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## Outcomes of a general hospital-based Home Parenteral Nutrition (HPN) program; report of our experience from a 26-year period

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### Abstract

**Background:** Home parenteral nutrition (HPN) was introduced in Spain in the late 1980s. Our hospital was a pioneering medical centre in this field.

**Aim:** Analyze outcomes of our HPN program.

**Methods:** Retrospective study of patients receiving HPN between 1986-2012. Study variables are expressed as frequency, mean  $\pm$  SD (range), median [interquartile range]. Parametrics, non-parametrics test and survival analysis ( $p < 0.05$ ) were applied.

**Results:** 91 patients (55 females and 36 males, mean age:  $50.6 \pm 5$  yrs.) who received HPN for an accrual period of 55,470 days (median: 211 days [range: 63-573]) were included. The most prevalent underlying condition was cancer (49.5%), with the commonest HPN indication being short bowel syndrome (41.1%). The most frequently used catheter type was the tunneled catheter (70.7%). The complication rate was 3.58/1,000 HPN days (2.68, infection; 0.07, occlusion; 0.07 thrombosis; and 0.59, metabolic complications). Complications were consistently associated with both the underlying condition and HPN length. Infections were most frequent within the first 1,000 days of HPN. Liver disease incidence was related to HPN duration. HPN could be discontinued in 42.3% of patients. Ten-year survival rate was 42%, and varied across the underlying conditions.

**Conclusions:** In the present series, the commonest reason for HPN was cancer. Our complication rate is in keeping with that reported in the literature. The overall survival rate was 42%, and varied across the underlying conditions.

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### RESULTADOS DEL PROGRAMA DE NUTRICIÓN PARENTERAL DOMICILIARIA (NPD) DE UN HOSPITAL GENERAL; ANALISIS DE 26 AÑOS DE ACTIVIDAD

#### Resumen

**Introducción:** La nutrición parenteral domiciliaria (NPD) se introdujo en España a finales de 1980. Nuestro hospital fue pionero en este campo.

**Objetivo:** Analizar los resultados de nuestro programa de NPD.

**Métodos:** Estudio retrospectivo de los pacientes que recibieron NPD entre 1986-2012. Las variables se expresan como frecuencias, media  $\pm$  DE (rango), mediana [intervalo intercuartílico]. Se aplicaron pruebas paramétricas, no paramétricas y análisis de la supervivencia ( $p < 0,05$ ).

**Resultados:** 91 pacientes (55 mujeres, edad media:  $50,6 \pm 5$  años). La duración total del tratamiento con NPD fue de 55.470 días (mediana: 211 días [rango: 63-573]). El diagnóstico principal y la indicación de NPD más frecuentes fueron el cáncer (49,5%) y el síndrome del intestino corto (41,1%). El tipo de catéter más utilizado fue el tunelizado (70,7%). La tasa de complicaciones totales fue de 3,58/1.000 días HPN (2,68 para infecciones; 0,07, oclusiones; 0,07 trombosis, y 0,59, complicaciones metabólicas) y se asoció al diagnóstico principal y la duración de la NPD. Las infecciones fueron más frecuentes en los primeros 1.000 días de NPD. La incidencia de hepatopatía se relacionó con la duración de este tratamiento. En el 42,3% de los pacientes se pudo suspender la NPD. La tasa de supervivencia global a los diez años fue del 42% con diferencias entre los diagnósticos principales.

**Conclusiones:** En nuestra serie, la razón más común para la NPD fue el cáncer. Nuestra tasa de complicaciones esta acorde con la literatura. La tasa de supervivencia global fue del 42%.

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## Abbreviation

HPN: Home Parenteral Nutrition.

ESPENHAN-CIF group: Home Artificial Nutrition and Chronic Intestinal Failure Group of the European Society for Clinical Nutrition and Metabolism.

NADYA-SENPE: Working Group on Home and Outpatient Artificial Nutrition of the Spanish Society for Parenteral and Enteral Nutrition.

SD: Standard deviation.

