Clinical Kidney Journal, 2023, vol. 16, no. 12, 2493–2502

https://doi.org/10.1093/ckj/sfad152
Advance Access Publication Date: 29 June 2023
Original Article

ORIGINAL ARTICLE

Opportunities to improve the management of anemia in peritoneal dialysis patients: lessons from a national study in routine clinical practice

Jose Portoles [1,2], Maria Luisa Serrano Salazar[3], Olga González Peña[4], Sandra Gallego Domínguez[5], Manel Vera Rivera [6], Jara Caro Espada[7], Alba Herreros García[8], Maria Antonia Munar Vila[9], Maria José Espigares Huete[10], Haridian Sosa Barrios [11], Vicente Paraíso[12], Loreto Mariscal de Gante[13], Maria Auxiliadora Bajo[14], Antonia Gueorguieva Mijaylova[15], Elena Pascual Pajares[16], Nuria Areste Fosalba[17], Laura Espinel[18], Fernando Tornero Molina[19], Soledad Pizarro Sánchez[20], Mayra Ortega Díaz[21], Aleix Cases [2,6,22] and Borja Quiroga [2,23]

[1]Nephrology Department, Hospital Universitario Puerta de Hierro, Facultad de Medicina, Universidad Autónoma de Madrid, IDIPHISA, Madrid, Spain, [2]Anemia Working Group of the Spanish Society of Nephrology, Spain, [3]Nephrology Department, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain, [4]Nephrology Department, Hospital Universitario Basurto, Bilbao, Spain, [5]Nephrology Department, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain, [6]Nephrology Department, Hospital Clinic, Barcelona, Spain, [7]Nephrology Department, Hospital Universitario Doce de Octubre, Madrid, Spain, [8]Nephrology Department, Fundación Puigvert, Barcelona, Spain, [9]Nephrology Department, Hospital Universitario Son Espases, Mallorca, Spain, [10]Nephrology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain, [11]Nephrology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain, [12]Nephrology Department, Hospital Universitario Henares, Madrid, Spain, [13]Nephrology Department, Hospital Universitario de la Princesa, Madrid, Spain, [14]Nephrology Department, Hospital Universitario La Paz, Madrid, Spain, [15]Nephrology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain, [16]Nephrology Department, Complejo Hospital Universitario de Toledo, Toledo, Spain, [17]Nephrology Department, Hospital Virgen de la Macarena, Sevilla, Spain, [18]Nephrology Department, Hospital Universitario de Getafe. Madrid, Spain, [19]Nephrology Department, Hospital Universitario Sureste, Madrid, Spain, [20]Nephrology Department, Hospital Universitario Rey Juan Carlos, Madrid, Spain, [21]Nephrology Department, Hospital Universitario Infanta Leonor, Madrid, Spain, [22]Medicine Department, Universitat de Barcelona, Barcelona, Spain and [23]IIS-La Princesa, Nephrology Department, Hospital Universitario de la Princesa, Madrid, Spain

Correspondence to: Aleix Cases; E-mail: acases@ub.edu

Received: 13.3.2023; Editorial decision: 25.6.2023

ABSTRACT

Background. Current guidelines establish the same hemoglobin (Hb) and iron biomarkers targets for hemodialysis (HD) and peritoneal dialysis (PD) in patients receiving erythropoiesis-stimulating agents (ESAs) even though patients having PD are usually younger, more active and less comorbid. Unfortunately, specific renal anemia [anemia in chronic kidney disease (aCKD)] trials or observational studies on PD are scanty. The aims of this study were to describe current aCKD management, goals and adherence to clinical guidelines, identifying opportunities for healthcare improvement in PD patients.

Methods. This was a retrospective, nationwide, multicentre study including patients from 19 PD units. The nephrologists collected baseline data, demographics, comorbidities and data related to anemia management (laboratory values, previously prescribed treatments and subsequent adjustments) from electronic medical records. The European adaptation of KDIGO guidelines was the reference for definitions, drug prescriptions and targets.

