



# *The cost of pharmacologic treatment in chronic renal disease*

**R. Pons, E. Torregrosa, J. Hernández-Jaras, H. García, A. Ríus, C. Calvo, J. Sánchez-Canel, M. Pin and F. Maduell**  
Nephrology Department. General Hospital of Castellón.

## SUMMARY

*The prevalence and incidence of end stage renal disease has increased considerably in the past years. We know that the cost of treatment of these patients is high. Limited information exists on care resource utilization for maintenance of patients before the initiation of replacement therapy.*

*The purpose of this study is determine the cost of pharmaceutic treatment during the predialysis phase. Pharmacy cost was analyzed for 200 patients controlled on outpatient nephrology departament. The mean age was 72.4 years, 59% were males, and the comorbidity distribution was: hypertension 87%, hyperlipidemia 56% and diabetes 35%.*

*The per-patient-per-month charges were 215,45 €, with a continous increase from 84.64 € on stage 1 to 352.59 € on stage 5 of chronic kidney disease. Erythropoiesis stimulants were reponsible of 46.5% of these cost. The most frequent prescribed medications were antihypertensive drugs, statins and iron preparations.*

*Patients with end stage renal disease generate significant cost during the predialysis period. The limited resources, and the growth of health care expeditures, particulary the spending for prescriptions drugs, are two of the major problems for Healt Care Systems. A better knowledge of the associated costs to the treatment of these patients will help us to increase our efficiency.*

Key words: **End stage renal disease. Predialysis. Cost. Treatment.**

## EL COSTE DEL TRATAMIENTO FARMACOLÓGICO EN ENFERMEDAD RENAL CRÓNICA

## RESUMEN

*La prevalencia e incidencia de la enfermedad renal crónica ha aumentado considerablemente a lo largo de los últimos años. Sabemos que el tratamiento de estos pacientes conlleva un elevado coste. Actualmente disponemos de una información limitada en relación a los recursos empleados en los cuidados de los pacientes en su etapa prediálisis.*

*El objetivo de este trabajo es determinar el gasto farmacéutico de los pacientes antes del inicio del tratamiento sustitutivo. Para ello analizamos el coste del tra-*

tamiento de 200 pacientes seguidos en la consulta externa de Nefrología. La edad media de la muestra fue de 72,4 años, siendo el 59% hombres, y con una comorbilidad distribuida en: hipertensión 87%, dislipemia 56% y diabetes 35%.

El gasto por paciente y mes fue de 215,45 €, observándose un incremento continuo desde 84,64 € en la fase I hasta 352,59 € en la fase V de la enfermedad renal crónica. Los estimulantes de la eritropoyesis fueron responsable del 46,5% de estos costes. Los fármacos prescritos con mayor frecuencia fueron hipotensores, hipolipemiantes y suplementos de hierro.

Los pacientes con enfermedad renal crónica generan un gasto significativo durante la etapa prediálisis. Los recursos limitados, y el crecimiento de los gastos sanitarios, particularmente los debidos a la farmacia, son dos de los principales problemas de los sistemas sanitarios. Un mejor conocimiento de los costes asociados al tratamiento de estos pacientes nos ayudará a incrementar nuestra eficiencia.

Palabras clave: **Enfermedad renal crónica. Prediálisis. Coste. Tratamiento.**

## INTRODUCTION

Patients with chronic renal disease on renal replacement therapy (CRDRT) account for 0.08% of the population in developed countries, whereas their treatment accounts for 1-2% of health care expenditures.<sup>1</sup> For Medicare, it has been calculated that CRDRT patients, representing approximately 0.5% of the system beneficiaries, consume 5% of total costs, approximately 10 fold as compared to the general population.<sup>2</sup> The first estimations in the case of individuals with pre-dialysis chronic renal disease (CRD) are even more evident. Phase 1-4 CRD patients account for 3.3% of the population assisted by Medicare, consuming 5.5-8% of health care budget, which represents 1.6-2.4 times more than CRDRT patients.<sup>3</sup>

Health care expenditure in Spain follows the same trend as other advanced nations, with a continuous and progressive increase since several years, being currently one of the main management problems both at an Autonomic and at a National level. The latest data from the Ministry of Health indicate that national pharmaceutical costs have gone up by 7.27% (8.68% in the Autonomous Community of Valencia), with a mean increase per prescription of 1.13%.<sup>4</sup> Extrapolating the cumulated annual cost of the population from the Community of Valencia, we may estimate that each inhabitant consumes between 200 and 230 € per year of prescribed medication (16.6-19.2 €/month).

