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Renal Safety Issues of Intravenous Iodinated Contrast Media Are Questionable

A Problemática da Nefrotoxicidade do Contraste Iodado Endovenoso É Questionável

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Keywords: Acute Kidney Injury/chemically induced; Contrast Media/adverse effects
Palavras-chave: Lesão Renal Aguda/induzido quimicamente; Meios de Contraste/efeitos adversos

INTRODUCTION

In a recent letter to the editor, the author rightly highlighted the potential interference of contrast media (CM) used in imaging studies with clinical laboratory tests, proposing an algorithm to manage these interactions.[1] We commend the author for this effort, but we believe it is crucial to address the underlying assumptions regarding the safety of intravenous contrast media, particularly its association with nephrotoxicity. Nephrotoxicity from intravenous iodine-based media remains a debated issue, with diverging views in the literature. We aim to expand on those concerns and hereby present a brief review of the current evidence on contrast-associated acute kidney injury (CA-AKI), or post-contrast acute kidney injury (PC-AKI), as well as our view of the evolving guidelines regarding its use in patients with kidney injury.

Contrast nephrotoxicity: a debatable topic

The aforementioned letter cites the European Society of Urogenital Radiology (ESUR) guidelines, which highlight potential safety issues with contrast media use, specifically mentioning the term 'nephrotoxicity'.[2] However, these guidelines, while alluding to "potential safety issues", do not offer explicit evidence on that matter. The safety of intravenous contrast regarding nephrotoxicity has been a topic of debate for decades, with more recent studies suggesting that the risk is often overstated.[3]

The term 'contrast-induced nephropathy' emerged in the 1950s, when renal failure was observed in some patients following intravenous injection of high-osmolar contrasts. Since then, modern low-osmolar iodine contrast agents have been developed to reduce nephrotoxicity. In fact, the definition of 'contrast-induced nephropathy' was redefined in 2019 to the less causally charged 'contrast-associated' AKI and then to 'post-contrast' AKI, highlighting the evolution in our understanding over the years.[4]

Post-contrast acute kidney injury: what is the evidence?

While the early studies lacked adequate control groups, making it difficult to establish a causal link, several recent observational studies and meta-analyses have been challenging the long-held belief that the low-osmolar iodinated contrast agents significantly increase the risk of AKI. For example, a recent meta-analysis found that intravenous contrast use was not significantly associated with an increased risk of AKI when compared to non-contrast computed tomography (CT) scans.[5] Specifically, the odds ratio for developing AKI was found to be 0.94 (95% CI: 0.83 to 1.07), suggesting that contrast-enhanced CT scans do not pose a significant risk in the majority of patients. Those studies are limited by the challenges of making causal assumptions in observational research due to their non-experimental nature, and randomized controlled trials (RCTs) have not yet been conducted because of ethical concerns. However, a recent quasi-experimental observational study found no association between intravenous contrast and long-term kidney injury.[6] This study used a regression discontinuity design to attenuate selection bias, which has remained the most problematic issue in observational studies on contrast media and kidney injury. This observational method reduces selection bias by establishing a threshold for the use of a given intervention (e.g., D-dimer levels in suspected pulmonary embolism as a guide for ordering angiographic chest CT) that does not depend on the typical confounding variables (e.g., age, GFR, and diabetes status, which are unrelated to the chosen threshold). Naturally, this study has limitations, namely the fact that the median eGFR was 80 mL/min/1.73 m^2 and they used an eGFR threshold of 45 mL/min/1.73 m^2 rather than lower values, thereby limiting the generalizability of their findings to high-risk patients.

More recently, a retrospective study analyzed approximately 15 000 patients with AKI at admission who had

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undergone intravenous contrast administration and found no association with persistent AKI or dialysis initiation, utilizing propensity-weighted and entropy-balanced statistical techniques in order to reduce selection bias and imbalances in measured covariates.[7] Dialysis initiation is likely the most concerning outcome of AKI after mortality, and this study supports the notion of renal safety with intravenous contrast. This study, like the others mentioned, is observational in nature and therefore limited by its lower level of evidence. However, considering the entire body of literature, the evidence from the studies with higher quality does not seem to indicate an association between intravenous contrast and AKI. Therefore, the burden of proof seems to be on the claim that such association is (still) real and clinically significant.

Ultimately, well-conducted, large and multicenter RCTs would be the ideal method to achieve proper group balance and avoid selection bias, but it remains uncertain whether such studies will ever be conducted.

Intra-arterial *versus* intravenous contrast: key differences

One important distinction to be made, often overlooked in discussions of contrast nephrotoxicity, is the difference between intravenous and intraarterial iodinated contrast administration.[8] While intraarterial iodinated contrast, commonly used in angiographic procedures, may pose a risk for renal injury, this risk is confounded by the invasiveness of the procedures themselves. For instance, vascular manipulation during an angiogram can induce renal ischemia, making it difficult to determine whether any resulting kidney injury is due to the contrast agent, the procedure, or a combination of both. Therefore, intraarterial CA-AKI is an even more difficult topic and we argue it should be studied and discussed separately from intravenous CA-AKI. For clarity, it is worth noting that some angiographic procedures, such as pulmonary angiography, are performed using venous puncture with intravenous iodinated contrast. The risks of contrast in these procedures are consistent with those discussed for intravenous iodinated contrast administration in general, as the route of administration does not differ in these cases.

Intravenous contrast in clinical practice: evolving guidelines

The current guidelines on contrast media use reflect this evolving understanding. The ESUR guidelines, as well as those from other major radiological and nephrology societies, have progressively relaxed their recommendations regarding the use of intravenous contrast in patients with chronic kidney disease (CKD). Notably, the 2020 consensus from the American College of Radiology and the National Kidney Foundation suggests that intravenous contrast should not be withheld from patients with an eGFR greater than 30 mL/min/1.73 m^2, a significant departure from earlier and more restrictive guidelines.[9] However, just as we have seen changes in the definition of CA- and PC-AKI over the years, we can imagine that this threshold may also be modified in the future based on the latest evidence. The significant clinical utility of angiographic CT in diagnosing potentially life-threatening conditions, especially in the acute context, cannot be overlooked.

Intravenous contrast in clinical practice: future algorithms, evidence, and guidelines

Clinical algorithms are designed to guide clinicians in practice. When it comes to intravenous contrast administration, it is essential to align its use with clinical patient data. While these tools can be beneficial, it is important to acknowledge the ongoing uncertainty surrounding contrast-associated renal safety. Such algorithms can support decision-making but should be applied with an understanding of the limitations in the available evidence, especially as the assumption that contrast media pose a significant risk of nephrotoxicity, even in patients with CKD, is increasingly being questioned.

A recent Canadian guideline, supported by the Canadian Association of Radiologists and developed by a multidisciplinary group including radiologists and nephrologists, states that the causality between contrast and kidney injury remains unproven. It recommends that even when eGFR ≤ 30 mL/min/1.73 m^2, the risks of CA-AKI should be balanced against the risks of delayed and suboptimal imaging.[10]

This research field would benefit from more comprehensive studies, ideally RCTs, to provide definitive answers on the long-term renal safety of contrast-enhanced imaging studies. In the meantime, clinicians must continue to balance the benefits of contrast-enhanced imaging against the potential risks, particularly in high-risk patients, with the notion that, as of late 2024, the burden of proof lays on those claiming that AKI is associated with intravenous contrast.

CONCLUSION

The nephrotoxicity of contrast media, particularly intravenous iodinated contrast, remains a topic of debate in the medical community. While older guidelines and clinical practices have tended to err on the side of caution, particularly in patients with CKD, recent evidence suggests that the risks associated with intravenous contrast may have been overestimated and, in present times, may even not be real. For most patients, including those with mild to moderate CKD, the benefits of contrast-enhanced imaging likely outweigh the risks. Ultimately, more research is needed, particularly in patients with AKI and eGFR below 30 mL/

min/1.73 m^2, to definitively determine the safety of repeated contrast exposures.

AUTHOR CONTRIBUTIONS

BVP, MB: Study conception and design, literature search, writing and critical review of the manuscript.

PCF: Writing and critical review of the manuscript.

All authors approved the final version to be published.

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Automated Adjustment of the Fraction of Inspired Oxygen (FiO_2) and the Time Spent in Normoxemia in Preterm Infants

O Ajuste Automático da Fração Inspirada de Oxigénio (FiO_2) e o Tempo em Normoxémia em Recém-Nascidos Prematuros

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ABSTRACT

Introduction: The challenge of maintaining normoxemia in preterm infants undergoing respiratory support and oxygen therapy has led to the development of closed-loop automatic control systems for FiO_2. The aim of this study was to assess the effectiveness of these systems in maintaining SpO_2 within a target range (90% - 94%) in preterm neonates receiving supplemental oxygen.

Methods: We conducted a single-centre prospective study over a three-year period (2020 - 2023) including preterm infants with a gestational age < 33 weeks who received supplemental oxygen within the first 24 hours of life and either invasive or non-invasive respiratory support. The closed-loop automatic control of FiO_2 used was the Predictive Intelligent Control of Oxygenation feature on Fabian® ventilators. Two groups were randomized and compared, one receiving automatic plus manual control of FiO_2, and the other receiving routine manual control. Uni- and multivariable regression analyses (linear or Poisson) were used to evaluate the association between the use of closed-loop automatic control of FiO_2 and the parameters of manual adjustments, hypoxemia, hyperoxemia, and normoxemia.

Results: The study included 89 patients, of which 45 received automatic plus manual control of FiO_2 and 44 received routine manual control. The first group required fewer manual adjustments of FiO_2, experienced fewer episodes of hypoxemia and hyperoxemia ($p < 0.002$), and spent more time with SpO_2 within the target range ($p < 0.001$), compared to the second group. After adjustment for confounding, the total time spent in normoxemia was higher when in automatic plus manual control of FiO_2 (β = 81.5; 95%CI: 47.9 - 115.2, $p < 0.001$).

Conclusion: The use of closed-loop automatic control of FiO_2 seems feasible and was associated with fewer episodes of hypoxia and hyperoxia, thereby maintaining SpO_2 within normal limits for longer periods. Additionally, it has been shown to be associated with a reduction in manual interventions.

Keywords: Infant, Premature; Hyperoxia; Hypoxia; Oxygen Inhalation Therapy

RESUMO

Introdução: O desafio de manter a normoxemia em recém-nascidos pré-termo submetidos a suporte respiratório e terapia com oxigénio levou ao desenvolvimento de sistemas de controlo automático em circuito fechado para a FiO_2. O objetivo deste estudo foi avaliar a eficácia destes sistemas na manutenção da SpO_2 dentro de uma faixa alvo (90% - 94%) em recém-nascidos pré-termo sob oxigénio suplementar.

Métodos: Conduzimos um estudo prospetivo unicêntrico ao longo de um período de três anos (2020 - 2023) incluindo recém-nascidos pré-termo com idade gestacional < 33 semanas que receberam oxigénio suplementar nas primeiras 24 horas de vida e suporte respiratório invasivo ou não invasivo. O dispositivo de controlo automático em circuito fechado da FiO_2 utilizado foi o Controlo Inteligente Preditivo da Oxigenação nos ventiladores Fabian®. Foram aleatorizados e comparados dois grupos, um que beneficiou do controlo automático mais manual da FiO_2 e outro que recebeu apenas controlo manual de rotina. A análise de regressão (linear ou de Poisson) uni- e multivariada avaliou a associação entre a utilização do controlo automático em circuito fechado da FiO_2 e os parâmetros de ajustes manuais, hipoxemia, hiperoxemia e normoxemia.

Resultados: Foram incluídos 89 pacientes, 45 receberam controlo automático em circuito fechado da FiO_2 e 44 receberam controlo manual de rotina. O primeiro grupo necessitou de menos ajustes manuais da FiO_2, apresentou menor número de episódios de hipoxemia e hiperoxemia ($p < 0,002$), e passou mais tempo com a SpO_2 dentro da faixa alvo ($p < 0,001$), em comparação com o segundo grupo. Após ajuste para variáveis de confundimento, o tempo total em normoxemia demonstrou uma associação significativa com o controlo automático em circuito fechado da FiO_2 (β = 81,5; IC95%: 47,9 - 115,2; $p < 0,001$).

Conclusão: O uso do controlo automático em circuito fechado da FiO_2 parece ser viável e estava associado a um menor número de episódios de hipóxia e hiperóxia, mantendo assim a SpO_2 dentro dos limites normais por períodos mais longos. Além disso, associou-se a uma redução do número de intervenções manuais.

Palavras-chave: Hiperoxemia; Hipoxemia; Oxigenoterapia; Recém-Nascido Prematuro

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KEY MESSAGES

- Maintaining normoxemia in preterm infants undergoing oxygen therapy presents a challenge, as their SpO_2 levels frequently fluctuate, spending extended periods within ranges classified as hypoxemia and hyperoxemia.
- The challenge of maintaining normoxemia has prompted the development of closed-loop automatic control (CLAC) systems for FiO_2.
- This prospective study assessed the effectiveness of CLAC of FiO_2, using the Predictive Intelligent Control of Oxygenation (PRICO) feature on Fabian® ventilators, in maintaining SpO_2 within a target range (90% - 94%) in preterm neonates receiving supplemental oxygen.
- Our results revealed that the use of CLAC of FiO_2 is feasible and is associated with fewer episodes of hypoxia and hyperoxia, thereby maintaining SpO_2 within normal limits for longer periods. Additionally, it has been shown to be associated with a reduction in manual interventions performed by nurses.

INTRODUCTION

Preterm infants of very low and extremely low birth weight at birth, due to their neurological and lung immaturity, require respiratory support and supplemental oxygen postnatally in order to maintain adequate peripheral oxygen saturation (SpO_2), as assessed by pulse oximetry. Maintaining normoxemia presents a challenge, as the SpO_2 levels of infants undergoing oxygen therapy frequently fluctuate, spending extended periods within ranges classified as hypoxemia and hyperoxemia. These conditions are associated with an increased risk of mortality and retinopathy of prematurity (ROP), respectively, underscoring the critical importance of maintaining appropriate oxygen saturation levels in this vulnerable population.[1,2]

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome (RDS) recommend maintaining the SpO_2 target between 90% and 94% for preterm infants receiving oxygen therapy.[3] Additionally, ventilator alarm limits should be set between 89% and 95%.[3] Intermittent hypoxemic episodes in preterm infants can result from worsening of the RDS, recurrent apnea, and active exhalation during mechanical ventilation.[4] Periods of hyperoxia often occur due to inadequate adjustment of the FiO_2 and may vary in duration. The challenge of maintaining normoxemia has prompted the development of closed-loop automatic control (CLAC) systems for FiO_2. These systems involve algorithms that use the patient's SpO_2 level to regulate the delivery of FiO_2 by the ventilator, thereby ensuring that SpO_2 remains within the desired range. Additionally, such automatic control systems alleviate the workload of nurses.

The primary objective of this study was to assess the effectiveness of CLAC of FiO_2 using the Predictive Intelligent Control of Oxygenation (PRICO) feature on Fabian® ventilators in maintaining SpO_2 within a target range in preterm neonates receiving supplemental oxygen, by measuring the time in minutes spent in normoxemia.

METHODS

This study was conducted prospectively over a three-year period (2020 - 2023) in a tertiary university neonatal intensive care unit (NICU), following authorization from the local ethics committee.

Preterm infants born with a gestational age of less than 33 weeks who required supplemental oxygen and either invasive or non-invasive respiratory support within the first 24 hours of life were included in the study. Infants affected by major congenital anomalies, chromosomal anomalies, those with hemodynamic instability, and those whose parents/guardians did not authorize participation in the study after explanation and request for informed consent were excluded.

The infants were sequentially included in the study based on the order of birth and were randomized 1:1 into two groups: one receiving automatic plus manual control (A+MC) of FiO_2, and the other receiving routine manual control (RMC) only. Randomization was based on a predetermined list created using the patient's inclusion number in the study, which corresponded to the group in which the patient was placed. This placement alternated between the two groups. The doctor who included the patient in the study had access to the predetermined list. Peripheral oxygen saturation was continuously monitored on the NICU monitor as per standard protocol, and a second oximetry sensor was placed for PRICO input in the neonates randomized to receive A+MC of FiO_2. Due to the nature of the intervention, it was not feasible to blind the study nurses and doctors. The manual control of FiO_2 was conducted by the responsible nurse after receiving the necessary information to participate in the study and maintain the FiO_2 at a target SpO_2 of 90% - 94%. Whenever nurses made a manual adjustment of FiO_2, they were required to record on a recording sheet the patient's SpO_2 and FiO_2 at that moment, along with the hour and minute of the adjustment, and the reason for the manual adjustment. During manipulations and

procedures performed on the neonates, the typical increases in FiO_2 and its control during the procedure were not recorded. The registration was conducted only during the first 24 hours of life. At 24 hours of life, registration was discontinued, and the children were then followed with standard treatment. Following our national practice, the nurse-to-patient ratio was 1:2.

The infants who underwent A+MC of FiO_2 used the PRICO feature on the Fabian® ventilator. Children who only used RMC did not benefit from automatic control technology, remaining solely reliant on manual adjustments made by the nurse in charge. The ventilators used in this study were the Fabian HFO® (Acutronic, Hirzel, Switzerland), equipped with PRICO technology. SpO_2 was assessed using the Radical Masimo® system (Masimo, Irvine, California, USA) with an average time of 8 seconds. The PRICO algorithm of the Fabian ventilator is a rule-based control scheme with proportion-integral-derivative characteristics that uses both the current SpO_2 and the trend SpO_2 measurement as inputs.[5,6] Detailed information on the algorithm is provided in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22397/15695). As the Fabian® ventilator requires SpO_2 input from a separate Masimo pulse oximeter, a second pulse oximeter was attached to the patient throughout the entire study period. Both pulse oximeters were placed in a post-ductal site.

To compare the two groups of infants in this study, we collected data on the following variables: mother's age, diseases and habits, pregnancy complications, use of antenatal corticosteroids and neuroprotection with magnesium sulphate, delivery mode, resuscitation maneuvers and Apgar scores, demographics, neonatal morbidities, including respiratory distress syndrome (RDS), pneumothorax, pneumonia, bronchopulmonary dysplasia (BPD, considered in this study oxygen dependency or ventilatory support at 36 weeks), hemodynamically significant patent ductus arteriosus (HS-PDA), early and late sepsis, meningitis, necrotizing enterocolitis (NEC), intra-ventricular hemorrhage (IVH), periventricular infarction (PVI), cystic periventricular leukomalacia (cPVL), retinopathy of prematurity (ROP), mortality, and length of NICU stay. This comprehensive set of data allowed for a thorough comparison between the two groups of infants in the study. Additionally, we gathered data on treatments, including surfactant administration, invasive mechanical ventilation, use of supplemental oxygen, oxygen requirement at discharge, medications (such as inhaled corticosteroids, bronchodilators and diuretics), duration of total parenteral nutrition (TPN), surgical closure of HS-PDA and placement of a ventriculoperitoneal shunt. The definitions and criteria used in the diagnosis of the mentioned conditions have been recently described.[7]

The resuscitation guidelines used were those from the Portuguese Society of Neonatology (available at www.lusoneonatologia.com), which have been updated in accordance with the European Resuscitation Council guidelines.[8] The ventilation practices used were as follows: non-invasive ventilation (NCPAP) was the preferred mode of ventilation in preterm infants with respiratory drive. Synchronized intermittent positive pressure ventilation (SIPPV) associated with volume guarantee (VG) was employed in cases of NCPAP failure or in preterm infants without respiratory drive. High frequency oscillatory ventilation (HFOV) at our center is typically employed as a rescue ventilation strategy. The strategy of permissive hypercapnia was advocated. Caffeine citrate was routinely administered from day one of life, regardless of apneas, until the infant reached 34 weeks of gestational age.

The primary outcome measured was the percentage of time spent within the target SpO_2 range. Additionally, a comparison was conducted for the number of FiO_2 adjustments between the two groups of children, with and without automatic FiO_2 control, and whether these adjustments were made in response to hypoxemia or hyperoxemia.

Statistics

Data collection and statistical analysis were performed using IBM SPSS® statistics 29.

Categorical variables were described using absolute and relative frequencies. Continuous variables with symmetric distribution were described using mean (± standard deviation), while continuous variables with asymmetric distribution were described using median (minimum-maximum). Chi-square or Fisher's exact test were applied to compare categorical variables, while independent t-test and Mann-Whitney U test were used for symmetric and asymmetric continuous variables, respectively. Poisson regression models were used to analyze count-based outcomes: total number of manual FiO_2 adjustments (Model 1), the number of hypoxemic episodes (Model 2), and the number of hyperoxemic episodes (Model 5). Results from Poisson regression were reported as incidence rate ratios (IRR) with 95% confidence intervals (CIs). For continuous outcomes, linear regression models were applied to evaluate total time spent in hypoxemia (Model 3), percentage of time below the target range (Model 4), total time in hyperoxemia (Model 6), percentage of time above the target range (Model 7), total time in normoxemia (Model 8), and percentage of time within the target range (Model 9). Results from linear regression were expressed as beta-coefficients (β) with 95% CIs. Multivariable models were adjusted for gestational age and birth weight to control for potential confounding factors. A p-value < 0.05 was considered statistically significant.

RESULTS

Over the course of the three-year study, a total of 89 patients were enrolled. Out of these patients, 45 received A+MC of FiO_2 within the first 24 hours of life, while 44 received CMR. Maternal and obstetrical data, delivery room management, as well as neonatal morbidity and mortality of both groups, are reported and compared in Table 1. The mean gestational age was higher in the A+MC of FiO_2 group

Table 1 – Maternal and obstetrical data, delivery room management, and neonatal morbidity and mortality of infants according to type (automated + manual *versus* routine manual) of FiO_2 control in the first 24 hours of life (part 1 of 2)

	Total (n = 89)	**A+MC of FiO_2** (n = 45)	**RMC of FiO_2** (n = 44)	***p*-value**
Maternal and obstetrical data				
Mother's age, mean (± SD)	31.79 (± 6.1)	32.1 (± 6.2)	31.4 (± 6.0)	0.612Ω
1st pregnancy, n (%)	43 (48.3)	23 (51.1)	20 (45.5)	0.593*
Multiple gestation, n (%)	20 (22.5)	10 (22.2)	10 (22.7)	0.954*
Antenatal steroids, n (%)	84 (94.4)	43 (95.6)	41 (93.2)	0.367**
- Full cycle, n (%)	61 (68.5)	33 (76.7)	28 (68.3)	0.325*
Neuroprotection ($MgSO_4$), n (%)	71 (79.8)	37 (82.2)	34 (77.3)	0.561*
Chronic diseases, n (%)	28 (31.5)	14 (31.1)	14 (31.8)	0.943*
Chronic arterial hypertension, n (%	6 (6.7)	4 (8.9)	2 (4.5)	0.677**
Gestational hypertension, n (%)	0	0	0	-
Preeclampsia/Eclampsia, n (%)	19 (21.3)	12 (26.7)	7 (15.9)	0.216*
HEELP syndrome, n (%)	0	0	0	-
DM 1, n (%)	1 (1.1)	1 (2.2)	0	0.999**
Placenta abruption, n (%)	3 (3.4)	2 (4.4)	1(2.3)	0.434**
Gestational diabetes, n (%)	11 (12.4)	9 (20)	2 (4.5)	0.050**
Fetal growth restriction, n (%)	18 (20.2)	8 (17.8)	10 (22.7)	0.561*
Rupture of membranes > 18h, n (%)	14 (15.7)	8 (17.8)	6 (13.6)	0.592*
Clinical chorioamnionitis, n (%)	13 (14.6)	5 (11.1)	8 (18.2)	0.345*
Histopathological chorioamnionitis, n (%)	20 (22.5)	8 (17.8)	12 (27.3)	0.283*
Smoking, n (%)	7 (7.9)	4 (8.9)	3 (6.8)	0.899**
Alcohol, n (%)	0	0	0	-
Drugs, n (%)	0	0	0	-
Delivery room management				
C-section, n (%)	63 (70.1)	32 (71.1)	31 (70.5)	0.946*
Male, n (%)	47 (52.8)	22 (48.9)	25 (56.8)	0.454*
Gestational age, mean (± SD)	28.8 (± 2.3)	29.4 (± 2.2)	28.2 (± 2.4)	**0.022**Ω
Birthweight, mean (± SD)	1222.2 (± 417.9)	1311 (± 458)	1131 (± 355)	**0.042**Ω
Positive pressure ventilation, n (%)	76 (85.4)	39 (86.7)	37 (84.1)	0.731*
ETT + MV, n (%)	35 (39.3)	16 (35.6)	19 (43.2)	0.461*
Early NCPAP, n (%)	55 (61.8)	31 (68.9)	24 (54.5)	0.164*
Oxygen, n (%)*	89 (100)	45 (100)	44 (100)	0.999**
Adrenaline, n (%)	3 (3.4)	2 (4.4)	1 (2.3)	0.999**
Apgar score				
≤ 5 at 1st minute, n (%)	22 (24.7)	9 (20)	13 (29.5)	0.297*
≤ 5 at 5th minutes, n (%)	3 (3.4)	2 (4.4)	1 (2.3)	0.999**

BPD: bronchopulmonary dysplasia; cLPV: cystic periventricular leukomalacia; DM: diabetes melitus; ETT + MV: endotracheal tube + mechanical ventilation; HELLP: hemolysis, elevated liver enzymes and low platelet count; HS-PDA: hemodynamically significant patent ductus arteriosus; IMV: invasive mechanical ventilation; IVH: intraventricular haemorrhage; n: number; NCPAP: nasal continuous distending pressure; NEC: necrotizing enterocolitis; O_2: oxygen; PDA: patent ductus arteriosus; PVI: periventricular venous infarction; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SD: standard deviation; TPN: total parenteral nutrition;
bold *p*: significant value; **Ω**: Independent *t* test; **ΩΩ**: Mann Whitney U test; *: Chi square test; **: Fisher's exact test.

(29.4 ± 2.2 weeks *vs* 28.2 ± 2.4 weeks, $p = 0.022$), as well as the mean birthweight (1311 ± 458 g *vs* 1131 ± 355 g, $p = 0.042$). No differences were observed in obstetric, delivery, and neonatal morbidity and mortality between the two groups. Infants in the A+MC of FiO_2 group required fewer manual adjustments of FiO_2 ($p < 0.001$), experienced fewer episodes of hypoxemia ($p < 0.001$) and hyperoxemia ($p < 0.001$), and spent more time with SpO_2 within the target range of 90% - 94% ($p < 0.001$) compared to those in the MC of FiO_2 group, as shown in Table 2. On the contrary, in the group of children receiving only routine manual FiO_2 control, a higher number of FiO_2 adjustments were needed ($p < 0.001$).

Uni- and multivariable analysis for strategies of control for FiO_2 is reported in Table 3. Total number of manual FiO_2 adjustments [IRR (95% CI) = 0.08 (0.05; 0.14)], number of hypoxemic episodes [IRR = 0.16 (0.09; 0.27)], total time in hypoxemia [β (95% CI) = -9.0 (-13.2; -4.9)], percentage of time below target range [β = -0.62 (-0.9; -0.3)], total time in hyperoxemia [β = -72.6 (-106.7; 40.8)], and percentage of time above target range [β = -4.7 (-7.0; -2.4)], were significantly associated with strategies of FiO_2 control, in the univariate analysis (all $p < 0.001$). The A+MC group also showed a significant increase in total time spent in normoxemia [β = 82.8 (49.2 - 116.3)], which remained significant in the adjusted analysis [β = 81.5 (47.9 - 115.2)] ($p < 0.001$).

DISCUSSION

Newborn preterm infants with respiratory disease often need extra oxygen, but it must be administered carefully to prevent the harmful effects of both low oxygen levels (hypoxia) and high oxygen levels (hyperoxia).[9] The manual adjustment of FiO_2 is known to result in a significant amount of time spent outside the target SpO_2 range.[10] Closed-loop

Table 1 – Maternal and obstetrical data, delivery room management, and neonatal morbidity and mortality of infants according to type (automated + manual *versus* routine manual) of FiO_2 control in the first 24 hours of life (part 2 of 2)

	Total (n = 89)	**A+MC of FiO_2** (n = 45)	**RMC of FiO_2** (n = 44)	***p*-value**
Neonatal morbidity and mortality				
RDS, n (%)	89 (100)	45 (100)	44 (100)	0.999**
Surfactant, n (%)	56 (62.9)	32 (71.1)	24 (54.5)	0.106*
BPD (O_2 at 36 weeks), n (%)	11 (12.4)	5 (11.1)	6 (13.6)	0.717*
IMV, n (%) Days of IMV, median (min - max)	25 (2-93)	45 (100) 25 (5-69)	44 (100) 25.5 (2 - 93)	0.999** 0.977ΩΩ
NCPAP, n (%)	80 (89.9)	40 (88.9)	40 (90.9)	0.752*
Days on CPAP, median (min - max)	22 (2 - 72)	21.5 (2 - 55)	23 (2 - 72)	0.937ΩΩ
Days with O_2 supplementation, median (min - max)	8 (1 - 95)	7 (2 - 80)	15 (1 - 95)	0.199ΩΩ
Need of O_2 at discharge, n (%)	1 (1.1)	1 (2.2)	0	0.989**
Days with PTN, median (min - max)	14 (4 - 107)	17 (5 - 76)	14 (4 - 107)	0.232ΩΩ
HS-PDA, n (%)	24 (27)	14 (31.1)	10 (22.7)	0.373*
PDA surgical closure, n (%)	3 (3.4)	2 (14.3)	1 (10)	0.999**
NEC stage ≥ 2, n (%)	4 (4.5)	2 (4.4)	2 (4.5)	0.999**
IHV stage 3, n (%)	15 (16.9	8 (17.8)	7 (15.9)	0.814*
PVI, n (%)	7 (7.9)	4 (8.9)	3 (6.8)	0.889**
cPVL, n (%)	5 (5.6)	4 (8.9)	1 (2.3)	0.361**
ROP stage > 2, n (%)	10 (11.2)	6 (13.3)	4 (9.1)	0.526*
Early-onset sepsis, n (%)	8 (9)	4 (8.9)	4 (9.1)	0.988**
Late-onset sepsis, n (%)	27 (30.3)	14 (31.1)	13 (29.5)	0.872*
Pneumonia, n (%)	11 (12.4)	5 (11.1)	6 (13.6)	0.717*
Meningitis, n (%)	1 (1.1)	1 (2.2)	0	0.999**
Days in NICU, median (min - max)	52 (17-111)	51.5 (17-105)	55 (20 - 111)	0.818ΩΩ
Deceased, n (%)	10 (11.2)	5 (11.1)	5 (11.4)	0.970*

BPD: bronchopulmonary dysplasia; cLPV: cystic periventricular leukomalacia; DM: diabetes melitus; ETT + MV: endotracheal tube + mechanical ventilation; HELLP: hemolysis, elevated liver enzymes and low platelet count; HS-PDA: hemodynamically significant patent ductus arteriosus; IMV: invasive mechanical ventilation; IVH: intraventricular haemorrhage; n: number; NCPAP: nasal continuous distending pressure; NEC: necrotizing enterocolitis; O_2: oxygen; PDA: patent ductus arteriosus; PVI: periventricular venous infarction; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SD: standard deviation; TPN: total parenteral nutrition;
bold *p*: significant value; **Ω**: Independent *t* test; **ΩΩ**: Mann Whitney U test; *: Chi square test; **: Fisher's exact test.

Table 2 – Manual adjustments of FiO_2, hyperoxemia, hypoxemia and time in normoxemia for the two groups automated + manual *versus* routine manual control of FiO_2 in the first 24 hours of life

	A+MC of FiO_2 (n = 45)	RMC of FiO_2 (n = 44)	*p*-value
Total no. of manual FiO_2 adjustments, median (min - max)	0 (0 - 4)	3.5 (0 - 12)	**< 0.001**ΩΩ
≥ 1 manual FiO_2 adjustments, n (%)[a]	10 (22.2)	36 (81.8)	**< 0.001***
HYPOXEMIC EPISODES			
No. of infants with hypoxemic episodes, n (%)	11 (24.0)	31 (70.5)	**< 0.001***
No. of hypoxemic episodes, median (min - max)	0 (0 - 4)	2 (0 - 8)	**< 0.001**ΩΩ
≥ 2 episodes, n (%)[a]	3 (6.7)	24 (54.5)	**< 0.001***
Total time in hypoxemia, median (min - max), minutes	0 (0 - 16)	8 (0 - 80)	**< 0.001**ΩΩ
≥ 8 minutes, n (%)[a]	3 (6.7)	23 (52.3)	**< 0.001***
% of time below target range, median (min - max)	0 (0 - 1.1)	0.6 (0 - 5.5)	**< 0.001**ΩΩ
≥ 1% below, n (%)[a]	1 (2.2)	11 (25.0)	**0.002***
HYPEROXEMIC EPISODES			
Number of infants with hyperoxemic episodes, n (%)	0 (0)	28 (63.6)	**< 0.001***
Nº of hyperoxemic episodes, median (min - max)	0 (0-0)	1 (0 - 6)	**< 0.001**ΩΩ
≥ 1 episodes, n (%)[a]	0 (0)	28 (100)	**< 0.001***
Total time in hyperoxemia, median (min - max), minutes	0 (0 - 0)	25 (0 - 480)	**< 0.001**ΩΩ
≥ 25 minutes, n (%)[a]	0 (0)	28 (100)	**< 0.001***
% of time above target range, median (min - max)	0 (0 - 0)	4.2 (0.3 - 33.3)	**< 0.001**ΩΩ
≥ 4% above, n (%)[a]	2 (4.4)	15 (34.1)	**<0.001***
NORMOXEMIA			
Total time in normoxemia, median (min - max), minutes	1440 (1424 - 1440)	1406 (936 - 1440)	**< 0.001**ΩΩ
% of time in normoxemia, median (min - max)	100 (98.9 - 100)	97.7 (65 - 100)	**0.103**ΩΩ

ΩΩ: Mann Whitney U test; *: Chi-square test; [a]: The cut-offs used to dichotomize the variables were the medians obtained from the manual adjustment parameters for hypoxemia and hyperoxemia, respectively.

automatic control delivery systems, emerging as a potential solution, have demonstrated advantages in crossover studies. They increase the percentage of time infants spend within the target SpO_2 range and reduce the need for manual FiO_2 adjustments in those receiving non-invasive or invasive respiratory support.[11-13] A recent systematic review and meta-analysis by Abdo *et al*, encompassing 13 trials, concluded that CLAC is rapid and effective in controlling infants' SpO_2, and it can help reduce the workload for nurses but should not replace clinical supervision.[14]

According to a survey conducted in the United Kingdom, CLAC systems for FiO_2 are not yet widely used in neonatology units.[15] There are still few studies on the long-term outcomes. In the study by Salverda H *et al*, no differences were found in neurodevelopment at two years of age between preterm infants who used CLAC during the entire period of oxygen therapy and those who did not use it.[16] The true long-term benefits for extreme premature children are also not yet known; however, trials are currently ongoing.[17]

Several algorithms for CLAC exist, with PRICO being the one used by Fabian® ventilators. It has already demonstrated superiority in previous studies, showing its effectiveness in maintaining saturations within the desired limits.[18] In our study, the PRICO algorithm used in preterm infants showed advantages in maintaining saturations within the desired range for longer periods, reducing episodes of hyperoxia and hypoxia, and decreasing the number of adjustments required by nurses. In fact, our study demonstrated a statistically significant association between the use of CLAC and a greater percentage of time spent in normoxemia, even when adjusted to other covariates, thereby reducing the periods above and below the established limits to 94% and 90%, respectively. Additionally, CLAC showed a statistically significant association with a lower number of FiO_2 adjustments made by nurses, thus proving to be a valuable aid in their work.

