appointed by the president but approved by congress and hold their office for life. Under the constitutional democracy, the USA grew through the doctrine of manifest destiny to expand across the North American continent and now includes 50 states including Hawaii and Alaska. A highly contentious two-party system stimulates heated debate among those who classify themselves as Democrats or Republicans. The purpose of this division is to engender productive discussion between those with differing ideas, but productivity in the USA is at its best when a cooperative spirit exists between party members.

The USA is a global superpower and among the wealthiest nations. The Brookings Institution reports that American households hold over US$ 98 trillion dollars of wealth (2018) and US$ 113 trillion dollars in assets. The households in the USA also hold US$ 15 trillion dollars in debt. A college-educated American has 4–5 times the wealth as one without such an education, and education through high school in the USA is compulsory. Those with a graduate or professional degree enjoy an eightfold increase in wealth over a high school graduate. Entrepreneurism in the USA, a capitalistic environment, has been historically very richly rewarded with 80% of the wealth distributed among 20% of the people [1]. The wealthy include inventors and creators. The USA is the founding home for Google, ExxonMobil, Walmart, Apple computer, Microsoft, IBM, ATT, and several other major entities known throughout the world.

Despite being established in 1630 by English refugees seeking religious freedom as the "city upon the hill," the USA was stained by slavery which denied justice and freedom to slaves of African descendancy until 1865. Although a vicious civil war led to the emancipation of blacks, the wealth and prosperity gap remained huge. In the years between 2013 and 2016, the net worth of Hispanic and black families has risen between 30% and 50% [2].

The USA has multiple problems yet to resolve – high crime is often committed with lethal firearms and the weaponization of America. The accessibility of weapons to those with severe mental health issues has created the problem of mass shootings that has yet to resolve. America is in the midst of an opioid crisis. The CDC reports that 4.8% of persons fail to obtain medical care due to costs. Although health care for medical emergencies is guaranteed by federal statute, 27.5 million US residents lack insurance coverage [3].

Brief History of Nephrology in the USA

Kidney disease is a worldwide and universal problem. It is impossible to speak about its history without referencing the contributions of scientists or physicians from many nations. The concept of dialysis was discovered in Scotland by Thomas Graham (1805–1869) who, in 1861, noticed a semipermeable membrane could separate colloids from crystalloids. He described that this method, which he termed dialysis, could separate salt and urea from the blood. However, this process would not be possible for 100 more years. Parallel to his observation was the discovery of the explosive, gun cotton, in 1846, and a tamer agent known as collodion. This substance was also a cellulose nitrate that was used for wound dressings and in the new field of photography. The film was also attempted in a dialysis experiment. In 1913, John Jacob Abel (1859–1938) and two assistants, Leonard George Roundtree (1883–1959) and Benjamin Turner (1871–1945), successfully completed a dialysis procedure in dogs using hirudin prepared from leeches with collodion membranes. A journalist for *The Times* of London coined the term "artificial kidney" to describe this event, and it was later mentioned in the January 12, 1914, edition of *The New York Times*. When the procedure was attempted in a human patient, it failed, and the concept was abandoned.

Dialysis would never have been possible without an anticoagulant. In 1916, Jay Maclean, a medical student volunteering in the Johns Hopkins laboratory of William Henry Howell, described an anticoagulant that was called heparin. Although it was first discovered in liver tissues, its main site of production is in the intestines and lung [4]. Collodion was replaced as a potential dialysis membrane by regenerated cellulose. Cellophane was not commercially profitable for DuPont until 1927 when a process was implemented that would make it waterproof. Meanwhile, in 1925, Erwin Freund founded the Visking company and used regenerated cellulose to wrap sausage. It was this product that found its way into the dialysis world [4, 5].

The news of heparin and Visking's sausage wrapping as potential products in the artificial kidney reached Willem Kolff of the Netherlands, who between 1939 and 1943 created a wooden rotating drum dialysis machine wrapped with 20 meters of sausage casing. His dialysis efforts were not met with success until 1945. After World War II, he sent prototype machines around the world. When speaking at Grand Rounds, he met George Thorn and John Merrill of the Peter Bent Brigham Hospital (The Brigham), who teamed with him to create a stainless steel version of the machine – the Kolff-Brigham kidney. By 1948, 40 stainless steel Kolff-Brigham kidneys were manufactured and shipped around the world [6].

By the 1950s, dialysis became more commonplace but was mainly used to treat acute renal failure – now termed acute kidney injury (AKI). Often, as a consequence of nephrotoxic medications, trauma, or surgery, dialysis would sustain the patient through a critical period and give the kidneys a chance to recover. While first considered a deluxe toy, dialysis proved itself a useful lifesaving procedure during the Korean War as a major tool to treat AKI related to battle field injuries.

Belding Scribner, a physician in Seattle, identified that the reason dialysis could only be performed temporarily was because of the access used. Along with engineer Wayne Quinton, he developed a U-shaped detachable Teflon shunt that could be placed in the artery and vein and connected to dialysis tubing for each treatment. In March 1960, he dialyzed Clyde Shields, a 39-year-old machinist. Shields lived an additional 11 years, initially dialyzing for 24 h every fifth day. His fifth patient, Tim Albers, survived an additional 36 years. Scribner and his patients demonstrated that dialysis could be useful not just for AKI but for patients with end-stage renal disease (ESRD). By January 1962, there were not enough dialysis beds to accommodate all of the chronic patients who needed therapy. Stringent criteria were established to determine who could qualify for lifesaving treatment. In November 1962, a journalist, Shana Alexander, published an article in *Life Magazine* titled "They Decide Who Lives, Who Dies: Medical Miracle and a Moral Burden of a Small Committee." This article was a wake-up call for the public that there was a therapy that would reverse an otherwise terminal disease yet a lack of resources available to provide for the need.

Scribner, as part of the Washington sector of dialysis innovation, played key roles in the development of home dialysis, the dialysis machine we use today, and, along with colleagues such as Joseph Eschbach, Henry Tenckhoff, and Wayne Quinton, made sentinel advances in the management of anemia, home peritoneal, and chronic dialysis care [7, 8].

John Putnam Merrill, an internist and cardiologist, initially scoffed at the "chore" of dialysis that he felt should be assigned to surgeons. But in accepting this chore, he created the subspecialty of nephrology. In the past several years, there has been a doubling in the number of nephrologists in the USA. In 1999, there were 4718 nephrologists, and in 2013, the last reporting period, there were 9007 nephrologists [9].

Merrill relegated the "chore" to fellows, namely, Eugene Schupak, Constantine "Gus" Hampers, and Ted Hagar. As fellows, their task was to purchase sausage casing from Oscar Meyer and wrap it around the drum and as well mix the chemicals for each dialysis procedure. The camaraderie between the trio survived their fellowship days. In 1965, the six dialysis stations at The Brigham could not provide for the burgeoning dialysis needs of the entire New England area, and additional programs were established by Hampers and Hagar at Normandy House, an extended care facility in 1966, and the Babcock Center in 1970. Care was provided at a fraction of the cost of hospital care. In 1968, National Medical Care (NMC) was established with approval of George Thorn, John Merrill, and Joseph E. Murray. It developed into a profitable business, and by 1970, NMC had four centers and generated profits of US$ 265,546 on 2 million dollars revenue. In 1984, NMC was purchased by WR Grace, and in 1996 it was sold to Fresenius Medical Care (FMC). It currently has a nearly US$ 23 billion market cap and owns or operates 3971 dialysis centers worldwide with its global headquarters in Bad Homburg, Germany [10].

Today, there are over 400,000 patients who dialyze in one of the 7749 dialysis centers in the USA. A majority dialyze within two major large dialysis organizations (LDOs), Fresenius or DaVita, which have 70% of the market share [11].