It is more and more frequent to read articles in medical-scientific journals making reference to financial and health care cost issues. This is just a reflection of the increasing concern of medical personnel on this issue of health care. Mean age of the population, in general, and of the renal pa-

tient in particular, has ever increased in recent years. This prolonged longevity results in higher prevalence of chronic diseases, two of the main reasons leading to increase medical prescription. Besides, in many cases these medications are costly because of being new, a third factor for putting up the price of treatments.<sup>5</sup> One of the main measures to halt and rationalize pharmaceutical costs is the introduction of generic drugs, a strategy that has become real in many neighbor countries.

The main goal of the present work has been to calculate the pharmaceutical expenditure of patients from an outpatient nephrology clinic that mainly takes care of patients in their period prior to replacement therapy. On the other hand, we have also focused on analyzing some of the demographic and clinical characteristics of these patients.

## PATIENTS AND METHODS

We carried out a retrospective study including CRD patients who visited the outpatient clinic between March of 2004 and February of 2005 (12 months total). Four patients were excluded; three for insufficient data, and a fourth one with a diagnosis of primary hypertension, with no pathological or functional renal impairments, leaving a final sample of 200 patients.

We have gathered the following variables:

- Demographic data: age, gender.
- Anthropometric data: weight, height, and body mass index (BMI).
- Laboratory data: calculated creatinine clearance in 24-hour urine sample

R. PONS y cols.

- Clinical or comorbidity data: diagnosis of arterial hypertension (AHT), diabetes mellitus, or dyslipidemia (DL).
- Prescribed treatment: drugs written on the patient clinical chart, including erythropoietin and darbepoietin.

All this information was obtained in a cross-sectional way at February 28<sup>th</sup> of 2005, including the latest data of each patient: anthropometrical, analytical, and of treatment, so that the results would be the more up to date as possible.

To obtain the price of medications patients received, including erythropoiesis stimulants (ES), we have used the pharmacological therapy guide MEDICUM®, 9<sup>th</sup> edition – 2004.

Pharmaceutical expenditure has been expressed as euros/patient/month, considering a month as 30 days. For each medication, we have calculated the price in euros/unit (tablet, capsule, pill, etc.), since many dispensation blisters do not include 30 units. Thus, in order to obtain the monthly cost for any drug, we have multiplied the price of one unit by the number of units consumed during 30 days. For calculating the units of ES, we have done the same but in this case we have multiplied units/week by 4.3 weeks to obtain total units consumed per month.

We calculated the comorbidity index by presence of AHT, DM and/or DL. Each diagnosis has been attributed one point, so that the highest comorbidity score a patient may have is 3, and the least is 0.

The study results are essentially descriptive. In case we needed to perform a statistical analysis, we used the SigmaStat® software.

## RESULTS

### Patients Characteristics

Mean age of the sample was 72.4 years, being compounded by 59% male patients (table I). A more

**Table I.** Demographic and laboratory data

|              | n          | Age         | % Male    | Cr Cl     |
|--------------|------------|-------------|-----------|-----------|
| <b>CRD 1</b> | 4          | 57          | 50        | 93        |
| <b>CRD 2</b> | 15         | 63          | 80        | 68        |
| <b>CRD 3</b> | 75         | 73          | 66        | 39        |
| <b>CRD 4</b> | 80         | 75          | 47        | 22        |
| <b>CRD 5</b> | 26         | 72          | 65        | 12        |
| <b>Total</b> | <b>200</b> | <b>72.4</b> | <b>59</b> | <b>32</b> |

Cr Cl: Creatinine clearance.

detailed analysis of the age variable shows that more than 75% of our patients are older than 65 years, and some 25% are older than 80 years. Since patients were on different CRD stages, we observed that 77.5% of them were on stages 3 and 4. As it was expected, the least numbered group of patients, only four, comprise stage 1 CRD, so that results related with this stage are anecdotic, being influenced by the high comorbidity of patients.