In our study, we originally intended to include premature children of lower gestational age and weight. However, the timing of patient inclusion coincided with the period of the COVID-19 pandemic, during which our unit experienced a significant decrease in admissions of extreme premature babies. As a result, the included infants had a higher

Table 3 – Unadjusted and adjusted regression analysis of FiO_2 regimens on oxygenation outcomes

	Unadjusted			Adjusted**		
	Coefficient*	95% CI	*p*-value	Coefficient*	95% CI	*p*-value
Model 1						
A+MC	0.08	0.05; 0.14	**< 0.001**	-	-	0.757
RMC	1.0					
Model 2						
A+MC	0.16	0.09; 0.27	**< 0.001**	-	-	0.450
RMC	1.0					
Model 3						
A+MC	-9.0	-13.2; -4.9	**< 0.001**	-	-	0.554
RMC	1.0					
Model 4						
A+MC	-0.62	-0.9; -0.3	**< 0.001**	-	-	0.563
RMC	1.0					
Model 5						
A+MC	-	-	0.832			
RMC						
Model 6						
A+MC	-72.6	-106.7; -40.8	**< 0.001**	-	-	0.065
RMC	1.0					
Model 7						
A+MC	-4.7	-7.0; -2.4	**< 0.001**	-	-	0.095
RMC	1.0					
Model 8						
A+MC	82.8	49.2; 116.3	**< 0.001**	81.5	47.9; 115.2	**< 0.001**
RMC	1.0			1.0		
Model 9						
A+MC	-	-	0.871	-	-	
RMC						

*: Beta-coefficients obtained by linear regression were reported, except in model 1, 2 and 5 which incidence rate ratios (IRR) coefficients were reported, obtained by Poisson regression analysis. **: Adjusted for gestational age and birth weight.
Model 1: Total no. of manual FiO_2 adjustments as dependent variable;
Model 2: No. of hypoxemic episodes as dependent variable;
Model 3: Total time in hypoxemia; Model 4: % of time below target range;
Model 5: No. of hyperoxemic episodes;
Model 6: Total time in hyperoxemia;
Model 7: % of time above target range;
Model 8: Total time in normoxemia;
Model 9: % of time in normoxemia;
-: coefficients not considered because *p*-value > 0.05.

gestational age than initially expected, and this is a limitation of our study. Less premature and consequently more stable infants may derive fewer benefits from CLAC of FiO_2 compared to those who are more premature and less stable. However, we anticipate that our results might be similar to those obtained from a sample of patients with a lower gestational age, as observed in previous studies.[18,19]

The intermittent hypoxia typical of preterm infants is associated with impaired growth, as well as possible longer-term cardiorespiratory instability and poor neurodevelopmental outcome.[20] Hyperoxia has been associated with and development of severe ROP, BPD, and brain injury.[21] Given that hyperoxia is neither natural nor random but rather an unintended consequence of the intervention, it is essential to develop means to prevent the excessive generation of free oxygen radicals and subsequent irreversible damage

to target organs.

While the reduction in nurses' workload associated with the use of CLAC of FiO_2 appears advantageous, it is important to highlight that nursing supervision throughout the shift is essential. Some scenarios may require the nurse's immediate action before the CLAC response time, such as in sudden apneas, or when the automatic control may accidentally end up being turned off.

The results of this study are important because they support the use of CLAC of FiO_2 throughout the entire period of mechanical ventilation with oxygen therapy, not just in the first 24 hours of life. However, there are still areas where this study can be deepened and continued, such as extending the protocol over a longer period and including neurodevelopmental assessments in the medium to long term.

None of the studies conducted to date have investigated whether automated control of FiO_2 can actually improve early and long-term respiratory and neurodevelopmental outcomes in preterm infants. Further large-scale studies are needed to assess the actual clinical relevance of these FiO_2 CLAC devices and to determine whether they should become the standard of care.

In conclusion, our study found that the use of CLAC of FiO_2 is feasible and is associated with fewer episodes of hypoxia and hyperoxia, thereby maintaining SpO_2 within normal limits for longer periods. Additionally, it has been shown to be associated with a reduction in manual interventions performed by nurses.

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AUTHOR CONTRIBUTIONS

GR: Study design, data collection, writing and critical review of the manuscript.

PS: Data collection and critical review of the manuscript.

FFL, RA: Statistical analysis of the data and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Hesitação e Recusa da Vacina Contra a COVID-19 entre Profissionais de Saúde: Estudo Transversal num Hospital Português

Hesitancy and Refusal of the COVID-19 Vaccine Among Healthcare Professionals: A Cross-Sectional Study in a Portuguese Hospital

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RESUMO

Introdução: A hesitação vacinal é reconhecida pela Organização Mundial da Saúde como uma das principais ameaças à saúde global, tendo adquirido contornos singulares no contexto da pandemia da COVID-19. Os profissionais de saúde são reconhecidos como uma das fontes de informação mais confiáveis relativamente à vacinação. A sua posição perante a imunização constitui um fator determinante da sua intenção de a recomendar a terceiros, com potencial repercussão na taxa de adesão à vacina na população geral. O objetivo deste estudo foi caracterizar do ponto de vista sociodemográfico os profissionais de saúde de um hospital terciário português que recusaram a vacinação contra a COVID-19 e analisar os motivos da hesitação/recusa e intenção de vacinação no futuro.

Métodos: Estudo observacional transversal conduzido em 2021, cuja população-alvo compreende os profissionais de saúde propostos a completar o esquema vacinal primário contra a COVID-19. Aos que recusaram a vacinação, foi solicitado o preenchimento do "Questionário de Não-Vacinação COVID-19", que incluía uma questão de escolha múltipla e um campo de resposta livre sobre os motivos da hesitação/recusa e a pretensão de vacinação no futuro. Foram analisadas as variáveis 'sexo', 'idade' e 'categoria profissional'.

Resultados: Entre os 6648 profissionais de saúde da amostra, 2,3% (n = 153) recusaram realizar o esquema vacinal completo. A média de idades foi de 46 anos (DP = 11), sendo a proporção, em cada grupo etário de 1,2% com ≤ 35 anos; 2,5% com 36 - 45 anos; 3,1% com > 45 anos. A taxa de recusa vacinal, entre o total de profissionais de cada sexo, foi de 2,3% no sexo feminino e 2,4% no masculino. Uma maior proporção de recusa ocorreu nos assistentes operacionais (n = 53, 4,0%) e assistentes técnicos (n = 13, 3,0%). Observaram-se 16 motivos de hesitação/recusa vacinal, sendo os mais relatados: receio de reações adversas (n = 31), investigação insuficiente das vacinas (n = 22), desconfiança na eficácia das vacinas (n = 25). Apenas 28,1% (n = 43) demonstraram intenção de vacinação no futuro.

Conclusão: Verificou-se uma elevada taxa de aceitação do esquema vacinal primário contra a COVID-19. A probabilidade de recusa vacinal foi semelhante entre ambos os sexos, mas superior em indivíduos com mais de 45 anos e nos assistentes operacionais. Destacaram-se os motivos de recusa vacinal que pressupunham preocupações relativas à segurança da vacina. Estudos adicionais são necessários para melhor compreensão das dinâmicas subjacentes à hesitação/recusa vacinal.

Palavras-chave: Atitude do Pessoal de Saúde; Hesitação Vacinal; Recusa de Vacinação; Vacinas contra COVID-19

ABSTRACT

Introduction: Vaccine hesitancy is recognized by the World Health Organization as a major global health threat. In the context of the COVID-19 pandemic, this issue has taken on unique dimensions. Healthcare professionals are considered one of the most reliable sources of information regarding vaccination. Their stance on immunization is a determining factor in their likelihood to recommend it to others, with potential repercussions for vaccination uptake rates in the general population. This study aimed to characterize the sociodemographic profile of healthcare professionals at a Portuguese tertiary hospital who declined COVID-19 vaccination and to analyze the reasons for hesitancy/refusal and future vaccination intentions.

Methods: A cross-sectional study was conducted in 2021, targeting healthcare professionals eligible for the completion of the primary COVID-19 vaccination schedule. Those who refused vaccination were asked to complete the "COVID-19 Non-Vaccination Questionnaire", which included a multiple-choice question and an open response field regarding reasons for hesitancy/refusal and future vaccination intentions. Variables analyzed included gender, age, and professional category.

Results: Among the 6648 healthcare professionals in the sample, 2.3% (n = 153) declined to complete the vaccination schedule. The average age was 46 years (SD = 11), with the proportion in each age group being 1.2% aged ≤ 35 years, 2.5% aged 36 - 45 years, and 3.1% aged > 45 years. The vaccine refusal rate among all professionals of each gender was 2.3% for females and 2.4% for males. A higher proportion of refusals was observed among healthcare assistants (n = 53, 4.0%) and technical assistants (n = 13, 3.0%). Sixteen reasons for vaccine hesitancy/refusal were identified, with the most frequently reported being fear of adverse reactions (n = 31), insufficient research on vaccines (n = 22), and distrust in vaccine efficacy (n = 25). Only 28.1% (n = 43) expressed an intention to be vaccinated in the future.

Conclusion: A high acceptance rate for the primary COVID-19 vaccination schedule was observed. The likelihood of vaccine refusal was similar between genders but higher among individuals over 45 years and operational support staff. The reasons for vaccine refusal that implied concerns about the vaccine's safety stood out. Further studies are needed to better understand the dynamics underlying vaccine hesitancy/refusal.

Keywords: Attitude of Health Personnel; COVID-19 Vaccines; Vaccination Hesitancy; Vaccination Refusal

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KEY MESSAGES

- A hesitação vacinal representa uma das principais ameaças à saúde global, tendo adquirido contornos únicos no contexto da pandemia de COVID-19 devido ao desenvolvimento e aprovação de vacinas em tempo recorde.
- Os profissionais de saúde, foco deste estudo, desempenham um papel crucial na promoção da confiança pública na vacinação, tornando essencial identificar e compreender os fatores associados à hesitação vacinal neste grupo.
- Apesar das preocupações relacionadas com a introdução emergente das vacinas, verificou-se uma elevada taxa de aceitação do esquema vacinal primário contra a COVID-19 entre os profissionais de saúde do estudo.
- A probabilidade de recusa vacinal foi similar entre os sexos, mas mais prevalente em indivíduos acima de 45 anos e assistentes operacionais, sendo motivada principalmente por preocupações com a segurança e eficácia das vacinas.
- O estudo foi conduzido em 2021, pouco após ser autorizada a utilização de emergência das vacinas, pelo que os resultados obtidos se enquadram num contexto específico e podem não refletir as crenças e atitudes atuais relativamente às vacinas contra a COVID-19.

INTRODUÇÃO

A vacinação desempenha um papel essencial na prevenção de um amplo espectro de doenças infeciosas, representando uma das intervenções mais eficazes e custo-efetivas em saúde pública. Estima-se que evita cerca de dois a três milhões de mortes anualmente a nível global.[1,2]

A hesitação vacinal, fenómeno que emergiu e evoluiu concomitantemente à prática da vacinação, configura-se como uma importante barreira aos potenciais benefícios proporcionados por esta medida, tendo sido reconhecida pela Organização Mundial da Saúde (OMS) como uma entre as 10 principais ameaças à saúde global.[2] Esta entidade complexa e dinâmica foi definida em 2015 pelo Strategic Advisory Group of Experts (SAGE) em imunização da OMS como o atraso na aceitação ou recusa de vacinas apesar da sua disponibilidade nos sistemas de saúde.[3] A sua manifestação é influenciada pela tríade epidemiológica que integra fatores contextuais, individuais e/ou de grupo, e fatores específicos das vacinas envolvidas.[3-6] De acordo com o "Modelo 3Cs" desenvolvido pelo grupo de trabalho SAGE, este último fator é determinado pela confiança na segurança e eficácia da vacina ou na entidade que a recomenda ou fornece, complacência relativamente à necessidade da mesma e conveniência no acesso à vacinação.[3-7]

No contexto da pandemia de COVID-19, causada pelo coronavírus SARS-CoV-2, a problemática da hesitação vacinal adquiriu contornos singulares. A rápida disseminação do vírus e o subsequente estado de emergência socioeconómica e humanitária global levaram à necessidade urgente de vacinas[8,9] as quais foram desenvolvidas e aprovadas para utilização a um ritmo sem precedentes.[10] Esta urgência gerou, desde logo, preocupações relativamente à sua eficácia e perfil de segurança,[8,11] que se manifestaram na forma de hesitação vacinal durante a implementação dos programas de vacinação, tanto na população geral como nos profissionais de saúde.[12-14]

Os profissionais de saúde são amplamente reconhecidos como uma das fontes de informação mais confiáveis no que diz respeito à vacinação.[15,16] A posição deste grupo perante esta medida preventiva constitui um importante determinante da sua intenção de a recomendar a terceiros, com potencial repercussão na taxa de adesão à vacina na população geral.[13,16-18] Por outro lado, a vacinação dos profissionais de saúde durante a pandemia de COVID-19 desempenhou um papel significativo na melhoria da situação epidemiológica global ao contribuir para a diminuição da incidência de infeção entre estes profissionais e das cadeias de transmissão entre estes e os doentes.[16,17]

O conhecimento das razões por detrás da hesitação/recusa vacinal entre profissionais de saúde é essencial para o desenvolvimento e implementação de estratégias de intervenção dirigidas e potencialmente mais eficazes de combate a esta problemática.

O presente estudo teve como objetivo caracterizar do ponto de vista sociodemográfico uma população de profissionais de saúde de um hospital terciário português que recusou a vacinação contra a COVID-19, analisar os motivos da hesitação/recusa e a sua intenção de vacinação no futuro.

MÉTODOS

Trata-se de um estudo observacional transversal cuja população-alvo compreendeu os profissionais de saúde de um hospital terciário português, realizado no ano de 2021.

No hospital em análise, todos os trabalhadores foram propostos a completar o esquema vacinal primário contra a COVID-19, constituído por duas doses da vacina Pfizer-BioNtech®.

Aos indivíduos que recusaram uma ou ambas as vacinas, foi solicitado o preenchimento do "Questionário de Não-Vacinação COVID-19" disponibilizado pelo Serviço de

Saúde Ocupacional, com o intuito de averiguar os motivos que justificaram esta decisão. O questionário foi elaborado após ampla revisão da literatura sobre os motivos frequentemente citados para a hesitação/recusa vacinal no geral e no caso específico da COVID-19.

O inquérito incluía uma questão relativa à causa da hesitação/recusa vacinal, oferecendo várias hipóteses de escolha, assim como um campo de resposta livre, sendo permitida a seleção de mais de uma opção (Fig. 1). Foi ainda questionada a pretensão de vacinação no futuro.

Foi realizada uma análise estatística descritiva, que incluiu o cálculo das frequências e/ou percentagens de ocorrência para as variáveis categóricas e média e desvio-padrão para as variáveis contínuas. As variáveis incluídas na análise foram o sexo, idade e categoria profissional. Foram consideradas cinco categorias profissionais: enfermeiros, médicos, assistentes operacionais, assistentes técnicos e técnicos de saúde. Na categoria "técnicos de saúde" foram incluídos os técnicos superiores de diagnóstico e terapêutica, farmacêuticos e técnicos superiores de saúde. Os restantes profissionais, com menor representação amostral, como pessoal dirigente, docentes, informáticos, técnicos superiores, entre outros grupos profissionais, foram agrupados numa única categoria denominada "outros".

Para analisar a associação entre as características sociodemográficas dos profissionais de saúde e a recusa vacinal foi realizada uma regressão logística. Através deste modelo estatístico foram calculadas as *odd ratios* (OR) para cada variável sociodemográfica e os respetivos intervalos de confiança a 95% (IC 95%). A análise da associação entre a categoria profissional e a recusa vacinal foi ajustada para a idade (em anos) e sexo. A análise estatística foi realizada através do *software* IBM® SPSS Statistics, versão 29.

Todos os dados foram anonimizados para garantir a privacidade dos participantes. A aprovação ética para o presente estudo (CES ULSSJ 35/2024) foi concedida pela Comissão de Ética da Unidade Local de Saúde de São João, localizada no Porto, em Portugal.

RESULTADOS

Dados sociodemográficos da população do hospital

A população do hospital em estudo era constituída

Por que motivo ainda não tomou a vacina contra a COVID-19?

- ☐ 1. Acho que a imunidade natural é melhor.
- ☐ 2. Não confio no Serviço Nacional de Saúde.
- ☐ 3. Não confio nas farmacêuticas.
- ☐ 4. Por gravidez/aleitamento.
- ☐ 5. Tenho medo de reações adversas.
- ☐ 6. Acho que as vacinas ainda não foram bem estudadas.
- ☐ 7. Desconfio do processo de produção das vacinas.
- ☐ 8. Tenho dúvidas acerca da eficácia da vacina.
- ☐ 9. Acredito na imunidade de grupo e portanto não preciso de tomar.
- ☐ 10. Tenho razões médicas que me impedem de tomar a vacina.
- ☐ 11. Já tive COVID-19.
- ☐ 12. Não quero tomar a vacina de uma marca específica.
- ☐ 13. Outro(s) motivo(s). Qual/Quais?

Figura 1 – Questão de escolha múltipla do "Questionário de Não-Vacinação COVID-19" relativa à causa da recusa vacinal

por um total de 6648 profissionais de saúde, que foram propostos a realizar o esquema vacinal primário contra a COVID-19. Observava-se uma maior representação do sexo feminino (73,8%) relativamente ao sexo masculino (26,2%). A média de idades era de 41 anos (DP = 11,11), com 31,5% (n = 2092) dos indivíduos com idade menor ou igual a 35 anos, 30,7% (n = 2039) com 36 - 45 anos e 37,9% (n = 2517) com mais de 45 anos. A população integrava 2495 enfermeiros, 1716 médicos, 1347 assistentes operacionais, 412 assistentes técnicos, 427 técnicos de saúde e 251 profissionais classificados como "outros". Os dados sociodemográficos da população do hospital encontram-se sistematizados na Tabela 1.

Recusa vacinal e as variáveis sociodemográficas

Entre os profissionais do hospital, 2,3% (n = 153) recusaram realizar uma (n = 3) ou ambas as doses (n = 150) do esquema vacinal primário.

Dos profissionais que recusaram a vacinação, 112 (73,2%) eram do sexo feminino e 41 (26,8%) do sexo masculino, correspondendo a 2,3% e 2,4% da população total de mulheres e homens, respetivamente. A média de idades dos profissionais que recusaram a vacinação foi de 46 anos (DP = 10,91). A proporção de recusa vacinal por intervalo de idade foi de 1,2% com idade menor ou igual a 35 anos (n = 25), 2,5% com 36 - 45 anos (n = 51) e 3,1% com mais de 45 anos (n = 77). Relativamente à categoria profissional, a proporção de trabalhadores que recusaram a vacina foi de 4,0% (n = 53) nos assistentes operacionais, 3,6% (n = 15) nos assistentes técnicos, 3,0% (n = 13) nos técnicos de saúde, 1,7% (n = 42) nos enfermeiros, 1,6% (n = 27) nos médicos e 1,2% (n = 3) nos profissionais classificados como "outros" (Tabela1).

Os profissionais de saúde apresentaram uma maior probabilidade de recusar a vacina à medida que a idade aumentava. Os indivíduos na faixa etária de 36 a 45 anos apresentaram uma probabilidade de mais de duas vezes de recusar a vacinação em relação ao grupo mais jovem (OR = 2,12; IC 95% 1,31 - 3,44), e a magnitude da associação era maior para os profissionais com mais de 45 anos (OR = 2,61; IC 95% 1,66 - 4,11). Relativamente à categoria profissional, e tendo os assistentes operacionais como categoria de referência, os enfermeiros apresentaram uma menor probabilidade de recusar a vacinação (OR = 0,45; IC 95% 0,29 - 0,69), assim como os médicos (OR = 0,48; IC 95% 0,29 - 0,77). Não se verificou uma associação clara entre o sexo e a recusa vacinal (OR = 1,00; IC 95% 0,69 - 1,44). A associação entre as características sociodemográficas dos participantes e a recusa vacinal encontra-se sistematizada na Tabela 2.

Motivos de recusa vacinal

Entre os indivíduos que recusaram ser vacinados, 26,1% (n = 40) optaram por não responder ao "Questionário

Tabela 1 – Caracterização sociodemográfica da população total e população que recusou a vacinação

	População total*	População que recusou vacinação**	Proporção de recusa vacinal na população total***
Variáveis	n (%)	n (%)	**%**
Sexo			
Feminino	4909 (73,8)	112 (73,2)	2,3
Masculino	1739 (26,2)	41 (26,8)	2,4
Idade (anos)			
≤ 35	2092 (31,5)	25 (16,3)	1,2
36 - 45	2039 (30,7)	51 (33,3)	2,5
> 45	2517 (37,9)	77 (50,3)	3,1
Categoria profissional			
Médicos	1716 (25,8)	27 (17,6)	1,6
Enfermeiros	2495 (37,5)	42 (27,5)	1,7
Assistentes operacionais	1347 (20,3)	53 (34,6)	4,0
Assistentes técnicos	412 (6,2)	15 (9,8)	3,6
Técnicos de saúde	427 (6,4)	13 (8,5)	3,0
Outros	251 (3,8)	3 (2,0)	1,2
Total	**6648**	**153**	**2,3**

*: Percentagens calculadas em relação à população total do hospital (n = 6648).
**: Percentagens calculadas em relação ao número total de indivíduos que recusaram a vacinação (n = 153).
***: Proporção de recusa vacinal para cada categoria das diferentes variáveis analisadas, calculada como o número de recusas dividido pelo total de indivíduos na população geral na respetiva categoria, refletindo o impacto da recusa vacinal em cada grupo.

Tabela 2 – Associação entre as características sociodemográficas dos participantes e a recusa vacinal

	OR	IC 95%
Sexo		
Feminino	1	
Masculino	1,00	0,69 - 1,44
Idade		
≤ 35 anos	1	
36 - 45 anos	2,12	1,31 - 3,44
> 45 anos	2,61	1,66 - 4,11
Categoria profissional*		
Assistentes operacionais	1	
Enfermeiros	0,45	0,29 - 0,69
Técnicos	0,81	0,43 - 1,50
Assistentes técnicos	0,87	0,48 - 1,56
Médicos	0,48	0,29 - 0,77
Outros	0,39	0,14 - 1,09

Nota: Os *odd ratios* (OR) e os intervalos de confiança (IC) a 95% apresentados são estimados por modelos de regressão logística.
*: Ajustado para a idade, em anos, e para o sexo.

de Não-Vacinação COVID-19", não indicaram nenhuma opção na questão relativa à razão da recusa ou mencionaram não ter motivo específico no campo de resposta livre.

Relativamente ao número de motivos evocados, 51,0% (n = 78) dos profissionais que recusaram a vacinação indicaram um motivo, 17,7% (n = 27) dois motivos e 5,2% (n = 8) três ou mais motivos.

Foram observados 16 diferentes motivos para a recusa vacinal, três dos quais foram indicados no campo de resposta livre. Os motivos de recusa mais relatados foram receio de reações adversas medicamentosas (n = 31), investigação insuficiente das vacinas (n = 22), desconfiança na eficácia das vacinas (n = 25), razões médicas (n = 16), gravidez ou amamentação (n = 15), infeção prévia por COVID-19 (n = 13) e preferência pela imunidade natural (n = 11).

Os motivos de recusa indicados e respetivas frequências encontram-se enumerados na Tabela 3.

Motivos de recusa vacinal e categoria profissional

Quando relacionados os motivos de recusa e a categoria profissional, verificou-se que a desconfiança na eficácia das vacinas foi a causa mais mencionada entre médicos (n = 5) e assistentes técnicos (n = 3). O receio de reações adversas medicamentosas foi a razão de destaque observada entre os assistentes operacionais (n = 17) e os técnicos de saúde (n = 4). A gravidez ou amamentação foi o motivo mais frequente entre os enfermeiros (n = 10).

A Tabela 4 resume a caracterização dos motivos de recusa vacinal de acordo com a categoria profissional dos respondentes.

Tabela 3 – Motivos de recusa vacinal

Motivos de recusa	n	%*
Preferência pela imunidade natural	11	7,2
Desconfiança no Serviço Nacional de Saúde	1	0,7
Desconfiança nas farmacêuticas	5	3,3
Gravidez/Amamentação	15	9,8
Receio de reações adversas medicamentosas	31	20,3
Investigação insuficiente das vacinas	22	14,5
Desconfiança no processo de produção das vacinas	5	3,3
Desconfiança na eficácia das vacinas	25	16,3
Crença na imunidade de grupo	5	3,3
Razões médicas	16	10,5
Infeção prévia por COVID-19	13	8,5
Preferência por vacina de outra farmacêutica	2	1,3
Cepticismo relativo à gravidade da COVID-19	3	2,0
Crenças religiosas/espirituais	2	1,3
Desconfiança na segurança da vacina	3	2,0
Reação adversa medicamentosa na 1.ª dose da vacina	1	0,7
Motivo pessoal não apurado	40	26,1

Nota: Como os participantes puderam selecionar múltiplos motivos de recusa, a soma das proporções apresentadas é superior a 100%.
*: O denominador utilizado corresponde ao total de profissionais de saúde que recusaram a vacinação (n = 153).

Tabela 4 – Motivo de recusa por categoria profissional

	M* n (%)	E* n (%)	AO* n (%)	AT* n (%)	TS* n (%)	O* n (%)	Total** n (%)
Preferência pela imunidade natural	-	3 (7,1)	4 (7,6)	3 (20,0)	1 (7,7)	-	11 (7,2)
Desconfiança no SNS	-	-	1 (1,9)	-	-	-	1 (0,7)
Desconfiança nas farmacêuticas	-	-	2 (3,8)	1 (6,7)	1 (7,7)	1 (33,3)	5 (3,3)
Gravidez/Amamentação	1 (4,4)	11 (26,2)	3 (5,7)	-	-	-	15 (9,8)
Receio de reações adversas medicamentosas	2 (8,7)	5 (11,9)	17 (32,1)	2 (13,3)	4 (30,8)	1 (33,3)	31 (20,3)
Investigação insuficiente das vacinas	3 (13,0)	4 (9,5)	12 (22,6)	2 (13,3)	1 (7,7)	-	22 (14,4)
Desconfiança no processo de produção das vacinas	2 (8,7)	1 (2,4)	1 (1,9)	-	-	1 (33,3)	5 (3,3)
Desconfiança na eficácia das vacinas	5 (21,7)	3 (7,1)	14 (26,4)	3 (20,0)	-	-	25 (16,3)
Crença na imunidade de grupo	-	1 (2,4)	2 (3,8)	1 (6,7)	1 (7,7)	-	5 (3,3)
Razões médicas	2 (8,7)	5 (11,9)	6 (11,3)	1 (6,7)	1 (7,7)	1 (33,3)	16 (10,5)
Infeção prévia por COVID-19	2 (8,7)	3 (7,1)	5 (9,4)	-	2 (15,4)	1 (33,3)	13 (8,5)
Preferência por vacina de outra farmacêutica	-	-	1 (1,9)	-	-	1 (33,3)	2 (1,3)
Cepticismo relativo à gravidade da COVID-19	1 (4,4)	-	2 (3,8)	-	-	-	3 (2,0)
Crenças religiosas/espirituais	-	-	1 (1,9)	-	1 (7,7)	-	2 (1,3)
Desconfiança na segurança da vacina	-	1 (2,4)	1 (1,9)	-	1 (7,7)	-	3 (2,0)
Reação adversa medicamentosa na 1.ª dose da vacina	-	-	-	-	1 (7,7)	-	1 (0,7)
Motivo pessoal não especificado	11 (47,8)	11 (26,2)	10 (18,9)	5 (33,3)	3 (23,1)	-	40 (26,4)

AO: assistentes operacionais; AT: assistentes técnicos; E: enfermeiros; M: médicos; O: outros; TS: técnicos de saúde.
Nota: Como os participantes puderam selecionar múltiplos motivos de recusa, a soma das proporções apresentadas pode ser superior a 100%.
*: O denominador utilizado no cálculo das percentagens corresponde ao número de indivíduos que recusaram a vacina em cada categoria profissional.
**: O denominador utilizado no cálculo das percentagens corresponde ao total de profissionais de saúde que recusaram a vacinação (n = 153).

Hesitação vacinal *versus* recusa firme

No que diz respeito à questão sobre a intenção de vacinação no futuro, 45,1% (n = 69) dos participantes responderam que não, 28,1% (n = 43) estavam dispostos a fazer a vacina no futuro, 4,6% (n = 7) afirmaram não saber, e 22,2% (n = 34) não responderam. Entre os 153 profissionais de saúde que recusaram uma ou ambas as doses da vacina, 30,4% (n = 34) dos indivíduos do sexo feminino demonstraram intenção de ser vacinados e 22,0% (n = 9) no caso do sexo masculino. Relativamente à categoria profissional, o desejo de vacinação no futuro foi de 100,0% (n = 3) na categoria "outros", 46,2% (n = 6) entre os técnicos de saúde, 38,1% (n = 16) entre os enfermeiros, 22,6% (n = 12) entre os assistentes operacionais, 18,5% (n = 5) entre os médicos e 6,7% (n = 1) entre os assistentes técnicos.

A Tabela 5 demonstra a distribuição da intenção de vacinação no futuro dos profissionais de saúde por sexo e categoria profissional.

DISCUSSÃO

A vacinação representa uma das medidas mais eficazes na mitigação da COVID-19, o que se refletiu de modo notório na evolução da pandemia após a sua introdução.[19] Apesar de a hesitação vacinal não constituir uma novidade na esfera da saúde pública, as circunstâncias singulares que envolveram as vacinas contra a COVID-19 resultaram

Tabela 5 – Intenção de vacinação no futuro

Intenção de vacinação no futuro*	Sim n (%)	Não n (%)	Não sabe n (%)	Não respondeu n (%)
Sexo				
Feminino	34 (30,4)	46 (41,1)	6 (5,4)	26 (23,2)
Masculino	9 (22,0)	23 (56,1)	1 (2,4)	8 (19,5)
Categoria profissional				
Médicos	5 (18,5)	13 (48,2)	-	9 (33,3)
Enfermeiros	16 (38,1)	15 (35,7)	2 (4,8)	9 (21,4)
Assistentes operacionais	12 (22,6)	28 (52,8)	2 (3,8)	11 (20,8)
Assistentes técnicos	1 (6,7)	10 (66,7)	1 (6,7)	3 (20,0)
Técnicos de saúde	6 (46,2)	3 (23,1)	2 (15,4)	2 (15,4)
Outros	3 (100,0)	-	-	-
Total	43 (28,1)	69 (45,1)	7 (4,6)	34 (22,2)

*: O denominador utilizado no cálculo das percentagens corresponde ao total de profissionais de saúde que recusaram a vacinação (n = 153).

na potenciação deste fenómeno.[20]

Dado o papel amplamente reconhecido dos profissionais de saúde como os agentes mais confiáveis no processo de promoção da vacinação, a hesitação vacinal neste grupo pode influenciar negativamente a posição dos demais em relação à vacina.[13,15-18] Torna-se, assim, essencial compreender as razões subjacentes a esta problemática como ponto de partida para uma atuação eficaz.

No presente estudo, procedeu-se à caracterização sociodemográfica dos profissionais de saúde de um hospital terciário português que recusaram a vacinação contra a COVID-19 e foram explorados os motivos dessa recusa e a sua intenção de vacinação no futuro.

Recusa vacinal e as variáveis sociodemográficas

Na população em análise, foi observada uma proporção de recusa vacinal de 2,3%. Este resultado é consistente com a maioria dos estudos sobre hesitação da vacinação contra a COVID-19 entre profissionais de saúde, os quais demonstraram elevadas taxas de aceitação da mesma.[13,17,21] No entanto, num artigo de revisão que incluiu 35 estudos de vários países, a prevalência de hesitação vacinal variou entre 4,3% e 72%,[17] o que poderá refletir diferenças socioculturais e/ou a colheita de dados em diferentes momentos no tempo.[22,23] Num outro estudo, que incluiu 3295 profissionais de saúde de 23 países, verificou-se uma hesitação vacinal de 15%, com 4% a recusar a vacina, contra 24,8% de hesitação vacinal verificada num ensaio realizado pelos mesmos autores na população geral.[13]

No que diz respeito ao sexo dos intervenientes, não se observou associação estatisticamente significativa entre este e a recusa vacinal. Relativamente à faixa etária, verificou-se uma maior probabilidade de recusa vacinal com o aumento da idade. Estas tendências não se verificaram em diversos estudos, nos quais o sexo masculino e a idade mais avançada foram fatores significativamente associados à intenção de vacinação.[13,24,25]

Quando a recusa vacinal foi analisada de acordo com a categoria profissional, os resultados demonstraram que os enfermeiros e médicos apresentaram uma probabilidade significativamente menor de recusar a vacinação em comparação com os assistentes operacionais. Apesar de a recusa vacinal ter sido inferior entre os técnicos de saúde, assistentes técnicos e outros profissionais de saúde, quando comparados com os assistentes operacionais, essa diferença não foi estatisticamente significativa.

