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Dar Voz aos Pais em Cuidados Intensivos Neonatais

Giving Voice to Parents in Neonatal Intensive Care

Maria Teresa DIONÍSIO [1], Ana FERRAZ [2], Alexandra DINIS [1]
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Palavras-chave: Comunicação; Pais; Relações Profissional-Família; Unidades de Cuidados Intensivos Neonatais
Keywords: Communication; Intensive Care Units, Neonatal; Parents; Professional-Family Relations

A comunicação entre os profissionais de saúde e as famílias é um pilar fundamental dos cuidados intensivos neonatais e pediátricos. Em contextos de grande complexidade emocional e clínica, como nas unidades de cuidados intensivos, os pais encontram-se particularmente vulneráveis e têm uma necessidade acrescida de informação clara, apoio emocional e participação ativa nas decisões sobre os cuidados dos seus filhos. A qualidade desta comunicação influencia diretamente a experiência parental, a relação estabelecida com a equipa e, potencialmente, os próprios desfechos clínicos, como já demonstrado em diversos estudos.[1,2]

Nas últimas décadas, os avanços tecnológicos e científicos nos cuidados intensivos neonatais e pediátricos transformaram radicalmente o cuidado prestado aos doentes críticos. Contudo, este progresso nem sempre foi acompanhado pelo desenvolvimento de políticas públicas e organização de cuidados que promovam cuidados centrados na família. Nos últimos anos, tem aumentado a consciencialização para a importância de avaliar a parentalidade em cuidados intensivos como parte integrante da atividade assistencial. Para que esta prática seja implementada de forma eficaz, é fundamental dispor de instrumentos de avaliação válidos, sensíveis ao contexto clínico e devidamente adaptados do ponto de vista linguístico e cultural.

Em Portugal, apesar dos questionários de satisfação parental e comunicação traduzidos e validados em português estarem a surgir agora, ainda se verifica uma lacuna entre a política instituída e a prática quotidiana. A escassez de vagas, a sobrecarga dos profissionais, a fragmentação da rede de atenção e a desigualdade regional, agravadas pela entrada de imigrantes ou migrantes cuja língua materna não é o português, e pelo turismo de saúde, ampliam ainda mais os desafios comunicacionais. Assim, torna-se urgente que as políticas de saúde incluam, de forma clara e operacional, diretrizes voltadas à comunicação efetiva e empática nos cuidados intensivos neonatais e pediátricos.

O artigo de Melo Parente *et al* agora publicado na Acta Médica Portuguesa, que apresenta a tradução e validação do questionário *Parents' Experiences of Communication in Neonatal Care* (PEC) para a população portuguesa, representa um contributo relevante nesta área.[3] O PEC é um instrumento conciso, desenvolvido no Reino Unido com o objetivo de medir especificamente a perceção dos pais relativamente à comunicação com os profissionais durante o internamento no período neonatal. Este trabalho surge, à semelhança de outros esforços realizados em Portugal, para medir a experiência parental de forma estruturada, nomeadamente a tradução e validação do *EMpowerment of PArents in THe Intensive Care*, na versão para a Neonatologia (EMPATHIC-N)[4] e na versão pediátrica (EMPATHIC-30).[5] O EMPATHIC-N avalia múltiplas dimensões da experiência dos pais - desde a comunicação e participação dos pais, até à organização, cuidados prestados e profissionalismo. O PEC, por sua vez, tem uma natureza mais dirigida à experiência da comunicação, com uma estrutura simples composta por 28 questões. Esta especificidade pode ser particularmente útil em contextos onde se pretende monitorizar ou melhorar de forma dirigida as práticas comunicacionais, por exemplo, no âmbito de um projeto de melhoria da qualidade. A sua brevidade favorece a aplicação sistemática em unidades com recursos limitados ou com maior rotatividade de doentes.

Ao serem validados para a população portuguesa, passam a estar disponíveis dois instrumentos com finalidades complementares para o período neonatal: um de carácter mais global (EMPATHIC-N), e outro de natureza específica e operacional (PEC). A escolha entre um e outro deverá ser orientada pelos objetivos da avaliação e pelos recursos disponíveis. Um terceiro questionário, o EMPATHIC-30, ficará no futuro disponível para a faixa etária pediátrica.

Medidas de incorporação de protocolos de comunicação, tais como reuniões familiares regulares e frequentes, uso de linguagem acessível e questionários de satisfação devem integrar as diretrizes nacionais de abordagem ao doente crítico e não devem ficar apenas no domínio da investigação. Os países que investiram em políticas públicas voltadas para a comunicação em cuidados intensivos,

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nomeadamente o Reino Unido e os Estados Unidos da América, registaram melhores desfechos clínicos, menor tempo de internamento e maior satisfação das famílias, além da valorização do trabalho multiprofissional.[6,7] A disseminação destes instrumentos pelas equipas de Neonatologia é um passo crucial para garantir cuidados mais humanos, participativos e centrados nas necessidades das famílias.

A validação do PEC em Portugal representa um passo importante no compromisso com a qualidade dos cuidados intensivos neonatais. Dar voz aos pais não é apenas um gesto de cortesia, é uma exigência ética e clínica num sistema de saúde que se quer centrado nas pessoas. Falar de comunicação em cuidados intensivos é, acima de tudo, falar de boas práticas clínicas, pelo que toda a política de saúde que se pretenda justa deve priorizar este tema.

CONTRIBUTO DOS AUTORES

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AF desempenha funções de liderança ou fiduciárias, remuneradas ou não remuneradas, na Sociedade Portuguesa de Neonatologia.

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Remote Consultations in Clinical Practice: A Review of Modalities and Current Challenges

Consultas Remotas na Prática Clínica: Uma Revisão das Modalidades e Desafios Atuais

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Keywords: Delivery of Health Care; Remote Consultation
Palavras-chave: Consulta Remota; Prestação de Cuidados de Saúde

Remote consultations have emerged as a critical component of healthcare delivery, particularly during the COVID-19 pandemic. While telemedicine has been around for decades, the global health crisis accelerated its adoption, pushing remote consultations from a convenient option to an essential practice. As we transition into a post-pandemic world, remote consultations are not merely a temporary measure but a fundamental shift in delivering care in an increasingly digital landscape. At its core, a remote consultation is an interaction between healthcare professionals and patients facilitated by technology, where physical presence is not required. These consultations can be conducted through various modalities, including text, audio, video, and combinations of these mediums. Understanding these classifications is crucial for optimizing their use in clinical practice and guiding innovation.

Text-based consultations, for instance, involve communication through messages that can be synchronous, such as real-time chat, or asynchronous, like emails or messaging platforms. While this method may be limited by the absence of visual and auditory cues, it provides a practical solution for follow-up care, medication adjustments, and addressing patient queries in areas with limited access to high-speed internet. For example, Eriksson *et al*[1] observed that text-based consultation improved access for patients needing frequent appointments and those with mental health problems, where efficiency gains among patients with simple cases were also noted. Moreover, recent advancements in artificial intelligence, particularly chatbots and large language models, have expanded the potential of text-based consultations by enabling automated patient triage, personalized health guidance, and real-time symptom assessment, improving accessibility and efficiency in remote healthcare settings. Audio-based consultations, typically conducted over the phone or through voice messaging apps, offer a more nuanced interaction by incorporating tone and inflection, which can convey important emotional and clinical information. Recently,[2] telephone-based consultations for adjuvant endocrine therapy (AET) were perceived as a promising strategy. The study concluded that nurse-led telephone-based motivational interviewing-guided consultations about AET were found to respond to participants' needs and enhance their perceptions of being informed and supported. On the other hand, video-based consultations closely mimic in-person visits by allowing real-time visual and auditory interaction. This modality has proven particularly effective in primary care, mental health, and specialties where visual cues, patient behavior, and non-verbal communication are critical to diagnosis and treatment. For instance, Steenbergen *et al*[3] designed a video-based eHealth program to reduce unplanned healthcare in the first six weeks after coronary artery bypass graft surgery. The strategy, comprising educational videos and video consultations, reduced unplanned healthcare use and hastened patient-reported recovery. Other emerging technologies, such as robotic-assisted telemedicine, biochemical remote diagnostics using portable biosensors, and Internet-of-Things-based health-monitoring devices (that enable remote monitoring of various health metrics, facilitating proactive and personalized care), also hold significant potential to enhance the accuracy and scope of remote consultations. These innovative solutions enable real-time patient monitoring, remote collection of biochemical markers, and even robotic-supported procedures, thus expanding clinical capabilities beyond traditional telemedicine limits (Table 1).

Combined modalities, which use a mix of text, audio, video, and images, represent the most comprehensive form of remote consultations. Nonetheless, regardless of the modalities, the rapid adoption of remote consultations has enhanced their potential to address several longstanding challenges in healthcare. One of the most significant advantages of remote consultations is their ability to improve access to care by transcending geographical barriers. For patients in rural or underserved areas, where healthcare

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Table 1 – Comparison of remote consultation emerging technologies: key characteristics, advantages, and limitations

	Key characteristics	Advantages	Limitations
Text-Based	Synchronous (chat) or asynchronous (emails, messaging)	High accessibility; suitable for follow-ups and simple queries	Lacks visual/auditory cues; risk of misinterpretation
Audio-Based	Telephone or voice messaging	Captures tone and emotional cues; effective for motivational interviewing	No visual assessment; limited contextual understanding
Video-Based	Live video interaction	Mimics in-person visits; allows visual and non-verbal communication	Requires stable internet; privacy concerns
Robotic-Assisted Telemedicine	Remote-controlled robotic systems for patient interaction	Enables presence in remote locations; useful in ICUs and surgical settings	High cost; requires trained personnel
Biochemical Remote Diagnostics	Portable biosensors for real-time biochemical marker analysis	Enables presence in remote locations; useful in ICUs and surgical settings	High cost; requires trained personnel
IoT-Based Health Monitoring	Wearable health devices and smart sensors	Enables continuous monitoring; real-time alerts for health deterioration	Data privacy concerns; accuracy variability

facilities are sparse, and specialists are few and far between, remote consultations offer a vital opportunity to receive timely medical advice, follow-up care, and specialist consultations without the need to travel long distances, which can be both costly and logistically challenging. Additionally, remote consultations are crucial in ensuring continuity of care, particularly in managing chronic conditions where regular monitoring and prompt intervention are essential. During the pandemic, routine care for chronic conditions,[4,5] post-operative follow-ups,[6] and mental health support[7] continued seamlessly through remote channels, highlighting the importance of these consultations in maintaining patient care even when in-person visits were impossible. Moreover, remote consultations offer unparalleled flexibility and convenience for patients and healthcare providers. Patients can schedule appointments around their daily lives without the need to take time off work or arrange childcare. For healthcare providers, remote consultations allow more flexible work hours and the ability to manage patient loads more efficiently. This flexibility enhances patient satisfaction and allows healthcare professionals to optimize their practice to accommodate their needs and those of their patients.

However, despite their numerous advantages, remote consultations are not without significant challenges.[8] Technological barriers remain critical, particularly in regions with limited internet connectivity or populations with reduced digital literacy. The lack of digital literacy substantially limits patient autonomy, frequently necessitating reliance on family members or caregivers to facilitate consultations, potentially compromising confidentiality. Furthermore, inadequate internet infrastructure may intensify healthcare inequalities, especially in rural or underserved areas, disproportionately affecting socio-economically vulnerable populations. Targeted policy interventions, including subsidies for internet access, provision of affordable telemedicine-compatible devices, and structured digital literacy programs, are essential to ensure equitable telemedicine access. Healthcare professionals also face considerable obstacles, including difficulties acquiring, implementing, and efficiently using telemedicine technologies in daily practice. Insufficient training and technical support can reduce provider efficiency, potentially causing frustration and negatively impacting patient outcomes and professional satisfaction. Additionally, the absence of a physical examination component poses risks of misdiagnosis or overlooked conditions. Although the careful integration of patient-shared multimedia tools, such as images and videos, and peripheral monitoring devices (e.g., home blood pressure monitors or glucometers), may partly mitigate these concerns, their effectiveness remains reliant on sufficient digital literacy and infrastructure availability.[9,10] Addressing these barriers requires targeted interventions, including improved patient and provider digital literacy, investments in technological infrastructure, policy support for equitable access, and comprehensive telemedicine training. Effective integration of remote consultations requires structured professional training and addressing usability challenges healthcare providers face.

Looking to the future, remote consultations have the potential to serve as a valuable complement within healthcare delivery, thoughtfully integrated alongside traditional face-to-face consultations rather than supplanting them. Emerging technological advancements, including artificial intelligence for patient triage, enhanced medical imaging analysis, biosensors, wearable health devices, and

interoperable healthcare platforms, could significantly enrich the capabilities of remote consultations. However, deploying these benefits requires carefully addressing barriers such as disparities in digital literacy, infrastructural limitations, confidentiality concerns, and ensuring comprehensive training for healthcare providers. It is essential to pursue structured educational initiatives, targeted policy measures, and strategic infrastructure investments, all specifically aimed at fostering equitable and optimal use of telemedicine. Rather than viewing remote consultations as an inevitable replacement, healthcare systems should strategically deploy them where they can most effectively enhance patient care. Ultimately, this balanced approach will strengthen healthcare delivery, making it more accessible, equitable, patient-centered, and efficient, while preserving and respecting the indispensable role of in-person clinical interactions.

COMPETING INTERESTS

The author have declared that no competing interests exist.

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Treatment of Locally Advanced and Metastatic Salivary Gland Cancer: A 10-year Experience of an Oncology Center in Portugal

Tratamento de Neoplasias das Glândulas Salivares Metastizadas ou Localmente Avançadas: Experiência de 10 Anos de um Centro Oncológico em Portugal

Ana Raquel TEIXEIRA [1], Cláudia AGOSTINHO [1], Catarina DIAS [1], Rita SOARES [1], Marta PINA [1], José DINIS [1,2], Luísa LOPES-CONCEIÇÃO [3,4,5], Cláudia VIEIRA [1,2]
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ABSTRACT

Introduction: Scientific evidence regarding salivary gland cancer systemic treatment is limited and the therapeutic approach to locally advanced or metastatic disease is mainly based on consensus. This study aimed to evaluate treatment patterns and outcomes in patients with advanced salivary gland cancer.

Methods: We conducted a retrospective cohort study in a comprehensive cancer center in Portugal, including adult patients diagnosed with primary malignant salivary gland tumors between 2012 and 2021. Data on demographics, tumor characteristics, treatments, and outcomes were collected from institutional cancer registries and electronic medical records. The study was approved by the institutional Ethics Committee.

Results: A total of 116 patients with salivary gland cancer were identified and, of these, 45 had locally advanced or metastatic disease: 24 received systemic anti-neoplastic treatment and 21 received best supportive care. One-year overall survival in systemic anti-neoplastic treatment group was 70% (*versus* 14% in best supportive care group, $p < 0.001$) and progression-free survival was 37%. The most commonly used systemic treatment was chemotherapy (n = 29, 59%). Seven patients (14%) received androgen deprivation therapy, and two patients (4%) received other targeted therapy (olaparib and erdafitinib).

Conclusion: Systemic treatment was associated with significantly improved survival in patients with advanced salivary gland cancer. Despite the heterogeneity of therapeutic approaches, including emerging biomarker-driven therapies, clinical decision-making remains largely consensus-based. These findings underscore the need for further research to support personalized treatment strategies and guide evidence-based care.

Keywords: Molecular Targeted Therapy; Salivary Gland Neoplasms/drug therapy

RESUMO

Introdução: A evidência científica relativa ao tratamento sistémico das neoplasias das glândulas salivares é limitada e a abordagem terapêutica da doença localmente avançada ou metastática baseia-se principalmente em consensos. O objetivo deste estudo foi avaliar os padrões de tratamento e os desfechos em doentes com carcinoma das glândulas salivares avançado.

Métodos: Realizámos um estudo de coorte retrospetivo num centro oncológico em Portugal, incluindo doentes adultos diagnosticados com tumores malignos primários das glândulas salivares entre 2012 e 2021. Os dados demográficos, as caraterísticas do tumor, os tratamentos e os resultados foram recolhidos a partir dos registos oncológicos institucionais e dos registos médicos eletrónicos. O estudo foi aprovado pela Comissão de Ética institucional.

Resultados: Foi identificado um total de 116 pacientes com neoplasias das glândulas salivares e, desses, 45 tinham doença localmente avançada ou metastática: 24 receberam tratamento antineoplásico sistémico e 21 receberam os melhores cuidados de suporte. A sobrevivência global a um ano no grupo que recebeu tratamento antineoplásico sistémico foi 70% (*versus* 14% no grupo que recebeu os melhores cuidados de suporte, $p < 0,001$) e a sobrevivência livre de progressão foi 37%. O tratamento sistémico mais frequentemente utilizado foi a quimioterapia (n = 29, 59%). Sete doentes (14%) receberam terapia de privação de androgénios e dois doentes (4%) receberam outra terapêutica dirigida (olaparib e erdafitinib).

Conclusão: O tratamento sistémico foi associado a uma melhoria significativa da sobrevivência em doentes com cancro avançado das glândulas salivares. Apesar da heterogeneidade das abordagens terapêuticas, incluindo as terapias baseadas em biomarcadores, a tomada de decisões clínicas continua a ser largamente baseada em consensos. Estes resultados sublinham a necessidade de mais investigação para apoiar estratégias de tratamento personalizadas e orientar os cuidados baseados na evidência.

Palavras-chave: Neoplasias das Glândulas Salivares/tratamento farmacológico; Terapia-Alvo

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KEY MESSAGES

- Significant overall survival benefit with systemic treatment: Patients with locally advanced or metastatic salivary gland cancer (SGC) who received systemic anti-neoplastic treatment had a one-year overall survival rate of 70%, compared to only 14% in those receiving best supportive care ($p < 0.001$).
- Diversity of systemic therapies employed: The study confirmed the variety of systemic treatments used, with chemotherapy being the most common (59%), followed by androgen deprivation therapy (14%) and emerging targeted therapies such as olaparib and erdafitinib.
- Emerging role of agnostic targeted therapies: The use of agnostic targeted therapies, although limited, demonstrates the potential of biomarker-driven approaches to improve outcomes in selected patient subgroups.
- Scarce evidence guiding clinical practice: The therapeutic approach to advanced SGC remains largely consensus-based, highlighting the need for further research.
- Foundation for future investigations: This study provides important data to explore personalized therapeutic strategies, including biomarker-driven treatments, and to develop more comprehensive clinical guidelines for this rare and heterogeneous cancer population.