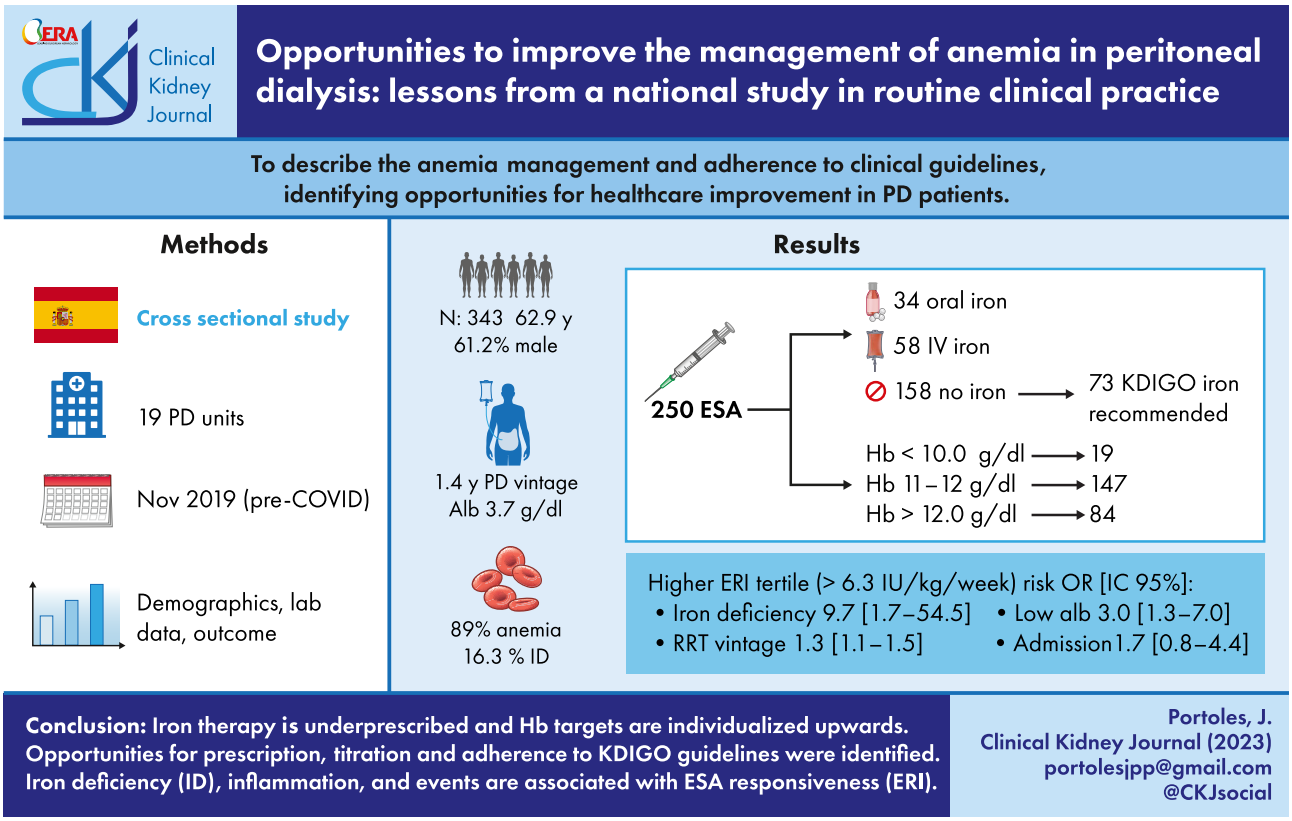
Results. A total of 343 patients (mean age 62.9 years, 61.2% male) were included; 72.9% were receiving ESAs and 33.2% iron therapy [20.7% intravenously (IV)]. Eighty-two patients were receiving ESA without iron therapy, despite 53 of them having an indication according to the European Renal Best Practice guidelines. After laboratory results, iron therapy was only started in 15% of patients. Among ESA-treated patients, 51.9% had an optimal control [hemoglobin (Hb) 10–12 g/dL] and 28.3% between 12–12.9 g/dL. Seventeen patients achieved Hb >13 g/dL, and 12 of them remained on ESA after overshooting. Only three patients had Hb <10 g/dL without ESAs. Seven patients (2%) met criteria for ESA resistance (epoetin dose >300 IU/kg/week). The highest tertile of erythropoietin resistance index (>6.3 UI/kg/week/g/dL) was associated with iron deficiency and low albumin corrected by renal replacement therapy vintage and hospital admissions in the previous 3 months.

Conclusion. Iron therapy continues to be underused (especially IV). Low albumin, iron deficiency and prior events explain most of the ESA hyporesponsiveness. Hb targets are titrated to/above the upper limits. Thus, several missed opportunities for adequate prescriptions and adherence to guidelines were identified.

LAY SUMMARY

Renal anemia is common in peritoneal dialysis (PD) patients. Current guidelines recommend how to diagnose and treat it with iron and erythropoiesis-stimulating agents (ESAs). Unfortunately, evidence in PD is weaker and most recommendations have been adapted from hemodialysis patients. Our retrospective study describes current anemia practices and the degree of adherence to clinical guidelines in a sample representing 12% of PD patients in our country. The key findings are: a relevant percentage of prescriptions do not conform to guidelines; and hemoglobin targets are titrated upwards, even above 12 g/dL in PD. Iron deficiency, malnutrition and previous events accounted for most of the ESA hyporesponse, and iron therapy (especially intravenous) continues to be underused. This should promote improvement strategies such as: structured dissemination of guidelines; clinical routes for in-hospital intravenous iron administration to PD patients; and computer-assisted prescription tools and early identification of ESA resistance or inflammation. Lastly, specific studies on anemia in PD patients are needed to generate reliable evidence to individualize prescriptions and targets in this population.

GRAPHICAL ABSTRACT



Keywords: anemia, erythropoiesis-stimulating agents, guidelines, hemoglobin target, peritoneal dialysis

INTRODUCTION

Anemia is a well-recognized complication in patients with chronic kidney disease (CKD). Its development is driven by several factors such as inadequate erythropoietin (EPO) production, iron deficiency, inflammation and high hepcidin levels (which impairs dietary iron absorption and mobilization from iron stores) and a shortened red blood cell survival, among others [1, 2]. Anemia prevalence increases with CKD progression, appearing in <20% of patients with CKD stage 3b, 78% in CKD stage 5 and >90% in dialysis patients [3–6]. In contrast, iron deficiency appears earlier in CKD and remains constant from CKD stages 3 to 5 at around 50% [4]. Interestingly, anemia treatment patterns differ in peritoneal dialysis (PD) and hemodialysis (HD) patients due to their different features. The HD technique is associated with significant blood losses through the extracorporeal circuit, as well as peristaltic blood pump–induced hemolysis, together with hemoconcentration at the end of the session. In contrast, PD patients are usually younger, more active and less comorbid, with lower inflammation, usually maintain better residual renal function (RRF) and do not experience episodes of hemoconcentration. Altogether, these differences determine that patients on PD have better anemia control, requiring lower doses of erythropoiesis-stimulating agents (ESAs) and iron than those on HD [5, 6].

It is well established that the presence of anemia in patients with CKD is associated with poorer quality of life and higher symptom burden (i.e. asthenia, reduced exercise tolerance, sleep disorders and fuzzy mind, among others) [7]. In addition, anemia is associated with an increased risk of adverse clinical outcomes [mortality, major adverse cardiovascular events (MACE), hospitalizations or CKD progression] [8]. Most of this evidence is based on HD and non-dialysis-dependent CKD (NDD-CKD) cohort studies. However, evidence on anemia prevalence and management in PD patients is scarce and recommendations are usually extrapolated from HD and NDD-CKD studies [9].

Current clinical guidelines establish the same hemoglobin (Hb) target with ESA in anaemic patients under both dialysis techniques [10], although the indication for individualization likely allows a wider Hb margin in PD patients vs HD patients, since they are usually younger and more physically active, the continuous technique is not associated with post-dialysis hemoconcentration, and they usually have a lower burden of cardiovascular disease, diabetes and other comorbidities [9, 10]. Unfortunately, we do not have randomized controlled trials evaluating the efficacy and safety of Hb normalization with ESA in PD patients, thus extrapolation from the results of randomized controlled trials in HD and NDD-CKD patients are needed [11–14].