Vários estudos demonstraram diferenças na intenção de vacinação entre grupos profissionais distintos.[26-29] Menores níveis de literacia em saúde foram associados a uma maior suscetibilidade à desinformação e desconfiança, correlacionando-se com uma maior hesitação vacinal.[25,30-32]

Considerando a heterogeneidade de profissões incluídas no grupo "profissionais de saúde", os níveis de literacia em saúde podem ser muito variáveis entre estes.[33] Estudos demonstraram que graus de escolaridade mais elevados estão associados a uma menor hesitação vacinal.[34] No entanto, esta evidência não foi consistente, uma vez que alguns trabalhos associaram níveis mais altos de educação a uma maior recusa vacinal,[35,36] enquanto outros não identificaram uma relação significativa entre as duas variáveis.[37] No presente estudo, apesar de não ter sido apurado o grau de escolaridade dos participantes, observou-se uma maior recusa vacinal entre os assistentes operacionais, onde são esperados menores graus de escolaridade e literacia em saúde. Por outro lado, um artigo de revisão demonstrou que o contacto direto com doentes com COVID-19 foi preditor de maior aceitação da vacina entre os profissionais de saúde,[17] fator este que pode variar significativamente

entre as diferentes categorias profissionais e mesmo dentro da mesma categoria profissional consoante o tipo de serviço hospitalar ou as tarefas executadas. Ser médico foi também associado, de forma significativa, a uma atitude de positiva relativamente à vacina,[13,38] tal como observado neste estudo.

Motivos de recusa vacinal

Na presente análise foram identificados 16 diferentes motivos de recusa vacinal. Entre os mais relatados destacaram-se o receio de reações adversas medicamentosas, investigação insuficiente das vacinas, desconfiança na eficácia das vacinas, razões médicas, gravidez ou amamentação, infeção prévia por COVID-19 e preferência pela imunidade natural.

Os diferentes motivos de recusa podem ser agrupados em grupos mais abrangentes, conforme observado nos estudos, que incluem preocupações com segurança e eficácia, desvalorização da necessidade da vacinação, desconfiança sistemática, crenças espirituais/religiosas, entre outros.[20,39]

Segurança das vacinas

Um dos fatores subjacentes à hesitação da vacina contra a COVID-19 frequentemente descritos na literatura consiste na preocupação relativamente à sua segurança.[39-41]

O rápido desenvolvimento e a aprovação emergente das vacinas, associados à convicção de que a tecnologia recente do mRNA não foi suficientemente investigada, são aspetos que contribuem para estas preocupações.[13,20,39,42,43] Neste contexto, muitos profissionais de saúde optaram por adiar a vacina até que mais dados sobre a sua segurança estivessem disponíveis.[39,44] No presente estudo, a ausência de investigação suficiente da vacina (n = 22) e a insegurança relativamente ao processo de produção das vacinas (n = 5) foram indicados como motivo para a recusa vacinal.

Entre os motivos que pressupõem desconfiança relativamente à segurança das vacinas, encontram-se frequentemente implicadas as questões relacionadas com reações adversas, comorbilidades e gravidez ou amamentação.[25,39]

O receio por reações adversas medicamentosas (n = 31) foi o motivo mais comummente mencionado no presente estudo. Esta preocupação foi frequentemente relatada como uma das principais causas de recusa vacinal, tanto na população geral como entre profissionais de saúde.[17,33,45] A ausência de estudos sobre os efeitos adversos a longo prazo foi apontada como a principal causa para esta preocupação.[42] Adicionalmente, a experiência de efeitos secundários no contexto de vacinação prévia contra a COVID-19 foi preditor de recusa de dose de reforço.[46]

As razões médicas (n = 16) constituíram outro problema de relevo na recusa vacinal. A imunização de indivíduos com condições médicas subjacentes representa uma questão complexa que resulta do balanço entre a maior suscetibilidade à COVID-19 nestes indivíduos e as preocupações relacionadas com o potencial impacto da vacina na doença,[47] sendo que a evidência na literatura sobre a relação entre o estado de saúde e a intenção de vacinação é mista.[48]

Apesar das recomendações do Centers for Disease Control and Prevention relativamente à vacinação contra a COVID-19 em grávidas ou lactantes,[49] este consistiu num fator de recusa vacinal (n = 15) nesta análise. Uma revisão sistemática demonstrou que os principais determinantes da hesitação vacinal nesta população são a ausência de informação suficiente e o receio relativo à segurança tanto para a mãe quanto para o filho.[50]

Eficácia das vacinas

A desconfiança na eficácia das vacinas, preocupação frequentemente relatada na literatura,[17] nomeadamente no que diz respeito à durabilidade da imunidade conferida,[51] esteve presente de forma considerável entre os motivos indicados pelos profissionais de saúde do hospital em análise (n = 25).

Vacinação desnecessária

A perceção de que a vacina contra a COVID-19 é desnecessária constitui um dos fundamentos implicados numa menor adesão vacinal na população geral e profissionais de saúde,[20,52] resultado de aspetos relacionados com a doença e fatores individuais.[49] Infeção prévia por COVID-19 (n = 13), preferência pela imunidade natural (n = 11) ou crença na imunidade de grupo (n = 5) estiveram entre os motivos referidos pela população que recusou a vacina, fatores estes frequentemente associados à convicção de que a vacina é dispensável.[14,53-55] Um estudo que envolveu mais de 65 000 profissionais de saúde nos Estados Unidos da América verificou, com significância estatística, uma menor taxa de vacinação entre os indivíduos com infeção prévia pelo SARS-CoV-2.[56] Esse fenómeno pode ser atribuído a uma perceção de maior proteção contra a COVID-19 entre estes indivíduos.[39]

O ceticismo perante o potencial curso grave da COVID-19 (n = 3) também esteve presente. Estudos demonstraram que uma perceção de risco reduzida é preditiva de uma menor adoção de comportamentos preventivos e de uma maior tendência a assumir riscos,[41] a qual se encontra mais evidente entre indivíduos jovens, saudáveis ou com infeção prévia pela COVID-19 associada a sintomas ligeiros.[20]

Desconfiança sistémica

A desconfiança no Serviço Nacional de Saúde (n = 1)

ou nas farmacêuticas (n = 5) também esteve presente entre os motivos de recusa vacinal. Descrença relativamente à integridade de organismos e instituições envolvidos na regulação e promoção da vacinação – nomeadamente agências governamentais, indústria farmacêutica e o sistema de saúde em geral – foi previamente relatada, por suspeitas de subversão dos mesmos em virtude da persecução de ganhos económicos secundários.[20,39,57] A recomendação de doses de reforço da vacina parece também ter contribuído para esta perceção.[39]

Crenças religiosas/espirituais

Crenças religiosas e/ou espirituais foram igualmente evocadas entre os profissionais de saúde (n = 2), aspeto frequentemente citado quando o custo moral da vacinação é percebido como superior aos benefícios em saúde potencialmente alcançáveis.[56,58]

Intenção de vacinação no futuro

No que diz respeito à intenção de vacinação no futuro, apenas 28,1% dos inquiridos revelaram estar dispostos a adotar esta atitude. A hesitação ou recusa vacinal podem ser contrariadas através de medidas que permitam atenuar os obstáculos à sua aceitação,[13] pelo que as intervenções orientadas para populações e preocupações específicas têm sido mais eficazes.[59] A intenção de vacinação tem aumentado ao longo do tempo, sendo esperado que esta tendência se mantenha, paralelamente à atualização contínua de elementos referentes à segurança e eficácia das vacinas.[13,39]

Limitações do estudo

O presente estudo apresenta algumas limitações. A população em análise tem uma dimensão limitada e é proveniente de um único hospital, pelo que a mesma pode não ser representativa dos profissionais de saúde no geral. Além disso, a partilha do mesmo local de trabalho pode propiciar a disseminação de opiniões e posições entre os pares, o que pode ter introduzido um viés de seleção.

Por outro lado, o estudo foi conduzido no ano de 2021, pouco tempo após ter sido autorizada a utilização de emergência das vacinas. Assim, os resultados obtidos enquadram-se num momento específico no tempo e podem não refletir as crenças e atitudes atuais relativamente às vacinas contra a COVID-19.

O formato de escolha múltipla pelo qual se optou para o questionário pode ter condicionado as respostas obtidas quanto aos motivos de recusa vacinal.

Constatou-se, ainda, que uma parcela considerável dos participantes não especificou o motivo da recusa vacinal, o que pode ter influenciado as frequências relativas obtidas para as diferentes razões evocadas, limitando a interpretação abrangente dos resultados. Adicionalmente, o estudo foi realizado ao longo de um ano, pelo que não foram avaliadas mudanças nas posições e perceções dos inquiridos em relação à vacinação que possam ter ocorrido posteriormente, sendo por isso desconhecido se a intenção de vacinação no futuro verificada à data do estudo corresponde à atitude efetivamente assumida pelo indivíduo.

Implicações práticas

Reconhecendo a relevância do tema da hesitação vacinal entre profissionais de saúde, considera-se pertinente propor estratégias que favoreçam a disseminação de informação, combatam a desinformação e promovam uma maior aceitação da vacinação neste grupo. O envolvimento ativo das chefias dos serviços e de outros líderes institucionais, bem como dos serviços de saúde ocupacional, poderá desempenhar um papel central no reforço da confiança na vacinação. Devem ser fomentadas abordagens baseadas no diálogo aberto, no respeito pelas experiências e preocupações individuais e na partilha de evidências científicas. Devem ser priorizadas as intervenções personalizadas, adaptadas aos grupos mais hesitantes e aos diferentes níveis de literacia em saúde com um enfoque na construção de uma comunicação transparente e honesta que reconheça e explique os potenciais efeitos secundários das vacinas. É igualmente fundamental destacar junto dos profissionais de saúde o papel que desempenham como modelos de adesão vacinal, sublinhando que as suas decisões e comportamentos têm um impacto direto na confiança do público e servem de exemplo para a sociedade. Complementarmente, a disseminação de materiais pedagógicos direcionados ao aumento da literacia em vacinação – através de canais internos de comunicação, cartazes, folhetos e palestras – poderão reforçar a aceitação e contribuir para um maior sucesso das campanhas de vacinação.

CONCLUSÃO

Verificou-se uma elevada taxa de aceitação do esquema vacinal primário contra a COVID-19 entre os profissionais de saúde em estudo. A probabilidade de recusa vacinal foi semelhante entre ambos os sexos, mas superior em indivíduos com mais de 45 anos e entre os assistentes operacionais.

Foram observados motivos diversificados para a recusa vacinal, destacando-se aqueles que pressupunham preocupações relativas à segurança da vacina. A desvalorização da necessidade da vacina e dúvidas relativamente à sua eficácia foram também frequentes. Menos de um terço dos participantes afirmou ter intenção de se vacinar no futuro. O cenário mutável da pandemia de COVID-19 e a disponibilização crescente de informação sobre as vacinas poderá ter modificado o panorama observado neste ou

outros estudos sobre hesitação vacinal. Dadas as limitações deste estudo, pesquisas adicionais deverão ser conduzidas no sentido de aprofundar a compreensão das dinâmicas subjacentes à recusa vacinal. O desenvolvimento de intervenções baseadas em dados objetivos e, por conseguinte, mais adaptadas ao público-alvo, permitirão respostas mais eficazes em futuros contextos semelhantes.

CONTRIBUTO DOS AUTORES

VT: Conceção e desenho do estudo, aquisição, análise e interpretação de dados, redação do manuscrito.

JA: Análise crítica e estatística dos dados, redação do manuscrito.

PM, PP: Desenho do estudo, colheita de dados.

SM, MM: Redação e revisão crítica do manuscrito.

RR: Redação e revisão crítica do manuscrito.

SP: Redação do manuscrito.

FS, CA: Revisão da literatura, redação e revisão crítica do manuscrito.

PN: Desenho do estudo, revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Differences in the Psychopharmacological Trajectories of School-Age Children with Attention-Deficit/Hyperactivity Disorder with and without Intellectual Disability

Diferenças nas Trajetórias Psicofarmacológicas de Crianças em Idade Escolar com Perturbação de Hiperatividade e Défice de Atenção com e sem Perturbação do Desenvolvimento Intelectual

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ABSTRACT

Introduction: Attention-deficit/hyperactivity disorder (ADHD) affects 5% - 7% of school-aged children, while intellectual disability (IDD) affects approximately 1% of the general population. Diagnosing and treating ADHD in individuals with IDD is challenging, not only due to communication difficulties but also because of psychiatric comorbidities that may be present. These factors can result in underdiagnosis of ADHD and increased prescribing of other psychotropic medications. The aim of this study was to determine differences in psychopharmacological treatment (number of prescribed psychostimulants, inefficacy, adverse effects) and in the number of comorbidities and other prescribed psychotropic drugs between patients with ADHD, with and without ID.

Methods: In the study, 845 children were included, divided into two groups: 574 with ADHD without ID and 271 with ADHD with ID. Microsoft® Excel® was used to calculate the Student's *t*-test, and statistical significance was assumed using the standard *p*-value of < 0.05.

Results: No significant differences were found in the average number of psychostimulants prescribed between groups ($p = 0.57$). Among those with ADHD without ID, 52.4% switched psychostimulants, while in the group with ADHD and ID, this change occurred in 56.1%. Statistically significant differences were found in the average number of other psychotropic medications prescribed per patient ($p < 0.05$) and in the number of antipsychotics prescribed ($p < 0.05$). Although our study showed more antipsychotic prescriptions for patients with ID compared to those without ID, some studies report similar use of antipsychotics between these groups. Additionally, the group with ID presented significantly more comorbidities than the group without ID ($p < 0.05$). These findings are aligned with the literature, which indicates a higher prevalence of psychiatric comorbidities in samples of patients with ID compared to those without ID (50% *vs* 18%).

Conclusion: Individuals with ID are diagnosed with more psychiatric comorbidities and are prescribed more psychotropic drugs. Additionally, more adverse effects and inefficacy with psychostimulants in ID populations require careful monitoring after initiation.

Keywords: Intellectual Disability; Antipsychotic Agents; Attention Deficit Disorder with Hyperactivity; Child; Psychotropic Drugs

RESUMO

Introdução: A perturbação de hiperatividade e défice de atenção (PHDA) afeta 5% - 7% das crianças em idade escolar, enquanto a perturbação do desenvolvimento intelectual (PDI) afeta cerca de 1% da população geral. Diagnosticar e tratar PHDA em indivíduos com PDI é desafiante, não só devido às dificuldades comunicacionais, como também às comorbilidades psiquiátricas que podem estar presentes, o que pode culminar no subdiagnóstico de PHDA e na maior prescrição de outros psicofármacos. Este estudo teve como objetivo determinar as diferenças no tratamento psicofarmacológico e no número de comorbilidades e de outros psicofármacos prescritos entre doentes com PHDA com e sem PDI.

Métodos: No estudo, foram incluídas 845 crianças, divididas em dois grupos: 574 com PHDA sem PDI e 271 com PHDA e com PDI. Foi usado o Microsoft® Excel® para calcular o teste *t* de *Student* e foi assumida a significância estatística usando o valor *standard* de $p < 0,05$.

Resultados: Não foram encontradas diferenças estatisticamente significativas no número médio de psicoestimulantes prescritos entre grupos ($p = 0,57$). Entre aqueles com PHDA sem PDI, 52.4% mudaram de psicoestimulante e, no grupo com PHDA e PDI, essa alteração ocorreu em 56.1%. Foram encontradas diferenças estatisticamente significativas no número médio de outros psicofármacos prescritos por doente ($p < 0,05$) e no número de antipsicóticos prescritos ($p < 0,05$). Apesar de o nosso estudo mostrar mais prescrições de antipsicóticos para doentes com PDI em relação aos doentes sem PDI, alguns estudos relatam um uso semelhante de antipsicóticos entre esses grupos. Além disso, o grupo com PDI apresentou significativamente mais comorbilidades do que o grupo sem PDI ($p < 0,05$). Este achado vai ao encontro da literatura, que mostra uma maior prevalência de comorbilidades psiquiátricas em amostras com PDI em comparação com amostras sem PDI (50% *vs* 18%).

Conclusão: Em suma, indivíduos com PDI apresentam mais comorbilidades psiquiátricas e recebem mais prescrições de psicofármacos. Além disso, a possibilidade de ocorrerem mais efeitos adversos e a ineficácia dos psicoestimulantes nas populações com PDI exigem uma monitorização cuidadosa após o seu início.

Palavras-chave: Antipsicóticos; Criança; Perturbação do Desenvolvimento Intelectual; Perturbação de Hiperatividade e Défice de Atenção; Psicotrópicos

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KEY MESSAGES

- Strengths: This study comprises a large sample (845 children) comparing ADHD with and without ID with a detailed analysis of comorbidities and pharmacological trajectories.
- Learning Points: There is evidence of higher prescription rates of antipsychotics and multiple psychotropic medications in children with ID. It is important to closely monitor adverse effects with multidimensional assessment.
- Limitations: This is a retrospective study with data extracted from potentially incomplete electronic records. This study lacks of adjustment for potential confounding factors and risk of clinical follow-up loss.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder, which affects approximately 5% - 7% of school-age children.[1] It is characterized by persistent inattention and/or hyperactivity and impulsivity with functional impairment in at least two contexts.[2]

Both psychopharmacological and behavioral interventions are options to manage ADHD symptoms. Stimulant medications, such as methylphenidate and lisdexamfetamine, have been first-line treatment options to target hyperactivity and attentional difficulties.[3] Furthermore, atomoxetine, a non-stimulant medication, has been used in place of stimulant medications, mainly when adverse effects of stimulant medications are poorly tolerated.[4]

The literature has shown that almost 66% of children with ADHD have at least one co-occurring condition, including anxiety, depression and/or sleep disorders.[5] In fact, among children with ADHD, up to 70% experience sleep problems. Fortunately, most ADHD patients have transient sleep problems, and only 10% have persistent problems over a 12-month period.[6] Since sleep problems have been associated with more severe ADHD symptoms, it is even more important to identify and manage sleep problems in children with ADHD. Efron *et al* found that 22% of children with ADHD were taking melatonin or clonidine for managing sleep problems.[7] The literature showed that children with ADHD have a significantly higher rate of impaired sleep compared to their healthy peers across most subjective sleep domains (e.g., bedtime resistance, sleep onset, night awakenings due to restlessness or movements, daytime sleepiness). Attention-deficit/hyperactivity disorder frequently co-occurs with primary sleep disorders such as restless legs syndrome, sleep apnea, and insomnia. Commonly, both pharmacological and non-pharmacological interventions are needed for treating sleep problems in children with ADHD.[8]

Intellectual disability (ID) is another neurodevelopmental disorder and is characterized by cognitive difficulties (reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from experience) as well as difficulties in conceptual, social, and practical areas of living.[2] The estimated prevalence rate of ID is around 1%.[9] There is a higher burden of psychiatric and neurodevelopmental disorders in people with ID, namely ADHD, with a prevalence rate between 6% and 16% in this population, which means three times higher than in the general population.[10]

The Wechsler Intelligence Scale for Children (WISC-III) is used to assess the intelligence quotient (IQ) between the ages of 6 and 16. It is an individually administered intelligence test that includes three composite IQ scores (Full Scale IQ, Verbal IQ, and Performance), four index scores (Verbal Comprehension Index, Perceptual Organization Index, Processing Speed Index, and Freedom from Distractibility Index) and 13 subtests (Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Coding, Picture Arrangement, Block Design, Object Assembly, Symbol Search, and Mazes).[11]

Diagnosis and treatment of ADHD in people with ID can be challenging because lower intellectual functioning can affect attention and behavior. Moreover, communication difficulties and psychiatric comorbidities could make the ADHD diagnosis even harder.[12] Missed diagnosis and lack of ADHD treatment in people with ID have shown to increase the use of other psychotropic medications such as antipsychotics.[13] Therefore, treatment of ADHD in people with ID is important to improve quality of life, reduce functional impairment, and prevent overuse of psychotropic medications.[12]

Moreover, ADHD and ID share some comorbidities, such as sleep disorders.[14] In fact, studies with adults with ID showed that they have an incidence of sleep disorders between 8.5% to 34.1%, with a serious sleep problem rate of 9.2%. According to a meta-analysis, there is evidence that melatonin enhances total sleep time and reduces the number of wake-ups per night in people with intellectual disabilities.[15]

This study aimed to understand whether there were significant differences between patients with ADHD with and without ID: in the psychopharmacological trajectory (number of prescribed psychostimulants, inefficacy, and adverse effects of psychostimulant medication), in the number of comorbidities, and in the prescribing of other psychotropic drugs.

METHODS

This study was conducted at the Childhood and Adolescence Mental Health and Psychiatry Department of Unidade Local de Saúde de Santo António. The study included all children aged 6 to 12 years old (inclusive) who had been referred to a Child Psychiatry consultation between 2013 and 2022, had received a diagnosis of ADHD according to the DSM-5, and had been treated with psychostimulant medication.

Data were collected by accessing the electronic clinical records of the selected patients. The study collected the following variables: sociodemographic information – age at the first consultation (6 - 12), sex (male or female) –, type of prescribed psychostimulant medication (immediate-release methylfenidate, extended-release methylphenidate, modified-release methyphenidate, lisdexamfetamine, atomoxetine), reason to change the psychostimulant (adverse effects, ineffectiveness, or both), other prescribed psychotropic drugs (antipsychotics, antidepressants, benzodiazepines), comorbid psychiatric diagnosis [oppositional defiant disorder (ODD)], specific learning disorders, sleep disorders, elimination disorders, communication disorders, autism spectrum disorder (ASD), anxiety disorders, depressive disorders), and IQ (40 - 130).

The Ethics Committee of Unidade Local de Saúde de Santo António approved this study.

Study sample definition

At the beginning of the study, 1453 children were identified. Of those, 608 were excluded: 431 children were excluded because they did not have WISC-III results in their electronic clinical files; 172 children were excluded because they scored between 70 and 79 on the WISC-III. In this context, it is important to note that ID implies an IQ below 70, although in WISC-III an IQ between 70 and 79 is already considered below normal. Finally, five children were excluded because they scored over 130 on the WISC-III, which is considered higher than normal IQ (giftedness). The final

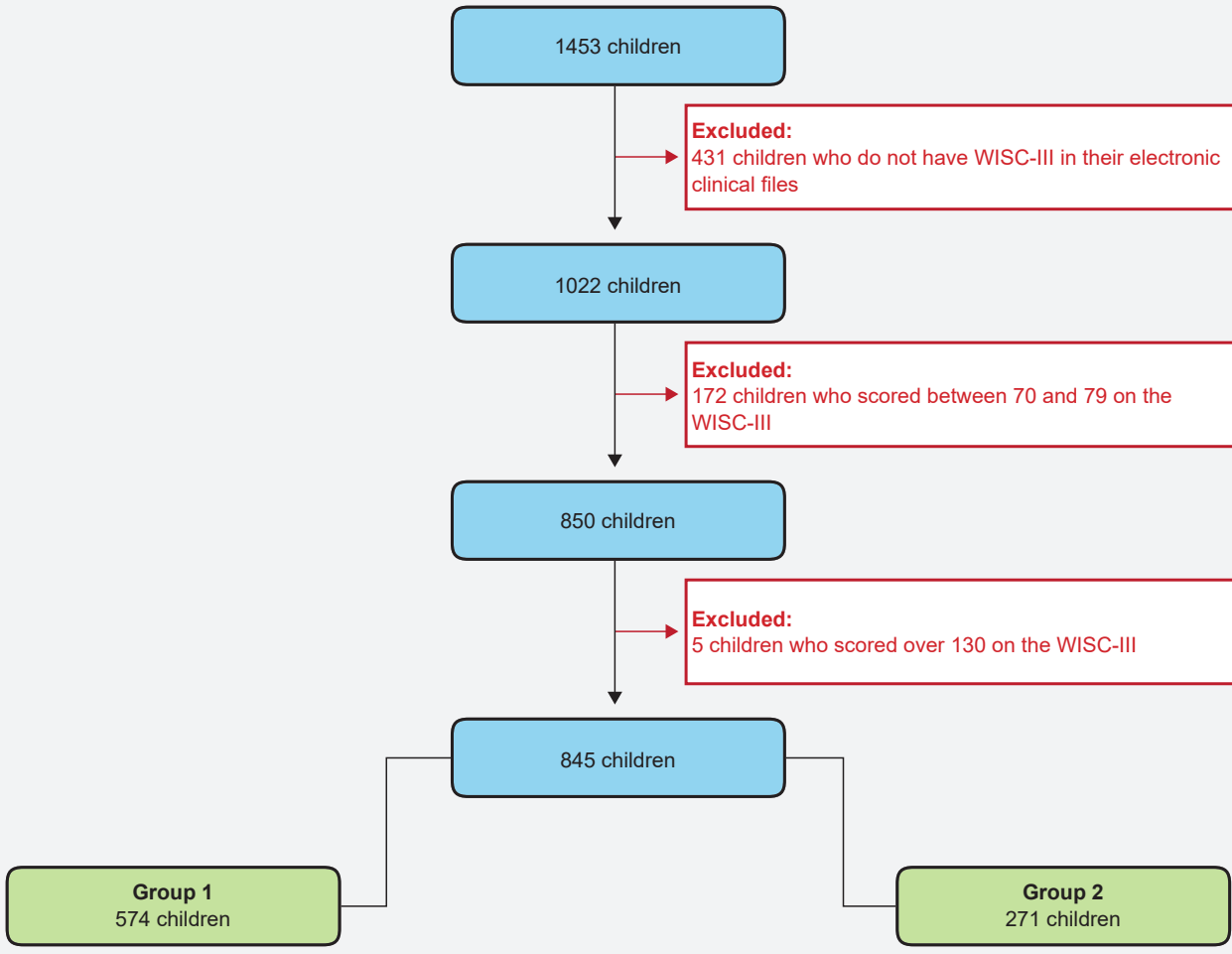

Figure 1 – Flowchart for study sample definition

sample size for the study was 845 children (Fig. 1).

Statistical analysis

The prescribed first-line medication, the need to change the psychostimulant medication or not, the reason for changing the psychostimulant medication, the class of other prescribed psychotropic drugs, and the comorbid diagnoses were coded as categorical variables.

The descriptive and simple comparative analysis was then performed using Microsoft® Excel®. Categorical variables were characterized by their absolute and relative frequencies. Microsoft® Excel® was also used to calculate Student's *t*-tests and calculate the various *p*-values of the experiment. The standard threshold of less than 0.05 was adopted for statistical significance.

RESULTS

Socio-demographic characteristics of the study population

In the group of children without ID, the average age was 8.1 years. This group was composed of 420 male children (73.2%) and 154 female children (26.8%). The average IQ in this group was 95.2 points, with a minimum IQ of 80 and a maximum IQ of 130.

Table 1 – First-line prescribed medicines by group

First-line medication		No. (%) of patients
ADHD without ID	Immediate-release methylphenidate (Rubifen®)	227 (39.5%)
	Extended-release methylphenidate (Concerta®)	176 (30.7%)
	Modified-release methylphenidate (Ritalina®)	140 (24.4%)
	Lisdexamfetamine	27 (4.7%)
	Atomoxetine	4 (0.7%)
ADHD with ID	Immediate-release methylphenidate (Rubifen®)	135 (49.8%)
	Modified-release methylphenidate (Ritalina®)	69 (25.5%)
	Extended-release methylphenidate (Concerta®)	58 (21.4%)
	Lisdexamfetamine	8 (2.9%)
	Atomoxetine	1 (0.4%)

Table 2 – Reasons to switch medication

Reasons to switch medication		No. (%) of patients
ADHD without ID	Ineffectiveness	217 (72.1%)
	Adverse effects	36 (12.0%)
	Ineffectiveness + adverse effects	48 (15.9%)
ADHD with ID	Ineffectiveness	102 (67.1%)
	Adverse effects	20 (13.2%)
	Ineffectiveness + adverse effects	48 (19.7%)

Table 3 – Most frequent adverse effects reported in each group

Adverse effects		No. (%) of patients
ADHD without ID	Loss of appetite	37 (44.0%)
	Apathy	26 (30.9%)
	Abdominal pain	11 (13.1%)
	Insomnia	11 (13.1%)
	Aggressiveness/agitation	11 (13.1%)
ADHD with ID	Loss of appetite	17 (25.0%)
	Apathy	13 (19.1%)
	Aggressiveness/agitation	8 (11.8%)
	Tics	7 (10.3%)
	Headache	6 (8.8%)

Note that some patients reported more than one adverse effect.

In the group of children with intellectual disability, the average age was 8.3 years. This group was composed of 194 male children (71.6%) and 77 female children (28.4%). The average IQ in this group was 62.5 points, with a minimum IQ of 40 and a maximum IQ of 69. In this group, 259 patients (95.6%) had a mild intellectual disability, with an IQ between 50 and 69, and 12 patients (4.4%) had a moderate ID, with an IQ between 35 and 49.

Clinical characteristics of the study population (Tables 1 - 6)

The average number of psychostimulants prescribed per child in the group without ID was 1.7. On the other hand, the average number of psychostimulants prescribed per child in the group with ID was 1.8. The means of both groups were compared using the t-test and the difference was not statistically significant (*p*-value = 0.57).

The most frequent first-line medication in the group without ID were immediate-release methylphenidate (Rubifen®) in 227 patients (39.5%), followed by extended-release methylphenidate (Concerta®) in 176 patients (30.7%), modified-release methylphenidate (Ritalina®) in 140 patients (24.4%), lisdexamfetamine in 27 patients (4.7%) and atomoxetine in four patients (0.7%). Similarly, the most common first-line medication prescribed in the group with ADHD and ID was immediate-release methylphenidate (Rubifen) in 135 patients (49.8%), followed by modified-release methylphenidate (Ritalina) in 69 patients (25.5%), extended-release methylphenidate (Concerta) in 58 patients (21.4%), lisdexamfetamine in 8 (2.9%) and atomoxetine in only one patient (0.4%).

In the group without ID, a total of 301 patients (52.4%) had to change treatment. In particular, 217 patients (72.1%) changed medication due to ineffectiveness, 36 patients (12.0%) changed medication due to adverse effects and 48 patients (15.9%) changed medication due to both ineffectiveness and adverse effects. In the group with ID, a total of 152 patients (56.1%) needed to change medication.

Table 4 – Other psychotropic medications and melatonin preparations prescribed by group

Other psychotropic medications		No. (%) of patients
ADHD without ID	Antipsychotics	121 (21.1%)*
	Antidepressants	60 (10.4%)
	Benzodiazepines	46 (8.0%)
	Melatonin preparations	81 (14.1%)
ADHD with ID	Antipsychotics	103 (38.0%)*
	Antidepressants	41 (15.1%)
	Benzodiazepines	23 (8.4%)
	Melatonin preparations	33 (12.2%)

*: statistically significant differences

Table 5 – Number of comorbidities by group

Type of comorbidities		No. (%) of patients
ADHD without ID	No	108 (18.8%)
	One	242 (42.2%)
	Two	150 (26.1%)
	Three	54 (9.4%)
	Four	14 (2.4%)
	Five	3 (0.5%)
	Six	2 (0.4%)
	Seven	1 (0.2%)
ADHD with ID	Only ID	83 (30.6%)
	ID + one comorbidity	118 (43.5%)
	ID + two comorbidities	49 (18.1%)
	ID + three comorbidities	15 (5.5%)
	ID + four comorbidities	5 (1.9%)
	ID + five comorbidities	1 (0.4%)

Table 6 – Type of comorbidities by group

No. of comorbidities		No. (%) of patients
ADHD without ID	ODD	195 (34.0%)
	Specific learning disorders	190 (33.1%)
	Sleep-wake disorders	93 (16.2%)
	Anxiety disorders	77 (13.4%)
	Elimination disorders	62 (10.8%)
	Communication disorders	52 (9.1%)
	ASD	44 (7.7%)
ADHD with ID	ODD	103 (38.0%)
	Sleep-wake disorders	39 (14.4%)
	Anxiety disorders	31 (11.4%)
	Communication disorders	30 (11.1%)
	Elimination disorders	29 (10.7%)
	ASD	29 (10.7%)

ASD: autism spectrum disorder; ODD: oppositional defiant disorder

In the case of 102 patients (67.1%), they changed medication due to ineffectiveness. Furthermore, 20 patients (13.2%) changed medication due to adverse effects and 48 children (19.7%) changed medication due to both ineffectiveness and adverse effects.

Our study found that the rate of side effects requiring changes was higher in the group with intellectual disability (13.2% + 19.7%) compared to the group without ID (12.0% + 15.9%). On the other hand, in terms of ineffectiveness, our study showed that a higher percentage of individuals without ID had to change medication due to ineffectiveness (72.1% + 15.9%) when compared to individuals with ID (67.1% + 19.7%).

The most frequent adverse effects in the group with ADHD without ID were loss of appetite (37/84; 44.0%), apathy (26/84; 30.9%), abdominal pain (11/84; 13.2%), insomnia (11/84; 13.1%) and aggressiveness/agitation (11/84; 13.1%). On the other hand, in the group with ID, the most frequent adverse effects were loss of appetite (17/68; 25.0%), apathy (13/68; 19.1%), aggressiveness/agitation (8/68; 11.8%), tics (7/68; 10.3%) and headaches (6/68; 8.8%).

Furthermore, the average number of other psychotropic drugs prescribed per patient in the group without ID was 0.55. Whereas the average number of other psychotropic drugs per patient in the group with patients with ID was 0.98. The means of both groups were compared using the *t*-test, and the difference was statistically significant (*p*-value < 0.05). The maximum number of other psychotropic drugs prescribed per patient in the group without ID was 9 and the maximum number of other psychotropic drugs prescribed per patient in the group with ID was 11.

Furthermore, the most prescribed pharmacological class after psychostimulants in group 1 was the antipsychotic class (prescribed in 121 patients; 21.1%), followed by the antidepressant class (prescribed in 60 patients; 10.4%) and the benzodiazepine class (prescribed in 46 patients; 8.0%). On the other hand, in the group of children with ADHD and ID, the psychotropic drugs prescribed along with psychostimulant medication were, in decreasing order of frequency: antipsychotics (in 103 patients; 38.0%), antidepressants (in 41 patients; 15.1%) and benzodiazepines (in 23 patients; 8.4%). Considering that the most prescribed pharmacological class after psychostimulants was antipsychotics, we compared the means of the number of antipsychotics prescribed in each group (0.29 in group 1 and 0.58 in group 2) using a *t*-test and the difference was statistically significant (*p*-value < 0.05).

