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Elements for economic evaluation on online Hemodiafiltration (OL-HDF) versus standard Haemodialysis to treat patients with End-Stage Renal Disease (ESRD)

Prof. Mario Del Vecchio
University of Medicine Florence - Bocconi Business University Milan, Italy

Dr. Guido Giordana
Fresenius Medical Care - NephroCare Coordination EMEALA

Dr. Luciano Pedrini
Seriate Hospital, Italy

Dr. Daniele Marcelli
Fresenius Medical Care - Medical Board EMEALA

Dr. Nicola Sisti
Bocconi Business University Milan, Italy

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M. Dobreva MSC
Fresenisus Medical Care

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Summary

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SUMMARY

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Executive Summary

In a recent survey among more than 6 000 nephrology professionals, almost half were in favour of the use of high-flux HD and HDF as their best option for extracorporeal dialysis therapy.

An analysis of clinical literature suggests that on-line HDF provides an increase in years of life gained, a reduction of adverse events, reduced hospitalizations, a reduced use of drugs and improved organizational efficiency. All the following elements have a direct impact on the Quality of Life of these patients:

- More effective blood purification with higher values of Kt/V (Kt/V ≥ 1.2): the better removal of uremic toxins reduces their impact on the metabolism and allows the patient to recover a better nutritional status, especially concerning protein balance;
- A normally fed patient is also a patient with a lower risk of immunosuppression and therefore is less likely to be hospitalized for infectious diseases;
- A demonstrated preservation of residual renal function for prolonged times;
- This improved metabolism also leads to a substantial recovery of nutritional status and an improvement in lipid profile and consequently slowes down the atherosclerotic process;
- An efficient control of anemia with reduced consumption of erythropoietin (EPO): patients treated with on-line HDF consume on average 30% less EPO and have a higher average hematocrit of 15% compared to patients treated with standard hemodialysis;
- An improvement of biochemical parameters such as the lipid profile allows some of the drugs (fibrates, statins, etc.), currently used in patients with ESRD to be prescribed less.

Moreover, the estimated incremental effectiveness (years of life gained and events avoided) of the innovative technology of on-line HDF compared to the HD reference technology allowed us to identify:

- A reduction of hospitalization days (both length of stay and intensiveness of treatments);
- An Improved Quality of Life (QoL): in addition to improved survival, patients on on-line HDF experience fewer side effects, a lower risk of future hospitalization, feel more energetic, have a better appetite (and are consequently better nourished and require less EPO) and sleep better at night. All these aspects result in a significant improvement in the QoL as perceived by the patient;
- A reduction of cardiovascular complications; an increase of intradialytic cardiovascular time of treatment;
- A reduction in the incidence of carpal tunnel syndrome; the effective removal of β_2-microglobulin consistently decreases the need for surgery for this condition which is extremely debilitating. This leads to an improvement in the quality of life of dialysis patients and a reduction of anti-inflammatory and painkiller consumption.

Considering the additional direct costs of on-line HDF therapy compared to HD Low-flux, its technological maturity, its increasing utilization in Europe it is clear that those costs are more than offset by the decrease in drug consumption and hospitalization rates, justifying the higher reimbursement for on-line HDF compared to other HD modalities.

In order to increase the utilization and dissemination of this technology, this slightly higher reimbursement should be introduced without limiting it to a specific patient population.

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EXECUTIVE SUMMARY

1. General overview of CKD and ESRD

BACKGROUND

More than 100 different diseases affect the kidneys. These diseases may appear early with different features such as pain, blood and/or protein in the urine, peripheral edema (swelling in the legs) and may remain undiagnosed until the patient recovers or the symptoms of renal failure develop. Most renal diseases are limiting and often occur with few, if any, symptoms or sequelae. Renal failure may be acute, and is reversible in some cases, when previously normal kidneys are affected by major injuries such as crash injuries, major surgery in the presence of severe infection or in all those cases in which the blood flow to the kidneys is compromised as in heart failure, haemorrhage, hypovolemia, and dehydration, where there is a reduction in blood pressure and the kidney is not vascularised. In these cases, renal support is needed only for days or weeks before normal renal function is restored. However, about half of these patients die during the illness because of other conditions.

More common is chronic irreversible renal failure in which the kidneys are slowly destroyed over months or years. Chronic irreversible renal failure slowly erodes kidney function and many patients resort to medical help late in their disease or even in the terminal stages of it. Tiredness, anemia, a feeling of being "run down" are often the only symptoms. Headache, breathlessness and perhaps angina if blood pressure is high, may also be a sign of kidney failure, or the prime cause of the renal disease. Ankle swelling may occur if the loss of protein in urine is particularly significant (1). The terminal stage of chronic kidney disease is End-Stage Renal Disease (ESRD), that is the irreversible deterioration of renal function to an extent that is incompatible with life without renal replacement therapy (RRT), either by dialysis or transplantation and it is the end result of progressive chronic renal failure (CRF) (2). Chronic Kidney Disease (CKD) is defined as the presence of kidney damage or a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 for 3 months or more. Markers of kidney damage include the presence of proteinuria or albuminuria, haematuria (after excluding other causes), or structural abnormalities confirmed by renal imaging. Population studies in various countries indicate that CKD affects as many as 1 in 10 adults, or over 500 million people worldwide (3). Approximately one-quarter to one-third of diabetics will develop diabetic nephropathy, making it one of the leading causes of CKD and ESRD. It is estimated that the number of people with diabetes will rise from 171 million in 2000 to 366 million in 2030, resulting in millions of new cases of CKD. The largest relative increases will occur in the Middle East, sub-Saharan Africa and India. In absolute numbers the countries with the largest projected number of cases in 2030 will be India (79 million), China (42 million) and the USA (30 million) (3-5).

INTRODUCTION

Chronic kidney disease (CKD) is defined by the presence of sustained abnormalities of renal function and results from different causes of renal injury. CKD can lead to a progressive loss of renal function, and may terminate in ESRD after a variable period of time following the initiating injury. ESRD occurs when kidney function is insufficient to sustain life and haemodialysis, peritoneal dialysis, or kidney transplantation is substituted for native kidney function. There are multiple causes of kidney damage that lead to the final common outcome of ESRD, characterized by hypertension, anaemia, renal bone disease, (also known as renal osteodystrophy), nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy. Because of the impact of ESRD on public health, interest has been shown for clinical and public health interventions that can delay or prevent the

CDK is defined as the presence of kidney damage or a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 for 3 months or more

occurrence of ESRD in individual patients and in high-risk populations with CKD. The National Kidney Foundation (NKF) – the Kidney Disease Outcomes Quality Initiative, the Clinical Practice Guidelines (KDOQI) - for Chronic Kidney Disease recommend to use the term CKD to define the presence of kidney injury and impaired kidney function. The NKF definition of CKD includes the presence of continuous impaired renal function for 3 or more months or renal injury shown by isolated anatomic, radiographic, biomarker, and urinary abnormalities that decrease the glomerular filtration rate (GFR), irrespective of the primary cause of the renal injury. In classifying CKD it is required that the clinician establish the presence or absence of renal injury estimated with GFR, and then determine that kidney disease has persisted for 3 or more months. Equations that convert the serum creatinine into an estimated GFR or creatinine clearance are available and should be used to avoid misinterpretation of serum creatinine values. An estimated GFR above 60 mL/min/1.73 m^2, in the absence of other anatomic, radiographic, or urinary abnormalities, does not lead to a classification of CKD. The National Kidney Foundation classification defines five stages of CKD identified by an increasing degree of impaired kidney function (Table 1.1).

As kidney damage progresses the remaining nephrons compensate for the reduction in nephron mass by increasing the single nephron filtration rate, and this hyperfiltration promotes further injury. At each stage of the process, patients may benefit from measures that delay or prevent the progressive loss of renal function, that avoid the waste product cumulating and decrease cardiovascular risk factors. The progression of kidney failure in patients with CKD needs to be monitored and those who reach CKD stage 3 require increased attention to keep hypertension, anaemia, renal bone disease and nutrition under control. Recognition and early identification of patients who advance to stage 4 and 5 CKD is important because a delayed treatment with ESRD has been associated with less than optimal vascular access placement, failure to manage renal bone disease and nutrition, poor anaemia control, impaired quality of life, and increased risk of severe hypertension, uremic symptoms,

TABLE 1.1

STAGES OF CHRONIC KIDNEY DISEASE

STAGE	DESCRIPTION	GFR (ML/MIN)
I	Kidney damage with normal GFR	> 90
II	Kidney damage with mild decrease in GFR	60-89
III	Moderate reduction in GFR	30-59
IV	Severe reduction in GFR	15-29
V	End-Stage Renal Disease (ESRD)	< 15 (or dialysis)

Source: National Kidney Foundation, 2011

TABLE 1.2

COMPLICATIONS DETECTED ACCORDING TO STAGES OF CKD

	STAGE IV (%)	STAGE III (%)	STAGE II (%)	STAGE I (%)
Hypertension	71	69	38	21
Anemia (Hb < 12 g / dl)	49	18	4	5
Peripheral vasculitis	22	23	4	3
Albumin < 3.5 g / dl	11	5	2	1
Calcium < 8.5 mg / dl	8	2	1	1
Phosphorus > 4.5 mg / dl	7	0	0	0

Source: National Kidney Foundation, 2011

pulmonary oedema, and immediate dialysis (6). Table 1.2 shows the complications for each stage. From the first to the fourth stage complications increase, especially hypertension, a cardiovascular complication already very common in dialyzed patients - who are increasingly elderly - that can increase kidney damage (7).

INCIDENCE AND PREVALENCE OF ESRD

Chronic Kidney Disease is becoming a global public health problem throughout the world and the costs of renal replacement therapy take up a significant share of health care budgets (8).

Population studies in various countries indicate that CKD affects as many as 1 in 10 adults, or over 500 million people worldwide

Population studies in various countries indicate that CKD affects as many as 1 in 10 adults, over 500 million people worldwide (3). Reported rates of incident ESRD across the globe show significant trends; rates have decreased in some countries, while rising or remaining stable in others. The USA, Taiwan and Japan continued to have some of the highest rates at 371, 347 and 287 respectively per million population (pmp) in 2009. Rates of less than 100 pmp were reported in Brazil, Iceland, Philippines, Finland, Russia and Bangladesh. Additionally, Japan and Taiwan continued to report the highest rates of prevalent ESRD at 2 205 pmp and 2 447 pmp, respectively in 2009. The next highest rate was reported by the USA at 1 811 pmp, followed by French-speaking and Dutch-speaking Belgium at 1 193 pmp and 1 141 pmp respectively. The lowest rates were reported by Bangladesh 140 pmp and Philippines 110 pmp (9).

Worldwide there are well over 2 million people on maintenance dialysis, and this number is projected to increase over 3 million.

Worldwide there are well over 2 million people on maintenance dialysis, and this number is projected to exceed 3 million by 2016 (Figure 1.1)

Haemodialysis (89%) is much more common than peritoneal dialysis (11%) as the treatment modality (3-5).

The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) - Registry Report includes data on Renal Replacement Therapy (RRT) from 55 National and Regional Registries in 30 countries in Europe and bordering the Mediterranean Sea (10). Renal Registries offer an important source of information on several aspects of CKD.

Indeed, they are useful in characterizing the ESRD population by describing the prevalence and incidence of ESRD, by identifying trends in mortality and disease rates, and by investigating relationships among patient demographics, treatment modalities, and morbidity (8). In 2009, the overall incidence rate at day 1 of RRT for ESRD among all registries reported by the ERA-EDTA Registries, providing aggregate data, was 121 per million population (pmp).

At Day 1 in 2009 the highest incidence rates of RRT for ESRD, among all registries providing aggregated data, were reported by Turkey (259 pmp), Portugal (240 pmp), whereas incidence rates below 100 pmp were reported by Estonia (51 pmp), Latvia (89 pmp), Montenegro (30 pmp), Russia (33 pmp) and the Ukraine (19 pmp) (Figure 1.2).

The incidence rate of RRT over the period 2004-2009, for countries and regions providing individual patient data of the ERA-EDTA Registry, adjusted for age and gender distribution is reported in Table 1.3.

As to the incidence rate of RRT by age group, the highest incidence rates in 2009 were reported in Italy and France (this is due to the mean age of patients), whereas Montenegro and Russia were among the countries reporting the lowest incidence rates (Figure 1.3).

Overall prevalence in all the registries reporting to the ERA-EDTA Registry was 623 pmp. The prevalence of RRT at 31 December 2009 in Portugal (1 507 pmp), France (1 091 pmp) and Spain (1 033 pmp) was highest. The lowest prevalence was reported by the Ukraine (101 pmp), Russia (170 pmp) and Montenegro (335 pmp) (Figure 1.4).

The mean age of prevalent patients on RRT at 31 December 2009 ranged from 47 years (Russia) to 68 years (Italy) (Figure 1.5).

The overall prevalence of RRT, adjusted for age and gender distribution is reported in Table 1.4 (10, 11).

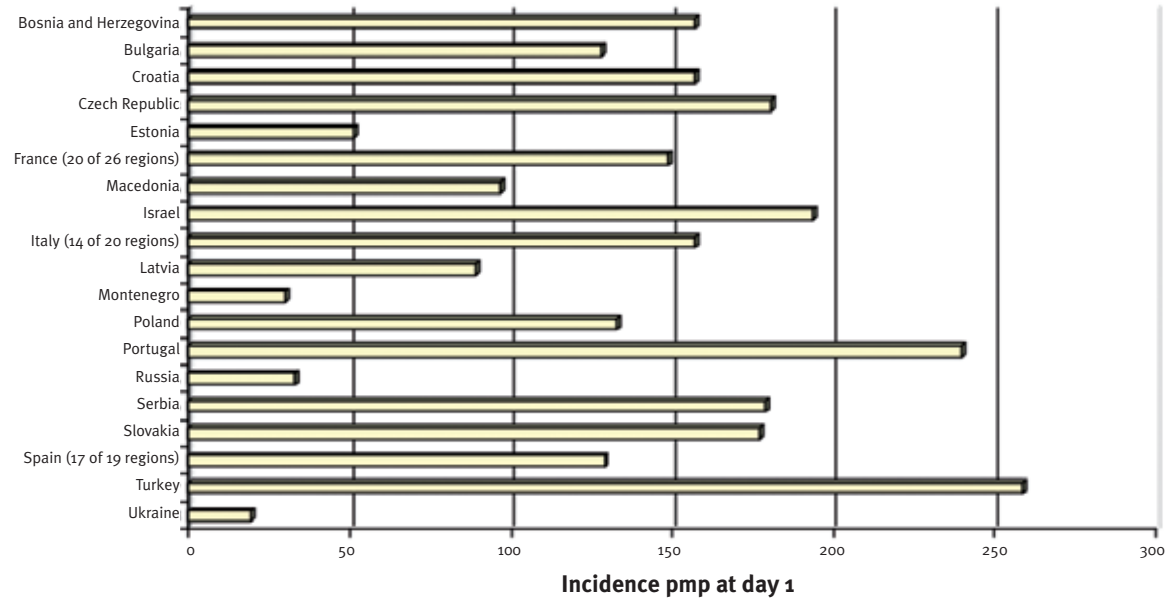
According to the Italian Society of Nephrology - Register of Dialysis and Transplants (SIN-RIDT) Annual Report 2009, the annual incidence of ESRD in Italy was 167 per million person-year and the median age at the beginning of dialysis was 70 years approx. in most Italian regions. The incidence and prevalence of ESRD in Italy per million people for each region referred to the year 2009 is shown in Table 1.5. The national average of prevalence was reported to be 765 per million people, while the regions with lower than average prevalence

FIGURE 1.1

EXPONENTIAL DEVELOPMENT OF PREVALENCE

FIGURE 1.2

INCIDENCE OF RRT PER MILLION POPULATION (PMP) AT DAY 1 IN 2009



Source: European Renal Association - European Dialysis and Transplant Association Annual Report, 2009

TABLE 1.3

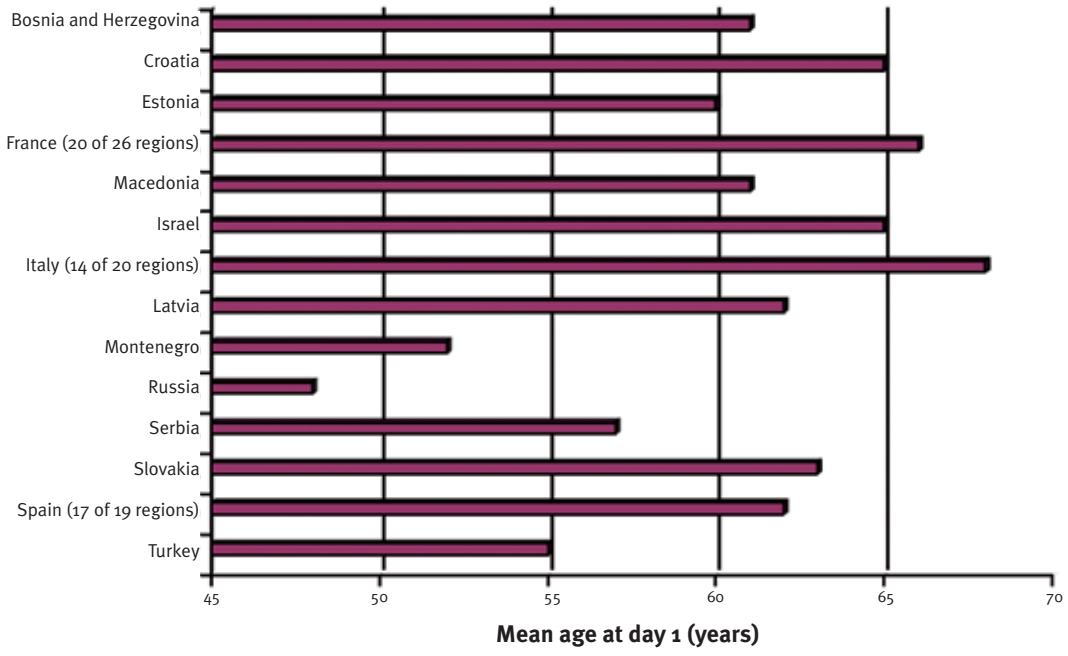
INCIDENCE OF RRT OVER THE PERIOD 2004-2009 PER MILLION POPULATION (PMP) AT DAY 1, ADJUSTED FOR AGE AND GENDER DISTRIBUTION

