Hemodialysis was born in 1945 to treat acute renal failure, and it has progressively become a rescue therapy for patients with chronic kidney disease (CKD) stage 5, otherwise doomed to death. During the years, technological innovations have led to improved dialytic tolerance, making possible to extend the treatment to a greater number of subjects. Low- and high-flux bicarbonate dialysis are nowadays the most frequent hemodialysis techniques; hemodiafiltration with different modalities, short daily and overnight hemodialysis are also widespread, each of them with peculiar characteristics. A recent randomized controlled clinical trial has identified high-flux hemodialysis as the best treatment for patients with low serum levels of albumin and for diabetics in comparison to low flux dialysis. Apart from the treatment of end-stage renal disease (ESRD), hemodialysis has new and important applications, including heart failure treatment and multiple myeloma. The need to provide hemodialysis patients a better quality of life has increased the interest in developing new techniques, such as the wearable artificial kidney, although still in initial clinical development. Apart from the treatment of end-stage renal disease (ESRD), hemodialysis has new and important applications, including heart failure treatment and multiple myeloma. The need to provide hemodialysis patients a better quality of life has increased the interest in developing new techniques, such as the wearable artificial kidney, although still in initial clinical development. The preclinical and clinical hard work ongoing in earlier stages of CKD should be able to obtain further relevant improvements and maybe avoid the need of hemodialysis itself.

Key words: Renal dialysis - Renal dialysis, history - Renal dialysis, adverse effects.

In 1945, in a little Dutch country hospital, Doctor Willem J. Kolff used the first artificial kidney, succeeding in treating a 67-year-old woman. Even if he overcame many practical difficulties, since there were no permanent access lines yet, and arterial and venous lines had to be inserted and removed at each dialysis, this first device was useful only in case of acute renal failure.

More than ten years later, Scribner, Quinton and Dillard were able to apply the artificial kidney to patients requiring long-term renal replacement therapy using a semi-permanent exteriorised arterio-venous shunt that could be used for repeated access to patients' circulation. The first long-term hemodialysis program began in Seattle, WA, in 1960 thanks to Shields and Gentry, while home dialysis started in London, Boston and Seattle four years later. In 1966, Brescia and Cimino created their famous subcutaneous arterio-
venous fistula (AVF): this gave a great boost to the development of chronic hemodialysis worldwide.\textsuperscript{3}

Many years have passed since the first age of hemodialysis and nephrologists have improved hemodialytic treatment thanks to the introduction of new techniques, obtaining a significant better quality of life for the patients. Many problems have been overcome but many aspects still need substantial improvement.

This review will go through hemodialysis’ history, focusing on the last hot topics of scientific discussion in the field as well.

**Epidemiology**

In the 1960s, at the dawn of nephrology, less than 800 patients could benefit regular hemodialysis in the United States, although more than 10,000 would have required such a rescue treatment. This discrepancy has been even bigger during the 1970s, when at least 20,000 subjects needed renal replacement therapy (RRT).\textsuperscript{4} At the beginning, the health systems could not afford hemodialysis for all the patients, leading to important ethical debate since the possibility to undergo RRT was – obviously – strictly associated with the chance to survive.

In the 1980s, hemodialysis could be offered to millions of chronic kidney disease (CKD) patients, otherwise doomed to death, in most of the countries of the world.

The epidemiological impact of CKD is nowadays a “Tsunami”, also because the management of CKD 5 patients is just “the tip of the iceberg”, since the incidence and prevalence of patients with any stage of CKD has dramatically risen in the last years. This aspect has been clearly reported by a prospective epidemiological study, which revealed a huge age-related increase in the incidence of CKD. Patients older than 75 years had an incidence rate more than twice that of patients aged 40-59 years (619 vs. 264 new cases per million population (p.m.p.) and almost seven times higher the one found in patients aged 20-39 years (619 vs. 92 new cases p.m.p.).\textsuperscript{5}

The Third National Health and Nutrition Examination Survey (NHANES III) program showed an increase of 15.9% in the crude estimate of CKD prevalence in the adult US population from 1988-1994 to 1999-2004 (14.5% and the 16.8%, respectively).\textsuperscript{6}

