Complex Chronic Disease in Pediatrics – Needs in The Last Year of Life

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Abstract

Published data on hospital use in the last year of life of a child with a life-threatening complex chronic disease (CCD) is scarce yet critical to inform the implementation phase of paediatric palliative care (PPC). We aimed to describe the last year of life of children with CCD, in terms of the clinic characteristics, hospital resources and the impact of referral to a hospital-based PPC team (PPCT). This is a quantitative, retrospective and comparative study of children with CCD (1–18 years of age), who died in a tertiary hospital between January 2016 and December 2020. We analysed the hospital resources in the last year, therapy and procedures in the last week of life, decision to limit treatment (DLT), place of death, referral to the PPCT and place to death, compared by number of CCDs. 72 patients (60% male) with a median age of 10.1 years were included. Most had ≥ 2 CCDs (58%) with cancer as the most common diagnosis (47%). The group with ≥ 3 CCD had longer hospital stays (p = 0.041). Of the 17 patients referred to the PPCT, there was a higher number of DLT (p < 0.001), greater use of the subcutaneous route (p < 0.001), a lower number of transfusions of blood products (p = 0.002) and a lower number of deaths in the Intensive Care Unit - ICU (p < 0.001). The ICU was the place where the highest number of deaths occurred (64% non-referred vs 6% referred, p < 0.001).

Conclusion: Early implementation of PPC optimises the use of hospital resources, minimises invasive procedures and therapies and develops effective and sustainable alternatives which are better suited to the needs of children and/or families.

What Is Known

- In recent years, there has been an increased prevalence of complex chronic disease (CCD), which has led to more specialised and prolonged medical care until the end of life.
- Most existing literature refers to adulthood and there are few paediatric studies on use of hospital resources and the invasiveness of procedures in the last year of life for children.

WHAT IS NEW:

- This study is one of the few to provide a comprehensive characterisation of the last year of life of children/adolescents with CCD.
- Timely referral to a specialised PPC team optimises the use of hospital resources, minimise invasive procedures and develop effective and sustainable alternatives which are better suited to the needs of children and/or families.

Introduction

In recent decades, the access to increasingly differentiated health care has greatly improved prognosis and life expectancy in many chronic diseases, causing a rise in their prevalence.1,2 Thus, there has been
an increased prevalence of CCD in children, which has led to an increase in more specialised and prolonged medical care\textsuperscript{3} and has highlighted the need to invest in pediatric palliative care (PPC).\textsuperscript{4,5}

Although most existing literature refers to adulthood, there are a few pediatric studies on the use of hospital resources in the last year of life of children with life-threatening CCD\textsuperscript{6,7} and the invasiveness of procedures.\textsuperscript{8,9,10,11}

Children with CCD at the end of their life form a substantial part of the main users of hospital resources.\textsuperscript{6} It is estimated that the majority (56\%) have two or more CCDs in the last year of life.\textsuperscript{7} This increased clinical complexity influences the consumption of resources, namely the increased number and duration of hospital stays,\textsuperscript{10} as well as the invasiveness of end-of-life procedures and therapies (invasive ventilation, resuscitation methods, renal replacement techniques and admission to or death in the ICU).\textsuperscript{1,11,12}

In this context, the existence of an individual advance care plan (ACP), which may involve decisions to limit treatment (DLT), is highly relevant. On the other hand, the involvement and approach of PPC appears to minimise the use of more invasive procedures and therapies in the last month of life.\textsuperscript{11,13,14}

In mainland Portugal, although the absolute numbers of admissions of pediatric patients are falling, the admissions of children with CCD have undergone a proportional increase. These cases seem to have a longer duration, are more costly and have a higher probability of death than admissions of children without CCD (a trend which is stronger when CCD \textgeq 2). The highest percentage of hospital episodes and deaths in Portugal may be due to the lack of alternatives to this care, namely at home and in the community.\textsuperscript{4}

The progressive implementation of PPC programmes, including home support, has enabled assessment of the impact of this type of care, both in the use of resources and place of death, and in the invasiveness of the therapies carried out.\textsuperscript{15,16} In Portugal, PPC has undergone a significant development in the last decade, with the creation of specialised teams being officially regulated in 2018.\textsuperscript{17}

It is thus timely to identify paediatric palliative needs in order to reinforce the implementation of PPC teams in the various hospital units with pediatric departments.\textsuperscript{18}

With this study, we aimed to describe the last year of life of children with CCD, regarding a) demographic and clinical characteristics, b) hospital resources used, c) invasiveness of procedures, d) place of death, and e) impact of referral to a Portuguese university hospital-based PPCT.