COUNTRY/REGIONS	2004	2005	2006	2007	2008	2009
	pmp	*pmp*	*pmp*	*pmp*	*pmp*	*pmp*
AUSTRIA	164	155	161	155	149	145
BELGIUM, DUTCH-SPEAKING	172	172	178	174	173	181
BELGIUM, FRENCH-SPEAKING	191	181	191	190	194	199
DENMARK	138	126	124	149	127	126
FINLAND	98	96	86	90	92	136
GREECE	186	181	182	174	180	182
ICELAND	90	85	84	94	89	111
NORWAY	107	106	107	120	119	121
SPAIN, BASQUE COUNTRY	121	112	101	105	97	117
SPAIN, VALENCIAN REGION	166	147	153	145	136	139
SWEDEN	119	116	124	123	116	119
THE NETHERLANDS	115	115	120	122	125	125
UNITED KINGDOM, ENGLAND	91	111	115	110	110	109

Source: European Renal Association - European Dialysis and Transplant Association Annual Report, 2008-2009

FIGURE 1.3

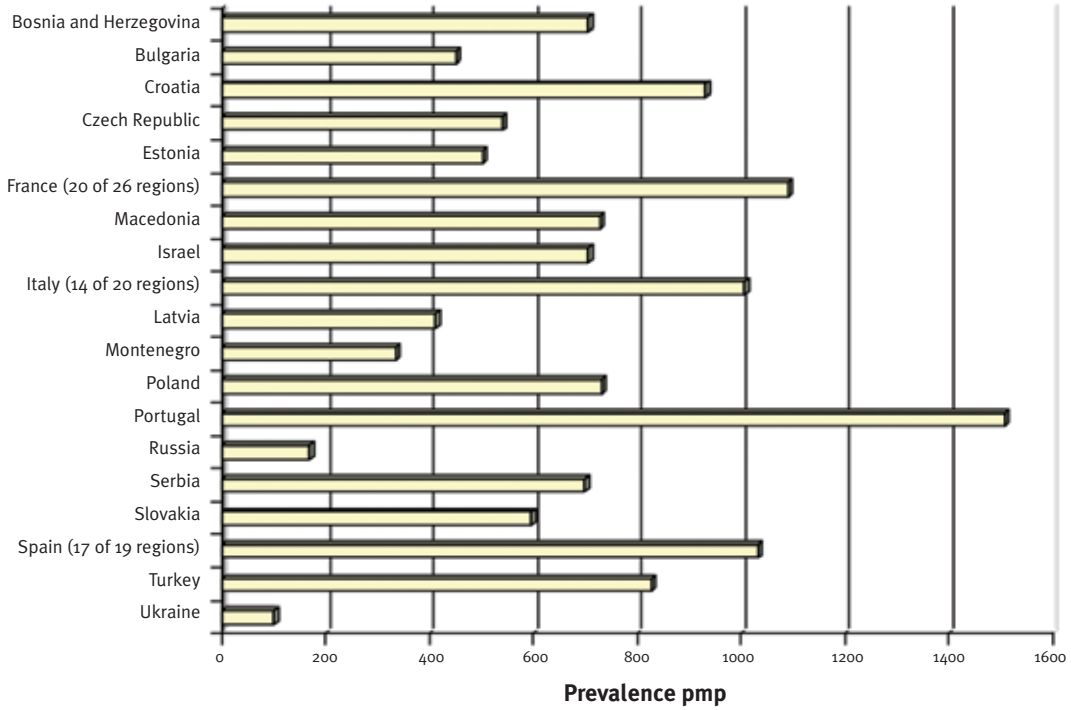
MEAN AGE (YEARS) OF PATIENTS STARTING RRT IN 2009



Source: European Renal Association - European Dialysis and Transplant Association Annual Report, 2009

FIGURE 1.4

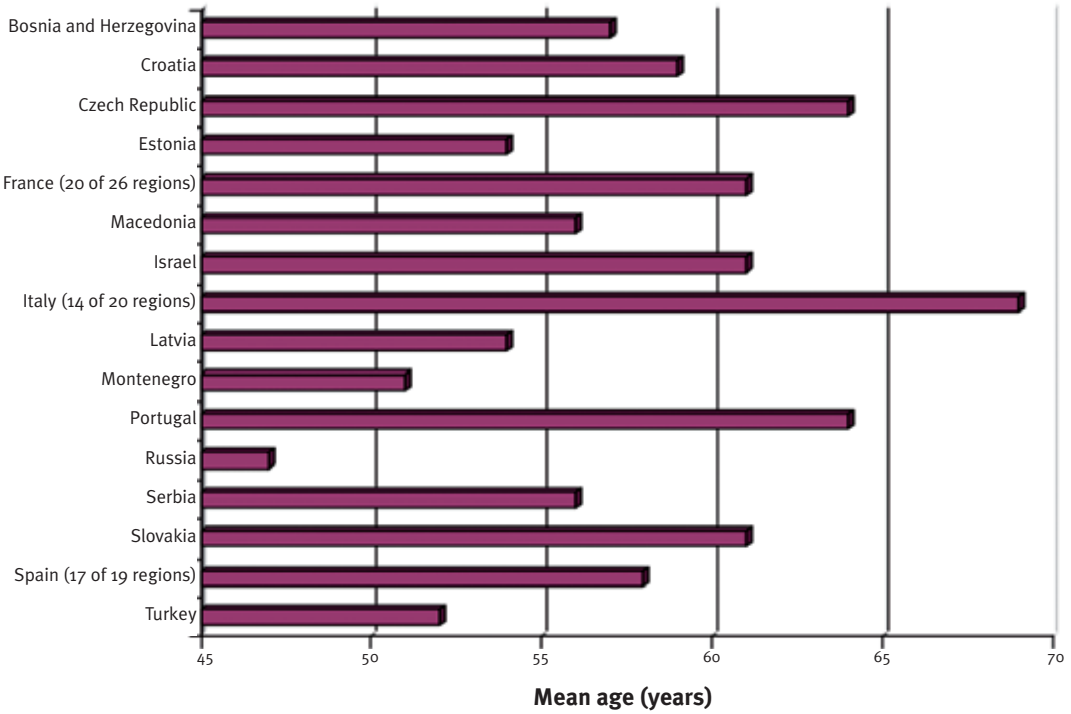
PREVALENCE OF RRT PER MILLION POPULATION (PMP) ON 31 DECEMBER 2009



Source: European Renal Association - European Dialysis and Transplant Association Annual Report, 2009

FIGURE 1.5

MEAN AGE (YEARS) OF PREVALENT PATIENTS ON RRT ON 31 DECEMBER 2009



Source: European Renal Association - European Dialysis and Transplant Association Annual Report, 2009

TABLE 1.4

PREVALENCE OF RRT ON 31 DECEMBER OVER THE PERIOD 2004-2009 PER MILLION POPULATION (PMP), ADJUSTED FOR AGE AND GENDER DISTRIBUTION

COUNTRY/REGIONS	2004	2005	2006	2007	2008	2009
	pmp	*pmp*	*pmp*	*pmp*	*pmp*	*pmp*
AUSTRIA	860	887	910	929	976	959
BELGIUM, DUTCH-SPEAKING	916	950	983	1 009	1 042	1 055
BELGIUM, FRENCH-SPEAKING	1 021	1 054	1 101	1 136	1 179	1 217
DENMARCK	777	786	794	831	848	833
FINLAND	682	704	711	723	740	747
GREECE	886	910	923	939	953	975
ICELAND	546	537	538	575	585	613
NORWAY	751	771	791	820	852	877
SPAIN, BASQUE COUNTRY	890	926	937	953	965	976
SPAIN, VALENCIAN REGION	1 085	1 076	1 077	1 113	1 135	1 099
SWEDEN	793	804	827	841	847	861
THE NETHERLANDS	734	760	794	818	854	898
UNITED KINDOM, ENGLAND	557	708	734	769	797	827

Source: European Renal Association - European Dialysis and Transplant Association Annual Report, 2008-2009

TABLE 1.5

INCIDENCE AND PREVALENCE OF ESRD IN DIFFERENT ITALIAN REGIONS IN 2009

REGIONS	INCIDENCE PMP	PREVALENCE PMP
ABRUZZO	148.6	**796.9**
BASILICATA	149.4	**789.6**
CALABRIA	149.3	**696.3**
CAMPANIA	232.1	**880.1**
EMILIA ROMAGNA	149.9	**741.0**
FRIULI VENEZIA GIULIA	207.4	**778.7**
LAZIO	159.8	**791.6**
LIGURIA	144.8	**750.0**
LOMBARDY	176.8	**722.0**
MARCHE	144.9	**743.8**
PIEDMONT	174.3	**675.2**
PUGLIA	164.8	**930.7**
SARDINIA	141.7	**842.5**
SICILY	219.1	**918.7**
TRENTINO ALTO ADIGE	115.7	**532.9**
TUSCANY	121.4	**728.4**
UMBRIA	171.0	**821.5**
VALLE D'AOSTA	172.1	**1076.7**
VENETO	112.0	**544.1**
ITALY	167.4	**764.6**

Source: Society of Nephrology-Italian Register of Dialysis and Transplants Annual Report, 2009

TABLE 1.6

INCIDENCE OF ESRD IN VARIOUS ITALIAN REGIONS IN 2006-2009

REGIONS	INCIDENCE 2006 (PATIENTS)	INCIDENCE 2009 (PATIENTS)	INCIDENCE GROWTH (%) 2006-2009
PIEDMONT	690	775	12%
VALLE D'AOSTA	17	22	29%
LOMBARDY	1 555	1 737	12%
TRENTINO ALTO ADIGE	100	119	19%
VENETO	516	550	7%
FRIULI VENEZIA GIULIA	254	256	1%
LIGURIA	277	234	-16%
EMILIA ROMAGNA	730	659	-10%
TUSCANY	368	453	23%
LAZIO	856	908	6%
ABRUZZO	231	199	-14%
BASILICATA	105	88	-16%
PUGLIA	603	673	12%
CALABRIA	278	300	8%
SARDINIA	221	237	7%

Source: Italian Society of Nephrology - Register of Dialysis and Transplant Annual Report, 2008-2009

were Trentino Alto Adige, Veneto, Piedmont, Calabria, Lombardy, Tuscany, Marche, Emilia Romagna and Liguria. Regions that were above the national average were Friuli Venezia Giulia, Basilicata, Lazio, Abruzzo, Umbria, Campania, Sicily, Sardinia, Molise, Puglia and Valle d'Aosta.

With regard to incidence, however, there were 7 210 new cases in 2009 compared to the 6 801 cases in 2006 (Table 1.6). This increased incidence is due to population aging and to the return to dialysis of transplant patients. The growth rates were higher than 10% for Tuscany, Valle d'Aosta, Piedmont, Lombardy, Trentino Alto Adige, Puglia while regions Abruzzo, Basilicata, Liguria, Emilia Romagna presented decreased values (12).

CAUSES OF ESRD (Table 1.7)

Autoimmune diseases

"Glomerulonephritis" describes a group of diseases in which the glomeruli (the filters which start the process of urine formation) are damaged by the body's immunological response to tissue changes or infections elsewhere. Together, all forms of nephritis can cause about 30% of renal failure. The most severe forms are therefore treated by suppressing the immune response; however, treatment makes a small impact on this group of patients.

TABLE 1.7

CAUSES OF ESRD
Diabetic ESRD
Glomerulonephritis
Renovascular disease
Pyelonephritis*
Polycystic kidney disease
Hypertension
Uncertain cause or glomerulonephritis unproven on biopsy

*including both prostatic hypertrophy and chronic pyelonephritis from childhood reflux nephropathy

Source: Italian Society of Nephrology- Register of Dialysis and Transplants Annual Report, 2009.

Systemic diseases

Although many generalized diseases such as Systemic Lupus, vasculitis, amyloidosis and myelomatosis can cause kidney failure,

the most important cause by far is diabetes mellitus (about 20% of all renal pathologies in many countries). In some patients, progressive kidney damage begins after some years of diabetes, particularly if blood sugar and high blood pressure have been poorly controlled.

High blood pressure

Severe hypertension damages the kidney but the damage can be prevented, and to some extent reversed, by early detection and early treatment of high blood pressure. The relationship between high blood pressure and kidney damage is being studied to see to what extent treatment to bring blood pressure to normal levels may reduce the incidence of ESRD in the patient target groups. Other factors may also be involved in this kind of kidney damage.

Obstruction

Anything which obstructs the free flow of urine can cause back-pressure on the kidneys. Much the commonest cause is the enlargement of the prostate in elderly men; although only a small proportion of them develop kidney failure, benign prostatic hypertrophy (BPH) is so common that it becomes a major cause of renal failure over the age of 70.

Urinary tract infections

Cystitis is a very common condition affecting about half the number of women at some time in their life and rarely has serious consequences. Further, infection of the urinary tract in young children or patients with an obstruction and other abnormalities of the tract or kidney stones may result in kidney failure.

Genetic disease

One common disease - Polycystic Kidney Disease (PKD) - and many rare inherited diseases affecting the kidneys account for about 8% of all kidney failure. Although present from birth, PKD often causes no symptoms until middle age or later. Our understanding of its genetic basis is rapidly improving and may lead to the development of effective treatment.

Prevention of chronic renal failure

The prevention of chronic irreversible renal failure is often impossible, but better control of diabetes and high blood pressure as well as relief of obstruction have much to offer, provided that the condition is recognised early in the course of the disease, before much renal damage has occurred. Screening for renal diseases has not been practised on the general population, because of the relatively low incidence of cases. Urine tests for protein or blood, or blood tests to assess the level of some substances normally excreted by the kidney such as creatinine and urea, are potentially useful methods to find out if populations at risk of renal failure can be identified.

The earliest possible assessment of patients likely to need RRT provides the greatest cost-effectiveness. This is reinforced by the growing awareness that medical and other complications frequently arise because of factors which could have been detected and modified had there been time for assessment. The surveillance of at-risk groups in general practice might help, bringing patients who will require RRT to the attention of nephrologists as early as possible. Indeed, hospital doctors in all specialties should be aware that mild renal failure requires prompt assessment by a nephrologist. Renal failure is often accompanied by other pathological conditions. Some of these are due to the primary disease: for example, diabetes causes renal failure, blindness and diseases of the nerves and blood vessels. Others, such as anemia, bone disease and heart failure are consequences of the renal failure. Coincidental diseases such as cardiovascular diseases, peripheral vascular disease, chronic bronchitis and arthritis are particularly common in older patients with renal failure. All these conditions (called collectively “co-morbidity”) can influence the choice of treatment for renal failure and may reduce its benefits. Expert assessment of the patient before ESRD can reduce co-morbidity and increase the benefit and cost-effectiveness of treatment. Thus early detection and the referral of patients at risk of renal failure is very important.

RENAL REPLACEMENT THERAPY (RRT)

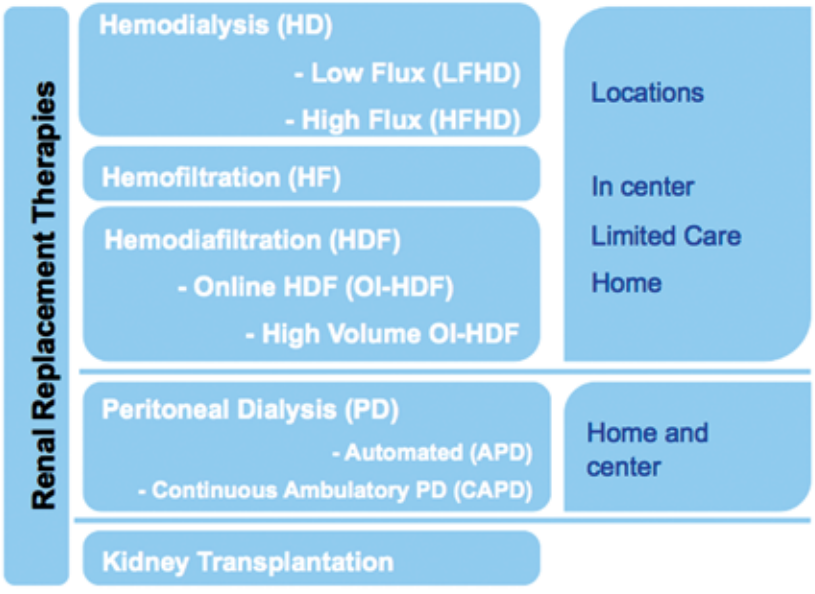
The term RRT is used to describe those treatments for ESRD where, in the absence of kidney function, the removal of waste product from the body is achieved by dialysis and other kidney functions are supplemented by drugs. It is also the term which covers the complete replacement of all kidney functions by transplantation. Patients with ESRD usually change treatment modalities during their time on RRT. They may begin with one form of dialysis, change to another and then receive a transplant; if the transplant fails they return again to dialysis. The modalities of treatment can therefore be seen as complementary (Figure 1.6).