The number of CKD 5 patients requiring RRT has also increased dramatically exceeding expectations. In 1984 Eggers et al.\textsuperscript{7} estimated that 117,200 patients would be receiving RRT by 2000, however that projection was modified in 1990 to between 209,000 and 274,000.\textsuperscript{8} Real data have not confirmed these forecasts: in 2000 in the US there were 378,862 patients undergoing any kind of RRT, with a point prevalence rate of 1,367 patients p.m.p.\textsuperscript{9} This rate was 3.1% more than that of the previous year, and 76% higher than that of 1990. A relevant rise of CKD 5 prevalence has been recorded also in European countries, even if of lower extent. The prevalence of Italian patients on RRT has constantly increased since 1996, reaching 864 p.m.p. in 2002 and 1,022 in 2004.

A parallel increase in the incidence of RRT has been observed in the US and in Europe. Just some years ago, the incidence of CKD 5 in the USA (333 p.m.p) was almost four times higher than that seen in 1980 and 40% more than that observed at the beginning of the 1990s.\textsuperscript{9} In other words, a 6-7% average annual increase has been observed in the number of new CKD 5 cases reported in the USA.\textsuperscript{10} Consistently with prevalence data, the European incidence rates are significantly lower than those registered in the USA.

In the last decades nephrologists have made important steps to face CKD natural course, thanks to the introduction of drugs working on renin-angiotensin system (angiotensin converting enzyme-inhibitors, angiotensin-receptor blockers, anti-aldosteronics, direct renin-inhibitors), effective treatments of glomerular diseases and some promising new therapies for glomerulonephritis and polycystic kidney disease. Despite our efforts to slow down the progression of CKD, we have not succeeded in stopping the increase of incident CKD 5 patients (even if the trend has been flattening).
The ageing of the general population is responsible for the striking increase in CKD patients. Nowadays, the great proportion of elderly patients mainly accounts for the increased incidence of people requiring RRT. Since 2000 in the USA the incident rate for patients over 75 years increased of 11%, with an incidence of 1 744 p.m.p.; the increase was only of 2.4% for younger patients (45-64 years).\(^{11}\) People aged >80 years had an average annual increase of 9.8%, doubling in less than ten years.\(^{12}\)

One possible explanation is that today mortality because of coronary heart disease and stroke has improved; surviving patients often develop hypertensive, atherosclerotic or athero-embolic kidney damage.

Another important reason for the progressive increase in the incidence and prevalence of RRT CKD is that the proportion of patients with diabetic ESRD has rapidly increased during the last years, also because RRT is well tolerated by these often compromised patients. The incident rate of patients with diabetes as renal underlying disease has moved from a small number in the 1980s to almost 160 p.m.p. in 2006.\(^{11}\)

Even if survival of hemodialysis patients has improved during the course of the years, thanks to the improvements in cardiovascular risk factors and diseases managements, it remains far from being satisfactory.

Diabetic CKD 5 patients have the worst outcome, largely due to cardiovascular causes: according to the United States Renal System (USRDS), in 1985 first-year mortality rate was 46/100 patient-years. It has significantly improved over the years, nearly halving in 2001 (25.1/100 patient-years).\(^{9}\) Adjusted annual mortality rate has also improved in prevalent patients, changing from 274.5 for 1 000 patients at risk in 1980 to 186.1 for 1 000 patients at risk in 2007.\(^{11}\)

When analyzing changes in hemodialytic population composition by primary diagnosis, besides the described increase in diabetic nephropathy - also valid for nephrosclerosis - it is worth to underline that the incident rate of CKD 5 due to glomerulonephritis continues to decrease (15.6% since 2000), reaching 26 p.m.p. On the contrary, at the beginning of hemodialysis era, glomerular disease was the most frequent cause of RRT, mainly because only young patients (in which this kind of disease is more common) could undergo such a “complicated therapy”.\(^{11}\)

Renal replacement therapy and intradialytic complications

At the beginning of dialysis era, when entering in a dialysis unit the scenario was characterized by people staying in Trendelemburg position, with nausea and vomiting, with a really bad tolerance of the treatment. Today, hypotension and gastric symptoms are much less frequent than in the past and the dialysis session is tolerated much better. Hemodialysis improvements in the chemical and microbiological characteristics have also made possible to reduce or make disappear some frequent complications typical of the first age of hemodialysis, such as the hard-water syndrome and pyrogenic reactions.