DaVita was started as Medical Ambulatory Care, Inc. in 1979 but was purchased by Donaldson Lufkin Jenrette in 1994. They recruited Victor Chaltiel (1941–2014), an ambitious businessman who was later a candidate for the mayor of Las Vegas. In 1994, the name changed to Total Renal Care (TRC) and became a public company the following year. It continued to expand, purchasing another dialysis company, Renal Treatment Centers in 1998. The integration was fraught with problems and TRC nearly went bankrupt. In recruiting a new CEO, Kent Thiry, the company reinvented itself and in 2000 emerged as DaVita. In July 2004, DaVita acquired Gambro Dialysis for 3.05 billion dollars and under Thiry became the second largest LDO. It currently has a market cap of US$ 9.3 billion [12]. It now has 2664 outpatient dialysis centers in the USA and 241 in other countries [13].

In 1997, the National Kidney Foundation (NKF), one of the largest national nephrology associations in the USA, published the first two in a series of clinical practice guidelines – the Dialysis Outcomes Quality Initiative – under the leadership of Garabed Eknoyan and Nathan Levin in an effort to standardize clinical and dialysis practices, improve outcomes and survival, and improve patient care efficiency by establishing a set of guidelines based on rigorous structured review and evidence-based medicine. The first guidelines centered around hemodialysis (HD) and peritoneal dialysis (PD) adequacy, anemia management, and vascular access. By 2000 the scope was broadened to encompass kidney disease, not just dialysis, and is presently referred to as the Kidney Disease Outcomes Quality Initiatives – KDOQI. In 2004, a worldwide guidelines project was established – Kidney Disease Improving Global Outcomes – KDIGO.

Renal Diseases in the USA

According to the Centers for Disease Control and Prevention (CDC), approximately 15% of US adults or 37 million people are estimated to have CKD. Most adults with CKD do not know they have it and should be referred for nephrology care when diagnosed. CKD is most prevalent in people aged 65 years or older (~38%), slightly more common in women (15%) than men (12%), and more common in non-Hispanic blacks than non-Hispanic Asians and whites. In regard to ESRD, African Americans are about three times more likely than whites to develop ESRD. Approximately 125,000 people in the USA started treatment for ESRD, and more than 726,000 individuals were on dialysis or living with a kidney transplant in 2016. Unfortunately, more than 240 individuals die on dialysis daily [14].

The leading causes of chronic kidney disease (CKD) in adults are diabetes and hypertension. A major risk factor for the development of CKD is the development of AKI. Among patients with AKI, 31% will develop CKD within a year [15]. Other risk factors also include obesity, heart disease, glomerulonephritis, cystic kidney disease, chronic interstitial nephritis, family history of kidney disease, congenital conditions, and medications. Among children and adolescents less than 18 years of age in the USA, glomerulonephritis and polycystic kidney disease are the main causes of ESRD (https://www.usrds.org/2018/download/v2_c07_ESRD_Pediatric_18_usrds.pdf) [15].

Kidney disease is the tenth leading cause of premature death in the USA. In the last period for which data is available, 2016, there were 124,675 newly reported cases of ESRD. This constitutes a plateau over the past 5 years. The lifetime risk of being diagnosed with ESRD is 4% in males and 2.9% in females and ranges from a low of 2.3% in white females to 8.1% in black males. There were 726,331 prevalent cases of ESRD in 2016, the number increasing by 20,000 per year. The prevalence is 9.5 times greater in Hawaiians and Pacific islanders and 3.7 times greater in blacks than in whites [15].

Over the past 15 years, the ESRD population unadjusted death rate has decreased by 27% and is now down to 134 per 1000 patient-years for ESRD. Forty percent to 50% of patients die during the first 3 years. Of the 30 million people in the USA with CKD, only 1.56% will ever reach dialysis [15].

Renal Replacement Therapy in the USA

Renal replacement therapy in the USA is done in centers via HD or at home with either PD or HD. When a patient with CKD has an estimated glomerular filtration rate (eGFR) less than 20 ml/min/1.73m^2, he or she is able to be listed and become eligible for a kidney transplant.

Sadly, in 2017, 35.4% of ESRD patients received minimal or no care from a nephrologist prior to starting dialysis. The mean eGFR at the initiation point of dialysis was 9.7 ml/min/1.73m^2 – down from 10.4 in 2010. Among incident patients, 87.3% began renal replacement therapy with HD and 9.7% with PD, and only 2.8% received a preemptive kidney transplant. Among prevalent dialysis patients, 29.6% have a functioning kidney transplant, 7.5% are treated with PD, and 63.15% of prevalent patients receive HD. Only 2.5% of patients do home HD [15].

Hemodialysis

Staff assisted in center is the most common therapy in the USA – comprising 86.9% of all starting patients. A third (33.4%) of incident patients received no pre-ESRD or little pre-ESRD nephrology care, and 80% of HD patients start dialysis using an indwelling catheter. Dialysis times are generally 4 h three times a week with a blood flow of 450 ml/min if a successful fistula is in place. While reuse of dialyzers was once popular (in 1997, 82% of dialysis facilities participated in a reuse program), it is rarely if ever in use today [16]. Hemodiafiltration is not generally offered in the outpatient dialysis setting. The typical patient dialyzes three times a week in a large dialysis center. Mortality in the dialysis population has been steadily declining in the past 15 years. The adjusted death rate has decreased by 29% with patients over the age of 65 years old comprising 44% of the population. The mortality rate is 166 per 1000 patient-years for the HD population [15].

Governance of the dialysis facility is typically represented by the facility administrator, the medical director, and for the 70% of patients dialyzing in one of the two largest dialysis facilities, Fresenius North America and DaVita Kidney Care, a corporate representative – generally the regional operations director. On a monthly basis, the interdisciplinary team comprised of a nephrologist, the social worker, dietitian, and renal nurse meets to discuss individual patient care. A facility health meeting made up of the medical director, the clinical coordinator, the facility administrator, social worker, and dietitian meets to discuss trends and the processes in place to advance facility quality and continually improve outcomes.

Home Hemodialysis

In 1963, John Merrill was able to demonstrate that patient's families could be trained to operate a dialysis machine and dialyze patients at home. The following year, Stanley Shaldon, while in London, was able to demonstrate that patients could not only successfully learn to manage their own dialysis but to dialyze overnight.

In Seattle, initial dialysis machines made use of a 380 liter stainless steel tank. The water and solutes were mixed and then stirred with canoe paddles. Albert "Les" Babb, a professor of nuclear and chemical engineering at the University of Washington, worked with Scribner to develop a machine that would mix fluid in a set ratio and recirculate it until it passed through the dialysis filter and could be discarded. The proportioning machine was born.

In 1964, Caroline Helm, a 16-year-old girl with lupus nephritis, developed the need for dialysis but did not qualify for in-center care because she fell below the minimum age of 18. But Caroline's father and Babb were friends, and for her, Babb developed a single patient machine with monitors and fail-safe devices. It even included a laminated front that would blend with the family furniture. This single patient proportioning machine became the prototype for nearly every dialysis unit now in existence. Two years later home dialysis was adopted in Seattle as a means of providing more dialysis to patients. Eventually 90% of Seattle patients were undergoing dialysis at home [17].

Despite its prominence in early dialysis care, home HD has not been utilized well in the USA. This may be due to multiple factors including lack of patients receiving pre-ESRD education. In a survey conducted by the American Association of Kidney Patients (AAKP), 32% responded that they were not educated about home dialysis. In the past 5 years, the percentage of patients who undergo home HD has been relatively flat, ranging from 1.6% in 2011 to 1.8% in 2016 [15].

Peritoneal Dialysis

Of the home modalities in the USA, PD is most often chosen by patients. Although it was in use for the management of AKI in the 1940s, PD catheters were stiff, and without a suitable access, it could not be considered for chronic therapy. In 1968, Henry Tenckhoff developed the silastic implantable catheter, which was later modified by adding Dacron cuffs, which is in use today [17].