In our study, the most prescribed drug class after psychostimulants was antipsychotics. However, the percentage of patients prescribed an antipsychotic in the ID group was higher than in the non-ID group (38.0% *vs* 21.1%). Additionally, the average number of antipsychotics prescribed in the ID group was significantly higher than in the group of individuals with normal IQ (0.58 *vs* 0.29; *p*-value < 0.05). Nevertheless, there is a 2016 study that showed that there were equal frequencies in the use of antipsychotics in patients with ADHD with and without ID.[16]

In the group of individuals without ID, melatonin preparations were prescribed to 81 individuals (14.1%). On the other hand, in the group of individuals with ADHD and ID, melatonin prescriptions were given to 33 individuals (12.2%). In our study, more melatonin preparations were prescribed to individuals without ID compared to those with ID (14.1% *vs* 12.2%). The difference in the prescribing of melatonin preparations between groups was not statistically

significant (Z-value = 0.655). This finding is different from what was found in the study by Osunsanmi *et al*, where a modestly higher prescribing of melatonin preparations was observed in the group with ID.[16]

In terms of comorbid psychiatric diagnoses, the average number of comorbidities in the group without ID was 1.4 diagnosis, with a maximum of seven comorbid diagnoses. Of the total, 108 patients (18.8%) did not have comorbidities. On the other hand, 242 patients (42.2%) presented another diagnosis, 150 children (26.1%) were diagnosed with two more mental disorders, 54 patients (9.4%) were diagnosed with three more mental disorders, 14 children (2.4%) presented another four diagnoses, three patients (0.5%) had five more diagnoses, two patients (0.3%) were diagnosed with six more mental disorders and only one child (0.2%) was diagnosed with seven other mental disorders. The most frequent comorbidities found in this group, according to DSM-5, were ODD (34.0%; 195/574), followed by specific learning disorders (33.1%; 190/574), sleep-wake disorders (16.2%; 93/574), anxiety disorders (13.4%; 77/574), elimination disorders (10.8%; 62/574), communication disorders (9.1%; 52/574) and ASD (7.7%; 44/574).

In terms of comorbid psychiatric diagnoses, the average number of comorbidities in the group with ID was 2.1 diagnoses, with a maximum of 6 comorbid diagnoses. In this group, 83 patients (30.6%) had only ADHD and ID, 118 children (43.5%) were diagnosed with one more mental disorder besides ADHD and ID, 49 patients (18.1%) had two more diagnoses besides ADHD and ID, 15 patients (5.5%) were diagnosed with three more mental disorders besides ADHD and ID, five children (1.8%) had four more diagnoses besides ADHD and ID and, finally, only one patient (0.4%) was diagnosed with five more diagnoses besides ADHD and ID. The most frequent comorbidities found in the group with ID, according to DSM-5, were ODD (38.0%; 103/271), followed by sleep-wake disorders (14.4%; 39/271), anxiety disorders (11.4%; 31/271), communication disorders (11.1%, 30/271), elimination disorders (10.7%; 29/271) and ASD (10.7%; 29/271). The means of the two groups in terms of number of comorbidities were compared using the t-test, and the difference was statistically significant (p-value < 0.05).

In our study, only 29 individuals with ADHD and ID had ASD (8.9%). However, there is a study with adult individuals that showed a prevalence of 73% of ASD in those with ADHD and ID. Furthermore, in this study, they found that anxiety disorders were the most common mental disorder reported (n = 65, 15%) followed by depression (n = 43, 10%).[17] The prevalence of anxiety disorders (11.4%) and depression (3.7%) in our study was considerably lower.

In a study with children and adolescents with ID, the most common comorbid psychiatric disorders were ADHD (64.9%), ODD (21.6%), anxiety disorders (18.0%), nocturnal enuresis (16.2%), conduct disorder (10.8%) and depressive disorder (6.3%).[16] In our study, we found a higher prevalence of ODD (38.0% *vs* 21.6%) but a smaller prevalence of anxiety disorders (11.4% *vs* 18.0%), depressive disorders (3.7% *vs* 6.3%) and elimination disorders (10.7% *vs* 16.2%).

DISCUSSION

There were no significant differences in psychostimulant prescribing between groups (1.7 *vs* 1.8 per child). Immediate-release methylphenidate was most common in both groups. Medication changes due to ineffectiveness were higher in the non-ID group (72.1%) compared to the ID group (67.1%), whereas changes due to adverse effects were higher in the ID group (33.0%) than in the non-ID group (27.9%).

The average number of other psychotropic drugs prescribed per patient was significantly higher in the ID group (0.98 *vs* 0.55). Antipsychotics were the most prescribed class after psychostimulants, more so in the ID group (38.0% *vs* 21.1%).

Comorbid psychiatric diagnoses were more prevalent in the ID group (average 2.1 diagnoses *vs* 1.4). Oppositional defiant disorder was most common in both groups, but the prevalence of other disorders varied between groups.

Unlike other studies in the literature, such as the study by Osunsanmi *et al*, where extended-release methylphenidate was the first-line ADHD treatment in individuals with ADHD and without ID (33.6% in both groups),[16] in our study immediate-release methylphenidate was the most commonly used first-line treatment in both groups. A possible explanation for this difference in our study is the fact that immediate-release methylphenidate in Portugal has a significantly lower cost compared to extended-release methylphenidate (the cost of a Rubifen® package with 50 tablets is €5.35 *versus* the cost of a Concerta® package with 30 tablets that is €15.49). Furthermore, this study focused on children who started the treatment before adolescence, which may have contributed to starting the treatment with lower doses, as the lowest dose of immediate-release methylphenidate is 5 mg, while the lowest dose of extended-release is 18 mg.

Our results are aligned with the existing literature in terms of side effects in the group with ID compared with the group without ID, which also indicates a higher-than-usual rate of side effects in children with intellectual disabilities.[18] Another study from 1991 showed that children with ADHD and ID who received short-acting methylphenidate were at higher risk of showing side effects such as tics and social withdrawal.[19] A more recent study showed that psychostimulants were associated with sleep difficulties, loss

of appetite and weight loss.[20] However, a systematic review from 2018 concluded that adverse effects from treatment with methylphenidate in children with ID ranged somewhere between 12% and 24%, although in some studies the rate was as high as 40% for some adverse effects,[21] which is comparable to the reported rate of adverse effects reported among non-ID children, which is on average around 12.5% - 24%.[22] This is consistent with a more recent study from 2020 that showed no major differences in type, nature, frequency, and intensity of side effects between the general and ID populations.[12]

Our ineffectiveness' rates are not consistent with previous studies in which, among patients with an IQ of 70 or less, only one of 17 patients achieved a Clinical Global Impression I (CGI-I) score of 1 or 2 thus being considered 'responder'; *versus* 20 of 26 patients with IQ 85 or greater.[12] In fact, a response rate to short-acting methylphenidate of 45% to 66% was shown for children with ADHD and ID, which is below the response rate for children with ADHD alone. Interestingly, an IQ above 50 predicted a better response to stimulants, while very low (severe, profound) IQ levels predicted a poorer response.[23]

A 2019 study found that 39.6% of children and adolescents with ID had one comorbid psychiatric disorder, 26.1% had two comorbidities, 10.8% had three comorbid psychiatric disorders, 1.8% had four comorbidities and another 1.8% had five comorbid diagnoses.[24] In terms of the number of comorbidities, we found that 30.6% of the children with ID had one comorbidity (ADHD), 43.5% were diagnosed with two more mental disorders, 18.1% had three comorbidities, 5.5% were diagnosed with four mental disorders besides ID, 1.8% had five comorbidities and only one patient (0.5%) were diagnosed with six mental disorders besides ID and ADHD.

The literature is indeed consistent in showing that the prevalence of comorbid psychiatric disorders is higher in ID samples than in samples with normal IQ. Dekker *et al* showed that 50% of children and adolescents with ID had a comorbid psychiatric disorder, while only 18% of children and adolescents with normal IQ had a psychiatric comorbidity.[25] Furthermore, Emerson *et al* showed that this prevalence was 36% for individuals with ID and 8% for individuals without ID.[26]

This study has the limitations of retrospective studies, and its findings should therefore be considered with caution. The evaluation of these cases relies solely on the available information in the clinical electronic reports which may be incomplete. Additionally, some children from our cohort may have become disengaged from our hospital's care and are currently receiving follow-up treatment at alternative healthcare facilities, posing challenges in terms of accessing comprehensive clinical information pertaining to these individuals.

Moreover, no adjustments were made for potential confounding factors between the two groups. As a result, caution must be exercised when interpreting the conclusions, as causal inferences cannot be drawn from the findings.

CONCLUSION

This study shows that individuals with ID have significantly more psychiatric comorbidities. Furthermore, it was concluded that the group with ID was prescribed more psychotropic medications, mainly antipsychotics, which were prescribed 1.5 times more often in this group compared to the group without ID. In the case of ADHD, diagnosing it is especially challenging in patients with ID due to some symptom overlap, so it is crucial to ask parents and teachers about ADHD symptoms and their impact on the child's functioning to establish an appropriate diagnosis and treatment plan. Finally, it is important to note that in the population with ID, there may be more adverse effects and greater inefficacy with psychostimulant medication, which require close monitoring after being started. To monitor possible side effects, the prescriber should assess blood pressure, heart rate, and weight at each appointment. Furthermore, the prescriber should ask about sleep habits, appetite, and other somatic symptoms such as headache and gastrointestinal distress.

AUTHOR CONTRIBUTIONS

FBM: Study design, data acquisition and analysis, writing of the manuscript.

VMM: Study design, writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

FBM received support from Humana for attending 26th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP) in Rio de Janeiro.

VMM has declared that no competing interests exist.

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PRIMARY-HF: Heart Failure Screening in Primary Care using Point-of-Care

PRIMARY-HF: Diagnóstico de Insuficiência Cardíaca em Cuidados de Saúde Primários com *Point-of-Care*

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ABSTRACT

Introduction: Heart failure is a major health challenge with high morbidity and socioeconomic burden, especially when diagnosis is delayed. In primary care, HF detection can be challenging due to symptoms overlapping with other conditions, limited access to diagnostic tools, and resource constraints. This study explores the use of natriuretic peptides (NT-proBNP) and point-of-care ultrasound (POCUS) with artificial intelligence integration as tools to improve HF screening and management in primary care. This study aims to determine whether NT-proBNP testing alone or combined with cardiac POCUS improves heart failure diagnosis and management in primary care settings, and to evaluate the cost-effectiveness of this approach.

Methods: This randomized controlled trial will involve patients aged 50 or older with suspected HF or cardiovascular risk factors, recruited across four primary care centers. Participants will be randomly assigned to one of four groups: standard of care (SoC), SoC with NT-proBNP, SoC with NT-proBNP and POCUS, and SoC with POCUS. Primary outcomes include new HF diagnosis, initiation of guideline-directed medical therapy, and improvement in health-related quality of life. Secondary outcomes include cost-effectiveness and the quality assessment of POCUS performed by trained primary care physicians. The integration of NT-proBNP and POCUS in primary care may enhance early heart failure diagnosis, optimize therapy, improve patient quality of life, and reduce healthcare costs associated with heart failure misdiagnosis and delayed treatment. This study could support the broader adoption of accessible diagnostic tools to improve heart failure management in primary care.

Keywords: Biomarkers; Echocardiography; Heart Failure/diagnosis; Heart Failure/diagnostic imaging; Natriuretic Peptide; Point-of-Care Systems; Primary Health Care

RESUMO

Introdução: A insuficiência cardíaca apresenta uma elevada morbilidade e um importante impacto socioeconómico, especialmente quando o diagnóstico é tardio. Nos cuidados de saúde primários (CSP), a deteção de insuficiência cardíaca é mais desafiante devido à sobreposição de sintomas com outras condições clínicas, ao acesso limitado a ferramentas de diagnóstico e às restrições de recursos. Este estudo explora o uso de péptidos natriuréticos (NT-proBNP) e ecografia *point-of-care* (POCUS) com integração de inteligência artificial (IA) como ferramentas para melhorar a seleção e gestão da insuficiência cardíaca nos CSP. O objetivo deste estudo é avaliar se a realização de testes de NT-proBNP combinados ou não com ecografia cardíaca POCUS melhoram o diagnóstico e a gestão da insuficiência cardíaca nos CSP, bem como avaliar a relação custo-eficácia desta abordagem.

Métodos: Este ensaio clínico controlado e randomizado incluirá pacientes com idade igual ou superior a 50 anos com suspeita de insuficiência cardíaca ou fatores de risco cardiovascular, recrutados em quatro centros de CSP. Os participantes serão aleatoriamente alocados a um de quatro grupos: *standard of care* (SoC), SoC com NT-proBNP, SoC com NT-proBNP e POCUS e SoC com POCUS. Os *outcomes* primários incluem novos diagnósticos de insuficiência cardíaca, início de terapêutica médica orientada por *guidelines* e melhoria na qualidade de vida relacionada com a saúde. Os *outcomes* secundários incluem a relação custo-eficácia e a avaliação da qualidade do POCUS realizado por médicos de CSP treinados. A integração do NT-proBNP e do POCUS em CSP poderá melhorar o diagnóstico precoce de insuficiência cardíaca, otimizar a terapêutica, melhorar a qualidade de vida dos pacientes e reduzir os custos de saúde associados ao diagnóstico incorreto e ao tratamento tardio da insuficiência cardíaca. Este estudo poderá vir a apoiar a adoção mais ampla de ferramentas de diagnóstico acessíveis para melhorar a gestão da insuficiência cardíaca nos CSP.

Palavras-chave: Biomarcadores; Cuidados Primários de Saúde; Ecocardiografia; Insuficiência Cardíaca/diagnóstico; Insuficiência Cardíaca/diagnóstico por imagem; Peptídeo Natriurético; Sistemas Automatizados de Assistência Junto ao Leito

INTRODUCTION

Background and rationale

Heart failure (HF) is a condition that poses a substantial clinical and socioeconomic burden. In Portugal, it is estimated that 16% of the population aged 50 or older suffers from heart failure, but only 10% of them are aware of their condition. These are preliminary findings from the Portuguese Heart Failure Prevalence Observational Study (PORTHOS), the largest and most recent epidemiological study on heart

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failure in Portugal.[1] In primary care, early identification of HF is challenging due to the overlap of symptoms with other conditions such as obesity, pulmonary disease, and general fatigue, which can obscure the clinical presentation. While recent policy changes have improved access to natriuretic peptide testing (NT-proBNP) in primary care, the use of advanced diagnostic tools, such as point-of-care ultrasound (POCUS), remains limited. Although echocardiography is accessible through conventional referral pathways, POCUS, as an immediate and practical tool for enhancing diagnostic precision in primary care, is not routinely available.[2,3]

Point-of-care ultrasound is already considered an extension of the physical examination presently carried out by family physicians in several countries, such as Norway, Canada, Germany, and Spain, where there is evidence of the utility of POCUS performed by family physicians for detecting cardiac abnormalities, such as left ventricular hypertrophy and structural anomalies.[4-6] These tools provide complementary information: NT-proBNP aids in the biochemical identification of heart failure, while POCUS offers real-time visualization of cardiac function and structure, helping in the confirmation or exclusion of heart failure, as well as in the identification of cardiac abnormalities that may require a prompt referral (e.g., severe valvulopathy, marked hypertrophy, segmental alterations, indirect signs of pulmonary hypertension or reduced left ventricular ejection fraction).

The primary objective of this study is to assess whether the integration of NT-proBNP testing and POCUS in primary care improves the diagnosis of HF, while improving HF guideline-directed medical treatment (GDMT), and patient's health status.

Trial design

This is a randomized controlled interventional trial, with four arms and an open-label design. The allocation ratio is 1:1:1:1, comparing different combinations of NT-proBNP testing and POCUS in heart failure diagnosis.

METHODS

Study setting

The study will be conducted across several primary care units in Portugal.

Training program for investigators in echocardiography

The training program will consist of theoretical and practical components, along with assessments to ensure proficiency:

1. Theoretical training:
   - Pre-test: Investigators will take a brief pre-test to assess their baseline knowledge of cardiac anatomy and echocardiographic principles.
   - Self-study: Investigators will complete four hours of self-study at home, focusing on cardiac anatomy, fundamental ultrasound concepts, and basic echocardiographic windows.
   - In-person learning: Following self-study, investigators will participate in four hours of in-person theoretical training led by two experienced family medicine physicians to reinforce the acquired knowledge and address any knowledge gaps identified in the pre-test.
2. Practical training:
   - Investigators will observe five POCUS echocardiographic tests performed by two trained family physicians (each with four months of practical training at a certified echocardiography laboratory, where they observed 200 echocardiograms and independently performed 50 complete echocardiograms, followed by the execution of over 400 cardiac POCUS during clinical practice).
   - Supervised tests: Investigators will perform five tests under supervision, with feedback sessions after each to identify and address areas for improvement.
   - Independent tests: Investigators will then conduct 10 tests independently. The images obtained will be reviewed by an expert cardiologist (European Association of Cardiovascular Imaging - EACVI accredited) to assess quality and accuracy.
   - Mentorship: Investigators will be assigned mentors (the family medicine physicians) who will provide continuous support during their independent phase.
3. Final assessment:
   - A theoretical examination will be conducted to assess knowledge retention and understanding.
   - Upon validation of both theoretical and practical skills, investigators will be certified as proficient in cardiac POCUS.

Eligibility criteria

- Inclusion criteria**:** Patients aged 50 years or older with suspected heart failure (based on signs and symptoms) or known cardiovascular risk factors (at least two of: diabetes *mellitus*, arterial hypertension, eGFR CKD-EPI < 60 mL/min, albuminuria, coronary artery disease or history of myocardial infarction or coronary revascularization, stroke or transient ischemic attack, atrial fibrillation or flutter, left ventricular hypertrophy (LVH) or Q waves on ECG, obesity with a BMI of 30 or greater).[7]
- Exclusion criteria: Patients with known heart failure

already under hospital management, terminal disease, severe comorbidities with life expectancy of less than one year, or inability to provide informed consent.

Interventions

The study involves four groups (Fig. 1):

- Group 1: Standard care (no NT-proBNP, no POCUS).
- Group 2: Standard care and NT-proBNP.
- Group 3: Standard care and NT-proBNP and POCUS.
- Group 4: Standard care and POCUS.

Initial assessment

Supervising physicians will carry out the initial assessment. Patients with suspected HF will be re-evaluated by investigators.

NT-proBNP Testing:

- If NT-proBNP < 100 pg/mL: HF is excluded.
- If NT-proBNP ≥ 100 pg/mL:
  - Physicians without POCUS: Request a conventional echocardiogram.
  - Physicians with POCUS: Perform POCUS and follow these criteria:
    - LVEF* < 50% or LVEF ≥ 50% with structural abnormalities (e.g., LVH** or LA enlargement***): Confirms HF.
    - Absence of these criteria: HF is excluded.
    - If uncertain, an echocardiogram is requested.

* LVEF obtained with the ultrasound AI generation;
** LV mass index ≥ 95 g/m^2 (female), ≥ 115 g/m^2 (male), or relative wall thickness > 0.42;
*** LA volume index > 34 mL/m^2 (sinus rhythm) or > 40 mL/m^2 (atrial fibrillation).

Monitoring adherence

Enrolled patients will be contacted at baseline, three, six, nine and 12 months (study close-out) for the application of the Kansas City Cardiomyopathy Questionnaire (KCCQ12)[8,9] and the *Medidas de Adesão ao Tratamento* (MAT) scale[10] to monitor their health status, quality of life, and treatment adherence. Physicians involved in the study will ensure adherence to the diagnostic and follow-up protocols. If a patient begins hospital follow-up for heart failure or requests to leave the study of their own free will, they will be excluded from the study.

Outcomes

- Primary outcomes:
  - New heart failure diagnosis.
  - Initiation of GDMT.
  - Improvement in health-related quality of life (measured by KCCQ12).
- Secondary outcomes:
  - Cost-effectiveness of NT-proBNP and POCUS in primary care.
  - Assessment of the quality of cardiac POCUS performed by trained family physicians.

Participant timeline

Explanation (Table 1):

- Enrolment phase (-t1):
  - Eligibility screening and informed consent will be conducted before the allocation.
- Allocation (timepoint 0):
  - Participants are randomly assigned to one of the four groups.
- Post-allocation assessments (t1 - t4):
  - At each timepoint (every three months), the KCCQ12 and MAT scale will be applied to monitor quality of life and adherence to treatment.
  - Outcome variables related to heart failure diagnosis, hospitalization, and other clinical outcomes will also be assessed at these intervals.

Sample size

The primary pragmatic comparison will be between Group 4 (Standard of Care + POCUS alone) and Group 1 (Standard of Care). Based on the following assumptions:

- An expected new HF diagnosis rate of 30% in Group 1 (Standard Care).
- An expected increase to 60% in new HF diagnosis with the addition of POCUS in Group 4.

To detect a doubling in the HF diagnosis rate with 80% power and an alpha level of 0.05, a minimum of 40 patients per group (160 total) is required. Randomization will be conducted in a 1:1:1:1 ratio, ensuring an even distribution of approximately 40 patients per group. The follow-up period will be 12 months, allowing clinicians sufficient time to optimize HF therapies or refer patients for hospital appointments if needed.

Comparisons between Group 4 and Groups 2 (Standard Care + NT-proBNP) and 3 (Standard Care + NT-proBNP + POCUS) will be exploratory, with the aim of determining non-inferiority. Since the proportions of GDMT initiation, specialty referral, and KCCQ-12 changes are dependent on new HF diagnoses, the power calculation is based exclusively on new HF diagnosis rates.

Recruitment

Recruitment will be carried out across multiple primary care units in Portugal. The strategy includes:

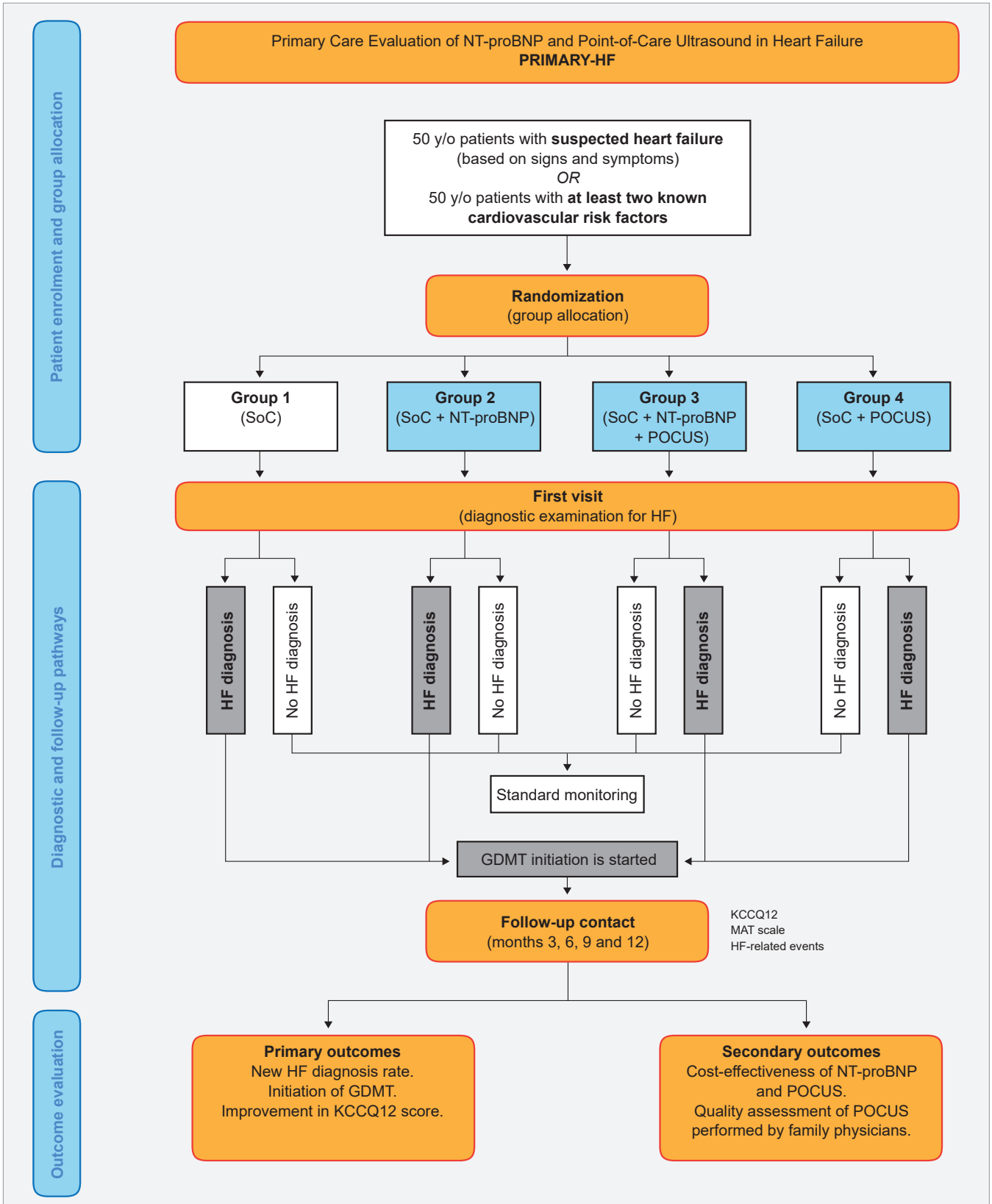

Figure 1 – Flowchart that illustrates the structure and process of the PRIMARY-HF study
GDMT: guideline-directed medical therapy; HF: heart failure; KCCQ12: Kansas City Cardiomyopathy Questionnaire 12; MAT: Medication Adherence Scale; POCUS: point-of-care ultrasound; SoC: standard of care.

1. Target population and enrolment:
   - Patients aged 50 or older with clinical suspicion of heart failure or known cardiovascular risk factors will be identified and recruited during routine visits by family physicians working at the participating primary care units.
2. Awareness campaigns:
   - Educational sessions will be organized at participating clinics to inform potential participants about the study's benefits and the role of NT-proBNP and POCUS in diagnosing heart failure.
3. Sustained recruitment efforts:
   - Recruitment is planned for a period of three months to ensure that the target sample size of 160 participants is achieved.
4. Retention measures:
   - Participants will be contacted regularly every three months for follow-up assessments (KCCQ12 and MAT scale). Flexible scheduling and reminder systems will be implemented to maximize retention and minimize dropout rates.

Methods: assignment of interventions

Sequence generation: The randomization sequence will be generated using a computer-based random number generator. The allocation ratio will be set to 1:1:1:1, ensuring an equal distribution of approximately 40 participants per group.

Allocation concealment mechanism: To maintain allocation concealment, sequentially numbered opaque sealed envelopes will be used. Each envelope will contain the assigned intervention group and will be opened only after the participant has provided informed consent and met all eligibility criteria.

Implementation: The randomization sequence will be generated centrally by the coordinating team at the Faculty of Medicine, University of Porto. Family physicians at each participating primary care site will be responsible for enrolling participants. Once eligibility is confirmed and informed consent is obtained, the assigned intervention group will be revealed by the site physician using the sealed envelope corresponding to the patient's sequence number.

Blinding: This is an open-label study, and neither the participants nor the physicians will be blinded to the intervention groups. Since the interventions (use of NT-proBNP testing and/or POCUS) are not amenable to blinding, all parties involved will be aware of the group assignments. No unblinding procedures are required.

Methods: data collection, management, and analysis

Data collection methods: data will be collected at baseline and during each follow-up visit (every three months for up to 12 months) using standardized electronic forms. The following measures will be taken to ensure data quality and consistency across all sites:

Table 1 – Timeline for the PRIMARY-HF study, detailing the enrollment, allocation, and follow-up assessments over a 12-month period. It includes eligibility screening, informed consent, intervention allocation, and evaluations such as KCCQ12 and MAT scale to monitor patient quality of life and adherence.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	**-t1**	**t0**	**t1** (3 months)	**t2** (6 months)	**t3** (9 months)	**t4** (12 months)
Enrolment						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS						
Group 1 (SoC)		X				
Group 2 (SoC + NT-proBNP)		X				
Group 3 (SoC + NT-proBNP + POCUS)		X				
Group 4 (SoC + POCUS)		X				
ASSESSMENTS						
Baseline variables		X				
KCCQ12 and MAT Scale			X	X	X	X
Outcome variables			X	X	X	X

GDMT: guideline-directed medical therapy; HF: heart failure; KCCQ12: Kansas City Cardiomyopathy Questionnaire 12; MAT: Medication Adherence Scale; POCUS: point-of-care ultrasound; SoC: standard of care

- Baseline assessment: Includes demographic and clinical variables such as age, medical history, NT-proBNP levels, and baseline KCCQ12 and MAT scores.
- Follow-up assessments: Conducted every three months using the KCCQ12 to monitor health-related quality of life and the MAT scale to evaluate treatment adherence.
- Additional variables: Any new heart failure diagnoses, changes in therapy, or hospitalizations will be recorded during follow-up.

To maintain data quality, physicians and study staff will receive training on data collection procedures. Regular monitoring visits by the coordinating team will verify the accuracy and completeness of collected data. Participants who discontinue the study will have their data analyzed up to the last follow-up point.

Economic impact assessment

Metrics

- Direct costs: Assess the reduction in the number of traditional echocardiograms performed.
- Indirect costs:
  - Patient time savings: Calculate the average time saved per patient by avoiding traditional echocardiograms and extrapolate this to the total number of patients in the study.
  - Opportunity costs: Assess opportunity costs related to lost work or daily activities due to additional tests and consultations, calculating the average cost per patient.

Data management: Data will be securely entered into a password-protected electronic database designed for clinical research. Key data management procedures include:

- Double data entry: To minimize errors, all data entries will undergo a double-entry process.
- Range checks and validations: Automatic range checks and data validation algorithms will ensure data consistency and accuracy.
- Data anonymization: all participant data will be anonymized before analysis, with unique identifiers stored separately in an encrypted file accessible only to authorized personnel.

Data will be stored on a secure server, with regular backups and restricted access. The study will comply with GDPR and local data protection regulations.

Statistical methods

Primary and secondary outcomes will be analyzed using the win ratio method as follows:

- Win ratio command: The hierarchical primary outcome will be tested using the 'winratio' package in Stata® with the command winratio id group, outcomes (newhf c > hftrt c > qol c >).
  - id: Unique patient identifier.
  - group: Dummy variable where '0' represents Group 1 (Standard Care) and '1' represents Group 4 (Standard Care + POCUS).
  - outcomes:
    - newhf: Categorical variable for new heart failure diagnosis, testing the hypothesis of a higher proportion of new diagnoses in Group 4 versus Group 1 at 12 weeks.
    - hftrt: Categorical variable assessing GDMT initiation or specialty referral at 12 weeks.
    - qol: Continuous variable representing the change in health status using KCCQ-12 scores from baseline to 12 weeks.

Subgroup analyses and additional tests

- Exploratory analyses will compare Groups 2 and 3 to Group 4 for non-inferiority, focusing on the effects of NT-proBNP and POCUS combined.
- Subgroup analyses will explore differential effects based on age, sex, and comorbidities.

Handling of missing data

- Missing data will be addressed using multiple imputation techniques to minimize bias. Sensitivity analyses will be conducted to compare outcomes with and without imputed data, ensuring robustness.

Methods: monitoring

Data monitoring: A formal data monitoring committee (DMC) is not required due to the low-risk nature of the study. The coordinating team at the Faculty of Medicine, University of Porto, in collaboration with the ethics committees, will oversee the study and conduct internal reviews.

Harms: All adverse events related to NT-proBNP testing and POCUS will be recorded during follow-up visits. Physicians will report any unintended effects to the coordinating team within 24 hours. The coordinating team will evaluate these events and decide on further action in consultation with ethics committees if necessary.

Auditing: No external audits are planned. However, the coordinating team will perform periodic internal audits to ensure compliance with the protocol and verify data accuracy.

Ethics and dissemination

Research ethics approval: The study protocol will be reviewed by the ethics committees of the health institutions where the intervention and data collection will take place and the ethics committee of the Faculty of Medicine, University of Porto. All procedures will comply with the Declaration

of Helsinki.

Protocol amendments: Any amendments to the study protocol will be submitted for approval to the ethics committees and communicated to investigators, participants, and registered trial platforms.

Consent or assent: Informed consent will be obtained from all participants before any study procedures begin.

Confidentiality: Participant data will be anonymized and stored in a secure, password-protected database.

Access to data: Access to the final dataset will be limited to the principal investigator and authorized personnel

Ancillary and post-trial care: There are no specific provisions for ancillary or post-trial care.

Appendices

Informed consent materials: A detailed informed consent form will be developed and provided to participants, outlining the study's purpose, procedures, risks, and benefits. The form will be available in Portuguese and reviewed by ethics committees for approval.

Biological specimens: If the study involves the collection of biological specimens (e.g., blood for NT-proBNP testing), procedures for collection, storage, and analysis will be established.

DISCUSSION

The aim of this clinical trial is to identify the most effective strategy for diagnosing HF and the most efficient approach to managing this condition. Recently published data from the PORTHOS study[1] found that 90% of patients with HF were unaware they had the disease, highlighting a significant gap in early diagnosis in Portugal.

The introduction of NT-proBNP and POCUS as diagnostic tools in primary care offers a practical and accessible solution, enabling more accurate screening and the early initiation of treatments. This study will not only test the clinical efficacy of these interventions but also their economic feasibility.

Additionally, the development of POCUS skills among family physicians represents an investment in continuous training, supporting faster diagnosis not only of HF but also of other conditions in the future.

In summary, this clinical trial has the potential to redefine the approach to HF diagnosis and management in Portugal. The results may serve as a foundation for adopting a more integrated, cost-effective, and patient-centered approach, which could be replicated in other primary healthcare settings.

TRIAL REGISTRATION

Unique Protocol Identification Number: PRIMARY-HF2024-NTBNP01. Trial Registration: To be submitted at ClinicalTrials.gov. Version 1.0 dated October 15, 2024.

AUTHOR CONTRIBUTIONS

JS, JPN, JPF, NC: Study conception and design, critical review of the manuscript.

MIMM, MC, TV, AG: Critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

JS received financial payments from Roche for advising.

TV received support for attending meetings and/or travel from the European Union of General Practitioners and Family Physicians (UEMO), the Portuguese Medical Association, the Bulgarian Association of Family Medicine, the BMJ Publishing Group, and DIA Europe; has a an unpaid position as President of the European Union of General Practitioners and Family Physicians (UEMO); is the Editor-in-Chief of Acta Médica Portuguesa, and receives a salary from the Portuguese Medical Association; receives honoraries from the BMJ Publishing Group as Associate Editor in the research team.