The most prevalent comorbidity diagnosis in our patients has been AHT, accounting for 87%, followed by dyslipidemia and diabetes mellitus, with 56% and 35%, respectively (Table II). Although they have not been included in the comorbidity index, we believe it is interesting to include other related data such as BMI and percentage of patients on anti-aggregants and with anti-coagulation therapy. The results obtained show a mean BMI leading to obesity diagnosis in all CRD stages but in stage 5. When looking at BMI distribution by quartiles, we have a more direct idea on the sample reality, with BMI values of 27, 30.5, and 33.8 corresponding to quartiles 25, 50, and 75, respectively. About the next parameter, anti-aggregation/anti-coagulation therapy, we may consider it as a cardiovascular risk marker since it is related with the presence of peripheral arteriopathy, coronary heart disease, or cerebrovascu-

**Table II.** Comorbidity data

|              | Comorbidity | % AHT       | % DM      | % DL      | % Anti-aggreg. | % Anticoag. | BMI         |
|--------------|-------------|-------------|-----------|-----------|----------------|-------------|-------------|
| <b>CRD 1</b> | 2           | 100         | 50        | 50        | 25             | 0           | 31.4        |
| <b>CRD 2</b> | 1.8         | 93          | 27        | 60        | 33.3           | 6.7         | 32.1        |
| <b>CRD 3</b> | 2.09        | 89.5        | 46        | 72        | 37             | 13          | 31.2        |
| <b>CRD 4</b> | 1.52        | 83.5        | 27        | 42.3      | 44.4           | 7.4         | 30.2        |
| <b>cRD 5</b> | 1.54        | 88.5        | 27        | 38.5      | 23             | 11.5        | 29.3        |
| <b>Total</b> | <b>1.76</b> | <b>87.1</b> | <b>35</b> | <b>56</b> | <b>31</b>      | <b>8.4</b>  | <b>30.7</b> |

% Anti-aggreg: % of patients on anti-aggregants, %Anti-coag.: % of anti-coagulated patients, %DL: % of patients with dyslipidemia, %DM: % of diabetic patients, %AHT: % of hypertensive patients, BMI: body mass index.

lar disease. The only related datum that we may foresee in this sense is the number of patients with atrial fibrillation, reaching approximately 10% of the subjects included in our study.

### Pharmaceutical expenditure

Total cost from prescriptions during one month for the 200 patients as a whole was 43,092 €, a figure that is halved, 27,074 €, if we exclude ES ( $p < 0.001$ ). These global figures result in mean cost per patient per month of 215.45 € and 115.40 €, respectively ( $p < 0.05$ ).

After patient distribution by CRD stages, we see a progressive increase of monthly cost, which is more pronounced if we considered ES (Table III).

When evaluating other possible factors affecting pharmaceutical expenditure of patients, we observe that gender and age are not determinant, a fact that may be subjected, in the second case, to high mean age of our sample.

About patients' comorbidity, we observed its importance in monthly cost of patients' treatment, if ES were excluded (table IV, fig. 1). In this way, the resulting mean monthly cost per patient was 50€, 92€, 121€, and 158€ for a comorbidity index of 0, 1, 2, and 3, respectively ( $p < 0.05$ ). When we incorporated the cost of ES, these differences vanished, with a mean cost between 195-236 € ( $p = NS$ ).

We decided to analyze in detail DM due to its known importance on morbidity and mortality of CRD patients. Sixty-six percent out of the 69 patients diagnosed with diabetes mellitus received insulin therapy, whereas 34.7% receive oral anti-diabetics, the most prescribed being repaglinide. Four patients had combined therapy with insulin and oral anti-diabetics. Table V summarizes the most important findings from these patients, and compares them with the remaining sample.