In Austin, Texas, during the 1970s, Robert Popovich and Jack Moncrieff pioneered the chronic ambulatory peritoneal dialysis (CAPD) procedures in use today. A further advancement was the development of plastic dialysis bags instead of glass bottles by Dimitri Oreopoulos in Toronto. Another pioneer, Zbylut Twardowski, developed a means to measure PD equilibrium and use it in patient management and a grading system for exit sites [18]. Automated peritoneal dialysis (APD) is possible because of the HomeChoice machine, created through the clever ingenuity of Dean Kamen in collaboration with Baxter.

PD has lower mortality rates than HD (153.5 vs 166.3 all cause prevalent mortality per 1000 patient-years). In 2017, 10.1% of incident ESRD patients started with PD. The prevalence of PD is only 7.1%. Most current figures demonstrate that in 2017 52,630 were undergoing either APD (the vast majority) or CAPD. In the years between 2001 and 2016, the adjusted mortality rate fell by 28% in HD but 43% in PD patients. The 3-year survival odds at 3 years are 70% for PD and 57% for HD. The lower mortality for PD may be explained by patient selection; those who select PD must have the dexterity and cognitive skills to manage it by themselves on a more or less constant basis. PD is more economical, and based on US Renal Data System (USRDS) data, a year of HD costs approximately US$ 72,000, while PD costs US$ 53,000 [15].

Government Involvement in Dialysis

By 1961, Belding Scribner had established the first outpatient dialysis unit in the world, a three-station outpatient center in the nursing residence basement of the Swedish Hospital. Soon, the center was at capacity, and the Seattle Artificial Kidney Center (now Northwest Kidney Center) was built. Of 30 candidates, only 10 could be accepted, and the rest would die. The *Life Magazine* feature by Shana Alexander highlighted the problem in 1962, and the veterans administration established 30 dialysis centers. Edwin Newman's 1965 NBC television documentary, "Who Shall Live?," sparked further interest in the program, and the Public Health Service set up a 5-year grant program, creating 12 more dialysis centers and 14 home programs the following year. When this program ended, it became regional. A government committee headed by Carl Gottschalk recommended government support for dialysis and kidney transplantation.

The National Association of Patients on Hemodialysis (NAPH) was created in October 1969 by Samuel Orenstein and William Blackton. They dialyzed together for 18 h a day in Brooklyn's Kings County Hospital dialysis unit and played a key role in persuading congress that dialysis could be feasible and safely done. In 1966, after undergoing dialysis training in Seattle, a young premed Stanford student, Andrew Peter Lundin, applied to medical schools across the country. Eli Friedman, Professor at SUNY Downstate Health Sciences University in Brooklyn and a pioneer in American dialysis, persuaded his admissions committee to accept Lundin, who while dialyzing alongside Orenstein and Blackton became a practicing academic nephrologist. He had been active in the NAPH from its beginnings and died in 2001. Simultaneously, George Schreiner, also a major pioneer in American dialysis and a member of the Gottschalk Committee, was involved in the National Kidney Foundation (NKF). He invited his neighbor Charles Plante to become their lobbyist, and together they crafted the legislative policies that would place dialysis as a Medicare benefit. Schreiner testified before congress 30 times. To demonstrate to the Wilbur Mills Ways and Means Committee that it was safe and feasible, a dialysis patient, Shep Glazer, daringly dialyzed before them in the committee room in 1971. The result of the Gottschalk Committee, AAKP, NKF, and several others was that in October 30, 1972, congress amended the Social Security Act to include dialysis benefits (Public Law 92-603). The law became effective in July 1973 and is now the highest source of support for kidney patients.

It was projected that annual dialysis costs would never top 250 million dollars. In 2016, 35.4 billion dollars was spent on all ESRD care and 7.2% of all Medicare claims. Of this portion, 28 billion dollars is spent on dialysis alone. It is the most important revenue source for large dialysis organizations like DaVita, which receives 69% of its revenue from Medicare.

The Medicare program is under the auspices of the Centers for Medicare and Medicaid Services (CMS) and tasked with both certifying ESRD facilities and monitoring and recertifying those that meet basic conditions for coverage. The original conditions were adopted in 1976, and the updated version was published April 15, 2008.

These conditions stress flexibility with respect to implementing facility-specific outcome measures. The goals are to ensure protection of patients' rights and physical safety, patient satisfaction and engagement in care, and the elimination of unnecessary administrative policies. The focus is on the "continuous, interdisciplinary, integrated care system that a dialysis patient experiences, centered around patient assessment, care planning, service delivery and quality assessment, and performance improvement." The burden of responsibility for implementing and continuing policies that meet these objections is tasked to the facility governing body and medical director. As outlined in §494.150, the medical director must participate in staff training and performance assessments, in the development, review, and approval of and adherence to patient care policies and procedures. These procedures pertain to safety, infection control, as well as patient admissions, transfers, and discharges. It is estimated that 87% of approximately 9000 nephrologists in clinical practice serve as a medical director (http://dialysisunits.com).

Dialysis Adequacy

Dialysis adequacy is determined in part by dialyzer membrane characteristics. Dialyzer technology rapidly moved from the large rotating drum to smaller and more compact devices. When in 1960 Clyde Shields was dialyzed, the device used was a parallel plate dialyzer that had been invented by Leonard Skeggs and Jack Leonards working in Cleveland. Frederic Kiil in Norway modified this dialyzer and made it popular for use when Scribner started the home dialysis program in 1964. Skeggs went on to invent the serial multiple analyzer (SMA), automating the chemistry analysis of serum samples and revolutionizing the way kidney disease could be identified. The coil dialyzer was developed by Kolff in 1956 after he moved to the USA and consisted of orange juice cans fitted to a Maytag washing machine. When Maytag forbad its commercial use, Travenol designed a machine of its own, the RSP (recirculating single pass) [4].

Although the hollow fiber technique was developed in the 1940s, it was never commercialized until Dow Chemical Company began to manufacture it for reverse osmosis. The hollow fiber technology was first used to manufacture cuprophane dialyzers by Cordis-Dow, in a joint venture with the Dow Chemical Company. However, biocompatibility was a problem as the cellulose-based dialyzers made of cuprophane or cellulose acetate led to amyloidosis. Union Carbide introduced polysulfones in 1965, and Fresenius capitalized on their superiority for clearing the beta microglobulins associated with amyloidosis. Hollow fiber membranes have now replaced all earlier dialyzers, and are highly efficient, biocompatible, and more compact.

In 1967, Frank Gotch, nephew of a legendary professional wrestler of the same name, along with John Sargent evaluated the characteristics of the Dow hollow fiber dialyzer and by 1974 had developed a kinetic modeling equation. Ten years after the introduction of chronic dialysis, there was no agreement as to what adequacy was. The National Cooperative Dialysis Study (NCDS) that began the following year was a prospective randomized trial performed to study the adequacy of dialysis. Patients were randomized to two different time-averaged urea concentrations, 50–90 mg/dL and 90–130 mg/dL. They were also randomized to shorter and longer treatment periods, 3 ± 0.5 and 5 ± 0.5 h. NCDS emphasized that the time on dialysis, the characteristics inherent in the dialyzer membrane, and the volume of distribution of total body water were functions of dialyzer clearance and time on treatment. Gotch concluded that Kt/V depended upon protein catabolism and was a predictor of dialysis failure. In 1985, the model suggested that the minimum adequate dose of three times weekly dialysis was single pool (sp) $spKt/V_{urea}$ of 1.0. For years nephrologists attempted to follow the NCDS strategy, a mistake falsely based on the age-old premise that urea was the major toxin of uremia. As dialysis treatments were shortened, the mortality rates rose.