**Materials And Methods**

**Study design and setting**
An observational, quantitative, retrospective and comparative exploratory study was carried out, involving children/adolescents with CCD who died in a Portuguese university hospital in the period from January 1, 2016 to December 31, 2020.

The children were identified by consulting the clinical files of children/adolescents who were designated “deceased” upon hospital discharge. Exclusion criteria for the study were children who died during their first year of life, adolescents aged 18 years or over and children who died suddenly.

To define CCD, we used the Feudtner et al.’s criteria, which include any medical condition with a duration of at least 12 months (unless death occurs first) and involve several different organ systems, or involve an organ system severely enough to require special pediatric care and a probable period of hospitalisation in a medical centre.14,19

Demographic (age and gender) and clinical variables were collected: main diagnosis (oncological, neurological/neuromuscular, cardiovascular, metabolic, congenital/genetic, respiratory, haematological/immunological, renal/urological and gastrointestinal), number of CCDs per patient, prognosis according to the Association for Children with Life-threatening or Terminal Conditions and their Families (ACT) (Table 1), resources used during the last year of life (duration of hospitalisations, main complementary exams, procedures and therapies used), characteristics of the last hospitalisation (origin on admission, duration of hospitalisation, cause of death and department in which the child died), presence of decision to limit treatment (DLT) and referral to a hospital-based PPCT.

| Category I | Life-threatening conditions for which curative treatment may be feasible but can fail, where access to palliative care services may be necessary when treatment fails, irrespective of the duration of that threat to life. On reaching long-term remission or following successful curative treatment, there is no longer a need for palliative care services. Examples: cancer, organ failures of heart, liver, kidney, transplant and children on long-term ventilation. |
| Category II | Conditions where premature death is inevitable; these may involve long periods of intensive disease-directed treatment aimed at prolonging life and allowing participation in normal activities. Children and young people in this category may be significantly disabled but have long periods of relatively good health. Examples: cystic fibrosis, Duchenne muscular dystrophy and SMA Type 1. |
| Category III | Progressive conditions without curative treatment options, where treatment is exclusively palliative and may commonly extend over many years. Examples: Batten disease, mucopolysaccharidoses and other severe metabolic conditions. |
| Category IV | Irreversible but non-progressive conditions causing severe disability leading to susceptibility to health complications and likelihood of premature death. Palliative care may be required at any stage and there may be unpredictable and periodic episodes of care. Examples: severe cerebral palsy, complex disabilities such as following brain or spinal cord injury. |

International Children's Palliative Care Network (ICPCN); Ministry of Health Secretariat of State Working Group Report (2014)20
The 365 days prior to the date of death were considered as the last year of life and the 7 days before death as the last week of life.

Days lasting at least 24 hours were counted in the total days of hospitalisation; some hospitalisations thus lasted less than 1 day, and are mentioned as having a duration of 0 days.

Assessment of the main procedures and therapies applied during the last week of life only included those that were re-started in these patients during this hospitalisation. As regards the selection of established sedative therapy, all prescribed drugs intended as sedatives were included, according to clinical records.

DLT, defined as abstention from or suspension of a certain treatment, given a terminal or irreversible clinical condition where the probability of harm was greater than the benefit for the patient, was considered as present when registered in the clinical file.

Authorisation was obtained from the Ethics Committee of the Hospital and University Center to carry out this work (reference number 093/CES).

**Statistical analysis**

Data were collected retrospectively from clinical files of patients (computerised records, accessed via the SClinico® program), and entered in anonymous format into an Excel database. IBM SPSS Statistics® software package (version 25.0) was used for all statistical analysis.

Quantitative variables (non-normal, assessed using Shapiro-Wilk tests) were described by the median, 1st quartile and 3rd quartile. Qualitative variables were represented by their absolute and relative frequencies.

To compare quantitative variables between three or more groups, the Kruskall-Wallis test was applied, after a previous assessment of normality in each group, and the respective multiple comparisons were evaluated. To test the association between qualitative variables, Fisher’s exact test was used. The significance level adopted for the study was 0.05.