Dialysis

Dialysis involves the cleansing or washing of the blood by the use of fluids which allow the toxic substances to leave the body by a route other than the kidneys; in addition it is possible to regulate the composition of the body fluids and the amount of water and salts in the body by altering the composition of the fluids used, and by pressure or other forms of filtration. There are various types of dialysis: hemodialysis, peritoneal dialysis, hemofiltration, hemodiafiltration. In hemodialysis, the patient's blood is pumped through the blood compartment of a dialyzer, exposing it to a partially permeable membrane. The dialyzer is composed of thousands of tiny synthetic hollow fibers. The fiber wall acts as the semipermeable membrane. Blood flows through the fibers, the dialysis solution flows around the outside of the fibers, and water and wastes move between these two solutions. The cleansed blood is then returned via the circuit back to the body. Ultrafiltration occurs by increasing the hydrostatic pressure across the dialyzer membrane. This usually is done by applying a negative pressure to the dialysate compartment of the dialyzer. This pressure gradient causes water and dissolved solutes to move from blood to dialysate, and allows the removal of several liters of excess fluid during a typical 3 to 5 hour treatment. In peritoneal dialysis, a sterile solution containing glucose is run through a tube into the peritoneal cavity, the abdominal body cavity around the intestine, where the peritoneal membrane acts as a semipermeable membrane. The peritoneal membrane or peritoneum is a layer of tissue containing blood vessels that lines and surrounds the peritoneal, or abdominal, cavity and the internal abdominal organs (stomach, spleen, liver, and intestines). The dialysate is left there for a period of time to absorb waste products, and then it is drained out through the tube and discarded. This cycle or "exchange" is normally repeated

FIGURE 1.6

RENAL REPLACEMENT THERAPIES - SPLIT AND LOCATIONS



4-5 times during the day (sometimes more often overnight with an automated system). Each time the dialysate fills and empties from the abdomen we have what is called one exchange. Dwell time is the time the dialysate stays in the patient's abdominal cavity and wastes, chemicals and extra fluid move from patient's blood to the dialysate across the peritoneum. A drain process is the process after the dwell time, when the dialysate full with waste products and extra fluid is drained out of the patient's blood. Ultra-filtration occurs via osmosis; the dialysis solution used contains a high concentration of glucose, and the resulting osmotic pressure causes fluid to move from the blood into the dialysate. As a result, more fluid is drained than was instilled. Peritoneal dialysis is less efficient than hemodialysis, but because it is carried out for a longer period of time, the net effect in terms of removal of waste products and of salt and water are similar to hemodialysis. Peritoneal dialysis is carried out at home by the patient. Although support is helpful, it is not essential. It does free patients from the routine of having to go to a dialysis clinic on a fixed schedule several times per week, and it can be done while travelling with a minimum of specialized equipment. Hemofiltration is a similar treatment to hemodialysis, but it makes use of a different principle. The blood is pumped through a dialyzer or "hemofilter" as in dialysis, but no dialysate is used. A pressure gradient is applied; as a result, water moves across the very permeable membrane rapidly, "dragging" along with it many dissolved substances, importantly the ones with large molecular weights, which are cleared less well by hemodialysis. Salts and water lost from the blood during this process are replaced with a "substitution fluid" that is infused into the extracorporeal circuit during the treatment. HDF is a term used to describe several methods of combining hemodialysis and hemofiltration in one process. HDF is the strategy enabling the high potential of hydraulic and solute permeability of synthetic membranes to be exploited at the highest level. The on-line production of unlimited amounts of sterile dialysate at a low cost has facilitaed its extensive utilization in recent years. However, to achieve the most efficient convective transport, the ultrafiltration rate must be forced towards its physical limits, while paying attention to the safety of the patient and to the integrity of the system. The infusion mode influences dialyzer performance and the efficiency of the technique. As opposed to standard and high-flux HD, increased removal of solutes in the small and middle molecular weight range was reported with on-line HDF in several recent studies. Some of these compounds have a pathogenic role or are markers of the most frequent long-term complications and causes of death in HD patients, such as dialysis related amyloidosis, cardiovascular disease, inflammation and malnutrition. Even in the absence of definite evidence, coming from large data base studies, there are strong indications to advocate for the use of this dialytic strategy, which combines the benefits of the high biocompatibility level of the membrane and the sterile dialysis fluid with an increased removal by convection of middle-molecular uremic toxins. A new mode of infusion in on-line HDF - the mixed infusion mode - is described here. This is able to achieve and maintain the maximum possible water and solute removal during the sessions through a feedback control of the trans-membrane pressure.

Renal transplantation

Renal transplantation replaces all the functions of the kidney, making erythropoietin (EPO) and vitamin D unnecessary. A single kidney is usually placed in the pelvis close to the bladder, and attached to a nearby artery and vein. The immediate problem is the body's acute rejection of the foreign graft, which has largely been overcome during the first months using drugs such as steroids and cyclosporine. These drugs and others, have many undesirable side-effects, including the acceleration of vascular diseases so that myocardial infarcts and strokes, are more common in transplant patients than in age-matched control groups. During subsequent years also, we witness a steady loss of transplanted kidneys due to a process of chronic rejection; the treatment of this is unsatisfactory and many patients require a second or even third graft over several decades, and have to rely on dialysis in the meantime. The main obstacle to a wider use of transplantation is the shortage of suitable kidneys to transplant. Although the situation could be improved, it is now clear that whatever social and medical structures

are present or legislation adopted, there is an inevitably and a significant shortage of kidneys from humans. This remains the case even if kidneys from the newly dead (cadaver kidneys) are retrieved with maximum efficiency, and living donors (usually, but not always, from close blood-relatives of the recipient) are used wherever appropriate. Experiments using animal kidneys are under-way but are still in the early stages. It will be some time before we know whether xenotransplantation, as this procedure is known, will contribute to the transplant program (1).

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2. Economic Impact of ESRD

The costs of renal replacement therapy are exceedingly high and are taking up a significant share of health care budgets. The prevalence of kidney failure worldwide continues to rise, and treatment is costly; thus, the economic burden of this illness is growing and the resources allocated to treatment are increasing. According to the U.S. Renal Data System (USRDS) Annual Report 2011, total Medicare costs in 2009 rose by 8%, to $491 billion; costs for ESRD rose by 3%, to $29 billion, accounting for 6% of the total Medicare budget. ESRD data for 2009, however, do not include Part D (costs of drugs), which amounted to $2 billion in 2008. In 2009, 38% of Medicare's ESRD dollars were spent on in-patient care, 35% on outpatient care and 21% on physician/supplier costs. After rising by 11% between 2007-2008, total Medicare expenditure for hemodialysis and transplant rose by 0.2% and 0.4% in 2009, to $21 billion and $2 billion, while costs for peritoneal dialysis fell by 3%, to $1 billion. Costs fell by less than 1% per person per year across modalities, to $82 285 for hemodialysis, $61 588 for peritoneal dialysis and $29 983 for transplant (13). Berger et al. compared healthcare costs in patients with ESRD beginning peritoneal dialysis (PD) or hemodialysis (HD), using a U.S. health insurance database in a retrospective cohort study. The median (IQR – indicates interquartile range) total per-patient healthcare costs were $43 510 higher among HD patients than among PD patients over 12 months ($173 507 vs. $129 997 P = 0.03). The median (IQR) per-patient inpatient costs were $39 851 for HD patients vs. $651 for PD patients (P <0.01); the corresponding values for other services were $73 392 vs. $70 642 for outpatient office visits (P = 0.53), $360 vs. $200 for Emergency Department (ED) visits (P = 0.29), $2 454 vs. $2 750 for outpatient (i.e. retail) pharmacy (P = 0.28), and $14 097 vs. $16 229 for all other services (P = 0.47). The difference in the total per-patient healthcare costs over 12 months was $80 709 (mean [95% CI], $263 001 vs. $182 292; (P = 0.04). The mean (95% CI) per-patient inpatient costs were $140 633 for HD patients and $79 175 for PD patients (P = 0.08); the corresponding values for other services were $81 046 versus $70 798 for outpatient visits (P = 0.48), $1 395 versus $848 for ED visits (P = 0.27), $4 196 vs. $6 679 for outpatient pharmacy (P = 0.15), and $35 731 versus $24 792 for all other services (P = 0.17) (14). In Canada, Lee et al. prospectively followed 166 dialysis patients to develop a description of costs and the resources required to treat ESRD patients on dialysis and to contrast differences in terms of resources required for various dialysis modalities. The study took the perspective of the health care purchaser. Overall annual costs of care in US dollars for in-center HD, satellite HD, home/selfcare HD and PD were $51 252, $42 057, $29 961 and $26 959 respectively (p < 0.001) (15). Icks et al. presented costs of dialysis in Germany from the perspective of the statutory health insurance, based on patient-level data in a population-based sample. The mean total dialysis-related cost in 2006 was 54 777 Euros (95% CI, 51 445-65 705) per patient year. The largest part of the costs (55%) was caused by the dialysis procedures, followed by the costs of medication (22%), hospitalization (14%) and transportation (8%). The total cost increased significantly with increasing age (16). In UK, Baboolal et al. used a mixing costing method to evaluate the cost of renal dialysis. The mean total annual cost of delivering automated PD (APD) or continuous ambulatory PD (CAPD) was substantially lower than that for HD. The annual maintenance costs for patients undergoing APD and CAPD were £21 655 and £15 570, respectively, compared with £35 023 and £32 669 for hospital-based HD and standard HD (SHD), respectively. The cost of home HD (HHD) for three sessions a week was £20 764 per year, which appears to be significantly cheaper than hospital-based HD. The main cost drivers for PD were the costs of solutions and management of anemia. For HD they were the costs of disposables, nursing, the overheads associated with running the unit and managing anemia (17). The Italian Research Institute Censis recently estimated the socio-economic costs of dialysis treatment. According to the website of the Italian Society of Nephrology in Italy there are 954 healthcare structures that provide dialysis treatment, amounting to 12 995 dialysis stations and 2 782 hospital beds for nephrology, equalling a number of 221 dialysis posts per million inhabitants and 49 nephrology hospital beds pmp. The distribution of these structures in the country

is variable. About 47% of dialysis structures and dialysis stations are present in the South (35% of Italian population), and most of them (55%) are located in the private sector. The second offering is in the North West (26% of the population), with 20% of the structures and the dialysis posts, 92% of which belong to the public sector, followed by the Centre (19% of the population), with the 19% of the structures and dialysis stations, 75% of which in the public sector. Lastly, there is the North East (19% of the population), with 14% of the structures and dialysis stations, 99% of which in the public sector. Overall, in Italy the supply of dialysis posts can be broken down as follows: 66% for the public sector and 32% in the private sector. The Censis study was conducted in 4 Italian regions, 2 in the North (Lombardy and Piedmont), 1 in the Centre (Lazio) and 1 in the South (Puglia) with the aim of representing the costs incurred by structures that provide dialysis. Attention was focused on the analysis of the unit cost of each treatment and results in terms of cost-effectiveness have allowed us to observe that as to direct costs, peritoneal dialysis (peritoneal dialysis, automated and continuous ambulatory peritoneal dialysis with a target around 15%-20%) is cheaper than extracorporeal dialysis. The components that contribute mostly to the cost formation for extracorporeal dialysis techniques are the costs for staff and service contracts; the latter having a significant impact on peritoneal methods as well, for which, however, the cost of staff is obviously less significant (Table 2.1).

Indirect costs are much higher for extracorporeal dialysis compared to peritoneal and transportation costs are particularly onerous in this category. An analysis of overall economic costs (direct costs + indirect costs) was carried out on a normal week-long course of treatment considering the high number of different parameters necessary to ensure the care of patients on dialysis (3 treatments a week were considered for patients receiving extracorporeal dialysis and 7 for those receiving peritoneal dialysis). This allowed us to state that the Continuous Ambulatory Peritoneal Dialysis (CAPD - 54.98.2) technique is, in general, less burdensome for health-care budgets (the cost estimated is in fact equal to € 490.77), followed by bicarbonate (and acetate) hemodialysis in limited-care units (HD-CAL - 39.95.2), with an estimated cost of € 588.96 per week. The social costs, basically constructed from hours lost by patients or their caregivers to undergo any treatment, are globally rather similar to those of the extracorporeal methods and CAPD, if in the first case, we consider the time transfers take to go to the center three times a week and in the second, the daily exchange that, even if carried out at home, is not negligible (Table 2.2). In this respect, the method that turns out to be less expensive is indeed automated peritoneal dialysis, which is carried out at night: the patient can rest during night therapy and the number of working hours lost is almost irrelevant. For this reason, and from the calculation of the total cost for week of therapy, APD emerges as the least expensive

TABLE 2.1

DIRECT COSTS FOR TREATMENT, THE AVERAGE OF THE FOUR ITALIAN REGIONS (AVERAGE VALUES IN EUROS)

	STAFF	MAINTENANCE	MATERIALS	EQUIPMENT (NOT IN SERVICE)	SERVICE	DRUGS*	TESTS	TOTAL DIRECT COSTS
HD	83.87	1.23	15.52	5.39	29.96	25.00	5.45	166.42
HD-Limited Care	44.73	1.71	.	1.28	40.02	20.96	-	118.70
HD-b	87.96	2.30	4.76	2.59	43.22	21.34	5.71	167.88
HDF	85.15	2.71	1.26	3.80	79.39	22.87	5.95	217.14
HDF-Limited Care	42.38	1.26	-	11.84	76.71	24.63	1.53	149.83
HDF-b	87.82	0.47	0.39	1.17	81.21	22.52	5.58	199.15
HF	88.11	2.39	2.45	4.37	86.44	26.99	5.95	234.70
APD	15.35	-	-	-	48.46	5.39	2.46	71.66
CAPD	15.50	-	-	-	30.65	6.68	2.47	55.30

* The cost of drugs is subject to significant variations in different regions under different mechanisms of delivery and redemption especially in relation to EPO, Source: Italian Research Institute Censis Report, 2009
HD-b (HD and biocompatible membranes)

TABLE 2.2

INDIRECT COSTS, ECONOMIC AND SOCIAL TREATMENT AND ECONOMIC COSTS AND TOTAL WEEKS OF TREATMENT, THE AVERAGE OF THE FOUR ITALIAN REGIONS (AVERAGE VALUES IN EUROS)

	TRANSPORT SERVICES	HOTEL SERVICES	GENERAL SERVICES	TOTAL INDIRECT COSTS FOR TREATMENT	TOTAL ECONOMIC COSTS PER TREATMENT (DIRECT + INDIRECT)	SOCIAL COSTS FOR TREATMENT	TOTAL ECONOMIC COSTS PER WEEK OF TREATMENT *	TOTAL ECONOMIC AND SOCIAL COSTS OF TREATMENT PER WEEK
HD	17.06	20.00	14.33	51.39	217.81	98.73	653.43	949.61
HD-Satellite Unit	24.04	17.70	35.88	77.62	196.32	98.73	588.96	885.14
HD-b	21.84	18.66	14.86	55.36	223.25	98.73	669.75	965.92
HDF	18.31	18.15	15.27	51.73	268.87	98.73	806.61	1,102.78
HDF-Satellite Unit	20.60	19.84	29.02	69.46	219.29	98.73	657.87	954.05
HDF-b	16.95	22.32	14.94	54.21	253.36	98.73	760.08	1,056.27
HF	20.29	20.47	16.01	56.77	291.47	98.73	874.41	1,170.60
APD	1.24	6.93	7.70	15.87	87.53	0.73	612.71	617.81
CAPD	1.24	6.93	7.24	14.81	70.11	40.64	490.77	775.27

* The techniques are performed in the hospital and CAL 3 times a week, those at home all day
Source: Italian Research Institute Censis Report, 2009

treatment of all (equal to € 617.81) (18).

In the lifecycle of RRT patients, home peritoneal dialysis is beneficial but can last until the peritoneum membrane can fulfil the osmotic function. **After 2-3 years, the patients, unless transplanted, have to switch to extracorporeal HD techniques** to continue living.

Therefore PD is limited in time and targets on average 15-20% of ESRD population only.

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3. Social Impact of ESRD

Patients with ESRD have a compromised Health-Related Quality of Life (HRQoL) and the burden of various other clinical problems. The association of HRQoL with mortality and morbidity in ESRD patients has given rise to the need of evaluating this impairment. Measuring HRQoL, following various interventions in ESRD treatment regimens, is increasingly being accepted and numerous studies and reviews have addressed this issue, using a variety of tools and instruments to assess the degree of impairment. Thong et al. have shown that a Self-rated health (SRH) item is an independent predictor of mortality in a large sample of incident patients with ESRD. Mapes et al. investigated whether indicators of HRQoL, assessed with Kidney Disease Quality of Life Short Form (KDQoL-SF), may predict the risk of death and hospitalization among the hemodialysis patients treated. The results of the study showed a highly significant association between lower HRQoL scores and higher risk of death and hospitalization. The KDQoL-SF physical component summary (PCS) score was the component most strongly associated with death and hospitalization. For each 10-point lower HRQoL score, the mortality risk (stratified by country and diabetes and adjusted) increased by 25% for the PCS, by 13% for the mental component score (MCS) and by 11% for the kidney disease component summary (KDCS). As to hospitalization, the adjusted RR values for each 10-point level HRQoL score were 1.15 for PCS, 1.06 for MCS and 1.07 for KDSC. Unruh et al. examined if the therapy under study affected physical functioning, vitality, Short Form-36 Health Survey (SF-36) physical and mental component summary scores, symptoms and problems associated with kidney disease, and sleep quality. The study suggested minimally significant changes in HRQoL measurements if the dialysis dose (Kt/V 1.45 vs. 1.05) of HD patients was increased or if high flux membranes were used, when utilizing the Index of Well-Being and the Kidney Disease Quality of Life-Long Form questionnaires. By using a Propensity Score (PS) analysis Kutner et al. investigated if there were differences in the quality of life of incident patients starting on HD or PD. The results showed that one year scores for the majority of health status and quality of life measures were not significantly different for HD and PD patients. Additionally, Albert et al. compared self-reported HRQoL and overall health status for HD and PD patients at the beginning of dialysis therapy and 1 year later. The findings suggest that there is no simple answer to the question of which dialysis modality can be expected to provide a better quality of life.

