



Nephrology in Argentina

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Area ¹	3,761,274 km ²
Population ²	44,361,150 (2018)
Capital	Buenos Aires
Three most populated cities ¹	1. Buenos Aires 2. Córdoba 3. Rosario
Official language ¹	Spanish
Gross domestic product (GDP) ³	912.09 billion USD (2018)
GDP per capita ¹	11,653 USD (2018)
Human development index (HDI) ³	0.825 (48° position)
Official currency	Argentinian peso
Total number of nephrologists	1200
National society of nephrology	Argentinian Society of Nephrology (SAN) www.san.org.ar
Incidence of end-stage renal disease ^{4,5}	2018 – 162 pmp 2019 – 160 pmp
Prevalence of end-stage renal disease ^{4,5} (on dialysis)	2018 – 676 pmp 2019 – 681 pmp
Total number of patients on dialysis (all modalities) ^{4,5}	2018 – 30,080 2019 – 30,610
Number of patients on hemodialysis ^{4,6}	2018 – 27,973 2019 – 28,608
Number of patients on peritoneal dialysis ^{4,6}	2018 – 1996 2019 – 2081
Number of renal transplantations per year ^{4,7}	2018 – 1329 2019 – 1576

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Introduction

Argentina, officially the Argentine Republic, is a sovereign country located in the southern and southeastern corner of the Americas. It adopts the form of a republican, democratic, representative, and federal government. Argentina is organized as a decentralized federal state, composed since 1994 by 24 self-governed states, being 23 provinces and the Autonomous City of Buenos Aires (CABA), the latter designated as the federal capital of the country. Each state has its own political autonomy, constitution, flag, and security forces. The 23 provinces maintain all power not delegated to the national state and guarantee the autonomy of their municipalities. It integrates the Mercosur – a commercial block of the southern South America countries, being one of the founders in 1991 – the Union of South American Nations (Unasur), the Community of Latin American and Caribbean States (CELAC), and the Organization of American States (OAS). In 2018, its Human Development Index was 0.830 and is ranked 48th worldwide, adjusted for the inequality that is 0.714 with a Gini coefficient of 42.7. In education, it has an investment budget of 5.1% of the GDP, with a population almost fully literate [1]. The Argentine economy is one of the most developed and important in South America. According to the World Bank, its nominal GDP is placed as

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21st in the world [2]. Due to its geopolitical and economic importance, it is one of the three Latin American sovereign countries that is part of the so-called Group of the Twenty and also integrates the group of the new industrialized countries (NIC). It has reached optimal levels of research and development in sciences, with five Nobel Prize winners, three of them associated to sciences. Its technological and scientific capacity has allowed to design, produce, and export satellites and build nuclear reactors. It is one of the 20 countries that have a permanent presence in Antarctica, being the one with the most permanent bases, 6 in total.

In relation to the health system, the first step was taken toward the recognition of public health as a problem of specific interest in 1943, with the creation of the National Directorate of Public Health and Social Assistance, which in 1949 became the Ministry of Health (MoH). Currently, the Argentine health system has 17,485 healthcare establishments including those managed by the public, social security, and private sectors. In Argentina there are 4.5 hospital beds per 1000 inhabitants, 3.94 doctors per 1000 inhabitants, and a total of 166,187 doctors [3].

Brief History of Argentine Nephrology

The history of Argentine nephrology has experienced several important moments, from the study of renin-angiotensin to the first renal transplant in Latin America.

In the 1930s, in the physiology laboratory at the Medical School of the University of Buenos Aires, Nobel laureates Bernardo Houssay and Juan Carlos Fasciolo began research applying the Goldblatt kidney model. They implanted an ischemic kidney from hypertensive dogs to nephrectomized normotensive dogs, which caused an increase in blood pressure, leading them to the assumption that a hypertensive substance was being continuously produced. This was the first experience that confirmed the presence of a humoral mechanism responsible for nephrogenic arterial hypertension [4]. Subsequently, Alberto Carlos Taquini confirmed the possibility that the substance released by the kidney acted directly on the blood vessels as well as that the increase in blood pressure that was observed after restoring the blood flow in ischemic kidneys was caused by the same vasopressor substance. Fasciolo, along with Eduardo Braun Menéndez in 1939, identified the hypertensive substance from venous blood from kidneys subjected to periods of ischemia. Extracted by acetone, it was thermostable and dialyzable and had a brief hypertensive effect, characteristics that differentiated it from renin. The Argentine team named this substance hypertensin. An enzyme-substrate reaction was postulated for the formation of hypertensin, which was denominated hypertensinogen (the substrate), renin (the enzyme), and hypertensinases (the enzymes responsible for degrading hypertensin). The discovery of the

Argentine team was limited to angiotensin, whereas Page and collaborators in the United States observed that a substrate was necessary for the pressor substance to be generated, the substrate being a globulin called hypertensinogen in Buenos Aires and renin activator in Indianapolis. Thus, a peptide substance was generated and named hypertensin in Argentina and in the United States angiotenin. Hypertensin and angiotenin turned out to be the same substance. In 1958, Braun Menéndez and Page agreed on a new nomenclature in Ann Arbor, so that the words angiotensin and angiotensinogen emerged [5].