All other authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Perceção da Qualidade de Vida Relacionada com a Saúde em Doentes com Acidente Vascular Cerebral numa Unidade de Cuidados Continuados Integrados: Um Estudo de Seguimento

Perception of Health-Related Quality of Life in Stroke Patients in a Continuing Care Unit: A Follow-Up Study

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RESUMO

O acidente vascular cerebral (AVC) continua a ser uma das principais causas de morte em Portugal, com uma prevalência de 8% em indivíduos com 50 ou mais anos de idade. Este estudo procurou avaliar a perceção de qualidade de vida (QoL) relacionada com a saúde em doentes com AVC, após alta da Unidade de Cuidados Continuados Integrados (UCCI), assim como os fatores que influenciam a QoL relacionada com a saúde. Foi realizado um estudo observacional, longitudinal com utentes de idade igual ou superior a 65 anos, com antecedentes de AVC e alta clínica, na zona Centro de Portugal. Foram avaliados em dois momentos: aos seis e aos 12 meses pós-alta da UCCI. Os dados foram recolhidos através de instrumentos de autopreenchimento, nomeadamente a versão portuguesa da *Stroke Scale Quality of Life* (SS-QoL). Considerando perdas de seguimento, foram incluídos um total de 128 indivíduos. Todas as dimensões da SS-QoL apresentaram melhorias dos seis para os 12 meses pós-alta. As variáveis "personalidade" e "capacidade mental" evidenciaram a melhor evolução. Os preditores psicológicos, físicos e cognitivos mostraram influência significativa na qualidade de vida pós-AVC, com ansiedade e depressão reduzindo a QoL, enquanto as capacidades funcionais e cognitivas a melhoraram. O presente estudo permite compreender a evolução da QoL destes utentes, incluindo os fatores mais afetados ao longo do tempo, e que influenciam a reabilitação pós-AVC.
Palavras-chave: Acidente Vascular Cerebral; Cuidados de Seguimento; Perceção; Qualidade de Vida; Reabilitação de Acidente Vascular Cerebral

ABSTRACT

Stroke continues to be one of the main causes of death in Portugal, with a prevalence rate of 8% in individuals aged 50 or over. The objectives of this study were to evaluate the perception of quality of life (QoL) related to health in patients with stroke, after discharge from the Integrated Continuing Care Unit (UCCI), and to evaluate the factors that influence health-related QoL. An observational, longitudinal and descJá agora riptive study was carried out with patients aged 65 years or older with a history of stroke and hospital discharge in central Portugal. They were observed in two time points: six and 12 months after discharge from the UCCI. Data was collected using self-completion questionnaires, namely the Portuguese version of the Stroke Scale Quality of Life (SS-QoL). Considering follow-up losses, a total of 128 individuals were included. All SS-QoL dimensions showed improvements from six to 12 months post-discharge. The variables "personality" and "mental capacity" showed the best evolution. The present study allows us to understand the evolution of the QoL of these users, including the most affected factors over time and that influence post-stroke rehabilitation.
Keywords: Aftercare; Perception; Quality of Life; Stroke; Stroke Rehabilitation

O acidente vascular cerebral (AVC) é uma doença cerebrovascular de início súbito, caracterizada pelo desenvolvimento repentino de sinais e sintomas neurológicos, que perduram por mais de 24 horas, sem outra causa aparente que não a de origem vascular. A causa de AVC pode ser isquémica – por oclusão de um vaso –, ou hemorrágica – por rotura de um vaso.[1,2] Os fatores de risco incluem, principalmente, a hipertensão arterial, a fibrilhação auricular e a diabetes *mellitus*.[3]

A maioria dos sobreviventes apresentam comorbilidades prévias a que se vêm juntar as sequelas do AVC, que determinam uma diminuição da autonomia nas atividades de vida diária, requerendo apoio na gestão das rotinas quotidianas e cuidados de reabilitação diferenciados.[4] Quanto mais precoce a abordagem e respetivo tratamento, maior a probabilidade de sucesso e prevenção de sequelas.[5]

Após alta hospitalar e chegada ao domicílio, a incapacidade funcional e as complicações médicas associadas têm consequências físicas, emocionais e sociais significativas nos sobreviventes de AVC e seus cuidadores.[6] Um dos principais objetivos nos cuidados a pessoas sobreviventes de AVC é melhorar e manter a qualidade de vida relacionada com a saúde (QoL). Para isso, é fundamental identificar os fatores que a influenciam, considerando que, com o envelhecimento, surgem multimorbilidades que dificultam a gestão da saúde.[7,8] O objetivo do presente estudo consiste em avaliar a perceção de QoL relacionada com a saúde e os seus preditores em doentes com AVC, aos seis e 12 meses após alta da Unidade de Cuidados Continuados Integrados (UCCI).

Foi realizado um estudo observacional, longitudinal e descritivo-correlacional com *follow-up* de um ano para avaliar a QoL em doentes com AVC que tiveram alta dos serviços de neurologia e/ou medicina de hospitais da zona

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Centro que foram admitidos numa Unidade de Cuidados Continuados Integrados do Centro de Medicina e Reabilitação. A avaliação ocorreu na admissão e alta hospitalar na UCCI, e aos seis e 12 meses após a alta. A população inicial incluiu 154 indivíduos com 65 anos ou mais, mas o *follow-up* foi concluído com 128 devido a 22 óbitos e quatro perdas de seguimento.

Os dados foram recolhidos entre agosto de 2020 e julho de 2022, usando um protocolo com instrumentos de autopreenchimento para obter informações sociodemográficas, clínicas e funcionais, como a idade, sexo, tipo de AVC e comorbidades. Na admissão na UCCI, foram usadas escalas como a *Modified Rankin Scale for Neurologic Disability* (mRANKIN), escala de Barthel, Escala Funcional de Ingestão Oral (FOIS) e Teste de Avaliação Cognitiva de Montreal para Demência (MoCA) para avaliar défices neurológicos, dependência funcional, independência diária, capacidade de ingestão alimentar e triagem cognitiva. Adicionalmente, foram usados os dados da *National Institutes of Health Stroke Scale* recolhidos na avaliação do doente no hospital de agudos. As reavaliações utilizaram as escalas Escala Internacional de Eficácia em Quedas (FES-I), Índice de Independência em Atividades da Vida Diária (KATZ), Escala Hospitalar de Ansiedade e Depressão (HADS) e *Stroke Scale Quality of Life* (SS-QoL) para medir preocupações com quedas, autonomia, ansiedade, depressão e a QoL. A análise da evolução da QoL foi realizada através do teste *t* de Student para amostras emparelhadas e regressão linear múltipla, com análises no SPSS.v.28 a um nível de significância de 5%.

O estudo incluiu 128 participantes, com idade média de 71,5 anos (40 - 94), sendo a maioria homens (n = 80, n = 99, 62,3%), aposentados (n = 100, 77,3%); a maioria tinha o ensino básico (77,9%) e era casada (n = 81, 63,3%).

Tabela 1 – Evolução dos utentes, comparação entre 6 meses e 12 meses

Variável	Admissão	Alta	6 meses	12 meses	Taxa de variação entre 6 e 12 meses
Apoio de marcha					
Nenhum	32 (25,0%)	34 (26,6%)	50 (39,1%)	46 (35,9%)	-3,2%
Marcha apoiada	47 (36,7%)	55 (43,0%)	51 (39,8%)	46 (35,9%)	-3,9%
Cadeira de rodas	37 (28,9%)	28 (21,9%)	18 (14,1%)	28 (21,9%)	+7,8%
Acamado	12 (9,4%)	11 (8,6%)	9 (7,0%)	8 (6,3%)	-0,7%
Sem afasia					
Afasia leve a moderada	33 (25,8%)	36 (28,1%)	27 (21,1%)	29 (22,7%)	+1,6%
Afasia grave	11 (8,6%)	9 (7,0%)	11 (8,6%)	7 (5,5%)	-3,1%
Mutismo, afasia global	16 (12,5%)	14 (10,9%)	-	1 (0,6%)	+0,6%
Permanência do doente após alta da UCCI					
Domicílio	-	84 (65,6%)	98 (76,6%)	94 (73,4%)	-2,2%
Lar	-	9 (7,0%)	16 (12,5%)	22 (17,2%)	+4,7%
UCMD	-	24 (18,8%)	12 (9,4%)	9 (7,0%)	-2,4%
ERPI	-	4 (3,1%)	2 (1,6%)	2 (1,3%)	-0,3%
RGA	-	6 (4,7%)	-	-	-
Hospital	-	1 (0,7%)	-	-	-
Fisioterapia			86 (67,2%)	56 (43,8%)	-23,4%
Escalas aplicadas					**Diferenças entre momentos**
FOIS; média (DP)	4,64 (1,75)	5,47 (1,56)	6,47 (1,21)	6,69 (1,03)	*p* = 0,001
MOCA; média (DP)	15,91 (5,17)	16,37 (4,77)	16,53 (4,57)	17,35 (4,23)	*p* = 0,009
HADS – Ansiedade; média (DP)	-	-	7,04 (5,85)	5,80 (4,11)	*p* = 0,057
HADS - Depressão; média (DP)	-	-	8,68 (5,29)	7,97 (4,73)	*p* = 0,541
FES; média (DP)	-	-	33,94 (16,23)	30,22 (16,38)	*p* = 0,004
KATZ; média (DP)	-	-	4,09 (1,88)	4,35 (1,89)	*p* = 0,302
NIHSS; média (DP)	6,82 (3,79)	4,51 (3,42)			*p* < 0,001
mRANKIN; média (DP)	3,06 (0,99)	2,24 (1,08)			*p* < 0,001
I.BARTHEL; média (DP)	38,57 (24,25)	64,24 (27,56)			*p* < 0,001

DP: desvio padrão; ERPI: estruturas residenciais para idosos; FES: Escala Internacional de Eficácia em Quedas; FOIS: Escala Funcional de Ingestão Oral; HADS: Escala Hospitalar de Ansiedade e Depressão; KATZ: Índice de Independência em Atividades da Vida Diária; MoCA: Teste de Avaliação Cognitiva de Montreal para Demência; RGA: reabilitação geral de adultos; UCCI: Unidade de Cuidados Continuados Integrados; UCMD: Unidade de Cuidados de Média Duração.

A Tabela 1 apresenta a evolução dos utentes em diversas variáveis ao longo do tempo, desde a admissão e alta na Unidade de Cuidados Continuados Integrados até os seis e 12 meses após a alta, incluindo o apoio de marcha, alterações na afasia, local de permanência pós-alta, fisioterapia e resultados de instrumentos de avaliação funcional e cognitiva. Observaram-se melhorias significativas nas dimensões "personalidade" (δ = 0,51) e "capacidade mental" (δ = 0,41); as dimensões "papel familiar", "disposição", "autocuidado", "papel social", "energia", "mobilidade" e "função do membro superior" também melhoraram, embora com pequenos efeitos; por fim, as dimensões "linguagem" e "visão" não apresentaram mudanças significativas dos seis para os 12 meses após a alta (Tabela 2).

A análise dos preditores da QoL em doentes pós-AVC revelou a influência significativa de fatores psicológicos, físicos e cognitivos sobre o bem-estar global, conforme evidenciado pelos resultados do modelo de regressão.

O R^2 foi de 0,69, ajustado para o número de preditores no modelo. O teste F revelou que o modelo era estatisticamente significativo [$F(6,119) = 48,65$; $p < 0,001$]. Os coeficientes do modelo indicaram que o valor de ansiedade da escala HADS registado aos seis meses [β = -2,047, $t(119) = -3,769$; $p < 0,001$], assim como o valor de depressão da escala HADS registado aos seis meses [β = -2,490, $t(119) = -4,801$; $p < 0,001$], tiveram um impacto negativo significativo sobre a QoL. O *score* da escala KATZ aos seis meses [β = 10,113; $t(119) = 6,859$; $p < 0,001$], o valor do teste de MoCA à data do AVC [β = 1,530; $t(119) = 2,915$; $p = 0,004$], o valor da escala de FOIS à data do AVC [β = 3,107; $t(119) = 2,022$; $p = 0,045$) e o índice de Barthel na alta da UCCI [β = 0,324; $t(119) = 2,924$; $p = 0,004$] revelaram um efeito positivo sobre o valor de *score* global da QoL.

Este estudo analisou a QoL em doentes com AVC, seis e 12 meses após alta da UCCI, identificando preditores significativos. Os resultados revelaram que a ansiedade e a depressão, medidas pela escala HADS, impactaram negativamente a QoL, com a ansiedade (β = -2,047; $p < 0,001$) e a depressão (β = -2,490; $p < 0,001$) associadas a uma redução no bem-estar global. Em contraste, as funcionalidades físicas e cognitivas, como a independência nas atividades diárias (KATZ, β = 10,113; $p < 0,001$) e a função cognitiva (MoCA, β = 1,530; $p = 0,004$), tiveram um impacto positivo significativo na QoL. A capacidade de deglutição (FOIS, β = 3,107; $p = 0,045$) e a independência funcional (Barthel, β = 0,324; $p = 0,004$) também contribuíram para a melhoria da QoL. Os resultados corroboram estudos anteriores, que identificam a importância de fatores como o apoio social, reabilitação e acesso a tratamentos de saúde na melhoria da QoL após o AVC. Considera-se que os programas de reabilitação devem iniciar-se o mais precocemente possível, integrando uma equipa multidisciplinar e a família do doente, de modo a ser possível atingir as melhorias desejadas na QoL dos utentes com AVC.

Algumas dimensões da SS-QoL não apresentaram melhorias significativas, como a "linguagem" e a "visão". Estes resultados poderão estar relacionados com a origem do AVC e défices potencialmente permanentes nessas áreas, ou com as limitações dos programas de reabilitação existentes.

Foi possível verificar uma melhoria significativa nas dimensões "papel social" e "capacidade mental". Não obstante, a par deste estudo, outros estudos demonstram melhorias em todas as dimensões da SS-QoL após alta das

Tabela 2 – Comparação da qualidade de vida, entrevista dos 6 para os 12 meses (n = 128)

Variável	6 meses	12 meses	*t*	*p*	Tamanho de efeito (delta Glass)
Escala SS-QoL					
Energia	6,92 (4,40); 3 - 16	7,70 (4,55); 3 - 15	-2,419	0,017	0,18 (Muito pequeno)
Papel familiar	8,25 (4,52); 2 - 25	9,33 (4,91); 1 - 25	-3,557	0,001	0,24 (Pequeno)
Disposição	15,30 (6,77); 3 - 25	16,52 (7,31); 3 - 32	-2,295	0,023	0,18 (Muito pequeno)
Personalidade	9,88 (4,96); 3 - 25	11,04 (5,29); 3 - 25	-2,799	0,006	0,23 (Pequeno)
Papel social	9,83 (5,35); 3 - 25	12,52 (6,75); 3 - 25	-5,324	< 0,001	0,51 (Médio)
Capacidade mental	6,95 (4,40); 3 - 16	8,77 (5,53); 3 - 25	-4,501	< 0,001	0,41 (Pequeno)
Linguagem	18,94 (6,08); 5 - 30	19,20 (6,87); 3 - 30	-0,447	0,656	NA
Mobilidade	18,39 (7,40); 4 - 30	19,51 (8,93); 4 - 64	-2,011	0,046	0,14 (Muito pequeno)
Função membro superior	15,02 (7,21); 3 - 30	16,28 (7,52); 3 - 30	-2,909	0,004	0,16 (Muito pequeno)
Visão	13,65 (3,26); 3 - 25	14,00 (3,91); 3 - 25	-1,306	0,194	NA
Produtividade	8,52 (5,06); 3 - 25	9,52 (6,00); 3 - 25	-2,727	0,007	0,20 (Pequeno)
Autocuidado	15,87 (6,97) 5 - 28	17,51 (8,34); 3 - 56	-2,929	0,004	0,23 (Pequeno)
Total SSQOL	141,62 (48,31)	159,70 (56,83)	-4,244	< 0,001	0,39 (Pequeno)

unidades de reabilitação. A análise dos preditores de QoL descritos no modelo de regressão revelou dados importantes sobre os fatores que influenciam significativamente a QoL em doentes após AVC. Com um R^2 ajustado de 0,69, o modelo mostrou que uma proporção substancial da variabilidade na QoL pode ser explicada pelos preditores incluídos. O teste F confirmou que o modelo é estatisticamente significativo, indicando que, coletivamente, os preditores escolhidos são capazes de prever a QoL de maneira eficaz.

Os resultados indicam que níveis mais altos de ansiedade e depressão, conforme medidos pela escala HADS aos seis meses após o AVC, estão negativamente associados com a QoL. Especificamente, a ansiedade (β = -2,047; $t(119) = -3,769$; $p < 0,001$) e a depressão (β = -2,490; $t(119) = -4,801$; $p < 0,001$) associaram-se a uma redução da QoL. Estes achados são coerentes com a literatura existente, que demonstra que sintomas psicológicos adversos podem reduzir a perceção de bem-estar e satisfação com a vida em sobreviventes de AVC. Intervenções que visam a saúde mental destes doentes podem, portanto, ser cruciais para melhorar a sua QoL.

Por outro lado, as funcionalidades físicas e cognitivas revelaram-se como preditores positivos significativos da QoL. O *score* da escala KATZ aos seis meses (β = 10,113; $t(119) = 6,859$; $p < 0,001$) mostrou o impacto mais forte, sugerindo que a independência nas atividades diárias é um determinante crítico da QoL. O valor do teste de MoCA à data do AVC (β = 1,530; $t(119) = 2,915$; $p = 0,004$), que avalia a função cognitiva, também foi um preditor significativo destacando a importância da preservação cognitiva na perceção de qualidade de vida. Similarmente, a capacidade de deglutição, medida pela escala FOIS à data do AVC (β = 3,107; $t(119) = 2,022$; $p = 0,045$), e a independência funcional, medida pelo Índice de Barthel à data da alta hospitalar (β = 0,324; $t(119) = 2,924$; $p = 0,004$), contribuíram significativamente para a QoL.

As limitações do estudo incluem o tamanho da amostra e a natureza observacional, que não permitem estabelecer causalidade. O estudo reforça a importância de intervenções que abordem aspetos físicos, cognitivos e psicológicos para melhorar a QoL pós-AVC. A avaliação da QoL relacionada com a saúde promove uma melhor compreensão, por parte dos profissionais de saúde, dos aspetos que perturbam o quotidiano dos utentes e o real impacto do AVC nas suas vidas.[9]

O AVC causa limitações funcionais complexas, afetando significativamente a QoL, devido às dificuldades nas atividades diárias. Este estudo revelou que, embora os doentes tenham registado melhorias em dimensões como "papel social", "personalidade" e "capacidade mental", facilitando a reintegração social, não foram percecionadas mudanças na "linguagem" e "visão". Estes resultados destacam a necessidade de personalizar e melhorar os programas de reabilitação pós-alta, maximizando os benefícios para todas as dimensões da QoL. Participar em programas de reabilitação mostrou-se essencial para promover a recuperação e o bem-estar global dos doentes.

CONTRIBUTO DOS AUTORES

JGG: Conceção e desenho do estudo, recolha e análise de dados, redação do manuscrito.

DF, MTV: Conceção e desenho do estudo, revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Serviços de Renovação da Terapêutica Crónica e Comparação com o Contexto Português

Chronic Disease Medication Services and Comparison with the Portuguese Context

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RESUMO

Ao longo dos últimos anos tem-se vindo a procurar a integração do farmacêutico comunitário na gestão de doentes crónicos, de forma a atenuar a pressão nos sistemas de saúde. De facto, os farmacêuticos não só são os especialistas do medicamento, como têm competências clínicas para promover a adesão à terapêutica e assegurar a monitorização do estado de saúde do doente crónico, principalmente no período entre consultas médicas. A renovação da terapêutica crónica nas farmácias comunitárias é um serviço farmacêutico que procura agilizar o acesso do doente à sua medicação sem deixar de ter cuidados de saúde adequados. Realizou-se uma revisão da legislação em vigor em diferentes países sobre o serviço de renovação da terapêutica crónica e sua comparação com a legislação portuguesa, propondo-se um protocolo de intervenção farmacêutica que otimize a prestação do serviço. O *Repeat Dispensing* do Reino Unido é o serviço que mais se assemelha ao de Portugal: necessitam ambos de prescrição médica por 12 meses, permitem o acesso ao histórico de prescrição (sem acesso a informação clínica), em nenhum deles é obrigatória a notificação do prescritor, ambos necessitam de consentimento informado e levam à criação de registos do processo. O *Adapt a Prescription* do Canadá é mais abrangente porque permite prescrições válidas por 24 meses, possibilita acesso a informação clínica e obriga à notificação do prescritor em 24 horas. O *Prescription Extension* da Irlanda é mais limitado porque não permite substituição terapêutica nem tem acesso ao histórico de prescrição nem a informação clínica, obrigando à notificação do prescritor em sete dias. Por sua vez, o *Continued Dispensing* da Austrália e o *Emergency Refills* dos Estados Unidos da América diferem bastante por não exigirem prescrição médica de longo prazo, aplicando-se quando não é possível obter uma prescrição válida e a recusa da dispensa da medicação pode ser uma ameaça à vida do doente. O serviço de Renovação da Terapêutica Crónica em Portugal surge como resposta às necessidades do sistema de saúde e é promissor nos cuidados de saúde prestados à população, concretamente na gestão terapêutica dos doentes crónicos.
Palavras-chave: Doença Crónica/tratamento farmacológico; Farmacêuticos; Prescrição de Medicamentos; Serviços Comunitários de Farmácia

ABSTRACT

Over the past few years, there has been a growing effort to integrate community pharmacists into managing chronic patients with chronic disease, to alleviate the pressure on healthcare systems. Pharmacists are not only experts in medicines but also have clinical skills to promote adherence to therapy and ensure monitoring of the health status of patients with chronic disease, especially in the period between medical appointments. Chronic disease medication renewal in community pharmacies is a pharmacy service that seeks to streamline patients' access to their medication while still receiving adequate healthcare. We conducted a review of the legislation in force in different countries regarding the chronic medication renewal service and compared it with Portuguese legislation, proposing a pharmacy intervention protocol that optimizes the provision of the service. Repeat Dispensing in the United Kingdom is the service that most resembles its counterpart in Portugal: both require a 12-month medical prescription, allow access to the prescribing history (without access to clinical information). In neither of them is notification of the prescriber mandatory, both require informed consent and lead to the creation of written records of the process. Canada's Adapt a Prescription is more comprehensive because it allows prescriptions valid for 24 months, enables access to clinical information, and requires notification of the prescriber within 24 hours. Ireland's Prescription Extension is more limited in that it does not allow for therapeutic substitution, nor does it enable access to prescribing history or clinical information, requiring notification of the prescriber within seven days. In turn, Australia's Continued Dispensing and the United States' Emergency Refills differ significantly in that they do not require a long-term medical prescription, namely in situations when it is not possible to obtain a valid prescription and refusal to dispense the medicine could be life-threatening to the patient. The Chronic Medication Renewal service in Portugal arises as a response to the needs of the healthcare system and has potential in the healthcare provided to the population, specifically in the therapeutic management of patients with chronic disease.
Keywords: Chronic Disease/drug therapy; Community Pharmacy Services; Drug Prescriptions; Pharmacists

INTRODUÇÃO

Nos últimos anos, tem-se verificado um aumento de doenças crónicas na população, que se traduzirá num desafio para os sistemas de saúde. De facto, nos países da Organização para a Cooperação e Desenvolvimento Económico (OCDE), em 2021, em média, mais de uma em cada três pessoas com 16 ou mais anos vivia com uma doença crónica, ocupando Portugal o terceiro lugar com a percentagem mais elevada (43,9%).[1] Por esse motivo, têm sido procuradas soluções que assegurem a sustentabilidade dos sistemas de saúde, nomeadamente, através do incentivo à criação de equipas multidisciplinares nas quais o farmacêutico pode desempenhar uma relevante função no suporte à gestão das doenças crónicas em tudo o que ao medicamento diz respeito.[1] Uma das soluções recentemente encontrada foi a implementação de novas diretivas que expandem as competências dos farmacêuticos comunitários.[2,3] O serviço de Renovação da Terapêutica Crónica, destinado a utentes da farmácia comunitária com

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patologias crónicas clinicamente estabilizadas (ex., hipertensão, diabetes, asma) e sob terapêutica de longa duração, vem fomentar a comunicação entre os médicos prescritores e os farmacêuticos, facilitando a sua cooperação na prestação de cuidados de saúde.[4] A inclusão do farmacêutico na gestão de doenças crónicas mostra-se uma mais-valia na otimização da acessibilidade aos medicamentos, na monitorização do estado de saúde dos doentes e na promoção da adesão à terapêutica.[2,5] Além disso, poderá ser fulcral de forma a aumentar os recursos em saúde, limitar prescrições inapropriadas e promover um uso seguro dos medicamentos, principalmente no período entre consultas médicas.[6,7] A presente revisão pretende explorar o que se entende por serviço de Renovação da Terapêutica Crónica através de uma revisão da legislação em vigor em diferentes países, uma vez que o modo de ação, os requisitos e os instrumentos acessíveis ao farmacêutico comunitário diferem.[2] Ademais, com base nesta revisão, tenciona-se propor um protocolo de ação de intervenção farmacêutica aquando do referido serviço, visto que o acesso a um protocolo estruturado é uma mais-valia para a otimização da prestação do serviço.

Foi definido como objetivo a identificação e comparação do serviço de renovação da terapêutica crónica em diferentes países e, depois de selecionadas as fontes de informação, foram definidos parâmetros a serem avaliados e comparados. A informação foi, posteriormente, sintetizada numa tabela comparativa. Sem limitações geográficas, foi realizada uma pesquisa de forma a definir quais os países a incluir na nossa análise. Para tal, foram utilizadas as seguintes palavras-chave: *"chronic medication renewal", "prescription renewal by pharmacists"* e *"pharmacist and chronic medication".* Foram usadas como base de dados a PubMed, o Google Scholar e os sítios web das entidades competentes dos países entretanto selecionados. Na análise foram incluídos os países onde o serviço de renovação crónica da terapêutica se encontra implementado de forma estruturada e regulamentada, tendo sido previamente definidos os parâmetros gerais a serem analisados em cada país, e que serviram de base para o reporte dos resultados. Na elaboração da presente análise comparativa foi analisada a legislação em vigor nos diferentes países abordados e foram consultados 26 artigos científicos, de forma a complementar a informação relativamente ao serviço de renovação da terapêutica crónica e as suas vantagens na prática clínica. Os resultados da pesquisa ficaram limitados aos idiomas português e inglês, o que se revela como uma limitação do presente estudo comparativo.

No âmbito da presente revisão vai ser descrito o serviço de renovação da terapêutica crónica e o respetivo protocolo de atuação no Reino Unido, Canadá, Austrália, Estados Unidos da América (EUA) e Irlanda, os cinco países que apresentaram o serviço implementado. No final será apresentada a realidade em Portugal.

O serviço de renovação da terapêutica crónica em diversos países

Reino Unido

No Reino Unido, mais de dois terços das prescrições médicas geradas são destinadas a doentes crónicos. Deste modo, surgiu o serviço *Repeat Dispensing*, que permite a renovação de uma prescrição sem que o médico prescritor precise de criar uma prescrição nova sempre que o doente crónico necessite da medicação a que está habitualmente sujeito.[8] A legislação deste serviço, criado em 2009, encontra-se no "*The National Health Service (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013"* e implica que os doentes estejam sujeitos a terapêutica de patologias crónicas clinicamente estabilizadas.[9,10]

Neste caso, a renovação da terapêutica crónica envolve uma prescrição criada pelo médico prescritor que contém as unidades dos medicamentos a serem dispensados num período de 12 meses. Além da dispensa, é necessário que o farmacêutico assegure que a condição do doente é estável e que a terapêutica continua segura e efetiva ou, caso contrário, é necessário consultar o médico e reavaliar a sua condição clínica. Antes da prescrição passível de renovação ser criada, o doente crónico deve dar o seu consentimento informado permitindo a partilha de informação acerca da sua terapêutica entre o prescritor e o farmacêutico.[4] No decorrer deste serviço, o farmacêutico deve comunicar ao médico todas as alterações clínicas relevantes inerentes ao estado de saúde do doente.[8,11-13]

Está estabelecido nas normas do serviço que o farmacêutico deve perceber junto do indivíduo se não há nenhum impedimento à dispensa da medicação. Para isso, foram estabelecidas questões que o farmacêutico deve colocar ao doente ou ao seu cuidador (Tabela 1).

No sistema eletrónico da farmácia comunitária é possível verificar a quantidade autorizada a ser dispensada, que depende da posologia do medicamento e do número de doses que contém.[4,14] Em casos excecionais, é permitido dispensar a quantidade equivalente a duas dispensas, desde que seja justificado pelo farmacêutico. É necessário realçar que existem medicamentos que não podem ser incluídos neste serviço, como substâncias controladas.[4,15] Além disso, alguns casos devem ser considerados contraindicações, como mudanças na condição clínica do doente ou alterações ao seu plano farmacoterapêutico, admissões hospitalares não planeadas nos seis meses anteriores ou doentes sujeitos a uma monitorização apertada.[4,16]

É obrigatório que o farmacêutico mantenha registos este serviço, nomeadamente das datas da dispensa e notas terapêuticas relevantes.[11] As normas aconselham que

Tabela 1 – Questões pré-definidas para o serviço *Repeat Dispensing* no Reino Unido

Questões a serem colocadas ao doente previamente à prestação do serviço *Repeat Dispensing*
- Ainda está a tomar todos os medicamentos presentes na prescrição renovável?
- Há algum medicamento de que não necessite este mês? (por ainda possuir unidades)
- Tem tido algum efeito adverso possivelmente decorrente da terapêutica instituída? (explicando os possíveis efeitos adversos inerentes à terapêutica)
- Nos últimos tempos, começou a tomar algum medicamento novo? (incluindo tanto medicamentos sujeitos a receita médica como não sujeitos a receita médica)
- Desde a data da última prescrição, consultou o médico prescritor ou outro profissional de saúde?
- Desde a data da última prescrição, o seu estado de saúde alterou-se?

seja implementado um meio de comunicação entre o prescritor e o farmacêutico, dando preferência ao *e-mail* para que todas as comunicações fiquem registadas.[4] Ao dispor do farmacêutico está uma plataforma para que possa consultar o histórico de prescrições do doente através do seu número nacional de saúde.[17]

Após uma alteração na legislação em fevereiro de 2019, os farmacêuticos passaram a ter permissão para dispensar um medicamento que difere do que consta na prescrição em termos de dosagem, forma farmacêutica ou dimensão da embalagem, durante períodos de indisponibilidade do medicamento.[18]

Canadá

No Canadá, a renovação da terapêutica crónica surge associada ao conceito de *Adapt a Prescription* e a legislação varia consoante a província. Considerando a legislação da província de British Columbia (BC), este serviço inclui a renovação de prescrições médicas e a substituição terapêutica.[19]

Quando foi implementado em 2008, este serviço estava limitado a certas classes terapêuticas e patologias. No entanto, a partir de 2022 essa lista foi alargada e os farmacêuticos passaram a poder renovar a terapêutica de praticamente todas as patologias crónicas.[20-22] Além disso, foi estabelecido um novo período de validade das prescrições médicas, que passou a ser de dois anos, com exceção de prescrições de substâncias controladas que passaram a ter um ano de validade.[21,22]

A diretiva n.º 58 da prática profissional do College of Pharmacists of British Columbia, designada "*Professional Practice Policy* – 58", contém as diretrizes necessárias para orientar os farmacêuticos na renovação da terapêutica crónica e estabelece que o farmacêutico deve certificar-se de que tem informação suficiente referente ao estado de saúde do doente, às suas doenças e fármacos.[19,23,24]

Antes de iniciar o processo, o farmacêutico deve assegurar-se de que a situação em questão reúne as condições que se seguem[25]:

- a prescrição médica anterior está completamente dispensada;
- o doente não possui medicação suficiente para cumprir o seu plano farmacoterapêutico;
- a condição do doente está estável;
- a terapêutica está instituída há mais de seis meses, na mesma dose e sem nenhuma intercorrência nesse período;
- a prescrição foi prescrita nos 24 meses anteriores e o prescritor continua a prescrever na província de BC.

Este processo apenas pode ocorrer em prescrições contidas no período de validade e as unidades de medicamento renovadas não podem corresponder a um período de tratamento que exceda essa data-limite.[19] No que diz respeito à dispensa de medicamentos distintos daqueles que a prescrição médica contém, também incluída no serviço denominado "*Adapt a Prescription"*, o farmacêutico pode alterar, em benefício do doente, a dosagem da forma farmacêutica, a sua formulação, a posologia ou realizar uma substituição terapêutica por um fármaco da mesma classe farmacológica desde que este se encontre aprovado para a patologia em causa e a prescrição não tenha sido já submetida a esse processo.[19,20,25] Existem algumas exceções, como é o caso de prescrições de medicamentos de quimioterapia que não podem ser renovadas nem ser alvo de substituição da terapêutica. As prescrições de psicotrópicos e substâncias controladas também não estão incluídas no processo de substituição terapêutica e apenas podem ser renovadas por tempo igual ou inferior ao que foi prescrito originalmente.[25]

O farmacêutico tem acesso a uma plataforma denominada *PharmaNet,* onde pode consultar o histórico de prescrições do doente nos 14 meses antecedentes e informação clínica relevante, de forma a aferir se a renovação da terapêutica é adequada.[24,26,27]

A legislação recomenda que o farmacêutico proceda à documentação de todo o processo de modo a registar o racional da sua decisão e apoiar o seu julgamento profissional.[24] Além disso, deve também obter o consentimento informado do doente ou do seu representante antes de

proceder à renovação e notificar o médico prescritor, no máximo 24 horas após a realização do serviço.[19]

Na província de BC existe um serviço de apoio à renovação de prescrições médicas, o *Provincial Prescription Renewal Support Service*, que pode ser utilizado em situações dúbias.[28]

Austrália

Na Austrália, entende-se *Continued Dispensing* como o serviço de renovação da terapêutica crónica.[29] Foi instituído em 2013 e permite que o farmacêutico dispense um medicamento sujeito a receita médica a um doente que não conseguiu obter uma prescrição válida. Isto distingue este serviço dos dois apresentados anteriormente, uma vez que, no caso do Reino Unido e do Canadá, era apenas exequível aquando da existência de uma prescrição médica válida e dentro do seu período de validade.