INTRODUCTION

Primary salivary gland tumors are a very heterogeneous entity, making their classification challenging.[1,2] The fifth edition of the World Health Organization (WHO) classification, introduced in 2022, identifies 39 salivary gland conditions grouped into four categories: non-neoplastic epithelial lesions, malignant and benign epithelial tumors and mesenchymal tumors specific to the salivary glands.[2,3] Approximately 20% of all salivary glands lesions are malignant and include 21 histologically subtypes.[1-3] This diversity results in distinct biological behaviors, influencing different treatment decisions and prognosis.[4]

Salivary gland cancers (SGC) are rare malignancies and account for 5% of all head and neck cancers.[4] They typically occur in the sixth and seventh decade of life.[5] Risk factors include history of prior head and neck cancer and cervicofacial radiotherapy (RT), industrial activity and smoking.[5] Nevertheless, only ionizing radiation is a well-established risk factor.[5] Globally, the estimated age-standardized incidence rate was 0.56 cases per 100 000, with 55 083 new cases in 2022.[6] Most SGCs are located in major salivary glands (parotid gland around 70%, submandibular gland 10% and sublingual gland < 1%).[1]

Surgery is the preferred treatment for localized SGC, with post-operative RT recommended in advanced stages.[5,7] Patients with locally advanced or metastatic (LAM) disease may receive systemic treatment, although evidence remains limited due to the rarity and heterogeneity of SGC.[5,7] Molecular profiling - using immunohistochemistry (IHC) and next-generation sequencing (NGS) - has helped identify LAM SGC patients who might benefit from targeted therapies.[8-10] Metastatic SGC is associated with a poor prognosis, with a median overall survival (OS) of 15 months and a 1-year OS of 54.5% across all subtypes.[5] For all these reasons, a multidisciplinary approach is recommended.[7]

The aim of this study was to review clinicopathologic characteristics, treatment and outcomes of a cohort of patients with major SGCs and LAM disease, treated at our comprehensive cancer center over 10 years.

METHODS

Setting and population

IPO-Porto is a highly differentiated institute, belonging to the Portuguese National Health Service and which provides specialized cancer care. It is a comprehensive cancer center, admitting around ten thousand new patients annually and providing healthcare to 50 thousand patients covering the entire cancer continuum, from diagnosis to treatment and follow-up.[11]

Study design and data collection

We identified a retrospective cohort of adult patients (age ≥ 18 years) diagnosed between 2012 and 2021 with primary malignant of major salivary gland tumors (topography codes C07-C08, according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems ICD-10) and any histology code from the International Classification of Diseases for Oncology ICD-O-3, except sarcomas).[12,13] Patients who participated in clinical trials were excluded from the study.

Information on demographics (sex and age), cancer (ICD-10 code, site, histological type and stage) and treatment (type, duration and response) characteristics was retrieved from the IPO-Porto Cancer Registry database and enhanced by reviewing electronic medical records (EMRs), specifically for information about the treatment response and disease progression from early stages. Vital status and date of death were assessed through the National Health Service database until 30 June 2024, allowing for a

minimum follow-up of 30 months since cancer diagnosis.

Statistical analyses

Sociodemographic, clinical and treatment characteristics are presented as counts and proportions and compared using the Chi-square test or Fisher exact test (whichever was appropriate), for categorical variables, or as median and percentiles 25 and 75 (P25 - P75) and compared using Mann-Whitney test, for continuous variables.

Overall survival (OS) was defined as the time between the date of diagnosis of LAM disease and the date of death due to any cause or to the date of censoring at the last time the subject was known to be alive. Progression-free survival (PFS) was defined as the time between the systemic treatment initiation with palliative-intent and the date of disease progression or death, whichever occurred first, and was censored at the last contact date for patients who neither have progression nor died. Survival curves were plotted using the Kaplan-Meier estimator and were compared using the log-rank test.

All analyses were performed using R version 4.1.2® (R Core Team, Vienna, Austria). Results were considered statistically significant for *p*-values less than 0.05.

Ethics

This study was approved by the local Ethics Committee of the IPO-Porto (code 101/2044). The need for patient informed consent was waived as the data comprised no unique personal identifiers and were extracted from the IPO-Porto Cancer Registry database and EMRs, and due to the retrospective nature of the study.

RESULTS

Patients and tumor characteristics

We identified 116 patients with major SGC treated in our center. Table 1 summarizes the main demographic, clinical, and treatment characteristics. The median age at diagnosis was 66 years, with seven patients (6%) under 40 years. The most common histologies were salivary duct carcinoma (n = 20, 17%), mucoepidermoid carcinoma (n = 18, 16%) and adenoid cystic carcinoma (n = 17, 15%). The parotid gland was the most frequent primary site (n = 95, 82%). Most patients (n = 93, 80%) received at least one curative-intent treatment, primarily surgery (n = 90, 78%), followed by adjuvant RT in 58 cases (50%) and adjuvant chemoradiotherapy (CRT) in six cases (5%). Adjuvant CRT was delivered in patients with advanced disease (pathological stage III-IVB). Among these, four (3%) presented perineural invasion, three (3%) presented lymphovascular invasion and two (2%) had positive surgical margins.

Disease recurrence occurred in 30 patients (26%): 12 (10%) had local recurrence, 22 (19%) had distant recurrence, and four (3%) experienced both.

Treatment group and outcomes

Among the 116 patients, 45 (39%) had LAM SGC, including 21 identified after disease recurrence [Appendix

Table 1 – Demographic and clinical characteristics of the overall population

	Overall (n = 116)
Age at diagnosis (years), **median** (P25 - P75)	66 (54 - 74)
Sex, n (%)	
Male	63 (54)
Female	53 (46)
Stage at diagnosis*, n (%)	
I	21 (18)
II	27 (23)
III	26 (22)
IVA	22 (19)
IVB	6 (5)
IVC	14 (12)
Primary tumor site, n (%)	
Parotid gland	95 (82)
Submandibular gland	20 (17)
Sublingual gland	1 (1)
Tumor histology, n (%)	
Salivary duct carcinoma	20 (17)
Mucoepidermoid carcinoma	18 (16)
Adenoid cystic carcinoma	17 (15)
Carcinoma, NOS	13 (11)
Squamous cell neoplasm	13 (11)
Acinar cell carcinoma	10 (9)
Adenocarcinoma, NOS	6 (5)
Epithelial-myoepithelial carcinoma	5 (4)
Small cell neuroendocrine carcinoma	4 (3)
Basal cell adenocarcinoma	3 (3)
Oncocytic carcinoma	3 (3)
Others	4 (3)
Curative-intent therapy, n (%)	
Yes	93 (80)
No	23 (20)
Recurrence (local and/or distant), n (%)	
Yes	30 (26)
No	86 (74)

NOS: not otherwise specified; P25: percentile 25; P75: percentile 75.
*: According to AJCC 8th Edition

1, Fig. 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Of these, 21 (47%) received only best supportive care (BSC group) and 24 (53%) received systemic treatment (ST group). Table 2 summarizes the main demographic, clinical, and treatment characteristics of both groups.

Significant differences were observed between the groups in terms of age, prior curative-intent treatment, and recurrence. Patients in the ST group patients were younger, more likely to have received prior treatment with curative intent and had a higher recurrence rate compared to those in the BSC group (p = 0.001, p = 0.024 and p = 0.011, respectively).

In the BSC group, the most common histologies were carcinoma not otherwise specified (NOS) and adenocarcinoma NOS (both n = 5, 24%). In the ST group, salivary duct carcinoma was the most frequent (n = 9, 38%). In both groups, the parotid gland was the most common primary site – 16 patients (76%) in the BSC group and 21 (88%) in the ST group.

By the end of follow-up, 20 deaths (83%) were recorded in the ST group and all 21 patients (100%) in the BSC

Table 2 – Comparison of demographic and clinical characteristics of patients with locally advanced or metastatic disease and receiving systemic therapy or best supportive care

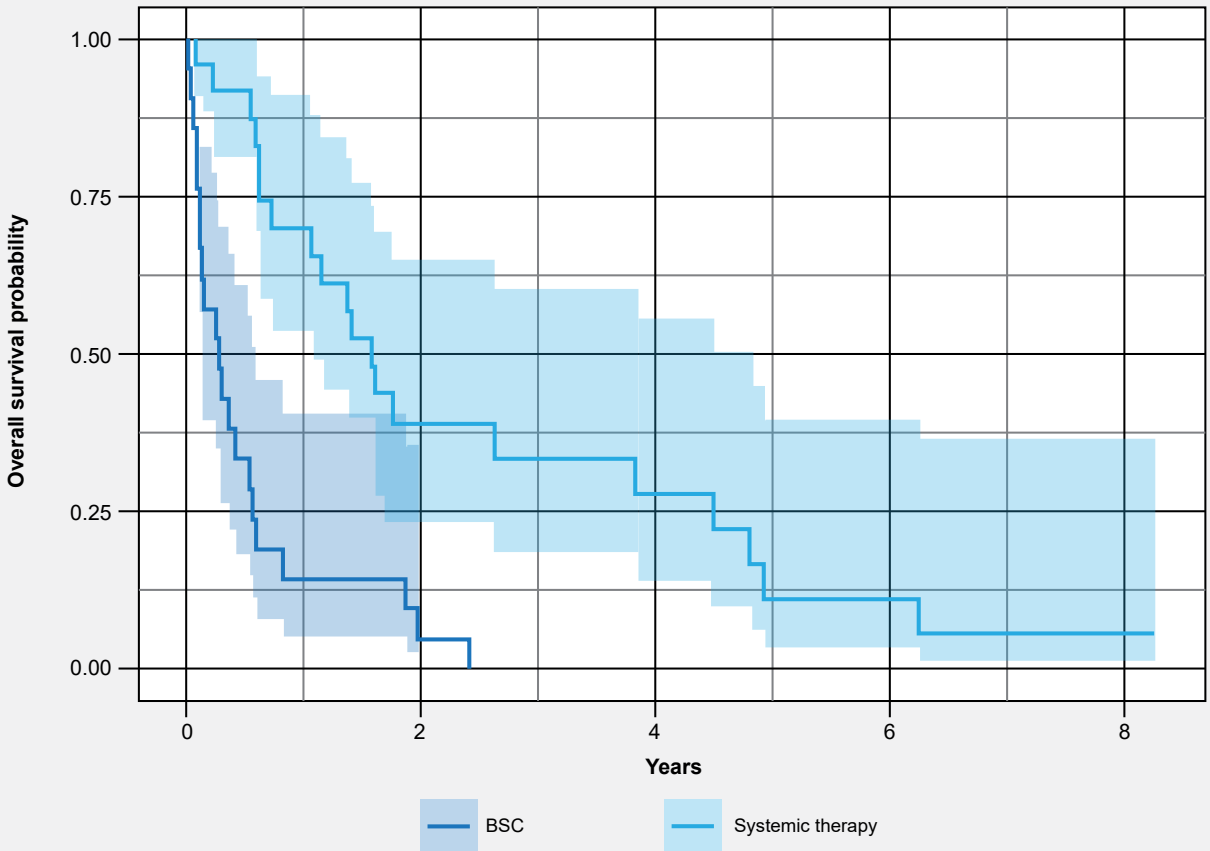
	Best supportive care (n = 21)	Systemic therapy (n = 24)	*p*-value
Age at diagnosis (years), **median** (IQR)	79 (66 - 87)	66 (56 - 71)	< 0.001
Sex, n (%)			
Male	11 (52)	17 (71)	0.334
Female	10 (48)	7 (29)	
Cancer stage at diagnosis*, n (%)			
II	1 (5)	1 (4)	0.725
III	4 (19)	5 (21)	
IVA	5 (24)	10 (42)	
IVB	3 (14)	2 (8)	
IVC	8 (38)	6 (25)	
Primary tumor site, n (%)			
Parotid gland	16 (76)	21 (88)	0.250
Submandibular gland	5 (24)	2 (8)	
Sublingual gland	0 (0)	1 (4)	
Tumor histology, n (%)			
Carcinoma, NOS	5 (24)	5 (21)	0.274
Adenocarcinoma, NOS	5 (24)	1 (4)	
Salivary duct carcinoma	4 (19)	9 (38)	
Squamous cell neoplasm	3 (14)	2 (8)	
Small cell neuroendocrine carcinoma	2 (10)	2 (8)	
Mucoepidermoid carcinoma	1 (5)	1 (4)	
Adenoid cystic carcinoma	0 (0)	3 (12)	
Acinar cell carcinoma	0 (0)	1 (4)	
Others	1 (5)	0 (0)	
Prior curative-intent treatment, n (%)			
Yes	7 (33)	18 (75)	0.012
No	14 (67)	6 (25)	
Recurrence, n (%)			
Yes	6 (29)	17 (71)	0.011
No	15 (71)	7 (29)	

NOS: not otherwise specified; P25: percentile 25; P75: percentile 75.
*: According to AJCC 8th Edition

group had died. Figure 1 shows a higher one-year overall survival (OS) in the ST group than in the BSC group [70%, 95% confidence interval (95% CI): 53% - 91% *vs* 14% (5% - 41%), $p < 0.001$]. The corresponding age- and stage-adjusted HR (95% CI) for the BSC group was 6.10 (2.54 - 14.67) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Male patients and patients diagnosed with cancer of parotid gland showed a significantly higher mortality [age-and stage-adjusted HR = 5.62 (2.00 - 15.78) and age-and stage-adjusted HR = 5.92 (2.31 - 15.17), respectively]. Absence of prior curative-intent treatment was associated with significantly higher mortality [HR = 9.98 (1.71 - 58.18)], as well as absence of disease recurrence [age-and stage-adjusted HR = 8.12 (1.79 - 36.89)]. Even though some differences in mortality were observed in other subgroups, the estimates did not remain statistically significant following adjustment for age and stage (Table 2).

Systemic treatment and outcomes

In ST group, 22 patients (92%) had metastatic disease and two patients had local recurrence. The most common sites of metastases were the lungs (n = 12, 50%), followed by non-locoregional lymph nodes (n = 10, 42%) and bone (n = 9, 38%) [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Five patients (21%) had metastases in three or more locations [Appendix 1, Table 2 (Appendix 1:



	BSC				
At risk	21	1	0	0	0
Events	0	20	21	21	21
	Systemic therapy				
At risk	24	7	5	2	1
Events	0	14	16	19	20

Figure 1 – Overall survival probability in best supportive care and systemic treatment groups
BSC, best supportive care

https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)].

Immunohistochemistry analyses of androgen receptor (AR) and HER2 were performed in 12 (50%) and 11 (46%) patients, respectively [Appendix 1, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Next-generation sequencing analysis was conducted in 11 patients (46%), identifying targetable mutations in eight patients (33%) [Appendix 1, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Two patients (8%) had a splice site alteration in AR-V7 in the AR gene.

A total of 49 systemic treatments were administered across up to seven lines. The median number of treatment lines was two (interquartile range 1 - 3) and six patients (25%) received at least three lines. Chemotherapy was the most frequently used treatment (n = 39, 80%), with platinum-based regimens preferred (n = 29, 59%) (Table 3). Monotherapy chemotherapy was used in 10 patients (20%). Androgen deprivation therapy (ADT) was chosen in seven patients (14%). Two patients received other targeted therapy: one received olaparib (2%) and another erdafitinib (2%).

Regarding best overall response, four (8%) achieved partial response (PR) and 28 (57%) had stable disease (SD) (Table 3). Eight patients (16%) had disease progression (DP) in the first disease response evaluation.

The one-year progression free survival (PFS) in ST group was 37% (Fig. 2).

DISCUSSION

In this study, we reviewed our 10-year experience in managing SGC. Most patients received upfront curative-intent treatment with surgery, followed or not by RT, in line with current guidelines.[6,7] However, some patients in our cohort received adjuvant concurrent CRT, which is not routinely recommended.[6,7,9] Retrospective data suggest that adjuvant concurrent CRT may improve locoregional control, although its impact on OS remains unclear.[14-17] Clinical trials in this setting are ongoing.[18]

Our recurrence rate (26%) was lower than most reports in the literature, which typically describes rates around 50%.[4,19] However, it aligns with findings from another Portuguese retrospective study, likely due to similarities in patient population and histological subtypes.[20]

In the LAM SGC subgroup, patients in the BSC group were significantly older than those in the ST group, had received prior curative-intent therapy and experienced fewer recurrences. This may reflect a later diagnosis in the BSC group. In addition, older patients usually present greater clinical frailty and more comorbidities, which may limit the initiation of systemic antineoplastic treatment.

Absence of prior curative treatment and absence of recurrence were associated with higher mortality, possibly reflecting more aggressive biological behavior and more advanced disease at diagnosis. Male sex and parotid gland location were also associated with higher mortality, which is consistent with the literature. Male patients are more frequently diagnosed with high-grade tumors and advanced disease, which may partly explain their worse outcomes.[21]

Table 3 – Systemic treatment and response evaluation

	1st LoT	2nd LoT	3rd LoT	≥ 4th LoT	Total
Type of treatment, n (%)					
Carboplatin + paclitaxel	17 (35)	3 (6)	0 (0)	0 (0)	20 (41)
Other platinum-based schemes	6 (12)	2 (4)	0 (0)	1 (2)	9 (18)
ADT	1 (2)	2 (4)	3 (6)	1 (2)	7 (14)
Monotherapy chemotherapy	0 (0)	6 (12)	2 (4)	2 (4)	10 (20)
Olaparib	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
CAPTEM	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Erdafitinib	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)
Total	24 (49)	14 (29)	6 (12)	5 (10)	49 (100)
Best overall response, n (%)					
PR	3 (6)	0 (0)	0 (0)	1 (2)	4 (8)
SD	15 (31)	8 (16)	3 (6)	2 (4)	28 (57)
DP	2 (4)	4 (8)	0 (0)	2 (4)	8 (16)
DCR	18 (37)	8 (16)	3 (6)	3 (6)	32 (65)
N/E	4 (8)	2 (4)	3 (6)	0	9 (18)
Total	24 (49)	14 (29)	6 (12)	5 (10)	49 (100)

ADT: androgen deprivation therapy; CAPTEM: capecitabine and temozolomide; DP: disease progression; DCR: disease control rate (partial response + stable disease); LoT: line of treatment; N/E: not evaluated; PR: partial response; SD: stable disease.