In 1955, Dr. Ruiz Guiñazú performed the first hemodialysis (HD) with a machine made entirely in the country, based on the Kolff-Brigham kidney model; in 1957 Professor Alfredo Lanari performed the first renal transplant in Latin America at the Institute of Medical Research associated to the University of Buenos Aires and the First Tissue Bank created through Law 17041 [6].

Inspired by the scientific activities of this institute, so-called the kidney club, the Argentine Society of Nephrology was founded on September 15, 1960 [7].

In 1965, Ondetti and Cushman began studying ACE inhibitors, based on the research by Sergio H. Ferreira of the Ribeirão Preto School of Medicine of the University of São Paulo, Brazil. Dr. Miguel Ondetti did his PhD thesis at the University of Buenos Aires and subsequently continued his research work in the Squibb Research and Development Laboratories in Argentina in the area of natural products, isolating and characterizing alkaloids of pharmacological importance. He succeeded to characterize the most relevant peptide of these compounds studied by Ferreira that received the generic name of teprotide and that was a competitive inhibitor of the enzymatic activity of ACE. In this way, Ondetti achieved the synthesis of polypeptides and related compounds finally characterizing the structure of captopril from the structure of the teprotide molecule. The identification of this compound in the 1970s had a profound social impact, as a new and effective method of hypertension control was achieved [8].

Simultaneously in 1962, Gianantonio published in *The Journal of Pediatrics*, under the title "Acute renal failure in infancy and childhood," detailing the experience in the diagnosis, treatment, and monitoring of 41 children with acute renal failure due to a disease named hemolytic uremic syndrome (HUS), previously described by Gasser in 1955. This was also the beginning of pediatric nephrology in Argentina, by Prof. Gianantonio who contributed significantly worldwide to the study of this pathology. The following year he performed peritoneal dialysis (PD) procedures for the first time in Argentina, saving many lives of children affected by HUS [9].

César Milstein also graduated from the University of Buenos Aires, making his doctoral thesis at that university, but he had to leave the country in 1962 due to the beginning of a military dictatorship and continued his studies in

Cambridge, where he published, in 1975 in the journal *Nature*, the article “Continuous Cultures of Fused Cells Secreting Antibody of Redefined Specificity,” together with G. Köhler, which would lead to the Nobel Prize in Medicine and Physiology in 1984. Monoclonal antibodies did not exist even in the imagination of the most expert immunologists, but their work allowed the development of new techniques and equipment and the advancement in the knowledge of infectious agents, in the diagnosis of diseases, and, more recently, in their application as a therapeutic agent and their impact on the results of transplants [10].

An increase in transplants in Argentina occurred toward the end of the 1970s, due to the discovery of new immunosuppressive drugs. In 1977, Law 21.541 was passed giving birth to the Single Coordinating Center for Ablation and Implant (CUCAI) as the national procurement agency in charge of the regulation of the activity. Between 1985 and 1996, the registration of CKD patients began with voluntary information, and the provided data represented 20–30% of the prevalent patients. Between 1990 and 1996, there was a significant increase in information, through the valuable contribution of the regional registries. In 1990, with the enactment of Law 23,885, CUCAI became the National Single Central Coordination Institute for Organ Removal and Implantation (INCUCAI), becoming a decentralized body as an autarchy and retaining its dependence on the MoH. In 1997, an agreement was established between INCUCAI and SAN that allowed the development of a patient registry with greater rigor and validity. The National Procurement and Transplant Information System of the Argentine Republic (SINTRA) is implemented in 2004, and a new stage begins in the registry era. Its implementation allowed to gather RRT information from the patients and centers (95%) and to register into a digital system [11].

In 2005, after an extensive parliamentary debate, Law 26.066 was approved incorporating the figure of the alleged donor for organ donations. The regulation, which established that every person over 18 years of age is considered a donor with the exception of those who have expressed their will not to be a donor, entered into force in 2006 and allowed the procurement activity to continue to rise. In 2010, the MoH, through INCUCAI and its procurement system, implemented the Renal Transplant Development Plan, which articulates actions at different levels to prevent, diagnose, treat, and follow-up CKD. Within this framework, the Hospital Donor Strategy was implemented, aiming to incorporate procurement as an activity of the hospitals themselves in order to increase the availability of organs and tissues for transplantation [12]. The year 2018 closed with an annual growth of 18% in terms of organ donation procedures, and this figure allowed Argentina to reach a rate of 15.75 donors per million inhabitants. Seventy-four percent of the organ donation procedures took place in public healthcare facilities. Of the 1681 organ transplants performed, 986 were renal transplants [13].

Kidney Disease in Argentina

Few studies have published the CKD prevalence in the general population of Argentina. These epidemiological analyses establish a prevalence of CKD between 10% and 12% of the general adult population [14].

Recently, prevalence studies have been published in special groups and in certain regions, such as the Santa Fe study whose CKD prevalence rate is 11.71% and 13.1% if considering pathological proteinuria. Another recent, multicenter study has reported a slightly lower rate close to 8.10% [15].