**Results**

In the paediatric hospital under study there were 137 deaths of children/adolescents during the five-year period (2016-2020). After applying the exclusion criteria, 72 were eligible for the study (53% of the total). Reasons for exclusion were children who died during the first year of life (29%) and adolescents aged 18 years or over (4%) and children who died suddenly (14%)

Of the children/adolescents included, 17 (24%) were referred to the PPCT. The time between referral and the date of death ranged from 0.25 to 24 months, with a median of eight months [Interquartile range (IQR) 0.625–9] of referral to and follow-up by the PPCT.

Most patients (59.7%) were male, with a median age of 10.1 years (IQR 4.4–13.4). It was found that 66.7% of the study population belonged to Category 1 in the ACT classification (Table 1), and the main
diagnosis was cancer in almost half (47.2%). The main reason for admission was worsening of the underlying disease/acute complications (63.9%). Most patients had $\geq 2$ CCDs (58.3%) and the highest number of deaths occurred in the ICU (48.6%) (Table 2).
### Table 2
Demographic and clinical characteristics of the 72 children/adolescents in the study

| Variable                      | Result         | Variable                      | Result         |
|-------------------------------|----------------|-------------------------------|----------------|
| Gender*                       | Result         | Number of CCD*                |                |
| Male                          | 43 (59.7)      | 1                             | 30 (41.7)      |
| Female                        | 29 (40.3)      | 2                             | 19 (26.4)      |
| Age (in years)*               | 10.1 (4.4, 14.3) | ≥ 3                          | 23 (31.9)      |
| ACT group*                    | Result         | Reason for admission*         |                |
| 1                             | 48 (66.7)      | Worsening of underlying disease/acute complications | 46 (63.9)      |
| 2                             | 6 (8.3)        | Scheduled exams or treatment  | 13 (18.1)      |
| 3                             | 7 (9.7)        | End-of-life care              | 7 (9.7)        |
| 4                             | 11 (15.3)      | Other                         | 6 (8.3)        |
| Main diagnostic group*        | Result         | Place of death*               |                |
| Oncological                   | 34 (47.2)      | ICU                           | 35 (48.6)      |
| Neurological                  | 12 (16.7)      | Cancer ward                   | 21 (29.2)      |
| Cardiovascular                | 11 (15.3)      | Paediatric ward               | 11 (15.3)      |
| Metabolic                     | 7 (9.7)        | ED                            | 5 (6.9)        |
| Congenital/Genetic           | 3 (4.2)        |                               |                |
| Haematological                | 2 (2.8)        |                               |                |
| Respiratory                   | 1 (1.4)        |                               |                |
| Gastrointestinal              | 1 (1.4)        |                               |                |
| Renal/Urological              | 1 (1.4)        |                               |                |

*n (%) and + Median (IQR). ACT=Association for Children with Life-threatening or Terminal Conditions and their Families; CCD=complex chronic disease; Emergency department=ED; Intensive care unit=ICU

Hospital resources used in the last year of life varied according to the type and number of CCD (Tables 3). The median total length of hospital stays was 54 days (IQR 18–109) and the median duration of the last
hospital stay was 14 days (IQR 4–36), with no differences between the diagnostic groups. The group of children with ≥ 3 CCDs had longer total hospital stays (median 66 days, IQR 22–181 vs 54 days, IQR 5–102 with 2 CCDs and 41 days, IQR 18–104 with 1 CCD; p = 0.041), with no differences between groups with 1, 2 and ≥ 3 CCDs regarding the duration of the last hospital stay or the length of stay in the ICU.