Ao efetuar este serviço, o farmacêutico deve reger-se pelas normas da Sociedade Farmacêutica Australiana e pela legislação vigente no seu estado. Considere-se o exemplo do regulamento 48 presente em *"Poisons Regulations 2018 – Statutory Rules 2018, No. 79"* que deve ser seguido pelos farmacêuticos a exercer no estado da Tasmânia.[30,31]

Inicialmente, este serviço aplicava-se apenas a contracetivos orais e estatinas; no entanto, ao longo dos anos, a lista de fármacos foi ampliada por razões emergentes, nomeadamente devido à pandemia de Sars-Cov-2 e a desastres naturais.[32,33] Atualmente, engloba grande parte do universo de medicamentos destinados a terapêuticas crónicas, sendo a lista temporária e revista periodicamente.[29,34]

É necessário cumprir diversos critérios, entre eles, não ter disponível uma prescrição válida, a terapêutica a ser renovada já ter sido prescrita anteriormente, encontrar-se estável e a terapêutica instituída mostrar-se segura, efetiva e apropriada. Além disso, após o início da terapêutica, o doente deve já ter sido observado pelo seu médico e deve ser garantido que a terapêutica não foi já renovada nos 12 meses anteriores. Outra das condições prende-se com o facto de o médico prescritor não estar disponível para criar uma nova prescrição médica, e nesses casos poder ser o farmacêutico a efetuar a renovação da terapêutica. A quantidade dispensada deve estar de acordo com a quantidade presente na prescrição anterior, normalmente correspondente a um ou dois meses de tratamento.[31] Para tornar este processo mais seguro, o farmacêutico comunitário tem acesso ao histórico clínico e farmacoterapêutico do doente na plataforma *My Health Record*.[35]

É obrigatório que o farmacêutico informe o médico prescritor da renovação da terapêutica até sete dias depois e que mantenha registos do processo, nomeadamente do racional que o apoiou nas decisões tomadas e detalhes de todas as comunicações feitas com outros profissionais de saúde.[31,36-38] Além disso, o doente ou o seu cuidador deve assinar uma declaração em como foi informado que lhe está a ser dispensada uma terapêutica sem apresentação de uma prescrição médica válida.[37]

Perante uma rutura de *stock* e indisponibilidade de medicamentos, o farmacêutico pode realizar uma substituição terapêutica, quer de dosagens alternativas quer de formulações. Para isto deve ser respeitado o formulário de substituição terapêutica, *Serious Scarcity Substitution Instruments* (SSSI).[39]

Estados Unidos da América

Também nos EUA existe legislação que permite a dispensa de medicamentos sem prescrição médica. No entanto, ainda se centra maioritariamente na dispensa de *emergency refills*, ou seja, dispensa de uma quantidade de medicamento que supre as necessidades de um curto período de tempo, o que difere do conceito de renovação da terapêutica crónica noutros países, como o Reino Unido.[40,41] Mudanças na legislação têm sido adotadas em vários estados desde 2016, data em que os estados pioneiros, Ohio e Florida, iniciaram a prestação do serviço.[40] Tomando como exemplo o estado de Colorado, este serviço aplica-se quando não é possível obter uma prescrição válida e a recusa da dispensa da medicação consiste numa ameaça à vida do indivíduo.[40,42,43]

Atualmente, nos EUA, existem dois conceitos distintos: o de dispensa de terapêutica de forma a dar continuidade ao plano farmacoterapêutico e o de dispensa de medicamentos numa situação excecional de emergência, sendo que se distinguem pela quantidade de medicamentos que é dispensada. Na primeira situação dispensam-se medicamentos que suprem 30 a 90 dias de tratamento e o farmacêutico deve garantir que existem prescrições anteriores da terapêutica e que a quantidade dispensada não excede a quantidade prescrita anteriormente.[2,40,42,43] Nos últimos anos, têm sido implementados modelos que conferem autoridade de prescrição e substituição terapêutica aos farmacêuticos, através de acordos com médicos prescritores, designados *Collaborative Practice Agreements*. No entanto, este cenário é pouco comum no contexto de farmácia comunitária.[44,45]

Irlanda

Na Irlanda, o processo de renovação da terapêutica crónica, até recentemente, era idêntico ao que é praticado nos EUA – *emergency supply*. Contudo, com o surgimento da dificuldade de acessibilidade a consultas médicas, originada pela pandemia de SARS-CoV-2, foram impulsionadas lterações na legislação. Porém, foi apenas em 2024 que o serviço de renovação da terapêutica crónica foi introduzido

de forma mais estruturada, designando-se '*Prescription Extension'*. Foram implementadas duas alterações: as prescrições médicas passaram a ter validade de 12 meses e os farmacêuticos passaram a ter permissão para aumentar a validade das prescrições para 12 meses, no caso de prescrições médicas emitidas a partir de 1 de março de 2024 com validade apenas de seis meses.[46-48]

Para perceber se é pertinente renovar a prescrição, o farmacêutico deve avaliar alguns fatores, entre eles a estabilidade do estado de saúde do doente, as suas doenças e parâmetros fisiológicos e bioquímicos relevantes. Outros critérios a ter em conta são a adesão à terapêutica, complexidade do plano farmacoterapêutico, apresentação de efeitos adversos, alterações recentes da terapêutica e uso correto dos medicamentos. De realçar que existem alguns medicamentos que não podem ser abrangidos por este serviço, nomeadamente substâncias controladas.[47,49,50]

A legislação recomenda que o farmacêutico documente todo o processo, bem como o seu racional e critérios inerentes ao doente e à sua terapêutica. Além disso, o farmacêutico deve informar o médico da renovação da prescrição no prazo de sete dias.[49-51] Quanto à comunicação entre o farmacêutico e o médico prescritor, prevê-se a implementação de um suporte operacional que permita a partilha de dados e informação de forma automática e integrada nos sistemas informáticos a que os prescritores e farmacêuticos têm acesso.[50]

Portugal

Após a análise do que se entende por renovação da terapêutica crónica em diferentes países, é possível agora perceber as diferenças e os aspetos comuns ao que é permitido fazer aos farmacêuticos comunitários em Portugal.

Inicialmente, em março de 2020, a Norma n.º 003/2020, publicada pela Direção-Geral da Saúde no contexto da pandemia de SARS-CoV-2, continha uma secção dedicada à dispensa de terapêutica crónica a doentes que não apresentassem receita médica. Foi uma medida excecional, posteriormente revogada, que permitia ao farmacêutico a dispensa de medicação para um prazo máximo de três meses.[52] Mais tarde, em 2023, foi publicada a Portaria n.º 263/2023, de 17 de agosto, que pretendeu simplificar o processo de renovação da terapêutica crónica de doentes clinicamente estabilizados e portadores de prescrição médica válida. Estas alterações traduziram-se no aumento de embalagens prescritas, que passaram a ser as necessárias para garantir o plano farmacoterapêutico durante 12 meses, sendo esta também a validade das prescrições.[53,54]

Outra das alterações implementadas foi as farmácias apenas poderem dispensar, no máximo, a quantidade necessária para garantir o tratamento durante dois meses, quantidade esta que é calculada pelo sistema informático através da posologia indicada pelo médico prescritor. Apenas em situações de extravio, perda e roubo de medicamentos ou ausência prolongada do país pode ser dispensada, pelo farmacêutico, uma quantidade superior à presente na legislação, desde que oportunamente justificada pelo farmacêutico. Os medicamentos abrangidos constam na lista de tratamentos de longa duração, estipulada na Deliberação n.º 32/CD/2021.[55] Está ainda referido na legislação que o farmacêutico, em caso de rutura ou indisponibilidade de medicamentos, pode dispensar formas farmacêuticas e/ou dosagens equivalentes à presente na prescrição médica.[53]

O farmacêutico comunitário passou a ter acesso ao histórico de prescrições e dispensas de cada doente nos últimos 12 meses. Para isto, é necessário que o farmacêutico esteja identificado no sistema informático da farmácia e no perfil do colaborador com o seu nome e número da carteira profissional e que o doente dê o seu consentimento através da apresentação do número nacional de utente e do código de acesso e dispensa, que é obtido através de uma mensagem escrita no telemóvel do doente.[56] Desta forma estão assegurados os requisitos éticos relacionados com o serviço.

Além disso, surgem novos instrumentos, associados ao serviço de Renovação da Terapêutica Crónica (RTC), que permitem a comunicação bidirecional entre o médico prescritor e o farmacêutico, nomeadamente o envio de notas terapêuticas através dos respetivos sistemas informáticos. As notas terapêuticas podem ser de dois tipos: 'dispensa' ou 'não dispensa'. Existem diferentes mensagens predefinidas, como é possível verificar na Tabela 2. A nota terapêutica enviada fica automaticamente associada à ficha do utente e pode ser consultado o histórico de notas terapêuticas enviadas e, se aplicável, a resposta do prescritor.[56]

Na legislação portuguesa referente a este serviço não estão previstos registos do serviço, ficando a critério do farmacêutico documentar a informação que considerar pertinente. Contudo, nas "Boas Práticas de Farmácia Comunitária" está descrito que devem ser efetuados registos de todos os dados relevantes relacionados com a terapêutica medicamentosa e intervenções realizadas.[57,58]

Análise comparativa do serviço de renovação da terapêutica crónica

Em seguida, é apresentada uma tabela comparativa do serviço de renovação da terapêutica crónica na qual estão representadas as semelhanças e diferenças do serviço em questão entre os países apresentados anteriormente (Tabela 3).

Como foi possível constatar, o processo de renovação da terapêutica crónica é visto de formas diferentes em diferentes países. No entanto, em todos eles, este novo serviço pretende responder às críticas associadas aos métodos

Tabela 2 – Notas terapêuticas do tipo 'dispensa' e 'não dispensa'

Notas terapêuticas	
Dispensa	**Não dispensa**
O doente apresenta queixas de efeitos secundários	Já tinha medicamento em casa
O doente apresenta problemas de adesão	Rutura de *stock* no armazenista
O doente referiu dificuldades na toma	Código do medicamento inexistente/incorreto
O doente toma um medicamento idêntico	A posologia prescrita não é possível
Quantidade insuficiente para a posologia e duração prescritas	O doente toma um medicamento idêntico
Sugeri consulta médica ao doente	O doente referiu que a dosagem não é a habitual
Outros	O doente não quer tomar o medicamento
	Alergias
	Reação adversa grave
	Interação grave
	Contraindicação grave
	Outros

tradicionais de gestão de prescrições médicas.[59] Assume especial relevância uma vez que as farmácias comunitárias se distinguem dos demais estabelecimentos de prestação de cuidados de saúde pela sua elevada acessibilidade.[60] Além disso, os farmacêuticos comunitários são profissionais dotados de competências técnico-científicas que permitem um acompanhamento adequado de indivíduos que apresentam doenças crónicas.[61]

Um serviço estruturado, como a renovação da terapêutica crónica, permite que os farmacêuticos consigam dar

Tabela 3 – Comparação do serviço de renovação da terapêutica crónica em diferentes países

	Reino Unido	**Canadá** (BC)	**Austrália**	**EUA**	**Irlanda**	**Portugal**
Nome do serviço	*Repeat Dispensing*	*Adapt a Prescription*	*Continued Dispensing*	*Emergency Refills*	*Prescription Extension*	RTC
Ano de implementação do serviço	2009	2008	2013	2016	2024	2023
Necessidade de prescrição médica válida	✓	✓	-	-	✓*	✓
Validade da prescrição	12 meses	24 meses	-	-	12 meses	12 meses
Substituição terapêutica	✓*	✓	✓* SSSI	-	-	✓*
Acesso a histórico de prescrição	✓	✓ *PharmaNet*	✓	-	-	✓
Acesso a informação clínica	-	✓ *PharmaNet*	✓ *My Health Record*	-	-	-
Acesso a canal de comunicação com o prescritor	-	-	-	-	-	✓
Notificação obrigatória do prescritor	-	✓ (< 24h)	✓ (< 7 dias)	✓ (consoante o estado)	✓ (< 7 dias)	-
Consentimento informado	✓	✓	✓	-	-	✓*
Criação de registos/ Documentação	✓	✓	✓	✓	✓	✓

O símbolo de verificação (✓) significa que os critérios estão comtemplados nos documentos pelos quais o serviço se rege. O símbolo asterisco (*) significa que, apesar do critério estar comtemplado no serviço de renovação da terapêutica crónica, condições específicas devem ser tidas em conta aquando do cumprimento do critério.
BC: British Columbia; EUA: Estados Unidos da América; RTC: renovação da terapêutica crónica; SSSI: *Serious Scarcity Substitution Instrument*.

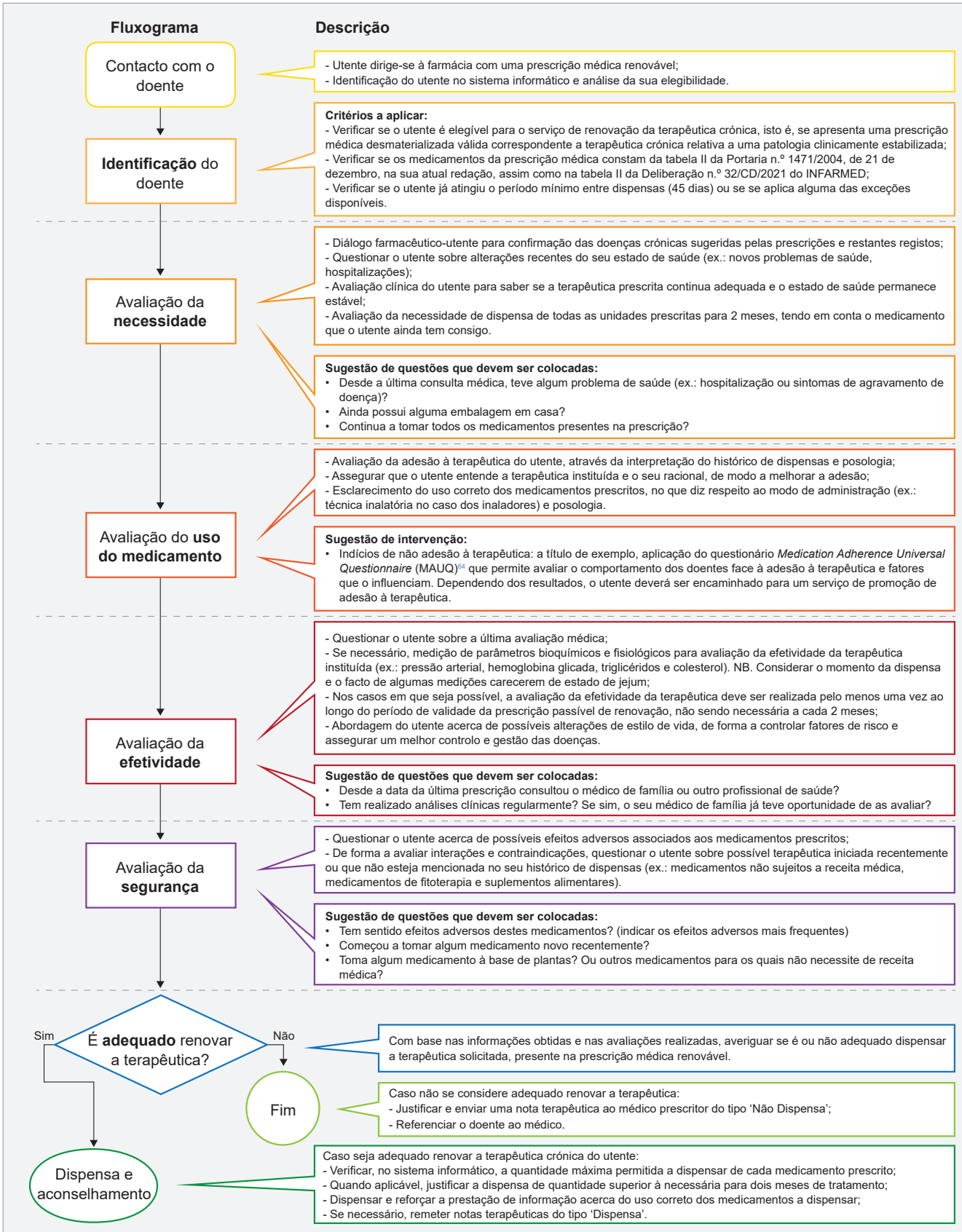

Figura 1 – Fluxograma de atuação no serviço de renovação da terapêutica crónica

resposta aos pedidos solicitados pelos utentes de forma a assegurar a acessibilidade permanente aos medicamentos necessários.[37] Além disso, oferece diversas vantagens aos doentes crónicos e ao sistema de saúde, nomeadamente um acesso facilitado a cuidados de saúde e, consequentemente, uma continuidade ininterrupta do plano terapêutico. Também para os profissionais de saúde traz vantagens, como a otimização da comunicação interprofissional e o incentivo à documentação e rastreabilidade dos serviços prestados. Todas as vantagens enunciadas refletem o impacto positivo que o serviço apresentou nos diferentes países que o implementaram.[62]

A renovação da terapêutica crónica apresenta diferentes regras consoante o país. Por sua vez, o papel que o farmacêutico desempenha no sistema de saúde difere consoante o país considerado, o que irá impactar diretamente o serviço. No entanto, em Portugal, a renovação da terapêutica crónica assemelha-se em grande parte à prática do serviço no Reino Unido. Espera-se que a implementação deste serviço facilite o acesso do doente à sua terapêutica crónica, ao mesmo tempo que reduz a carga administrativa inerente à prescrição e assegura a monitorização do doente por um profissional de saúde.

Refletindo nas ferramentas que estão acessíveis ao farmacêutico nos países abordados, nomeadamente no Canadá e na Austrália, é possível antecipar que o acesso a um histórico de informação clínica do utente poderia ser uma mais-valia na prestação do serviço na sua componente clínica. Além disso, como perspetiva futura de otimização da comunicação e cooperação multidisciplinar entre o farmacêutico e o médico prescritor, a obrigatoriedade de notificar o médico da prática do serviço, tal como acontece nos restantes países (com exceção do Reino Unido), seria uma vantagem.

Proposta de fluxograma para o serviço de renovação da terapêutica crónica

Apesar de a Ordem dos Farmacêuticos ter introduzido uma norma geral do serviço de RTC, esta não prevê a inclusão de diretrizes detalhadas que permitam delinear um protocolo de atuação.[63] Tendo em conta as diretrizes presentes na Portaria n.º 263/2023, de 17 de agosto, e de forma a esquematizar os componentes da intervenção farmacêutica descritos na Norma Geral da Ordem dos Farmacêuticos, é proposto um fluxograma, com o objetivo de diminuir possíveis erros associados a este serviço e apoiar o farmacêutico nas suas tomadas de decisão (Fig. 1).

É necessário realçar que existem possibilidades de otimização do serviço, nomeadamente no que diz respeito à falta de acesso a informação clínica, uma vez que o histórico de prescrições e dispensas não é suficiente para delinear um histórico clínico completo do doente e estabelecer se é ou não apropriado realizar a renovação da terapêutica. Uma das soluções seria a criação de uma plataforma com um histórico clínico com um maior nível de detalhe que permitisse que o farmacêutico tivesse acesso a diagnósticos já estabelecidos, objetivos terapêuticos, resultados de análises clínicas e outra informação clínica relevante.[64,65]

Face à recente implementação do serviço, em Portugal, não é possível tirar conclusões sobre a plataforma de comunicação entre o médico prescritor e o farmacêutico. No entanto, esta aparenta ser uma vantagem, uma vez que constitui um canal direto de comunicação com o médico prescritor, permitindo que situações que necessitem de avaliação médica sejam facilmente reportadas.[66] Além disso, será importante proceder a uma revisão das notas terapêuticas existentes e da necessidade de criação de novas. Um dos exemplos centra-se na nota terapêutica: "O doente toma um medicamento idêntico". Neste caso, o conceito de medicamento idêntico não se encontra definido de forma clara; de qualquer modo, devido aos riscos associados à duplicação da terapêutica, deveria ser reavaliado se esta nota se deveria incluir no grupo predefinido de *'dispensa'*.

CONCLUSÃO

Através desta revisão, e apesar de algumas limitações do serviço, é possível perceber as vantagens que a RTC veio trazer ao sistema de saúde em Portugal e aos doentes crónicos. É fundamental ter presente que, apesar de a introdução deste serviço ter sido de enorme importância, poderá haver margem para expandir a inclusão ativa do farmacêutico comunitário na gestão dos doentes crónicos. Será necessário que as autoridades competentes efetuem uma monitorização do serviço através de estudos e análises da prestação do serviço, de forma a otimizar a sua prática. Deve ser encarado como uma oportunidade para os sistemas de saúde, na medida em que incentiva a criação de equipas multidisciplinares com vista a otimizar a prestação de cuidados em saúde.

CONTRIBUTO DOS AUTORES

MCB: Revisão da literatura, conceção e redação do manuscrito.

SPB: Revisão da literatura e redação do manuscrito.

HMF: Revisão crítica do manuscrito.

IVF: Conceção e revisão crítica do manuscrito.

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Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Symmetrical Neck Swelling After Percutaneous Coronary Intervention

Edema Cervical Bilateral Após Intervenção Coronária Percutânea

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ABSTRACT

Cervical edema after iodinated contrast media administration can raise the suspicion of a hypersensitivity reaction, but other diagnoses must be considered. The authors present a rare case of a man who, during the diagnostic investigation of a patient with thoracic pain developed severe submandibular swelling and local pain after a percutaneous coronary intervention with iodinated contrast media. The cervical computerized tomography revealed enlargement of the submandibular glands with adjacent fat stranding, suggesting contrast-induced sialadenitis. In the allergology department skin prick tests, intradermal tests and epicutaneous test with suspected iodinated contrast media and alternative were performed, which were negative. Drug provocation tests with alternative iodinated contrast media were negative. Different approaches can be considered when approaching these patients. Our algorithm includes the evaluation of a potential hypersensitivity reaction with a skin test and drug provocation test with alternative iodinated contrast media.
Keywords: Contrast Media; Edema; Iodine/adverse effects; Sialadenitis/chemically induced

RESUMO

A reação de hipersensibilidade deve ser considerada perante o desenvolvimento de edema cervical após a administração de um meio de contraste iodado. Contudo, devem ser avaliados outros diagnósticos diferenciais. Os autores apresentam um caso raro de um homem, que durante a realização de uma intervenção coronária percutânea com meio de contraste iodado para estudo de dor torácica, desenvolveu um edema e dor submandibular bilateral. A tomografia computadorizada cervical revelou aumento das glândulas submandibulares com densificação da gordura adjacente, sugestivo de sialadenite induzida por contraste. No serviço de imunoalergologia, foram realizados testes cutâneos por picada, intradérmicos e epicutâneos com o meio de contraste iodado suspeito e alternativo, que foram negativos. A prova de provocação com meio de contraste iodado alternativo foi negativa. Assim, podem ser consideradas diferentes abordagens no estudo destes doentes. O nosso algoritmo incluiu avaliação de uma potencial reação de hipersensibilidade com testes cutâneos e prova de provocação com meio de contraste iodado alternativo.
Palavras-chave: Edema; Iodo/efeitos adversos; Meio de Contraste/efeitos adversos; Sialadenite/induzida quimicamente

INTRODUCTION

Iodinated contrast media (ICM) were first implemented in clinical practice in the early 1900s for diagnostic purposes and disease surveillance.[1] Even though adverse reactions to ICM are relatively frequent they are typically mild and can arise from either toxicity or hypersensitivity responses.[2] The frequency of immediate and non-immediate hypersensitivity reactions is described in approximately 0.5% - 3.0% of the exposed patients.[3]

Cervical swelling following the administration of ICM may suggest a potential hypersensitivity reaction, but other diagnoses must be considered: ductal obstruction of salivary glands, trauma, acute infection, neoplasia or contrast-induced sialadenitis (CIS).[4]

Contrast-induced sialadenitis was first described in 1956 by Miller and Sussman, who coined the term 'iodide mumps', likening the facial glandular swelling to viral parotitis.[5] It remains an uncommon reaction to ICM and fewer than 80 cases have been reported to date.[5,6] In the present case, sialadenitis developed from one to 24 hours after administration of ICM and took four to 84 hours to resolve.[4,7] Clinical manifestations were characterized by swelling of the salivary glands and pain.[7] The etiology is not fully known, but may be due to high concentrations of ICM in the salivary glands, causing local inflammatory edema, which leads to the obstruction of the salivary duct.[7] The study by Lee *et al* identified the main risk factors that contribute to the development of CIS after neurovascular procedures, finding higher incidence in the female sex, the volume and type of contrast agent used and the duration of the procedure.[8]

The diagnosis of CIS is primarily based on clinical observation and is corroborated by ultrasound of the salivary glands.[4] Other imaging techniques such as computed tomography may be considered.[4]

A correct diagnosis is essential. Additional exposure to ICM should be avoided, as it is likely that sialadenitis will recur. However, there are no absolute contraindications if urgent life-saving interventions are necessary.

CASE REPORT

We present the case of a 77-year-old male patient referred for evaluation at the Allergology department due to facial edema associated with the administration of ICM.

The patient had a personal history of hypertension, dyslipidemia, and recurrent episodes of thoracic pain. The usual medication was zofenopril 30 mg, atorvastatin 10 mg and

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tamsulosin 0.4 mg. No history of atopy or allergic disorder, such as food, drug or latex allergy.

During the study of thoracic pain, the patient underwent a percutaneous coronary intervention with iopromide 769 mg/mL (Ultravist®), with a total administered dose of 70 mL. Ten hours later, he developed severe submandibular swelling and local pain, without other symptoms. The patient was observed in the emergency department. There were no changes in the blood count, renal function, liver enzymes and C-reactive protein; the cervical CT (without contrast) revealed an enlargement of the submandibular glands with adjacent fat stranding, suggestive of edematous changes (Fig. 1). The patient was treated with a short course of corticosteroids (40 mg prednisolone) with complete resolution on day five. The patient had had a prior exposure to ICM (iopromide) without any adverse reactions.

He was referred to our Allergology department for study of hypersensitivity to ICM. The skin prick tests (SPT), intradermal tests (ID) and epicutaneous test (ET) were conducted in accordance with the European Academy of Allergy & Clinical Immunology (EAACI) and European Network for Drug Allergy (ENDA) guidelines.[9] The SPT with iopromide (769 mg/mL) and iomeprol (714 mg/mL), ID test with iopromide (1/10) and iomeprol (1/1) and ET with iopromide (1/1) and iomeprol (1/1) were negative at the 20 minutes (SPT and ID), and 48 hours reading (ID and ET).

The drug provocation test (DPT) with alternative ICM, iomeprol (Iomeron®), was performed. The DPT with iomeprol was carried out, using incremental doses at one-hour intervals across two sessions separated by one week (5 mL > 10 mL > 15 mL on the first day and 10 mL > 20 mL > 30 mL on the second day, which amounted to a cumulative dose of 90 cc) was negative.

DISCUSSION

Our patient developed bilateral cervical angioedema 10 hours after ICM administration. The differential diagnosis of trauma, infection, ductal obstruction and neoplasms of the salivary glands were excluded based on the clinical history, analytical study and tomographic findings.

Considering the clinical history and time of onset of symptoms after a known trigger, the hypothesis of hypersensitivity to ICM was considered. To investigate a potential hypersensitivity to iopromide, allergological studies (SPT, ID and ET) were carried out, all with negative results, making the diagnosis of ICM hypersensitivity less likely. Considering the cervical CT findings of submandibular gland edema with adjacent fat stranding, but absence of edema in subcutaneous cellular tissues, a characteristic of edema in allergic reactions, the most probable entity was CIS.[10,11]

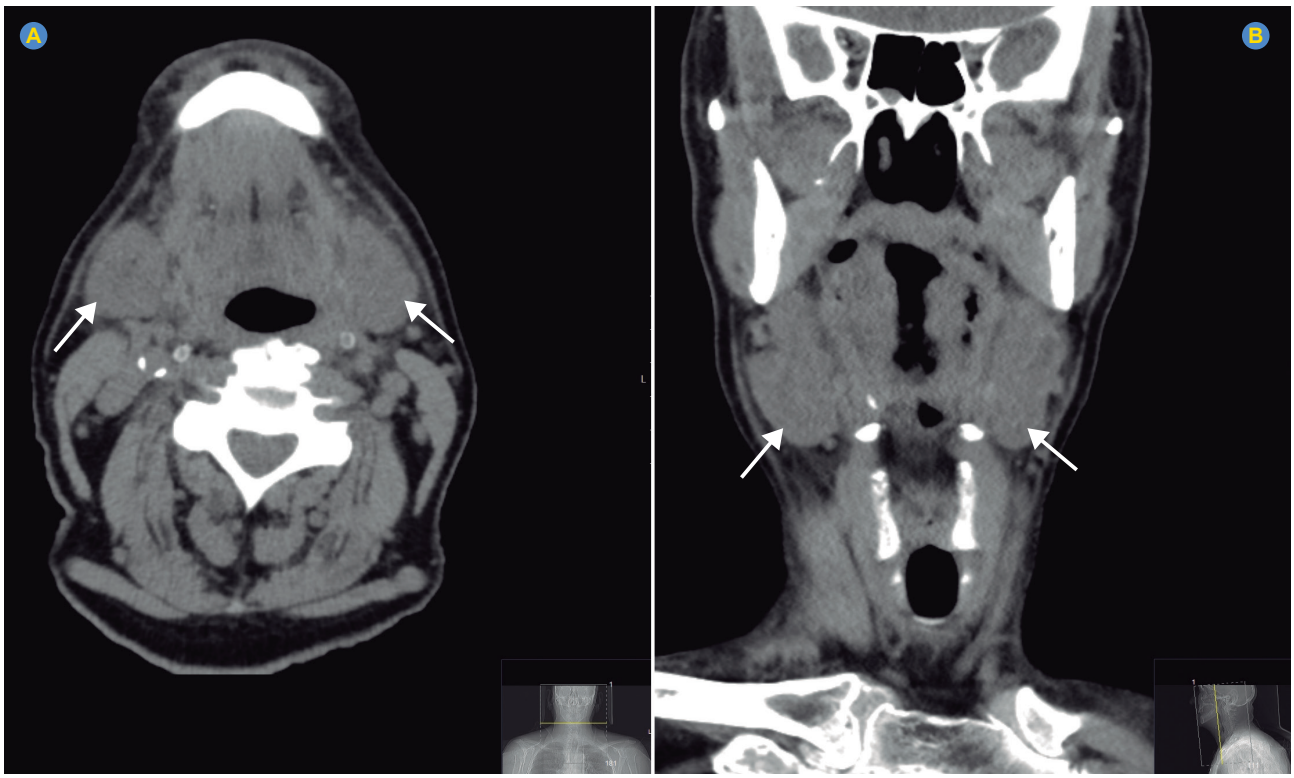

Figure 1 – Axial (A) and coronal (B) submandibular sialadenitis. Non-contrast computerized tomography images reveal enlargement of the submandibular glands with adjacent fat stranding, suggestive of edematous changes. Nonspecific bilateral submandibular lymph nodes are also observed. No obstructive calculi are identified.

The submandibular glands are the most commonly affected salivary glands in this context, as described in our clinical case, followed by the parotid glands, sublingual glands and, in rare cases, involvement of the thyroid, lacrimal gland, and pancreas has been reported.[4,11,12]

The pathophysiology of CIS is debatable; initially it was associated with a mechanism mediated by immunoglobulin E.[4] However, it is now believed that the condition is due to the toxic accumulation of iodine in the ducts of the salivary glands, triggering an inflammatory reaction and consequent obstruction of the salivary duct.[7,13] Premedication with antihistamines and corticosteroids was not proven to prevent episodes of sialadenitis.[7,11]

Current treatments for CIS are supportive therapy and the administration of anti-inflammatory agents, with the expectation that symptoms can fully resolve within a few hours to two weeks.[11,14] In our case, pain and edema of the submandibular glands resolved within five days of treatment with prednisolone.

The management of CIS remains a topic of debate. However, many reported cases indicate that the condition is generally benign and self-limiting, although there is a tendency for recurrence.[11]

The risk of recurrence with the administration of the same contrast is high. A literature review published in 2018 described nine cases of recurrence of sialadenitis after administration of different forms of low-osmolarity non-ionic iodinated contrast media.[12] Other studies suggested there was a lower risk with contrasts with low osmolarity and high solubility.[7]

Due to the risk of recurrence, the patient refused the DPT with the suspected ICM, so the DPT with alternative ICM was performed. The DPT – performed with Iomeprol, a monomeric, non-ionic ICM with low chemotoxicity, osmolality, and viscosity, and high solubility in water compared to other non-ionic ICM – was negative.[1,2]

The benign course of this syndrome should not limit the use of iopramide, but the use of iomeprol should be favored due to the patient's tolerance.

In conclusion, CIS is considered an uncommon reaction to ICM. The condition is typically benign and self-limiting and, although the administration of ICM is not contraindicated in life-saving situations, the risk of recurrence of sialadenitis is high. In the clinical case presented, after evaluating potential hypersensitivity reactions with skin tests, the DPT was performed with alternative ICM, which was negative. Although iopromide administration is not contraindicated, the authors consider that DPT with lower osmolarity ICM can be considered, thus providing the patient with a safer alternative.

AUTHOR CONTRIBUTIONS

LPD: Study design, data analysis and interpretation, writing of the manuscript.

ACC, CM: Data analysis and interpretation, writing of the manuscript.

MJS: Study design, critical review of the manuscript.

All authors approved the final version to be published.