The government in consensus with the scientific societies has been continuously developing programs that promote healthcare strategies aimed at preventing and addressing CKD in its primary stages through the PAIER (Program for the Comprehensive Approach to Renal Diseases), mentioning a special approach to the attention of the CKD stage, in order to promote registration policies on the waiting list prior to dialysis and a management model for people with advanced CKD [16]. This program has probably collaborated with the development of preemptive renal transplants, so called because these patients have never received chronic dialysis as RRT, increasing from 51 transplants in 2008 to 116 in 2017.

The number of people who submitted to RRT reached 40,899 patients, 69.8% with dialysis and 30.2% transplanted. Twenty-one percent of the patients are on renal transplant waiting list, and less than 20% of them were transplanted within 1 year of evaluation [12].

Acute Renal Injury and Critical Care Nephrology

Acute kidney injury (AKI) data are based on epidemiological studies from developed countries, where the incidence is assessed in eminently urban environments [17]. This situation is completely different from that of developing countries in which AKI develops in eminently suburban and rural settings, where the incidence is significantly higher. The population distribution in our country according to the last census of 2010 is represented by a very marked phenomenon, where the Autonomous City of Buenos Aires is the most densely populated region with 14,185 inhabitants/Km², while the province of Santa Cruz is represented by 1.1 inhabitants/km². Given the absence of specific epidemiological data, if we projected the epidemiological figures reported in the literature, we would estimate the AKI incidence from 84,000 to 630,000 patients per year, of which approximately 22,386 to 163,800 will acutely require some type of RRT [18].

Based on the RIFLE and AKIN criteria, a multicenter study of 627 patients from 9 ICUs conducted in Argentina found that, respectively, 69.4% and 51.8% presented some degree of AKI. The overall 90-day mortality was 40.9%

(RIFLE) and a markedly increased number of patients with severe degree of renal failure (71.1%) [19].

As a relevant fact of endemic diseases causing AKI, we find *Hantavirus* infection and HUS syndrome as the most common causes in the pediatric age. In 1995, a family outbreak of pulmonary syndrome caused by *Hantavirus* in southern Argentina led to the discovery of the Andes virus. In 1998, in the city of El Bolsón and in Bariloche, interhuman transmission was documented for the first time [20]. This zoonosis is presented as (1) epidemic nephritis, (2) hemorrhagic fever with renal syndrome in Europe and Asia, whose mortality reaches 10%, and (3) cardiopulmonary syndrome caused by *Hantavirus*, the most serious of all with an average mortality of 30%, in the Americas. This last form is frequent in Argentina, and besides the severity of the cardiopulmonary component, AKI due to multi-organ failure may occur. Lethality presents a trend of decline from 60% in 1988 to 33% in 2018. More than 70% of people with *Hantavirus* infection live in rural sectors, and also approximately 70% of them carry out activities in the agricultural-forestry sector.

The latest hantavirus outbreak began on November 14, 2018, with one case with an epidemiological nexus of previous environmental exposure; this patient attended a social event, with five attendees of the same event presenting hantavirus with the onset of symptoms at week 47 and 48 epidemiological (18/11–01/12). Twenty-five total cases (23 confirmed, 2 suspects) were reported by January 10, 2019, and 9 persons died confirming interhuman contagion [21].

In relation to HUS, Argentina has the highest incidence in the world. This disease is endemic with an annual incidence of 10 cases/100,000 children under 5 years old. As a consequence, HUS is the main pediatric cause of AKI and the second of CKD in our country, in addition to being responsible for 9% of kidney transplants in children and adolescents. The toxin has been isolated from beef and its derivatives. Argentina has very high levels of meat consumption per capita, and children begin to eat meat at an early age. There is suspicion of an association between the consumption of undercooked meat and infection by the *Escherichia coli* bacteria producing Shiga toxins [22].

Treatment with a product consisting of fraction F (ab) 2 of equine immunoglobulin obtained from hyperimmune sera is currently under development in the country, generating the product INM-004 lot 3945. Preclinical studies have been conducted in vivo where no clinical alterations or side effects associated with treatment were evidenced. In the murine model, the product managed to rescue the animals from the toxic effect even when administered 48 h after administration of the toxin. Currently, the first use in human, prospective, randomized, and placebo-controlled two-stage trial is under development to assess the safety, tolerability, and pharmacokinetics. The trial is authorized to be submitted to the regulatory entity (ANMAT) awaiting its results by 2020 [23].

In the context of critical care nephrology, the RRT modality options available include conventional HD, intermittent online hemodiafiltration (HDF), veno-venous hemofiltration, and PD performed in ICUs.

Renal Disease in Pediatric Population

There are 12,333,747 children under 18 years of age (30, 74%) in Argentina. According to the national dialysis registry, there are 559 patients under the age of 19 on chronic dialysis, 166 in PD, 185 in HD, and 13 in HDF [24].

Eighty-nine (25%) of these children are on the waiting list for kidney transplantation, and another 19 patients are on the waiting list for preemptive kidney transplantation [24].