In 1985 Gotch et al.\(^{13}\) demonstrated in the American National Cooperative Dialysis Study (NCDS) that patient morbidity and treatment failure were partially related to inadequate dialysis dose. Some years later, Held et al.\(^{14}\) showed a linear correlation between higher dialysis doses and lower mortality rates. Thanks to these observations, the quantification of the delivered dialysis dose became of paramount importance. In the following years, it has become clear that also the length of dialysis is crucial. The choice of biocompatible dialytic membranes and high flux also began to play a relevant role, since early epidemiological studies suggested that semisynthetic membranes and high fluxes may reduce morbidity and mortality in dialysis patients.\(^{15, 16}\) However, previous observations were not confirmed by other studies,\(^{17-19}\) which found only an association with lower relative risk of carpal tunnel syndrome surgery.\(^{16, 18}\)

The introduction of bicarbonate instead of acetate dialysate buffers, the frequent use of ultrafiltration control monitors and the knowledge of the intradialytic sodium kinetic have
led to significant improvements in cardiovascular stability during the hemodialytic treatment, reducing the occurrence of severe intradialytic hypotension. The assessment of the dry weight and the prevention of volume overload have always been particularly difficult in the management of hemodialysis patients. A wrong evaluation of these parameters can lead to relevant complications, such as hypotension or – the other side around – to hypertension, especially during the course of the treatment.

Since a positive sodium balance plays the most important role in the genesis of hypertension, the first useful step to control blood pressure in CKD patients is to look for an adequate sodium balance.20 Besides a low sodium diet, intradialytic sodium removal should be equivalent to interdialytic sodium gain: this strategy assures a normal extracellular volume for the patient. Sodium removal is the sum of diffusive flux (the direction of which is regulated by the diffusive gradient between sodium plasma water and dialysate sodium concentrations) and convective flux (from the patient to the dialysate). Thus, the dialysate sodium prescription is one of the most important factor regulating sodium balance. Theoretically, a hyponatric dialysate can be used in patients requiring losing sodium by diffusion. However, this practice, which has been used in the past, should be generally avoided as it can cause cellular overhydration due to osmotic fluid shift from the extracellular to the intracellular compartment leading to intradialytic hypotension.20 Hypermatric dialysate is more frequently used than isonatric or hyponatric solutions because it avoids excessive sodium losses with ultrafiltration, thus preventing the onset of intradialytic hypotension. If the sodium concentration in the dialysate is higher than the patient’s predialysis plasma sodium concentration, sodium is given via diffusion so that the difference in concentrations equalizes. However, hypermatric dialysis can lead to insufficient net sodium removal, which can result in the development of refractory hypertension and intradialytic hypotension. In addition, hypermatric dialysis can increase the sense of thirst, resulting in high water intake during the interdialytic period.20

Considering that interdialytic sodium and water load varies from one uremic patient to another, the dialytic treatment should be individualized in order to correct sodium and water removal by adjusting the sodium content in the dialysate. The application of the single pool sodium kinetic model allowed to determine the dialysate sodium concentration required to obtain the end-dialysis plasma water sodium concentration necessary to achieve a zero sodium balance over the treatment cycle.21, 22 It was soon clear that the single pool sodium kinetic model was not useful for everyday clinical practice, since it required the determination of the plasma water sodium concentration at the beginning of each dialysis session. For this reason, the sodium conductivity kinetic model helped nephrologists in evaluating intra- and interdialytic sodium balance. Plasma conductivity can be considered a surrogate of plasma sodium, which can be estimated on-line without any blood samples and laboratory determinations, giving an immediately available value. The conductivity kinetic model as a surrogate of sodium kinetic model can predict quite precisely the end-dialysis plasma sodium concentration (with an imprecision <1.4 mEq/L).23