IQ: Interquartile range.

i.e.: "id est", that is.

e.g.: "exempli gratia", for example.

MCT: Medium Chain Triglycerides.

LCT: Long Chain Triglycerides.

PICC: Peripherally Inserted Central Catheter.

MBD: Metabolic Bone Disease.

## Introduction

Home parenteral nutrition (HPN) gives rise to long-term survival of patients with permanent or transient intestinal failure.<sup>1</sup> More than 45 years have passed since this modality of nutritional support was first used in 1967.<sup>2</sup> In most countries, HPN is most often hospital-based and is generally delivered by specialized multidisciplinary teams.<sup>3</sup>

According to data from the 2011 survey by the Home Artificial Nutrition and Chronic Intestinal Failure Group of the European Society for Clinical Nutrition and Metabolism (ESPENHAN-CIF group),<sup>4</sup> HPN prevalence lies within the range of 3.25-66 patients/million. In Spain, HPN prevalence, as estimated based on data from the voluntary register of the Working Group on Home and Outpatient Artificial Nutrition of the Spanish Society for Parenteral and Enteral Nutrition (NADYA-SENPE), has been increasing since the register was first opened, with the prevalence rate being of 4.06 patients/million in 2012,<sup>5</sup> and an unequal distribution throughout the country.<sup>6</sup>

The major HPN complications are those associated with the venous catheter (i.e. infection, occlusion and venous thrombosis) and those of metabolic nature (i.e. liver disease and metabolic bone disease).<sup>7</sup>

In order to share our group's experience, herein we report the outcomes of a general hospital-based HPN program covering a 26-year period; that is, since the program was first implemented in our hospital.

## Aim

Analyze outcomes of our HPN program.

## Methods and materials

A longitudinal retrospective study including all patients treated at the Hospital General Universitario

Gregorio Marañón (Madrid, Spain) who received HPN between January 1986 and October 2012 was conducted. Study data were collected from both medical records and the HPN register of the NADYA-SENPE group ([www.nadya-senpe.com](http://www.nadya-senpe.com)). Data collection was compliant with the Law on Protection of Personal Data (Spanish Organic Law 15/1999). More than one HPN episode for each patient was allowed. A new HPN episode was identified when HPN administration was suspended for longer than 3 months regardless of the reason (e.g. protracted hospital stay, attempt to HPN discontinuation).

Data statistical analysis was conducted by patient for the following variables: age at HPN initiation, underlying condition (diagnosis), number of catheters, clinical evolution and survival. Data analysis was carried out by HPN episode for the following variables: HPN indication, type of catheter, patient activity and independence levels and number and type of HPN-associated complications.

The diagnosis of catheter-related infectious complications was performed in accordance with the definitions by the Center for Disease Control.<sup>8</sup> Catheter occlusion was defined as either impossibility of infusing any fluid or drawing blood through the catheter or need of exerting an excessive pressure or both. The diagnosis of central venous thrombosis was made based on clinical data (i.e. thorax, shoulder or neck pain with signs suggestive of venous occlusion with ipsilateral arm edema or superior vena cava syndrome) and confirmation by upper limb venography or Doppler sonography.<sup>9</sup> The diagnosis of HPN-associated liver disease was established based on an 1.5-fold elevation of the upper limit of normal persisting for at least 6 months in serum levels of two of the following parameters: -glutaryl transferase, alkaline phosphatase and/or conjugated bilirubin.<sup>10</sup> In some instances, liver disease diagnosis was made by liver biopsy. Metabolic bone disease (MBD) was defined as skeletal fragility due to abnormal bone quality either in asymptomatic patients or in patients presenting with bone pain and/or fracture.<sup>11</sup> MBD was diagnosed by adhering to the WHO criteria, which define osteopenia as a T-score between -1 and -2.5 standard deviations (SD) and osteoporosis as a T-score below -2.5 SD.