Because of the lack of strong evidence on the management of anemia in CKD (aCKD) in PD, the Spanish Society of Nephrology undertook a real-world study to evaluate the anemia prevalence, prescription patterns and adherence to current guidelines recommendations.

MATERIALS AND METHODS

The PD-anemia study is a nationwide, non-interventional, retrospective, clinical real-world study that included 19 PD units in Spain. The Anemia Working Group of the Spanish Society of Nephrology designed and conducted the study. The study included all prevalent PD patients that were active in the technique in November 2019 for at least 3 months. We chose this timeframe to avoid COVID-19 pandemic-related interference. Exclusion criteria were having received a previous kidney transplant and being on PD due to a cardiorenal syndrome with diuretic resistance and a residual renal function >20 mL/min/1.73 m^2.

At baseline, nephrologists in charge of the patients collected demographical data, cause of CKD, comorbidities, data on PD prescriptions (i.e. PD technique, Kt/V), anemia treatments and laboratory values from the different structured PD–electronic medical records (PD-EMR) available in every regional healthcare system. We did not ask for reasons for not prescribing ESA or iron in those patients who were not receiving it. Data on ESAs and iron prescriptions during the previous 4 months and their adjustments in the follow-up visits after knowing laboratory values was also collected. All values were included in a dedicated database for the analysis. The ESA resistance index (ERI) was calculated as a dose-response score defined as epoetin dose [international units (IU) per kg per week] per g/dL of Hb. Darbepoetin dose in µg/kg/week was transformed to epoetin using a 1 to 200 conversion factor [14, 15]. ESA resistance in this study was defined as a subcutaneous ESA dose >300 U/kg/week or an ERI ≥12.7 U/kg/week/Hb g/dL [15]. We also performed an analysis of factors associated with the higher ERI tertile.

Anemia was defined as Hb <13 g/dL in men and Hb <12 g/dL in women, or any Hb under ESAs treatment according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [10]. The European Renal Best Practice (ERBP) position statement suggested adapting the KDIGO recommendation for ESA treatment to the European population [16], suggesting achieving and maintaining Hb levels between 10 and 12 g/dL, but individualizing the target according to the comorbidities of the patients. However, Hb values >13 g/dL should not be intentionally aimed for during ESA therapy.

Absolute iron deficiency (ID) was defined as a transferrin saturation index (TSAT) <20% and serum ferritin concentration <100 ng/mL [16]. Functional iron deficiency (FID) was defined by a TSAT ≤20% and normal-elevated ferritin levels [16].

The indication for iron therapy prescription was defined according to the EBRP position statement [16]. (1) Among patients with CKD with anemia who are not on iron or ESA therapy, a trial of intravenous (IV) iron or a 3-month oral iron trial was prescribed , with a switch to the IV route if oral iron was unsuccessful or not tolerated in the case of an absolute iron deficiency (TSAT < 20% and serum ferritin < 100 ng/mL) (2) if an increase in Hb concentration without starting ESA treatment was desired and TSAT was < 25% and ferritin was < 300 ng/mL and (3) among patients treated with ESA if an increase in Hb concentration or a decrease in ESA dose was desired and TSAT was < 30% and ferritin was < 300 ng/ mL . The upper limit of TSAT of 30% and of serum ferritin of 500 ng/mL should not be intentionally exceeded [16].

Statistical analysis

We calculated a sample size of 265 to estimate the percentage of patients with Hb on target, considering a prevalence of 75% of PD patients on ESAs and 72% of them on target [5, 10] with a precision of 5% in a two-tailed test. Continuous variables were expressed as means and standard deviations (SD) or median and interquartile range (IQR), and categorical variables as valid percentages. Comparisons between groups were performed using the Chi-square or Fisher's exact tests for qualitative variables and Student's *t*-test/analysis of variance or Mann–Whitney/Kruskal–Wallis tests for quantitative variables. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. A *P*-value <.05 was considered statistically significant. To analyse factors associated with ESA hyporesponse, we selected the higher tertile of ERI (low response) as the main variable, and we performed a univariate logistic regression to estimate the odds ratio for each associated factor. This analysis was followed by a backward/forward multivariate model incorporating all variables that resulted in a *P*-value of <.10, in addition to all clinically relevant variables. The final model selected was that which was simplest and yielded the maximum R^2 value.

The statistical package STATA 14.0 (Stata Statistical Software: Release 14, Stata Corp. LP, College Station, TX, USA) was used for the statistical analysis.

Compliance with ethics guidelines

Study protocols were approved by Hospital Puerta de Hierro Ethics Committee (n 157/21) and were conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization guidelines for Good Clinical Practice, and any other applicable local health and regulatory requirements.

RESULTS

Baseline characteristics

We included 343 patients with a mean age of 62.9 (SD 14.4) years, 61.2% male, and a median PD vintage of 1.4 (IQR 0.7–2.6) years. Anemia was present in 89.0% of the whole sample [Hb 11.7 (1.3) g/dL, ferritin 259 (148.8–456) mg/dL and TSAT in 29.5% (SD 10.9)] (Table 1).

ESA treatment patterns

Among the 343 included patients, 72.9% were on ESA treatment and 33.2% were receiving iron therapy (Table 1). The type of ESA was unique for each PD unit, with most patients receiving darbepoetin [77.2%, median dose 1.0 (0.6–1.7) µg/kg/month] followed by epoetin α [22.8%, median dose 133.3 (85.1–290.2) IU/kg/month] (Table 1).

Patients on ESA treatment were more frequently female ($P = .001$), more commonly were shifted from a previous HD technique ($P = .02$), and had a lower renal Kt/V ($P = .007$). Regarding analytical values, patients on ESA had higher Hb levels ($P < .001$), higher ferritin ($P = .02$) and lower serum albumin levels ($P = .002$) (Table 1).

Iron treatment patterns

Of the 343 patients, 11.9% had FID and 4.4% absolute ID. Patients on ESA treatment showed a lower prevalence of absolute ID but higher prevalence of FID (Table 2).