In reference to the frequency of comorbidities in maintenance HD, 17.9% have arterial hypertension, the mean PTHi is 606 pg/ml, 20% present with normal bone remodeling (>155 < 300 pg / ml PTHi), the average albuminemia is 3.82 gr/dl with 19.1% of patients with albumin <3.50 gr/dl, and the average hemoglobin is 10.49 gr/dl [24].

It is interesting to observe that the most commonly used dialysis modality by age groups, between 0 and 4 years, is PD in 86.7%; between 5 and 9 years PD in 77.6%; between 10 and 14 years HD in 59.4%; and finally between 15 and 18 years HD in 81%.

The HD mortality when adjusted by gender and presence of diabetes was 6.47% in PD vs. 3.28% in HD between 0 and 9 years and 2.39% in PD vs. 3.20% in HD between 10 and 19 years, in 2017 [24].

The first pediatric renal transplant in Argentina was performed in 1961; since then the programs have been growing. There are 11 pediatric units that perform kidney transplants primarily in Buenos Aires. In 2017, 148 pediatric patients under 18 years of age were transplanted (105 living donors).

There are 120 pediatric nephrologists (78% women), 58% living in and around Buenos Aires. In 4 of the 23 provinces, there is no permanent pediatric nephrologist. To become a pediatric nephrologist requires complete training in clinical pediatrics, followed by a pediatric nephrology scholarship. The University of Buenos Aires also offers a scholarship program. The title of specialist is granted by the local association of doctors in each district, the Argentine Society of Pediatrics, or the University of Buenos Aires. Within the public system, the pediatric fellow receives a monthly remuneration during the full scholarship [25].

Glomerulopathies

The SAN has developed a national registry of glomerulopathies, being the largest provider in the country the one in the areas of Buenos Aires and the Province of Buenos Aires, having together collected a total of 1714 biopsies. The clini-

cal presentation syndromes are nephrotic syndrome (36.2%), asymptomatic urinary abnormalities (25%), rapidly evolving renal failure (9.3%), nephrotic range proteinuria (6.3%), CKD (6.7%), AKI (6.2%), nonrecurrent macroscopic hematuria (2.2%), HUS (0.3%), and unreported ones (4.7%). In relation to the distribution of the pathologies, 52.6% are primary, 37.9% secondary, 4% undetermined, 2.7% vascular, 2.6% tubular, and 0.2% miscellaneous [26].

The six most frequent primary glomerulopathies correspond to focal and segmental glomerular sclerosis (22.4%), mesangial (17.4%), membranous (13.8%), minimal change disease (8.3%), mesangial non-IgA (6.2%), and mesangiocapillary glomerulonephritis type I (6.0%), whereas within secondary glomerulopathies, most of them were grouped in the category secondary to autoimmune disease (85%) (SLE, 85%; extra GN capillary, 6%; necrotizing, 1%), secondary to gammopathy (6%), secondary to metabolic/hereditary disease (5%), secondary to non-streptococcal infection (2%), secondary to neoplastic disease (1%), and hepatopathy (1%) [26]. Currently, the practice of renal biopsies is not done routinely due to operational, economic, and/or bureaucratic difficulties.

Renal Replacement Therapy (RRT) in Argentina

Argentina has developed a national information system (SINTRA) to collect, filter, process, create, and distribute data on donation and transplantation activities. This tool allows the whole management of the donation and transplantation procedures. Standards related to donor detection, donor maintenance with life support, procurement, selection of recipients, compatibility testing, storage and transportation of organ, tissues, and cells, as well as allocation and screening for transmissible diseases of the deceased donor have been established by national consensus.

During 2017, 7236 new patients entered maintenance dialysis corresponding to a crude rate of 164 pmp and an adjusted rate of 154.8 pmp [24]. The number of patients and the crude rate increased in relation to the values of the previous years. Almost 400 (394) patients are foreigners and their countries of origin being Paraguay, Bolivia, Chile, Italy, Uruguay, and Peru. In the last 10 years, more than 5000 patients with other nationalities have been treated with RRT in Argentina [24].

As of December 31, 2017, almost 30,000 (29,700) patients were treated with maintenance dialysis, corresponding to a crude rate of 674 pmp and an adjusted rate of 637 pmp. The number of patients has had a constant growth since 2004, but not the gross rate that stagnated between 2013 and 2016, rising again in 2017. The adjusted rate decreased from 2013 to 2017 [24].

In relation to the incident patients, fewer patients were admitted in the last 4 years, and they were in worse clinical

conditions when admitted. The ESRD patients entering RRT for the first time is younger every year, more anemic, in worse nutritional conditions, has greater use of transient catheters as first access for HD (72.3% of catheter admissions in 2017, the highest percentage since 2004), and has increasing percentage of unvaccinated anti-hepatitis B.

In relation to diabetes as a cause of CKD, there is a sustained increase in incident patients reaching the maximum rate ever (four out of ten new incident patients), being the first cause of admission and with the highest growth since 2004 according to the latest published data, reaching 59 pmp with certain regional differences [24].