To address the impact of the changes implemented in our clinical practice over the 26-year period covered by the study, we took into account that: (1) initially, HPN solutions were elaborated at the Hospital pharmacy, and since 1998 the hospital reached an agreement with a pharmaceutical company, which delivered HPN solutions at patients' home; (2) In January 2007, we started using lipid formulations composed of mixtures of medium chain triglycerides (MCT), long chain triglycerides and 3, rather than 50% MCT/LCT mixtures; and (3) since 2009, tunneled catheters in use have been sealed with saline solution instead of sodium heparin, with the sealing being maintained with heparin in subcutaneous reservoir catheters.

To address the relationship of variable underlying condition (i. e. diagnosis) to survival, all types of malignancy on either active or palliative therapy were unified together in the variable *malignant neoplasms*, while under the variable *other underlying conditions* motility abnormalities and congenital disorders were brought together since no patients on HPN died from a condition included in the latter variable.

For data statistical analysis, the absolute and relative (percentage) frequency, mean, standard deviation (SD), median, range, and interquartile (IQ) indexes were used. Sample normality was tested by means of Kolmogorov-Smirnov test for independent samples. T-Student,<sup>2</sup> Kruskal-Wallis and Mann-Whitney tests, ANOVA and bivariate correlations were used as well. Survival was analyzed by Kaplan-Meier method and the log rank test. To determine the impact of HNP-related factors on survival, both univariate and multivariate analyses were conducted. The variables gender, age, diagnosis and catheter-related infectious and liver complications were included in the univariate analysis, whereas Cox regression model was used to estimate predictive values for death. Then, factors showing statistical significance were included in the multivariate analysis. Statistical significance was set at  $p < 0.05$ . All statistical tests were conducted by means of the software package IBM SPSS® Statistics 21.

## Results

### Patients' characteristics

A total of 91 patients (36 males and 55 females) were included in the study. There were 116 HNP episodes (mean and SD:  $1.27 \pm 0.67$  per patient; range: 1-5 episodes). The distribution by number of HPN episodes was: 80% of patients with 1 episode, 15.4% with 2 episodes, 2.2% with 3 episodes and only 1.1% achieved 4 and 5 episodes. Mean age at HPN initiation was  $50.6 \pm 15$  years (range: 3 months-83 years). The most frequent diagnosis was the neoplasms on palliative therapy in the 34.1%, followed by neoplasms on active therapy and radiation enteritis (15.4%), mesenteric ischaemia (12.1%), Crohn disease (5.5%), motility abnormalities (2.2%), congenital anomalies (1.1%) and other diagnoses (14.3%). The total duration of HPN was 55 470 days (median per patient: 211 days [IQ: 63-573]; median per HPN episode: 184 days [IQ: 59-531]). Significant differences in mean HPN duration across the underlying conditions were found ( $p = 0.007$ ). The most common indication for HPN was short bowel syndrome (41.1%) (fig. 1). Patients' activity level was normal in 18.8% of cases and limited in 71.8%, with 8.5% of patients being bedridden or confined to the armchair. Patients' independence level was complete in 49.6% of cases and limited in 48.7%. Both activity and independence levels were correlated with the underlying condition ( $p < 0.001$ ).

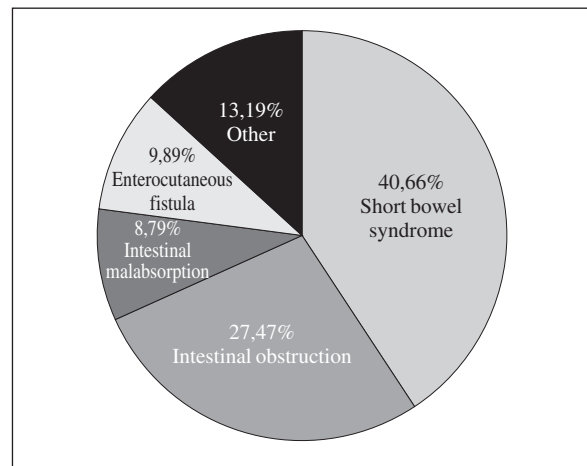


Fig. 1.—Distribution of patients by HPN indication.