Two-thirds of the patients were not receiving any iron supplementation. IV iron was more frequently prescribed than the oral route (20.7% vs 12.5%). Ferric carboxymaltose was the first

Table 1: Patients' characteristics, dialysis data and laboratory results by ESAs prescription and whole sample.

	All ($n = 343$)	No ESA ($n = 93$)	ESA ($n = 250$)	P-value
Age (years)	62.9 (14.4)	62.5 (12.0)	63.1 (15.6)	.7
Male (%)	61.2	75.3	56	.001
Charlson's comorbidity index	5.4 (2.6)	5.2 (2.3)	5.5 (2.8)	.4
CKD etiology (%)				.1
Glomerular	22.6	21.5	23.2	
Diabetes mellitus	18.6	11.8	21.2	
HTN/nefroangiosclerosis	14.2	12.9	14.8	
APKD	12.1	16.1	10.4	
Interstitial	7.5	5.4	8.4	
Other/unknow	25.3	32.26	22	
Dialysis				
Dialysis vintage (years)	1.5 (0.7–2.7)	1.4 (0.7–2.4)	1.5 (0.7–2.8)	.9
Previous HD (%)	14.8	7.5	17.5	.02
PD vintage (years)	1.4 (0.7–2.6)	1.4 (0.7–2.4)	1.4 (0.7–2.6)	.9
Renal Kt/V renal	1.1 (0.8)	1.3 (0.9)	1.0 (0.8)	.007
Peritoneal Kt/V	1.2 (0.5)	1.0 (0.5)	1.2 (0.5)	.9
Weekly total Kt/V	2.3 (0.7)	2.3 (0.8)	2.2 (0.7)	.9
Iron therapy				.068
No iron (%)	66.8	76.3	63.2	
Oral iron (%)	12.5	9.7	13.6	
IV iron (%)	20.7	14.0	23.2	
ESA treatment				
Darbepoetin (%)	56.3		77.2	NA
Epoetin (%)	16.6		22.8	NA
ERI (IU/week/kg/Hb)			4.1 (2.3–7.6)	NA
Anemia (%)	89	60.2	100	NA
Absolute ID (%)	4.4	8.2	3.0	.044
FID (%)	11.9	5.7	14.2	.035
Hemoglobin distribution				<.001
Patients with Hb <9 g/dL (%)	2.3	2.2	2.4	
Patients with Hb 9–10 g/dL (%)	4.1	1.1	5.5	
Patients with Hb 10–11 g/dL (%)	17.8	7.5	21.6	
Patients with Hb 11–12 g/dL (%)	34.1	25.8	37.2	
Patients with Hb 12–13 g/dL (%)	28.3	32.3	26.8	
Patients with Hb >13 g/dL (%)	13.4	31.2	6.8	
Laboratory values				
Hb (g/dL)	11.7 (1.3)	12.4 (1.5)	11.5 (1.1)	<.001
Ferritin (ng/mL)	259 (148.8–456)	231.5 (114–375)	285 (160–504)	.02
TSAT (%)	29.5 (10.9)	30.5 (12.0)	29.1 (10.4)	.3
C-reactive protein (mg/L)	1.4 (0.4–4.8)	1.1 (0.4–2.9)	1.5 (0.4–6.2)	.3
Albumin (g/dL)	3.7 (0.5)	3.8 (0.4)	3.7 (0.5)	.002
Folic acid (ng/mL)	6.6 (4.3–10)	5.5 (4.4–9.0)	7 (4.2–11.7)	.2
Vitamin B_{12} (pg/mL)	551.4 (211.3)	582.6 (214.3)	540.8 (210.0)	.2

Data are shown as mean and (SD) or median and (IQR) or columns percentage.
APKD: autosomal polycystic kidney disease; HTN: hypertension; NA: not applicable.

choice (84.8%, cumulative median dose in the previous 4 months was 500 mg), followed by iron sucrose (13.0%, cumulative dose in the previous month was 200 mg). As shown in Table 2, we found significant differences between groups according to the iron prescription in the Charlson comorbidity index (greater), dialysis vintage (longer), renal Kt/V (lower), ferritin (higher), C-reactive protein (higher), albumin (lower) and Hb (higher) among those who received IV iron. ESA-treated patients received more frequently oral iron (13.6% vs 9.7%) and IV iron (23.2% vs 14.0%) than those without ESA ($P = .07$) (Fig. 1).

Among the 158 patients on ESA treatment but without an iron prescription, 53 had indication for iron prescription according to the ERBP, with 7 of them having absolute ID. Indeed, in 45 patients (84.9%) iron treatment was not prescribed after knowing the TSAT and ferritin results at the follow-up visit. If KDIGO recommendations were applied (i.e. iron use if TSAT <30% and ferritin <500 ng/mL for ESA-treated patients), the untreated patient rate would be even higher, 73 instead of 53 patients.

All patients with absolute ID on oral iron prescription were switched to IV iron after knowing the laboratory results. None of the 18 patients with more than 3 months on oral iron prescription and within the limits of guidelines were switched to IV as suggested by the European guidelines to improve efficacy.

Guideline target adherence

According to the EBPG recommendation, most ESA-treated patients (147/250) had an optimal Hb control within the 10–12 g/dL range. However, in 67 of the 250 patients, Hb was in the 12–12.9 g/dL range and in 17/250 Hb was above the limit of 13 g/dL. Mean ESA dose was higher among patients in the lower ranges of achieved Hb (Fig. 2).

Table 2: Patients' characteristics, dialysis data and laboratory results classified by iron therapy.