The percentage of insulin-dependent diabetics prior to the onset of maintenance dialysis reaches 76% of the diabetic incidents with a progressive increase in insulin prescription in recent years; only 55% received insulin at the time of admission to maintenance dialysis in 2004.

HD is the most frequent RRT modality in incident patients (94%), but PD has shown a significant growth in the last 11 years, from 3.9% to 6.5% of the total admissions. Capital Federal, Neuquén, and Chaco are the districts with the highest percentage of patients starting in PD: 15%, 12%, and 12%, respectively [24].

The average estimated initial glomerular filtration rate (GFR) was 8.7 ml/min/1.73 m², and 7.7% presented a GFR \geq 15 ml/min/1.73m² according to the 2017 data.

In relation to comorbidities, 70% present with some degree of anemia, with average hematocrit values of 27.6–27.7%. Only 35% of patients start with hematocrit \geq 30%. Half of the new patients have protein malnutrition with hypoalbuminemia (<3.5 g/dL) which is a predictor of greater immediate mortality. The overweight-obesity population comprises 57% of the incident patients, and 84% of the patients present with arterial hypertension on admission [24]. Almost 40% (39%) of the incident patients are vaccinated for hepatitis B, 0.3% have positive HBsAg, 1.2% anti-HVC positive, and 0.8% anti-HIV positive. There has been a significant increase in the number of anti-HIV incident patients admitted to dialysis in the last 2 years (8 positive patients per 1000 incident patients) when compared to previous years [24].

A very significant increase in the use of the non-tunneled transient catheter, as first access to HD, has been observed, from 59% in 2004 to 72% in 2017. In contrast, the use of native fistula as first access fell very significantly in the same period (from 35% to 22%). Patients with asthma or chronic obstructive pulmonary disease accounted for 7.6% of new patients in maintenance dialysis in 2017, no difference with the previous years. Tobacco was consumed by 18% of the population admitted to maintenance dialysis in 2017, a tendency toward greater smoking, contrary to the expectations based on the implementation of active measures against smoking in Argentina. Active tuberculosis or a history of tuberculosis had a significant decrease, representing 1.1 of every 100 patients admitted to maintenance dialysis in 2017 [24].

In relation to the prevalence, diabetic nephropathy is the most frequent etiology with the highest growth since 2004, reaching 187 pmp in 2017, whereas unknown etiology is the second with 127 pmp in 2017 [24].

In relation to the dialysis modality, HD is the most frequent modality in 94% of the patients, while PD showed significant growth in the last 11 years, going from 3.9% to 6.5% of the total reflecting the data of the incident patients' data [24].

Online HDF has been performed in Argentina since 2014. The growth of this technique has been significant in the short period, from 184 patients in 2014 to 1688 patients in 2017, representing 5.7% of the prevalent population in maintenance dialysis.

In relation to comorbidities in prevalent patients, anemia is present in 61.9% of the patients, hemoglobin ≥ 11 , and < 13 g/dL in 38.1% of the patients with EPO doses up to 105 IU/Kg/week [24]. The percentage of prevalent patients with arterial hypertension increased significantly in 2016–2017, without distinction of gender, age, etiology, body mass, or dialysis modality, except for the youngest group in maintenance dialysis (0–19 years), in which it decreased. Forty percent presented values of systolic BP > 140 and diastolic BP > 90 mmHg. The percentage of patients treated with hypotensive medication increased in the last 2 years, although the percentage of hypertensive patients who do not receive antihypertensives (29%) remains high. The prevalence of positive HBsAg is 1.0%, anti-HCV 2.4%, and anti-HIV 0.9%. More than half of the population (58%) in chronic dialysis have anti-HBs values at protective levels. Cardiovascular disease presented the following frequency: coronary heart disease 8.0%, heart failure 16.0%, cerebrovascular disease 7.0%, and finally peripheral vascular disease 30.8% of the prevalent population in maintenance dialysis.

Peritoneal Dialysis

About 2000 (1936) patients were treated with PD in 2017, achieving a growth of more than 100% in 10 years (952 patients in 2007); 471 patients out of those 1926 started PD in 2017. The annual growth was 10% for the biennium 2016–2017.

There are certain differential characteristics between patients on PD compared to HD, according to data published by the Argentine Registry. PD patients are younger (32% are 60 years or older vs. 51% in HD), consist of more female (54% vs. 42% in HD), and have less diabetics (16% vs. 28% in HD). In relation to comorbidities, the average hemoglobin value was 10.94 g/l, albumin 3.62 g/l, and i-PTH 463, and 31.3% were hypertensive, 6.6% presented with coronary insufficiency, 10.5% have heart failure, and 18% have peripheral vascular disease. The percentage of PD

patients positive for HBsAg was 1.18%, anti-HVC 2.24%, and 1.41% anti-HIV [24].

The crude mortality rate in 2017 was 10.2% (202 deaths, with 1883.6 patients' years of risk exposure) and adjusted mortality (by age and etiology by indirect standardization) of 15.16%. The crude mortality rate in diabetic patients was 16.3% in females vs. 26.6% in males.

An interesting fact to point out was the improvement of the adjusted mortality results in PD in recent years, going down from 20% in 2007 to 15.16% in 2017 [24].