In 1989, the Dallas Conference on Morbidity and Mortality in Hemodialysis was held and demonstrated that mortality rates decreased when dialysis times increased. The results resulted in the creation of a randomized control trial to determine the appropriate time for dialysis. The HEMO study looked at spKt/V groups of 1.71 and 1.32 and in 2001 concluded that a high dose offered no advantage; the NKF KDOQI guidelines have since established the minimum delivered $spKt/V_{urea}$ to be 1.2 and the target spKt/V to be 1.4 per HD session in patients treated three times a week. In the USA, these goals are being met. Only 3.5% of prevalent dialysis patients have a spKt/V less than 1.2. Nearly half of the patients (49%) have a spKt/V between 1.2 and 1.59, and 47.4% have a spKt/V greater than 1.6.

The frequency and duration of dialysis have been quantified and studied by Dialysis Outcomes and Practice Patterns Study (DOPPS). In the USA, 96.6% of patients currently dialyze three times a week. There has been no trend. It has also been shown that shortening the length of dialysis sessions is associated with a higher mortality rate. DOPPS has looked at 5203 prevalent dialysis patients and found that 30.8% dialyze less than 210 min, 39.6% dialyze between 210 and 240 min, and 29.7% dialyze over 4 h. In 2010, 22.4% of patients dialyzed over 240 min, representing an upward trend.

The Arteriovenous Access

In 1966, Michael Brescia and James Cimino along with Kenneth Appel and Baruch Hurwich reported a technique to create a fistula between the artery and vein in the arm and successfully cannulate it with a #14 needle. Cimino later reported he got the idea from a surgical procedure developed at the Mayo Clinic in the 1930s to increase blood flow in the limbs of polio victims (Oct 1, 2006, Renal and Urology News). The procedure has been a success and continues to be the gold standard for access. In the USA, 73.2% of accesses are arteriovenous (AV) fistulas.

Synthetic vascular grafts created from a stretched form of polytetrafluoroethylene (Gore-Tex) has been in use since around 1969 and substituted for the Brescia-Cimino fistula 16.6% of the time in the USA [15]. They do not last as long or permit as high a blood flow and have a higher rate of infection when compared to AV fistulae.

Patients are recommended to have AV fistulas in place for their access as part of a national vascular access improvement initiative – the Fistula First Initiative (FFI) – established in 2003 by CMS. Through education and support, the rate of fistula placement has steadily improved. However, still many fistulas that are placed fail [19], and as a result, 12.1% of US patients require dialysis through a catheter [20]. The continued use of a catheter is the result of either patient preference, exhaustion of sites, or lack of stability to undergo access surgery. Some patients have extensive peripheral vascular disease by the time they reach the point of requiring dialysis; thus it becomes difficult to place permanent access.

Catheter disadvantages include an increased incidence of infection and a lower maximum blood flow than other forms of access. They also have higher hospitalization rates and are costlier, mainly because a nurse is required to initiate treatment in catheter patients. In addition to complications, the presence of a dialysis catheter is associated with a higher mortality rate in dialysis patients.

The ideal scenario is for patients to be closely followed and carefully managed by the nephrologist for several years, receive extensive education regarding dialysis modalities, and after making a selection, transition to dialysis with a permanent access in place. Unfortunately, this is not always the case. Patients who have not been adequately educated on dialysis modalities during the earlier stages of disease often present to a hospital acutely ill but only rarely have a fistula placed during the initial admission because of financial payment disincentives. Patients with ESRD secondary to hypertension are less likely than diabetic patients to receive pre-ESRD education. Furthermore only 13.3% of patients who received pre-ESRD education received dietary instruction. Patients without education were less prepared for dialysis and more likely to start with an indwelling catheter rather than the preferred AV fistula. USRDS reports data from 2016 that 80% of newly diagnosed patients initiate HD with a catheter and that at 90 days 69% are still using the catheter. Only 17% of patients initiate dialysis with an AV fistula in the USA. It is a relief to know that at the end of 2 years 71% of HD patients have a working AV fistula in place. Around 50% of incident patients start dialysis with an eGFR between 5 and <10 ml/min/1.73m^2, while around 29% initiate treatment when the eGFR is between 10 and <15 [15].

Poor access planning and surgical technique are both barriers to higher fistula rates, and 39% of fistulas fail to sufficiently mature for use. Of those that do mature, the median time to first use is 108 days. AV access accounts for 9.2% hospitalizations, 8.5% readmissions within 30 days, and 7.6% of emergency room admissions [15]. Although, historically, the emphasis has been to place an AV fistula, elderly patients have a slower maturation time and a higher degree of access failures and require more careful planning. Additionally, some patients may not have adequate arterial blood flow because of peripheral vascular disease [15].

Hospitalizations

Despite the conditions for coverage and their requirement that continuous quality improvement processes be put into place, some indicators that reflect both increased expenses to the Medicare system and quality of life for patients are not improving rapidly and signify that an ongoing challenge exists. According to the July 2014 DOPPS data, the mean percentage of ESRD facilities with hospitalization claims over a 6-month period was 38.4%. The percentage of ESRD beneficiaries with at least one hospitalization claim was 12.9% [8].

In 2016, Medicare was the primary spender for US – 10.2 *billion of in patient care. That was nearly as much as it spent as the US* – 11.1 billion as primary payer for outpatient services. The USRDS reports that adjusted hospital admission rates have declined 15% over the past 9 years, from 2.0 to 1.7 per patient-year. Reasons for hospitalizations often relate to the complexity of comorbidities attendant in a population that reaches the most advanced stages of disease. The serum albumin is an index of chronic illness [21]. The USRDS reported that in a sample of HD patients from May 2017, 18.9% had serum albumin levels less than 3.5 g/dL.

The most likely cause for a hospital encounter in ESRD patients is infection [15]. The number of hospital days per patient-year for infection is 3.6. Septicemia is the most frequent cause of admission, readmission, and emergency visit – 9.3%, 8.6%, and 9.2%, respectively [15]. The risk of having bacteremia in a patient on HD is 26 times higher than in the general population, and the dialysis catheter is the most common site of infection [22]. Newer therapies are emerging to reduce the incidence of catheter-related infections. The ClearGuard HD antimicrobial barrier cap was compared with the Tego connector plus Curos disinfecting cap and demonstrated a significantly lower incidence of blood stream infection (0.28 vs 0.75 positive blood cultures/1000 central venous catheter days $p = 0.001$) [23].

Hospitalizations are highest in the first year of dialysis, suggesting that CKD education and preparation for either a preemptive transplant or the desired modality may lessen transition costs even further [15].

Even more daunting is the frequency of 30-day readmissions for hospital patients. Roughly 37% of patients who were admitted to the hospital were readmitted within 30 days between the periods of 2014 and 2016. This percentage is relatively steady; between 2007 and 2011 39% were readmitted. The USRDS demonstrates that readmissions for cardiovascular disease are 39.2%. Many (45.8%) of the readmissions are to treat cardiovascular in contrast to a new condition, a reflection of the chronicity of this disorder. Although constituting only 2.6% of the reasons for hospitalization, 41.9% of those sustaining an acute myocardial infarction account are readmitted following discharge. Stroke patients are also frequently readmitted, 40.9%. Stroke patients also have a 30-day post-discharge mortality of 7.8% [15].

The expense of end of life treatment practices in the USA for patients with ESRD is increasing. Despite that 23.3% of ESRD patients withdraw from dialysis, and 26% enroll in hospice care before death, and 39% of ESRD patients die in the hospital. Fifty-five percent are seen by at least 10 physicians and 62% by at least 5 specialties during their final 90 days. Most recently, the median number of days these ESRD patients spend in the hospital is 15 days. Sixty-three percent of patients with ESRD are admitted to a critical care unit during the final 90 days of life. The median cost in the year of death per person of ESRD patient was $103,932 in 2015, with $7687 being in the final week of life [15].