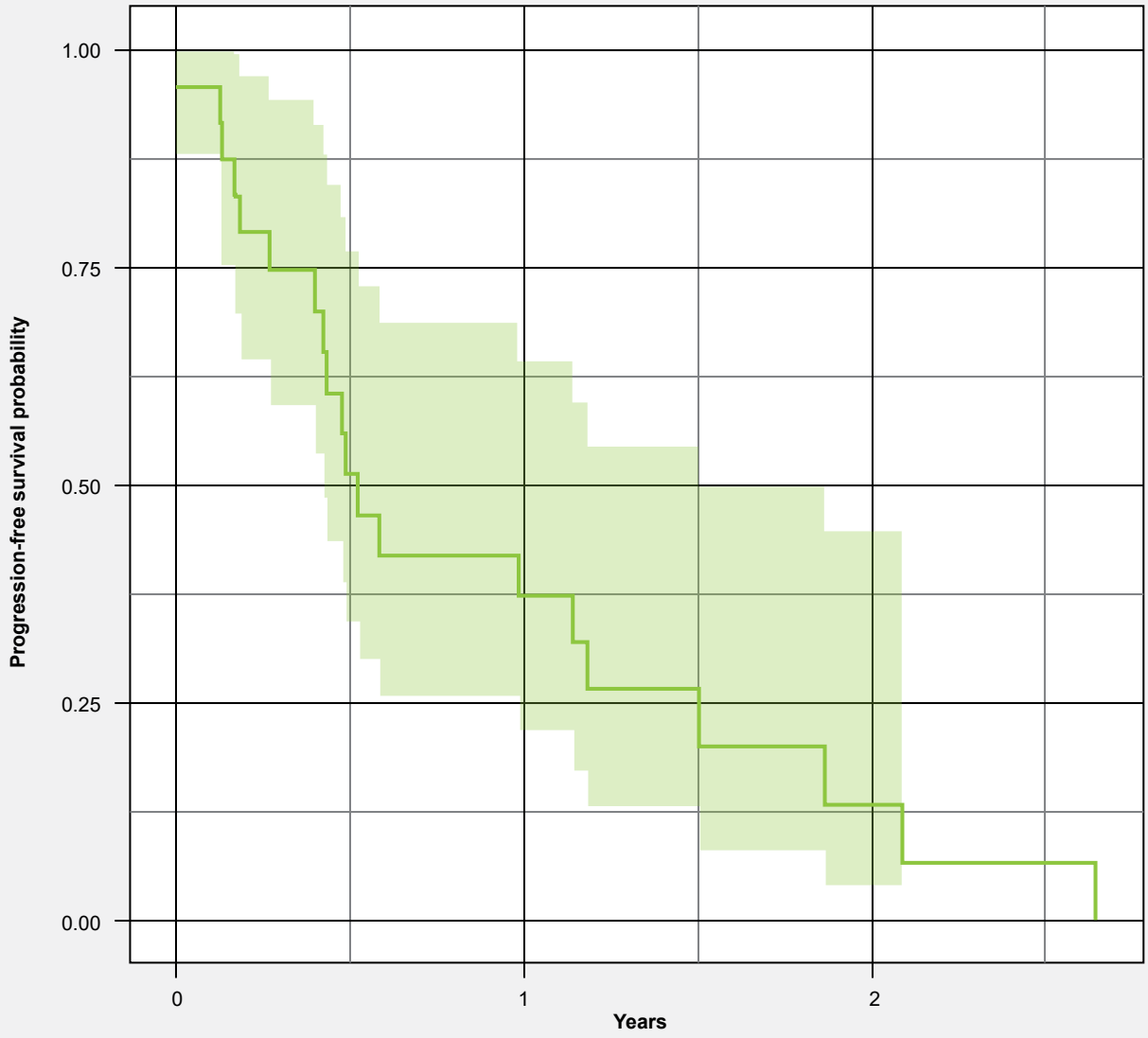


Figure 2 – Progression-free survival probability in systemic treatment group

Additionally, although many parotid tumors are benign, this site can harbor aggressive malignant subtypes such as high-grade mucoepidermoid carcinoma or carcinoma ex pleomorphic adenoma.[22] Nevertheless, the wide confidence intervals observed suggest variability or uncertainty in the estimates, likely due to factors such as small sample size or variability in the data.

Systemic treatment for advanced SGC remains challenging due to the heterogeneity of tumor subtypes and diverse biological behavior.[5] In our cohort, chemotherapy was the most frequent treatment, consistent with expert recommendations and findings from other cohort studies.[5,19] Platinum-based chemotherapy is widely used in this context, with reported objective response rate (ORR) between 27% and 50%.[18,23,24] Common regimens include platinum combined with taxane (docetaxel or paclitaxel), CAP (cyclophosphamide/ doxorubicin/ cisplatin) or platinum combined with vinorelbine, gemcitabine or fluorouracil.[5,18,23,24] Another treatment option is single-agent chemotherapy, as paclitaxel monotherapy, with lower objective response rates (0%

- 20%).[5,18,24] We reported four cases of neuroendocrine carcinoma (NEC), two patients in BSC group and two patients in ST group, both of whom received carboplatin/etoposide. Neuroendocrine carcinoma of the SGC (small or large cell carcinoma) is a rare subtype (1% - 3%) and is associated with aggressive clinical behavior.[25,26] The parotid gland is the most common location, as observed in our cohort, although NEC of the sublingual gland has also been reported.[27]

Evaluation of AR and HER2 status is recommended in advanced SGC, as both represent potential therapeutic targets.[23] Androgen receptor status should be assessed by IHC and HER2 expression by IHC and/or in situ hybridization (ISH).[23] Of note, this information was unavailable for some patients in the ST group, likely due to referral from other centers or insufficient tumor material for analysis. Furthermore, in certain cases, such as neuroendocrine carcinoma, this assessment is not clinically relevant.

For AR-positive tumors, ADT – either with combined androgen blockade (CAB) or antiandrogen monotherapy – is a treatment option in the first-line setting or beyond.[5,18] A phase two study of first-line CAB (bicalutamide and leuprorelin acetate) reported an ORR 42% and a clinical benefit rate of 75%.[28] Following ADT resistance, another phase two study showed benefit in the use of abiraterone/prednisone plus luteinizing hormone releasing hormone (LHRH) analog, with an ORR of 21% and a disease control rate of 63%.[29] To our knowledge, there are no prospective studies comparing ADT versus chemotherapy in first-line setting. However, a retrospective study including 58 patients reported similar overall-survival (OS) with both treatments but higher response rates for ADT.[30]

In HER2-positive SGC, HER2-target therapies are used both in first- or subsequent-line treatment.[18] In the first-line setting, the preferred regimen is trastuzumab combined with a taxane, with an ORR 70% reported for trastuzumab-docetaxel in salivary duct carcinoma.[5,31] Evidence supporting the addition of pertuzumab to this combination remains limited.[23] More recent data suggest that the antibody-drug conjugate T-DM1 may be more effective in this setting, with an ORR of 90%.[5,23] In our cohort, no HER2-positive cases were identified, possibly due to the exclusion of patients enrolled in clinical trials.

In addition to AR and HER2 status, tumor genomic profiling may contribute to a more precise diagnosis and a personalized treatment in LAM SGC.[8,32,33] Up to 50% of patients may present actionable mutations or fusion genes.[5] In our cohort, erdafitinib and olaparib were used as off-label treatment.[34,35] Erdafitinib was used in a case of acinic cell carcinoma harboring FGFR3-TACC3 fusion, who presented disease progression in the first imaging assessment. A 217 patient-phase two study demonstrated the clinical benefit of Erdafitinib in previously treated and advanced solid tumors with FGFR alterations (ORR 30%), which included rare cancers such as SGC (n = 5, 2%).[36] Olaparib was prescribed to a patient with a salivary duct carcinoma and an ATM mutation, who maintained stable disease for nine months. Evidence on the efficacy of PARP inhibitors in ATM-mutated tumors is conflicting. The PROfound clinical trial showed benefit of Olaparib in men with metastatic castration-resistant prostate cancer previously treated and who had alterations in the ATM gene.[37] In the other hand, a tumor-agnostic phase two study demonstrated no efficacy in the ATM cohort but it did not include any patient with SGC.[38]

Our study has some limitations. First, it was conducted at a single comprehensive cancer center in Northern Portugal, which may limit the generalizability of the findings. Additionally, the small number of patients receiving targeted therapies, combined with the heterogeneity of histological subtypes and treatment approaches, restricts the ability to draw definitive conclusions about treatment efficacy. Lastly, molecular testing was not consistently performed across the cohort, potentially underestimating the use of biomarker-driven therapies. Nevertheless, our center is the largest in the country, treating patients from diverse regions and varied sociodemographic backgrounds. Consequently, the findings likely reflect a wider real-world scenario despite these limitations. We suggest prospective studies to validate our results and further explore the efficacy of agnostic therapies in biomarker-selected subgroups.

CONCLUSION

In our cohort, patients who received exclusively BSC were older and less likely to have undergone prior curative-intent therapy. We also confirmed the heterogeneity of systemic treatments for SGC and illustrated the use of agnostic therapeutics in this setting. We believe earlier implementation of NGS in advanced SGC could improve patient outcomes by enabling access to targeted therapies and achieving better clinical responses. Based on our experience, we propose a practical therapeutic algorithm (Fig. 3) to assist clinicians in the initial management of advanced SGC. We recommend the initial evaluation of disease behavior. In cases of stable or indolent disease, surveillance is recommended until progression. For progressive disease, AR and HER2 status should be assessed. Androgen receptor-positive tumors may be treated with androgen deprivation strategies such as aLHRH combined with bicalutamide or abiraterone/prednisolone. HER2-positive tumors are managed with chemotherapy plus trastuzumab or T-DM1. For tumors AR- and HER2-negative, comprehensive tumor genetic profiling should be performed and treatment should be guided accordingly. In the absence of targetable mutations, chemotherapy remains the standard treatment option.

Given the rarity and heterogeneity of these tumors, collaborative national or multicenter registries are essential to generate robust, generalizable data. Furthermore, multidisciplinary tumor boards play a critical role in interpreting molecular results and guiding personalized treatment strategies.

Prospective studies are needed to validate our findings and further explore the efficacy of agnostic therapies in biomarker-selected subgroups.

AUTHOR CONTRIBUTIONS

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

CA, CD, RS, MP, JD, CV: Study design and critical

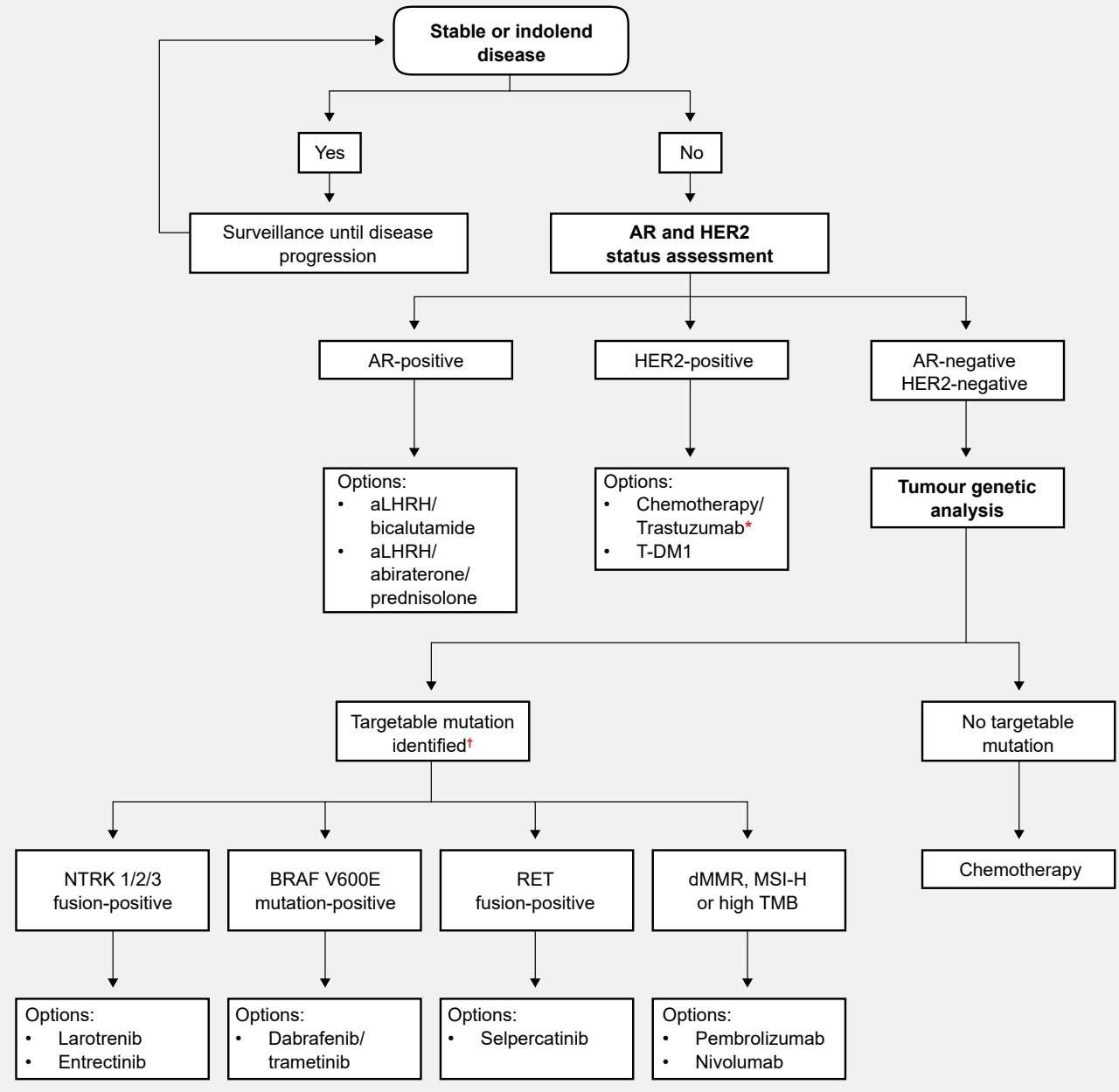


Figure 3 – Suggested systemic therapy algorithm of locally advanced or metastatic salivary gland cancers, based on our experience
AR: androgen receptor; dMMR: mismatch repair deficient; HER2: human epidermal growth factor receptor 2; MSI-H: microsatellite instability high; NTRK: neurotrophic tyrosine receptor kinase; RET: rearranged during transfection; TMB: tumor mutational burden.
* Upon disease progression, consider other anti-HER2 drugs;
† Mentioned only examples of actionable genetic alterations and other target therapies could be used (we recommend discussing these cases by a molecular tumor board).

review of the manuscript.

LLC: Statistical analysis 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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Awareness and Barriers to Guideline Adherence: Slovenian Family Physicians Survey and Qualitative Feedback

Conhecimento e Barreiras na Adesão às Normas de Orientação Clínica: Questionário a Médicos de Família Eslovenos e *Feedback* Qualitativo

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ABSTRACT

Introduction: Clinical practice guidelines are essential for standardizing care, yet adherence in primary care remains inconsistent globally. The aim of this study was to assess the use of clinical guidelines by family physicians in Slovenia for diagnosing and managing common conditions, to explore factors influencing guideline awareness and decision-making, and to identify barriers to adherence.

Methods: A nationwide cross-sectional study surveyed family medicine specialists and trainees across public and private practices in rural and urban Slovenia. Participants completed an online questionnaire to evaluate their awareness of professional guidelines (27 guidelines made by Slovenian healthcare professionals). Furthermore, they were tested on guideline-aligned decisions (five clinical vignettes). The last question in the survey was an open-ended question on the main obstacles associated with the use of clinical guidelines.

Results: Out of 660 physicians surveyed, only 57 respondents completed the questionnaire in full (8.6% response rate). Guideline awareness varied significantly (average 60.8%), with higher knowledge of guidelines for relatively common conditions (e.g., 96% for arterial hypertension *versus* 12% for polycythemia *vera*). Correct clinical decisions according to guidelines were made in 65.2% of cases (lowest average scores for osteoporosis, 57.9%, highest for dyspepsia, 69.7%). Minimal statistically significant differences emerged between family medicine specialists and trainees (decisions regarding peripheral arterial occlusive disease, $p = 0.024$), public or private practice types (decisions regarding low urinary tract symptoms, $p = 0.037$), and urban or rural practice settings (decisions regarding chronic obstructive pulmonary disease, $p = 0.008$ and $p = 0.016$). Answers to the open-ended question were divided into six categories according to the content: organizational limitations (lack of time and availability of guidelines), limitations related to the characteristics and quality of guidelines, team members' lack of knowledge or work based on experience, complex patients, non-cooperative patients, and financial limitations.

Conclusion: On average, family physicians in Slovenia make clinical decisions according to guidelines in 65.2% of cases. Organizational constraints, notably workload and time pressures, are the leading obstacles to guideline adherence. Interventions such as extended consultation times, centralized digital guideline repositories, and annual update seminars are recommended. Our study highlights the need for broader research to validate strategies for enhancing guideline implementation and adherence in primary care.

Keywords: Clinical Decision-Making; Family Practice; Guideline Adherence; Slovenia; Surveys and Questionnaires

RESUMO

Introdução: Apesar de as normas de orientação clínica serem essenciais para harmonizar os cuidados, a adesão nas unidades de cuidados de saúde primários permanece inconsistente a nível global. Este estudo teve como objetivo a avaliação da utilização de normas de orientação clínica por médicos de família na Eslovénia para o diagnóstico e tratamento de patologias comuns, e a identificação dos fatores que influenciam o conhecimento das normas de orientação clínica, a tomada de decisões e das barreiras à adesão.

Métodos: Estudo transversal de âmbito nacional junto de especialistas em Medicina Geral e Familiar e de médicos internos de Medicina Geral e Familiar a trabalhar em centros de saúde públicos e privados em áreas rurais e urbanas da Eslovénia. Os participantes completaram um questionário *online* para avaliar o seu conhecimento sobre normas de orientação clínica (27 normas de orientação clínica elaboradas por profissionais de saúde eslovenos). Posteriormente, avaliaram-se as decisões tomadas em relação à sua conformidade com as normas de orientação clínica em vigor (cinco casos clínicos). O último item do questionário foi uma pergunta de resposta aberta sobre os principais obstáculos associados ao uso das normas de orientação clínica.

Resultados: De um total de 660 médicos, apenas 57 completaram o questionário na íntegra (taxa de resposta de 8,6%). O conhecimento sobre as normas de orientação clínica variou significativamente (média de 60,8%), com maior conhecimento das normas sobre patologias relativamente comuns (por exemplo, 96% para hipertensão arterial *versus* 12% para policitemia *vera*). Em 65,2% dos casos foram tomadas decisões clínicas corretas e de acordo com as normas (pontuações médias mais baixas para osteoporose, 57,9%, mais altas para dispepsia, 69,7%). Diferenças mínimas estatisticamente significativas emergiram entre especialistas em medicina geral e familiar e internos (decisões sobre doença arterial periférica, $p = 0,024$), contextos de prática pública ou privada (decisões sobre sintomas do trato urinário inferior, $p = 0,037$), e contextos de prática urbana ou rural (decisões sobre doença pulmonar obstrutiva crónica, $p = 0,008$ e $p = 0,016$). As respostas à pergunta aberta foram divididas em seis categorias: limitações organizacionais (falta de tempo e disponibilidade de diretrizes), limitações relacionadas com as características e qualidade das normas, falta de conhecimento dos membros da equipa ou trabalho baseado na experiência, doentes complexos, doentes não colaborantes e limitações financeiras.

Conclusão: Em média, os médicos de família na Eslovénia tomam decisões clínicas de acordo com as normas de orientação clínica em 65,2% dos casos. Os principais obstáculos à adesão às normas são as restrições organizacionais, principalmente a carga de trabalho e pressões de tempo. São recomendadas intervenções, tais como tempo de consulta prolongado, repositórios digitais centralizados de normas de orientação clínica e seminários anuais de atualização. O nosso estudo destaca a necessidade de mais investigação para validar as estratégias de melhoria da implementação e adesão às normas de orientação clínica nos cuidados de saúde primários.

Palavras-chave: Adesão às Diretrizes; Eslovênia; Inquéritos e Questionários; Medicina Geral e Familiar; Tomada de Decisão Clínica

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KEY MESSAGES

- A nationwide survey of Slovenian family physicians provides insights into clinical guideline awareness and decision-making.
- A mixed-methods design using clinical vignettes and open-ended feedback enriches quantitative and qualitative findings.
- Organizational challenges, including excessive workload and limited consultation time emerged as major barriers.
- The small sample size (57 respondents, 8.6% response rate) and use of only five vignettes may limit the study's generalizability.
- The findings underscore the need for targeted interventions, such as extended consultation times and centralized digital guideline repositories.