Hemodialysis-induced hypovolemia is the most important cause of intradialytic cardiovascular instability. Some studies have evaluated the critical blood volume reduction responsible for the onset of symptomatic hypotension;24 automated control systems have been proposed to maintain a constant blood volume reduction rate through dialysis session.25-28 A blood volume monitor (BVM) has been developed to analyze blood density and give information about the relative blood volume. BVM determines an automatic feedback control of the ultrafiltration rate and this helpful mechanism prevents blood volume from reaching critical levels. As shown,29 using BVM the incidence of intradialytic symptoms in hypotensive-prone patients has been reduced from 40% to 32%. Other factors have been related to intradialytic hypotension, like the shape of the relative
blood volume signal, which depends on different ultrafiltration rates during the dialytic session. Andrulli et al.\textsuperscript{30} reported that a large initial decrease in relative blood volume predicts symptomatic hypotension, even if the presence of a critical relative blood volume was not confirmed.

Today many methods have been developed and used to monitor hydration in hemodialysis: the evaluation of the diameter of the inferior vena cava, the application of bioimpedance and the measurement of plasma levels of natriuretic peptides. However, all these possibilities have not a well defined clinical role yet and further inquiries are needed to improve their accuracy.\textsuperscript{31}

Besides the phenomenon of intradialytic hypotension, nephrologists have to face sometimes intradialytic hypertension, another clinical cardiovascular complication of dialytic session. This is more frequent than thought, with an estimated prevalence of 5% to 15%. Patients with intradialytic hypertension are more likely to be older, treated with a greater number of antihypertensive drugs, having a lower dry weight and levels of serum creatinine, serum albumin and phosphorus than patients whose systolic blood pressure decreasing or not changing with hemodialysis.\textsuperscript{20} Mechanisms potentially involved in the onset of intradialytic hypertension include extracellular volume overload, increased cardiac output, changes in electrolyte levels, activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, and endothelial dysfunction. Unfortunately, its treatment is still uncertain, despite that this complication is associated with a poor outcome, with a two-year all cause mortality rate higher than that of normotensive patients.\textsuperscript{32} The most important treatment approach for intradialytic hypertension is adequate sodium and fluid removal, as previously described.\textsuperscript{20}

Considering the latest technologies, BVM has been used to manage hypertension and fluid balance. Blood volume tracking – which guides relative blood volume along an individually pre-set relative blood volume trajectory by continuously adjusting the ultrafiltration rate and dialysate conductivity – is able to reduce blood pressure in hemodialyzed hypertensive patients.\textsuperscript{33} However, well-conducted randomized controlled clinical trials are still needed to determine pathophysiologic mechanisms and define the best treatment approach for intradialytic hypertension.

**Modalities of renal replacement therapy**

One of the aims of hemodialysis is to remove solutes that are usually excreted by the kidneys. In observational trials, convective therapies – in comparison with diffusive therapies – seemed to be associated with reduction of serum beta2-microglobulin and incidence of dialysis-related amiloidosis, slower decrease of residual renal function, improvement of lipid profiles, lower mortality and possible positive effects on anemia, cardiovascular mortality, nutritional status, incidence of infections and peripheral nerve conductivity.\textsuperscript{34}

In 2002, the primary analysis of the Hemodialysis (HEMO) study – a prospective, randomized trial evaluating benefits from high-efficiency and high-flux hemodialysis in comparison with standard hemodialysis\textsuperscript{35} – showed that greater urea removal reduced the relative risk of mortality by only 4% (not statistically significant); similar results were observed for high-flux hemodialysis (8% reduction). The secondary analysis revealed a reduction of the relative mortality risk by 32% in high-flux patients being on hemodialysis for more than 3.7 years.\textsuperscript{36, 37} However, the HEMO study design has some flaws, since high-flux dialyzers were used without very high convective clearances and dialyzers were reused till twenty times.