### HPN characteristics and complications

A total of 146 catheters were used (mean:  $1.8 \pm 1.5$  per patient; range: 1-9). The most frequently used venous catheter was the tunneled catheter (70.7% of patients), followed by the reservoir catheter (28.4%). In our series, only one peripherally inserted central catheter (PICC) was used. The type of catheter was correlated with the underlying condition ( $p = 0.001$ ).

The total number of complications was 199 (mean complication rate/1,000 HPN days: 3.58). Catheter-related infectious complication rate was 2.68/1,000 HPN days, while catheter-related non-infectious complication rate was 0.31 (0.07/1,000 HPN days for occlusion, 0.07/1,000 HPN days for venous thrombosis, and 0.17/1,000 HPN days for other complications, such as catheter wear or rupture). Infectious complication incidence was highest within the first 1,000 HPN days (fig. 2) ( $p < 0.001$ ) (RHO = 0.47). Also, a correlation between infectious and thrombotic complications was found ( $p < 0.001$ ).

Metabolic complications were seen in 28.6% of cases. Eight patients (8.8%) developed liver complications with varying clinical evolution: 4 had mild liver disease without cholestasis, and 2 of them died from their underlying condition; 4 patients had severe liver disease with attendant cholestasis (2 of them died due to HPN-associated liver failure, 1 experienced clinical improvement when lipids were removed from the HPN solution, and 1 child is pending hepatointestinal transplantation). Median HPN duration before the development of liver disease was 279 days (IQ: 165-1013). Liver complications were correlated with HPN duration ( $p < 0.05$ ).

In 17 patients who had a bone density test done while on HPN, the mean lumbar T-score was  $-2.37 \pm 1.4$ , while mean femoral neck T-score was  $-2.41 \pm 1.03$  (table I). Furthermore, MBD was correlated with the underlying condition ( $p = 0.012$ ) and patients' independence level ( $p = 0.02$ ). Differences in MBD

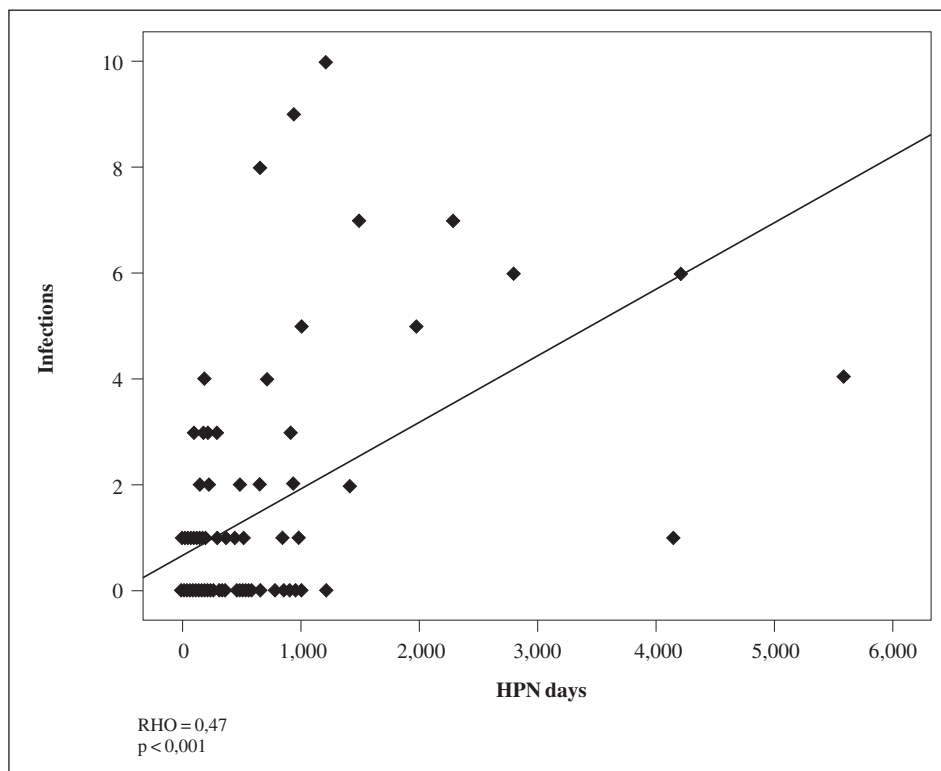


Fig. 2.—Infectious complications by HPN duration.