INTRODUCTION

Clinical practice guidelines represent evidence-based recommendations often derived from the highest available levels of high-quality evidence regarding procedural efficacy. These guidelines are developed through multidisciplinary collaboration among leading specialists across medical disciplines and often incorporate input from patient advocacy organizations.[1] A report from the American College of Cardiology/American Heart Association Task Force identified a gap in the literature in terms of guideline use improving patient outcomes.[2]

National clinical guidelines comprise a comprehensive framework of healthcare services and procedural recommendations designed to ensure equitable access to essential and clinically justified medical services without discrimination. They also encompass economic evaluations of workforce requirements, logistical and organizational implementation strategies, and risk management protocols. Slovenian national guidelines form the foundation of national healthcare programs and require formal approval from the Health Council of the Slovenian Ministry of Health.[3]

Global research has consistently demonstrated suboptimal adherence to clinical guidelines among physicians, with European adherence rates not exceeding 70%.[1] A notable German study revealed significant variations in guideline awareness across medical specialties, with cardiologists showing the highest awareness of hypertension guidelines (37.1%), followed by internists (25.6%) and family physicians (18%).[1] Awareness was found to correlate primarily with the duration of private practice experience rather than the urban or rural location of practice. Adherence rates also varied by condition, with 63% of German physicians reporting adherence to hypertension guidelines and only 32% following hyperlipidemia treatment guidelines.[1] Another study found that at least 20% of clinical cases encountered in clinical practice were not covered by clinical guidelines.[4] While 100% adherence is unrealistic, the optimal adherence rate for a primary care system remains undetermined.

Adherence to evidence-based clinical guidelines in primary care remains a significant challenge in modern medical practice. The aim of this study was to assess the awareness and knowledge of clinical guidelines among family physicians in Slovenia, specifically regarding their use of guidelines to inform diagnostic and treatment decisions for common conditions in daily practice. It also sought to evaluate physicians' awareness of the existence and content of disease-specific guidelines. Furthermore, the study analyzed whether factors such as family medicine traineeship (FMTs) or family medicine specialist (FMSs) status, practice location (urban *versus* rural), and ownership type (public *versus* private) affect guideline awareness and knowledge of their content.

An open-ended question was included to move beyond predefined categories of commonly cited barriers and instead capture authentic, practice-based reflections from experienced clinicians. Additionally, another aim of this study was to identify potential barriers to guideline adherence and propose practical solutions to improve consistency in their application. Understanding these patterns and challenges is crucial for developing targeted interventions that enhance guideline adherence and, consequently, improve the quality of primary healthcare delivery.

METHODS

This cross-sectional study was conducted among FMSs and FMTs in Slovenia. The manuscript was elaborated in agreement with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines.[5] The target population included FMSs and FMTs working in various regions of Slovenia and employed in both public and privately owned healthcare institutions. Ethics committee approval was obtained from the Slovenian National Medical Review Board (0120-470/2020/6). Informed consent was obtained on the survey landing page, where participants were provided with information about the number of questions, the nature and storage of collected data, the study's investigators, and its purpose. Data were securely collected and stored using 1ka, an open-source online survey platform.[6]

The survey instrument was developed internally by the

research team without external templates. It comprised demographic questions, clinical vignettes, and a single open-ended question addressing the main obstacles to the use of clinical guidelines. The vignettes were elaborated based on Slovenian national guidelines (detailed in the 'Methods' section below) and recommendations for the most common conditions encountered by FMSs. No validated questionnaires addressing this specific topic were available.

Usability and technical functionality were pre-tested using the 1ka platform. The electronic questionnaire underwent internal testing among research group members before field deployment.

The survey was not open to the public. Access was restricted to invited participants via a shared URL, which was not individually personalized for each respondent. The survey was not password-protected.

Initial recruitment was conducted via email invitations sent directly by the research group to a random selection of FMTs and FMSs, and email addresses were obtained through internet search. Additionally, the Medical Chamber of Slovenia (MCS) distributed the survey invitation to all FMTs registered in their database.

Study recruitment was carried out in two phases using a convenience sampling strategy. This strategy was employed as it offers easier operational logistics, readily available study participants and faster data collection. The main drawback of such sampling is the potential introduction of bias, as those who are more readily available could misrepresent actual subgroups in the target population. As this study aimed to set the basis for further research, the aforementioned risk of bias was acceptable. In the first phase (March 31st, 2021), the MCS distributed the questionnaire link to 632 FMTs and FMSs listed in its email database. To further extend reach within the target population, the questionnaire was also shared in a Facebook group for FMTs (396 members) and the closed Facebook group of the 30th modular training program (32 members), part of the formal family medicine traineeship.[7] The second recruitment phase (October 6th, 2021) targeted healthcare institutions. Twenty-six public healthcare centers (PHCs) were randomly selected from 58 PHCs across Slovenia (representing a 45% sampling rate). The management teams at these centers were asked to distribute the questionnaire to their employed FMTs and FMSs. Twenty-three out of 26 PHCs agreed to participate. Additionally, recruitment was extended to private contractors working within the public primary care system. Survey invitations were sent to 42 randomly selected privately owned practices across various Slovenian regions, identified via the Professional Association of Private Doctors and Dentists of Slovenia's online registry.

Participation in the survey was voluntary, and no incentives were offered. URL links sent out to participants were not unique. Additionally, we did not ask participants for their name or identifiable information. Data collection occurred during two intervals: from February 25th, 2021, to June 25th, 2021, and from October 6th, 2021, to January 6th, 2022. The survey did not employ randomization of question order or adaptive questioning techniques.

The first page of the survey presented the study invitation and informed consent statement, followed by the survey questions, which were organized across nine pages. No completeness checks were enforced before submission; participants could return to previous pages to review or amend their responses.

The respondents' IP addresses were logged during the survey to reduce the likelihood of multiple submissions by the same individual. However, no additional measures, such as log file analysis or response-block tracking, were implemented to identify or prevent duplicate entries. Respondents were not required to register for survey participation.

Incomplete responses were excluded from the final analysis. Timestamps were not used to track response duration, and no statistical adjustments or corrections were applied to the dataset.

Slovenian primary healthcare system

The Slovenian primary healthcare system has served as a model for many other countries.[6] It is organized and administered by local municipalities.[7] The system offers a comprehensive range of preventive, diagnostic, curative, rehabilitative, palliative, and health promotion services.[7] Definitions of key terms relevant to the Slovenian healthcare system and this study are provided in Table 1. Each patient in Slovenia has a family medicine specialist, typically located near the patient's residence. The FMSs function as gatekeepers to the healthcare system, referring patients to specialist services when necessary. Before 2001, the system was primarily staffed by general medicine practitioners. Between 2000 and 2001, it was restructured into an FMS-based model.[8] Under the previous system, general practitioners did not complete internships. A one-year residency was followed by a 'state professional' examination.[8] The current program, in place since 2001, requires four years of postgraduate training: two years in secondary or tertiary care settings, and two years in general practice under the supervision of an experienced mentor.[8] As of 2024, there were 1096 active family medicine specialists and 272 family medicine trainees in Slovenia.[9]

Clinical vignettes

The first section of the survey listed 27 national guidelines, recommendations, and care proposals developed in Slovenia. Participants were asked to indicate which of these

Table 1 – Term definitions: Slovenian primary healthcare system

Family medicine trainee	Medical doctor doing residency in Family Medicine, after doing an internship.
Family medicine specialist	Specialist medical doctor who has done four-year residency in Family Medicine and passed state professional exam.
General medicine specialists	Title of a physician before 2000 and new residency program, who has done one-year family medicine residency and passed the state professional exam.
Public sector	Community public health centers whose ownership structure is by the local municipalities.
Private contractor	Medical practices which are owned by a private company (mostly owned by the FMSs themselves) and hold a concession from local municipalities for public service.
Concession	A contract with the National public health insurance institute that allows the concessionaires to charge their service to the public health insurance scheme. The medical practices are privately owned, but healthcare is publicly funded.
Primary healthcare level	Health care at a pre-hospital level.
Secondary healthcare level	Health care at a hospital level.
Tertiary healthcare level	Health care at a university hospital level.

they were familiar with, without requiring in-depth knowledge of their contents.

Clinical vignette cases were elaborated using the following Slovenian guidelines: guidelines for men with lower urinary tract symptoms due to benign prostatic hyperplasia,[10] osteoporosis,[11] peripheral arterial disease,[12] dyspepsia,[13] helicobacter pylori infection,[14] and chronic obstructive pulmonary disease (COPD).[15]

Each case consisted of a brief clinical scenario followed by several potential management actions. Participants were asked to indicate whether the action was recommended by the corresponding guideline and whether it reflected their actual clinical practice. Guideline adherence was defined as correctly identifying the guideline-recommended management actions within each vignette.

Statistical analysis

The quantitative data were categorical and are presented as frequencies with corresponding percentages. Statistical analyses were conducted using IBM® SPSS Statistics for Windows®, version 28.0.[16] Statistical significance was defined as $p < 0.05$.

Chi-square tests were performed to evaluate whether family physicians adhered to clinical guidelines at expected rates. Additional chi-square analyses were used to compare adherence rates between FMTs and FMSs to determine whether trainees adhered to guidelines more consistently than specialists in clinical practice.

Qualitative analysis

The final survey item was an open-ended question, analyzed through descriptive qualitative content analysis using a deductive approach. A categorization matrix was developed based on a review of existing literature, professional experience, and the collected dataset. Responses were manually coded into six distinct thematic categories related to guideline adherence. This process enabled the identification of the most cited factors contributing to guideline non-adherence in daily family medicine practice.

RESULTS

Study characteristics

Among the total number of survey accesses (n = 660), 277 respondents (42.0%) initiated the questionnaire, and 57 participants completed it (8.6% of total accesses; 20.6% of surveys initiated). The sample characteristics are summarized in Table 2. The majority of respondents were women, with FMS comprising the largest professional group. Most participants were aged between 31 and 40 years.

Participants were geographically distributed across all Slovenian regions, with the highest representation from the Podravska, Gorenjska, and Osrednjeslovenska regions.

Guideline recognition

Considerable variability in guideline awareness was observed, depending on the specific guidelines in question (Table 3). Physicians reported the highest levels of familiarity with guidelines for the management of diabetes, arterial hypertension, anaphylaxis, and osteoporosis. In contrast, the least recognized guidelines were those related to tear film disorders, dry eye syndrome, and polycythemia vera. On average, 60.8% of physicians reported awareness of the listed guidelines.

Table 2 – Demographic characteristics of survey respondents (n = 57)

Characteristic	n	%
Sex		
Female	37	65
Male	20	35
Professional status		
Family medicine specialists*	34	60
General medicine specialists*	9	16
Family medicine trainees	14	25
Age group (years)		
< 30	7	12
31 - 40	22	39
41 - 50	12	21
51 - 60	10	18
> 61	6	11
Location		
Urban	29	51
Rural	28	49
Employment type		
Public sector	49	86
Concessionaire	8	14
Academic roles		
Student mentor	24	42
Trainee mentor	17	30
University professor	3	5
No academic roles	13	23
Status		
Specialist	43	75
Trainee	14	25

* The Slovenian system recognizes both FMS, a new program from 2000 onward, and general medicine specialists, an old program before 2000; both work on primary care as GPs

Guideline adherence

Correct clinical decision-making in line with guideline recommendations was observed in an average of 65.2% of cases (Table 4). Statistically significant results are shown in Fig. 1.

A statistically significant difference between FMT and FMS was identified in one clinical vignette concerning peripheral arterial disease. Specifically, regarding the statement "Would not prescribe antiplatelet therapy for asymptomatic patients with reduced Ankle Index", 72.0% (n = 31) of FMS responded correctly according to guidelines, compared to 36.0% (n = 5) of FMT (p = 0.024; Fisher's exact test).

Significant differences were also observed in the management of chronic obstructive pulmonary disease. Urban-based physicians demonstrated higher adherence to diagnostic guidelines (72.0%, n = 21) than rural-based physicians (36.0%, n = 10; p = 0.008; Fisher's exact test). Conversely, rural physicians were more likely to prescribe bronchodilators for suspected COPD (75.0%, n = 21) compared to their urban counterparts (41.0%, n = 12; p = 0.016; Fisher's exact test). No other significant differences in management decisions were identified based on geographic location.

A statistically significant difference based on practice ownership was found in the management of lower urinary tract symptoms. Physicians working in privately owned practices were more likely to request bladder diaries (50.0%, n = 4) compared to those in public healthcare institutions (14.3%, n = 7; p = 0.037; Fisher's exact test). No additional significant differences between public and private sector physicians were identified.

Open-ended question responses (qualitative analysis)

A total of 57 completed surveys yielded 177 individual responses to the open-ended question regarding barriers to guideline adherence. These responses were categorized into six thematic categories.

First category: organizational constraints

- Excessive workload, time constraints: Respondents noted that often, "you know what is right, but you don't do what is right, you do what is faster". Working at multiple sites was also identified as a contributing factor to overload. Some comments reflected a desire to return to more traditional, patient-centred care, exemplified by the statement: "Let's give family medicine back to the family doctor!".
- Guideline accessibility: Respondents called for a "duty of regional medical associations for timely information" and "rapid computerized format" for guidelines. While pharmaceutical companies sometimes issue educational materials, respondents said, "It is questionable whether such tools can be considered reliable guidelines and recommendations". Suggestions included "annual refresher courses" focused on primary care and clear guidelines delineating the responsibilities of family physicians versus specialists.
- Dysfunctional healthcare system: Physicians frequently attributed guideline nonadherence to systemic inefficiencies: "Unacceptable waiting times often force shortcuts and deviations from established protocols, which can lead to serious mistakes". Consequently, "you must see a patient multiple times to carry out one guideline-recommended measure".

Table 3 – Guideline recognition (rate of physicians answering they know the guideline)

Guideline for	n	%
Type II diabetes	55	96%
Arterial hypertension	55	96%
Anaphylaxis	54	95%
Osteoporosis	54	95%
Men with lower urinary tract symptoms due to benign prostatic hyperplasia	49	86%
Dyspepsia	48	84%
Guidelines for resuscitation	48	84%
Dementia	47	82%
Chronic obstructive pulmonary disease	46	81%
Community-acquired pneumonia	46	81%
Pain in adult cancer patients	46	81%
Asthma	44	77%
Peripheral arterial disease	40	70%
Migraine	36	63%
Preparation of diabetic patients for colonoscopy	35	61%
Venous thrombosis	35	61%
Chronic venous insufficiency	34	60%
Preventing NSAID and antiplatelet therapy-induced gastrointestinal damage	30	53%
Diabetic retinopathy	30	53%
Painful shoulder	25	44%
Abdominal aortic aneurysm	23	40%
Chronic kidney disease in adults	18	32%
Head injuries	14	25%
Carpal tunnel syndrome	10	18%
Polycythemia vera	7	12%
Dry eye	5	9%
Teary eye disorders	3	5%

Respondents also described challenges in communication with secondary care and difficulties reconciling specialist instructions with existing guidelines.

- Poor digitalization: Participants identified inadequate digital decision-support tools and the absence of integrated guideline resources within electronic patient records as barriers. Suggestions included embedding direct guideline links into patient management software and standardizing health records to facilitate continuity of care across institutions.

Second category: poor guideline quality

Many physicians expressed dissatisfaction with the existing guidelines, describing them as too lengthy, insufficiently adapted to the realities of Slovenian primary care, and inconsistent across specialties. Some respondents felt that certain common conditions lacked appropriate guidelines, while others doubted their clinical relevance, stating: “Guidelines are not medicine” and “guidelines are nonsense”.

Third category: knowledge/education/experience

Respondents highlighted a lack of awareness about available guidelines, insufficient training opportunities for

Table 4 – Correct clinical decisions (rate of physicians answering in accordance with the guidelines)

Clinical vignette case	%
Prostate hyperplasia	68.6
Osteoporosis	57.9
Peripheral artery disease	62.5
Dyspepsia	69.7
Chronic obstructive lung disease	67.3

both physicians and nursing staff, and a general underemphasis on guideline use during medical education and postgraduate specialization. Several physicians noted that "we have too few quality training sessions for family doctors". Some doctors prefer to rely on their established habits, personal beliefs, and "experiences that have taught them why they decide differently" rather than following guidelines.

Fourth category: patient complexity

Several respondents noted that guideline recommendations are often difficult to apply to complex, multimorbid patients, particularly in the absence of guidelines for multimorbidity management. A strong emphasis was placed on a patient-centred approach, the complexity of care, and the need for individualized and holistic treatment rather than strict adherence to guidelines alone.

Fifth category: patient cooperation

Participants observe that constant treatment changes due to guideline updates can lead to a loss of patient trust. Patients often have "different expectations than those promoted by guidelines" and may resist their implementation by refusing diagnostic tests or, conversely, demanding referrals to secondary care. "Following guidelines sometimes requires saying 'no' to a patient, which some doctors are unwilling to do".

Sixth category: financial constraints

Physicians highlighted limited access to diagnostic tests due to insurance restrictions and insufficient funding for laboratory services and medical equipment. This financial gap between clinical recommendations and available resources further contributed to deviations from guidelines.

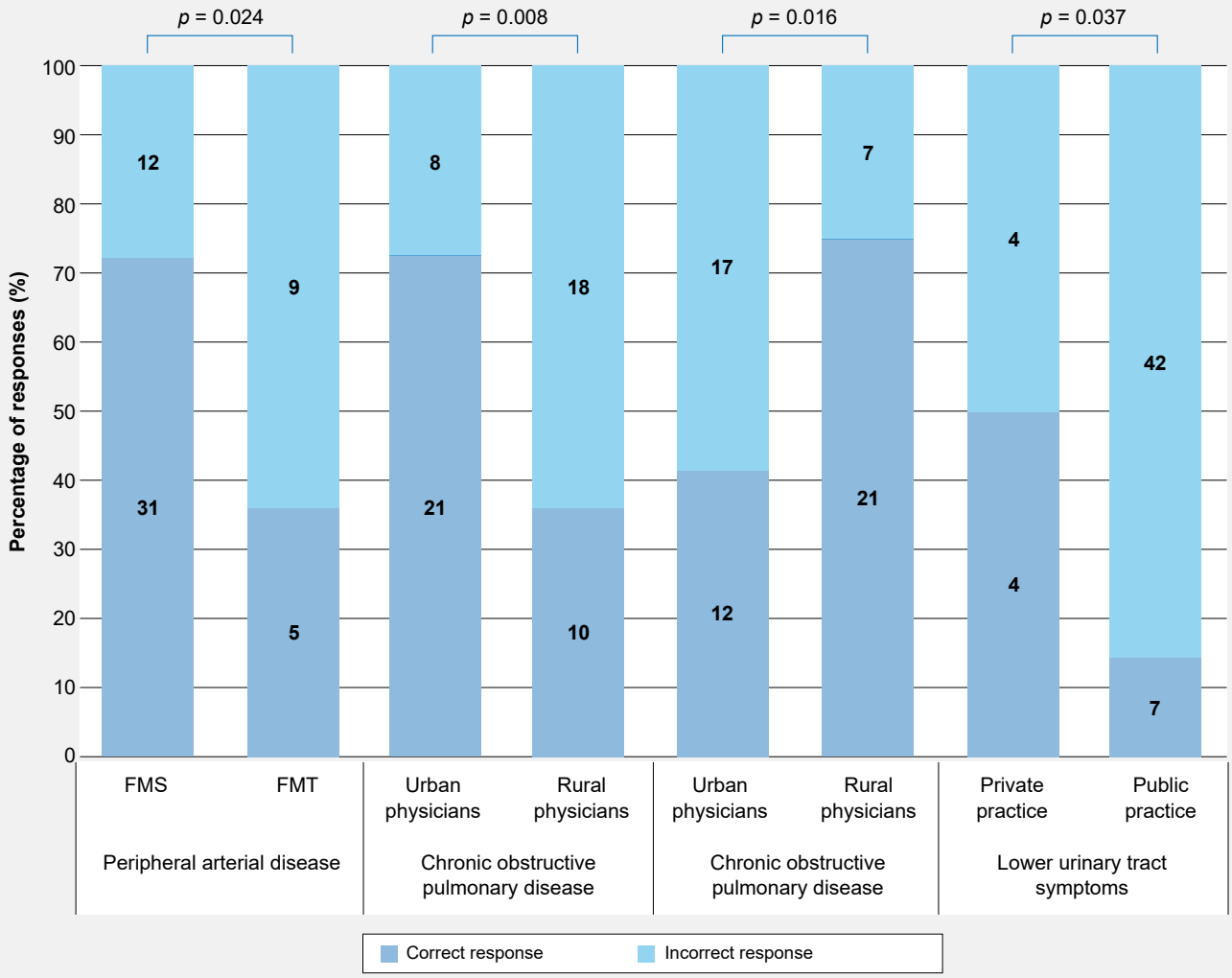

Figure 1 – Statistically different results of subgroup comparison based on guidelines thematic area with significance shown as *p* value

DISCUSSION

This cross-sectional survey study represents the first comprehensive assessment of guideline awareness and adherence across multiple clinical domains within Slovenian primary care. Our findings suggest there is considerable variability in primary care physicians' recognition of clinical guidelines, ranging from 5.0% to 96.0%, with higher recognition rates observed for guidelines addressing common disorders. Using five clinical vignettes, we evaluated both theoretical knowledge and practical application of these guidelines, revealing notable discrepancies between awareness and clinical practice. Barriers to adherence were predominantly organizational, underscoring systemic challenges that require targeted interventions to improve the integration of evidence-based practices in primary care.