**Table III.** Pharmaceutical cost

|              | €/pt/month<br>(ES excluded) | % pt with<br>ES | €/pt/month<br>(ES included) |
|--------------|-----------------------------|-----------------|-----------------------------|
| CRD 1        | 84.64                       | 0               | 84.64                       |
| CRD 2        | 84.72                       | 6.7             | 98.21                       |
| CRD 3        | 111.37                      | 24              | 153.62                      |
| CRD 4        | 120.1                       | 31              | 257.39                      |
| CRD 5        | 126.7                       | 74.6            | 352.59                      |
| <b>Total</b> | <b>115.40</b>               | <b>46.5</b>     | <b>215.45</b>               |

€/pt/month: Euros per patient per month, ES: eritropoyesis stimulants, % pt with ES: Percentage of patients treated with eritropoyesis stimulants.

Among pharmacological groups, ES are, by large, the main responsible of pharmaceutical expenditure of CRD patients, comprising 46.5% of the whole. In order to obtain more friendly user data, we decided to carry out an analysis of the influence of the remaining drugs, excluding ES. In this way, we may see how the cost of treatment received by the patient depends by large of hypotensive drugs, hypolipidemic agents, and drugs related with management of bone disease secondary to CRD (Fig. 2). As expected, the percentage influence of the latter is more evident in the last stage of CRD, mainly in the subgroup of patients with stage 5 CRD who will start on renal replacement therapy, in whom this cost accounts for up to 31.5% of patient's pharmaceutical expenditure.

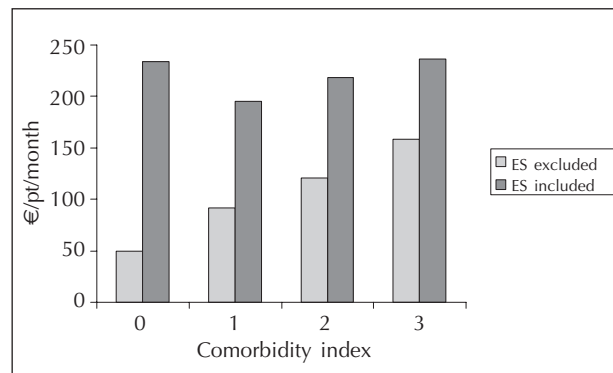
As for hypotensive drugs, the most frequently used ones are loop diuretics (47%) and calcium-channel blockers (41%) (Fig. 3). Sixty-five percent of patients received treatment with ACEI or ARA-II. For managing their blood pressure, patients consume an average of 2.2 hypotensive drugs.

As for the whole pharmacological groups, hypotensive drugs are the most frequently prescribed (87%), followed by hypolipidemic drugs (53%) and oral iron (51%) (fig. 4).

**Table IV.** Comorbidity and treatment cost

|          | n  | Age | Cr Cl | €/pt/month<br>(ES excluded) | €/pt/month<br>(ES included) |
|----------|----|-----|-------|-----------------------------|-----------------------------|
| <b>0</b> | 12 | 81  | 18    | 50                          | 235                         |
| <b>1</b> | 64 | 73  | 29    | 92                          | 195                         |
| <b>2</b> | 82 | 71  | 32    | 121                         | 218                         |
| <b>3</b> | 42 | 70  | 37    | 158                         | 236                         |

€/pt/month: Euros per patients per month. ES: eritropoyesis stimulants. Cr Cl: Creatinine clearance.



**Fig. 1.**—Comorbidity and treatment costs.

**Tabla V.** Characteristics of diabetic patients

| Diabetes                 | YES  | NO   | p      |
|--------------------------|------|------|--------|
| €/pt/month (ES included) | 248  | 200  | NS     |
| €/pt/month (ES excluded) | 145  | 100  | < 0.05 |
| Mean Age                 | 73   | 71   | NS     |
| % Male                   | 60   | 58   | NS     |
| Cr Cl                    | 35   | 30   | < 0.05 |
| BMI                      | 32.2 | 30   | < 0.05 |
| Comorbidity Index        | 1.55 | 1.35 | < 0.05 |
| % Hypertensive           | 91.2 | 85   | NS     |
| % with ACEI/ARA II       | 81   | 56   | < 0.05 |
| % Dyslipidemic           | 66   | 49   | < 0.05 |

€/pt/month: Euros per patients per month. ES: eritropoiesis stimulants. Cr Cl: Creatinine clearance. BMI: body mass index.