One year after starting dialysis, patients on both HD and PD reported improvements in nearly all aspects of general functioning and psychological well-being. The major difference with PD and HD modalities seem to be in the degree of satisfaction with the therapy: PD patients generally reporting greater satisfaction and a less negative impact of the therapy (19-37). This study showed a greater satisfaction of PD patients with their therapy. Furthermore PD patients believed that their treatment had a lower impact on their lives than HD patients. A few studies, some preliminary, suggested that treatment of anemia, selected modifications in the dialysis treatment regimen, treatment of depression and exercise programs have resulted in improved HRQoL assessments. Treatment of sleep disturbances and pain may also have a positive effect. Many studies have evaluated the relationship between anemia and HRQoL. A review by Leaf et al. concluded that erythropoietin therapy provided a significant improvement in various HRQoL domains. In studies using the Short Form (SF-36) Health Survey domains, the most dramatic improvements were noted in physical symptoms, vitality, energy, and performance. Smaller improvements were noted in social functioning and mental health, while little, if any, improvement was observed in emotional health or pain relief.

Additional sectors of health showing possible improvements with erythropoietin therapy include sleep, cognitive functioning, and sexual functioning. One of the principal changes in patient-reported outcome is recovery time after a dialysis session. Linsday et al. reported a dramatic decrease in recovery time for patients treated with more frequent dialysis compared to the conventional HD 3

times per week. This change strongly correlates with improvement in various HRQoL domains. Preliminary data of a FREEDOM study suggest an improvement in many HRQoL domains with a 6 times per week home HD: a significant decrease in Back Depression Inventory scores, an increase in physical and mental components of SF-36 and a dramatic reduction in recovery time after a dialysis session. More frequent HD also impacts another domain associated with impaired HRQoL: sleep difficulties. Hanly et al. showed that converting patients from conventional 3 times per week HD to nocturnal 6 or 7 times per week HD lead to a reduction in the frequency of apnea and hypopnea from 25 to 8 episodes per hour of sleep. Patients on on-line HDF experience fewer side effects, feel more energetic, have a better appetite (and are consequently better nourished and require less erythropoietin) and sleep better at night. All these secondary aspects result in a significant improvement in the QoL as perceived by the patient. About 25-30% of ESRD patients have a diagnosis of clinical depression. The presence of depressive symptoms is associated with increased morbidity and mortality and with reduced HRQoL. A structural exercise program may also have a beneficial effect on HRQoL in CKD patients. Exercise programs can improve the reduced physical functioning of CKD patients, which in turn can result in an improvement of various HRQoL parameters. Chronic pain is common for patient with ESRD, and significantly impacts HRQoL (38-62).

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4. Effectiveness of on-line HDF

The uremic syndrome encompasses a constellation of symptoms and metabolic derangements and is attributed to the retention in the body of a large number of compounds which are normally excreted by healthy kidneys and can be toxic per se or only at the high concentration found in uremia. These compounds are called uremic toxins when they interact negatively with biologic functions. Knowledge of the dependence of uremic abnormalities on specific toxic solute concentrations is still incomplete, so it is difficult at this time to define the precise role of all compounds in uremic derangements. However, a systematic classification of uremic solutes has been compiled by the European Uremic Toxin Work Group (EUTox) according to their characteristics, molecular weight and/or electro-chemical binding, which potentially influence their removal pattern during dialysis (63, 64). Three main physico-chemicals group of uremic toxins have been recognized: 1) free water-soluble low-molecular-weight solutes (MW<500 D), such as urea, creatinine, uric acid and several guanidine compounds; 2) middle-molecular solutes, (MW>500 D up to 30 kD), among which several peptides such as β_2-Microglobulin, myoglobin, cystatin C, clara cell protein 16, retinol-binding protein and cytokines as interleukins and Tumor Necrosis Factor α are included; 3) protein-bound solutes, mostly characterized by a MW<500 D, such as pentosidine, homocysteine, hippuric acid, p-cresylate, indoxyl sulphate, and others.

Free water-soluble low-molecular-weight solutes

Urea (MW 60 D) is a recognized marker of this category of toxins for its biological and metabolic characteristics and the ease with which it is detected and measured in blood. The fractional excretion index of urea removal during dialysis (Kt/V) has become the most used index of the adequacy of dialysis treatment (65). Removal of urea and of all free small molecular-weight solutes mainly occurs by diffusion and, thus, is very effective during low-and high-flux HD. However, online HDF has been shown to further increase urea and creatinine removal, and higher Kt/V urea has been reported for HDF treatment compared to HD at matched treatment duration and operational conditions. The Phosphate (P) molecule falls into the category of water-soluble low-molecular weight toxins (MW 96 D) but, for its hydrophilic characteristics, is surrounded by an aqueous cover which considerably increases its effective molecular weight. Moreover, P is mainly distributed within cells and is not freely diffusible into the extracellular space. For these reasons its elimination characteristics are different from those of urea and other small-molecular weight toxins and its intradialytic kinetics is more similar to that typical of middle molecules (66-72).

HDF as compared to standard HD has been shown to increase P removal during single treatment sessions and to establish a lower basal level in the medium-long term. This was demonstrated in several controlled studies and in large data base observational experiences (71, 73-77).

Middle-molecular solutes

Beta$_2$-Microglobulin (β_2-M, 11 800 D) has been recognized as the most suitable marker of middle molecular uremic toxins of similar molecular weight by the European Best Practice Guidelines Expert Group. Its pre-dialysis level was shown to predict mortality in the randomized Hemodialysis Study (HEMO) and in a Japanese prospective trial (78-80). It has been demonstrated that β_2-M removal is greater during a session of HDF than on low-flux and high-flux HD (67-69, 81). On HDF, β_2-M removal correlates with the convection volume of the session (66, 69). While β_2-M basal level is reported to progressively increase with time in chronic patients on RRT with low-flux HD, observational and randomized studies have shown that the β_2-M level remains stable (82) or may be reduced (83) in patients on high-flux HD, and even significantly decreases with time in patients switched to on-line HDF (66, 71, 83) or HF (84, 85). This effect is most pronounced when residual renal function is absent (86). Besides β_2-M, other uremic compounds of the larger molecular spectrum were removed to a greater extent in HDF

with all the available highly permeable and biocompatible membranes. This was shown for myoglobin (17 kD) (67), factor D (24 kD) (70, 84) a complement fraction abnormally high in patients with renal failure, and other complement fractions, such as fraction Ba (33 kDa) (87), C3a (9 kD) and C5a (11 kD) (88). On-line HDF has also been associated with increased removal and/or reduced production of pro-inflammatory cytokines such TNF-a (17 kD) (89, 90), interleukins 1-6-8 (17 kD) (89-93) and proinflammatory CDl4+/CD16+ cells (89), and with the improvement of variables related to endothelial dysfunction (94), oxidative stress, and antioxidant capacity (95, 96). Moreover, two randomized crossover studies demonstrated a potent effect of high-flux membranes on lipoprotein and lipid profiles (97) and a significant reduction in triglycerides and increase in high-density lipoprotein concentrations as a long-term effect of on-line HDF with high-flux membranes, which was not shown with standard HD (71).

Protein-bound solutes

During dialysis protein-bound solutes follow a multicompartmental kinetics similar to that of the middle molecules in spite of their generally low molecular weight, as a possible consequence of their protein-binding and metabolic transformation. A substantial part of the removal of these compounds occurs by diffusion. As such, pentosidine (MW 379 D) was removed to a similar extent (70%) with low-flux and high-flux membranes and long-term lower basal levels were only observed in patients on high-flux polysulfone, possibly as a consequence of a reduced oxidative stress promoted by this membrane (98). On the contrary, high-flux and low-flux polysulfone resulted having a similar plasma level of homocysteine (135 D) in a 3-month longitudinal study, despite the greater removal per session obtained with the high-flux membrane (99). More recently, observational and randomized controlled studies have shown that both standard HDF and on-line HDF applied in the long term were able to reduce homocysteine level to a greater extent than low-flux HD (71, 84, 100, 101). Variable reduction ratios have been reported for asymmetric dimethylarginine (ADMA, 202 D) during low-flux HD and HDF, but without a significant long-term change in its basal level with both techniques (71, 84, 100). Convection was shown to positively impact protein-bound toxin removal because HDF was able to increase p-cresol clearance without leading to excessive albumin loss (102). Similar removal (40% to 50%) of p-cresyl sulphate (MW 187 D, protein-binding ±95%) and indoxyl sulphate (MW 212 D, protein-binding ±90%) was reported during HD and HDF sessions with high-flux membranes (103,104). On HDF, removal of different solutes was inversely proportional to the percentage of protein binding and ranging from 4% in the case of carboxy-methyl-propyl-furanpropanoic acid (CMPF, MW 240 D, protein binding ±100%) to 74% in the case of hippuric acid (MW 179 D, protein binding ±50%) (105). A clear effect of flux on such compounds, as well as on homocysteine, was shown with the use of large pore “superflux” polysulfone and triacetate cellulose membranes (106, 107) at the expense, however, of having significant albumin loss. The longitudinal application of online post-HDF was recently shown to result in a consistent and progressive decline of the basal level of some protein-bound uremic solutes, particularly those with the strongest protein binding (p-cresylsulfate and CMPF), and this effect was not observed in the patient group on high-flux HD (108).

CLINICAL EFFECTS

Several protein-bound and middle-molecular solutes have a pathogenic role or are markers of the most frequent long-term complications and causes of death in HD patients. Data from a number of clinical studies suggest that the use of online HDF may be associated with an enhanced removal and reduced basal levels of these compounds that might be of relevance in the pathogenesis of uremic and cardiovascular complications. So, online HDF may promote a whole array of potential beneficial effects which individually are believed to improve clinical outcome. β_2-Microglobulin accumulation and oxidation is retained as the main cause of dialysis related amyloidosis. A lower basal β_2-M level, established in patients treated for a long time with high-flux membranes and on-line HDF, not only resulted in a lower incidence and progression of this invalidating systemic disease (109-111) but, outstandingly, has been associated to a significant lower risk of mortality in HD patients, independent of

treatment duration, diabetes, malnutrition and chronic inflammation (79, 80). Additionally, a lower phosphate level achieved in patients on long-term convective treatments (71, 73, 76, 77) supported by appropriate pharmacological therapy may help prevent the progression of mineral metabolic disorders caused by secondary hyperparathyroidism (71), and of the accelerated atheroarteriosclerotic lesions which are the main cause of morbidity and mortality in uremic patients. Indeed, the phosphate level has been associated with mortality in several authoritative studies (112, 113). Thus, on-line HDF may lead, with time, to a potentially improved outcome, given that the amount of β_2-M and phosphate removal is greater than in high-flux therapy and leads, in time, to lower basal levels of these uremic toxins. Several protein-bound solutes have been found to be toxic in vitro (114-116), and some of them have also been associated with adverse outcomes in dialysis patients, such as atherosclerosis (117), cardiovascular disease (118), infectious disease (119), and neurological abnormalities (120). In particular, the free p-cresol serum concentration is a predictor of general mortality in the HD patient group (121). P-cresyl sulfate, the main in vivo metabolite of p-cresol, promotes vascular disease in uremia as a consequence of its pro-inflammatory effect on unstimulated leucocytes. This leads to oxidative stress and, consequently, atherosclerosis (116). Since, convective strategies can result in significantly reduced plasma levels in these protein-bound compounds (102, 105), they may be beneficial for patient outcome. Both uncontrolled and randomized studies have reported decreased erythropoietin resistance and a lower need for its administration in patients treated with online HDF (71, 77, 122, 123), possibly as an effect of the increased removal of middle molecular inhibitors of erithropoiesis (124, 125).

In this respect, aided by the use of ultrapure dialysis fluid, Online HDF may play a role in the control of anemia in uremic patients by creating a more biocompatible environment with fewer toxic and inflammatory stimuli. Intradialytic hypotension is frequently observed during HD and is associated with regional wall motion abnormalities of the left ventricle and myocardial stunning (126). Repeated episodes can contribute to myocardial damage and cardiomyopathy. On-line HDF and HF have been associated with improved haemodynamic stability and blood pressure control in some studies (127-129), but not in others (130). However, this effect, rather than to a greater removal of unknown hypertensive factors, seems mainly due to the large amount of cooler substitution fluid infused in on-line HDF which causes thermal energy loss within the extracorporeal system and so avoids vasodilatation caused by heat accumulation (131).

EFFECTS ON OUTCOME

The hypothesis that the enhanced removal of larger solutes obtained with high-flux membranes may result in improved hard clinical end-points, has been confirmed in a number of observational studies, and in two large data-base randomized trials. The **HEMO study** showed no difference in survival between low- and high-flux HD in the overall study population. However, a reduced rate of death for cardiac causes or cerebrovascular disease in patients treated with high-flux membranes, as well as **longer survival** in patients undergoing high-flux HD **for >3.7 years** were observed in post hoc subgroups analyses. Moreover in a Kaplan-Meier survival analysis, patients in the predominant HDF group had significantly better survival figures compared with those of the predominant high-flux HD group ($P < 0.001$). Median survival was 3.4 yr (95% confidence interval [CI] 3.0 to 3.8) for those who were on predominantly high-flux HD and 7.2 yr (95% CI 6.1 to 8.3) for those who were on predominantly HDF (132-134).

Similarly, a primary analysis of the **European Membrane Permeability Outcome (MPO) study** showed improved survival of high-flux HD in patients with albumin level ≤ 4 g/dL and of diabetic patients in a secondary analysis (82). Moreover, a post-hoc analysis of the German 4D study and a large observational French study (135-136) showed greater survival in patients treated with high-flux as compared to low-flux HD. The evaluation of the impact of HDF on hard clinical end points is still underway. However, available evidence suggests a definite benefit from convective treatments as compared to low- and high-flux HD. A small Italian randomized study showed better survival in patients on HF compared to low-flux HD over a 3-year period (85).

Some observational and registry studies reported similar findings: in a retrospective analysis of the European Dialysis Outcomes and

Practice Patterns Study **(DOPPS)**, Canaud et al. reported a significant **35% lower mortality risk** in patients on high-efficiency HDF (volume exchange 15-25 litre per session), compared to low- and high-flux HD (137).

In a **British study** by Vilar *et al.* a **reduced hazard of death of 0.66** was reported in 232 patients who were treated solely by HDF compared with 637 patients who solely used high-flux HD (138).

In the **RISCAVID** prospective study a survival benefit was associated with online HDF over standard HD; however, only 5% of the HD population used high-flux membranes (93). Jirka et al. also reported similar results from data collected through the **EuCliD® network** with a **mortality reduction of 35%** compared with an HD group (139).

What proportion of the HD group used high-flux membranes was not specified. In conclusion, medium-long-term application of on-line high-efficiency HDF compared to low- and high-flux HD results in enhanced removal and lower basal levels of small, medium and protein-bound uremic solutes, some of which are retained as markers or causative agents of several uremic derangements, mainly inflammation, secondary hyperparathyroidism, dyslipidemia and cardiovascular disease.

Probably, many of the benefits attributed to HDF potentially result from a general reduction of uremic toxicity. This might be the link with the clinical benefits reported in patients undergoing chronic HDF which eventually contributes to improving patient survival, as suggested by published observational studies.

ON-LINE HDF AS TREATMENT MODALITY

The percentage of patients with ESRD on HDF therapies was around 5% worldwide in 2010 (around 90 400 patients), slightly higher if compared to 2009. The utilization of HDF as a treatment modality is quite varied in the various regions. Comparing the ratio of HDF patients in a region in relation to the total number of HD patients, Central (17%), Western (18%) and Northern Europe (24%) were the most relevant HDF regions in the world, while Eastern Europe had a share of 10% HDF patients. The regional percentage value increased in Central Europe (from 15% in 2009 to 17% in 2010), Western Europe (from 15% to 18%), Northern Europe (from 22% to 24%) and Eastern Europe (from 9% to 10%). On-line HDF was by far the predominant HDF therapy, representing over 90% of the global HDF patient population in 2010 (Table 4.1).

Table 4.2 illustrates the key HDF countries in which HDF patients account for more than 13% of all HD patients. Treating 67% of all its HD patients with HDF, Switzerland remains at the top among European countries. The country was able to even increase its share of HDF patients by 5 percentage points while Slovenia massively increased its HDF patient share to around 65% as well.