In our assessment of 27 selected guidelines, physicians recognized an average of 60.8%, a figure comparable to findings from Sweden (60.0%).[8] Similar recognition rates have been observed in other health professions, such as dentistry, where 68.0% of dentists reported familiarity with clinical guidelines.[9] The range of guideline recognition was substantial, from 5.0% for tear film disorders to 96.0% for arterial hypertension and type 2 diabetes. These results align with Slovenia's documented disease burden, where circulatory diseases and diabetes represent major public health concerns.[17,18] Interestingly, the only study on guideline adherence in Slovenia was conducted in 2007, which showed that only 9.3 % of patients were managed according to guidelines for hypertension. This pattern highlights a recurrent issue identified in the international literature: less prevalent or complex conditions, such as primary aldosteronism, are more likely to be overlooked or inadequately managed due to limited physician familiarity with the corresponding guidelines.[10]

Disease management between FMS and FMT differed only in antiplatelet therapy for asymptomatic patients with reduced Ankle index. As antiplatelet and anticoagulation therapy is complex and requires special education, it is possible that FMT did not yet receive that knowledge and have responded incorrectly.[11] It is also possible that due to selection bias introduced by convenience sampling a larger portion of FMT who are not familiar with guidelines were chosen. This lack of knowledge can be addressed by additional training in antiplatelet and anticoagulant therapy.

When comparing disease management by practice location, a significant difference was identified in the management of chronic obstructive pulmonary disease. Urban physicians demonstrated greater adherence to diagnostic guidelines, while rural physicians were more likely to prescribe bronchodilators empirically for suspected COPD. This finding is consistent with studies from the United States, which report that rural primary care physicians face additional barriers to guideline adherence due to factors such as large geographic distances, differing patient epidemiology, and challenges in care coordination.[12] These studies also highlighted disparities in patient expectations and healthcare-seeking behavior between urban and rural populations.[12] This could be addressed by educating rural physician more often on this topic in their local environments, making it easier for them to attend such educational events. While our study did not explore these contextual factors in depth, these international findings suggest relevant avenues for future research to better understand and address these differences in the Slovenian context.

The observed difference in lower urinary tract symptom management between physicians in privately owned and public sector practices was limited and should be interpreted with caution, given the small sample size. In general, differences between private and public primary care practices in Slovenia have been attributed to variations in management structures[13], although overall clinical performance is typically comparable. We believe that this indicates good quality of care for both ownership structures in Slovenia. As healthcare digitalization advances and debates around funding and healthcare service delivery continue, it will be important to evaluate how different organizational models and generational workforce preferences[14] influence patient care quality and guideline implementation.

Previous studies have proposed various strategies to enhance guideline implementation in primary care settings.[15] Our findings emphasize that organizational constraints remain the primary barrier to effective guideline integration, consistent with existing literature.[15,16,19] In the Slovenian context, physicians recommended solutions including establishing working standards that allow for longer patient consultations, improving guideline accessibility through centralized digital repositories, and involving practicing primary care physicians in guideline development to ensure practical applicability. These suggestions parallel recommendations from qualitative research conducted in Canada,[20] Germany,[4] Sweden,[17] and The Netherlands.[18]

This study has several limitations. The modest sample size may have limited the ability to detect certain trends or differences, and the small group sizes could have exaggerated observed effects. The convenience sampling may have introduced bias into our results, warranting further research with better sampling strategies in the future. Additionally, the use of an IP-based system to prevent duplicate responses may have inadvertently restricted participation from clinics sharing workstations, potentially underestimating the response rate. The employed questionnaire was developed for this study, as no validated instrument was available, and its psychometric properties were not formally assessed. Moreover, the length and cognitive demand of

the questionnaire could have led to respondent fatigue, particularly towards the end, with no mechanism to measure this effect. Data collection occurred during the COVID-19 pandemic, which may have influenced guideline awareness and adherence patterns as physicians prioritized emergent care needs. Finally, while clinical vignettes are a well-established research tool, real-time analysis of electronic health records and metadata might offer a more accurate assessment of guideline adherence in clinical practice.

Future research should investigate whether proposed interventions at both the organizational and guideline development levels lead to measurable improvements in guideline recognition and adherence which was also recommended by other authors.[4] Given that much of the existing research on guideline implementation is over a decade old, there is a clear need to revitalize this field with studies reflecting contemporary clinical realities, updated guidelines, and evolving socioeconomic factors. There is also a lack of studies comparing patient outcomes when guidelines are adhered to and where they are not, warranting further exploration.[2] Additionally, few studies have explored differences in guideline knowledge and application across various career stages, which could offer valuable insights into the design of targeted continuing medical education strategies.

CONCLUSION

This study found a variable awareness of clinical guidelines among family physicians in Slovenia, with an average recognition rate of 60.8%. Physicians adhered to guideline-recommended clinical decisions in 65.2% of cases. Organizational constraints emerged as the predominant barrier to guideline adherence. Recommended strategies for improving adherence include extending consultation times, improving access to diagnostic services, developing centralized digital guideline repositories, implementing annual update seminars, and introducing digital tools to facilitate guideline navigation and integration into clinical workflows. These findings underscore the need for broader, high-quality research to evaluate the effectiveness of interventions aimed at enhancing guideline implementation in primary care settings.

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PREVIOUS AWARDS AND PRESENTATIONS

The detailed and complete qualitative analysis of this research was presented at a nursing conference in Novo Mesto, Slovenia, in 2022. The conference was held in the Slovenian language.

AUTHOR CONTRIBUTIONS

LP: Drafting, writing, and critical review of the manuscript.

NKR: Conceptualization, methodology, investigation, data collection, formal analysis, visualization, and project administration.

VI: Conceptualization, methodology, investigation, resources, data curation, validation, supervision, and project administration.

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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Development and Validation of the "Physical Functional Impact Index on Chronic Pain" (PFIICP): A Formative Model Approach

Desenvolvimento e Validação do "Índice de Impacto Funcional Físico na Dor Crónica" (IIFFDC): Uma Abordagem de Modelo Formativo

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ABSTRACT

Introduction: The development and validation of reliable and valid instruments to assess chronic pain and its impact on daily functioning are crucial in both clinical and research settings. The aim of this study was to develop and validate the scale 'Physical Function Impact Index on Chronic Pain' – PFIICP, a novel 12-item questionnaire designed to evaluate the physical functional impact on chronic pain.

Methods: A formative measurement model was used. In comparison with other established scales that have emotional, cognitive and social considerations, PFIICP is designed to be more objective, as it focuses only on the relationship between physical performance and the subject's pain.

Results: Data were collected from n = 285 patients at baseline and n = 58 patients at follow-up (3 - 6 months later). Spearman's rho correlations between the 12 items ranged from 0.153 to 0.793, all statistically significant ($p < 0.05$), indicating that each item contributes uniquely to the construct. The intraclass correlation coefficient (ICC) for test-retest reliability was 0.788 (95% CI: 0.731 - 0.833), demonstrating good stability over time. Convergent validity was supported by strong Pearson correlations with established measures, including the Brief Pain Inventory (BPI; r = 0.739, $p < 0.05$) and the Pain Disability Index (PDI; r = 0.739, $p < 0.05$).

Conclusion: These findings suggest that the PFIICP is a robust tool for assessing the functional impact of chronic pain through a formative model approach.

Keywords: Chronic Pain; Pain Measurement; Quality of Life; Reproducibility of Results; Surveys and Questionnaires

RESUMO

Introdução: O desenvolvimento e a validação de instrumentos fiáveis e válidos para avaliar a dor crónica e o seu impacto no funcionamento diário são cruciais tanto em contextos clínicos como de investigação. Este estudo teve como objetivo desenvolver e validar a escala 'Índice de Impacto Funcional Físico da Dor Crónica' IIFFDC, um novo questionário de 12 itens concebido para avaliar o impacto funcional físico na dor crónica.

Métodos: Foi utilizado um modelo de medida formativo. Em contraste com outras escalas bem estabelecidas que apresentam considerações emocionais, cognitivas e sociais, a IIFFDC, de forma a ser objetiva, foca-se apenas na relação entre a atividade física e a dor crónica do individuo.

Resultados: Foram recolhidos dados de n = 285 doentes no início do estudo e de n = 58 doentes no seguimento (3 - 6 meses depois). As correlações rho de Spearman entre os 12 itens variaram entre 0,153 e 0,793, todas estatisticamente significativas ($p < 0,05$), indicando que cada item contribui de forma única para o constructo. O coeficiente de correlação intraclasse (ICC) para a fiabilidade teste-reteste foi de 0,788 (IC 95%: 0,731 - 0,833), demonstrando uma boa estabilidade ao longo do tempo. A validade convergente foi apoiada por fortes correlações de Pearson com medidas estabelecidas, incluindo o *Brief Pain Inventory* (BPI; r = 0,739, $p < 0,05$) e o *Pain Disability Index* (PDI; r = 0,739, $p < 0,05$).

Conclusão: Estes resultados sugerem que o IIFFDC é uma ferramenta robusta para avaliar o impacto funcional da dor crónica através de uma abordagem de modelo formativo.

Palavras-chave: Dor Crónica; Inquéritos e Questionários; Medição da Dor; Qualidade de Vida; Reprodutibilidade dos Resultados

KEY MESSAGES

- Development and validation of the Physical Function Impact Index on Chronic Pain (PFIICP), a 12-item questionnaire designed to evaluate the physical functional impact on chronic pain.
- Results suggest strong correlations between the 12 items, indicating that each item contributes uniquely to the construct.
- Strong convergent validity with the Brief Pain Inventory and the Pain Disability Index.
- Validation was done in a public general hospital; More studies are needed to validate the questionnaire in different settings.
- The PFIICP is a robust tool for assessing the functional impact of chronic pain through a formative model approach.

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INTRODUCTION

Chronic pain is one of the primary reasons to seek healthcare, namely at the level of primary healthcare services. It has a prevalence rate of approximately 37% in the Portuguese population[1] and in a recent study,[2] its prevalence in primary healthcare in mainland Portugal was estimated at 33.6%. As expected, in its origin, pain was mostly musculoskeletal, located in the lower back and lower limbs.[2] It is widely recognized that the assessment of the functional consequences of chronic pain in the individual, considering both the person's organic structure (body segments) and the physical functional implications (body functions) in the individual's activities and participation in their daily environment, as defined in the International Classification of Functioning, Disability, and Health[3,4] is of great relevance. However, to quantify objectively a specific action performed by someone is inherently difficult to establish and reproduce.

The present study aimed to develop and validate a new tool, the 'Physical Function Impact Index on Chronic Pain' (PFIICP), designed to promote objectivity and practicality. This instrument was designed to be as objective as possible and it focuses on the relationship between physical performance and pain, considering only the body functionality and the limitations resulting from the subjects' chronic pain. Furthermore, as it is based on the anatomical representation of the body, its applicability is intuitive for any healthcare professional. For comparative validity, we used two validated questionnaires in Portuguese: the Brief Pain Inventory (BPI) and the Pain Disability Index (PDI). Although these questionnaires do not specifically address (in detail) the physical functional impact of pain on the individual, they do approach the interference of pain in a general set of daily activities, professional issues and quality of life.

The assumption of the measurement model – whether reflexive or formative – is critical, as it directly influences the interpretation of the results and the psychometric properties of the instrument.[5] Reflexive models assume that latent constructs cause observed variables, while formative models posit that the construct is an aggregation of specific dimensions represented by the observed variables. Clarifying the type of model used is particularly important in the field of pain research, where constructs such as 'functional impact' may be better represented as aggregations of distinct facets rather than as underlying causes of observed indicators.[6]

The PFIICP was developed to assess the physical functional activities associated with chronic pain. Unlike traditional reflective models, where latent constructs cause observed variables, the PFIICP employs a formative measurement model, wherein the latent construct ("physical functional impact of chronic pain") is defined and formed by the observed variables (12 items). This approach aligns with the understanding that the construct of interest is not an independent entity but rather an aggregation of specific dimensions based on segments of the human body and their corresponding physical functions such as upper body *versus* lower body physical limitations or walking *versus* sitting or lying down.[5]

Since daily life, professional activities, and social participation are based on the functional performance of the human body (and its different segments), it is assumed that it is this functional impact that truly weighs on an individual's daily quality of life, particularly for those who suffer from chronic pain.

The PFIICP is an intuitive tool that is easy to use in health care, particularly in Primary Health Care, as it is the translation of a set of functions that correspond to the body diagram. It leaves out psychological concepts and emotional experiences that are certainly important in those who experience pain, but it objectively translates the repercussions of pain at the present time, so that it can be properly quantified.

METHODS

Instrument development and pre-test

The development of the PFIICP results from a literature review of existing and validated metrics for functional assessment and quality of life. In addition, we consulted five experts in the chronic pain domain on the adequacy of the items that compose the scale and on whether they would fit for the purpose of developing an instrument that is not only more objective but also more user-friendly. In informal discussions, we sought to explore whether the proposed items made the appropriate correspondence between the action (function) and the body segments involved in the most common pain syndromes, namely using a body diagram of pain location. The experts agreed on the adequacy of the final version of the scale.

To test its applicability, we then performed a simple pre-test. For that purpose, 10 individuals, recruited from the general population, accepted to respond to the questionnaire to ensure comprehension and the time needed to fill in the questionnaire (the goal was less than five minutes). After very minor adjustments, the instrument proved suitable to be tested and validated.

Participants

Data were collected from n = 285 patients (91 men and 194 women; aged between 21 and 90 years old) attending their first consultation at the Pain Unit at Unidade Local de Saúde de Braga (Hospital de Braga), between March 2024 and March 2025. A subset of n = 58 patients (17 men and 41 women) completed a second evaluation, according to

the scheduled clinical appointments (generally three to six months later) and after clinical individual orientation, including any kind of analgesic treatment purposed (e.g., pharmacological, physical or psychological).

The participants were adults aged ≥ 18 years diagnosed with chronic pain lasting three or more months[7-9] followed in the consultation for that same reason, without any diagnostic restriction (assumption of chronic pain as a diagnosis for frequency of that same consultation) and who agreed to participate in the study.

Ethics committee approval was obtained from the institutional review board (ID:13_2024), and informed consent was provided by all participants.

Instruments

The PFIICP: A self-reported 12-item questionnaire designed to assess the functional impact of chronic pain. Each item evaluates a distinct aspect of daily functioning affected by pain, scored on a Likert scale (0 - 10) using the verb form to express the action. Higher scores indicate greater functional impairment.

The questionnaire uses a visual representation of the human body to facilitate self-reporting, ensuring that respondents can easily identify areas of concern.

I.

Figure 1.

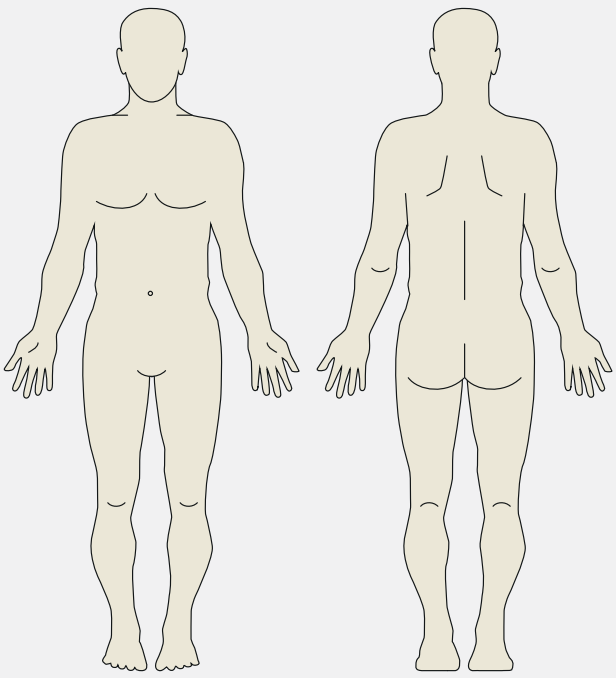

Figure 1 – Human body representation

II.

1. Personal care (washing, dressing, ...)
2. Working (or studying)
3. Sitting or lying down
4. Standing (orthostasis)
5. Changing position (getting up/sitting down; getting in and out of a vehicle/bathtub)
6. Walking
7. Going up/down (stairs)
8. Carrying loads or weights (for example, a shopping bag)
9. Handling objects (for example, writing, buttoning...)
10. Chewing/brushing teeth
11. Urinating or defecating
12. Engaging in sexual activity

The assessment of participants included the validated Portuguese versions of the following questionnaires:

- The Brief Pain Inventory.[10,11] The BPI assesses the intensity of pain at its worst, best, average, and current levels, according to an 11-point numerical rating scale (NRS), where 0 = 'no pain' and 10 = 'worst pain imaginable'. It also gathers information on pain treatments, perception of relief, and pain interference. The latter dimension includes general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life, also using an 11-point NRS (0 = 'no interference'; 10 = 'completely interferes').
- The Pain Disability Index.[11,12] The PDI measures the overall impact of pain on seven activities of daily life, using an 11-point scale ranging from 0 (no disability) to 10 (total disability). The seven activities cover vital aspects (eating, sleeping, or breathing), physical (personal care), and social aspects (social activities, family and/or household responsibilities).
- The BPI and the PDI were used in clinical trials to measure the response to treatment. In a study by Azevedo *et al*,[1] the BPI and the PDI were used to evaluate the effectiveness of pharmacological and non-pharmacological therapies in pain management for patients with chronic pain. They helped monitor the reduction in pain intensity and improvement in quality of life, providing essential data for assessing treatment effectiveness.