The Membrane Permeability Outcome (MPO) study\textsuperscript{38} is a recent, multicenter, prospective, randomized, controlled, clinical trial evaluating the effects of membrane permeability on survival in incident hemodialysis patients with low (≤4 g/dL) or normal albumin (>4 g/dL). It specifically included a sicker patient population, in order to show the possible role of high-flux dialysis on
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patients’ survival with enough statistical power. The study did not show any significant effect of membrane permeability on survival in the population as a whole, but found a relative risk reduction of mortality of 37% in the low albumin group with high-flux dialysis. Interestingly, a secondary analysis of the MPO study reported that diabetic patients on high-flux dialysis, independently of albumin levels, had an adjusted relative risk mortality reduction of 38% in comparison with those on low-flux treatment.

Today, thanks to this recent study, nephrologists are aware that high-risk hemodialysis patients – diabetic or with albumin level ≤ 4 g/dL – will improve their survival with the use of high-flux membranes. This treatment could be useful also in low-risk patients, delaying long-term hemodialysis related complications.

The editorial comment to the MPO study underlined the novelty of information about the possibility that high-flux hemodialysis could give a moderate benefit in reducing mortality in comparison with low-flux hemodialysis. Positive effects of high-flux dialysis in hypoalbuminemic patients are also recognized, even if this finding was not shown by the HEMO study. MPO study results should be read “as a supporting rationale for the use of high-flux dialysis membranes if they are financially affordable”.

The European Renal Best Practice (ERBP) Advisory Board recently published a position paper taking into consideration the results of the MPO study, and its relevancy on dialysis strategy. The MPO study provided a high grade evidence of improved survival using high-flux membranes in high-risk patients identified by serum albumin ≤40 g/L; the same was true for serum beta2-microglobulin reduction. Since findings about better survival come from a secondary analysis, their degree of evidence is only of low-moderate grade. Following the results of the MPO study, the ERBP Advisory Board gave strong recommendation (level 1A) to the use of high-flux dialysis for high-risk patients, also considering the small incremental extra cost of high-flux filters, the high prevalence of albumin ≤40 g/L at the beginning of dialysis and the reduction in beta2-microglobulin. The authors did not change recommendation on high-flux in low-risk patients (level 2B).

In hemodiafiltration (HDF), diffusive and convective transports are both present allowing effective removal of small and middle molecules. This therapy is a combination of hemodialysis and hemofiltration, which was introduced to overcome the low clearance of small solutes by hemofiltration by adding a diffusive component.

Canaud et al. compared HDF with standard hemodialysis in a prospective observational trial of 2165 patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Compared with low-flux hemodialysis, HDF was associated with a 35% reduction of the adjusted relative risk of mortality. Possible reasons explaining this data could be found in increased removal of small and middle molecules (not cleared by low-flux hemodialysis), improved intradialytic cardiovascular stability and higher biocompatibility profile with less bioactivation and secondary inflammation associated with HDF therapy. However, a bias by indication could not be ruled out.

Some observational trials have pointed out the benefits of on-line HDF on phosphate and beta2-microglobulin removal, hemodynamic stability, erythropoietin resistance, nutritional parameters, dialysis-related amyloidosis, quality of life and mortality. However, possible on-line HDF advantages have not been demonstrated yet in adequate randomized controlled trials. The results coming from three different randomized prospective studies, taking place in Holland (the Dutch Convective Transport Study – CONTRAST), in France and in Italy (the Italian Convective Study) are awaited. Preliminary results of the Italian Convective Study have shown better cardiovascular stability with HDF.

To perform on-line HDF safely, dialysis units require sterile and non-pyrogenic fluids for infusion. Moreover, patients need adequate vascular accesses to obtain blood flow of 300 to 400 mL/min.

Going back to the roots of nephrology,
1964 was an important year, since the first unattended overnight home hemodialysis was performed. Nocturnal hemodialysis (performed five to seven nights a week for 6 to 12 hours per session) and short daily hemodialysis (five to seven days per week for 1.5 to 3 or more hours per session) have been developed in recent years. There are no data available about prevalence of daily or nocturnal hemodialysis, even if these modalities can be considered as a small percentage of the great number of hemodialysis patients.