Heart Disease and Volume

In 2009, a 20th anniversary meeting of Dallas Conference on Morbidity and Mortality was held on April 23, at the Sheraton Boston Hotel to look at factors that were determining patient care. At the time the meeting was held, dialysis mortality was 20% per year with hospital costs exceeding $20,000 per patient. Less than 20% of patients were rehabilitated. Myocardial fibrosis emerged as a major culprit in the high mortality and was felt as the result of poor blood pressure control and a failure to achieve euvolemia. It was acknowledged that normalization of blood pressure and intravascular volume was difficult with conventional dialysis and that in addition to modifying dialysis schedules, reducing sodium and repeated dietary counseling would be necessary [24].

In the USA, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocker (ARB) therapy is prescribed in 59.9% of patients with heart failure. Cardiovascular disease occurs in 64.5% of patients with CKD who are ≥66 years old. It is associated with a shortened survival; only 59% of patients ≥66 years old with stage 4–5 CKD who sustain an acute myocardial infarction survive 2 years. When it is present, congestive heart failure is an independent mortality risk factor in CKD and is associated with a 2-year survival probability of 77.8%. 23.8% of CKD patients have atrial fibrillation, but around 50% of patients with heart failure and CKD have atrial fibrillation. In the USA, 30.9% of patients with atrial fibrillation and CKD are treated with anticoagulants. Peripheral vascular disease occurs in 25.2% of CKD patients, and a stroke or transient ischemic attack is also more common, occurring in 16.1% of CKD patients in contrast to 6.7% of patients ≥66 years old without CKD [20].

Using DOPPS data and looking at treatment times and ultrafiltration rates in 22,000 HD patients, Saran et al. published in 2006 that every 30-min longer period on HD was associated with a 7% lower relative risk of mortality (RR = 0.93 $p < 0.0001$). Ultrafiltration removal of over 10 ml/kg per hour was associated with a higher relative risk of mortality (RR = 1.09 $p = 0.02$) and an odds ratio for intradialytic hypotension of 1.30 ($p = 0.045$) [20]. In 2015, Flythe et al. published that post-dialysis weights that exceeded the target by 2 kg in at least 30% of treatments were associated with an adjusted hazard ratio of 1.28 (95% CI 1.15–1.43) and completing dialysis treatments with a weight below the target weight by 2 kg resulted in an adjusted hazard ratio of 1.22 (95% CI 1.05–1.4) for all-cause mortality [25]. It is well established that removing volume at high ultrafiltration rates is associated with a higher mortality [26]. Greater than 13 ml/kg/hour is associated with a relative risk of mortality of 1.59 (95% CI 1.29–

1.96) [27]. In the Feb 2019 DOPPS study, of 5145 patients, the intradialytic weight loss was 2.68% per treatment. For a 70 kg patient, this would compute to 1.88 kg, which if removed over a 4-hour treatment would be 470 ml/hour or 6.7 ml/kg/hour [20]. Regrettably, many hospital visits are for volume overload. The hospitalization rate for cardiovascular disease is 2.6 per patient-year and represents a continued challenge for nephrologists [15].

CKD Mineral and Bone Disorder (CKD-MBD)

Among complex disorders associated with advancing kidney disease are those that surround the metabolism of the tightly regulated divalent cation, calcium. As kidney disease advances, the renal tubular cell production of 1-alpha hydroxylase decreases, resulting in a marked decrease in the hydroxylation of 25-hydroxyvitamin D (3) to its active form. Active vitamin D is essential for cell differentiation, the modulation of immune responses, and both the transcellular and paracellular absorption of calcium from the gastrointestinal tract [28]. It participates in a feedback loop that controls the synthesis of parathyroid hormone (PTH), an 84 amino acid that regulates calcium absorption from bone through an indirect stimulation of osteoclasts. In CKD, the elevated serum phosphorus stimulates FGF23 to rise and modulate phosphorus excretion, but as the disease progresses, the serum phosphorus also rises. The high serum phosphorus turns on transcription factors that deposit calcium into the media of vascular smooth muscle cells. In the patient with abnormal kidneys, bone calcium falls, and calcium abnormally deposits in the blood vessel media. This pathology results in vascular calcification, aortic valve disease, vascular stiffness, and increased bone fractures [29]. Management strategies are to reduce serum phosphorus and prevent or treat the rise in PTH. Popular therapies are the use of phosphate binders, vitamin D analogs, and a calcimimetic.

In the USA, the most popular vitamin D receptor analog is doxercalciferol, being used 84.2% of the time in the DOPPS dialysis sample, as compared with 15.8% use for paricalcitol. At the time of reporting, calcitriol use was zero. Twenty-nine percent of dialysis patients are on a calcimimetic, although in its oral form, cinacalcet, it was sometimes poorly tolerated. A newer parenteral calcimimetic, etelcalcetide, is in use 6.1% of the time [20].

Serum phosphorus remains a challenge to control. 23.5% of dialysis patients are in the 3.5–4.5 mg/dL range, while 26.3% are between 4.6 and 5.5 mg/dL. 42.7% have serum phosphorus values greater than 5.5 mg/dL and in 22.4% are between 5.0% and 5.4% [20].

Serum Potassium

In 61.0% of ESRD patients the serum potassium is between 3.5 and 4.9 mEq/L, and in 23%, it is between 5.0 and 5.4 mEq/L. 11% have a serum potassium greater than 5.5 mEq/L. An elevated potassium greater than 5.5 mEq/L indicates for the most part either dietary indiscretion or inadequate dialysis, and for years the standard has been to supplement selected patient with persistent hyperkalemia with sodium polystyrene sulfate [20]. Now, there are now two newer medications that have been successfully tested in the ESRD population. In patients with multiple episodes of hyperkalemia, patiromer on a daily basis statistically reduces the serum potassium by −0.5 mEq/L over a follow-up period, the median of which was 141 days [30]. Sodium zirconium cyclosilicate was studied in an ESRD population on a once daily basis on non-dialysis days. Forty one percent (41.2%) in the zirconium responded compared to 1.0% of placebo. Serious adverse events were roughly the same 7% vs 8% in the zirconium and placebo groups. Both groups had comparable interdialytic weight gains, and the drug was well tolerated [31].

Renal Transplantation

Valley Forge General Hospital was a major casualty center for battlefield injuries near Philadelphia during World War II. It was here that the noted plastic surgeon, Joseph E. Murray, working as an Army surgeon, developed a keen interest in immunology and the skin. On December 23, 1954, Murray, now a surgeon at the Peter Bent Brigham Hospital, performed the first kidney transplant. It was between 24-year-old identical twins, and the recipient lived an additional 9 years without immunosuppression. He also pioneered cadaveric transplantation and the use of immunosuppressants in organ transplantation. In 1990, he was awarded the Nobel Prize in Physiology or Medicine.

Today, there are 231 transplant centers in the USA. As of December 31, 2016, there were 81,418 dialysis patients waiting for a transplant. 20,161 transplants were performed in 2016, 28% from living donors. There were 215,061 patients who have a functioning kidney transplant as of that date. The probability of 1-year survival with a living related donor is 99% and 96% for a deceased donor [15].

Kidney transplantation consists of either living or deceased donors. Advances have been made in both, yet there is a wide gap between those persons who are on a waiting list and the numbers of available kidneys. With respect to living donors, kidney-paired donations have enabled families and friends to indirectly donate to an individual when the kidney is not a biocompatible match. They can thus donate to a second individual who is a compatible recipient provided a prospective donor for that individual can donate back. While even more complex pairing systems can be arranged, the net result is that each recipient receives a biocompatible living donor kidney, even if from a stranger.