Table 3

| Total duration of hospitalisations (days) | p | Duration of the last hospitalisation (days) | p |
|-----------------------------------------|---|-------------------------------------------|---|
| Total sample (n = 72)*                  | 54 (18, 109) | 14 (4, 36) | 3 (0, 11) |
| Main diagnostic group*                  | | | | |
| Oncological (n = 34)                    | 68 (36, 109) | 23 (13, 48) | 5 (0, 12) |
| Neurological (n = 12)                   | 31 (16, 151) | 5 (1, 13); | 1 (0, 7) |
| Cardiovascular (n = 11)                 | 26 (8, 48) | 6 (3, 26) | 10 (1, 26) |
| Metabolic (n = 7)                       | 43 (4, 239) | 38 (4, 74) | 1 (0, 5) |
| Congenital/Genetic (n = 3)              | 91 (1, 235) | 0·106 | 3 (1, 19) | 0·081 | 5 (1, 15) |
| Haematological (n = 2)                  | 91 (91,91) | 46 (35,57) | | 31 (15,46) |
| Respiratory (n = 1)                     | 247 (247, 247) | 16 (16, 16) | | 17 (17, 17) |
| Gastrointestinal (n = 1)                | 103 (103, 103) | 28 (28, 28) | | 10 (10, 10) |
| Renal/Urological (n = 1)                | 1 (1, 1) | 1 (1, 1) | | 0 (0, 0) |
| No. of CCDs*                            | | | | |
| 1 (n = 30)                              | 41 (18, 104) | 15 (4, 27) | 4 (0, 11) |
| 2 (n = 19)                              | 54 (5, 102) | 0·041 | 17 (4, 54) | 0·836 | 3 (1, 7) |
| ≥ 3 (n = 23)                            | 66 (22, 181) | 16 (2, 47) | | 6 (0, 16) |

*Median (IQR). CCD = Complex chronic disease; Intensive care unit=ICU

Table 4 compares the results of hospital resource use during the last week of life in the groups of patients referred and not referred to the PPCT. Regarding pharmacological therapy, differences were found between the two groups, with less administration of inotropic agents in the group of patients referred to
PPCT (12% vs. 62%, p = 0.001). In the latter group, the subcutaneous route was proportionally more used (53% vs. 0%, p < 0.001), with a preference for the intravenous route in non-referred patients (100% vs. 61%, p < 0.001). It should be noted that the use of the intraosseous route in one of the referred patients occurred during admission to the ED, in an unforeseen exacerbation and in which the PPCT was not contacted.

The group of referred patients underwent a smaller number of invasive procedures [resuscitation methods (0% vs. 27%, p = 0.015), endotracheal intubation (6% vs. 44%, p = 0.004), central venous catheter (18% vs. 53%, p = 0.013)] and artificial/substitutive therapy [invasive ventilation (6% vs. 15%, p = 0.001) and blood product transfusion (12% vs. 55%, p = 0.002)]. On the other hand, there was greater use of oxygen therapy in referred patients (94% vs. 63%, p = 0.030). Regarding end-of-life planning, about half (52.8%) of the clinical files of patients were designated DLT, with this practice being more frequent in patients referred to the PPCT (94% vs. 40%, p < 0.001).
Table 4
– Main procedures and therapies carried out in the last week of life

| Variables                      | Total sample | Not referred to the PPCT (n = 55) | Referred to the PPCT (n = 17) | p     |
|--------------------------------|--------------|-----------------------------------|-------------------------------|-------|
| Pharmacological therapy*       |              |                                   |                               |       |
| Inotropic                      | 36 (50)      | 34 (61.8)                         | 2 (11.8)                      | 0.001 |
| Opioids                        | 60 (83.3)    | 44 (80)                           | 16 (94.1)                     | 0.271 |
| Route of administration        |              |                                   |                               |       |
| Transdermal                    | 16 (22.2)    | 14 (25.5)                         | 2 (11.8)                      | 0.327 |
| Subcutaneous                   | 9 (12.5)     | 0 (0.0)                           | 9 (52.9)                      | < 0.001|
| Endovenous                     | 67 (93.1)    | 55 (100.0)                        | 12 (70.6)                     | < 0.001|
| Intraosseous                   | 4 (5.6)      | 3 (5.5)                           | 1 (5.9)                       | 1.000 |
| Intrathecal                    | 2 (2.8)      | 2 (3.6)                           | 0 (0.0)                       | 1.000 |
| Invasive procedures *          |              |                                   |                               |       |
| Resuscitation methods          | 15 (20.8)    | 15 (27.3)                         | 0 (0.0)                       | 0.015 |
| Endotracheal intubation         | 25 (34.7)    | 24 (43.6)                         | 1 (5.9)                       | 0.004 |
| Surgery                        | 12 (16.4)    | 12 (21.8)                         | 0 (0.0)                       | 0.057 |
| Biopsy                         | 2 (2.8)      | 2 (3.6)                           | 0 (0.0)                       | 1.000 |
| CVC                            | 32 (44.4)    | 29 (52.7)                         | 3 (17.6)                      | 0.013 |
| Drain                          | 6 (8.3)      | 6 (10.9)                          | 0 (0.0)                       | 0.325 |
| Artificial/replacement therapy*|              |                                   |                               |       |
| Invasive ventilation           | 29 (40.3)    | 28 (50.9)                         | 1 (5.9)                       | 0.001 |
| Non-invasive ventilation       | 15 (20.8)    | 14 (25.5)                         | 1 (5.9)                       | 0.100 |
| Oxygen therapy                 | 53 (73.6)    | 37 (67.3)                         | 16 (94.1)                     | 0.030 |
| Transfusion of haemoderivatives| 32 (44.4)    | 30 (54.5)                         | 2 (11.8)                      | 0.002 |
| Renal replacement techniques   | 11 (15.3)    | 10 (18.2)                         | 1 (5.9)                       | 0.440 |