With regard to absolute numbers in the EMEA region, Germany and Italy are the countries with the largest HDF patient populations, with respectively 9 800 and 7 640. What becomes obvious is that within the top 15 EMEA countries with the largest HDF populations only two countries have considerable numbers of patients

TABLE 4.1

DISTRIBUTION OF HD AND HDF PATIENTS IN 2010

	NUMBER OF HD PATIENTS	NUMBER OF HD PATIENTS ON HDF MODALITIES	% OF HD PATIENTS ON HDF MODALITIES	NUMBER OF HD PATIENTS ON ON-LINE HDF
Central Europe	95 700	15 900	17%	15 900
Western Europe	140 600	24 800	18%	22 500
Northern Europe	9 500	2 240	24%	2 240
Eastern Europe	142 500	14 500	10%	13 200
Total Europe	**388 300**	**57 440**	**15%**	**53 840**
Total including RoW	1 810 000	90 400	5%	82 000

Source: On-line Hemodiafiltration: The Journey and the Vision. Sichart JM, Moeller S, 2011 (140)

TABLE 4.2

DISTRIBUTION OF HDF PATIENTS IN THE EUROPEAN COUNTRIES WITH LARGEST RELATIVE HDF POPULATIONS IN 2010

COUNTRY	NUMBER OF HD PATIENTS	TOTAL NUMBER OF PATIENTS ON HDF MODALITIES	% OF PATIENTS ON HDF MODALITIES
Switzerland	2 980	2 000	67%
Slovenia	1 380	910	65%
Slovakia	2 880	1 580	55%
Portugal	9 940	4 780	48%
Hungary	5 500	2 300	42%
Czech Republic	5 350	1 760	33%
Finland	1 520	470	31%
Belgium	6 750	2 040	30%
Greece	8 930	2 630	29%
Sweden	2 930	810	28%
Austria	3 960	1 070	27%
Serbia	4 190	1 060	25%
Norway	990	250	25%
Denmark	2 030	400	20%
Netherlands	5 160	1 000	19%
Spain	21 700	3 900	18%
Italy	46 600	7 640	16%
United Kingdom	24 100	3 430	14%
France	36 800	4 950	13%
Germany	76 600	9 800	13%

Source: On-line Hemodiafiltration: The Journey and the Vision. Sichart JM, Moeller S, 2011 (140)

TABLE 4.3

DISTRIBUTION OF CONVENTIONAL AND ON-LINE HDF PATIENTS IN THE EUROPEAN COUNTRIES WITH LARGEST HDF POPULATIONS IN 2010

	TOTAL NUMBER OF PATIENTS ON HDF MODALITIES	% OF PATIENTS ON CONVENTIONAL HDF	% OF PATIENTS ON ON-LINE HDF
Germany	9 800		100
Italy	7 640	25	75
France	4 950		100
Portugal	4 780		100
Spain	3 900	5	95
United Kingdom	3 430		100
Greece	2 630	50	50
Hungary	2 300		100
Belgium	2 040		100
Switzerland	2 000		100
Czech Republic	1 760		100
Slovakia	1 580		100
Turkey	1 410		100
Austria	1 070		100
Serbia	1 060		100

Source: On-line Hemodiafiltration: The Journey and the Vision. Sichart JM, Moeller S, 2011 (140)

TABLE 4.4

GROWTH OF HDF PATIENTS FROM 2004 TO 2010

HDF PATIENTS	2004	2005	2006	2007	2008	2009	2010	% 2004-2007	% 2007-2010	% 2004-2010
Global Total	43 590	46 920	50 290	59 130	65 880	77 350	90 430	11%	15%	13%
EMEA Total	25 120	27 740	28 860	36 470	43 410	50 050	59 440	13%	18%	15%

Source: On-line Hemodiafiltration: The Journey and the Vision. Sichart JM, Moeller S, 2011 (140)

on conventional HDF (Italy and Greece). As a result the predominant HDF treatment mode within EMEA is on-line HDF with a share of over 94% of all HDF patients (Table 4.3).

Observing the development of HDF patient numbers on a global scale between 2004 and 2010, the number of HDF patients increased by around 13% every year. While between 2004 and 2007 the average growth was around 11% every year, while there was a reported growth of around 15% every year between 2007 and 2010.

The two HDF modalities have shown opposite trends. While on-line HDF patient numbers have strongly increased over the last seven years at a rate of around 20% per annum, the number of patients treated with conventional HDF decreased by around 11% every year. So on-line HDF patient numbers increased in this time from around 27 000 patients to around 82 000 patients. In the meantime patient numbers treated with conventional HDF dropped from almost 17 000 patients in 2004 down to around 8 500 in 2010 (140).

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5. Organizational Issues of on-line HDF

Hemodiafiltration (HDF) is an established treatment modality that is getting increasingly popular since it now offers an optimal and affordable form of renal replacement therapy in chronic renal disease patients. The online production of substitution fluid by "cold sterilization" (ultra-filtration) of dialysis fluid gives access to virtually unlimited amounts of sterile and nonpyrogenic intravenous-grade solution.

The incorporation of the online HDF module into the dialysis proportioning machine hardware is beneficial: first, it simplifies the handling procedure compared to bag use; second, it secures the process by enslaving the infusion module to the safety regulation of the HDF monitor; third, it allows practitioners to regularly check the physical integrity of the ultra-filters by means of a built-in air pressure test.

TECHNICAL REQUISITES AND HYGIENE HANDLING

The safety of Online HDF relies upon strict and permanent conditions of use and handling. Compliance with guidelines is the only way to prevent adverse effects and to guarantee the success of the Online HDF program. The use of ultrapure water (UPW) to feed the HDF machine is a basic requirement for ol-HDF. Several studies have updated our knowledge of the water treatment system required. UPW is a high-grade quality water which has been developed mainly to satisfy the needs of the semiconductor industry. For HDF purposes, UPW refers to reverse-osmosis-treated water (one or more stages of reverse osmosis in series) with a resistivity in the range of 0.1–5.0 MΩ/cm with a very low level of bacterial and endotoxin contamination, i.e. < 100 CFU/l and endotoxin Limulus amebocytelysate (LAL) < 0.03 endotoxin units (EU)/ml. The production and distribution of UPW to HDF machines may take place with several water treatment options. Distribution pipes must be adequately designed to prevent stagnation, to eliminate dead ends and other recontamination sites. Permanent recirculation of treated water through a closed loop circuit with a microfiltration system is required when a buffer tank is used. The use of specifically designed HDF and European-Community-certified machines is necessary.

Several certified Online HDF machines are presently available on the European market. Basically, these Online HDF machines share common features that include an infusion pump with a flow-measuring system, a dialysate ultrafilter module (usually two certified ultrafilters in series) placed onto the hydraulic circuit of the machine and an enslaving system feedback control by the machine alarm detection system. The infusate module is a captive part of the machine which is disinfected simultaneously with each process of the HDF machine. In some machines, a built-in pressure test (bubble point) is performed periodically by the HDF monitor to check the integrity of the ultrafilter membrane.

The infusate module consists in an adjustable pump running up to 200 ml/min with a counter calculating the total amount of fluid infused into the patient. The safety of the infusion module is linked to the general warning system of the HDF monitoring apparatus. Ultrapure dialysate flowing into the dialysate compartment of the hemodiafilter is produced through an ultrafilter (UF1) placed just at the exit site of the dialysate.

A fraction of the fresh dialysate (100/800 ml/min) produced by the proportioning HDF system is diverted by the infusion pump and infused into the blood of the patient (either postfilter or prefilter infusion). The ultra-purity of the infusate is then secured by a second-stage ultra-filtration (UF2) before it is infused into the patient. In this configuration, infusate flow diverted from the inlet dialysate is compensated by an equivalent ultrafiltration flow taken from the patient through the hemodiafilter within the fluid balancing chamber. Ultrafilters are an integral part of the HDF machine that are disinfected after each run and changed periodically.

Online cold sterilization of biological fluids is based on a membrane filtration process (ultrafilter). However, it is important to recall that the retentive capacity of an ultrafilter is restricted to certain conditions of use. The use of UPW, sterile electrolyte concentrates and frequent disinfection of the HDF machine

reducing the bacterial contamination level are basic requirements to prevent ultrafilter bacterial overflow. Hygiene handling is a crucial measure to ensure the HDF system is permanently safe. Measures needed to maintain the bacterial contamination at a low level have two targets: one is to maintain the ultrapurity of water feeding the HDF machines by means of a frequent disinfection of the water treatment system, a destruction of biofilm by chemical agents and/or thermochemical disinfection, by changing filters and disposable tubings at regular intervals and by a permanent recirculation of UPW in the distribution system; the other is to prevent recontamination and bacterial proliferation in the HDF machine by means of frequent disinfection, use of sterile liquid concentrate or powder and periodical changes of the ultrafilters. Quality monitoring of the dialysate and the infusate is mandatory to detect early microbiological contamination of the system. The microbiological inventory of water, dialysate and infusate should be performed according to best practice guidelines and pharmacopeia regulations. Sampling methods, culture media and sensitive microbiological methods have been validated and published elsewhere. Endotoxin content (infusate and dialysate) should be assessed using a sensitive LAL assay with a threshold detection limit of 0.03 EU/ml. Information concerning microbiological monitoring must be stored to prove the quality of treatment. Such rules must be considered as a part of the good medical practices for ol-HDF.

BEST CLINICAL PRACTICES

Vascular Access

Patients treated with Online HDF require an access capable of delivering an extracorporeal blood flow of at least 350 ml/min, and preferably higher, on a reliable basis. High blood rate facilitates the ultrafiltration flow and reduces the transmembrane pressure (TMP) problems during the session.

Hemodiafilter

A high-flux, high-efficiency dialyzer is required. The membrane must have a high hydraulic permeability (ultrafiltration coefficient K_{UF} > 50 ml/h/mm Hg), high solute permeability (mass transfer-area coefficient K_oA urea > 600 and β_2-Microglobulin > 60 ml/min) and large surface of exchange (1.50-2.10 m^2).

Prescription and Substitution Fluid Volume per Session

The conventional Online HDF treatment schedule is based on 3 dialysis sessions lasting 4 hours each per week (12 h/week). In this relatively short treatment time, it is of paramount importance to ensure high blood flows (400 ml/min) coupled with high dialysate and/or infusate flow rates in order to optimize solute exchange. By increasing the frequency and/or duration of HDF sessions, it is also possible to achieve a more physiological and more effective treatment.

Follow-Up and Monitoring of Patients Treated with On-line Hemodiafiltration

Follow-up and monitoring of ol-HDF-treated patients are exactly the same as those of patients treated with regular conventional hemodialysis. Dialysis adequacy targets as recommended by the Kidney Disease Outcome Quality Initiative and the European Best Practice Guidelines should be equivalent in terms of extracellular fluid volume control, blood pressure control, minimum dialysis dose delivered (urea Kt/Vdp > 1.2), uremia control, acidosis and hyperkaliemia correction, phosphorus, calcium and parathyroid hormone control, and anemia correction. On a regular basis, Online HDF provides a higher solute removal rate as compared to conventional low- and high-flux hemodialysis for low- and middle-size uremic toxins including β_2-Microglobulin. On a long-term basis, this higher efficacy translates into a reduction of the time-averaged concentration of blood

β_2-Microglobulin, meaning that this middle-size marker should be routinely incorporated in the criteria to evaluate dialysis adequacy. Due to the high volume of fluid exchanged per session (25-50 l/session) clinicians are also recommended to follow the inflammatory profile of ol-HDF-treated patients on a monthly basis (e.g. high-sensitivity C-reactive protein) and check the nutritional markers (albumin and transthyretin). Thanks to ol-HDF, however,

reaching minimum international adequacy standards is quite easy due to the better hemodynamic stability and the higher solute removal capacity of the method.

Microbiological Monitoring

The ultrapurity of the bicarbonate-based dialysate and infusate produced by Online HDF machines relies on three components: first, a well designed and bioengineered water production and delivery system; second, a strict application of hygienic rules to undertake regular disinfection procedures of the water treatment system and the proportioning HDF machines; third, a planned monitoring of the microbiological inventory of the complete chain of treatment. Disinfection procedures and the frequency with which the water treatment system and Online HDF machines are monitored may vary from country to country according to specific health authority regulations. The overall aim is to ensure the quality and safety of the Online HDF method at any time. Best clinical practice guidelines recommend to perform a complete disinfection of the hydraulic circuit of the Online HDF machine (chemical, heat or mixed) after each run. A new sterile tubing set for the infusate line is requested at each new HDF session. Periodical changes of the ultrafilters installed on inlet dialysate and infusate lines should be performed according to manufacturer instructions or earlier in case of technical failure. Disinfection of the water treatment system and water distribution circuit should be performed, as a minimum, on a monthly basis. The type of disinfection (chemical, heat or mixed) and periodicity of disinfection procedures may vary from centre to centre but should adhere to manufacturer recommendations in all cases, and should be adapted to microbiological results. More frequent disinfection actions (daily or weekly) of the water distribution pipe using heat or mixed heat/chemical procedures appear to be the optimal way of preventing bacterial contamination and biofilm formation. Monitoring the microbiology of the water treatment Online Purification Cascade and Online HDF machines should comply with best practice recommendations and country-specific rules. All recommendations have been reported in detail in the European Best Practice Guidelines and ISO 23500. They represent the most comprehensive and updated guidelines that need to be applied to guarantee the safety of the Online HDF method. Water feeding the HDF machines should be checked weekly during the validation phase and at least monthly during the surveillance and maintenance period. Dialysate and infusate produced by proportioning Online HDF machines should be checked at least every 3 months. Microbiological monitoring should include the culture of water and/or dialysate and the determination of endotoxin content. Descriptions of the sampling method, culture media and delay for observation have been published elsewhere.

At present, Online HDF modalities offer the most effective renal replacement modality for ESRD patients. High-flux Online HDF allows the delivery of a high “dialysis dose” based on the conventional urea marker. By enhancing the convective fluxes, Online HDF enlarges the spectrum and increases the uremic toxin mass removed. Online HDF improves the hemocompatibility profile of extracorporeal renal replacement modalities and reduces inflammation in CKD-5 patients. Online production of substitution fluid reduces the cost of treatment and simplifies the technical aspect of the method compared to other HDF modalities using reinfusion bags. In addition, by giving access to an unlimited amount of high-quality intravenous fluid, the online HDF concept opens new therapeutic options (feedback control of volemia, automation of priming and restitution). These unique properties should give online HDF a leading position in ESRD therapeutic options so as to enhance the overall efficacy of renal replacement therapy and to improve the global care of end-stage renal failure patients (141).

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6. Cost-effectiveness of on-line HDF

The methodology of cost-effectiveness is recognized internationally as a tool used to evaluate the cost of a health intervention in relation to its effectiveness (e.g. technology, medical device, drugs). A modern application uses this methodology in a counter-economic way, to convert the effectiveness of a new treatment into an estimate of the price to be paid for the intervention itself.

As regards new medical devices or applications, it has been observed that, in Italy as in other European countries, the reimbursement system does not envisage innovative techniques and/or technologies, leading to a lack of incentives for innovation or the adoption of more cost-effective medical therapies.

Therefore, the price that can be calculated for a new medical device on the basis of the cost-effectiveness criterion is only used as general reference (which, consequently, is not binding) to indicate whether the price that the Italian NHS has agreed to pay is too high or acceptable in relation to the effectiveness of the device. The appropriate use of public money takes place when expenditure is proportionate - or even small - compared to the amount of health produced by the intervention.

OBJECTIVES

Evaluating the additional cost (incremental cost) and additional effectiveness (incremental effectiveness), which Online HDF brings in comparison with HD.

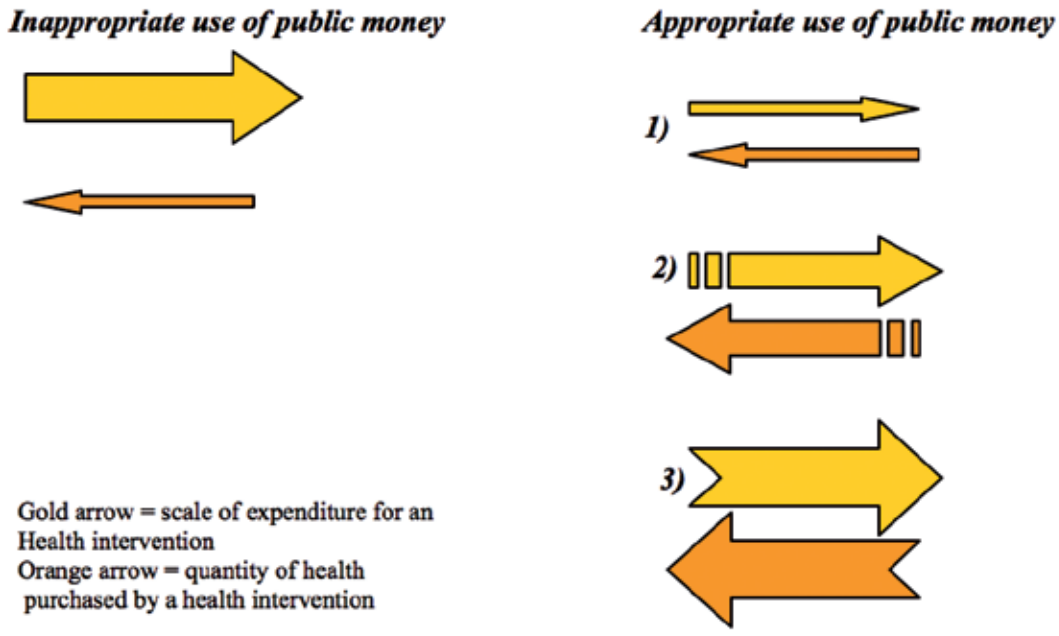
METHODOLOGY

From a methodological point of view the following steps were performed:

1. identification of therapeutic prescription
2. analysis of clinical literature and identification of innovative technology A (ol-HDF) and technology of reference B (HD);
3. comparison between the innovative technology A (ol-HDF) and the technology of reference B in terms of clinical benefit;
4. estimated incremental effectiveness of the innovative technology A (ol-HDF) versus technology of reference B (HD) (142).

CLINICAL COMPARISON

High mortality rates among CKD patients on HD therapies have been recognized for some



time. A number of strategies to improve patient outcomes have been considered, including refinement of clinical prescription and dialysis technology on which dialysis therapy is so dependent. In particular, considerable attention has been devoted in recent years on treatment duration, frequency and modalities, in an attempt to not only overcome the effects of uremia but also of a multitude of related co-morbid conditions accompanying CKD. Efficient elimination of a broad spectrum of accumulated uremic retention solutes ("uremic toxins"), small and large, constitutes the core objective of all HD therapies. As uremic toxicity begins to be better understood, the significance of the removal of larger compounds, classified as middle molecules (MM) and known for some time to play a role in the uremic syndrome, has been realized. Advances in membrane and machine technology have further facilitated the establishment of high-flux dialysis (HF-HD) as the predominant form of HD treatment.