## DISCUSSION

We have currently available an amount of literature evaluating and quantifying the financial impact of stage 5 CRD patients on renal replacement therapy.<sup>2,6-9</sup> Most of these studies mention pharmaceutical cost related to dialysis therapy, and essentially to erythropoietin, which comprises more than 50% of total pharmacy costs. In the cases in which somehow pharmaceutical cost is analyzed as a whole, it accounts for 16-21% of total cost associated to a patient. In a study carried out by our group,<sup>9</sup> in which costs associated to different kinds of hemodialysis are analyzed, pharmacy accounts for 13.4% of the hemodialysis session; approximately 24\_ per treatment (310 €/patient/month).

On the other hand, we may find studies indicating that slowing CRD progression may have a beneficial economic impact.<sup>10,11</sup> McLaughlin<sup>11</sup> did an

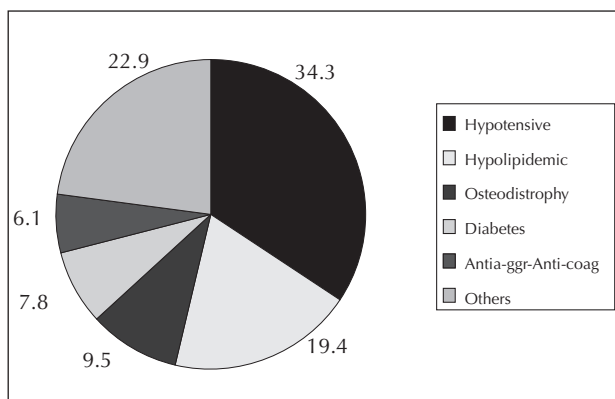


Fig. 2.—Percentage of expenditure by pharmacological group.

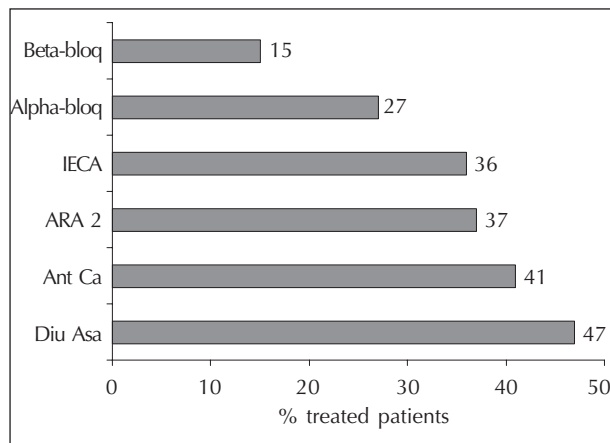


Fig. 3.—Hypotensive drugs.

estimation of the evolution of 1000 patients with creatinine clearance of 20 mL/min throughout 5 years. Patients receiving nephrologic care consumed 20% less costs, as compared to those referred late, partially due to the selection of cheaper replacement therapies.

Peter<sup>12</sup> retrospectively analyzed health care cost during 24 months before dialysis onset, showing an acute cost increase within 6 months before dialysis, hospitalization being the main reason. Diabetic patients also had greater resource consumption than those with cardiovascular disease and those initiating hemodialysis (as compared to those on peritoneal dialysis or transplantation), although the latter group is composed by older patients with higher comorbidity.

However, as Mendelssohn<sup>13</sup> states in his work, although it seems evident that multidisciplinary care before dialysis is beneficial, «the financial issue in predialysis care is in its childhood.»