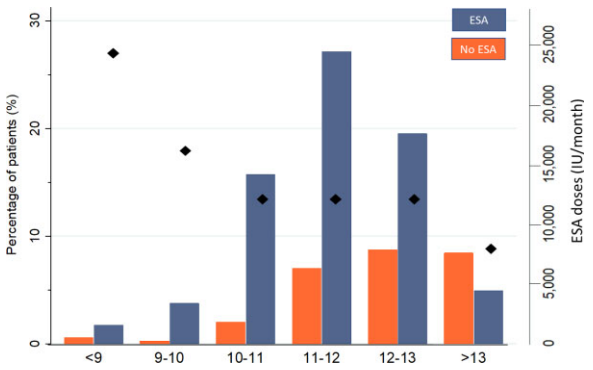
	IV iron ($n = 71$)	Oral iron ($n = 43$)	None ($n = 229$)	P-value
Age (years)	62.7 (15.7)	63.6 (15.6)	62.9 (13.8)	.944
Male (%)	62.0	60.5	61.1	.986
Charlson's comorbidity index	6.2 (3.2)	5.7 (3.0)	5.1 (2.3)	.013
CKD etiology (%)				.530
Glomerular	24.0	25.6	21.8	
Diabetes mellitus	15.5	23.3	18.8	
HTN/nefroangiosclerosis	11.3	23.3	13.5	
APKD	12.7	7.0	12.7	
Interstitial	7.0	2.2	8.7	
Other/unknown	14.1/15.5	2.3/16.3	8.7/14.0	
Dialysis				
Dialysis vintage (years)	1.8 (1.1–3.5)	1.3 (0.5–3.2)	1.4 (0.7–2.5)	.029
Previous HD (%)	21.1	16.3	12.7	.208
PD vintage (years)	1.7 (1.0–3.5)	1.4 (0.4–3.2)	1.4 (0.7–2.4)	.03
Renal Kt/V renal	0.9 (0.7)	0.9 (0.7)	1.2 (0.8)	.01
Peritoneal Kt/V	1.2 (0.5)	1.3(0.5)	1.1 (0.5)	.140
Weekly total Kt/V	2.2 (0.5)	2.3 (0.5)	2.3 (0.7)	.182
ESAs treatment				.007
Darbepoetin (%)	69.0	72.1	49.3	
Epoetin (%)	12.7	6.98	19.7	
ERI (IU/week/kg/g/dL)	6.3 (3.4–10.1)	3.8 (2.6–6.8)	3.5 (2.1–6.5)	.001
Anemia (%)	93.0	95.4	86.9	.136
Absolute ID (%)	7.4	4.7	3.4	.382
FID (%)	15.9	16.3	9.7	.242
Hb distribution				.044
Patients with Hb <9 g/dL (%)	2.8	2.3	2.2	
Patients with Hb 9–10 g/dL (%)	11.3	4.7	1.8	
Patients with Hb 10–11 g/dL (%)	9.9	27.9	18.3	
Patients with Hb 11–12 g/dL (%)	36.6	32.6	33.6	
Patients with Hb 12–13 g/dL (%)	26.8	23.3	29.7	
Patients with Hb >13 g/dL (%)	12.7	9.3	14.4	
Laboratory values				
Hb (g/dL)	11.6 (1.4)	11.4 (1.2)	11.8 (1.3)	.09
Ferritin (ng/mL)	407 (238–557)	228 (120–358)	254 (145–446.5)	.002
TSAT (%)	28.8 (12.1)	26.9 (8.7)	30.2 (10.8)	.155
C-reactive protein (mg/L)	2.3 (0.75–16.7)	1.1 (0.3–3.0)	1.2 (0.4–3.6)	.001
Albumin (g/dL)	3.5 (0.5)	3.7 (0.4)	3.8 (0.5)	<.001
Folic acid (ng/mL)	6.4 (3.6–12.7)	8.5 (4.3–20)	6.7 (4.5–9.3)	.622
Vitamin B_{12} (pg/mL)	556.0 (208.0)	605.2 (339.1)	542.8 (192.1)	.534

Data are shown as mean and (SD) or median (IQR) or columns percentage.
APKD: autosomal polycystic kidney disease; HTN: hypertension.

	No Iron	Oral Iron	IV Iron	TOTAL
ESA	158 (46.1)	34 (9.9)	58 (16.9)	250 (72.9)
No ESA	71 (20.7)	9 (2.6)	13 (3.8)	93 (27.1)
TOTAL	229 (66.8)	43 (12.5)	71 (20.7)	343 (100)

ESA: erythropoiesis stimulating agent, IV: intravenous.

Figure 1: Combined anemia treatment, ESA and iron (IV or oral) for full-analysis data set.

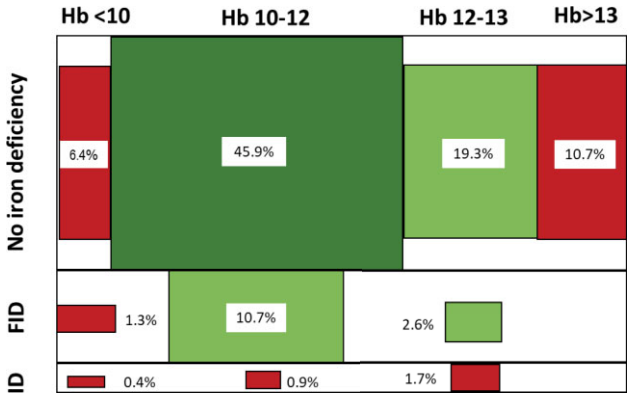


ESA: erythropoiesis stimulating agent.

Figure 2: Hb categories considering ESA prescription or not and mean ESA dosage. Darbepoetin doses were converted to international units using a 1 to 200 conversion factor.

Nephrologists did not withdraw ESA in 12 of the 17 patients with Hb >13 g/dL, despite the recommendations of the guidelines. Nor was the ESA dose reduced in 20 of the 45 patients with Hb between 12 and 12.9 g/dL. Treatment with ESA was not started in only 3 of the 19 with Hb <10 g/dL.

We analysed the subgroup of patients who were receiving ESAs. The combined distribution by Hb levels and ferrokinetic



ID: iron deficiency; FID: functional iron deficiency; Hb: hemoglobin (g/dl); ESA: erythropoiesis stimulating agent. The area represented in the squares is proportional to the percentage

Figure 3: Patient's distribution (%) of iron deficiency according to Hb ranges among those under ESA treatment.

targets is summarized in Fig. 3. We did not find any statistical differences in Hb targets among those that received different ESAs (darbepoetin or short-acting rHuEPO).