Worldwide, over half of all HD patients are treated today with high-flux membranes. This transition from low-flux dialysis (LF-HD) to HF-HD is an assertion of the clinical need to remove large compounds that accumulate in uremia. An open, prospective, randomized controlled trial Membrane Permeability Outcome (MPO) conducted by Locatelli et al. involving 738 patients in 59 centres from 9 European countries demonstrated a survival benefit for HF-HD compared to LF-HD, particularly in a dialysis population with increased risk of morbidity and mortality (patients with low serum levels of albumin and for diabetics). Other randomized clinical trials in Europe have evaluated HDF and HD; the overall hypothesis of these RCTs is to determine if there is an improvement in clearing MMW solutes during online HDF, a better correction of the uremic environment, a decrease in cardiovascular damage, a decrease in cardiovascular morbidity and mortality (Table 6.1).

In recent years, there has been a further steady shift towards on-line hemodiafiltration (ol-HDF), a derivative of HF-HD that relies predominantly on the mechanism of convective solute transport across HF membranes for the enhanced removal of larger substances (143). On-line HDF is an alternative to the conventional HD proposed for ESRD patients, and aims at improving patient outcomes in terms of morbidity, quality of life, and mortality. First, HDF increases dialysis efficacy by enlarging the molecular weight spectrum of uremic toxins up to middle and large solutes; second, HDF ameliorates the clinical tolerance of sessions and the quality of life; and third, HDF improves the biocompatibility of the HD system by combining the use of high flux synthetic membranes and ultrapure dialysis fluid purity (Figure 6.1).

Online hemodiafiltration has caused a lively debate since most of the currently published studies have not been able to show a definitive and clear-cut improvement in survival or hospitalization rates. However, as is the case with most medical devices it is practically impossible to design a true randomized unbiased trial.

Furthermore, the various comorbidities of the patients make it even more difficult to compare outcomes in observational studies.

There are a number of confounding factors which limit the comparability between studies or even make observations and conclusions from studies irrelevant:

- EPO use has changed repeatedly in the last years, ESA have evolved, different brands and doses are used, and the recommended hemoglobin levels have been restated several times in the guidelines.
- The aging of the population in general has led to a growing number of patients but also to an increase of the average age of the patient population, thus bringing about an overall increase in comorbidities and need for hospitalization.
- In dialysis the type of medical devices used – the dialyzer or the machine used - are only a small part of the variables which are present. Duration and frequency of treatment, which are critical for the quality of the treatment, vary between different centers and even between one specialist and another.
- Large randomized and blinded trials to compare effectiveness are not performable, for all the reasons stated above, but also because of ethical issues.

For example even high-flux HD was suggested over 20 years ago. The medical community was convinced of its superiority to low flux, but recent clinical trials such as the HEMO trial, still fail to prove superior survival. This has been the case with on-line HDF as well.

For example the most important attempt to make a meta-analysis of all the trials performed – the Cochrane collaboration review (144) – concluded that the results from 20 studies in

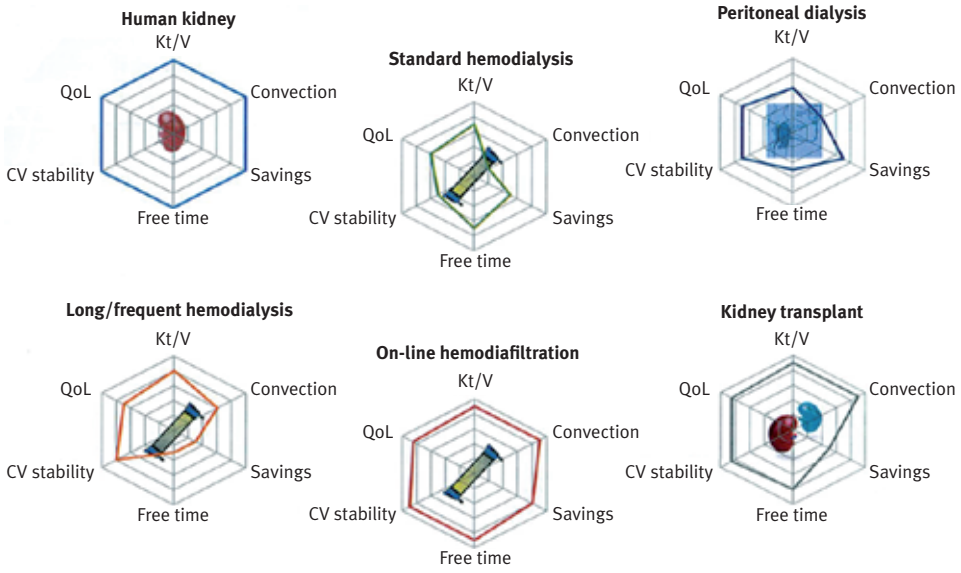
TABLE 6.1

RANDOMIZED CLINICAL TRIALS IN EUROPE EVALUATING HDF AND HD

STUDY	MODALITY CONTROL GROUP	NUMBER OF PATIENTS	PRIMARY ENDPOINT
CONTRAST (76)	Low-flux HD	715	Mortality
Canaud et al (146)	High-flux HD	Target ± 600	Intradialytic morbidity
Bolasco (155)	Low-flux HD, HF and ol-HF	146	Hemodynamic stability
Turkish study	High-flux HD	782	Cardiovascular morbidity and Mortality
ESHOL (156)	HD (94% high-flux)	939	Mortality
FINESSE (157)	High-flux HD	Target ± 120	Uraemic Neuropathy

FIGURE 6.1

RADAR GRAPH DESCRIBING THE PERFORMANCE OF SIX DIFFERENT CONDITIONS: NORMAL KIDNEY, STANDARD HD, PD, LONG/FREQUENT HD, ON-LINE HDF AND KIDNEY TRANSPLANT



Source: On-line Hemodiafiltration: The Journey and the Vision. Gatti E, Ronco C, 2011

the literature with a total of over 600 patients, showed that no superiority of one system over the other is evident and suggested further studies to be performed in order to support HDF use over HD. Further, the attempt of Witzemann et al. (145) to follow 44 randomized patients yielded no satisfactory results. Indeed, neither the size of the patient cohorts nor the duration of the studies were sufficient to draw any general conclusion.

Health and regulatory authorities have approved Online HDF for Renal Replacement Therapy (RRT) in Europe provided that specific EU-certified HDF machines are used and water purity complies with the level of microbiological purity defined in the European Best Practice Guidelines. To increase the safety and the security of these methods, some countries have reinforced this regulation by issuing a specific sanitary regulation for online HF/HDF methods (e.g. France). All dialysis facilities performing Online HDF treatment must therefore comply with technical requirements and water monitoring specified by these guidelines. In this day and age, it is amazing to note that despite technological advances featuring ol-HDF, the prevalence of HDF-treated patients amounts to approximately 10% of all dialysis patients,

despite several clinical studies have reported beneficial effects of HDF methods.

These positive clinical effects may be grouped into several major categories as follows: improvement in hemodynamic stability and blood pressure control; prevention and or delayed occurrence of β_2M-amyloidosis; improvement of metabolic profile; improvement of anemia correction and status management in HD patients, reduction of hospitalization and mortality.

Anemia correction

Renal anemia is a common feature of HD patients, requiring the use of EPO in 80% to 100% of patients. Although still controversial, it has been shown that anemia was improved and EPO needs reduced in patients treated by high-efficiency HDF. This very interesting effect has been reported in patients who were switched from low-flux HD to high-flux HDF modalities. These observations suggest that high-efficiency HDF methods might remove some erythropoietic inhibitor substances (146). Note also that anemia correction was associated with a reduced inflammation state of the patient. Anemia of CKD is a major complication that occurs early in the development of CKD, with severity increasing as renal function deteriorates. Most of the patients with stage 5-CKD and requiring renal replacement therapies in the form of dialysis have anemia, which contributes to poor quality of life. Anemia in CKD is attributed primarily to an insufficient nephric output of erythropoietin (EPO) and unavailability of iron leading to decreased erythropoiesis. Its correction, essentially by pharmaceutical intervention with erythropoiesis-stimulating agents (ESA) and intravenous (i.v.) iron supplements, is an important component of CKD management but adds significantly to the high overall costs of treating patients with advanced CKD. Treatment of anemia in CKD has become a highly contentious topic, with growing concerns regarding the precise targets, safety, clinical evidence, questionable benefits and costs of present anemia management practices. Compared to standard dialysis including High-flux HD, Online HDF has been shown to improve the anemic status of CKD patients by significantly increasing Hb to target levels at reduced maintenance doses of EPO. Two further studies showed that when patients are switched from conventional HD to ol-HDF, significantly higher hematocrit (Hct) and Hb levels were reached with the Online HDF treatment modality. Switching patients from conventional HD to Online HDF was associated with a reduction in the EPO dose needed to reach a higher mean Hct level. In a study in which patients on conventional HDF were changed to ol-HDF, an EPO dose reduction of 30% was observed after the switch to ol-HDF, with a significant increase in Hb and Hct levels during the Online HDF treatment (143).

Improvement of hemodynamic stability

Rapid removal of solutes and fluids may result in symptomatic hypotension, which is the most common acute complication of HD. Twenty percent to 30% of dialysis sessions are complicated by dialysis hypotension and associated symptoms of muscle cramps, nausea, vomiting, and headache. Elderly patients and those with diabetes, as well as those with autonomic insufficiency and structural heart disease, are particularly affected. Reduction in the frequency of this complication could contribute significantly to improving the quality of life of ESRD patients.

Less intradialytic hypotension also permits adequate fluid removal, helping restore euvolemia and ensuring better blood pressure control, as well as achieving the prescribed treatment time and delivering the prescribed dialysis dose.

Several observational studies suggest better intradialytic hemodynamic stability when patients are treated by convective therapies, including HDF.

A meta-analysis of randomized controlled studies confirmed that systolic blood pressure during the dialysis session was significantly higher, and the maximal drop in systolic pressure was less significant with convective modalities as compared with HD. The precise mechanisms by which HDF maintains arterial pressure during dialysis sessions are not completely understood. One theory is that an increase in peripheral vascular tone (arterial and venous) and in the vascular refilling rate is caused by the neutral thermal balance, particularly with high-volume exchange. Several other factors may contribute to this hemodynamic adaptation during HDF, although they remain speculative, including high sodium concentration of the substitution dialysis fluid, release of vasoconstrictor mediators, clearance of vasodilator mediators, and improvement of sympathetic activity

which helps heart rate adaptation and vascular resistance (147). Improvement of hemodynamic stability was repeatedly reported in the elderly population and/or heart-compromised patients prone to dialytic hypotensive episodes. In a short comparative study, Mion et al. reported a significant improvement of blood pressure stability in HDF vs. HD.

Interestingly, these results were achieved despite a higher ultrafiltration rate in the HDF group. Several studies have confirmed a better intradialytic hemodynamic stability when patients were treated by convective therapies (HF, HDF) compared with HD. The beneficial effects of HDF seem to be mainly due to the neutral thermal balance that is achieved in HDF, particularly with high fluid volume exchange. Although not completely understood, this positive effect of HDF is clearly related to a better peripheral vasomodulation effect, which entails a negative thermal balance, but other factors as well, such as the high sodium concentration of the infusion fluid and the removal of vasodilating mediators. Intradialytic symptomatology and post-dialysis fatigue are reduced with HDF methods, particularly when these are applied on a daily basis. Improvement of dialysis tolerance is an important component of the beneficial effects of HDF that contribute significantly to ameliorating the quality of life of ESRD patients.

Blood pressure control

Blood pressure control is achieved similarly to that of high-flux HD. This beneficial cardiac effect is mainly due to intradialytic hemodynamic stability, which allows a normal volemia to be restored. Longer sessions and compliance to sodium diet restrictions may facilitate the achievement of this goal. Regular application of HDF has been associated with a reduction of left ventricular hypertrophy contributing to a better preservation of cardiac function.

Hemocompatibility

Hemocompatibility is improved with ol-HDF. Several prospective studies have shown that the behaviour of markers of the acute-phase reaction (CRP, IL1, IL6, IL1, IL6 RA and albumin) improved or remained stable over time in HDF modalities. This positive effect results from the combined use of a synthetic biocompatible membrane, ultrapure dialysis fluid, and the "passivation" of the membrane by the protein coating layer. Prevention of inflammation is now becoming a crucial concern to reduce the incidence of dialysis-related complications in long-term dialysis patients (146). In June 2004, a prospective observational study "RISchio CArdiovascolare nei pazienti afferenti all'Area Vasta In Dialisi (RISCAVID) performed on a large HD population in the north-western region of Tuscany, Italy, assessed the different parameters of chronic inflammation. RISCAVID was started with the aim of investigating the link between traditional and non-traditional risk factors on mortality and morbidity. 757 patients representing the whole HD population of 1 235 0,62 inhabitants were included. Each of the 15 dialysis facilities of this region provided, at the start of the study, blood samples from all patients to determine inflammatory markers and data on patients' demographic characteristics, renal history, laboratory values, co-morbidity disease, dialysis techniques, vascular access prescriptions and outcomes (this was repeated every 6 months). Three papers have been published to date on the basis of the results of the RISCAVID database. The first described the role of chronic inflammation and the impact of different HD modalities on morbidity and mortality rates. The second focused on the erythropoietic response to a erythropoiesis-stimulating agents (ESA) treatment and the factors involved in resistance to ESA. The third examined the clinical relevance of serum mineral derangements, and the impact of different therapeutic strategies on mineral metabolism and mortality (148).

Recent studies have suggested that high-flux therapies including Online HDF might contribute to a longer and better *preservation of residual renal function*. Interestingly, this positive effect appears now comparable to that observed in peritoneal dialysis patients. Although this phenomenon is not completely understood or proved, it might result from a reduction of the inflammation state and from a reduced incidence of intradialytic hypotension episodes (149).

Prevention or delayed occurrence of β_2M-amyloidosis

The prevention or delayed occurrence of β_2M-amyloidosis in long-term-treated ESRD patients has been evidenced in several large

retrospective studies. Locatelli and co-workers have shown in a study that the use of high-flux membranes and convective dialysis modalities including HDF had a beneficial impact on the development of β_2M-amyloidosis, reducing its incidence by 50%. Koda and co-workers have shown, in a large retrospective cohort study comparing the use of low-flux and high-flux membranes, that the incidence of carpal tunnel syndrome, defined as the first symptom of β_2M-amyloidosis, was reduced by 50% during the use of high-flux membranes. Schwalbe and co-workers have similarly reported, in a retrospective study comparing 2 vintage periods of dialysis, that the incidence of carpal tunnel syndrome and amyloid cysts declined with the increased use of high-flux membranes and that there was an improvement in the microbiological purity of the dialysis fluid. In these studies, the beneficial effect of convective clearances due to internal filtration was partly compounded by the improvement of the overall dialysis quality, including the extended use of hemocompatible membranes and a better purity of dialysis fluid. In these retrospective studies, several confounding factors interfere and mask the precise role of convective therapies in the protective effect described.

Growth retardation

Children with ESRD are a major concern. Conventional HD alone has not been able to correct their delayed development. A recent study based on a daily Online HDF treatment has shown that this schedule is able to correct growth retardation in children with CKD. This beneficial effect is achieved by combining greater treatment efficacy, the enhancement of dietary and caloric intakes and the better correction of internal milieu disturbances (acidosis, calcium and phosphate control). The combined use of growth hormone, erythropoietic stimulating agents and Online HDF provides now the opportunity to normalize growth rate in CKD kids (149).

Dyslipidemia and oxidative stress

A dyslipidemia profile, oxidative stress, and AGEs (Advanced Glycosilation Endproducts) reported in dialysis patients contribute to accelerating atherosclerosis. The regular use of high-flux membranes in HD or in HDF has been shown to improve lipid profile and to reduce oxidative stress and AGEs concentrations. Such a beneficial effect may be partly due to the improved biocompatibility of the dialyzer and the ultrapurity of the dialysate. Note that the increased loss of natural antioxidant substances (vitamin C, E, selenium, etc.) may annul part of the beneficial effects of high-flux convective modalities. To prevent the increase of oxidative stress by HDF modalities, it is highly desirable to supplement patients with natural antioxidant substances (146).

Caloric and/or protein malnutrition

This is observed in about one third of dialysis patients. Several recent studies have shown that the use of high-flux methods including HDF may have a positive impact on the nutritional state when compared to low-flux membranes. Anthropometric parameters, such as dry weight, body mass index, and albumin figures, tend to increase over time in patients treated with convective therapies. This is associated with an increase in dietary protein intake as evaluated by the urea generation rate. One must recognize that this positive effect might result from the combined effects of the use of high-flux membranes with ultrapure dialysate and more speculatively with the removal of anorexia-inducing uremic toxins.

Hospitalizations are frequent among dialysis patients, and reducing repeat hospitalizations could decrease costs and improve outcomes. Hospitalizations are frequent for end-stage renal disease (ESRD) patients treated with dialysis. In 2006, dialysis patients had averaged nearly two hospital admissions per patient-year. Furthermore, hospitalizations of ESRD patients cost the US health-care system $31 billion between 2002 and 2006, which represented more than one-third of the total costs of treating ESRD over this time period. Many of these hospitalizations were probably repeated hospitalizations, defined as hospitalizations that occur within a short period (for example, 30 days) following a previous hospitalization. Preventing such repeated admissions would reduce overall costs due to hospitalization and would also probably increase the overall health of the dialysis patient, as each hospitalization can have adverse consequences, including worsening anemia, malnutrition, infection, and possibly, in-hospital mortality. In addition, reducing repeated hospitalizations could

potentially dramatically improve the quality of life of dialysis patients, which may be as important as health outcomes from the perspective of patients and their families. The rate of hospitalization is high for all dialysis patients who have a high prevalence of co-morbidity conditions and treatment-related complications. Rates and characteristics of the most prevalent causes for new hospitalization are displayed on Table 6.2 (150).