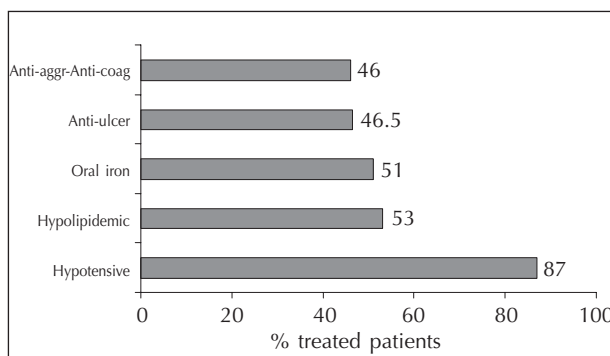


Fig. 4.—Anti-aggregants and oral anticoagulation agents.



Smith<sup>14</sup> compared stages 2-4 CRD patients with other with no renal disease assisted by a health care organization. Throughout the observation period (5.5 years) CRD patients had significantly higher costs, and although there is no particular reference to pharmaceutical cost, he did indicate that they had 1.9-2.5 more prescriptions than the control group.

In his work published in 2002<sup>15</sup> and 2003<sup>16</sup>, London followed up 1936 patients during the 12 months before starting replacement therapy, observing that patients had an average pharmacy expenditure of 125\$/month, the most frequently used drugs being loop diuretics and ACEIs. When comparing pharmacy costs between treated and non-treated patients with ES, he did not find statistically significant differences (157 vs. 122\$/patient/month). However, when studying anemia management, he observed that only 10.5% are treated with erythropoietin in spite anemia being diagnosed in 47.4% of the cases, a fact that probably accounts for this lack of cost difference between both groups. The monthly cost in our study for non-ES treated patients has been 115.4\_/patient/month, whereas the percentage of ES-treated patients (similar to percentage of anemic patients) was 46.5%, a finding very similar to that found by London in his work.

In another study published in 2003, Robbins<sup>17</sup> distributed 2114 patients into three periods: predialysis (from month 6 to month 2 before replacement therapy onset), peri-dialysis (from one month before to one after dialysis onset), and postdialysis (2-3 months after dialysis onset). In this case, monthly pharmacy cost for each period was 206, 227, and 222\$ per patient. Nine to thirty-one percent of the patients were treated with erythropoietin during months before dialysis, with no reference to percentage of anemic patients. There are only 11.4% of patients on ACEIs therapy, although 35% of the patients were diabetics. In our case, 81% of diabetics, with a prevalence similar to that of Robbins' population, are treated with ACEI or ARA-II agents.

Our study is limited by the small number of patients in the first two stages of CRD, a fact that is a logical picture of our working reality. The increase in pharmaceutical expenditure as CD advances is an indisputable fact, characterized by the need for ES, and for the increasing usage of other drugs such as chelating agents or calcitriol. Patients' age has not been a determinant factor in pharmaceutical expenditure, a situation that may have been conditioned by the lower comorbidity of older patients and by the limited group of patients younger than 65 years (n = 38). In any case, according to our results, pharmaceutical expenditure of CRD patients is 6-12 times

higher than that of the general population, a fact that we should consider when selecting one or the other therapeutic options.

Our daily duty should be supported in evidence-based medicine, which will provide us with the necessary efficiency to justify each one of our decisions. We currently have available the Guidelines on Kidney and Cardiovascular Disease of the Spanish Society of Nephrology.<sup>18</sup>

Maybe in this way we will overcome the clinical-financial dilemmas as the already posed with diabetic nephropathy management<sup>19</sup> of selecting between ACEIs or ARA-II, with some interesting conclusions.

## CONCLUSIONS

Financial cost derived from treating chronic renal disease patients is paramount, both because of the high prevalence of this condition and because of the associated comorbidity.

We are currently facing a problem with therapeutic prescription, largely due to the big therapeutic armamentarium that pharmaceutical companies has made available. As Kronick<sup>20</sup> states in a recent editorial, «it is hard to find money, but expending correctly is even harder.»

Once generic drugs have been incorporated, the following step may be to question who should pay the cost difference between a generic drug and a *trade-mark*,<sup>22</sup> since it has been shown that there are no efficacy differences between both.