**Table I**  
*Distribution of metabolic bone disease in HPN patients*

<i>Bone densitometry during HPN</i>		
	<i>Lumbar spine % (patients)</i>	<i>Femoral neck % (patients)</i>
Normal	26,3 (5)	15,8 (3)
Osteopenia	26,3 (5)	36,8 (7)
Osteoporosis	47 (9)	47,4 (9)

between males and females at lumbar ( $p = 0.04$ ) and femoral ( $p = 0.02$ ) levels were found.

Overall complications were correlated with both the underlying condition ( $p = 0.001$ ) and HPN duration, with a 6-fold increment in the risk of complication development for patients on HPN for more than 180 days as compared with those on HPN for less than two months ( $p = 0.001$ ).

When the first 13 years were compared with last 13 years of our HPN experience, we encountered a significant increase in the use of HPN for cancer (45.1% increment), Crohn disease (5.5%) and radiation enteritis (6.6%) ( $p = 0.004$ ), whereas the HPN use for mesenteric ischaemia or motility abnormalities remained stable. Additionally, overall mean complication ( $p = 0.01$ ) and catheter-related complication rates, both infectious and non-infectious ( $p < 0.001$ ), declined during the last 13 years. We found no significant differences in the emergence of tunneled catheter-related complications following the switch from heparin to saline for catheter

sealing. Since the introduction of the lipids - MCT/LCT/ 3 mixtures, the catheter-related non-infectious complication rate has dropped (from 1.1/1,000 HPN days to 0.8/1,000 HPN days,  $p < 0.05$ ).

#### *Clinical evolution and survival analysis*

Based on clinical evolution outcomes, 30 patients (42.3%) were weaned off HPN following intestinal adaptation; 3 (4.2%) developed end-stage chronic renal failure and were switched to intradialytic parenteral nutrition; 11 (15.5%) discontinued treatment due to other reasons; and 27 (38%) died. At present, 20 patients remain on HPN. Overall survival rate at 1, 3 and 5 years after HPN initiation was 72%, 58% and 42%, respectively. In the case of patients suffering from a non-malignant condition, 10-year survival rate was 65%. We found statistically significant differences in survival across the underlying conditions (fig. 3). The univariate analysis results showed that the underlying condition and catheter-related infectious complications significantly influence mortality (table II). In the multivariate analysis, only the variable underlying condition showed to independently influence survival ( $p < 0.05$ ).

#### **Discussion**

Currently, HPN is widely recognized as a safe, efficient therapy whose development has paralleled both parenteral