Anemia is an important characteristic of patients with chronic renal failure and has a considerable effect on morbidity and on the hospitalization rate. In study of Bonforte at al. of the Nephrology and Dialysis Unit in Desio (Milan)-Italy found that Online HDF has a significantly higher effect on anemia than standard HD. They reviewed the cases of 45 patients (mean age 54; M/F 30/15; mean time on hemodialysis 109 months) on Online HDF for 26 months (average time). A high incidence of critical patients was selected for their age (age > 65 years; n=14) and the presence of co-morbidity factors such as diabetes mellitus (n=9), intradialytic hypotension (n=12), time on hemodialysis > 60 months (n=21), carpal tunnel deposits (n=6) and high body size (n=13). Authors selected 35 patients who had spent at least 12 months on HD and Online HDF.

Table 6.3 shows the results of their study: Online HDF patients had a significantly lower hospitalization rate. The reasons for admission were the following (HD versus HDF): infection 78% vs. 22% ($p < 0.05$), cardiovascular disease 70% vs. 30% ($p < 0.05$), haemorrhage and surgery 80% vs. 23% ($p < 0.05$). Patients on Online HDF, in addition to having a significantly lower hospitalization rate, enjoyed anemia improvement and higher cardiovascular stability (the use of biocompatible membranes may play an important

TABLE 6.2

MOST PREVALENT PRIMARY DIAGNOSIS FOR HOSPITALIZATION

	NEW HOSPITALIZATIONS PER PATIENT YEAR	MEDIAN LENGTH OF STAY (DAYS)	PROBABILITY OF REPEAT HOSPITALIZATION (%) [a]
Infection	0.22	7	25.3
Access related	0.14	4	24.1
Volume overload	0.07	4	29.4
Chest pain	0.07	4	28.1
Shortness of breath	0.06	4	30.4
Congestive heart failure	0.05	5	28.8
Cardiovascular disease [b]	0.04	5	26.2
Hypertension	0.03	4	28.0
Nausea and vomiting	0.03	4	30.3
Peptic ulcer disease	0.02	5	24.5
Abdominal pain	0.02	5	29.2
Myocardial infarction	0.02	6	28.5
Fever and chills	0.02	5	27.0
Hypotension	0.02	5	29.0
Weakness	0.02	5	28.3
Altered mental status	0.02	6	31.3
Anemia	0.02	4	31.2
Hyperkalemia	0.02	3	24.3
Coronary artery disease	0.02	5	21.8
Bleeding	0.01	5	23.9
Other causes	0.57	5	26.6

[a] Hospital visit within 30 days after discharge from a new hospitalization
[b] Excluding myocardial infarction, congestive heart failure, and coronary artery disease, Source: International Society of Nephrology, 2009

TABLE 6.3

MOST PREVALENT PRIMARY DIAGNOSIS FOR HOSPITALIZATION			
	HD	OL-HDF	
Total follow-up (months)	890	890	
N° hemodialysis	11 203	11 203	
N° hospitalizations	64	39	**p < 0.05**
Hospitalization days	393	266	n.s

Source: Bonforte G, Zerbi S et al. Nephrology and Dialysis Unit - Desio (Milan) - Italy, 2001 (151)

role). Therefore the association between Online HDF and a lower risk of hospitalization leads to significant cost savings and an improvement of the patients' Quality of Life (151).

Mortality

All the above-mentioned effects have an impact on hospitalization and quality of life. The scientific community has been discussing mortality figures for years, but more and more findings tend to confirm a mortality decrease of around 35% for high efficiency and high volume HDF (>15 liters reinfusion volumes) compared to standard LF HD. A summary on mortality studies was recently published (Table 6.4) (152).

COST COMPARISON

In the economic evaluations of health programs, the costs can be divided into direct costs and productivity losses. Direct costs, that refer to the consumption of health care services not directly attributable to the disease or the program being evaluated, are divided into medical direct costs and non-medical direct costs. Productivity losses refer instead to the reduction of production due to disability or premature death. Direct medical costs include all costs incurred by the Health Care System, or third payers (private insurance if it exists), to organize and run the program and are related to the health resources used in the cycle of prevention, diagnosis, treatment and rehabilitation; typical examples are the drugs, equipment, tests and hospitalizations.

The non-medical direct costs are those incurred by the patient and his family as the cost of transport to access the program and the cost of assistance provided by relatives (informal care). It is a view shared by several authors that when evaluating the effectiveness of health programs (Online HDF vs. HD) the calculation should take into account only medical costs and not indirect costs. To be conservative, therefore, we should exclude non-health related cost components such as informal care, transportation and lost productivity.

The analysis of direct medical cost allows us to highlight that the two dialysis treatments today, after the many technical improvements developed during the last 20 years, differ by a scale of 20-30%; since staffing and major fixed costs (infrastructure, location, utilities, general expenses) do not vary according to the dialysis method. The only variations in direct medical costs are related to equipment, materials, and water testing (Table 6.5).

The table shows that the costs of staff, equipment and drugs are identical for both dialysis techniques while the costs of tests and equipment are higher for ol-HDF, revealing a difference in costs between the two methods in the range of 16.5% and 34% which mainly depends on the materials and lab test used for water (ultrapure dialysate).

EUROPEAN REIMBURSEMENT OVERVIEW

When looking at the reimbursement of HD/HDF therapies, a distinction should be made between structure and rate; the reimbursement structure is the system that defines who is eligible to receive reimbursement for the dialysis service and how the financial resources should be distributed to the different providers, while the reimbursement rate is the amount of money paid to the service provider for the provision of specific dialysis services and products.

Reimbursement structures and reimbursement rates vary widely within and between countries. Their structures are

TABLE 6.4

CLINICAL EVIDENCE ON HEMODIAFILTRATION

REFERENCE	DESIGN	INTERVENTION/ THERAPIES	NUMBER OF PATIENTS	EFFECT/ PRIMARY END POINT	REMARKS
HEMO study (132-133)	RCT	High-flux <-> low-flux HD	1 846 921 on high-flux	No difference	Positive effect of high-flux in subgroup
MPO study (82)	RCT	High-flux <-> low-flux HD	647 318 on high-flux	No difference	Positive effect of high-flux in subgroup
Subanalysis of 4D study (135)	RCT	Study on effect of statin	648 241 on high-flux	Improved survival in high-flux (41%)	*Post hoc* analysis
Chauveau et al. (136)	Prospective observational	High-flux <-> low-flux HD	650 305 on high-flux	Improved survival in high-flux (38%)	
DOPPS (137)	Prospective observational	HD <-> HDF	2 165 263 on HDF	Improved survival in HDF (35%)	Only in infusate >15 l per session
EuCliD (139)	Prospective observational	HD <-> olHDF	2 564 394 on HDF	Improved survival in HDF (37%)	
Bosch et al. (158)	Retrospective observational	HD <-> HDF (double high-flux)	183 approx. 25 on HDF	Improved survival in HDF (60%)	Control based on USRDS data
RISCAVID study (93, 148)	Prospective observational	HD <-> HDF	757 303 on HDF	Improved survival in HDF (22%)	
Santoro et al. (85)	RCT	HD <-> HF	64 32 on HF	Improved survival in HF	Small study
Vilar et al. (138)	Retrospective observational	HD <-> HDF	858 232 on HDF	Improved survival in HDF (34%)	Predominantly on HDF
CONTRAST (76)	RCT	HD <-> olHDF	Target approx 700	All cause mortality	Ongoing
Canaud et al. (146)	RCT	HD <-> olHDF	Target approx 600	Intradialytic mortality	Ongoing
Italian study (155)	RCT	HD <-> olHDF <-> olHF	146	Hemodynamic stability	Ended

Modified from: Blankestijn et al, 2010 (152)
HD: hemodialysis; HDF: hemodiafiltration; HF: hemofiltration; olHDF: on-line hemodiafiltration; RCT: randomized controlled trial.

TABLE 6.5

DIRECT MEDICAL COSTS FOR TREATMENT (RELATIVE VALUES)

	HD	OL-HDF
Staff	58.73	58.73
Materials	31.10	46/60
Equipment	5.21	5.2 /6.9
Drugs	1.82	1.82
Tests	0.33	2/3.6
Others	2.81	2.81
Total costs	100.00	116.5/134

Source: derived from CENSIS data, 2009

TABLE 6.6

REIMBURSEMENT MODALITIES FOR HDF THERAPIES IN 2010

	COUNTRY	TOTAL NUMBER OF PATIENTS ON HDF MODALITIES	AS % ON COUNTRY DIALYSIS PATIENTS
Group 1	Slovenia	910	65%
	Slovakia	1 580	55%
	Czech Republic	1 760	33%
	Greece	2 630	30%
Group 2	Serbia	1 060	25%
	Spain	3 900	18%
	Italy	7 640	16%
	United Kingdom	1 320	7%
	Russian	1 400	7%
Group 3	Switzerland	2 000	67%
	Portugal	4 780	48%
	Hungary	2 300	42%
	Finland	470	31%
	Belgium	2 040	30%
	Sweden	810	28%
	Austria	1 070	27%
	Netherlands	1 000	20%
	France	4 950	13%
	Germany	9 800	13%
	Romania	550	7%

Source: On-line Hemodiafiltration: The Journey and the Vision. Moeller S, 2011 (140)

primarily influenced by regulatory aspects and source of funding while reimbursement rates are primarily influenced by components including treatment mode, provider type, payer type, place of treatment, patient characteristics/ status, regional agreements, regulatory aspects, quality & outcome aspects.

Components included in the "base" reimbursement in most countries are core disposables, machines, infrastructure, physician fees, nursing services, standard pharmaceuticals (e.g. heparin) but don't include special pharmaceuticals (e.g. EPO, iron, phosphate binders), diagnostics, laboratory tests, vascular access, transportation and hospitalization.

Depending on the mode of treatment (standard HD, HDF, on-line HDF) the reimbursement can be independent of the mode of treatment in countries such as France, Germany, Portugal or dependent of the mode of treatment in countries such as Italy, Spain, United Kingdom; when the reimbursement is dependent on the mode of treatment, it is generally higher for the non-standard therapies (HDF/on-line HDF).

Similarly, according to the type of provider (public or private providers), the reimbursement can be independent of the type of provider in countries such as Germany, Portugal or dependent of the type of provider in countries such as France, Italy, Spain, United Kingdom. When reimbursement is dependent of the type of provider, it is generally higher for public providers.

Moreover in some countries (e.g. Germany) the reimbursement can depend on patient age and/or co-morbidities (e.g. diabetes, HIV), and in countries such as Italy and Spain, regional authorities can define their own reimbursement structures/rates, depending on local conditions, while in some countries (Portugal, Germany) quality aspects (treatments and outcomes) influence reimbursement policies.

In the majority of the European countries, there is no special reimbursement defined for HDF treatments. Of the 34 European countries in which

HDF is performed the 20 countries with more than 400 patients are displayed in Table 6.6. The countries have been grouped into 3 categories.

Group 1: Countries currently having a special reimbursement for HDF therapies without restrictions;

Group 2: Countries currently having a special reimbursement for HDF but a limited one and with restrictions according to the type of provider (only for private or only for public entities) or region;

Group 3: Countries without any specific reimbursement for HDF therapies.

In the cases of Slovenia, Slovakia, the Czech Republic and Greece, the additional reimbursement for HDF can vary from around 30% - 50% of the standard high-flux HD reimbursement. In many countries where the HDF premium is offered, the percentage of HDF is limited (to for example 20% of all treatments) in order to keep the overall dialysis cost under control, but the result is that of limiting potential economic savings on overall patient costs (153).

7. Case study

RESULTS BASED ON A 7-YEAR OL-HDF IMPLEMENTATION STRATEGY OVER A LARGE ITALIAN POPULATION.

An analysis of the clinical literature suggests that Online HDF provides an increase in the years of life gained, a reduction of adverse events, reduced hospitalizations, reduced use of drugs, improved organizational efficiency.

Today, monitoring the quality and variability of practice patterns adequately is generally considered a priority. Continuous Quality Improvement (CQI) programs, Clinical Performance Guidelines (GPGs), Clinical Performance Measures (CPMs) and Patient Safety Initiatives are examples of efforts to reduce variability in medical practice, improve clinical outcomes and address both the quality and cost of medicine.

After the release of the "Adequacy of Haemodialysis Guideline" by the Renal Physician Association in 1996 and "Dialysis Outcome Quality Initiative (DOQI) Guidelines" by the National Kidney Foundation in 1998, several scientific societies (EDTA, British Renal Association, Italian Society of Nephrology, etc.) produced their own guidelines, and Fresenius Medical Care (FME) could not remain inactive in this field.

For this reason, and aware of its duty to continuously monitor and guarantee the quality of the care delivered to patients treated in its dialysis units, FME developed a monitoring system, called European Clinical Database (EuCliD), so that the European FME clinics can participate in an officially recognized monitoring system.

Observations on 8 800 patients-years performed by the EuCliD® Network (from 2005 to the end 2011) were used to verify observed data in the studies mentioned before (DOPPS, Bonforte *et al.* (151) RISCAVID, MPO, Contrast, etc.) concerning the beneficial outcome of on-line HDF compared to High flux-HD, a more challenging comparison than with Low Flux HD.

Specific attention was devoted to Italian network data as on-line HDF technology was extensively implemented ever since 2005 (from 23% to 94% of cases in 2010) and the number of observed patients grew from 1 275 in 2005 to 1 474 in 2011 (Table 7.1) (154).

All trends shown are not adjusted by comorbidities or age.

A comparison could have been done with all data collected in 23 Europe and Latin American countries as well, for a total of more than 35 000 patients and treatments of the EuCliD® network.

- **The average age** of patients in Italy increased between 2005 and 2011 by 2.2 years making Italian patients at the end of 2011 3.9 years older compared to those of the FME European network, with ages of 67.6 vs. 63.7 years respectively.
- **Patient age** > 75 increased from 29% in 2005 to 35% in 2010.
- **Diabetic patients** increased by 20% up to 26%.
- **Patients with neoplasm** increased from 7% to 10%.
- **Utilization of HDF on-line** increased from 23% in 2005 to 94% in 2010; (in 2011 the decrease in HDF was due to the extension of prevalence to regions where the therapy has legal limitations).
- **The Kt/V (dialysis dose)** increased to a very high level (compared to the European guidelines target: eKt/V> 1.2 in 80% of patients) (Figure 7.1) up to 1.75 in average.

These parameters show a progressive increase in the fragility of the population, also compared to the overall network.

Nonetheless, other most important outcomes like hospitalization and gross mortality remaied stable.

Improvements have been noted in EPO consumption per patient despite neoplasm incidence.

- **Active patients on transplant list**: the proportion of active patients on transplant waiting lists is co-related to the proportion of patients in better clinical conditions (patients without severe co-morbid conditions).