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The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

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A Case of Unilateral Bertolotti's Syndrome

Um Caso de Síndrome de Bertolotti Unilateral

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Keywords: Low Back Pain; Lumbar Vertebrae
Palavras-chave: Dor Lombar; Vértebras Lombares

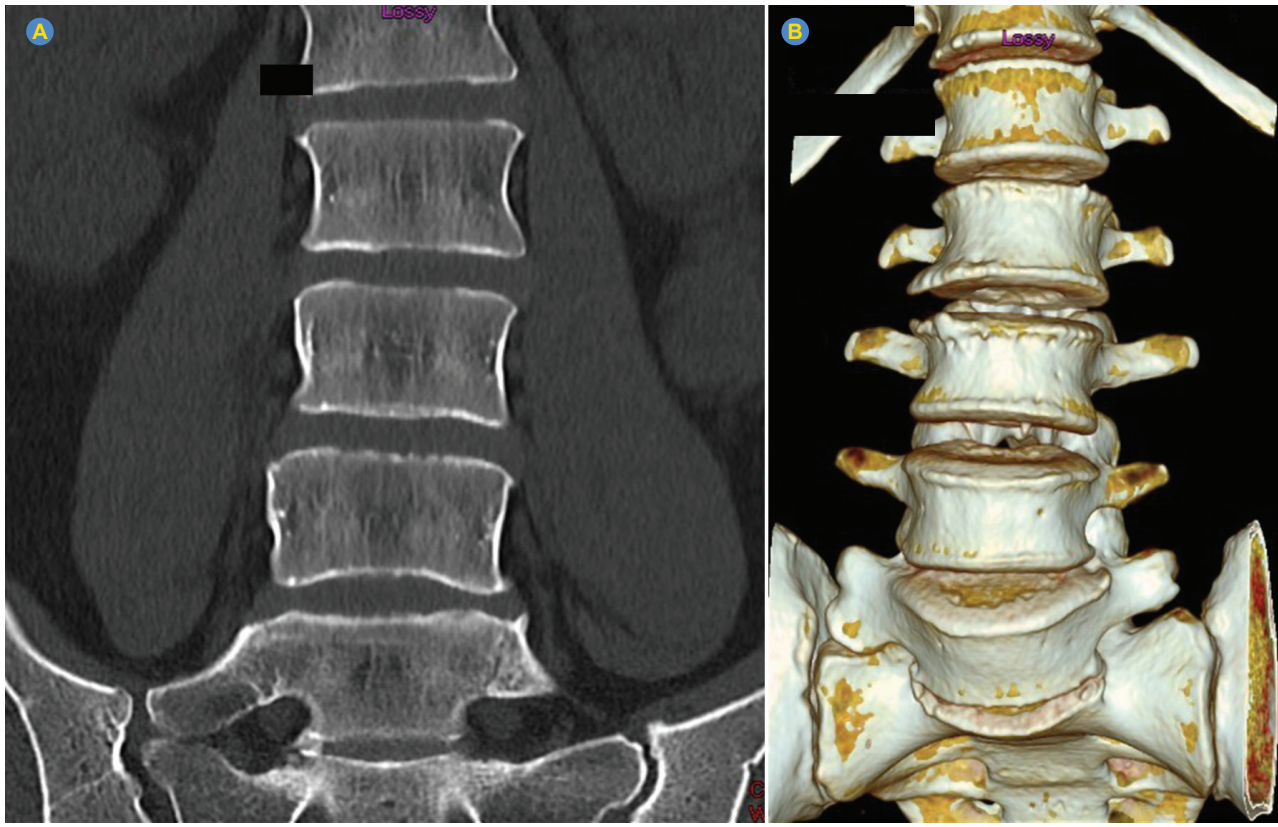

Figure 1 – Sacralization of the lowest right lumbar vertebral body originating the lumbosacral transitional vertebra compatible with Bertolotti's syndrome

A 47-year-old woman with chronic low back pain presented with right hip paresthesia extending to the ipsilateral lower limb, causing significant physical limitation. The lumbosacral computed tomography scan (Fig. 1A) and three-dimensional reconstruction (Fig. 1B) showed an abnormal connection between the lowest lumbar vertebra (L5) and the sacrum on the right side of the spine, compatible with a congenital condition called lumbosacral transitional vertebra (LSTV) defect and, consequently, Bertolotti's syndrome.[1-4] Bertolotti's syndrome typically manifests as chronic low back pain with associated symptoms such as sacroiliac joint, groin and hip pain, reduced back mobility, and radiculopathy.[1,2] Since its diagnosis requires clinical and imaging assessments, with the presence of LSTV, its incidence is still unclear.[1,3] Both images show the connection between the right transverse process and the sacrum on the right side of the spine. The initial treatment is conservative (physical and pharmacological therapies).[1,4] Epidural steroid injections,

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radiofrequency ablation, and surgery are considered second-line treatments.[1,4]

AUTHOR CONTRIBUTIONS

RMG: Study design, data collection, literature search, writing and critical review of the manuscript.

JCG: Study design, literature search, writing and critical review of the manuscript.

MPP: Writing and critical review of the manuscript.

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All authors approved the final version to be published.

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PATIENT CONSENT

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Practical Guidance on the Detection of *NTRK* Fusions in Sarcomas: Current Status and Diagnostic Challenges

Orientações Práticas sobre a Deteção de Sarcomas de Fusão *NTRK*: Estado Atual e Desafios Diagnósticos

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ABSTRACT

Sarcomas are a rare and heterogeneous group of mesenchymal malignant tumors and account for approximately 1% of all adult cancers and around 20% of all pediatric solid tumors in Europe. Technology advances have enabled a more accurate and efficient characterization of the molecular mechanisms underlying the pathogenesis of sarcoma subtypes and revealed novel and unexpected therapeutic targets with prognostic/predictive biomarkers, namely the neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion. The *NTRK* fusion assessment has recently become a standard part of management for patients with unresectable locally advanced or metastatic cancers and has been identified in various tumor types. In the more prevalent adult and pediatric sarcomas, *NTRK* fusions are present in 1% and 20%, respectively, and in more than 90% of very rare subsets of tumors. The inhibition of TRK activity with first-generation TRK inhibitors has been found to be effective and well tolerated in adult and pediatric patients, independently of the tumor type. Overall, the therapeutic benefit to those patients compensates for the difficulties of identifying *NTRK* gene fusions. However, the rarity and diagnostic complexity of *NTRK* gene fusions raise several questions and challenges for clinicians. To address these issues, an expert panel of medical and pediatric oncologists, radiologists, surgeons, orthopedists, and pathologists reviewed the recent literature and discussed the current status and challenges, proposing a diagnostic algorithm for identifying *NTRK* fusion sarcomas. The aim of this article is to review the updated information on this issue and to provide the experts' recommendations and practical guidance on the optimal management of patients with soft tissue sarcomas, infantile fibrosarcoma, gastrointestinal stromal tumors, and osteosarcoma.
Keywords: Gene Fusion; Oncogene Proteins, Fusion/genetics; Receptor, trkA/genetics; Sarcoma/genetics

RESUMO

Os sarcomas são um grupo raro e heterogéneo de tumores mesenquimatosos malignos, e constituem um dos principais grupos de cancros raros na Europa, representando cerca de 1% de todos os cancros em adultos e cerca de 20% de todos os tumores sólidos pediátricos. Os avanços tecnológicos permitiram uma caracterização mais precisa e eficiente dos mecanismos moleculares subjacentes à patogénese dos subtipos de sarcoma e revelaram novos e inesperados alvos terapêuticos e biomarcadores prognósticos/preditivos, nomeadamente o gene de fusão do recetor tirosina cinase neurotrófico (*NTRK*). A avaliação da fusão de *NTRK* foi incluída, recentemente, na gestão de doentes com cancros localmente avançados irressecáveis ou metastáticos e foi identificada em vários tipos de tumores de adultos e pediátricos. Nos sarcomas mais prevalentes diagnosticados em adultos e pediátricos, as fusões de *NTRK* estão presentes em 1% e 20%, respetivamente, e em mais de 90% dos subconjuntos de tumores muito raros. A inibição da atividade de TRK com inibidores de primeira geração tem-se mostrado eficaz e bem tolerada em doentes adultos e pediátricos, independentemente do tipo de tumor. Globalmente, o benefício terapêutico para estes doentes compensa as dificuldades em identificar os genes de fusão de *NTRK*, sendo que a raridade e a complexidade diagnóstica dos genes de fusão de *NTRK* levantam várias questões e desafios para os médicos. Para abordar estas questões, um painel

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de oncologistas médicos e pediátricos, radiologistas, cirurgiões, ortopedistas e patologistas reviram a literatura recente e discutiram o estado atual e os desafios, propondo um algoritmo de diagnóstico para identificar sarcomas de fusão de *NTRK*. Este artigo pretende apresentar uma revisão da literatura atual sobre o tema e fornecer as recomendações dos especialistas e orientações práticas para a gestão de doentes com sarcomas de tecidos moles, fibrossarcoma infantil, tumores do estroma gastrointestinal e osteossarcomas.
Palavras-chave: Fusão Génica; Proteínas de Fusão Oncogénica/genética; Receptor trkA/genética; Sarcoma/genética

INTRODUCTION

Sarcomas are a rare and heterogeneous group of mesenchymal malignant tumors, accounting for approximately 1% of all adult cancers and 20% of all pediatric solid tumors.[1-6] These tumors can occur in virtually any anatomic site, arising in either soft tissue (~80%) or bone (~20%).[1–5]

Complete surgical resection with or without pre-and postoperative therapies is the standard treatment for most localized sarcomas.[1,7] In locally advanced, metastatic, or recurrent settings, treatment may involve a combination of strategies, including systemic therapy and local approaches.[1,8] The clinical management of sarcomas remains challenging due to their heterogeneity, aggressive nature, and different responses to current treatment options.[7,9]

Technological advances have enabled a more accurate and efficient characterization of the molecular mechanisms underlying the pathogenesis of sarcomas and revealed novel therapeutic targets and prognostic/predictive biomarkers.[1,7,10–12] The discovery of neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions as sarcoma oncogenic drivers led to new personalized therapies for a subset of patients in the form of tropomyosin receptor kinase (TRK) inhibitors, improving clinical outcomes.[1,12–15]

The *NTRK* fusion assessment has recently become a standard for patients with unresectable locally advanced or metastatic cancers.[16] These fusions can be detected using a variety of methods, including tumor deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) sequencing and plasma cell-free DNA profiling.[1,13,17]

Although rare in most common tumor types, *NTRK* fusions are recurrent in certain tumors such as secretory carcinoma of the salivary gland, secretory carcinoma of the breast, thyroid cancers, congenital mesoblastic nephroma, pediatric melanoma, infantile gliomas and infantile fibrosarcoma, where they can be present in > 90% of cases.[1,15,18] In contrast, *NTRK* fusions have been identified in < 1% of other adult and pediatric sarcomas.[1,15,18]

The rarity and diagnostic complexity of *NTRK* gene fusions raises several questions and challenges for clinicians. To address these issues, an expert panel of Portuguese medical and pediatric oncologists, radiologists, surgeons, orthopedic surgeons, and pathologists reviewed the recent literature and discussed diagnostic challenges of patients with soft tissue sarcomas, infantile fibrosarcoma, gastrointestinal stromal tumors (GIST), and osteosarcoma.

The aim of this article is to present updated information on this issue and the experts' proposal of a diagnostic algorithm for *NTRK* fusion sarcomas for practical guidance on the optimal management of these patients.

OVERVIEW OF *NTRK* FUSION CANCER

Etiology of *NTRK* Cancers

The *NTRK* gene family includes three members: *NTRK1* (chromosome 1q23.1), *NTRK2* (chromosome 9q21.33), and *NTRK3* (chromosome 15q25.3), that encode transmembrane TRK proteins TRKA, TRKB, and TRKC, respectively.[1,19] Tropomyosin receptor kinase proteins are expressed in the adult's peripheral and central nervous systems (CNS), and during embryonic development.[20]

Under normal physiological conditions, TRK proteins bind to neurotrophic family ligands leading to downstream signaling that is critical for the normal development and function of the peripheral and CNS.[1,19,21] However, *NTRK* genes may undergo chromosomal rearrangements due to intra- and inter-chromosomal translocations of the kinase portion of *NTRK1/2/3* with an unrelated gene.[20,22] These gene fusions lead to the constitutive activation/expression of chimeric TRK proteins, which have oncogenic properties by driving uncontrolled cell proliferation and tumor growth in a variety of tissues.[20,22]

Neurotrophic tyrosine receptor kinase fusions were first found in colon carcinoma[23] and later described for the first time in pediatric fibrosarcomas, namely the *ETV6::NTRK3* fusion.[24] Currently, there are over 80 different fusion partners identified in a wide range of tumor types.[23–25] In rare cancers, the most common detected gene fusion is *ETV6::NTRK3*, while in the more common, the *NTRK* genes can be found with a large number of different partners, with the *NTRK1* gene usually having more fusion partners than *NTRK2* and *NTRK3* genes.[26,27]

NTRK gene fusions in soft tissue sarcomas

Soft tissue sarcomas comprise a heterogeneous group of cancers with different responses to treatment, which ultimately confer an aggressive behavior, poor prognosis, and a five-year overall survival (OS) rate of 65%.[28,29] Disease management should be performed by a multidisciplinary team in a sarcoma reference center. Among the underlying causes of soft tissue sarcomas, *NTRK* gene fusions account for only 1% of cases.[28–32]

Infantile fibrosarcoma

Infantile fibrosarcoma is a rare pediatric tumor that usually occurs in the first year of life. It forms in connective tissue and, in almost 50% of cases, arises in the extremities of the body, followed by the head, neck, and trunk.[33,34] The tumor often presents a fast-growing period, but it rarely metastasizes. Resection of the tumor with clean margins is the mainstay of treatment, although 48% - 62% are considered unresectable.[34] Chemotherapy has been shown to improve OS in infantile fibrosarcoma by improving the ability to remove the tumor. Infantile fibrosarcoma are tumors with a high prevalence of *NTRK* fusions.[13] *ETV6::NTRK3* fusion is the most common fusion and, together with other variants, is present in about 90% of infantile fibrosarcomas.[24,35,36] This implies a new therapeutic target for these patients.

Gastrointestinal stromal tumors

Gastrointestinal stromal tumors are rare tumors characterized by usually small gastroesophageal or duodenal nodules with a progression risk associated with tumor size and mitotic index.[37,38] In adults, GIST typically occurs in patients aged 60 - 65 and frequently harbor *KIT* or *PDGFRA* mutations.[38,39] Pediatric GIST is mainly characterized by loss of function mutations in succinate dehydrogenase (SDH) genes, encoding the subunits of the SDH enzyme.[40] Regarding *NTRK* gene fusion frequency, screening of 24 GIST lacking *KIT* or *PDGFRA* mutations showed one *NTRK* fusion-positive tumor (4.2%).[41] However, another study of targeted sequencing data from 738 GIST did not found cases with *NTRK* rearrangements. More comprehensive large-scale studies are needed to confirm *NTRK* fusion incidence in GIST.

Osteosarcoma

Osteosarcoma has an overall incidence of 0.3 cases per 100 000/year and occurs most frequently around the knee in adolescents and in the craniofacial bones in adults.[42] High-grade osteosarcoma patients usually develop metastases in the lungs and distant bones.[43] *NTRK* fusions appear to be rare in bone sarcomas, as suggested by a study comprising 354 bone tumors that did not find *NTRK* gene fusion after immunohistochemistry screening.[44,45]

ASSESSMENT OF *NTRK* FUSIONS IN SARCOMAS

Technologies for testing *NTRK* fusions

New *NTRK* gene fusions are being discovered regularly, resulting from the emergence of new screening methodologies.[30] The most common technologies to detect, directly or indirectly, *NTRK* fusions in tumor tissues are immunohistochemistry (IHC), reverse transcriptase polymerase chain reaction (RT-PCR), fluorescence *in situ* hybridization (FISH), next-generation sequencing (NGS) of DNA and/or RNA, and NanoString nCounter technique.

Immunohistochemistry

Immunohistochemistry is a valuable screening tool in clinical environments with limited access to NGS platforms. Regarding other methods, IHC has several benefits, namely time- and tissue-efficiency with an overall good cost-effectiveness.[46] This technique is highly sensitive for detecting *NTRK1/2* fusions but sub-optimal for *NTRK3* fusions (sensitivity < 79%).[16] The anti-TRKA and pan-TRK antibodies can be used to spot elevated TRK expression compared to the low TRK levels observed in control cells.[15,16,46] These antibodies enable the detection of the gene fusions at the protein level, allowing to distinguish between expressing (detectable) and non-expressing (non-detectable) *NTRK* fusions. The staining pattern can be correlated with the subcellular location of the *NTRK* fusion partner. However, TRKA/B/C proteins are physiologically expressed in some healthy cells, like neural and muscle tissue, making it difficult to evaluate the presence of *NTRK* fusions in tumors derived from or involving such organ systems. Additionally, sample preparation can lead to false negatives. Hence, internal and external controls, such as endothelial cells and positive cell lines, are highly recommended. The absence of standard criteria for immunohistochemistry evaluation complicates the interpretation of IHC data; thus, positive results should be followed with a molecular method to further confirm the presence of *NTRK* fusion.[16]

Although international guidelines recommend confirmation of positive TRK IHC with a targeted RNA analysis, up-front testing with a targeted RNA analysis should be preferred in some scenarios since there is limited evidence available regarding the use of IHC in detecting *NTRK* gene alterations in routine practice.[1,15,47,48]

Reverse transcriptase polymerase chain reaction

Reverse transcriptase polymerase chain reaction is a well-established technique to measure the expression of fusion transcripts implicated in a wide variety of sarcomas.[49–51] This method employs a 3' primer annealing to an *NTRK* kinase domain and a 5' primer annealing to a fusion partner, flanking the fusion region.[52] In the presence of the targeted region, the aid of fluorescent signaling probes at each PCR cycle allows detecting the DNA amplification with high sensitivity and specificity.[52] Reverse transcriptase polymerase chain reaction can also be used for quantitative reporting of tumor burden or post-treatment monitoring. One disadvantage of RT-PCR is the need to design a set of primers for each gene fusion transcript that, together with an increasing number of 5' fusion partner genes, reduces the applicability of a multiplex RT-PCR assay.[53] Moreover, it is restricted to known fusion partners, which can lead to false negatives in

the case of an unknown fusion partner. Thus, RT-PCR is usually used as a confirmatory test.

Fluorescence *in situ* hybridization

Fluorescence *in situ* hybridization is a quick and inexpensive conventional technique to study chromosomal rearrangements and is widely available in many laboratories.[49,54] In FISH, fluorescently labeled DNA probes anneal to specific regions within or flanking a gene(s) of interest to detect the fusion gene events.[54] To bypass the need to develop many FISH probes for each fusion partner gene, a break-apart FISH probe for each *NTRK* gene is used. This approach allows the observation of several fusion targets in one sample using different fluorochromes and the detection of novel fusions with yet uncharacterized fusion partners.[55] This is a sensitive and powerful technique, and a positive FISH result is sufficient to establish the diagnosis of a *NTRK*-positive tumor.[56] However, the fusion partner gene is not identified, and the expression of *NTRK* fusions is not confirmed. Moreover, false positives may occur due to unproductive rearrangements or aberrant probe hybridization, and false negatives may result from FISH probes failure to detect some rearrangements derived from small genomic deletions.[16,55,57]

Next-generation sequencing of DNA and/or RNA

Next-generation sequencing allows precise and simultaneous evaluation of multiple genomic events including detection of NTRK gene fusions. In some assays, it can also detect novel fusion partners.[30] This method has variable levels of sensitivity depending on the assay and computational pipelines.[16] RNA-based NGS is currently the gold standard for the identification of *NTRK* gene fusions because, with the splicing out of introns, it becomes more precise, specific, highly sensitive, and simplified in terms of technical requirements.[58,59] Conversely, DNA-based NGS is less accurate, especially in *NTRK2* and *NTRK3* genes.[58] Besides identifying novel fusion partner genes, the exon involved, and the precise breakpoint, RNA-based NGS also allows to discriminate between in-frame and out-of-frame rearrangements, inferring transcript functionality, and gene expression levels. Additionally, this method relies on sample preparation and RNA integrity and quality, which is particularly critical in bone sarcomas, where fixation and demineralization procedures can result in RNA degradation.[60]

NanoString nCounter technique

NanoString nCounter is a multiplex nucleic acid hybridization technology that enables reliable and reproducible assessment of the expression of up to 800 genes or 228 gene fusions in 12 samples in a single assay. The technique works well with a variety of starting materials from fresh or formalin-fixed tissues, cell lysates or biological fluid samples.[61]

nCounter is a cost-effective technique, with high specificity and sensitivity for detecting *NTRK* fusions, with a high concordance rate with RNA-based NGS assays.[62] However, it is unsuitable for biomarker discovery and, when compared to other methods, may be less sensitive to gene expression variability.[63]

Strategy and screening algorithms

Considering the vast number of *NTRK* gene fusions already identified and the high heterogeneity of tumor types and stages, efficient identification of *NTRK* fusions can be demanding and of utmost importance in order to select the patients that are more likely to benefit from therapy and to rule out other potential drivers of tumorigenesis. Several screening algorithms and recommendations have been developed to provide a reliable diagnosis without unnecessary further testing and improve the time to treatment.[1,2] In Fig. 1, we propose a diagnostic algorithm adapted to real-world clinical practice to identify such patients.

Generally, in histologically confirmed localized sarcomas detected during early stages with complete surgical excision, *NTRK* fusion testing is not fundamental for disease management and may not be considered routine clinical practice. The exception is infantile fibrosarcoma, which has a high prevalence of *NTRK* fusions[7] and should have a confirmatory test such as NGS or FISH. If NGS is not possible, a first screen using IHC pan-TRK can be performed.

In the case of tumors with an elevated recurrence risk, *NTRK* fusion testing using NGS platforms should be conducted to plan the most appropriate therapies.

For locally advanced, unresectable tumors and/or metastatic disease, where alternative therapies are insufficient, testing for *NTRK* gene fusions is certainly advantageous. Patients with identified *NTRK* fusions can benefit from first-line TRK inhibitors.

Rare cancer types that commonly harbor *NTRK* gene fusions, such as infantile fibrosarcoma and inflammatory myofibroblastic tumors should always be tested for *NTRK* fusions. In these cases, a positive result by NGS or FISH is sufficient to provide a diagnosis, whereas a positive staining by IHC pan-TRK should be confirmed by NGS to exclude false positives.

In sarcomas with other genetic drivers, *NTRK* fusion testing is mainly performed for academic and research purposes rather than clinical practice.

A two-step approach involving an IHC pan-TRK screening and confirmatory NGS testing provides a reliable and cost-effective way of detecting *NTRK* gene fusions. However, pathologists should always adapt these algorithms whenever needed for individual clinical circumstances for

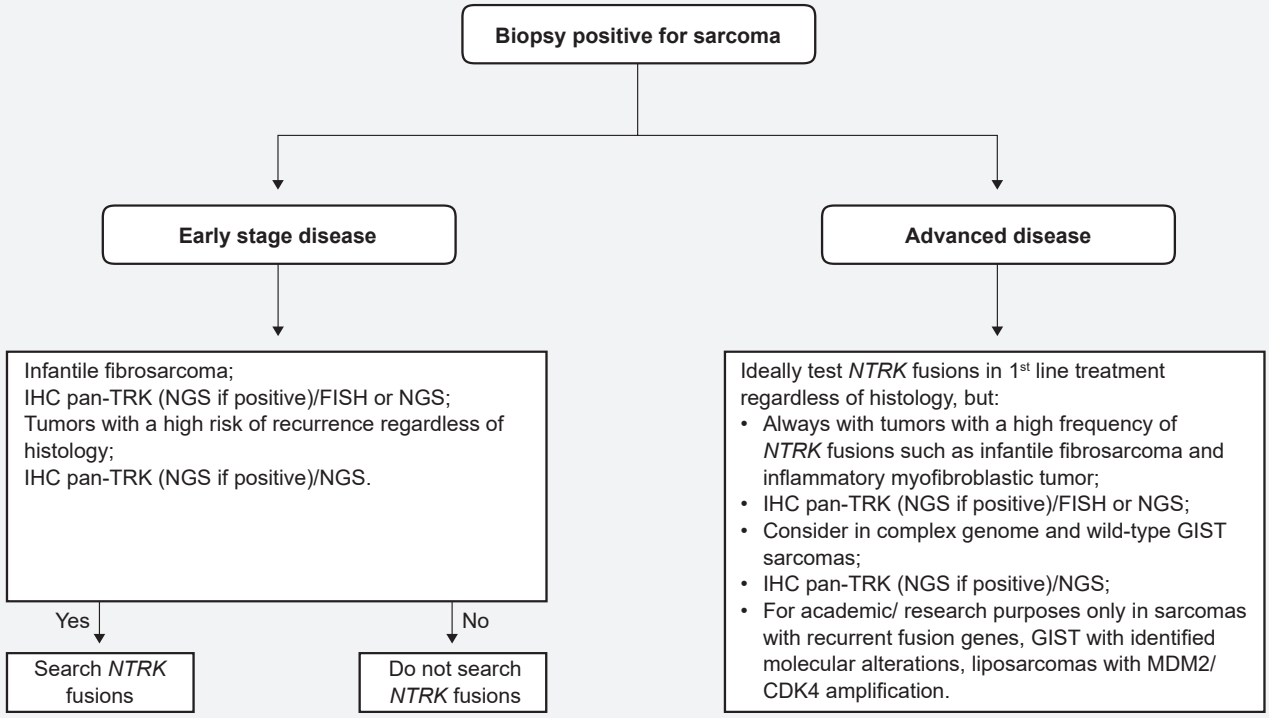

Figure 1 – *NTRK* diagnostic algorithm
FISH: fluorescence *in situ* hybridization; GIST: gastrointestinal stromal tumors; IHC: immunohistochemistry; NGS: next-generation sequencing; *NTRK*: neurotrophic tyrosine receptor kinase; TRK: tropomyosin receptor kinase

benefit of patient's healthcare.

CLINICAL MANAGEMENT OF *NTRK*-FUSED SARCOMAS

Therapies for patients with TRK fusion sarcoma

Several small molecules, grouped into multi-kinase inhibitors or more-selective TRK inhibitors, with different levels of affinity to the TRK domain, are currently in clinical trials (CTs) and some are already approved.[64] Many of them have demonstrated efficacy in *NTRK* fusion-positive solid tumors.[31] The multi-kinase inhibitor group includes entrectinib, crizotinib, cabozantinib, lestaurtinib, ponatinib, nintedanib, merestinib, MGCD516, PLX7486, DS-6051b, and TSR-011.[31] The most specific TRK inhibitor is larotrectinib, the first FDA-approved TRK inhibitor. Larotrectinib and entrectinib are now the first-generation of TRK inhibitors approved for adult and pediatric patients who have a solid tumor with a *NTRK* fusion and no acquired-resistance mutations, which is metastatic or unresectable and a relapse prior to therapy, or without satisfactory alternative treatment options.

FIRST-GENERATION TRK INHIBITORS

Larotrectinib

Larotrectinib is a highly effective and highly selective pan-TRK inhibitor,[2,65] with a binding affinity capacity of more than 100-fold when compared with a panel of several kinases.[66] It has demonstrated a robust tumor-agnostic effect in various sarcomas, including osteosarcoma, dedifferentiated chondrosarcoma, GIST, infantile fibrosarcoma and other soft tissue sarcomas (adult fibrosarcoma, inflammatory myofibroblastic tumor, infantile myofibromatosis, lipofibromatosis, malignant peripheral nerve sheath tumor, myopericytoma, spindle cell sarcoma, high-grade endometrial stromal tumor, and synovial sarcoma).[1,65]

On the clinical setting, larotrectinib has demonstrated a high efficacy profile in a pooled analysis of the first 55 consecutively enrolled patients of three phase I/II clinical trials (CTs) in adult and pediatric TRK fusion-positive cancers, regardless of patient age or tumor type.[57] The overall response rate (ORR) was 75%, the median time of response was 1.8 months and, after one year, 71% of responses were ongoing, with 55% of all patients remaining progression-free.[56] In a recent pooled analysis of the same CTs, including 159 patients with TRK fusion-positive cancer aged from < one month to 84 years and treated with larotrectinib, an objective response of 79% (95% CI 72 - 85) was reported, with 16% having complete responses.[68]

Larotrectinib is available in oral, liquid, or capsule formulations with similar pharmacokinetics, which allows proper administration in infants and children.[69] Additionally,

the treatment is well tolerated, and no grade 4/5 adverse events (AEs) nor related deaths were attributed to the treatment.[69,70] The most common AEs were fatigue, dizziness, anemia, increased liver enzyme levels, hematological toxicity, arthralgia/myalgia, and vomiting.[56,68-71]

More recently, long-term follow-up studies demonstrated that larotrectinib leads to a median OS of > 36 months with an increased survival benefit and a favorable extended safety profile,[72,73] thus contributing to a clinically significant impact in the quality of life (QoL) of 90% of adult and 67% of pediatric patients.[74]

Larotrectinib is also able to cross the blood-brain barrier producing objective and durable responses in subsets of patients with primary CNS tumors or brain metastases from non-CNS solid tumors.[75-78]

The role of larotrectinib may also be extended to a neoadjuvant setting, shifting to a new treatment paradigm for patients with a locally advanced *NTRK* fusion-positive tumor that, without this alternative, would face morbid surgery. Two children with locally advanced infantile fibrosarcoma avoided a possible amputation after larotrectinib treatment substantially reduced the tumor, thus enabling a limb-sparing surgery instead.[56] Four other patients with partial responses underwent surgical resection of the tumor, avoiding morbid surgery. Three of them were classified as a pathological complete response after no viable tumor was detected on the microscopic examination.[69,79]

Entrectinib

Entrectinib is a multi-kinase inhibitor targeting pan-TRK, ROS1, and ALK kinases, with IC50 values in the nanomolar range between 0.1 and 1.7 nM,[80] among other structurally similar off-target kinases.[81] Besides adult and the recent approval for > one month-old pediatric patients with *NTRK* fusion-positive solid tumors, entrectinib is also FDA-approved for patients with *ROS1* fusion-positive metastatic non-small cell lung cancer (NSCLC).[82]

The regulatory and efficacy data for entrectinib approval were based on three phase I/II CTs, comprising a 54-patient analysis. The patients were adults with advanced or metastatic *NTRK* fusion tumors, including with baseline CNS metastases. The ORR was 59%, and the median duration of response was 12.9 months.[83] Long-term follow-up studies showed an increased ORR of 63.5% and response duration of 20 months, supporting that entrectinib is able to induce clinically meaningful improvements with durable systemic and intracranial responses.[84,85]

Entrectinib is available in an oral capsule formulation and is well tolerated, the most common treatment-related AEs being grade 1 or 2 and non-serious, like weight gain, anemia, and fatigue; the most common serious AEs were nervous system disorders, in 4% of patients.[85]

Regarding the pediatric population, entrectinib leads to an objective ORR of 86% in patients with recurrent or refractory solid tumors, including primary CNS tumors.[86] Only 32.4% of patients had to reduce the dosage, and 8.8% discontinued drug-treatment, in both cases, due to AEs.[87] Entrectinib can reduce tumor burden and produce rapid and durable responses, with a progression-free survival of 17.5 months, in children and adolescents.[86,88]

Considering QoL, patients harboring *NTRK* fusion tumors treated with entrectinib reported a stable health status, with a tendency to improve clinical outcomes.[89]

Larotrectinib and entrectinib also provide improved clinical results when compared with prior therapies, and they are progressively being integrated into national and international clinical practice guidelines for the treatment of *NTRK* fusion positive tumors.

Next-generation TRK inhibitor

Tumors treated with first-generation TRK inhibitors can develop resistance to therapy, resulting from resistant mutations. If the resistance is off target (activation of compensatory signaling pathways), patients might benefit from an inhibitor directed to the activated signaling pathway to manage the disease progression.[90]

The resistance mutations can also be on-target when they occur within the TRK kinase domain.[91] These alterations can cause further structural changes on the kinase domain or alter the ATP-binding affinity, reducing the ability of first-generation TRK inhibitors to bind to the TRK kinase domain. Next-generation agents are being developed not only to address on-target resistance but also to maintain the potency against wild-type TRK fusion proteins.[92–94]

Selitrectinib/LOXO-195, a highly effective and sensitive TRK kinase inhibitor, was evaluated in two patients, both with advanced-stage *NTRK* fusion-positive cancers, after acquired resistance to larotrectinib. One patient experienced a rapid clinical response with a reduction of tumor burden and only dizziness as treatment-related AE. The other patient, after an initial partial response to selitrectinib, experienced respiratory distress resorting to hospitalization and her condition worsened afterwards.[93] Considering the CTs results, selitrectinib/LOXO-195 was not moved forward.

Repotrectinib is a highly potent inhibitor against ROS1, ALK, and TRK inhibitors. A proof-of-concept case, harboring an acquired resistance mutation in the *NTRK3* gene, experienced a rapid and robust response within the first few days of treatment with a reduction of tumor burden. After a slow disease progression and, consequently, dose escalation, this patient re-established disease control.[92] More recently, cellular assays showed that repotrectinib is 10-fold more potent against wild-type and mutated TRKA, B, and C proteins than selitrectinib.[94] Repotrectinib has shown

promising results in inhibiting most on-target *NTRK* resistance mutations, and currently, is in phase I/II CTs to establish safety, dosing, and clinical efficacy.[94]

ISSUES AND QUESTIONS ON *NTRK* FUSION SARCOMAS

Testing difficulties

Each molecular diagnosis technique has advantages and disadvantages. Testing decisions should ultimately be made based on the type of tumor and the resources available, including the quality and quantity of biopsy material and equipment accessibility.[16]

Although costly, RNA-based NGS is the gold standard to test *NTRK* gene fusions in sarcomas. IHC is well accepted as a pre-screening tool, but it gives a high rate of false-negative staining in the case of *NTRK3* fusions. RT-PCR and FISH are highly sensitive techniques; however, the former only detects previously known *NTRK* gene fusions, while the latter may not detect some rearrangements derived from small genomic deletions.[16,18,96]

These technologies are optimized to work in formalin-fixed paraffin-embedded sample tissue, and it is important to have an image-guided biopsy to collect the material.[30,51,55]

More recently, some technologies have been developed to take advantage of liquid biopsies, from which circulating tumor cells and circulating cell free tumor DNA/RNA can be harvested.[96,97] Circulating tumor DNA represents a non-invasive approach that allows monitoring tumor recurrence or progression throughout treatment. However, the sensitivity level of this method will vary with the cell shedding capacity of the tumor and, consequently, with the amount of material for detection in circulation.[97]

The FISH and IHC methods have already been optimized to directly detect gene rearrangements in filtration-enriched circulating tumor cells from NSCLC.[96] Still, validation from other groups is needed before clinical implementation.

Genetic variability and mutations

A variety of *NTRK* alterations, other than fusions, have been identified in 14% of several tumor types, including point mutations, amplifications, deletions, and splice variants.[98] Data showing the response of tumors with non-fusion *NTRK* alterations treated with TRK inhibitors is still limited. A case-report presented one patient with an *NTRK* amplification that exhibited a partial response of short duration; however, none of the tumors with *NRTK* point mutations responded to treatment.[69] Another described a patient with a metastatic esophageal squamous cell carcinoma harboring an *NTRK1* amplification treated with larotrectinib. Initially, the patient showed a partial response of the primary and metastatic tumors, but 3.5 months later, the disease progressed.[99]

CONCLUSION

Since *NTRK* fusions are present in 1% to 20% of the more prevalent adult and pediatric sarcomas, and more than 90% of very rare subsets of tumors, patients eligible for TRK inhibitors are a minority within the overall number of cases of patients with sarcoma.[1,18] Nevertheless, the inhibition of TRK activity with first-generation of TRK inhibitors is effective and well tolerated in adult and pediatric patients, independently of the tumor type.[69,70,87]

The therapeutic benefit to those patients compensates for the difficulties of identifying *NTRK* gene fusions. Accordingly, pathologists play a critical role in the diagnosis and assessment of patients with cancer. Several clinical guidelines and *NTRK* gene fusion testing recommendations have been developed to help identify *NTRK* fusion-positive cancers.[63,100] Following these diagnostic algorithms, pathologists should consider the optimal use of tumor tissue and testing prioritization when tumor tissue is limited, such as small biopsies and cytological samples.