Kidneys that have been harvested from decedents are allocated to recipients by computer matching, managed through the Organ Procurement and Transplantation Network (OPTN) under strict policies. OPTN is government based and managed by the United Network for Organ Sharing (UNOS). Recipients are active candidates on a registered waiting list. To fairly allocate how deceased donor kidneys are appropriated, they are first indexed. The computer instruction set compares the data on the deceased organ donor with data on the waiting list and ranks candidate recipients according to OPTN policies. Since the time spent on the waiting list is counted toward the appropriation priority, early referral is advised. The Kidney Donor Profile Index (KDPI) established in 2014 combines a variety of donor factors into an index that helps establish how long the donor kidney is expected to function. The lower the score the better the predicted function. In general, 65% of deceased donor kidneys have KDPI between 21% and 85% and can be expected to function around 9 years, while a KDPI greater than 85% may be predicted to function only greater than 5½ years. The Estimated Post-Transplant Survival (EPTS) score is assigned to all active patients on the waiting list. It is based on the patient's time on dialysis, whether or not they are diabetic, whether or not they have had a previous kidney transplant, and their age. The score ranges from 0% to 100%. The ETPS score is used in tandem with the KDPI to match kidneys that have a longer predicted survival with appropriate candidates. Thus, an EPTS score of 20% or less will receive a higher priority of kidneys with a KDPI of 20% or less. In 2017 there were 92,685 patients on the waiting list for a kidney transplant [32].

Age in and of itself is not an exclusion for transplantation. In 2017, 23% of all US transplants were performed in persons over 65 years old. In 2018, there were 21,157 transplants recorded in the OPTN registry. Of these, 4419 were over 65 years old. 8259 transplants (38%) were performed in persons between the ages of 50 and 64. The trend toward transplanting older patients has increased. In 1988, only 212 of the 8878 transplants in the registry were in persons above age 65 [32].

The waiting time for a kidney transplant is a concerning long-term trend, as the time continues to increase. In 2017, 37.8% waited on the list over 3 years. 16.6% of patients have been on the list greater than 5 years [32]. The 2014 kidney allocation system (KAS) allows patients to start their waiting list time from the date of first dialysis.

There are racial disparities among prevalent transplant patients. When related to the number of prevalent African American patients on HD (141,383), only 44,002 have a functioning transplant (31%). This compares to 60% of white, 40% of Hispanic, and 59% of Asians. The reasons for these disparities are complex and may in part relate to provider awareness. The UNOS kidney allocation system changes that were implemented in December 2014 were designed to increase fairness in allocating kidneys and to also reduce the racial disparities. Disparities are being further addressed by the establishment of a clinical trial that involves educational materials for the staff and patients in 600 US dialysis facilities with low wait-listing [33]. However, all-cause graft loss in deceased donor kidney transplants has decreased from 51.4% to 30.6% [34].

Immunosuppression related to kidney transplantation is generally driven by the center's protocol. Most commonly, in high-risk patients – African Americans, panel-reactive antibody tests greater than 20%, or who lost a previous transplant because of immunologic reasons – thymoglobulin is initiated intraoperatively. Tacrolimus is given as initial therapy when the fall in serum creatinine is 30% from baseline or when function delayed is started at the completion of thymoglobulin to a target of 50–75% of goal level until a recovery in kidney function. Our center also uses mycophenolate mofetil (MMF) and corticosteroids. In non-high-risk patients, daclizumab or basiliximab is used instead of thymoglobulin. A steroid sparing can be used with thymoglobulin induction in non-high-risk patients. Our center uses tacrolimus with a goal of 8–10 ng/mL for the first 30 days and 7–9 ng/mL for the next 60 days. From the 90th day to the completion of 1 year, our goal is 6–8 ng/mL and 4–8 ng/mL after 1 year. We also use MMF and prednisone – 30 mg daily for the first 2 weeks and tapering by 5 mg every 2 weeks until 10 mg daily. At the 180th day, patients with good graft function who are not on a steroid-sparing regimen are placed on 5 mg daily of prednisone. Our protocol also addresses anti-infectious, gastrointestinal, cardiac, and osteoporosis prophylaxis.

Pediatric Nephrology

The pediatric nephrologist encounters a different spectrum of disease than adult counterparts, as they must diagnose and treat a variety of congenital disorders as well. Congenital anomalies of the kidney and the urinary tract (CAKUT) occur as a disruptive process of urologic development and account for the majority of cases of CKD and ESRD in children. The malformations vary from renal agenesis to horseshoe kidneys and duplication of the ureter [35]. The number of children with ESRD has decreased from 17.5 per million to 12.9 per million by 2017. The total number of incident ESRD patients under 21 years old was 1319 for 2017. Of those 51.3%

received HD, 27.8% PD, and 20.8% a renal transplant. There are currently 9667 prevalent ESRD patients, 16.6% of whom are on HD and 10.1% on PD. 73.3% have received a kidney transplant. 44.7% of patients under 21 years old receive pre-ESRD for greater than 12 months, but there are still 19.1% of pediatric patients who receive no care at all. In contrast to adults, the mean eGFR for pediatrics is 14.0 ml/min/1.73m^2. 41.5% receive dietary care.

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry of dialysis patients demonstrates that focal segmental glomerulosclerosis occurs in 14.3% of patients, while a dysplastic or hypodysplastic kidneys occur 13.9% of the time. The third most common cause of renal abnormalities in children is obstructive uropathy, which occurs 12.6% of the time. Reflux nephropathy occurs in 3.5% of patients, hemolytic uremic syndrome in 3.0%, while chronic glomerulonephritis and congenital nephrotic syndrome occur in 2.9 and 2.6 percent of dialysis patients. The NAPRTCS database reveals that pediatric dialysis patients initiating dialysis have a height z-score < 2 standard deviations less than average and are hypertensive. The most common cause of death was cardiopulmonary disease with young age, growth deficits, and black race predicting a poorer prognosis for survival. Survival increased significantly between the 2002–2011 and the earlier 1992–2001 cohorts [36].

Other Renal Diseases

The nephrologist follows a variety of kidney disorders as part of his or her daily routine. These include glomerular disorders, inherited disease, interstitial nephritis secondary to medications, and acid-base/electrolyte abnormalities. Hospital-based nephrologists deal with fluid management and a variety of critical care issues, acute acid-base disorders and AKI. These next few paragraphs will highlight a few of these conditions.

The incidence of glomerular disorders was examined in 2016 in a Medicare and an employer health plan. It was found that the incidence of secondary glomerular disease – that related to a primary non-renal systemic disorder – was 134 per 100,000 in the Medicare cohort and 10 per 100,000 in the employer health plan. Primary glomerular disorders occurred in 57 per 100,000 in the Medicare and 20 per 100,000 in the health plan cohorts. Primary glomerulonephritis patients are more likely to progress to ESRD than secondary glomerulonephritis patients in both the health plan 46.2 vs 19.5 and Medicare 72.9 vs 24.1. Data for Medicare demonstrated that the death rate was higher in secondary glomerulonephritis patient 186.1 vs 127.2 in the Medicare population. It was also noted that hospitalization rates were substantially higher in glomerulonephritis patient [37].

The prevalence of kidney stones in the USA is 10.6% for men and 7.1% for women. The incidences of kidney stones rise with age, peaking in 60–69-year-old men at 19.1% and women 9.4%. Kidney stones are more common in a southern latitude with a higher sunlight index. It is not clear whether oxalate in vegetables is associated with a higher kidney stone incidence. However, the incidence rises with sugar-sweetened sodas, animal protein intake and supplemental calcium (in men), and decreased fluid intake. It decreases with increased fluid intake, increased dietary calcium intake, coffee and tea consumption, and fresh fruit intake. Kidney stones are associated with cardiovascular disease, the metabolic syndrome, hypertension, and diabetes. They are associated with CKD. As expected, kidney stone patients have a higher hospitalization rate, especially emergency department visits [38].