Several authors have reported positive effects of frequent hemodialysis (short daily or long nightly) in comparison with standard treatment on quality of life, nutritional status and blood pressure control. Moreover, an analysis on 117 patients treated by short daily hemodialysis showed a better survival rate (61%) than that observed in conventional hemodialysis population. Another pooled evaluation on 415 patients treated by short daily hemodialysis for 1006 patient-years showed a 2-3 times better survival rate and a predicted 50% survival time 2.3-10.9 years longer than that of the matched three times weekly hemodialysis patients from the USRDS 2005 Data Report. Unfortunately, heterogeneity in the study population is an important limitation of this analysis.

Johansen et al. recently compared survival and hospitalization among patients receiving frequent hemodialysis (nocturnal and short daily hemodialysis) with conventional hemodialysis. Primary outcomes were risks for all-cause mortality and for the composite outcome of mortality or cerebro-cardiovascular events. Mortality risk and risk for mortality or major morbidity event was lower with nocturnal treatment in comparison with standard hemodialysis; when analyzing short daily hemodialysis, a trend in risk of death reduction – although non-significant – was found.

Starting from the hypothesis that short daily hemodialysis could be more physiological than standard hemodialysis, Punal et al. compared clinical effectiveness and quality of life of the two different modalities in a systematic review including 17 original articles (without any randomized clinical trial and with a low overall quality score). A better hypotension control, together with a reduction of medications requirements, including anti-hypertensive drugs, erythropoietin dosage and phosphate binders, was found with short daily dialysis compared with standard therapy. No differences have been reported in the incidence of vascular access related complications. The review also found an improvement in quality of life when patients were moved from conventional to daily dialysis, complaining less nausea, vomiting, cramps and hypertensive crises, and reporting a better physical and mental health status. The London Study showed similar results.

At present, no clinical randomized trials on daily versus standard hemodialysis have been performed because of obvious problems in randomizing patients to such a different techniques. Lee et al. performed a comparison between varying combinations of in-center hemodialysis frequency and session length. Cost-effectiveness ratio increased with the number of hemodialysis treatments per week; dialysis schedules requiring more frequent in-center hemodialysis could become cost-neutral only with a 32-43% decrease in the cost of hemodialysis session. The authors concluded that the possibility of developing more frequent hemodialysis strategies on a large scale is strictly related to significant improvements in the economic model underlying the delivery of hemodialysis.

**Special indications for hemodialysis**

In addition to kidney failure, hemodialysis treatment indication has been broadened to other pathological conditions, such as refractory heart failure, anasarctic hepatic disease and acute intoxication. Another application of hemodialysis concerns renal failure secondary to multiple myeloma cast nephropathy, which is a consequence of abnormal higher free light chains (kappa and/or lambda) concentrations in the kidney tubules, produced by tumoral plasma cell proliferation. Patients with acute renal failure and myeloma used to
be treated by plasma exchange and less frequently by peritoneal dialysis, in order to remove the excess of free light chains, despite the fact that trials did not show relevant positive effects. In 2007, Hutchison et al. demonstrated that daily and extended hemodialysis with a high cut-off dialyzer (Gambro HCO 1100) is able to remove a large amount of free light chains. In a single-center, prospective study, the same group tested the efficacy of chemotherapy plus extended hemodialysis with a high cut-off dialyzer in reducing serum free light chains in 19 patients with multiple myeloma and renal failure requiring dialysis treatment. Dialysis schedule included five days of eight-hour daily hemodialysis, eight hours on alternate days for the following twelve days and than six hours three times per week. This extended hemodialysis schedule was supplied by infusion of human albumin, calcium and magnesium to replace the amount lost. Serum free light chain concentrations were early reduced in 13 patients, who also became dialysis independent in a time range varying from two weeks to four months (median of 27 days). Chemotherapy and extended hemodialysis were associated with a great reduction in serum free light chain concentrations in patients with myeloma cast nephropathy, with a recovery of renal function in more than 70% of the patients. Considering these promising results, the EuLITE trial (European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy) - a multicenter randomized controlled study - has been designed in order to evaluate the role of high cut-off hemodialysis membranes in addition to bortezomib in giving independence from RRT at three months from recruitment in patients with cast nephropathy and renal dysfunction requiring dialysis.