ERI and associated factors

Only seven patients (2%) fulfilled criteria of ESA resistance (>300 IU/kg/week) and 10.9% exceeded the pre-specified limit of 12.7 IU/kg/week/g/dL dose. Patients in the highest ERI tertile (ERI >6.3 IU/kg/week) had higher C-reactive protein levels (2.3 vs 1.3 mg/dL, $P = .04$), lower residual renal function (renal Kt/V 0.9 vs 1.2, $P = .01$), more iron deficiency (absolute: 6.5% vs 0%, functional: 13% vs 9%; $P = .03$) and lower serum albumin (3.5 vs 3.8 g/dL, $P = .005$) in comparison with the lowest tertile (0.3–2.7 UI/kg/week). The multivariate model to identify factors associated with being in the highest tercile of ERI included: iron deficiency [odds ratio (OR) 9.7, 95% confidence interval (CI) 1.7–54.5; $P = .01$]; low albumin tertile (OR 3.0, 95% CI 1.3–7.0; $P = .01$), RRT vintage (years) (OR 1.3, 95% CI 1.1–1.5; $P = .001$) and a previous hospital admission (OR 1.7, 95% CI 0.8–4.4; $P = .2$).

Patients with ESA resistance had previously received more red blood cell transfusions (7.5% vs 0%) and had had more hospital admissions (8.4% vs 2.5%, $P = .01$). Despite higher IV iron prescription (35.4% vs 10.8%, $P = 0.001$), these patients showed a numerically lower TSAT (28.1% vs 30.3%; $P = .2$) and higher ferritin levels (337.5 vs 256.1 ng/mL; $P = .1$). Interestingly patients with cancer had higher ERI [8 (7–9) vs 5 (3–7); $P < .001$], but a similar percentage of ESA resistance.

DISCUSSION

Our study describes real-world anemia management, Hb and iron biomarkers targets, and adherence to current ERBP guidelines [16] in a national sample representing 12% of all prevalent PD patients in Spain. We identified an underuse of iron therapy, the need for more accurate ESA dose adjustments, and a tendency to maintain Hb levels in the upper target range. Thus, we identified several areas for improvement of anemia management in this population.

Most of our ESA-treated patients achieved the recommended Hb target between 10 and 12 g/dL. Beyond this upper limit, we considered that those in the Hb range between 12 and 12.9 g/dL could be adequately treated requiring only a downward titration of the ESA dose, before reaching the strict indication to withdraw ESA if Hb exceeds 13 g/dL as also considered in previous studies [5, 16, 17]. Following the EBPG position paper on the KDIGO anemia guidelines, clinicians should guide their treatment with ESA therapy individualizing the Hb target according to the patient characteristics [17, 18]. Functional status, comorbidities and ESA dosage are some of the characteristics suggested for an accurate Hb target selection. Other guidelines, such as the National Institute for Health and Care Excellence (NICE), also suggest the consideration of the patient's perspectives for a better stratification of the Hb target [19].

An important and unsolved issue in the current anemia guidelines is the lack of differentiation between dialysis techniques in their recommendations. In addition, as evidence based on clinical trials is very scarce on PD, nephrologist and guidelines extrapolate results from HD. However, this may not be the correct approach, as PD patients are usually younger and more active, receive a continuous technique, do not suffer post-dialysis hemoconcentration, have lower comorbidities (such as cardiovascular disease or diabetes) and need lower doses of ESA [16, 18]. On the other hand, less than a tenth of the patients had an Hb <10 g/dL and in most cases an ESA was prescribed afterwards.

Some of these missed opportunities for more accurate anemia management may be due to work overload or insufficient awareness of the problem of anemia. Likely, the aid of decision support tools may improve our results. Previous experiences with artificial intelligence models or computer-assisted decision tools in HD have shown that the integration of therapies and laboratory results (ranges and trends) with events and comorbidities can improve the efficiency of anemia management and reduce the workload [20, 21].

In terms of prevalence of anemia and achievement of Hb targets, our results agree with other national registries such as the Swedish National CKD Registry or the PD-DOPPS (Dialysis Outcomes and Practice Patterns study) [5, 17]. However, these studies may be difficult to extrapolate to our reality. Our multicentre study fits in our real-world evidence with a systematic inclusion and a more precise approach to routine clinical practice. This can offer a more realistic result with valuable results for planning health policy interventions.

Iron prescription continues to be the Achille's heel in the treatment of anemia in PD patients. Despite that, few patients

with absolute iron deficiency were not receiving iron therapy; the prescription of iron as a support to ESAs is somewhat worse. In fact, although guidelines are not a strict enforceable framework, we found under-prescription of iron (IV or oral) specifically in those under ESA, who may benefit from ESA dose reductions and costs savings, but more importantly from the potential dose-dependent adverse effect of ESAs [15, 22–24]. *Post hoc* analysis of randomized controlled trials on Hb targets in NDD-CKD (CREATE, TREAT and CHOIR [12–14]) have shown that the highest risk is associated with lower Hb levels achieved and higher ESA doses [23, 24]. Furthermore, iron deficiency is associated with thrombocytosis, which may further increase the thrombotic risk in ESA-treated patients, as suggested by Streja *et al*. [25]. In fact, in a classical editorial of Hung *et al*. the role of iron treatment concomitant with ESA therapy was stressed [26]. This underuse of iron prescription probably reflects a lack of awareness or an "epocentric" view but represents a missed opportunity for improving anemia management. The preferred protocol for iron administration is high-dose iron at long intervals, with a median dose of 500 mg over 4 months. We cannot extrapolate the total annual dose as the dose titration depends on subsequent laboratory values. A previous study by our group with a 1-year follow-up reports a mean annual dose of 1700 mg for the correction of iron deficiency and maintenance of iron stores in patients with PD [27].

The benefits of an iron prescription targeted to an upper ferritin and TSAT targets on HD were confirmed in the PIVOTAL trial [28]. Patients randomized to a pro-active IV iron strategy (up to ferritin 800 ng/mL) achieved significant reductions in MACE and myocardial infarction without increasing the risk of infections or arteriovenous fistula thrombosis versus a reactive IV iron strategy (only when ferritin levels fall below 200 ng/mL). Indeed, past concerns on the potential risks derived from iron therapy have been questioned in a recent KDIGO controversy [18]. Data in NDD-CKD patients also confirm the safety of the IV iron strategy [29]. Unfortunately, we do not have randomized clinical trials of IV iron therapy in PD patients.