In this manuscript, we have reviewed the etiology of *NTRK* cancers and gene fusions in soft tissue sarcomas, namely infantile fibrosarcoma, GIST, and osteosarcoma, and the therapies for patients with TRK fusion sarcoma, including first- and next-generation TRK inhibitors. We reviewed the technologies for testing *NTRK* fusions and discussed the diagnostic challenges. Aiming at optimizing clinical management of these patients we propose a diagnostic algorithm for identifying *NTRK* fusion sarcomas (Fig. 1).

In Portugal, evidence is limited due to regulatory issues. Despite the most recent data and the consensus among the participants in this working group, there is no public coverage in Portugal for these medicines, limiting patients' access to therapeutics. Real-world evidence studies will be essential to demonstrate the improvement in survival with QoL for sarcoma patients with *NTRK* fusion.

AUTHOR CONTRIBUTIONS

All authors participated in the consensus-elaboration meeting and contributed to the diagnostic algorithm elaboration, paper revision and validation.

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IF received research funding from PharmaMar and Roche.

AF received honoraria for presentations from Novartis, AstraZeneca and Gilead; support for attending meetings and travel from Pfizer and Gilead; participated on an advisory board from AstraZeneca, Daichi and Lily; has a leadership role in the Portuguese Oncologic Study Group.

JL received honoraria for meeting presentations from Thermofisher; honoraria for manuscript preparation from Roche; research funding from Thermofisher.

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Carcinoid Complexity: A Syndrome Revealing Lung Tumor and Heart Disease

Complexidade Carcinoide: Uma Síndrome que Revela um Tumor Pulmonar e Doença Cardíaca

Keywords: Carcinoid Heart Disease; Carcinoid Tumor; Lung Neoplasms; Somatostatin Analogs
Palavras-chave: Doença Cardíaca Carcinoide; Neoplasias do Pulmão; Tumor Carcinoide

Dear Editor,

Lung carcinoid tumors (LC) account for 20% - 25% of all neuroendocrine tumors (NETs) and 1% - 2% of all cases of lung cancer.[1,2] About 20% to 30% of patients have disseminated disease at diagnosis, presenting with carcinoid syndrome (CS), and of these, about half have carcinoid heart disease (CHD).[2,3]

The authors present the case of a 79-year-old man, a former smoker, who was admitted to the emergency department due to shortness of breath and tiredness on minor exertion and productive cough starting one month before. The patient was admitted with a suspected respiratory infection and therefore started an empirical antibiotic regimen, but worsened over time, with dyspnea for progressively minor efforts and anasarca. Diagnostic tests were carried out detecting a progressive increase in NT-proBNP levels (up to 4300 pg/mL – reference value 0 – 125 pg/mL) and a transthoracic echocardiogram demonstrated dilated right cavities and left atrium, with decreased overall RV systolic function, mild to moderate tricuspid regurgitation, with an estimated pulmonary artery systolic pressure of about 82 mmHg – normal mPAP 14 ± 3 mmHg) (Fig. 1) and a minor pericardial effusion, predominantly posterior. Considering the hypothesis of CS as a presentation of a disseminated carcinoid tumor, a thoraco-abdominopelvic computed tomography (CT) revealed a mass in the right lower lobe, with approximately 50 mm in the longest axis, mediastinal and hilar adenopathy, and numerous hepatic nodules that captured contrast. Diagnostic tests included: measurement of serum chromogranin A (326 ng/mL) and urinary 5-HIAA (12.5 mg/24 hours), both high; bronchoscopy, with histology of the biopsies carried out suggestive of a typical lung carcinoid tumor, expressing chromogranin and Ki67 (about 1%); brain CT and PET/CT with gallium 68 (^{68}Ga-DOTATOC PET/CT) that showed a malignant tumor lesion (Fig. 2) with overex-pression of somatostatin receptors in the lymph nodes, liver, and bones. Given the findings, the patient was diagnosed with a primary bronchopulmonary carcinoid tumor with liver and bone metastasis and was proposed for therapy with octreotide every four weeks.

Although there was initial symptomatic improvement, the ^{68}Ga-DOTATOC PET/CT performed to assess the response showed extensive splenic metastasis and progression of lymph node metastasis, leading to initiation of second-line therapy with everolimus, which was suspended 15 days after the first dose due to adverse effects. At the time of writing, the patient was under surveillance, with symptomatic treatment with octreotide. This case highlights the diagnostic and therapeutic challenges of CS and the importance of an integrated approach using biochemical screening, imaging, and echocardiography to guide diagnosis and treatment.

AUTHOR CONTRIBUTIONS

SRL: Study design, writing of the manuscript.
JB, MIMVL: Data analysis and interpretation.
SV: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki

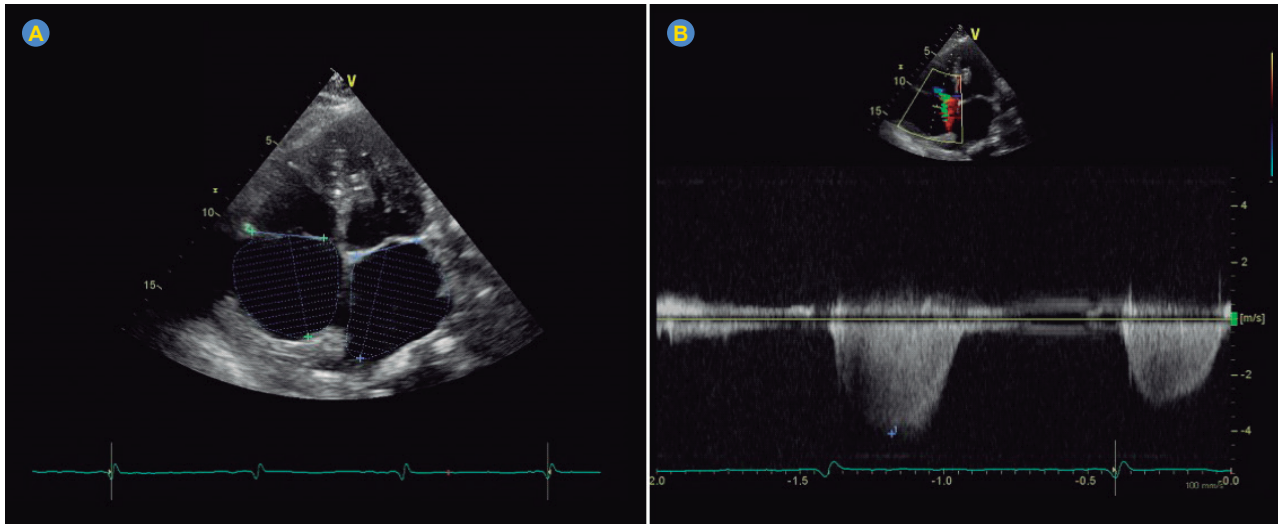

Figure 1 – Transthoracic echocardiogram demonstrating dilated right cavities and left atrium (A); mild to moderate tricuspid regurgitation, with an estimated pulmonary artery systolic pressure (ePASP) of about 82 mmHg (B).

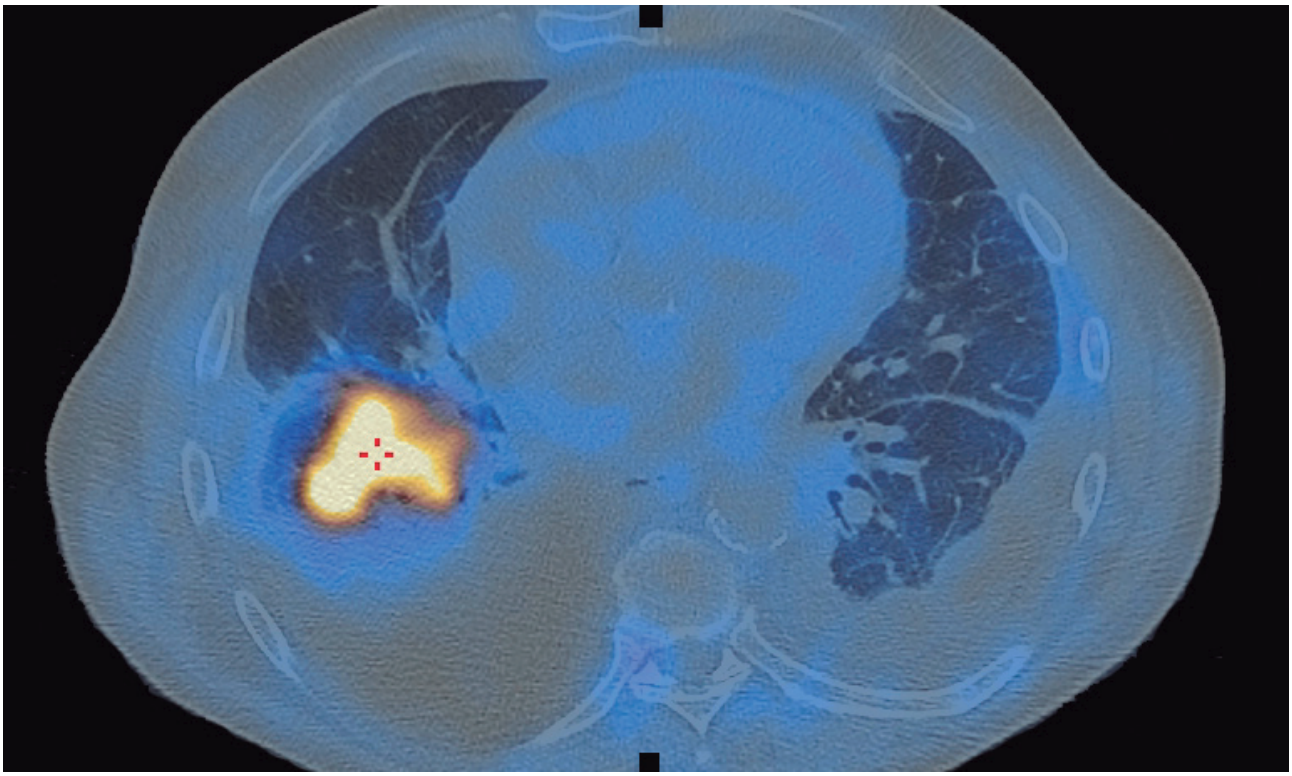

Figure 2 – PET-CT with gallium 68 showing uptake in the right lower lobe (SUVmax = 12.3)

Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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EBV-Associated Cytotoxic Peripheral T-cell Primary Pulmonary Lymphoma

Linfoma Primário Pulmonar de Células Citotóxicas Periféricas T Associado ao EBV

Keywords: Epstein-Barr Virus Infections/complications; Lung Neoplasms; Lymphoma, T-Cell; T-Lymphocytes, Cytotoxic
Palavras-chave: Infecções pelo Vírus Epstein-Barr/complicações; Linfoma de Células T; Linfócitos T Citotóxicos; Neoplasias dos Pulmões

Dear Editor,

Primary pulmonary lymphomas (PPL) are extremely rare, comprising less than 1% of all lymphomas and less than 0.5% of all primary lung cancers.[1] When they occur, they are usually B-cell lymphomas.[1,2] Primary T-cell lymphomas of the lung are exceedingly rare, with only a few case reports described in the literature. We present a case of a primary pulmonary T-cell lymphoma to highlight its clinical and radiological characteristics and the challenges in its diagnosis and treatment.

A 43-year-old white woman, smoker and with a history of mild asthma and Behçet's disease under azathioprine, presented with left pleuritic chest pain. Initial chest radiography was unremarkable. Two weeks later, she developed a fever, productive cough and exertional dyspnea. Reevaluation with chest CT showed multiple bilateral consolidations and ground-glass opacities (Fig. 1A). Lab results revealed elevation of C-reactive protein and lactate dehydrogenase. Despite empirical antibiotics and systemic corticosteroids, there was no improvement. Bronchoscopy and bronchoalveolar lavage were unremarkable. A CT-guided transthoracic biopsy showed small lymphoid cells with scant cytoplasm and slightly irregular basophilic nuclei, and necrosis (Fig. 1B), which, combined with the immunohistochemical staining results, allowed for the diagnosis of an Epstein-Barr Virus (EBV)-associated peripheral cytotoxic T-cell lymphoma by a pathologist specialized in lymphomas. The patient's condition deteriorated rapidly, and she passed away shortly after being transferred to the hematology department.

Primary pulmonary lymphoma is defined as a lymphoma confined to the lung, with or without lymphatic hilar involvement at the time of the diagnosis or up to three months after.[1,2] This type of lymphoma, particularly of T-cell origin, poses a diagnostic challenge due to its rarity (either as PPL or through secondary involvement of the lung) and overlapping clinical presenting features with more common respiratory infections.[1] Clinically, men seem to be slightly more affected than women[1,2] and the mean age at diagnosis is around 60 years.[1] Radiologically, it may present as a solitary or as multiple nodules, ground-glass opacities, or consolidation with air bronchogram.[2] Unilateral involvement is more common, although bilateral cases can occur in about 10% of cases.[1] The prognosis is generally poor, with a rapid clinical deterioration.[3] Immunosuppression and EBV infection may play a role in its pathogenesis.[4] There is no established treatment protocol, although cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)-based chemotherapy is generally used.[4] Early diagnosis and treatment initiation are crucial.

The aim of this case is to raise awareness of this entity which requires high clinical suspicion, emphasizing the importance of a timely and accurate diagnosis to increase the chances of better outcomes.

AUTHOR CONTRIBUTIONS

AN, LM, MJC: Study conception and design, data acquisition, analysis and interpretation, writing and critical review of the manuscript.

JP: Study design, data acquisition, analysis and interpretation, writing and critical review of the manuscript.

CC: Study conception and design, data interpretation, critical review of the manuscript.

All authors approved the final version to be published.

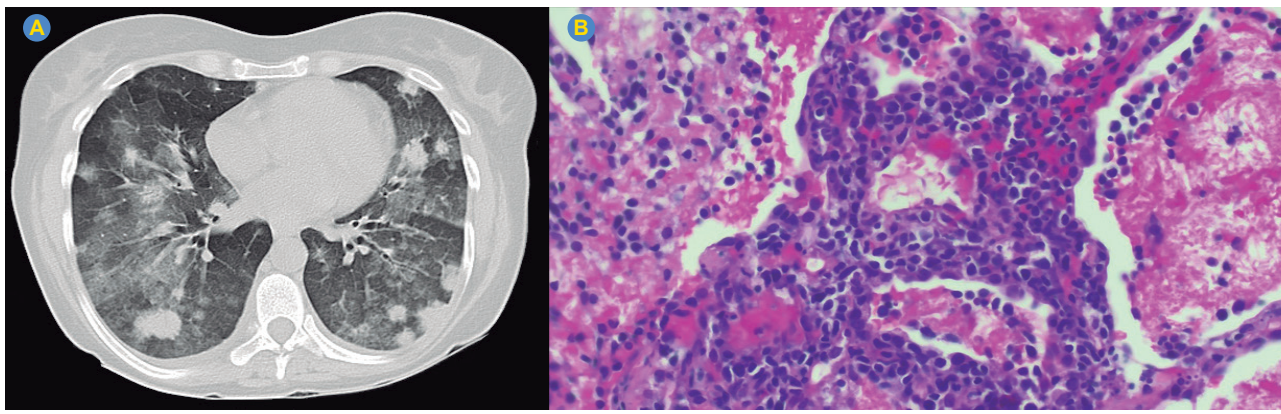

Figure 1 – Chest CT revealing multiple bilateral foci of consolidation, some of which with a nodular pattern and with air bronchogram, associated with areas of ground glass and mosaic pattern, with predominant distribution on the lower thirds of both lungs (A). Lung tissue with infiltration by small lymphoid cells with scant cytoplasm and slightly irregular basophilic nuclei, and necrosis (H&E, 400x) (B). Immunohistochemical staining revealed positivity for CD3, CD8, CD2, TIA-1, and BCL-2 and negativity for CD20, CD5, CD7, CD30, TdT, MUM-1, CD10 and BCL6. EBER was also positive (not displayed).

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Consent obtained from the patient's legal representative.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Anemia Sideroblástica Congénita e Sobrecarga de Ferro em Idade Avançada

Congenital Sideroblastic Anemia and Iron Overload in Older Age

Palavras-chave: Anemia Sideroblástica/congénita; Hiperferritinemia; Sobrecarga de Ferro
Keywords: Anemia, Sideroblastic/congenital; Hyperferritinemia; Iron Overload

As anemias sideroblásticas (AS) enquadram-se num grupo de distúrbios da eritropoiese, caracterizado pela presença de sideroblastos em anel na medula óssea. As causas adquiridas incluem síndrome mielodisplásica, neoplasias mieloproliferativas, consumo de álcool, entre outras. Das causas congénitas, a anemia sideroblástica ligada ao X (ASLX) é a mais comum. Tipicamente resulta de mutações do gene *ALAS2* (envolvido na síntese do heme), cursa com anemia microcítica e afeta jovens ou adultos do sexo masculino. Alguns doentes respondem ao tratamento com vitamina B6.[1,2]

Descrevemos o caso de um doente do sexo masculino, com 67 anos, referenciado ao seviço de hematologia por hiperferritinemia, anemia microcítica e alterações no esfregaço de sangue periférico (ESP). O doente não tinha antecedentes transfusionais ou antecedentes familiares de anemia conhecidos e era assintomático. Do estudo efetuado, destacava-se: anemia microcítica hipocrómica [Hb 9,5 g/dL (VR: 13 - 18), HTC 33,8% (VR: 43 - 55), VGM 56,9 fL (VR: 87 - 103), MCHC 28,1 g/dL (VR: 28 - 36)], RDW 25,4% (VR: 11 - 16), eritrócitos 5,94 x 10^{12}/L (VR: 4,4 - 6,0), reticulócitos 0,96% (VR: 0,5 - 2,5), índice reticulocitário 0,5 (VR: > 2), sugestivo de distúrbios na maturação eritroide; ESP: dimorfismo eritrocitário; elevação das transamínases (3-4xLSN) e gama GT (2xLSN), ferro sérico 214 ug/dL (VR: 53 - 167), transferrina 172 mg/dL (VR: 200 - 360), ferritina 4665 ng/mL (VR: 20 - 250), saturação de transferrina (ST) 89% (VR: 20 - 50); ecografia abdominal: discreta esplenomegalia e esteatose hepática; eletroforese Hb normal; pesquisa de mutações genéticas associadas a hemoglobinopatias ou hemocromatose negativa. A ressonância magnética abdominal mostrou sobrecarga de ferro hepática [25,2 mg/g de peso seco (N < 2,0 mg/g)].

Foi instituída quelação de ferro com desferasirox 360 mg bid/PO. Após dez meses de tratamento, mantinha ferritina > 3000 ng/mL, ST 149%, Hb 9,5 g/dL e hepatoesplenomegalia, optando-se por introduzir desferoxamina 3x/semana/SC. Após três meses, verificou-se descida da ferritina para 1700 ng/mL, ST 92%, Hb e transamínases estáveis. O estudo genético, com painel do metabolismo do ferro e porfiria, detetou a variante *ALAS2.c.1447G>T;p.*

Tabela 1 – Diagnósticos diferenciais de hiperferritinemia de acordo com mecanismo fisiopatológico

Hiperferritinemia		
Aumento da síntese de L-ferritina	**Libertação de ferritina por destruição celular**	**Aumento da produção de ferritina por sobrecarga de ferro**
• Etilismo • Neoplasias • Doença de Gaucher • Síndrome hereditária de hiperferritinemia-cataratas • Hiperferritinemia hereditária benigna	• Doenças hepáticas • Doenças autoimunes • Infeções	• Hemocromatose hereditária (gene HFE) • Variantes não-HFE: doença da hemojuvelina (gene *HJV*), hepcidina (gene *HAMP*), Recetor 2 da transferrina (gene *TFR2*), ferroportina (gene *SLC40A1C*), aceruloplasminemia (gene *CP*) • Eritropoiese ineficaz (talassemias, anemia sideroblástica) • Dependência de transfusões (anemia falciforme, talassemias, anemia hemolítica, neoplasias hematológicas) • Dieta rica em ferro • Tratamento com ferro endovenoso • Doenças hepáticas • Porfiria cutânea tarda

Ala483Ser (em hemizigotia), não descrita na literatura, no entanto, variantes no gene *ALAS2* com as mesmas características estão associadas a ASLX. O mielograma evidenciou 22% sideroblastos em anel, corroborando o diagnóstico. Manteve-se seguimento e convocou-se os familiares para estudo.

A hiperferritinemia pode ter diversas etiologias (Tabela 1). Na presença de sobrecarga de ferro, importa excluir hemocromatose hereditária, anemias relacionadas com eritropoiese ineficaz e/ou dependência de transfusões.[3]

As anemias sideroblásticas predispõem a sobrecarga de ferro secundária à eritropoiese ineficaz e transfusões. Está recomendado iniciar tratamento se ferritina > 500 – 1000 ng/mL, transfusão de > 10 - 12 concentrados eritrocitários, ou conteúdo de ferro hepático > 5 mg/g de peso seco (flebotomias ou quelação de ferro se anemia).[4]

As autoras pretendem evidenciar uma patologia rara que se pode manifestar por anemia, hiperferritinemia e sobrecarga de ferro, sublinhando a necessidade de tratamento individualizado.

CONTRIBUTO DOS AUTORES

MG: Colheita e interpretação de dados, conceção e redação do manuscrito.

FF: Colheita e interpretação de dados, conceção e revisão crítica do manuscrito.

As autoras aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

As autoras declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

CONFIDENCIALIDADE DOS DADOS

As autoras declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

As autoras declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Otimização de Referenciações Hospitalares: Da Sobrecarga à Solução

Optimizing Hospital Referrals: From Overload to Solution

Palavras-chave: Cuidados Primários de Saúde; Encaminhamento e Consulta; Hematologia; Hospitais Terciários; Portugal
Keywords: Hematology; Hospitals, Tertiary; Referral and Consultation; Portugal; Primary Health Care

Exmo. Editor,

Os hospitais terciários portugueses enfrentam uma sobrecarga considerável, evidenciada pelo facto de o aumento da atividade hospitalar verificado no Serviço Nacional de Saúde (SNS) se revelar insuficiente para dar resposta à procura.[1] Este desequilíbrio resulta num tempo médio de espera de 113 dias para consultas especializadas, com apenas 51,6% de cumprimento do tempo máximo de resposta garantido.[2]

A otimização da articulação entre os cuidados de proximidade e cuidados especializados poderá atenuar estes constrangimentos, pois estima-se que a adoção de critérios de referenciação (CR) mais rigorosos possa reduzir em 30% a carga de trabalho nos hospitais terciários,[3] otimizar a alocação de recursos e diminuir em 25%[3] as consultas desnecessárias, sobretudo se complementada por formação contínua e consultoria remota.[4]

Para avaliar este problema, analisaram-se 258 pedidos de consulta de hematologia pediátrica recebidos entre janeiro e junho de 2023 num hospital terciário em Lisboa. Verificou-se que 26% desses pedidos não cumpriam os CR institucionais (Tabela 1), originando 13% de recusas. Entre os 212 doentes efetivamente avaliados em consulta, 30% não apresentavam alterações hematológicas, incluindo 21% cujos motivos de referenciação já estavam resolvidos ou não se confirmaram. Constatou-se ainda que 52% receberam alta após uma ou duas consultas, enquanto 18% mantiveram seguimento essencialmente para correção de ferropenia.

Estes resultados corroboram o relatado em estudos prévios,[3,4] sugerindo que muitos destes casos poderiam ter sido tratados nos serviços de proximidade.

Nesse sentido, foi implementada uma intervenção alinhada com as diretrizes da Organização Mundial da Saúde,[5] composta por: (1) revisão dos CR, através da inclusão de critérios baseados em risco e da exclusão de condições benignas ou autolimitadas; (2) capacitação dos referenciadores, com programas de formação contínua que incluem ferramentas práticas, como *checklists* e algoritmos de decisão; e (3) criação de uma consultoria remota especializada para a discussão de casos mais complexos.

Concluindo, a otimização das referenciações revela-se fundamental para promover uma utilização mais racional

Tabela 1 – Critérios institucionais de referenciação de hematologia pediátrica

Categoria	Critério
Alterações no hemograma[a]	- Anemia (Hb < P5 para idade e sexo), exceto anemia ferropénica
	- Macrocitose (VGM > P95 para idade)
	- Policitemia (Hb > P95 para idade e sexo)
	- Trombocitopenia (Plaquetas < 150 000/L)
	- Neutropenia (Neutrófilos < 1500/L)
	- Citopenias combinadas
	- Trombocitose (Plaquetas > 500 000/L)
Hemoglobinopatias	- Hemoglobinopatia suspeita ou confirmada
	- Portadores de hemoglobinopatias
Alterações da coagulação	- Tempo de protrombina ou tempo de tromboplastina parcial ativado prolongado[a]
	- Déficit suspeito ou confirmado de fatores da coagulação
	- História de hemorragias recorrentes ou desproporcionadas para o contexto clínico
Trombofilia	- Trombofilia suspeita ou confirmada
	- TEV não associado a fatores de risco major[b]
	- Dois ou mais episódios de TEV
	- TEV em locais atípicos[c]
	- AVC isquémico fora do período neonatal
	- Púrpura fulminans, suspeita ou confirmada
	- Avaliação antes do início anticoncetivos com estrogénios, na fase pré-concecional ou antes de cirurgia ortopédica, caso história familiar de trombofilia hereditária ou trombose em idade jovem

[a]: em pelo menos 2 determinações distintas;
[b]: cateter venoso central, trauma major, cirurgia major ou imobilização prolongada;
[c]: território esplâncnico (veias porta, hepática, esplénica, mesentérica) ou cerebral;
AVC: acidente vascular cerebral; Hb: hemoglobina; P5: percentil 5; P95: percentil 95; TEV: tromboembolismo venoso; VGM: volume globular médio.

dos recursos disponíveis e assegurar cuidados de saúde de elevada qualidade. A aplicabilidade transversal desta estratégia em outras especialidades reforça o seu potencial contributo para o aperfeiçoamento global do sistema de saúde em Portugal.

CONTRIBUTO DOS AUTORES

SV: Desenho do estudo, colheita e interpretação de dados, escrita do manuscrito.

TP: Desenho do estudo, colheita e interpretação de dados.

SB, PK, RM: Desenho do estudo, interpretação de dados, revisão crítica do manuscrito.

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PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Ramsay Hunt Syndrome: Clinical Presentation, Diagnostic Challenges, and Treatment Efficacy

Síndrome de Ramsay Hunt: Apresentação Clínica, Desafios Diagnósticos e Eficácia do Tratamento

Keywords: Herpes Zoster Oticus/diagnostic imaging; Magnetic Resonance Imaging; Tomography, X-Ray Computed
Palavras-chave: Herpes Zóster Ótico/diagnóstico por imagem; Ressonância Magnética; Tomografia Computorizada

Dear Editor,

Ramsay Hunt syndrome (RHS), first described by James Ramsay Hunt in 1907, is a rare condition caused by the varicella zoster virus,[1,2] affecting approximately five in 100 000 individuals, typically aged 20 - 30, with no sex differences.[3] It involves the facial and vestibulocochlear nerves due to their proximity, leading to symptoms such as facial paralysis, ear pain, herpes vesicles, and occasionally vertigo, nausea, or nystagmus. Compared to Bell's palsy, RHS often presents with more severe paralysis and delayed rash onset in 14% of cases, complicating diagnosis.[1]

We present the case of a 73-year-old man with a 15-day history of right-sided facial muscle weakness, intense right ear pain, and vesicular eruptions in the external auditory canal and auricle. He had a medical history of diabetes *mellitus*. Physical examination revealed loss of right frontal sulci, difficulty closing the right eye, and mouth deviation to the left. A computed tomography scan revealed an inflammatory process in the tympanic membrane on the right side. A magnetic resonance imaging (MRI) scan detected an inflammatory neuropathy of the right VII cranial nerve (facial nerve) within the internal auditory canal, along with right sided otomastoidopathy and inflammatory changes in the external auditory canal and auricle on the right. Polymerase chain reaction (PCR) detected the varicella zoster virus, confirming RHS. The patient was treated with oral prednisone (1 mg/kg/day for five days, tapered over 10 days), oral acyclovir (800 mg five times daily for seven days), and facial rehabilitation. He showed improvement within 10 days and was symptom-free six months later.

The histopathology of RHS varies with its progression. Post-mortem studies show necrosis of the dorsal ganglion branches in acute cases, while chronic cases reveal fibrosis in the vestibular ganglia.[1] A diagnosis of Ramsay Hunt syndrome relies on clinical history, physical examination, and supportive imaging.[1] While MRI can identify nerve inflammation,[4,5] PCR offers higher sensitivity when using mononuclear blood cells, as demonstrated in the presented case, or samples from the geniculate area.[1] Short-term complications of RHS include corneal abrasions, exposure keratopathy, depression, social anxiety, and the potential spread of chickenpox to unvaccinated or immunocompromised individuals. Long-term complications, such as synkinesis (involuntary contractions), postherpetic neuralgia, vesicular scarring, and persistent psychological effects, are possible but were absent in this case. Treatment typically involves antiviral therapy, with acyclovir being the primary agent. Combining antivirals with steroids has shown better outcomes in improving facial control (70.5%) compared to antiviral monotherapy (68%).[3]

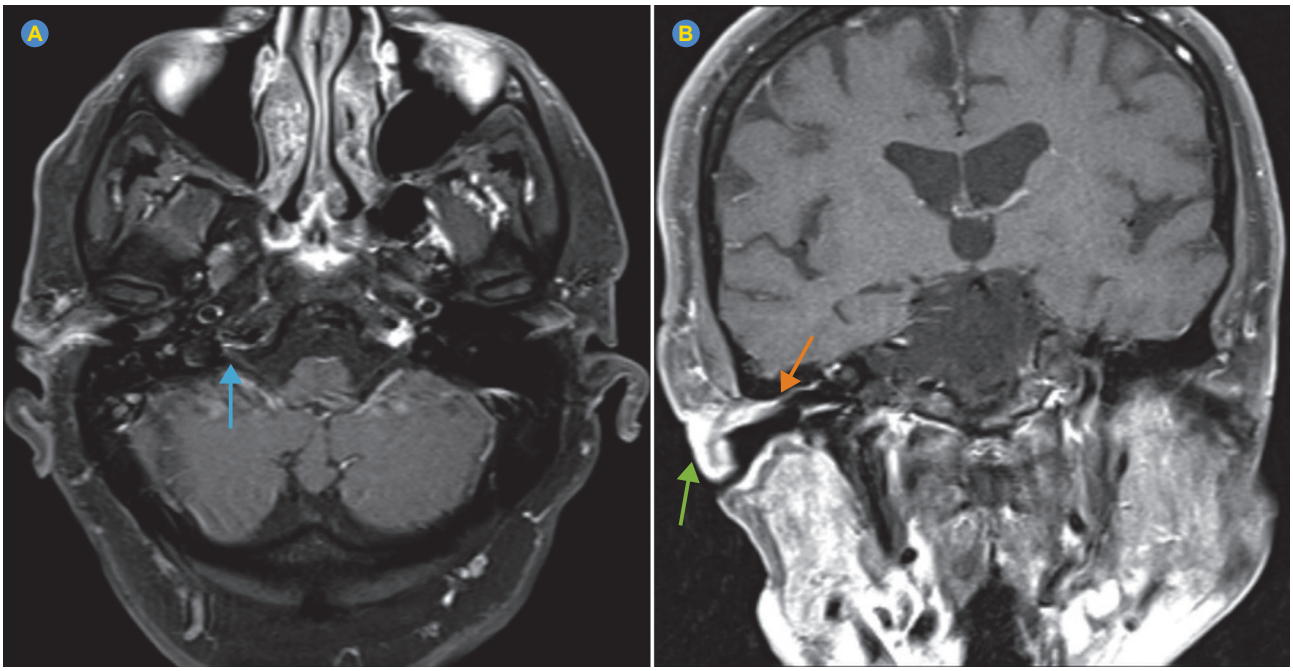

Figure 1 – Magnetic resonance imaging T1 post-contrast sequence in axial section (A) and coronal section (B) demonstrating focal enhancement of the canalicular right facial-vestibulocochlear nerve complex (blue arrow) and an avid enhancement of the right external auditory canal (orange arrow) and external ear/ pinna (green arrow)

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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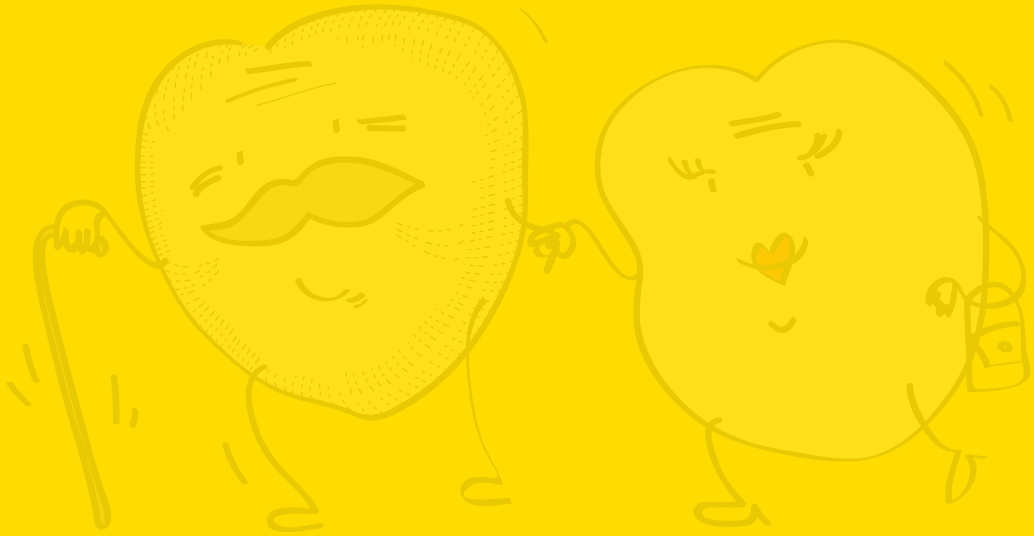

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