The PD costs are pending, being affected by the economic crisis of the country and the devaluation of its currency, since the inputs (disposable material) reflect 60% of the cost and are imported.

Hemodialysis

In 2017, 27,764 patients were treated with HD, achieving a growth close to 20% in 10 years (23,266 patients in 2007); almost 7000 (6765) patients entered HD (93.49% of total 2017 incident patients in dialysis). The HD growth was 3% in the biennium 2016–2017. In relation to comorbidities, the average hemoglobin value was 10.59 g/l, albumin 3.76 g/l, i-PTH 517, and 40.5% were hypertensive, 8.2% presented with coronary insufficiency, 16.5% have heart failure, and 29.4% have peripheral vascular disease. In reference to prevalence of viral infections, 0.88% were positive for HBsAg, 2.62% anti-HVC, and 0.83% anti-HIV [24].

In relation to HD adequacy, average KT/V was 1.56, whereas 76.4% presented K/TV greater than 1.3. Patients with permanent vascular access managed to reach higher average K/TV. In relation to vascular accesses distribution, 68.8% have native arteriovenous fistula, 13% grafts, 7.7% permanent tunneled catheters, and 10.4% non-tunneled transient catheters. In regard to the use of tunneled and transient catheters in different populations, there is a greater frequency of use at the extremes of life: 35.4% between 0 and 19 years and 43.7% between 65 and over 75 years [24].

The crude mortality rate was 18.16% (5038 deaths, with 27,736 patients' year of exposure to risk) in 2017. The gross mortality rate for diabetic patients was 26.6% in females vs. 26.14% in males [24].

Considering the HD population registered from January 2005 to December 2015, the probability of survival under dialysis treatment in the short (1 year), medium (5 years) and long term (10 years) is 80%, 40%, and 18%, respectively. When we select the subgroup of HD patients in the transplant waiting list, the results are 92%, 70%, and 44%, respectively [24].

The gross mortality rate of both techniques (HD and PD) decreased between 2016 and 2017, resulting in 17.7 deaths per hundred patients at risk per year. The adjusted global

mortality rate also decreased last year, being 16.26 deaths per hundred patients at risk year. Adjusting for age, gender, and diabetic nephropathy, PD patients from 2011 onwards have presented significantly lower mortality than HD patients in Argentina.

In Argentina, 100% RRT coverage is guaranteed, with financing originating from the public subsector (82%) and private (18%) [24].

The financing of the admission to maintenance dialysis relies fundamentally on eight payers representing 99.4% of the total in 2017, with very similar percentages from 2004 to 2016 (always greater than 99.2%). PAMI is the largest payer in the number of incident dialysis patients per year, followed by all other institutions like Provincial Social Works, Trade Union Social Works (ex SSSAPE), provincial subsidies, Incluir Salud (ex PROFE), prepaid, other social works, and finally the public health system [24].

A recent cost study shows that the main categories and their impact on the costs of the chronic HD session are human resources (44%), disposable material (11%), real estate (8%), and transportation (8%). The cost of one chronic HD session was estimated at 2693 Argentinian pesos (170.12 USD). In the case of one HDF session, the same main cost categories were observed, although their relative magnitude changes: human resources (35%), disposable material (25%), real estate (7%), and transportation (6%). The estimated cost of the HDF session was 3372 Argentinian pesos (213.01 USD) [27].

Kidney Transplant

In Argentina, a total of 13,185 renal transplants, performed between 1998 and December 31, 2016, have been registered. The great majority (89%) corresponds to adult donors and 11% to pediatric donors [12]. Argentina offers national and international training programs to harmonize the practices of professional staff working with organ donation and procurement activities. Several technical cooperation agreements have been signed with many countries, mainly in Latin American, and joined international forums in the field of transplantation. Public or private health institutions must be accredited for procurement and transplantation, and health professionals must be certified (Law 24,193). There are 59 centers authorized for renal transplantation distributed throughout the country but in greater number in the federal capital (17), Buenos Aires, (10) and Córdoba (6) [28].

Brain death must be certified by the criteria of complete brain death in accordance with the law. The law only allows the donation of organs from related living donors, with no additional incentives for donors. Organ trafficking is prohibited and punishable by law. The Argentine system guarantees transparency, traceability, and the quality of the procedure.

The percentage of cadaveric kidney transplant or related living donor has increased 74% in the last 14 years, from 765 in 2004 to 1329 in 2017. Considering all types of kidney transplants, the rate per million inhabitants rose from 20.0 up to 30.2 from 2004 to 2017, resulting in a 51% growth, having its maximum value (30.5) in 2013. The gross renal transplant rate in the maintenance dialysis population increased from 3.4 to 3.8 transplants per 100 patients at risk year, between 2005 and 2017. There are currently geographical differences, being Buenos Aires the city with the highest gross rate, 7/100 patients at risk year. Drawing a comparison of unadjusted rates with international data reported from the rest of the world, it will be observed that Argentina, with 28 pmp in 2016 (last year published), is placed at 34th position out of 64 countries that publish data in the USRDS Registry [29].