Our results also show that IV iron administration is underused, despite the fact that the IV route is more effective in increasing Hb levels, but prescribed somehow less than the oral route [30]. As PD is a home dialysis technique, IV iron administration can be a challenge. However, as we have shown previously, IV iron can be administered during the outpatient visit, safely using the same venous line used for blood collection, and saving time [27]. Furthermore, in most PD clinics ferric carboxymaltose was used, thus allowing a high-dose, low-frequency strategy as proposed by the NICE guidelines [19].

Few patients (2%) meet the strict EBPG criteria for ESA resistance, but we did find some patients with a high ERI as suggested in recent papers [31]. In our experience, ERI is the best way to define the response to ESA treatment. Iron deficiency, malnutrition-inflammation and previous events were associated with a poorer response to ESAs, confirming previous results [32]. The role of inflammation as an ESA-resistance mechanism in CKD has been previously demonstrated in HD and NDD-CKD patients, but evidence in PD is scarce. Therefore, early identification of inflammation and correction, when possible, may improve ESA response, which may translate into a benefit in terms of mortality, burden of disease and cost of care [7, 31, 33].

Peritonitis among other infections may induce transient resistance to ESAs. Our group has reported previously a rate of 0.55 episodes per patient year at risk [34]. Longer follow-up studies are better to identify this relationship. We have not found an association between peritonitis and ESAs response, probably due to short follow-up period. Instead, we found association with hospital admission for any cause during the previous 3 months as a confounding variable in our multivariate analysis for higher ERI (resistance).

Iron deficiency, low serum albumin after correcting by renal replacement therapy vintage and recent hospital admission event accounted for the majority of ESA hyporesponses. Given the cross-sectional design of our study, we cannot infer causality and only describe the association.

Our study has some limitations to be acknowledged. First, the retrospective design and the classical bias associated. Secondly, this is a study based on a representative sample (12%) of the entire cohort of Spanish PD patients, which does not necessarily represent anemia management in other countries. However, the sample is well powered, data have been collected by nephrologists using structured electronic medical records, with few missing data, and therefore the results and conclusions are robust. Another strength of the study is that it reflects the real clinical practice, identifying opportunities for improving anemia management. Third, dates for inclusion were intentionally marked in Q4 2019 to avoid the bias derived from the management of PD patients during year COVID-19 pandemic. Lastly, since some new treatments for anemia (i.e. hypoxia-inducible factor stabilizers) were not available at the time of the study, our results need to be considered within that context.

CONCLUSIONS

In summary, the most relevant findings of our study have been: first, a significant percentage of prescriptions does not conform to guidelines; second, Hb targets titrated upwards even above 12–13 g/dL in PD patients; third, iron deficiency, low albumin and previous events account for most of ESA hyporesponsiveness; and fourth, iron therapy continues to be underused, especially in case of IV iron for patients at home dialysis.

This should promote improvement strategies such as: structured dissemination of guidelines; clinical routes for in-hospital administration of IV iron to home-therapy patients; computer-assisted prescription tools implemented in EMR and early identification of ESA resistance or inflammation.

Lastly, specific studies on anemia management in PD patients are needed to generate reliable evidence to individualize prescriptions and objectives for these patients, who are very different from those in HD centres.

ACKNOWLEDGEMENTS

We thank the cooperation of the Anemia working group (Grupo de Anemia de la Sociedad Española de Nefrologia GAS-S.E.N.) and the GCDP (Grupo Centro de Diálisis Peritoneal) in the study. We gratefully acknowledge the methodology and data assistance of Paula López Sánchez BSc, PhD.

FUNDING

This study was co-funded by Unrestricted Grants from FRIAT renal foundation, Nipro and Vifor CSL Inc. through Fundación SENEFRO and IDIPHISA.

AUTHORS' CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article,

take responsibility for the integrity of the work, and have given their approval for this version to be published.

CONFLICT OF INTEREST STATEMENT

J.P. and B.Q. have received support for travel, consultancy and speaker fees from CSL Vifor, Astellas and GSK. A.C. has received grants from CSL Vifor, consultancy fees from CSL Vifor, AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, GSK, Lilly, Novo Nordisk and Otsuka, and speaker fees from CSL Vifor, Astellas, Amgen, Bayer, GSK, Novo Nordisk or Sanofi Mexico, as well as travel grants from Astellas, AstraZeneca or GSK outside the submitted work.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant-level data, clinical-level data and protocols upon request to SENEFRO Foundation (senefro@senefro.org).