Hemodialysis vascular access

Since the great idea from Brescia and Cimino, long time has passed by and this surgical field of nephrology has undergone important changes. First, the ageing of the dialytic population and the increase of diabetes and atherosclerotic vascular disease made more difficult the adequate and timely preparation of the hemodialysis vascular access.

In the middle of 1970s, bovine graft fistulas have been created in patients in which autogenous AVF were not feasible. Some years later, permanent catheters were shown to be effective as a prolonged tool for hemodialysis vascular access. These advances - in addition to the epidemiological changes already reported - caused a rapid increase in graft and catheters use, while a reduction of AVF creation was the predictable consequence.

In 2000, the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines indicated native AVF as the preferred permanent vascular access for hemodialysis and suggested that at least 50% of new CKD 5 patients should have a primary AVF (and 40% of prevalent patients). The use of permanent catheters, which should be reserved to less than 10% of patients, was discouraged. Unfortunately, the DOPPS underlined that guidelines adherence in everyday clinical practice varies among different countries. DOPPS data collected in 2002 showed that more than 75% of hemodialysis patients in Japan, Italy, Germany, Spain and France had an AVF, and 10% or less of the patients were dialyzed using a graft. The other side around, in the United States a significant lower percentage of AVF (30%) together with an extremely high presence of grafts (42%) were observed. Data about permanent and temporary catheter use also vary greatly among countries.

The DOPPS also investigated outcomes related with the use of hemodialysis catheters, which has been associated with a 5 to 7-fold higher risk of vascular access infection, lower hemoglobin concentrations and increased risk of hospitalization and mortality. All these negative outcomes rose patient care costs.

In 2003, accordingly with K/DOQI guidelines goals, the centers for Medicare and Medicaid services with the ESRD networks
gave birth to the so called “fistula first initiative”, a National Vascular Access Improvement Initiative. The project would like to increase the use of AVF for hemodialysis. In 2007 its objective was updated, aiming at 65% of prevalent patients with an AVF within two years. The “fistula first initiative” was appreciated in the nephrologic world and had positive consequences, as underlined by the DOPPS vascular access data analysis from 1996 to 2007. In the United States AVF use increased from 24% to 47% and grafts decreased from 58% to 28%.

In 2006 K/DOQI clinical practice guidelines for vascular access recommended that 65% of hemodialysis patients should use AVF, while catheters should be limited to less than 10% of the dialytic population.

One of the main challenge of nephrologists in everyday clinical practice should be vascular access creation and follow-up, in order to provide efficient dialysis therapy. AVF (or graft as a second option) should be preferred to catheters. The need of a safe vascular access together with required experience in its management represent the most limiting factors to the possible types of home hemodialysis.

A (critical) look at the future

In December 2007, the Lancet published an original article which was considered somehow revolutionary for the management of hemodialysis patients. Davenport et al. evaluated the safety and efficacy of a wearable hemodialysis device in a group of eight patients regularly undergoing hemodialysis. Mean treatment time was 6.4 hours, anticoagulation was obtained with unfractioned heparin and patients usual vascular access was used. The authors did not find any relevant cardiovascular complication or negative alterations in serum electrolytes concentration and acid-base balance. Blood and dialysate flow and also the clearance rates of urea and creatinine were significantly lower than those we can obtain with standard hemodialysis, even if the authors suggested these variables can be improved increasing the total time of dialysis treatment. Fluid removal required to reach the dry weight was not an aim of that pilot study. No cases of hemolysis were reported, while the vascular access clotted in two cases and once the needle moved from the fistula without bleeding thanks to a safety mechanism. The authors underlined the promising role of the device, considering the efficacy and safety data achieved and the potential in improving intradialitic cardiovascular stability as a consequence of the slow rate of ultrafiltration, since the wearable device should used for long period during every day or all the day long.

The patients did not report any complaints and were satisfied, being possible for them to sleep, move and eat at the same time. They also required very short time to recover after the end of the dialysis treatment compared to the usual discomfort associated with standard hemodialysis. Although needing confirm regarding the overall applicability of the wearable device, the conclusions of the authors emphasized its possible role in delivering a new and better quality of dialytic treatment to CKD 5 patients.