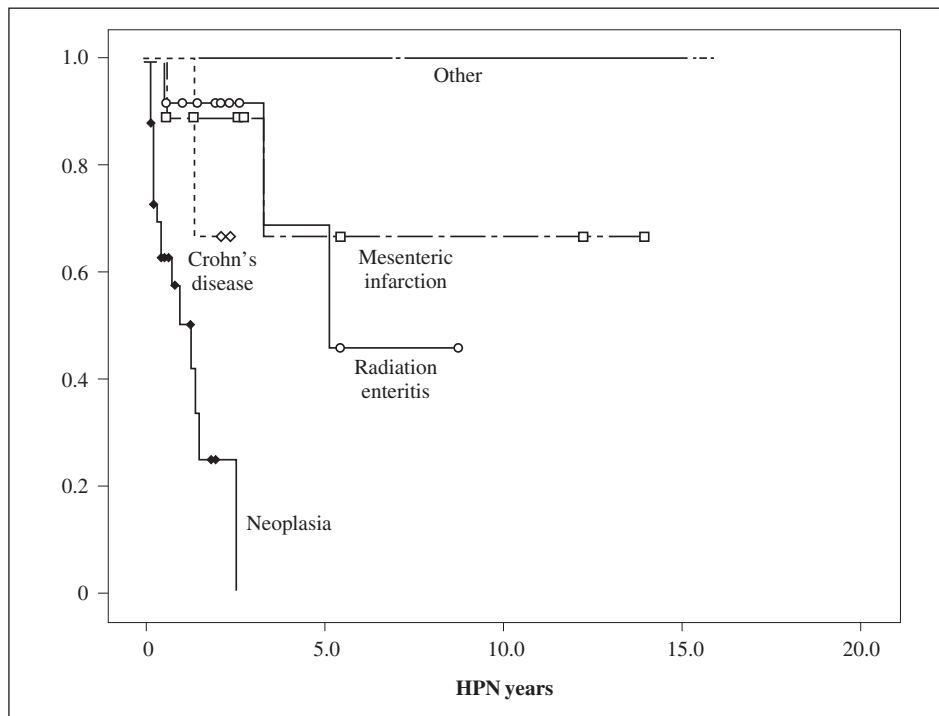


Fig. 3.—Survival by underlying condition.

**Table II**  
Effect of the addressed variables on survival

Variable	Group/rank	Hazard ratio (95% CI)	P-value
Diagnosis	Neoplasias	1	
	Radiation enteritis	0,72 (0,01-0,37)	0,002
	Crohn's disease	0,23 (0,03-1,72)	0,15
	Mesenteric infarction	0,52 (0,008-0,35)	0,002
	Others	No event	
Catheter-related infectious complications	Lineal	0,27 (0,11-0,64)	0,003
	No	1	
	1	0,34 (0,11-1,03)	0,057
	> 1	0,23 (0,08-0,65)	0,005

nutrition evolution itself (e. g. catheters, formulas) and healthcare providers' improved knowledge and practical experience.<sup>12</sup> In the present paper, we look back over our HNP experience with a large patient cohort that has been investigated by means of a long-term follow-up.

In our series, the most frequent HPN indication was short bowel syndrome, which concurs with findings reported from other series in Spain, Europe and the United States.<sup>13</sup> In some countries, malignancy has now replaced benign conditions as the most usual etiology of intestinal failure leading to HPN.<sup>12,14</sup> However, the use of HPN in patients with terminal cancer has obvious cultural and religious implications, and widely varies from one country to another. Indeed, in certain European countries, benign conditions, such as Crohn disease, intestinal ischaemia and intestinal pseudoobstruction, continue to be the most commonly diagnosed underlying conditions in HPN patients.<sup>15</sup>

In the present series, the most frequently used catheter type was the tunneled catheter, followed by the reservoir and PICC catheters, which coincides with the standards in Spain.<sup>5,16</sup> The tunneled catheter is of first choice for patients with underlying benign condition, whilst the reservoir catheter is still the most widely used in cancer patients, probably because this type of catheter allows access compatibility for intravenous chemotherapy; however, this is not the case in all the countries reported in the literature.<sup>14</sup>

Catheter-related infectious complications were the most common in our patients, with a rate of 2.68/1,000 HPN days, which is slightly higher than the average incidence of 1-2 episodes/1,000 catheter days reported in earlier series,<sup>17</sup> but lies still within the standard range (i.e. 0.38-4.58 episodes/1,000 catheter days).<sup>18</sup> Catheter-related infectious complications were most commonly seen within the first 1,000 HPN days, which



is a reflection of patients' learning curve for catheter care, as previously reported by other authors.<sup>19</sup>

Among the catheter-related mechanical complications, occlusion is the most prevalent one.<sup>20</sup> This complication may be caused by deposition of fibrin, lipids or drugs infused through the catheter and/or calcium-phosphorus precipitation. Occlusion may be either total or partial, thereby it may be symptomatic or asymptomatic. In the present study, occlusion rate was 0.07/1,000 HPN days, which is lower than that reported in the literature (0.071 occlusions/catheter/year).<sup>7</sup> Of note, another remarkable catheter-related non-infectious complication is the central venous thrombosis, which in our series yielded a rate similar to that reported in the literature.<sup>21,22</sup>