  During the period taken into consideration, the inclusion criteria of patients were extended, but while the total number of patients for all countries remained stable around 6 000 individuals, the population of patients on transplant waiting-lists observed, increased by

TABLE 7.1

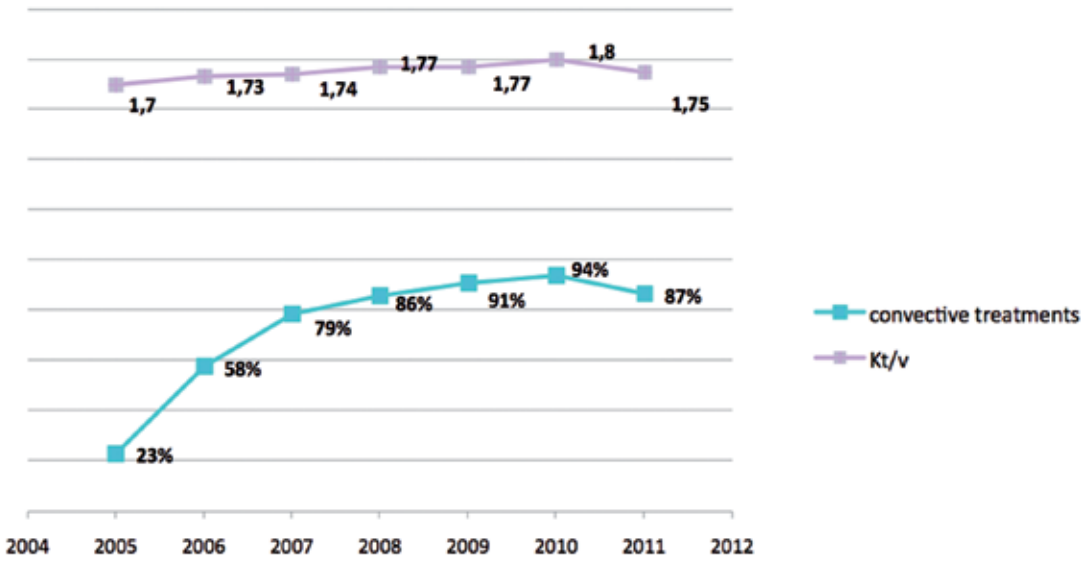
DESCRIPTION OF DEMOGRAPHICS, MAIN DIALYSIS FEATURES, MAIN THERAPIES, CO-MORBIDITY AND TRANSPLANT WAITING LIST STATUS OF THE PATIENTS ON DIALYSIS IN ITALY

	2005	2006	2007	2008	2009	2010	2011	Δ 2005- 2011
Patients	1 275	1 334	1 324	1 210	1 170	1 042	1 474	199
Mean age	65.4	66	66.2	66.9	67.3	67.5	67.6	2.2
Pt age >75 years (%)	29%	30%	32%	34%	35%	36%	35%	21%
Pts on high-flux filters (%)	93%	99%	98%	100%	100%	99%	99%	6%
Convective treatment % (HDF online)	23%	58%	79%	86%	91%	94%	87%	276%
Kt/v	1.7	1.73	1.74	1.77	1.77	1.8	1.75	3%
Time on dialysis (mean years)	6.18	6.02	6.18	6.18	6.36	6.36	6.37	0.19
β2-microblobulin (mg/L)	25.2	25.4	24.2	23.6	23.5	21.8	20.7	-18%
Vascular access (catheter,%)	10%	9%	14%	15%	18%	19%	22%	220%
Pts active on transplant list (%)	5%	13%	14%	14%	15%	17%	20%	277%
Diabetics (%)	20%	22%	23%	24%	26%	25%	26%	30%
Pts with neoplasm%	7%	7%	7%	8%	9%	9%	10%	37%
Pts on ESA	75%	78%	78%	89%	92%	90%	82%	9%
ESA dose (U/kg/wk mean)	116.6	130.5	129.3	128	117.6	110.6	102	-12%
Pts on IV iron therapy (%)	53%	82%	96%	98%	93%	93%	85%	32%
Iron IV dose (mg/wk mean)	80.2	75.4	81.5	80.3	79.5	77	77.1	-4%

Source: European Clinical Database - EuCliD®, 2012

FIGURE 7.1

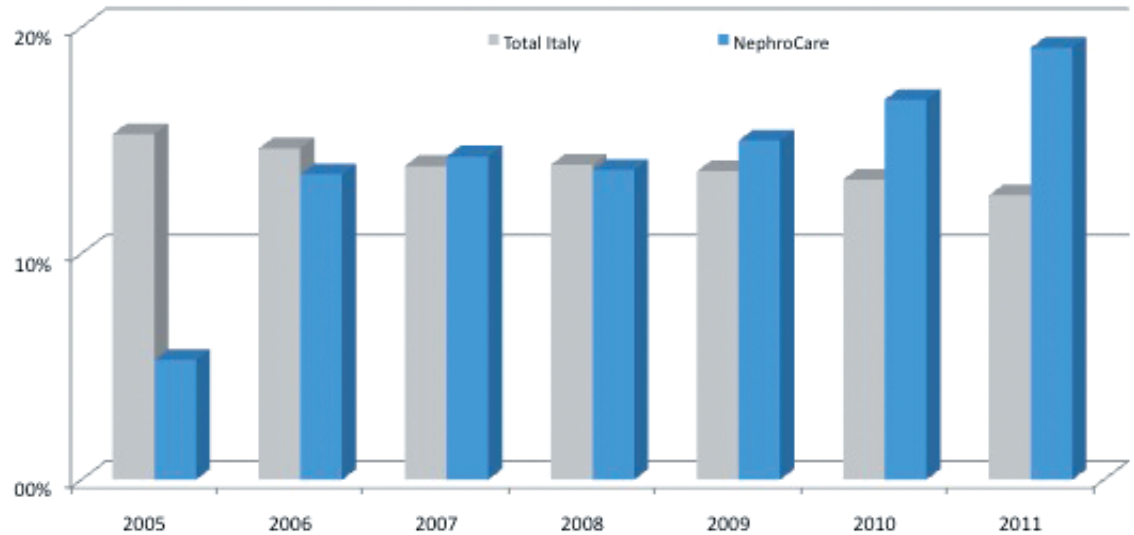
DIALYSIS EFFECTIVENESS INDICATOR



PATIENTS IN TX LISTS	2005	2006	2007	2008	2009	2010	2011
Waiting patient list all Italy	6 223	6 213	6 128	6 407	6 538	6 624	6 542
Country Italy as %	15.3%	14.7%	13.9%	13.9%	13.6%	13.3%	12.6%
NephroCare Italy as %	5.3%	13.5%	14.3%	13.7%	15.0%	16.8%	19.1%
delta	-10.0%	-1.2%	0.4%	-0.2%	1.4%	3.5%	6.5%

FIGURE 7.2

ACTIVE PATIENTS ON TRANSPLANT LIST COMPARED TO NATIONAL TREND



Source: EuCliD and www.misisterosalute.it

FIGURE 7.3

ANAEMIA MANAGEMENT (ESA)

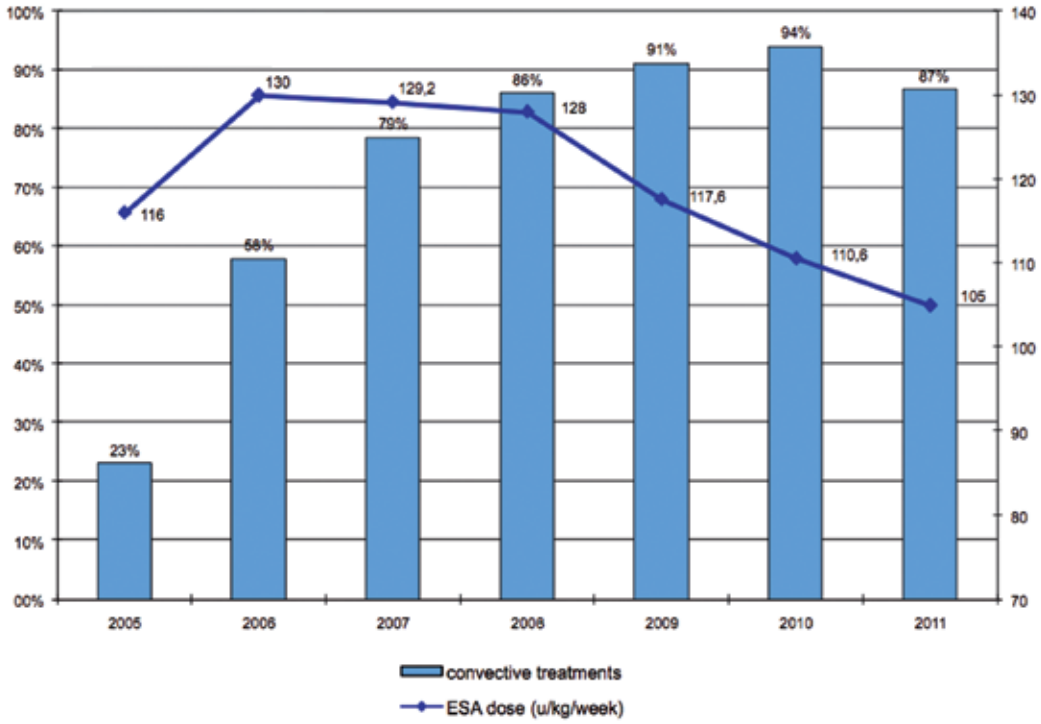
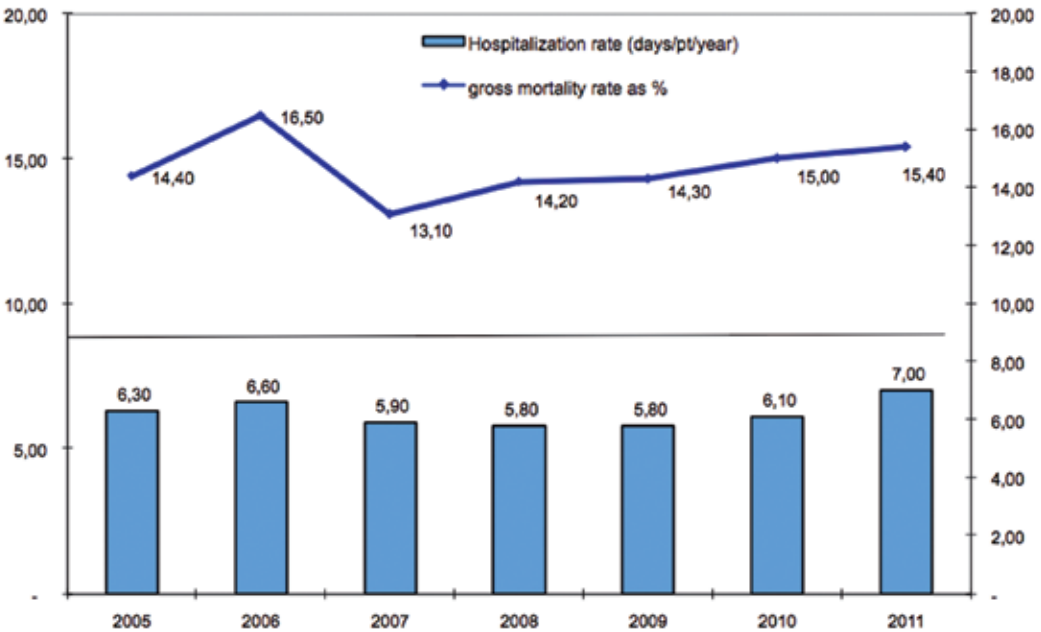


FIGURE 7.4

HOSPITALIZATION AND GROSS MORTALITY RATE



Source: EuCliD® and Ministry of Health statistics on hospital stays (SDO)

around 277% (Figure 7.2) (Ministry of Health Statistics).

- **ESA and IV iron** are the main therapies related to anaemia management: as expected a progressive decrease in dosage was observed (from 130 UI/kg/week in 2006 to 102 in 2011, while the level of haemoglobin remained in the same range as suggested by international and national guidelines) (Figure 7.3).
- The figure for **mean days of hospitalization** (despite the aging population) remained stable around 6/day/patient/years, compared to the national level of 9.7 days. **This saved more than 3 500 hospital days/years, 1 400 man days** (for patients under 75 y.o.) **or around 1000 working days were recovered** (patiens under 65 y.o).
- **Gross mortality**: During the period considered the gross mortality rate remained stable and in line with the national and regional registries (Figure 7.4).

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Glossary

ARTERIOVENOUS FISTULA: Surgical connection of an artery and a vein, usually in the forearm. This is created in patients who will need haemodialysis, so that the vein will grow thicker to allow for repeated needle sticks. In most haemodialysis patients, this is the best option.
AUTOMATED PERITONEAL DIALYSIS (APD): Dialysis solution is introduced through a permanent tube in the abdomen and flushed out either every night while the patient sleeps.
BLOOD PRESSURE: The force that blood puts on arteries and veins as it flows through them.
CHRONIC KIDNEY DISEASE (CKD): Any condition that causes reduced kidney function over a period of time. CKD is present when a patient's glomerular filtration rate remains below 60 milliliters per minute for more than 3 months or when a patient's urine albumin-to-creatinine ratio is over 30 milligrams (mg) of albumin for each gram (g) of creatinine (30 mg/g). CKD may develop over many years and lead to end-stage renal disease.
CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD): A form of peritoneal dialysis that does not need a machine. With CAPD, the blood is always being filtered. The dialysis solution passes from a plastic bag through a catheter and into the abdomen. The dialysis solution stays in the abdomen with the catheter sealed. After several hours, the person using CAPD drains the solution back into a disposable bag. Then the person refills the abdomen with fresh solution through the same catheter to begin the filtering process again.
CONTINUOUS CYCLING PERITONEAL DIALYSIS (CCPD): A form of peritoneal dialysis that uses a machine. This machine automatically fills and drains the dialysis solution from the abdomen. A typical CCPD schedule involves three to five exchanges during the night while the person sleeps. During the day, the person using CCPD performs one exchange with a dwell time that lasts the entire day.
CREATININE: A waste from meat protein in the diet and muscle use. Creatinine is removed from the blood by healthy kidneys, and leaves the body in urine. When kidneys do not work correctly, creatinine levels in the blood increase.
CYST: An abnormal sac filled with gas, fluid or a more solid material. Cysts may form in kidneys or in other parts of the body.
DIABETES MELLITUS: A condition when a person has high blood sugar. This is from a lack of working insulin, a hormone used to turn glucose (sugar) into a form your body can use.
DIALYSITE: A liquid used to clean waste from the blood in the two major kinds of dialysis.
DIALYSIS: The process of cleaning wastes from the blood artificially. This job is normally done by the kidneys. If the kidneys fail, the blood must be cleaned artificially with special equipment. The two major forms of dialysis are haemodialysis and peritoneal dialysis.
DIALYZER: A part of the haemodialysis machine. The dialyzer has two sections that are separated by a membrane. One section holds dialysate, and the other section holds the patient's blood.
ELECTROLYTES: Chemicals in the body that result from the breakdown of sodium, potassium, magnesium and chloride. Healthy kidneys control the amount of electrolytes in the body. When kidneys fail, electrolyte levels get out of balance, which can cause serious health problems.
END-STAGE RENAL DISEASE (ESRD): Total chronic kidney failure. When the kidneys fail, the body retains fluids and harmful wastes. A person with ESRD needs dialysis or a kidney transplant to take over the work of the failed kidneys.
ESTIMATED GLOMERULAR FILTRATION RATE (eGFR): A measure of how well the kidneys are working. An eGFR is based on a person's creatinine level, age, sex and race.
EXCHANGE: A cycle in peritoneal dialysis when dialysate fills the abdominal cavity, stays there for a certain dwell time and empties to prepare for another cycle.
GLOMERULONEPHRITIS: Inflammation of the glomeruli. Most often, it is caused by an autoimmune disease, but it can also be caused by infection.
GLOMERULUS: A tiny set of looping blood vessels in the nephron, the part of the kidney where blood is filtered.

HAEMODIALYSIS (HD): A way to clean wastes and extra fluid from the blood using a machine. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The filtered blood then flows through another set of tubes back into the body. This helps to replace the work of the kidneys after they have failed. haemodialysis is the most common kind of dialysis.

HAEMODIALYSIS-LIMITED ASSISTANCE CENTRES (HD-CAL): CALs are dialysis services managed by nurses, with a remote supervision of a Hospital Hemodialysis Departments (HHD) . The HHD physicians define the HD prescriptions (dialysis duration, ideal weight loss, pharmacological therapy) during periodic control visits, while the day by day management is carried on by nurses. Although CALs may represent an efficient solution to the organizational burden of the disease, they require to tightly monitor the quality of the delivered treatment by the HHD responsible.

HAEMODIAFILTRATION (HDF): Hemofiltration is sometimes used in combination with hemodialysis, when it is termed hemodiafiltration. Blood is pumped through the blood compartment of a high flux dialyzer, and a high rate of ultrafiltration is used, so there is a high rate of movement of water and solutes from blood to dialysate that must be replaced by substitution fluid that is infused directly into the blood line. However, dialysis solution is also run through the dialysate compartment of the dialyzer. The combination is theoretically useful because it results in good removal of both large and small molecular weight solutes.

HAEMOFILTRATION (HF): It's a renal replacement therapy similar to hemodialysis which is used almost exclusively in the intensive care setting. Thus, it is almost always used for acute renal failure. It is a slow continuous therapy in which sessions usually last between 12 to 24 hours and are usually performed daily. During hemofiltration, a patient's blood is passed through a set of tubing (a filtration circuit) via a machine to a semipermeable membrane (the filter) where waste products and water are removed. Replacement fluid is added and the blood is returned to the patient.

HAEMODIAFILTRATION-LIMITED ASSISTANCE CENTRES (HD-CAL): Haemodiafiltration in limited assistance centres.

HAEMODIAFILTRATION-pb (HDF-pb): Haemodiafiltration with very biocompatible and high permeability membranes.

HYPERTENSION: High blood pressure. This can be caused by too much fluid in the blood vessels or by narrowing of the blood vessels. Hypertension is the second leading cause of kidney failure. It can also be caused by kidney disease.

KIDNEYS: Bean-shaped organs that filter wastes and extra fluid from the blood. People usually have two, and they are located on either side of the spine, just under the ribcage. The waste and fluid filtered by the kidneys is called urine and is delivered to the bladder through the ureters.

KIDNEY STONE: A small, hard crystal that forms from certain chemicals that build up on the surfaces of the kidney, renal pelvis or ureters.

MEMBRANE: A thin layer of tissue that lines a body cavity or separates two body parts. Membranes can act as filters, allowing some things to pass through while keeping others where they are. The membrane in a dialyzer filters waste from the blood.

NEPHRECTOMY: Surgical removal of a kidney.

NEPHRITIS: Inflammation of the kidney.

NEPHROLOGY: A branch of medicine concerned with diseases of the kidneys.

NEPHROLOGIST: A doctor who treats kidney problems and high blood pressure.

NEPHRON: A tiny unit in the kidney that filters waste and extra fluid from the blood. Each kidney contains about 1 million nephrons.

NEPHROTIC SYNDROME: A condition where too much protein is in the urine and too little protein is in the blood. This causes swelling. There are two types of nephrotic syndrome: childhood and adult.

PERITONEAL DIALYSIS: Filtering the blood by using the lining of the abdominal cavity, or belly, as the filter. A cleansing liquid, called dialysis solution, is drained from a bag into the abdomen. Fluid and wastes flow through the lining of the abdominal cavity and remain "trapped" in the dialysis solution. The solution is then drained from the abdomen, removing the extra fluid and wastes from the body. The two main types of peritoneal dialysis are continuous ambulatory peritoneal dialysis and continuous cycling peritoneal dialysis.
POLYCYSTIC KIDNEY DISEASE (PKD): An inherited disorder that causes many grape-like clusters of fluidfilled cysts to form in both kidneys over time. These cysts destroy working kidney tissue. PKD may lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD).
RENAL: Of the kidneys. A renal disease is a kidney disease. Renal failure means that the kidneys have stopped working.
RENIN: An enzymemade by the kidneys to help control blood pressure and the amount of fluid in the body.
TRANSPLANT: Replacement of a diseased organ with a healthy one. A kidney transplant may come from a living donor or someone who has just died.

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