In the Newsletter Transplant, Argentina reported 29.8 pmp for 2017, when in reality the figure is 30.2 pmp. Argentina ranks fourth in the American continent, behind the United States, Canada, and Uruguay [30].

In relation to kidney transplants during 2019, 1576 were paid by the most important social security funders: *National Institute of Social Services for Retired and Pensioned* (PAMI) with 357 and *Incluir Salud* (a federal program, public payer), with 266 transplants [28].

Nephrology Practice in Argentina

Annually, approximately 4000 young doctors apply for medical training positions in the different jurisdictions of the country [31].

The most frequent pathways to train as a medical specialist are the medical residence/fellowship or the university postgraduate degree. Of the 2440 professionals who have certified their specialty in the Ministry of Health of Argentina between 2008 and 2013, 57% did so at the end of an accredited medical residence/fellowship and 25% at the end of the university postgraduate degree.

In order for the degrees to have national validity, the universities which grant them must necessarily be accredited by the National Commission for University Evaluation and Accreditation (CONEAU), within the jurisdiction of the Ministry of Education and the Residency Accreditation System (SNARES) of the Ministry of Health. Both agencies are in charge of the of health specialists training programs.

The nephrologist training in Argentina requires a year of internal medicine, 3 years of nephrology, and one year of professional practice, which are articulated with different time loads in each year of the program. The internal medicine module can be incorporated into residence or certified independently. The specialty of nephrology is recognized in the 24 jurisdictions.

In order to enter medical residence in the public sector, a single medical exam is carried out concentrating the applicants of 21 states institutions dependent on the MoH. In 2018, 48 medical residence positions were offered to training in different specialties. Nephrology training is only available in 12 of the 24 states.

Among the physicians who apply for training positions by specialty, only 0.13% choose nephrology, with pediatrics (32%), general medicine (18%), and anesthesia (12%) being the most applied to [27].

The nephrologist working in a private dialysis unit earns approximately 6 USD per hour and a maximum of 1152 USD per month. In the public sector, the salary is approximately 1200 USD per month plus social benefits (paid holidays, retirement, etc.). New nephrologists entering the labor market have few opportunities in established kidney transplant programs and public nephrology services, facing great vulnerability when dealing with multinational dialysis providers or national networks. Moreover, many nephrologists own their own dialysis centers. National dialysis entrepreneurs are grouped together in the Confederation of Dialysis Associations of the Argentine Republic, which is a non-profit civil association, founded on May 8, 1997, by the Provincial Dialysis Associations of the Argentine Republic with the purpose of addressing, collectively, scientific and educational actions in nephrology and dialysis and in defense of the rights of the centers and establishments that make up the associations.

Multinational networks (Fresenius, Diaverum, and Baxter) treat the majority of patients on maintenance dialysis and are also grouped in an association called the Argentine Chamber of Renal Therapy.

According to the national dialysis center registry in 2020, there are 596 dialysis centers. There are 503 privately owned dialysis centers: 112 are owned by FMC (10,498 patients), 40 are owned by Diaverum (3515 patients), 194 are associated with the confederation of dialysis centers in Argentina (7989 patients), and 182 are independent (7006). In the public sector, there are 68 dialysis centers (1617 patients) [28].

The value of the monthly payment for the entire benefit of HD, including EPO, vascular access, and the patient transport, is 1102 USD (66,169.28 Argentinian pesos in exchange for 60 pesos for 1 USD, January 2020), and in PD, including EPO, peritoneal access, and antibiotics, it is 1186 USD (71,179.95 Argentinian pesos in exchange for 60 pesos for 1 USD, January 2020). There is a delay in reimbursement, which leads to serious difficulties in the operation of the dialysis centers (PAMI and IOMA 60 days of delay, *Incluir Salud* and MoH of the province of Buenos Aires 240 days), which results in economic difficulties for private dialysis units and the nephrologists working in these clinics.

In an HD center, the responsible medical director must be a specialist in nephrology with no less than 2 years of dialysis experience, after having obtained the title of specialist. Nephrologists must ensure that the correct dialysis prescription as well as the clinical follow-up of the patient undergoing dialysis are executed daily, at a rate of 1 every 40 patients. In case of nonavailability of a nephrologist, the acting physician must have demonstrated dialysis treatment experience for a period of at least 6 months. In relation to nursing staff, their training and education must be certified by the medical director. The ratio of staff present during each dialysis shift must not be less than one to five patients [32].

In PD, the physician responsible for the unit must have a nephrology specialist title granted by the competent authority as well as dialysis therapy experience of 2 years and not less than 3 months of experience in chronic PD in a PD service recognized by the SAN. In the case of pediatric chronic PD, the physician responsible should be a pediatric nephrologist or have a backup pediatric nephrologist for consultation, whenever needed. Nursing staff must be registered in the MoH with certified dialysis training. The nursing staff ratio should not be less than 1 nurse per 20 adult patients, whereas in pediatrics the ratio should not be less than 1 nurse per 15 patients [32]. The dialysis units must also have a psychologist, dietitian, and social worker in relation to the number of patients and at the discretion of the medical management. Each dialysis center has a continuous improvement program supported by the medical directorate and implemented by a quality committee constituted by the medical director, nursing officer, nephrologist, social worker, dietitian, psychologist, and representatives of the administrative and maintenance areas.