Data collection

The PFIICP was administered via a self-reported questionnaire before entering the medical appointment without any kind of time restriction. Participants were presented with a visual representation of the human body, alongside the 12 items, allowing them to rate the specific aspects of

daily functioning on chronic pain.

No external observers influenced the responses, ensuring that the data reflected genuine patient perceptions.

The use of self-reported measures requires careful consideration of potential common methodological biases, which may arise from factors such as social desirability, mood states, or item characteristics. To minimize these biases, the PFIICP was designed with clear and concise items, avoiding ambiguity and reducing the likelihood of misinterpretation.

Statistical analysis

Spearman's rho correlations were calculated to examine the relationship between individual items and the total PFIICP score. Test-retest reliability was assessed using the intraclass correlation coefficient (ICC). Convergent validity was evaluated through Pearson correlations with the BPI and PDI. All analyses were conducted using JASP (Version 0.19.2). Statistical significance was set at $p < 0.05$.

Normality tests (Shapiro-Wilk) were performed for all items and the total PFIICP score. The results indicated moderate deviations from normality in some items, which was expected due to the ordinal nature of the scale. To mitigate possible limitations, we supplemented the analyses with nonparametric methods, such as Spearman correlations and the Wilcoxon Signed-Rank test to assess responsiveness.

To assess the relative independence between items, we performed a multicollinearity analysis using the variance inflation factor (VIF).

RESULTS

Item contribution

Spearman's rho correlations between the 12 items pairs ranged from 0.153 to 0.793, with all correlations being statistically significant ($p < 0.05$). These results indicate that each item contributes meaningfully to the construct, albeit with varying degrees of importance (Table 1). The multicollinearity analysis confirmed the independence of the items, with VIF values < 4.5 for all items, considered acceptable, ensuring that the items represent distinct dimensions without significant redundancies.

This characteristic is particularly important in formative models, where the items represent distinct dimensions of the latent construct rather than being reflections of a single underlying dimension.

Test-retest reliability

The ICC for the PFIICP scores between baseline and follow-up assessments was 0.788 (95% CI: 0.731 - 0.833), indicating good temporal stability. To further address the suitability of ICC for ordinal data, additional item-level analyses using Spearman's rank correlation coefficients were conducted between the initial and follow-up assessments. These analyses confirmed the scale's temporal stability, reinforcing its reliability as a measure of chronic pain's physical functional impact.

It is important to note that traditional internal consistency metrics, such as Cronbach's alpha coefficient, are not applicable to the PFIICP due to its formative model-based structure. In this approach, the items represent distinct and independent dimensions that contribute to the latent construct, without the expectation of high correlation between them.

Table 1 – Spearman's rho Correlations between items and PFIICP/IIFFDC global score; Variance Inflation Factor (VIF) of PFIICP/IIFFDC items.

Item	I01	I02	I03	I04	I05	I06	I07	I08	I09	I10	I11	I12	PFIICP	VIF
I01	--													2.293
I02	0.535***	--												1.676
I03	0.511***	0.384***	--											1.942
I04	0.510***	0.459***	0.526***	--										2.808
I05	0.634***	0.439***	0.625***	0.640***	--									3.083
I06	0.552***	0.462***	0.492***	0.667***	0.657***	--								3.604
I07	0.564***	0.488***	0.461***	0.701***	0.677***	0.793***	--							4.330
I08	0.534***	0.616***	0.446***	0.582***	0.555***	0.579***	0.683***	--						2.486
I09	0.538***	0.334***	0.322***	0.259***	0.376***	0.333***	0.338***	0.439***	--					1.926
I10	0.366***	0.197**	0.300***	0.234***	0.265***	0.214***	0.218***	0.211***	0.563***	--				1.849
I11	0.300***	0.153*	0.305***	0.229***	0.304***	0.208***	0.250***	0.207***	0.361***	0.533***	--			1.650
I12	0.313***	0.374***	0.375***	0.343***	0.358***	0.326***	0.309***	0.342***	0.269***	0.265***	0.411***	--		1.445
PFIICP	0.760***	0.647***	0.675***	0.705***	0.764***	0.723***	0.748***	0.726***	0.655***	0.552***	0.537***	0.603***	--	

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

The application of measures such as Cronbach's alpha, which assume high intercorrelations between items (typical of reflective models), could result in artificially low values, incorrectly suggesting a lack of reliability. Thus, methods more appropriate to the formative nature of the PFIICP were chosen, such as multicollinearity analysis (VIF) and the assessment of temporal stability through the intraclass correlation coefficient (ICC).

Convergent validity

Pearson correlations revealed strong associations between the PFIICP and the BPI ($r = 0.739$, $p < 0.05$) and PDI ($r = 0.739$, $p < 0.05$). These high correlations confirm the PFIICP's ability to capture similar constructs measured by these established instruments, providing evidence for convergent validity.

Exploratory analysis of responsiveness

An exploratory analysis of responsiveness was conducted to evaluate the PFIICP's ability to detect changes in the functional impact of chronic pain over time. This analysis was based on individual variations between baseline and follow-up assessments, conducted three to six months later. Participants who received significant interventions during the follow-up period were excluded to minimize external influences. The Wilcoxon Signed-Rank Test revealed no statistically significant changes in PFIICP scores over time ($z = 1.043$, $p = 0.299$). The effect size, measured by the matched rank biserial correlation, was small ($r = 0.166$, $SE = 0.158$), with a 95% confidence interval ranging from -0.144 to 0.446. These findings suggest minimal change in PFIICP scores over time without interventions. While the changes were not statistically significant, the small effect size indicates potential sensitivity to detect clinically meaningful changes in future studies with stricter control of interventions. The exploratory nature of this analysis highlights the need for longitudinal studies to further validate the PFIICP's responsiveness.

DISCUSSION

The present study provides initial validation evidence for the PFIICP, a novel 12-item questionnaire designed to assess the impact of physical functional activities on chronic pain. By adopting a formative measurement model, the PFIICP reflects the multidimensional nature of chronic pain's consequences, with each item contributing uniquely to the overall construct.

The wide range of Spearman's rho correlations (0.153 - 0.793) underscores the heterogeneity of the PFIICP items. While some items (e.g., I05) showed stronger associations with the total score, weaker correlations (e.g., I11) do not necessarily imply redundancy (even though this item may need further revision, namely in semantic terms). In formative models, items are not required to be highly intercorrelated, as they represent distinct facets of the construct.[5] Instead, their relevance lies in their theoretical alignment with the concept of functional disability caused by chronic pain, a functionally complex network of diverse aspects considered in these 12 different items.

The ICC value of 0.788 suggests that the PFIICP produces consistent results over time, which is crucial for longitudinal studies or clinical monitoring. This level of reliability indicates that the PFIICP can consistently track changes in patients' functional status.

Although the results of the exploratory responsiveness analysis did not reach statistical significance, the small effect size observed ($r = 0.166$) suggests that the PFIICP may have potential sensitivity to detect clinically relevant changes in future studies, especially with greater control of interventions performed during the follow-up period. It is important to note that this analysis complements the assessment of temporal consistency (stability of scores without interventions) by exploring the instrument's ability to capture individual variations in functional impact associated with changes in the clinical status of participants.

The strong correlations between the PFIICP and the BPI/PDI highlight the instrument's ability to measure constructs aligned with existing gold-standard measures. The construction and validation of this scale intends to objectify pain in clinical practice in terms of the physical repercussions on the individual's daily life. On the one hand it facilitates the interpretation of the healthcare provider who applies it, given that it is based on the affected body segments and, on the other, it allows the construction of an expected network of interactions of these same physical repercussions that result in the individual chronic pain.

The index is a practical, quick to answer (four minutes) and useful tool to objectify the real consequences of chronic pain of each person, their need for health care and ultimately, the social and economic costs that this means, mainly the need to resort to differentiated health care in hospital pain units, with increased costs of referral, use of specialized human resources and highly complex techniques. Because it is an objective, reproducible and reliable indicator of repercussion of pain, it can be assumed as a severity screening instrument and an indicator of the quality of care provided and, subsequently, a potential factor in the creation of public policies of general interest, given the scale of pain in the Portuguese society.[1,2]

Although the relatively small sample size, due and carried out in a real consultation context and respecting the regular appointments, may limit generalizability for the follow-up analysis, the inclusion criteria were very broad, particularly in terms of age and definition of chronic pain lasting

three months or more as the pathology, which minimized bias.

However, given the fact that the validation was done in a Pain Unit of a public general hospital, more studies are needed to validate the questionnaire in the general population in different settings.

Finally, the assumption of a formative model considers that the construct is defined by the unique contributions of each item rather than by their shared variance.[5] This approach reduces the risk of spurious relationships arising from methodological biases (e.g., social desirability bias, memory bias, acquiescence bias, fatigue effect),[13] as the focus is on the relevance and representativeness of the items rather than their internal consistency.

CONCLUSION

The PFIICP demonstrates promising psychometric properties as a tool for assessing the functional impact of chronic pain. Its adoption as a formative measurement model reflects the multifaceted nature of chronic pain's consequences. With promising test-retest reliability and convergent validity, the PFIICP holds potential for use in both clinical practice and research. Further studies are warranted to refine the instrument and evaluate its performance across diverse populations.

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AUTHOR CONTRIBUTIONS

FA, NS: Study design, writing of the manuscript.

PT: Data analysis and interpretation, 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

FA is the president of Associação Portuguesa para o Estudo da Dor (APED).

NS is the president of the Portuguese Agency for Clinical Research (AICIB).

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ACTA MÉDICA PORTUGUESA
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Da Preconceção à Amamentação: O que Pensam os Profissionais de Saúde e as Mulheres sobre a Suplementação Vitamínica

From Preconception to Breastfeeding: What Healthcare Professionals and Women Think about Vitamin Supplementation

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RESUMO

Na gravidez, os hábitos saudáveis, como uma dieta equilibrada e suplementação vitamínica, são essenciais para a saúde materno-fetal. As deficiências nutricionais podem causar malformações fetais, sendo que organizações como a Direção-Geral da Saúde recomendam a suplementação com ácido fólico e iodo. Contudo, as diretrizes para outros micronutrientes, como o ferro e o zinco, são menos claras, gerando dúvidas entre profissionais de saúde. Um estudo descritivo realizado entre março e agosto de 2023 avaliou a perceção de médicos, farmacêuticos e mulheres sobre a suplementação. Entre os 230 médicos entrevistados, 89,1% destacaram a importância da consulta pré-concecional, sendo o ácido fólico o suplemento mais recomendado. Na gravidez, 81,7% prescreveram ácido fólico, 49,6% ferro e 60,4% iodo. Contudo, apenas dois terços das mulheres relataram suplementação no pós-parto, evidenciando uma lacuna nos cuidados nesta fase. Entre os 433 farmacêuticos, 48% acreditam na necessidade de maior intervenção no aconselhamento sobre suplementação, especialmente no pós-parto, quando a procura por informações aumenta. Das 1107 mulheres inquiridas, 49% não realizaram consulta pré-concecional, muitas vezes obtendo informações de fontes informais, o que prejudica a adesão às recomendações médicas. Apesar da alta adesão à suplementação na gravidez, fatores como o custo e o receio de efeitos adversos ainda são barreiras. É essencial melhorar o aconselhamento antes, durante e após a gravidez, com estratégias personalizadas que envolvam médicos, farmacêuticos e programas comunitários, visando melhores resultados materno-fetais.

Palavras-chave: Aconselhamento; Amamentação; Cuidado Pré-Concepcional; Equipa de Cuidados ao Doente; Gravidez; Suplementos Nutricionais; Vitaminas

ABSTRACT

Pregnancy is a period when adopting healthy habits, such as a balanced diet and vitamin supplementation, is crucial for maternal and fetal health. Nutritional deficiencies can lead to fetal malformations, and organizations like the Directorate-General of Health recommend supplementation with folic acid and iodine. However, guidelines for other micronutrients, such as iron and zinc, remain less defined, causing uncertainty among healthcare professionals. A descriptive study conducted between March and August of 2023 assessed the perceptions of doctors, pharmacists and women regarding supplementation. Among the 230 physicians interviewed, 89.1% emphasized the importance of preconception consultations, with folic acid being the most recommended supplement. During pregnancy, 81.7% prescribed folic acid, 49.6% iron, and 60.4% iodine. However, only two-thirds of women reported postpartum supplementation, highlighting a gap in care during this phase. Among the 433 pharmacists, 48% recognized the need for greater involvement in advising on supplementation, particularly in the postpartum period, when the demand for information increases. In a survey of 1107 women, 49% did not attend a preconception consultation, often relying on informal sources for information, which hampers adherence to medical recommendations. Despite high adherence to supplementation during pregnancy, factors such as cost and fear of side effects remain barriers. Improving counselling before, during, and after pregnancy is essential, with tailored strategies involving doctors, pharmacists, and community programs to achieve better maternal and fetal health outcomes.

Keywords: Breast Feeding; Counseling; Dietary Supplements; Patient Care Team; Preconception Care; Pregnancy; Vitamins

A gravidez é um período em que as mulheres tendem a adotar hábitos mais saudáveis, incluindo cuidados com a dieta, com o objetivo de prevenir complicações e promover a saúde do feto. O desenvolvimento fetal depende diretamente da ingestão alimentar materna, sendo os défices nutricionais causas conhecidas de malformações e patologias fetais.[1]

A Direção-Geral da Saúde (DGS) destaca a importância do aconselhamento pré-concecional e da suplementação com micronutrientes, mantida durante a gravidez, devido à sua relação com o bem-estar materno-fetal, aconselhando o uso de ácido fólico na preconceção e durante o primeiro trimestre, para prevenir defeitos do tubo neural, e de iodo na preconceção e durante a amamentação exclusiva.[2,3]

O American College of Obstetricians and Gynecologists reforça a suplementação de ácido fólico e a avaliação dietética da grávida para assegurar o suprimento de nutrientes essenciais, como o cálcio, ferro, vitamina A, B12, D e outros.[4] Entretanto, diretrizes para outros micronutrientes, como o ferro, zinco e vitamina E, são menos claras.[2,5]

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Informações contraditórias sobre a segurança e eficácia dos suplementos nutricionais geram dúvidas entre profissionais de saúde, refletindo-se na prática clínica e na prescrição.[1]

Foi realizado um estudo observacional e descritivo entre março e agosto de 2023, através de entrevistas e questionários *online*. O objetivo foi avaliar a perceção dos profissionais de saúde e mulheres portuguesas sobre suplementação vitamínica na preconceção, gravidez e pós-parto.

MÉDICOS

Características sociodemográficas

Foram entrevistados 230 médicos de Ginecologia/Obstetrícia, 83,5% (n = 192) especialistas. Destes, 25% trabalhavam no Sistema Nacional de Saúde, 24% no setor privado e 51% em ambos.

Consulta de planeamento familiar/preconceção

Do total, 89,1% informaram sobre a importância da consulta pré-concecional; 90,4% promoveram estilo de vida saudável e 57% avaliaram hábitos alimentares. Suplementação recomendada: ácido fólico e iodo (42,1%), apenas ácido fólico (49%) e multivitamínicos (27%). Apenas 0,9% não recomendou suplementos (Fig. 1).

Consulta pré-natal e orientação pós-parto

Na consulta pré-natal, 81,7% prescreveram ácido fólico no primeiro trimestre, 49,6% prescreveram ferro nos segundo e terceiro trimestres e 60,4% prescreveram iodo. Foram prescritos multivitamínicos a 39% das grávidas, e a 38,3% a prescrição de suplementos foi baseada em análises. No pós-parto, 39,1% dos médicos recomendaram a toma de ferro, 38,7% recomendaram a toma de iodo, 37,4% recomendaram a toma de multivitamínicos e 16,1% não recomendaram suplementação (Fig. 1).

PROFISSIONAIS DE FARMÁCIA

Foram entrevistados 433 profissionais de farmácia. Destes, 30% foram abordados sobre suplementação por mulheres na preconceção e 69% foram abordados por mulheres no pós-parto (Fig. 1).

Sobre o seu papel, 48% consideraram que deveriam ser mais interventivos, 25% consideraram o seu aconselhamento indispensável, e 27% afirmaram restringir-se ao esclarecimento e venda de medicamentos prescritos.

MULHERES

Características sociodemográficas

Foram inquiridas 1107 mulheres, 78,4% com filhos, recrutadas através de um inquérito *online* anónimo, exclusivamente em português, disponibilizado através das redes sociais. A participação foi voluntária, não remunerada e o consentimento para a participação foi fornecido durante o preenchimento do questionário.

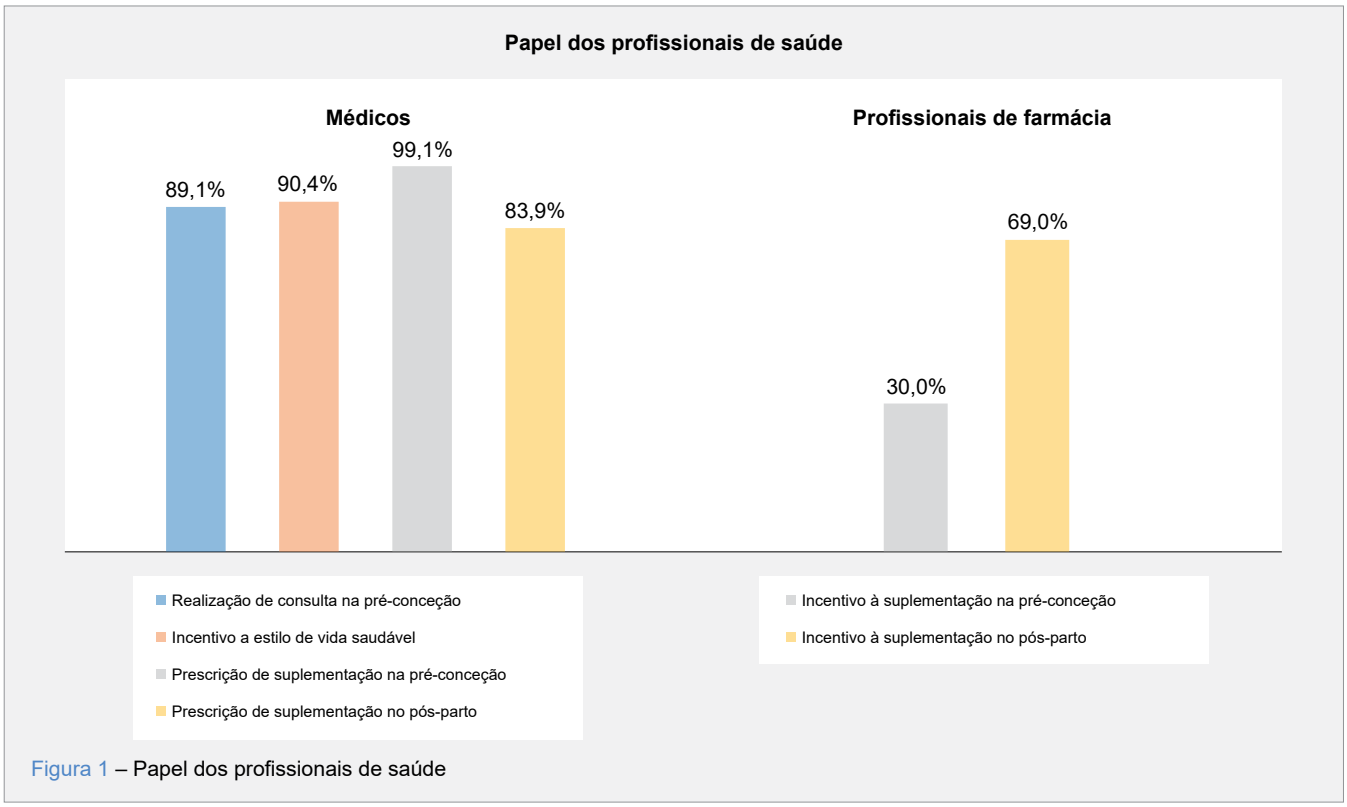

Figura 1 – Papel dos profissionais de saúde

Consulta de planeamento familiar/preconceção

Metade das mulheres inquiridas (49%) não realizou consulta pré-concecional. Entre as que realizaram, 85,6% iniciaram pelo menos um suplemento, 59,5% receberam recomendações sobre hábitos alimentares e suplementos e 55,4% receberam informação sobre hábitos de saúde (Fig. 2).