The most efficient preventive strategy for catheter occlusion is washing with normal saline after use. We did not find any differences in the tunneled catheter-related complication rate following the introduction of saline sealing as a standard practice, thereby we are not in a position to provide convincing data to determine whether or not tunneled catheters should be heparinized, because such data collection would have required a different study design. We did corroborate that, as reported elsewhere,<sup>23</sup> catheter infection is a risk factor for occlusion.

Liver disease is a major parenteral nutrition metabolic complication.<sup>12</sup> The prevalence of liver abnormalities (e. g. steatosis, cholestasis) in the HPN series from 1970s has been reportedly high, with 25-100% of patients being affected and progressing to advanced liver disease (i. e. cirrhosis, liver failure) in 15-40% of cases. HPN-associated liver disease has declined in most recently reported series,<sup>7</sup> as is the case in ours. In the present study, a relationship between this complication and the underlying condition or bowel rest (i. e., patients with no oral intake) was not found; however, this association has been reported by other authors.<sup>24</sup> This discrepancy is likely to be due to the low liver disease incidence in our series. On the contrary, we did find a relationship of liver disease to HPN length.<sup>25</sup> In recent studies, the use of lipid solutions containing 3 fatty acids has resulted in both decreased liver disease incidence and improved clinical evolution.<sup>26,27</sup>

Metabolic bone disease (MBD) is a common HPN complication.<sup>11</sup> In our series, only 18.7% of patients had a density bone test done, which prevents drawing any conclusions about the actual prevalence of this complication. The results from studies with long-term follow-up reported in the literature suggest that metabolic bone disease may affect 84% of patients (43% osteopenia, 41% osteoporosis and 10% pathologic fracture).<sup>28</sup> In our series, we found a consistent relationship between MBD and its well-established risk factors, such as gender and lacking physical activity. The role of HPN in bone mass loss remains unknown. HPN-associated bone mass loss is thought to be of multifactorial origin, and it is likely to greatly depend on the underlying condition causing intestinal failure.<sup>29</sup>

Improving quality of life of patients during HPN is becoming increasingly important, as suggested by the growing interest of authors in research on HPN-related life quality.<sup>14,30</sup> In the present study, only 18.8% of patients on HPN had normal activity, which is consistent with findings from other studies.<sup>31</sup>

Our study shows that HPN resulted in a mean survival longer than 11 years in patients with underlying conditions other than cancer, which is similar to findings in other European and USA series.<sup>13, 32</sup> This comes to confirm the HPN role as a first line therapy for chronic intestinal failure. In the present investigation, the diagnosis (i. e. the underlying condition) turned out to be the only independent variable that significantly influenced survival.

The major drawbacks of our study are all related to the retrospective design and the excessive length of the time period covered. The comparative analysis of the HPN complications that had been emerging within the different time periods covered in our study following the implementation of certain measures (e. g. the switch to lipid solution, sealing of tunneled catheters with normal saline) is a reflection of our own learning curve for the prevention, control and management of such complications, as described in previous reports.<sup>20,33</sup> Furthermore, additional changes have been being introduced in our clinical practice over time that may have had a significant impact on HPN complications in a manner that we were not able to control in the present study, including the canalization of central venous catheters by the interventional radiologist under ultrasound/radiological control in replacement of blind puncture or dissection performed by the surgeon or the change in the antiseptic solution by switching to chlorhexidine. These changes may have contributed to the overall good clinical outcomes found in our series.

Given the low prevalence of both intestinal failure, similar to that of rare diseases, and HPN, it is recommended that such patients be treated at reference medical centres by a highly experienced multidisciplinary team in order to reduce complication rate and improve survival.<sup>15,20,34</sup>

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