The wearable hemodialysis device could lead to several improvements in patients management, reducing hyperkalemia, mineral bone disease, acid-base disorder, erythropoiesis stimulation agents, phosphate binders and antihypertensive drugs need, as showed by long daily hemodialysis.

It should be underlined that since the 1970s – which means just some years after the birth of chronic hemodialysis program – many attempts to improve patient quality of life have been done, including the development of a wearable device. However, it was not possible to efficiently overcome relevant troubles related to device dimension and weight, the need of portable energy sources and of big quantity of dialysate water and the important condition of achieving adequate solute clearances. Moreover, the problem of the vascular access management was unsolved.

The article of Davenport et al. was considered revolutionary by some scientific journals, considering the “new device” as the future of RRT. The accompanying editorial
comment on the Lancet underlined that the described wearable artificial kidney was the “small first step in the long road to wearable blood-cleansing devices”.73 In Eknoyan’s opinion, the application of nanotechnology and molecularly engineered membranes with selective permeability characteristics to dialysis research made possible the progress from the early attempts.73

Other authors did not agree with the content of wearable hemodialysis device article, since the claimed originality and priority were not considered true,74 especially when compared with the early work of Murisasco in the 1980s.72 Also the peer review process has been criticized as not able to outline previous publications not cited by Davenport et al.75 The fact that conventional home hemodialysis and overnight unattended home hemodialysis were not mentioned as means to improve the quality of dialysis treatment were other hot points of scientific debate.76

Anyway, besides pro and contra comments about wearable hemodialysis device, further studies are needed to better understand the real feasibility of nowadays “new means” for delivering high quality hemodialysis treatment.

Conclusions

We can be proud of the improvements made in this field in more than 60 years and in particular during the last decades, with many important and positive changes. We started from the “13 lucky survivors”, who became the first chronic hemodialysis patients at the Royal Free Hospital in January 1965, to the current huge number of people who survive worldwide thanks to hemodialysis using the best modalities we know.

Scientific medical progress will inexorably go on and future will be certainly characterized by other great changes, allowing the improvement of our patients’ quality of life and, more importantly, outcome.

One day we will be able to say that “future dialysis” is “no more dialysis”, avoiding the need of RRT.

Riassunto

Emodialisi: passato, presente, futuro

Nata nel 1945 per trattare i casi di insufficienza renale acuta, l’emodialisi si è progressivamente diffusa e affermata come terapia salvavita per i pazienti affetti da insufficienza renale cronica severa, altrimenti destinati a una prognosi infausta. Nel corso degli anni, le innovazioni tecnologiche hanno permesso di poter nettamente migliorare la tolleranza dei pazienti al trattamento emodialitico, potendolo estendere a un sempre maggiore numero di soggetti. La bicarbonato dialisi, low- e high-flux, è oggi la più frequente modalità di prescrizione emodialitica, ma si stanno sviluppando anche l’emodiafiltrazione nelle sue diverse accezioni, l’emodialisi breve quotidiana e quella lunga notturna, ognuna delle quali presenta peculiari caratteristiche. Un recente studio clinico randomizzato controllato ha identificato la dialisi high-flux come il miglior trattamento da instaurare nei pazienti con albuminemia più bassa e nei diabetici. L’emodialisi nella pratica clinica ha anche trovato nuove e rilevanti applicazioni, come nel campo della tempa dello scompenso cardiaco e del mieloma multiple. La necessità di garantire ai pazienti emodializzati una migliore qualità di vita ha dato impulso allo sviluppo di nuove tecnologie, come il rene indossabile, tuttavia ancora in fase di iniziale valutazione clinica. In sessanta anni abbiamo assistito a una sostanziale evoluzione del trattamento emodialitico, che ha determinato rilevanti cambiamenti nella storia clinica dei pazienti uremici. La speranza è che il fervido lavoro in fase pre-clinica e clinica attualmente in corso nelle fasi più precoci della malattia renale cronica possa portare ad ulteriori miglioramenti e rendere possibile non dover più ricorrere alla terapia emodialitica.

Parole chiave: Emodialisi - Emodialisi, storia - Emodialisi, effetti collaterali.

References

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Cavalli