Consulta pré-natal e pós-parto

Durante a gravidez, 83,1% das mulheres realizaram suplementação (Fig. 2). Destas, 76,8% fizeram-no durante mais de três meses. Os suplementos mais comuns foram o ácido fólico (72%), ferro (54%), iodo (19%) e vitamina D (10%). No pós-parto, 81,9% realizaram consulta de puerpério, e 64% suplementaram na amamentação, sobretudo com ferro e iodo (Fig. 2).

As sociedades médicas destacam a importância da consulta pré-concecional. Neste estudo, 89,1% dos médicos abordaram o tema, o que traduz resultados semelhantes aos recolhidos a nivel internacional.[5] Durante a consulta, a promoção de um estilo de vida saudável e a prescrição de suplementos foram temas recorrentes, conforme recomendações da DGS.[2] Contudo, observou-se discrepância entre a perceção das mulheres e dos médicos, sugerindo que os temas podem ser abordados superficialmente.

No puerpério, a prescrição de iodo não foi universal, apesar dos benefícios verificados no desenvolvimento cognitivo da criança.[2] A literatura mostra que os cuidados no pós-parto são frequentemente negligenciados em comparação à gravidez.[6] No presente estudo, apenas dois terços das mulheres relataram suplementação no pós-parto.

Entre os profissionais de farmácia, metade reconheceu a necessidade de maior intervenção no aconselhamento. O aumento da procura de informação durante o pós-parto reflete a escassez de fontes seguras nesse período. A proximidade do farmacêutico com a comunidade destaca seu papel essencial no aconselhamento, mas é necessário capacitar estes profissionais com informação fidedigna.[7]

Metade das mulheres não realizou consulta pré-concecional, o que impacta negativamente a adesão à suplementação.[8] A gravidez não planeada, que corresponde a 37% dos casos em Portugal, e a prescrição informal de suplementos são fatores relevantes.[9] Muitas mulheres obtêm informações através de amigos ou das redes sociais, comprometendo a adesão às recomendações médicas.[5]

Neste estudo, a consulta pré-concecional mostrou ser determinante para a adesão à suplementação, com a maioria das mulheres a iniciar pelo menos um suplemento. Em contraste, outro estudo indicou que a suplementação é menos frequente na preconceção do que na gravidez, sendo que os profissionais acreditam que não existe um correto aconselhamento das mulheres pelos pares.[5]

Durante a gravidez, as taxas de suplementação observadas são semelhantes em estudos portugueses e internacionais. A suplementação com ácido fólico no primeiro trimestre atingiu os 90,8% em estudos portugueses.[1,8] As Como principais obstáculos à suplementação destacam-se não apenas os custos associados, baixos rendimentos maternos e dificuldade de acesso aos cuidados de saúde, mas também a falta de orientação médica, dúvidas sobre a sua eficácia e receio de efeitos adversos.[5,10]

Apesar da alta adesão à consulta pós-parto, apenas dois terços das mulheres relataram suplementação nesse

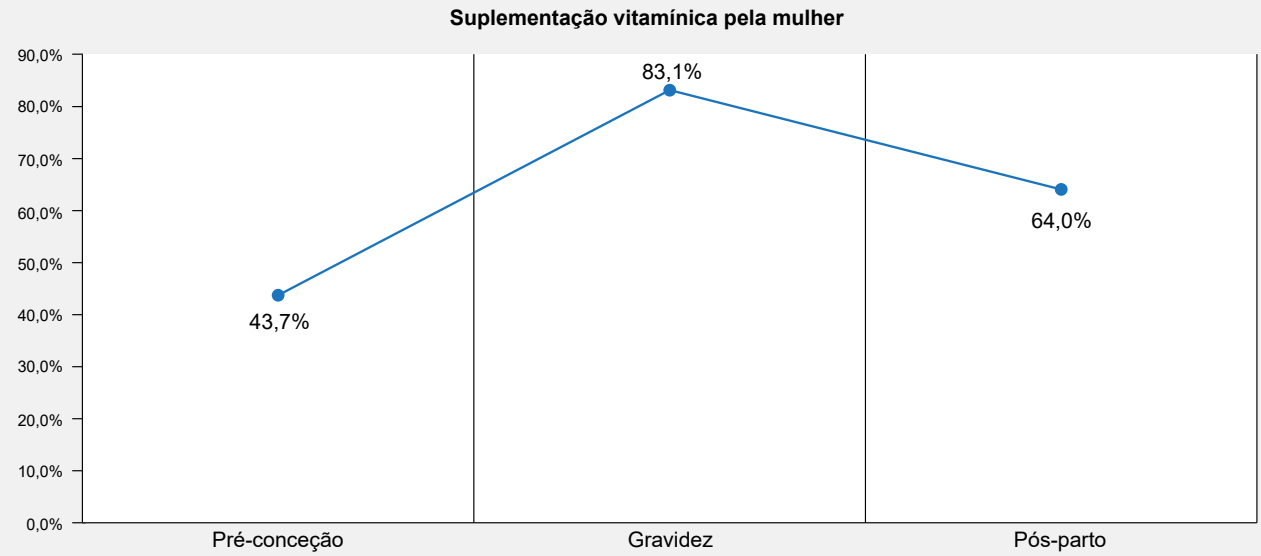

Figura 2 – Realização de suplementação vitamínica pela mulher

período, valor abaixo do esperado, destacando a necessidade de maior foco nos cuidados do puerpério.

A maioria dos médicos de Ginecologia/Obstetrícia reconhece a importância da consulta pré-concecional, porém, muitas mulheres não a realizam. A prescrição de suplementação foi satisfatória durante a gravidez, mas insuficiente no puerpério, especialmente quanto ao iodo na amamentação. Importa referir que no presente estudo não foram incluídos os médicos de Medicina Geral e Familiar, que desempenham um papel relevante na prescrição de suplementação, sobretudo em contextos de gravidez de baixo risco, o que poderá constituir um viés na interpretação dos resultados.

A procura por informação em farmácias duplica no pós-parto, sugerindo lacunas no aconselhamento médico nesse período. É essencial educar e aconselhar mulheres em idade fértil sobre suplementação vitamínica antes, durante e após a gravidez. Estratégias personalizadas, através de profissionais de saúde, programas comunitários e recursos informativos são fundamentais para melhorar os cuidados reprodutivos e os resultados materno-fetais.

CONTRIBUTO DOS AUTORES

MS: Recolha e análise de dados, escrita do manuscrito.

FS, JGB, AC: Revisão crítica do manuscrito.

TB: Recolha e análise de dados, escrita e revisão crítica do manuscrito.

Todas 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.

CONFLITOS DE INTERESSE

JGB recebeu pagamento ou honorários por palestras, apresentações, agências de palestrantes, redação de manuscritos ou eventos educacionais da Kernpharma.

AC recebeu honorários de consultoria da Bial; recebeu pagamento ou honorários por palestras, apresentações, agências de palestrantes, redação de manuscritos ou eventos educacionais da Organon, Theramex, Gedeon Richter, Bayer e Kern Pharma; recebeu apoio para viagens da Gedeon Richter, Organon, Bayer, Tecnimede, Theramex e Lilly; participou em conselhos de monitorização da segurança dos dados ou conselhos consultivos da Bayer, Organon, MSD, Tecnimede e Astellas; possui funções de liderança ou fiduciárias em SPDC, SPG e SPODOM, remuneradas ou não remuneradas.

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

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Advancing Access to Intestinal Microbiota Transplant: Bridging the Gap Between National Practices and the European Strategy

Facilitar o Acesso ao Transplante de Microbiota Intestinal: Alinhar as Práticas Nacionais com a Estratégia Europeia

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ABSTRACT

Clostridioides difficile is an opportunistic pathogen that can cause a range of conditions, from asymptomatic carriage to severe illness, posing a significant public health threat due to its high mortality rates and substantial healthcare costs. Traditional treatment options, including antibiotics, often fail to eradicate the infection, leading to recurrent cases that severely impact patients' lives. Intestinal microbiota transplant (IMT) has emerged as an effective strategy for decolonizing pathogenic agents, demonstrating safety and efficacy, particularly in treating recurrent *Clostridioides difficile* infection (rCDI). Despite its potential, access to IMT is limited due to safety concerns, logistical challenges, and a lack of proper guidance, underscoring the urgent need for structured intestinal microbiota banks (IMBs). These organized facilities are crucial for the collection, screening, processing, and distribution of intestinal microbiota preparations, thereby facilitating the clinical application of IMT. In this narrative review, we discuss the relevance of applying IMT for the treatment of rCDI in Europe, with a focus on Portugal. We highlight the existence and distribution of IMBs across Europe and their importance in improving access to IMT. This review also addresses the challenges in creating an IMB and the development of such a structure in Portugal as a centralized repository for high-quality, standardized microbiota preparations, making IMT accessible for national hospitals. Additionally, it emphasizes the need to raise awareness among healthcare providers and the public to support the broader adoption of IMT.
Keywords: Clostridioides difficile; Clostridium Infections; Europe; Fecal Microbiota Transplantation; Gastrointestinal Microbiome

RESUMO

Clostridioides difficile é um agente patogénico oportunista capaz de causar desde condições assintomáticas até doenças clínicas graves, representando uma significativa ameaça à saúde pública devido às suas elevadas taxas de mortalidade e aos substanciais custos associados aos cuidados de saúde. Os tratamentos tradicionais, incluindo antibióticos, muitas vezes falham em erradicar a infeção, o que leva a recorrências que afetam de forma significativa a qualidade de vida dos pacientes. O transplante de microbiota intestinal (TMI) surgiu como uma estratégia eficaz para a descolonização de agentes patogénicos, demonstrando segurança e eficácia, especialmente no tratamento de infeções recorrentes por *Clostridioides difficile*. Apesar do seu grande potencial, o acesso ao TMI é limitado devido a questões de segurança, desafios logísticos e à ausência de diretrizes claras, o que destaca a necessidade urgente de bancos de microbiota intestinal (BMI). Estas estruturas são essenciais para a recolha, rastreio, processamento e distribuição das preparações de microbiota intestinal, facilitando, assim, a implementação clínica do TMI. Nesta revisão narrativa, discutimos a relevância da aplicação do TMI no tratamento de infeções recorrentes por *C. difficile* na Europa, com especial enfoque em Portugal. Destacamos a existência e distribuição dos BMI na Europa e a sua importância na melhoria do acesso ao TMI. Esta revisão aborda também os desafios da criação de um BMI em Portugal, destacando a importância de um repositório centralizado de preparações de microbiota padronizadas e de alta qualidade, tornando o TMI acessível aos hospitais nacionais. Adicionalmente, sublinha a necessidade de sensibilizar os profissionais de saúde e o público em geral para apoiar a adoção mais ampla do TMI.
Palavras-chave: Clostridioides difficile; Europa; Infecções por Clostridium; Microbioma Intestinal; Transplante de Microbiota Fecal

INTRODUCTION

Over the past decade, intestinal microbiota transplantation (IMT), also known as fecal microbiota transplantation, has become a key area of biomedical research. It is based on restoring the disrupted gut microbiota of the patient by transferring processed fecal material and its microbiota from a healthy donor to the patient.[1] Robust scientific evidence has demonstrated the safety[2] and efficiency of this procedure, particularly for the treatment of recurrent *Clostridioides difficile* infection (rCDI).[3]

Clostridioides difficile is an opportunistic pathogen responsible for infections that can range from asymptomatic carriage to severe conditions, posing a significant public health concern due to its high mortality rates and associated healthcare costs.[4]

Numerous questions arise regarding IMT application in clinical practice, particularly concerning the perceptions and acceptance among physicians and patients, as well as operational and logistical challenges related to donor selection, material preparation, distribution, and delivery of IMT, along with the absence of oversight support and dedicated centres.[5]

This narrative review aims to critically evaluate the

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pertinence of IMT application in the context of rCDI in Europe and Portugal, identify best practices for the provision of IMT material, and underscore the importance of establishing sustainable infrastructures for the continuous supply of IMT, ensuring its ongoing availability in clinical practice.

METHODS

This narrative review follows a systematic approach to literature selection, with relevant studies identified through a comprehensive PubMed search using key terms like "fecal microbiota transplant", "Clostridioides difficile infection", and "microbiota banks". To ensure thoroughness, the search was supplemented by manually screening reference lists from pertinent studies. In alignment with the upcoming European Union new rules on substances of human origin (SoHO legislation), the term 'Intestinal Microbiota Transplantation' will be used instead of 'Fecal Microbiota Transplantation' since the "intestinal microbiota" is the substance of human origin that is regulated by the European Commission.

Intestinal microbiota transplant for recurrent *Clostridioides difficile* infection in Europe and Portugal

Clostridioides difficile is a Gram-positive anaerobic bacterium. *Clostridioides difficile* infection (CDI), has been recognized as a leading cause of healthcare-associated infections and imposes a substantial burden to public health and health-related costs globally.[6] However, it is acknowledged that CDI can also be acquired in the community by young, healthy individuals without prior exposure to antibiotics or hospitals.[7] The main factors increasing the risk of CDI include age, immunosuppression, hospitalization, and the use of antibiotics.[8,9]

The burden of healthcare-associated CDIs in acute care hospitals in the European Union and European Economic Area (EU/EEA) was estimated at 123 997 cases annually according to the European Center for Disease Prevention and Control (ECDC) surveillance report.[10] The direct attributable costs were estimated to be between €5798 - €11 202/episode,[11] with a total estimated burden of €3 billion per year in the EU.[12] Moreover, recurrent CDI has a particularly significant impact, both economically and in terms of strain on healthcare resources, underscoring the importance of identifying the most cost-effective strategy for its prevention and treatment.[13]

Antibiotic therapy is considered the standard treatment for CDI, although other therapies, such as IMT may be considered depending on disease severity and recurrence.[14] Substantial evidence in real-world practice,[15] supported by large-scale clinical trials and long-term follow-up studies[16,17] emphasize the efficacy and safety of IMT in rCDI, with clinical resolution rates approaching 90% across multiple studies,[18,19] and demonstrated effectiveness in preventing further relapses.[20] Moreover, in a network meta-analysis, Rokkas *et al* identified IMT as the most effective treatment for rCDI, outperforming other interventions, including standard antibiotics like vancomycin and fidaxomicin.[21] Thus, IMT not only demonstrates superior clinical resolution but also offers additional benefits by reducing the reliance on antibiotics, thereby minimizing the risk of development of antimicrobial resistance.[22] Additionally, IMT contributes to the restoration of a healthy gut microbiome, enhancing gut microbial balance and functionality.

From an economic perspective, data from a well-established IMT program in Denmark suggests that the average cost of an IMT procedure in a public hospital – whether administered via colonoscopy or nasojejunal tube – was €3095. This investment yielded a 42% reduction in hospital costs related to rCDI within the first year, primarily driven by fewer hospital admissions and shorter lengths of stay.[23] Moreover, in comparison to standard care for first or second episodes of CDI, the hospital observed €1645 lower costs over a 26-week period for patients treated with IMT, due to fewer admissions, reduced hospital contacts, and decreased medication use.[24]

Nevertheless, a Europe-wide survey conducted in 2019, across 31 IMT centers, in 17 countries, reported that only 1077 IMT procedures were performed for treating CDI, covering just 10% of the approximately 12 400 patients estimated to be eligible for this treatment each year. The authors concluded that there is a significant gap in IMT coverage, suggesting "the need to increase the IMT activity in Europe by at least 10-fold to meet the true, indicated need".[25]

In Portugal, the epidemiology of CDI has been documented.[26] Most patients are over 70 years old, 49.1% of the cases are classified as healthcare associated and 44% of primary episodes were community-associated. The primary risk factor for developing CDI was antibiotic exposure, affecting 86.0% of patients. These findings are consistent with reports from other European countries.[27] The study by Nazareth *et al* identified 385 cases of primary CDI across six public hospital centers in Portugal, revealing that 2.6% of these patients experienced multiple recurrences, providing a national framework of potential candidates for IMT. However, it was acknowledged that the rate of recurrent episodes is likely underestimated, as only hospitalized patients within the participating hospitals were included in the surveillance.

Data on IMT performed in Portuguese healthcare institutions is currently unavailable, and there is no national documentation regarding the number of transplants conducted in Portugal. Our literature review identified only a limited number of published studies on this subject, all of which involved hospital-based treatments with IMT prepared

on-site. In a single-case study, IMT was performed as a decolonization strategy in a patient infected with multidrug-resistant bacteria. In this case the donor was a relative.[28] In an observational study that included 28 patients treated with IMT between June 2014 and January 2017, to assess the safety and efficacy of IMT for the management of refractory and recurrent CDI, donors were unrelated volunteers selected and screened based on medical history and laboratory testing.[29] The same hospital team conducted a retrospective analysis to investigate intestinal decolonization of carbapenamase-producing Enterobacteriaceae in patients screened as positive for these resistant bacteria and undergoing IMT between 2014 and 2019.[30] Nonetheless, it is important to consider that additional patients in Portugal may have been treated with IMT and those cases may not be documented. However, it is reasonable to assume that the national results regarding the use of this microbiota-based therapy are significantly lower compared to those in other European countries.[25] The absence of an easy access to intestinal microbiota preparations could be one of the reasons that limits the use of IMT.

Additionally, limited awareness among healthcare providers and insufficient guidance from local regulatory authorities on procedure regulation[31] could also be limiting patient access to this life-saving therapy.