Polycystic kidney disease is a single gene disorder that is autosomal dominant, reportedly prevalent in 1 in 400 to 1 in 1000 live births, and has been calculated to affect greater than 10 million persons worldwide. In the USA, the incidence has been studied in Olmstead County and is 2.06/100,000 person-years. In a rare variant, the prevalence is estimated to be 1 in 26,500 live births in North, Central and South America [39].

Alport syndrome is a rare X-linked disease that in 805 of patients is caused by mutations in the COL4A5 gene, affecting type 4 collagen in glomeruli. It leads to progressive renal failure, is associated with hearing loss, and occurs mainly in men [40]. Clinical trials for therapy related to Alport syndrome are underway.

Diseases such as Bartter syndrome (prevalence 1/1,000,000) and Gitelman syndrome (prevalence 1/40,000) are uncommonly encountered by the nephrologist. They are each caused by gene mutations that affect tubular transport in either the thick ascending limb, as in Bartter syndrome, or the distal convoluted tubule [41]. Other disorders such as Fabry disease are uncommon. Nephrologists in both an inpatient and an outpatient setting must deal with hemo-mediated kidney injury, acute kidney injury, and interstitial nephritis that are related to drug-induced nephrotoxicity. Treatments vary, but acute kidney disorders are usually reversible by removing their underlying cause [42].

Nephrology Practice in the USA

In the USA, after completing 2–3 years of nephrology fellowship, individuals start clinical practice in either private or academic sectors. Some graduates may pursue an extra year of fellowship to specialize in transplant and then pursue one of the above two models for transplant practice.

In the private practice spectrum, physicians either go in to solo practice or join smaller- to medium-sized groups ranging from 2 to 4 partners or larger groups with 5+ individuals. Each practice consists of physicians and physician extenders that see patients in the clinic, dialysis centers, hospitals, and often in interventional access centers. Private practice is more likely to be associated with business opportunities that include ownership or joint ventures into dialysis clinics (15.7% vs 4.1%), ambulatory surgery centers, and interventional access centers (5% vs 2.5%) than academic practices. Private practice physicians also participate in medical directorships (33.9% vs 15.6%) but conduct clinical research trials less commonly (8.3% vs 57.4%). Some private practice physicians elect to assume teaching responsibilities in local medical schools and may opt for non-tenured clinical tract with respect to academic appointments. Almost half (47.1%) of the physicians elect to join either a group practice nephrology or multispecialty clinic. 52.9% of men and 38.7% of women elect to go into private practice. 60.6% of group practice nephrologists have weekend call 13 times or more each year, in contrast to only 24.1% academic nephrologists. 39.1% of group and 18.1% of academic nephrologists have night call greater than 26 or more weeks per year. The average annual salary for the private practice nephrologist is US$ 207,176 vs US$ 176,438 for academia [43].

In the academic model, individuals join nephrology departments at large academic centers and balance duties between clinical practice, research, and training. Naturally, in the academic setting, direct involvement with trainees exists, providing excellent opportunities for teaching and for shaping future nephrologists. With respect to research, academic nephrologists conduct either clinical research or basic science investigations, and some combine both along with clinical practice. A tenured appointment for an academic position offers much greater security than a clinical appointment. About half (47.1%) of nephrologists completing their renal fellowship training enter academic medicine, the same as for private practice. 53.8% are women and 42.4% are men. 5.8% of fellows align with neither tract. Academic physicians receive more support for career development opportunities (37.3% vs 16.9%) and Visa sponsorships (18.6% vs 13.6%). Sign-on bonuses (28% vs 5.1%) and income guarantees (33.2% vs 16.9%) are more likely to accompany private group practice in contrast to academia. Academic physicians are less likely to be dissatisfied with work hours (23.5% vs 35%) and work life balance (26.1% vs 33.6%). Academic nephrologists are more likely to recommend nephrology to medical students and residents (81% vs 69.7%) [43].

Regardless, unfortunately women are currently paid less than men in both settings $206,043 vs $175,152. According to an ASN survey, 25% of all nephrologists are unhappy with their salaries but find the intellectual challenges and relationships with patients highly rewarding [43].

Salaries for dialysis nurses in the USA vary but are generally between US$ 72,000 per year and US$ 95,000 per year. Nurse practitioners are compensated at a higher rate, around US$ 107,000 per year [44].

Future Perspectives of Nephrology in the USA

We have come a long way from 1961 when Belding Scribner established the first outpatient dialysis unit in the world. It was not until 12 years later, during Richard Nixon's reelection campaign, that Congress passed Public Law 92-603 extending Medicare coverage to individuals with ESRD requiring HD or transplantation.

What followed PL 92-603 was various policy and payment models over the years to improve patient care and physician reimbursement. Since then, dialysis has become the most expensive item that Medicare reimburses, and there are challenges for the program to add value as well as improve the quality of life and well-being for ESRD patients. Recently, there has been more movement and encouragement for increasing preventative care and education in CKD and improving access and rates of kidney transplantation. What is being evaluated is incorporating various incentives to help build this framework and improve access to care for this vulnerable population. A major impetus is on home dialysis. Thus, we have come full circle, as the original models of dialysis therapy envisioned strong home programs.

However, despite that patients are starting dialysis at an older age, the trends toward mortality in dialysis are improving as we discover better ways to care for patients. As our population ages, renal replacement therapy must adapt to accommodate the need for quality life and a minimized burden of care.

As we advance care, we will discover several innovations along the way. An innovation initiative known as KidneyX (https://www.kidneyx.org) is a public-private partnership between the US Department of Health and Human Services and the American Society of Nephrology. It recently awarded a $75,000 prize to a team of collaborators, Shuvo Roy and William Frissell, to accelerate their development of an implantable dialysis device. Victor Gura, a nephrologist in Los Angeles, has developed an ergonomic miniature dialysis machine that is wearable. His machine weighs less than 10 pounds, is operated by 9-volt batteries, and uses less than 400 ml of fluid. A clinical trial was conducted between 2014 and 2016 [45].

The innovative concepts to manage patients with ESRD lie in the field of bioengineering, where steps in developing bioengineered organs and tissues for clinical use are being investigated [46]. Teams are investigating how to harvest stem cells from a prospective kidney transplant and implant them into the blastocyst of an animal made deficient of kidney genes. As the animal develops, a phenotypic human kidney is generated that is immunologically compatible with the recipient and can be transplanted back. A proof of concept has been demonstrated by implanting pluripotential stem cells from a mouse into a Sall1-targeted anephric rat [47]. Other tissues and organs are being studied by other groups, and technical challenges are slowly being hurdled [48].

Conclusion

Nephrologists in the USA provide dialysis care to over 450,000 patients and manage over 200,000 functioning transplants. The fascinating development of technologies makes the care of patients with ESRD gratifying. Despite our advances, we face major challenges – the burdensome cost of care, the lack of patients being started with a fistula, the fact that many patients are not being started on the modality they would choose if they were educated on their choices and managed earlier in the course of their disease, and the association of cardiovascular disease with CKD and the lack of transplantable kidneys. Efforts to increase home dialysis and education of CKD patients are underway. While it may sound like science fiction, there are several initiatives to develop more innovative ways to provide wearable and implantable dialysis machines and even to grow human kidneys for transplantation in another animal. Overall, the future to improve kidney disease is promising.