The EPIRCE study will show us the underwater part of the iceberg that we will have to face. With the outcomes in hand, we will be able of doing an appropriate health care planning and ask our managers the necessary resources to direct the future tract of chronic renal disease.

This work has been made possible, partially, thanks to the collaboration grant from Roche Laboratories to our Department.

## REFERENCES

1. Manns B, Taub K, Donaldson C: Economic Evaluation and End-Stage Renal Disease: from Basics to Bedside. *Am J Kid Dis* 36: 12-28, 2000.
2. Ploth D, Shepp P, Counts C, Hutchinson F: Prospective Analysis of Global Costs for Maintenance of Patients With ESRD. *Am J Kid Dis* 42: 12-21, 2003.
3. Hunsicker LG: The consequences and cost of chronic kidney disease before ESRD. *J Am Soc Nephrol* 15: 1363-1364, 2004.
4. Nota de Prensa del Ministerio de Sanidad y Consumo del 21-feb-05. Página web: <http://www.msc.es>

## R. PONS y cols.

5. Steinbrook R: The Prescription-Drug Problem. *N Engl J Med* 346: 790, 2002.
6. Rodríguez-Carmona A, Pérez Fontán M, Valdés Cañedo F: Estudio comparativo de costes de las diferentes modalidades de diálisis. *Nefrología* 16: 539-548, 1996.
7. Martín Hernández R: Aspectos económicos del tratamiento con diálisis de la IRCT. *Nefrología* 16: 81-92, 1996.
8. Martín Hernández R: Análisis de los costes en nefrología: situación actual y perspectivas de futuro. *Nefrología* 18: 40-51, 1998.
9. Hernández-Jaras J, García H, Bernat A, Cerrillo V: Aproximación al análisis de costes de diferentes tipos de hemodiálisis mediante unidades relativas de valor (URV). *Nefrología* 20: 284-289, 2000.
10. Trivedi H, Pang M, Campbell A y cols.: Slowing the Progression of Chronic Renal Failure: Economic Benefits and Patient's Perspectives. *Am J Kid Dis* 39: 721-729, 2002.
11. McLaughlin K, Manns B, Culleton B y cols.: An Economic Evaluation of Early Versus Late Referral of Patients With Progressive Renal Insufficiency. *Am J Kid Dis* 38: 1122-1128, 2001.
12. Peter W, Kahn S, Ebben J, Pereira B, Collins A. Chronic Kidney disease: the distribution of health care dollars. *Kidney Int* 66: 313-321, 2004.
13. Mendelssohn DC. Coping with the CKD epidemic: the promise of multidisciplinary team-based care. *Nephrol Dial Transplant* 20: 10-12, 2005.
14. Smith DH, Gullion CM, Nichols G, Keith DS, Brown JB. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. *J Am Soc Nephrol* 15: 1300-1306, 2004.
15. London R, Solis A, Goldberg G, Wade S, Ryu S: Health Care Resource Utilization and Impact of Anemia Management in Patients With Chronic Kidney Disease. *Am J Kidney Dis* 40: 539-548, 2002.
16. London R, Solis A, Goldberg G y cols.: Examination of Resource Use and Clinical Interventions Associated With Chronic Kidney Disease in a Managed Care Population. *J Manag Care Pharm* 9: 248-255, 2003.
17. Robbins JD, Kim JJ, Zdon G y cols.: Resource use and patient care associated with chronic kidney disease in a managed care setting. *J Manag Care Pharm* 9: 238-247, 2003.
18. Guías SEN: Riñón y Enfermedad Cardiovascular. *Nefrología* 24 (Supl. 6), 2004.
19. Mitch WE: Treating Diabetic Nephropathy – Are There Only Economic Issues? *N Engl J Med* 351: 1934-1936, 2004.
20. Kronick R: Financing Health Care – Finding the Money Is Hard and Spending It Well Is Even Harder. *N Engl J Med* 352: 1252-1254, 2005.
21. Scherer FM: The Pharmaceutical Industry – Prices and Progress. *N Engl J Med* 351: 927-932, 2004.