*n (%). CVC= Central venous catheter; PPCT=pediatric palliative care team, TPN = Total parenteral nutrition
Variables | Total sample | Not referred to the PPCT (n = 55) | Referred to the PPCT (n = 17) | p
---|---|---|---|---
TPN | 10 (13.9) | 10 (18.2) | 0 (0.0) | 0.104
Decision to limit treatment* | 38 (52.8) | 22 (40.0) | 16 (94.1) | < 0.001

*n (%). CVC = Central venous catheter; PPCT = pediatric palliative care team, TPN = Total parenteral nutrition

Referral to the PPCT seems to be influenced by the main diagnosis group (Table 5, p = 0.003), with the neurological group being the most referred, constituting 41.2% of all referrals. Patients with ≥ 3 CCDs were more often referred than patients with less clinical complexity (p = 0.036), representing 41.2% of referrals. There was also an association between non-referral to the PPCT and death in the ICU in the last year of life (p < 0.001). Of the group of 17 referred patients, only one died in the ICU, compared with 35 out of 55 non-referred patients (63.6%).
Table 5
- Impact of main diagnosis group, no. of CCDs and death in ICU on referral to the PPCT

| Variables                  | Total sample | Not referred to the PPCT (n = 55) | Referred to the PPCT (n = 17) | p       |
|----------------------------|--------------|-----------------------------------|------------------------------|---------|
| Main Diagnostic Group*     |              |                                   |                              |         |
| Oncological                | 34 (47.2)    | 31 (56.4)                         | 3 (17.6)                     |         |
| Neurological               | 12 (16.7)    | 5 (9.1)                           | 7 (41.2)                     |         |
| Cardiovascular             | 11 (15.3)    | 10 (18.2)                         | 1 (5.9)                      |         |
| Metabolic                  | 7 (9.7)      | 4 (7.3)                           | 3 (17.6)                     |         |
| Congenital/Genetic         | 3 (4.2)      | 2 (3.6)                           | 1 (5.9)                      | 0.003   |
| Respiratory                | 1 (1.4)      | 1 (1.8)                           | 0 (0.0)                      |         |
| Haematological             | 2 (2.8)      | 1 (1.8)                           | 0 (0.0)                      |         |
| Gastrointestinal           | 1 (1.4)      | 1 (1.8)                           | 0 (0.0)                      |         |
| Renal/Urological           | 1 (1.4)      | 0 (0.0)                           | 1 (5.9)                      |         |
| No. of CCDs*               |              |                                   |                              |         |
| 1                          | 30 (41.7)    | 23 (41.8)                         | 7 (41.2)                     |         |
| 2                          | 19 (26.4)    | 18 (32.7)                         | 1 (5.9)                      | 0.036   |
| ≥ 3                        | 23 (31.9)    | 14 (25.5)                         | 9 (52.9)                     |         |
| Deaths in ICU*             | 36 (50.0)    | 35 (63.6)                         | 1 (5.9)                      | <0.001  |

*n (%)  CCD = Complex chronic disease; PPCT = Hospital PPC support team; ICU = Intensive care unit

Discussion

This work is one of the few studies on the use of hospital resources in the last year of life of children/adolescents with CCD and the first in the country to assess the impact of PPC teams.