References

1. Brookings Institute. 15 December 2019. Available from: https://www.brookings.edu/.
2. Changes in U.S. family finances from 2013 to 2016: evidence from the survey of consumer finances: The Federal Reserve System. Available from: https://www.federalreserve.gov/publications/files/scf17.pdf.
3. National Center for Health Statistics. 15 December 2019. Available from: https://www.cdc.gov/nchs/fastats/access-to-health-care.htm.
4. Fadem SZ. Issues in dialysis. 1st ed. New York: Nova Science Publishers; 2012. 361 p.
5. Cameron JS. The prehistory of haemodialysis as a treatment for uraemia. G Ital Nefrol. 2016;33(Suppl 66):33.S66.2.
6. Murphy WP Jr, Swan RC Jr, Walter CW, Weller JM, Merrill JP. Use of an artificial kidney. III. Current procedures in clinical hemodialysis. J Lab Clin Med. 1952;40(3):436–44.
7. Blagg CR. Belding Hibbard Scribner—better known as Scrib. Clin J Am Soc Nephrol. 2010;5(12):2146.
8. Blagg CR. The 50th anniversary of long-term hemodialysis: University of Washington Hospital, March 9th, 1960. J Nephrol. 2011;24(Suppl 17):S84–8.
9. Chronic Kidney Disease (CKD) Surveillance System – Centers for Disease Control and Prevention (CDC). 12 December 2019. Available from: https://nccd.cdc.gov/ckd/Default.aspx.
10. Fresenius Medical Care AG & Co. KGaA (FMS). Available from: https://finance.yahoo.com/quote/FMS/.
11. Shinkman R. The big business of dialysis care. NEJM Catalyst. 2016 https://catalyst.nejm.org/doi/full/10.1056/CAT.16.0826.
12. DaVita Inc. (DVA). Available from: https://finance.yahoo.com/quote/DVA/.
13. DaVita Inc 2018 Form 10-K Annual Report. 2018.
14. Chronic Kidney Disease in the United States – 2019. Atlanta: Centers for Disease Control and Prevention; 2019. Available from: https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf.
15. U.S. Renal Data System. USRDS 2018 annual data report volume 2: end-stage renal disease in the United States. Bethesda: National Institute of Health; 2018.
16. Denny GB, Golper TA. Does hemodialyzer reuse have a place in current ESRD care: "to be or not to be?". Semin Dial. 2014;27(3):256–8.
17. Fadem SZ. Milestones in dialysis in issues in dialysis. New York: Nova Science Publishers; 2012.
18. Prowant BF, Schmidt LM, Twardowski ZJ, Griebel CK, Burrows LK, Ryan LP, et al. Peritoneal dialysis catheter exit site care. ANNA J. 1988;15(4):219–23.
19. Ackad A, Simonian GT, Steel K, Parisi C, Mancini S, Douglas C, et al. A journey in reversing practice patterns: a multidisciplinary experience in implementing DOQI guidelines for vascular access. Nephrol Dial Transplant. 2005;20(7):1450–5.
20. DOPPS practice monitor: reporting contemporary trends in US dialysis practice. Ann Arbor: Arbor Research Collaborative for Health; 2019 [updated 2019, May]. Available from: https://www.dopps.org/dpm/.
21. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. J Am Soc Nephrol. 2010;21(2):223–30.
22. Suzuki M, Satoh N, Nakamura M, Horita S, Seki G, Moriya K. Bacteremia in hemodialysis patients. World J Nephrol. 2016;5(6):489–96.
23. Brunelli SM, Van Wyck DB, Njord L, Ziebol RJ, Lynch LE, Killion DP. Cluster-randomized trial of devices to prevent catheter-related bloodstream infection. J Am Soc Nephrol. 2018;29(4):1336–43.
24. Parker TF 3rd, Glassock RJ, Steinman TI. Conclusions, consensus, and directions for the future. Clin J Am Soc Nephrol. 2009;4(Suppl 1):S139–44.
25. Flythe JE, Kshirsagar AV, Falk RJ, Brunelli SM. Associations of posthemodialysis weights above and below target weight with all-cause and cardiovascular mortality. Clin J Am Soc Nephrol. 2015;10(5):808–16.
26. Flythe JE, Brunelli SM. The risks of high ultrafiltration rate in chronic hemodialysis: implications for patient care. Semin Dial. 2011;24(3):259–65.
27. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int. 2011;79(2):250–7.
28. Christakos S, Dhawan P, Porta A, Mady LJ, Seth T. Vitamin D and intestinal calcium absorption. Mol Cell Endocrinol. 2011;347(1–2):25–9.
29. Chistiakov DA, Sobenin IA, Orekhov AN, Bobryshev YV. Mechanisms of medial arterial calcification in diabetes. Curr Pharm Des. 2014;20(37):5870–83.
30. Kovesdy CP, Rowan CG, Conrad A, Spiegel DM, Fogli J, Oestreicher N, et al. Real-world evaluation of patiromer for the treatment of hyperkalemia in hemodialysis patients. Kidney Int Rep. 2019;4(2):301–9.
31. Fishbane S, Ford M, Fukagawa M, McCafferty K, Rastogi A, Spinowitz B, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. J Am Soc Nephrol. 2019;30:1723–33.
32. National Data – Organ Procurement and Transplantation Network. Richmond: UNOS; 2019.

33. Patzer RE, Smith K, Basu M, Gander J, Mohan S, Escoffery C, et al. The ASCENT (allocation system changes for equity in kidney transplantation) study: a randomized effectiveness-implementation study to improve kidney transplant waitlisting and reduce racial disparity. Kidney Int Rep. 2017;2(3):433–41.
34. Purnell TS, Luo X, Kucirka LM, Cooper LA, Crews DC, Massie AB, et al. Reduced racial disparity in kidney transplant outcomes in the United States from 1990 to 2012. J Am Soc Nephrol. 2016;27(8):2511–8.
35. Nicolaou N, Renkema KY, Bongers EMHF, Giles RH, Knoers NVAM. Genetic, environmental, and epigenetic factors involved in CAKUT. Nat Rev Nephrol. 2015;11(12):720–31.
36. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
37. Wetmore JB, Guo H, Liu J, Collins AJ, Gilbertson DT. The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. Kidney Int. 2016;90(4):853–60.
38. Ziemba JB, Matlaga BR. Epidemiology and economics of nephrolithiasis. Investig Clin Urol. 2017;58(5):299–306.
39. Bergmann C, Guay-Woodford LM, Harris PC, Horie S, Peters DJM, Torres VE. Polycystic kidney disease. Nat Rev Dis Primers. 2018;4(1):50.
40. Kashtan CE, Ding J, Gregory M, Gross O, Heidet L, Knebelmann B, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport syndrome research collaborative. Pediatr Nephrol. 2013;28(1):5–11.
41. Caberto S, Fadem S. In: Fadem S, editor. Genetic renal tubular disorders in essentials of chronic kidney disease. New York: Nova Science Publishers; 2015.
42. Rastogi A, Arman F, Asaturyan A, Ameen K, Singhal R. Other causes of chronic kidney disease. In: Fadem S, editor. Essentials of chronic kidney disease. New York: Nova Science Publishers; 2015.
43. Quigley L. E S. report on a survey of nephrologists in early years of practice. Washington, DC: George Washington Health Workforce Institute; 2018.
44. Salaries.com. Available from: https://www.salary.com/research/salary/benchmark/staff-nurse-rn-renal-dialysis-salary/.
45. Gura V, Rivara MB, Bieber S, Munshi R, Smith NC, Linke L, et al. A wearable artificial kidney for patients with end-stage renal disease. JCI Insight. 2016;1(8):e86397.
46. Nichols JE, La Francesca S, Vega SP, Niles JA, Argueta LB, Riddle M, et al. Giving new life to old lungs: methods to produce and assess whole human paediatric bioengineered lungs. J Tissue Eng Regen Med. 2017;11(7):2136–52.
47. Goto T, Hara H, Sanbo M, Masaki H, Sato H, Yamaguchi T, et al. Generation of pluripotent stem cell-derived mouse kidneys in Sall1-targeted anephric rats. Nat Commun. 2019;10(1):451.
48. Roelen BAJ. Regenerative medicine: taming the chimaera. Stem Cell Rep. 2018;11(4):849–51.