This quality committee evaluates, on an annual basis, the implementation of the different programs to improve vascular or peritoneal access, among others. The committee for its evaluations will take as a reference the average national results published by the Argentine Registry of Dialysis and by those suggested by the SAN [32].

The annual results obtained will be communicated to the members of the renal team in each center as well as the objectives proposed for the following period. The reports will remain available for internal and external audits.

Hemodialyzers may be reused; however, the dialyzer efficiency must be controlled by measuring the residual fiber bundle volume, which must be maintained above 80% of the initial reference value. The reference values must be included in a folded book of nonremovable sheets, although it can be kept in a computerized record, as long as it is encrypted.

In the case that it is decided to reuse the dialyzer, reprocessing must be done in a physical environment used exclusively for that purpose; anti-HCV-positive patients' dialyzers must be reprocessed in a separate, properly identified sector.

Disposal of hemodialyzers used in positive B patients is recommended, whereas in the case of patients with HIV-positive serology, discard is mandatory in each session [32].

Although the government's dialysis guidelines do not mention the number of reuses allowed for one dialyzer, it is usually discarded after 20 times of use.

Highlights of Nephrology in Argentina

On March 28, 2015, the Favaloro Institute performed the first cross renal donation kidney transplant in Latin America. On October 12, 2017, through a resolution published in the *Official Gazette*, INCUCAI was authorized to incorporate this type of operations. The new transplant law (No. 27447, 2018) among other points incorporates the cross renal donation procedure. Before the law was enacted, there were two transplant options in Argentina: a cadaveric kidney donor or a living one. If the kidney was donated by a living donor, it should be related to the patient via a family bond, and if that link did not exist, a judicial process had to be claimed in order to authorize the transplant.

Among the different compatibilities that must exist between the patient and the donor, the most important ones are blood and tissue compatibility. Cross transplantation is a modality that allows a patient who has a potential noncompatible living donor to still receive a living donor transplant. It was reported in a paper by Rapaport in 1986 and first implemented in South Korea in 1990. The new legal framework creates a system where patients with their noncompatible living donors can be registered, and the INCUCAI is responsible for finding compatible pairs [33].

Another point to note is related to the HUS, a serious disease of great importance for our country public health and for which there is no approved medication in the world. It is the local development of an innovative biological medicine with the potential to become the first treatment to block Shiga toxin (Stx) and prevent progression to HUS.

The National Administration of Drug, Foods and Medical Devices (ANMAT) has incorporated this new drug into its "Program for Support to Innovation in Medicines and Health Products" and has also been presented to the European regulatory authorities (EMA) and United States (Food and Drug Administration, FDA) in the form of "scientific advice" and "pre-IND meeting" respectively, incorporating the suggestions of the three entities into the final design. In addition, the drug has been designated as an orphan drug in Europe and the United States. The Phase II/III clinical study is currently in progress evaluating the efficacy and safety of this drug to block Shiga toxin serum in pediatric patients at risk of developing HUS. The study is being carried out in public and pri-

vate centers in different parts of the country, hoping that the results will allow to prevent HUS progress in a few years.

Future Perspectives of Nephrology in Argentina

The main current challenge for nephrology in Argentina, as in the rest of the world, is to increase the interest among medical graduates in choosing the specialty.

Furthermore, the need to increase the reimbursement of therapies related to nephrology and repeated economic crisis conspire to the stability and development of nephrology in Argentina. The fact that a large part of the available jobs is in dialysis units facing financial problems makes it difficult for new doctors to choose this complex specialty, requiring many years of study and an inadequate salary. Access to new technologies also faces economic difficulties for everyone, including the population in need of access to them. Argentina has had several possibilities for the development of its economy and science in its past history as a country. We now hope that a new era of enlightenment may come forth and allow the development of our specialty.

Conclusion

Nephrology in Argentina has a good organization through the various associations that regulate the nephrologist formation (CONEAU and SNARES). The SAN does an excellent job fully involved in the training of nephrologists through prestigious continuing education programs (PRONEFRO) and fundamentally being a professional pillar of the Chronic Dialysis Registry in SINTRA with INCUCAI.

Basic sciences in Argentina have demonstrated the impact of their discoveries on the renin-angiotensin system and the subsequent development of captopril and monoclonal antibodies. Today, the National Commission of Research Science and Technology (Conicet) together with a private national laboratory (Inmunova) is on its way to establish the first treatment for HUS.

The national system of organ and tissue procurement has achieved a sustained impact over time and on the perception of citizen security. Laws have accompanied this development. Quality programs have accompanied the development of dialysis units, and an improvement in the mortality of diabetic patients on chronic dialysis has been achieved.

The path of nephrology in Argentina has been paved over the past years. However, much still remains to be done, and as the tango song of Enrique Santos Discépolo [34] says, "*lleno de esperanzas el camino que los sueños prometieron a sus ansias.*"

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