The main diagnostic groups were oncological, neurological and cardiovascular, similar to those described in previous studies.\(^1,3,4,6\) The low prevalence of congenital disease (cardiopathies, genetic/polymalformative syndromes) and metabolic disease may be related to the fact that children under one year of age were excluded, and in this period, there is a higher prevalence of these diagnostic groups (about 50%).\(^8\) Metabolic diseases, together with neurological and genetic diseases, constitute
50% of children with a need for PPC and as a group, these diseases are an important cause of death at 
paediatric age (up to 60%).\textsuperscript{4,12}

Our results suggest that the use of hospital resources by children with CCD in the last year of life varies 
according to the type and complexity of their clinical condition.

On the other hand, similar to that portrayed in the literature, it can be seen that most children/adolescents 
died in an invasive environment.\textsuperscript{6,10,15,17} In the last week of life, a high percentage of patients used a CVC, 
received transfusions of blood products, were under IV and underwent resuscitation methods, surgical 
interventions and renal replacement techniques. In most cases, the intravenous route was the most 
frequent.

The international literature suggests that patients referred to PPC have shorter hospital stays, fewer 
invasive procedures\textsuperscript{11} and thus reduced consumption of resources, lower percentage of drug 
administration,\textsuperscript{6,7,15,16} improved symptom control,\textsuperscript{21} earlier decisions in end-of-life planning\textsuperscript{14} and a 
greater feeling of support and satisfaction for families.\textsuperscript{21} As regards the place of death, the scientific 
evidence also points to a lower number of deaths in the ICU of children with CCD accompanied by PPC 
teams.\textsuperscript{11,16}

Our study corroborates this evidence, as we found fewer invasive therapies and procedures (resuscitation 
methods, endotracheal intubation, CVC placement, invasive ventilation, transfusion of blood products) 
and a greater number of DLT in patients referred to the PPCT.

Regarding place of death, the ICU was the most frequent, similar to that described in other studies,\textsuperscript{1,5,22} 
which can be justified either by the absence of an ACP or by the option of optimising symptom control in 
a unit with greater vigilance and professionals with greater experience in handling more specific 
therapies.\textsuperscript{18} However, death in this department was rare and was clearly lower in patients referred to the 
PPCT (only one in 17 patients compared to 2 out of 3 of those not referred), confirming the reduction in 
healthcare costs when these patients are referred to the PPC teams.\textsuperscript{10,13,22}

Therefore, the importance of early referral to PPC teams should be highlighted, with a certifiable impact 
on the preparation of the ACP, adequacy of resources and improved quality of care provided, in keeping 
with the preferences of the patient and their family.\textsuperscript{13} Other studies have shown that family members and 
health professionals prefer an early approach to the ACP, which would ideally be discussed at diagnosis 
and/or in a phase of greater stability of the disease and would remain a dynamic process throughout the 
evolution of the disease. They also show that drawing up an ACP that respects the family's goals and 
values seems to be associated with less suffering for children with CCD at the end of life.\textsuperscript{12}

As limitations of our study we point out the fact that it is a retrospective analysis; the sample was small 
and it was impossible to determine the stage of the evolution of the disease, which may justify the use of
more or fewer invasive procedures and therapies. Furthermore, the clinical records did not always allow a complete interpretation of the therapy performed.

In conclusion, the present work is one of the few to provide a characterisation of the last year of life of children/adolescents with CCD in terms of the use of hospital resources at the end of life, and to analyse the impact of referral to PPC.

We found that there is a high level of consumption of hospital resources by children with CCD in the last year of life. Timely referral to a specialised PPC team enables a more adequate and effective response to the needs of these children and allows a more appropriate use of hospital resources.

It is therefore important to continue to raise awareness about the needs of patients with CCD at paediatric age during the last year of life, and to promote the education of health professionals on this topic and to reinforce PPC programmes which involve different levels of health care.

**Abbreviations**

ACT - Association for Children with Life-threatening or Terminal Conditions and their Families

CCD - complex chronic diseases

CVC - central venous catheter

DLT - decision to limit treatment

ED – emergency department

ICU – intensive care unit

IQR – interquartile range

PPC - pediatric palliative care

PPCT – pediatric palliative care team

TPN - Total parenteral nutrition

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**Authors Contributions:**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Andreia Nogueira, Diana Correia and Marisa Loureiro]. Data interpretation and critical reviewing were performed by [Barbara Gomes and Cândida Cancelinha]. The first draft of the manuscript was written by [Andreia Nogueira] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Ethics approval:**

This is an observational study. The Coimbra Hospital and University Center Research Ethics Committee has confirmed that no ethical approval is required.

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