REFERENCES

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol* 2012;**23**:1631–4. https://doi.org/10.1681/ASN.2011111078
2. Portolés J, Martín L, Broseta JJ *et al.* Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. *Front Med (Lausanne)* 2021;**8**:642296. https://doi.org/10.3389/fmed.2021.642296
3. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014;**9**:e84943. https://doi.org/10.1371/journal.pone.0084943
4. Wong MMY, Tu C, Li Y *et al.* Anemia and iron deficiency among chronic kidney disease stages 3-5ND patients in the Chronic Kidney Disease Outcomes and Practice Patterns Study: often unmeasured, variably treated. *Clin Kidney J* 2019;**13**:613–24. https://doi.org/10.1093/CKJ/SFZ091
5. Evans M, Bower H, Cockburn E *et al.* Contemporary management of anemia, erythropoietin resistance and cardiovascular risk in patients with advanced chronic kidney disease: a nationwide analysis. *Clin Kidney J* 2020;**13**:821–7. https://doi.org/10.1093/CKJ/SFAA054
6. Cases A, González de Antona Sánchez E, Cadeddu G *et al.* Epidemiology and treatment of renal anemia in Spain: RIKAS retrospective study. *Nefrologia* 2022; in press. https://doi.org/10.1016/j.nefro.2022.04.001
7. Pergola PE, Pecoits-Filho R, Winkelmayer WC *et al.* Economic burden and health-related quality of life associated with current treatments for anemia in patients with CKD not on dialysis: a systematic review. *Pharmacoecon Open* 2019;**3**:463–78. https://doi.org/10.1007/s41669-019-0132-5
8. Palaka E, Grandy S, Van Haalen H *et al.* The impact of CKD anemia on patients: incidence, risk factors, and clinical outcomes-a systematic literature review. *Int J Nephrol* 2020;**2020**:7692376. https://doi.org/10.1155/2020/7692376
9. Portolés J, Gallegos-Villalobos Á, López-Gómez JM *et al.* Implementation of clinical guidelines and compliance with target hemoglobin levels in peritoneal dialysis. *Nefrologia* 2013;**33**:140–2. https://doi.org/10.3265/Nefrologia.pre2012.Nov.11776
10. McMurray JV, Parfrey PS, Adamson JW *et al.* Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;**2**:279–335. https://doi.org/10.1038/kisup.2012.37
11. Besarab A, Bolton WK, Browne JK *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;**339**:584–90. https://doi.org/10.1056/nejm199808273390903
12. Singh AK, Szczech L, Tang KL *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**:2085–98. https://doi.org/10.1056/nejmoa065485
13. Drüeke TB, Locatelli F, Clyne N *et al.*; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;**355**:2071–84. https://doi.org/10.1056/NEJMoa062276
14. Pfeffer MA, Burdmann EA, Chen C-Y *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**:2019–32. https://doi.org/10.1056/NEJMOA0907845
15. Weir MR. Managing anemia across the stages of kidney disease in those hyporesponsive to erythropoiesis-stimulating agents. *Am J Nephrol* 2021;**52**:450–66. https://doi.org/10.1681/ASN.2020050556
16. Locatelli F, Bárány P, Covic A *et al.* Kidney Disease: Improving Global Outcomes guidelines on anemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant* 2013;**28**:1346–59. https://doi.org/10.1093/ndt/gft033
17. Perlman RL, Zhao J, Fuller DS *et al.* International anemia prevalence and management in peritoneal dialysis patients. *Perit Dial Int* 2019;**39**:539–46. https://doi.org/10.3747/pdi.2018.00249
18. Babitt JL, Eisenga MF, Haase VH *et al.* Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving global Outcomes (KDIGO) Conference. *Kidney Int* 2021;**99**:1280–95. https://doi.org/10.1016/J.KINT.2021.03.020
19. Ratcliffe LEK, Thomas W, Glen J *et al.* Diagnosis and management of iron deficiency in CKD: a summary of the NICE guideline recommendations and their rationale. *Am J Kidney Dis* 2016;**67**:548–58. https://doi.org/10.1053/J.AJKD.2015.11.012
20. Barbieri C, Molina M, Ponce P *et al.* An international observational study suggests that artificial intelligence for clinical decision support optimizes anemia management in hemodialysis patients. *Kidney Int* 2016;**90**:422–9. https://doi.org/10.1016/J.KINT.2016.03.036
21. Brier ME, Gaweda AE, Aronoff GR. Personalized anemia management and precision medicine in ESA and iron pharmacology in end-stage kidney disease. *Semin Nephrol* 2018;**38**:410–7. https://doi.org/10.1016/j.semnephrol.2018.05.010
22. Vaziri ND, Zhou XJ. Potential mechanisms of adverse outcomes in trials of anemia correction with erythropoietin in chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**:1082–8. https://doi.org/10.1093/ndt/gfn601
23. McCullough PA, Barnhart HX, Inrig JK *et al.* Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. *Am J Nephrol* 2013;**37**:549–58. https://doi.org/10.1159/000351175
24. Solomon SD, Uno H, Lewis EF *et al.*; Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) investigators. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med* 2010;**363**:1146–55. https://doi.org/10.1056/NEJMoa1005109

25. Streja E, Kovesdy CP, Greenland S *et al*. Erythropoietin, iron depletion, and relative thrombocytosis: a possible explanation for hemoglobin-survival paradox in hemodialysis. *Am J Kidney Dis* 2008;**52**:727–36. https://doi.org/10.1053/j.ajkd.2008.05.029
26. Hung SC, Tarng DC. ESA and iron therapy in chronic kidney disease: a balance between patient safety and hemoglobin target. *Kidney Int* 2014;**86**:676–8. https://doi.org/10.1038/ki.2014.179
27. Portolés J, Durá-Gúrpide B, Merino-Rivas JL *et al*. Effectiveness and safety of ferric carboxymaltose therapy in peritoneal dialysis patients: an observational study. *Clin Kidney J* 2021;**14**:174–80. https://doi.org/10.1093/ckj/sfz153
28. Macdougall IC, White C, Anker SD *et al*. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019;**380**:447–58. https://doi.org/10.1056/NEJMOA1810742
29. Macdougall IC, Bock AH, Carrera F *et al*.; FIND-CKD Study investigators. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anemia. *Nephrol Dial Transplant* 2014;**29**:2075–84. https://doi.org/10.1093/ndt/gfu201
30. Shepshelovich D, Rozen-Zvi B, Avni T *et al*. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis* 2016;**68**:677–90. https://doi.org/10.1053/j.ajkd.2016.04.018
31. Cizman B, Smith HT, Camejo RR *et al*. Clinical and economic outcomes of erythropoiesis-stimulating agent hyporesponsiveness in the post-bundling era. *Kidney Med* 2020;**2**:589–99.e1. https://doi.org/10.1016/J.XKME.2020.06.008
32. López-Gómez JM, Portolés JM, Aljama P. Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. *Kidney Int* 2008;**74**:75–81. https://doi.org/10.1038/ki.2008.523
33. Mazzaferro S, D'Alonzo S, Morosetti M. Unmet needs about iron deficiency in peritoneal dialysis: a Delphi consensus panel. *BMC Nephrol* 2022;**23**:336. https://doi.org/10.1186/S12882-022-02969-3
34. Portolés J, Janeiro D, Lou-Arnal LM *et al*. First episodes of peritoneal infection: description and prognostic factors. *Nefrologia* 2013;**33**:316–24. https://doi.org/10.3265/Nefrologia.pre2013.Feb.11733

Received: 13.3.2023; Editorial decision: 25.6.2023