Intestinal microbiota transplant for microbiome related diseases

Beyond CDI, repairing the gut microbiota through IMT has opened novel therapeutic avenues for a number of potentially dysbiosis-related diseases.[32,33] Dysbiosis can be defined as an alteration in the composition or function of the gut microbiome[34] and it can be driven by several host and environmental factors.[35] Dysbiosis has been strongly associated with inflammatory bowel diseases (Ulcerative colitis and Crohn's disease),[36] but also with antibiotic-associated diarrhea,[37] metabolic disorders,[38] autoimmune diseases[39] and neurological disorders.[40]

While IMT has demonstrated effectiveness in treating rCDI, its potential in other clinical contexts remains uncertain. Data are limited to small, heterogeneous clinical trials, lacking the consistency needed to identify specific microbiome-derived therapeutic agents and the underlying mechanisms of action.[41,42] The human gut microbiota is a complex and diverse community of microorganisms that interact through metabolic, immune, and neuroendocrine pathways, making it difficult to pinpoint causal relationships between specific microbes and health outcomes.[43,44] Achieving consistent, long-term success with IMT is also challenging due to the gut microbiota's resilience. Donor's bacteria often fail to establish permanently, with recipients' microbes frequently returning to baseline after a few weeks.[45-47] Additionally, environmental factors like diet and medication can rapidly alter gut microbiota, adding potential confounding. Individual microbial signatures, shaped by unique environmental experiences, further contribute to varied responses among patients with similar diagnoses.[48,49]

Despite these challenges, several clinical trials have expanded our understanding of human microbial communities, underscoring new directions for research in this field. De Groot *et al* have shown that the donor's microbiota profile can affect metabolic outcomes after IMT.[50] In turn, Kootte *et al* concluded that the recipient's microbiota profile at baseline was decisive in defining the success of the engraftment.[45] In turn, Li *et al* suggested that donor-host interactions do not depend on the taxonomic affiliation of species nor on differences in relative abundance between donor and recipient species, but rather on an immune-based compatibility, with specific strains showing superior dominance over native species while others exhibit a resistance capacity.[51] While preliminary, these findings are promising and are encouraging further research across Europe (Table 1).[52]

Intestinal microbiota banks

The use of IMT in routine clinical practice requires a robust infrastructure reliant on voluntary donors, which has led to the emergence of intestinal microbiota banks (IMBs) as a model for scaling access to this treatment.[53] These banks have been fundamental in advancing IMT procedures, shifting from fresh stool preparations sourced from relatives, handled in basic laboratory settings, to frozen preparations or capsules containing carefully selected processed feces from anonymous, healthy donors.[54] Additionally, published guidelines from scientific consensus reports on donor identification, screening, and IMT-optimized protocols have been crucial in establishing best practices and defining a standardized model for IMBs.[55-57]

Intestinal microbiota banks are centralized facilities that provide ready-to-use donor intestinal microbiota preparations (IMP), minimizing the challenges regarding IMT production, distribution, and application.[58] They may operate at an institutional (e.g., university, hospital-based), national, or international level and are currently settled in several European countries.[56] Ideally, an IMB ensures that the IMT can be delivered safely, at scale, guaranteeing its wide access. This is possible through the centralization of donor selection, material processing and safety monitoring, functioning in a similar way to a blood bank.[59] The centralization of donors makes it possible to adopt systematic measures for donor identification and data protection, rigorous screening for transmittable diseases and pathogens, anonymization, long-term traceability of the product/raw material and the possibility of linking the patient to the specific administered

Table 1 – (section 1 of 2) Active clinical trials related to intestinal microbiota transplant (searched terms: "microbiota transplant | Not yet recruiting; Recruiting studies | Interventional studies) | Europe | Registered on clinicaltrials.gov"). In all studies, intestinal microbiota is the substance derived from human donors, reinforcing the need of microbiota banks for advancing the knowledge in the field of other diseases. Some studies were registered using the term "FMT", but in accordance with the new terminology adopted in this review, the intervention in the table is named as "IMT".

Country	Intervention	Condition	Identifier
Austria	IMT	Obesity	NCT06268990
	IMT	Acute graft-versus-host-disease after allogeneic hematopoetic stem cell transplantation	NCT03819803
	IMT combined with Atezolizumab plus Bevacizumab	Patients who failed to respond to prior immunotherapy for advanced hepatocellular carcinoma	NCT05750030
Belgium	IMT	Decolonization of Gram-negative multi-resistant organisms	NCT04188743
Denmark	IMT	Chronic diarrhea in patients with systemic sclerosis	NCT06333795
	IMT	Treatment-naïve patients with newly diagnosed chronic inflammatory diseases	NCT04924270
	IMT	Liver cirrhosis	NCT04932577
	IMT	Eradication of multidrug resistant organisms in the intestine	NCT05742074
	IMT	Anorexia nervosa	NCT05834010
	IMT	Microscopic colitis	NCT05998174
	IMT capsules	Checkpoint Inhibitor-mediated diarrhea and colitis	NCT06206707
	IMT and FVT	Restoration of the gut microbiome after cesarean section	NCT06264219
Finland	Lyophilized capsulated autological IMT	Gut microbiome restauration after treatment with antibiotics	NCT06250413
	IMT	Postoperative Crohn's disease	NCT04637438
	IMT	Initial clostridioides difficile enteritis	NCT05257538
	IMT	Irritable bowel syndrome associated food intolerance	NCT05361785
	IMT	Optimal route of IMT for irritable bowel syndrome	NCT05874830
	IMT	Prevention of recurrent urinary tract infections caused either by sensitive *E. coli* or ESBL-*E. coli*	NCT06050148
	IMT (maternal fecal transplant)	Preterm infant intestinal microbiota development	NCT06227845
France	IMT capsules	Severe irritable bowel syndrome	NCT06433180
	IMT	Prophylaxis of recurrent pouchitis after IMT in ulcerative colitis with ileo-anal anastomosis	NCT03524352
	IMT	Prevention of allogeneic hematopoietic stem cell transplantation complications and particularly draft-versus-host disease	NCT04935684
	IMT capsules	Eradicate colonizing emergent superbugs (multi-drug and extensive-drug resistant Gram negative bacteria)	NCT05035342
	IMT	IMT as a maintenance treatment following anti-TNF agent withdrawal in Crohn's disease patients	NCT04997733
	IMT capsules (MaaT033®)	Axial spondyloarthritis patients resistant to conventional treatment	NCT05654753

IM: intestinal microbiota; IMT: Intestinal microbiota transplant; CDI: clostridioides difficile infection; FVT: fecal virome transplantat; ESBL-*E. coli*: extended-spectrum beta-lactamase *escherichia coli*

product, active recruitment and donor loyalty program.[58] Material processing must be described in standard operating procedures, under a quality control program, including good manufacturing/laboratory practices, ensuring that the IMTs administered are consistent, safe, and traceable.[60] Moreover, with standardized preparation and storage methods, the risk of contamination and variability can be drastically reduced, leading to more predictable and effective treatments. At the same time, safety monitoring, one of the main concerns in IMT practice, requires the development of a suitable risk management system with all the critical steps along the process properly characterized, capable of

Table 1 – (section 2 of 2) Active clinical trials related to intestinal microbiota transplant (searched terms: "microbiota transplant | Not yet recruiting; Recruiting studies | Interventional studies) | Europe | Registered on clinicaltrials.gov"). In all studies, intestinal microbiota is the substance derived from human donors, reinforcing the need of microbiota banks for advancing the knowledge in the field of other diseases. Some studies were registered using the term "FMT", but in accordance with the new terminology adopted in this review, the intervention in the table is named as "IMT".

Country	Intervention	Condition	Identifier
Germany	Fecal filtrate transplantation *VS* IMT	Mild to moderate active ulcerative colitis	NCT03843385
Hungary	Fecal filtrate transplantation *VS* IMT	Multiple recurrent CDI	NCT04960306
Italy	IMT capsules	Hepatic encephalopathy	NCT06368895
	IMT	Patients with mild-to-moderate ulcerative colitis	NCT05739864
	Autologous IMT	Ameliorate nintedanib-induced diarrhea in patients with idiopathic pulmonary fibrosis	NCT05755308
	IMT	Eradicate intestinal colonization by carbapenem-resistant enterobacteriaceae	NCT05791396
	IMT	Relieve symptoms of irritable bowel syndrome without constipation	NCT05803980
	IMT	Relieve symptoms of irritable bowel syndrome with constipation	NCT05803993
	IMT	Recurrent CDI and ulcerative colitis: single infusion *versus* sequential approach	NCT06071312
Netherlands	IMT	Ulcerative colitis	NCT05998213
	IMT	Convert the response to immunotherapy in immune checkpoint inhibitors refractory metastatic melanoma patients	NCT05251389
	Lyophilized IMT capsules in combination with pre- and probiotics	Non-alcoholic steatohepatitis	NCT05821010
Norway	IMT	Axial spondyloarthritis	NCT06451588
	IMT derived from feces of clinical responders	Cancer patients who have failed immunotherapy	NCT05286294
Poland	IMT	Prophylaxis of necrotizing enterocolitis (premature infants)	NCT06333405
	IMT	Decolonize antibiotic - resistant bacteria	NCT06156956
Romania	IMT	Liver cirrhosis	NCT06478602
Spain	IM capsules	Recurrent diverticulitis	NCT06687382
Switzerland	IMT capsules	CDI first episode and first recurrence	NCT05266807
United Kingdom	IMT capsules	Cirrhosis	NCT06461208
	IMT	Primary sclerosing cholangitis	NCT06286709
	IMT	Intestinal microbiota transplant prior to allogeneic stem cell transplant	NCT06355583

IM: intestinal microbiota; IMT: Intestinal microbiota transplant; CDI: clostridioides difficile infection; FVT: fecal virome transplantat; ESBL-*E. coli*: extended-spectrum beta-lactamase *escherichia coli*

addressing risk identification, prevention, and minimization.[61]

A number of well-established IMBs in Europe have already published reports of their experience as IMT providers. Lacking a product-specific regulatory support, most IMBs, relying on formal or informal guidance from their health authorities, reported finding support in the National Tissues Act and the EU Tissues and Cells Directive (2004/23/EC), and in expert consensus reports when planning the most appropriate framework for assessing the quality, safety and traceability of donor feces.[59,62–65] It is also implied in most published reports that donor recruitment programs are challenging, especially due to the low eligibility rate and excessive costs of screening.[64] Nevertheless, following strict donor selection criteria, standardized processing and storage of IM suspensions, and consultation by a multidisciplinary team of IMT experts, results in safe and effective application of IMT, as reported by the Netherlands Donor Feces

Bank.[65] Intestinal Microbiota banking has proven to be cost-effective for two main reasons. First, one donor can serve for multiple IM donations, eliminating the restriction of having on-demand single-donation IMT procedures, resulting in better profitability of donor screening processes.[66] Secondly, laboratory costs can be significantly reduced due to the large amounts of samples collected from donor blood and feces.

Universal intestinal microbiota banking has emerged in Europe as a reliable source for IMT, and the best strategy to suppress the need for the product, both in clinical practice and in research. These banks are funded through a combination of national and European funds, grants, private investments, and donations. However, some of the western countries that face a high burden of microbiome-related diseases (e.g., intestinal bowel disease, obesity, and antibiotic-resistant infections), such as Portugal, are underrepresented in translational microbiome research. The Europe-wide survey conducted by Baunwall *et al* revealed that IMBs are concentrated in central axis countries,[25] showing a clear imbalance in the access to IMT, compromising both its use as therapy and in clinical research.

Establishing Portugal's first intestinal microbiota bank

Recognizing the absence of a national IMB and its crucial role in addressing public health issues, a multidisciplinary team initiated the establishment of the first Portugal IMB in 2020. Based at NOVA Medical School (NMS|FCM, UNL) and in partnership with YourBiome®, a spin-off of NOVA University, the project aims to support physicians and advance scientific knowledge by providing high-quality donor IMP. The working group, comprised of translational microbiome experts, research scientists, and specialists in infectious diseases and gastroenterology, is committed to improving education and awareness among physicians and patients. The goal is to foster greater confidence and willingness to perform the procedure while consistently prioritizing ethical standards and patient safety.

Following the European model, the Portuguese IMB draws on the experiences of existing IMBs and expert consensus reports, while adhering to the latest guidelines to establish a standardized biobanking process. The Portuguese IMB ensures the availability of high-quality, standardized IMP and enhances patient safety through rigorous screening protocols. These protocols are designed to minimize the risk of transmitting microbiome-related conditions and improve microbiota quality, leading to more predictable and effective treatment outcomes. This was possible by harnessing the extensive expertise and knowledge of the multidisciplinary team of collaborators, many of whom are leading experts with published, high-impact contributions in the field of microbiota research.[67-69] The Portuguese IMB is currently recruiting donors and is also providing IMP for distribution across several national hospitals. This initiative aims to improve access to IMT for patients with recurrent or refractory CDI and ensure equitable distribution among those clinically indicated for treatment.

Regulation

Products of human origin, as complex as feces, have a high potential risk of infecting the recipient. A careful and substance-specific regulatory approach especially targeted for the critical steps in the process is necessary. The European Union's Competent Authorities for Tissues and Cells have recognized that intestinal microbiota falls outside the scope of the Human Tissue Directive 2004/23/EC,[70] prompting discussions on revising the legislation to address new substances of human origin. In 2022, the European Commission (EC) adopted the proposal for a regulation on quality and safety standards for substances of human origin (SoHO)[71] intended for human application, and in April 2024 the regulation was approved by the European Parliament. This new regulation, to be effective from 2027, in which the IM is included, intends to implement the conditions for harmonization across Member States. The new regulation for SoHO, which reflects the experience of regulatory networks for blood products and/or tissues and cells, provides specific regulatory standards to ensure adequate quality and safety for intestinal microbiota transplantation, particularly in the context of regulation and inspection of IMBs, for donor protection and management, and for the implementation of a robust bio-surveillance system. Furthermore, the European Centre for Disease Prevention and Control has been tasked with developing technical guidelines for donor testing and deferral strategies, standardizing safety measures across member states and facilitating cross-border procedures to narrow gaps in availability.

It is expected that at some point, microbiota-derived drugs may supplant the complete donor intestinal ecosystem, but for now, conventional IMT remains the most suitable treatment, particularly for those with rCDI. Intestinal microbiota banks will remain a vital source of microbiota-based preparations for IMT, while analyzing long-term data on gut microbiome manipulation will shed light on the effects of IMT developments and policy changes.[72]

Final considerations and perspectives

Recognition of the beneficial therapeutic effect of IMT, particularly for the treatment of rCDI, has prompted scientific societies to issue recommendations and guidelines endorsing this life-saving therapy. Despite these advancements, its broader potential remains unclear. The medical and scientific community should support the establishment of IMBs, ideally staffed by multidisciplinary teams

responsible for clinical protocols, ongoing oversight, and dissemination of best practices, thereby enhancing both knowledge and confidence among practitioners. Intestinal microbiota banks must stay up to date with emerging scientific evidence, addressing technical, safety, and ethical considerations. Special emphasis should be placed on IM interactions within organ axes and other ecological niches in the human body to proactively prevent undesirable microbiota-mediated responses. Additionally, to support the establishment of IMBs and strengthen their structure, it is crucial to develop a regulatory and strategic framework at the national level, that promotes broad and equitable therapeutic access in line with established standards. Even though the adoption of the SoHO Regulation will harmonize guidelines for donor screening , each country still needs to develop specific guidelines and establish its own screening panel based on its unique social, cultural and epidemiological context, in addition to the general recommendations.

A significant challenge in establishing an IMB relies in raising public awareness about the critical role of the human microbiota in health and disease. The transfer of knowledge between the scientific and medical communities and the general public is therefore essential to enhance donor recruitment efforts. Also, the healthcare and scientific communities must come together to properly define relevant terms, rather than perpetuating the use of concepts and words that can lead to misinterpretation. For example, terms like “feces” or “stool” should not be routinely associated with the therapeutic use of the IM, as they may convey a misleading or trivialized understanding to the general public.

There has been a paradigm shift in global public health strategy for the treatment of *Clostridioides difficile*, transitioning from the traditional reliance on antibiotics to the use of IMTs. To ensure optimal care, it is crucial to stay aligned with this evolving approach and the development of new microbiota-based therapies, avoiding delays in adopting modern treatment advancements. As awareness of IMT as a therapeutic option grows, denying patients access due to unfamiliarity to the procedure or logistical constraints may increase unsupervised, ‘home-made’ procedures using unscreened feces from friends or relatives, raising the risk of inadvertently transplanting harmful pathobionts. It is crucial to raise awareness, improve education, and increase familiarity with IMT among healthcare practitioners, especially regarding its technical aspects, encouraging clinicians to critically review the literature, ensuring evidence-based clinical decisions. Simultaneously, managing patient perceptions and expectations is essential for the broader acceptance of IMT.

Understanding microbiome-mediated health and disease mechanisms is essential for developing new clinical microbiome-based interventions. While alternative approaches like defined consortia and IMT-like products are under development, donor-derived IMT currently remains unmatched. Dedicated structures for Intestinal Microbiota Banking are essential for addressing urgent public health challenges related to gastrointestinal disorders and beyond, while also contributing to the development of robust scientific evidence. Looking ahead, gut microbiota-based therapy is expected to evolve toward more accessible and standardized treatments, including oral formulations with well-defined ingredients, clear mechanisms of action, and proven safety profiles. Future advancements may emphasize personalized microbiome restoration, tailoring treatments to individual patient needs based on clinical assessments.

AUTHOR CONTRIBUTIONS

LD, DP, CM: Writing and critical review of the manuscript.

HP, PP, CC: 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

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ACTA MÉDICA PORTUGUESA
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Reactive Infectious Mucocutaneous Eruption: A Rising Enigma

Erupção Mucocutânea Infeciosa Reativa: Um Enigma em Ascensão

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ABSTRACT

Reactive infectious mucocutaneous eruption is a rare condition that predominantly occurs in pediatric patients following a respiratory infection, most commonly caused by *Mycoplasma pneumoniae*. It is characterized by prominent mucositis, usually with minimal or absent skin involvement. We present the case of a nine-year-old male admitted with severe oral mucositis and a penile lesion compromising bladder emptying. During hospitalization, dispersed cutaneous lesions emerged along with bilateral conjunctival hyperemia. The etiological investigation detected *Mycoplasma pneumoniae* in respiratory secretions, with positive IgM and IgG serology. Treatment included azithromycin, intravenous immunoglobulin and methylprednisolone, resulting in progressive clinical improvement. This case highlights the importance of recognizing reactive infectious mucocutaneous eruption. It can be challenging to differentiate from Stevens-Johnson syndrome, but it tends to have a more favorable clinical course. Early initiation of supportive care and multidisciplinary support are crucial for a good prognosis.
Keywords: Exanthema; Mucositis; Mycoplasma pneumoniae

RESUMO

A erupção mucocutânea infeciosa reativa é uma entidade rara que ocorre predominantemente em idade pediátrica após uma infeção respiratória, na maioria dos casos causada por *Mycoplasma pneumoniae*. Caracteriza-se por mucosite exuberante, com envolvimento cutâneo escasso. Descreve-se o caso de uma criança de nove anos internada por quadro de mucosite oral exuberante e lesão ao nível da glande com compromisso do esvaziamento vesical. Durante o internamento, desenvolveu lesões cutâneas dispersas e hiperemia conjuntival bilateral. A investigação permitiu a deteção de *Mycoplasma pneumoniae* nas secreções respiratórias, com IgM e IgG específicos positivas. O tratamento incluiu azitromicina, imunoglobulina endovenosa e metilprednisolona endovenosa, resultando em melhoria progressiva e recuperação completa sem sequelas. Este caso pretende alertar para o diagnóstico de erupção mucocutânea infeciosa reativa. O diagnóstico diferencial com síndrome de Stevens Johnson e outras toxidermias pode ser difícil, apresentando a erupção mucocutânea infeciosa reativa uma evolução clínica mais favorável. O início precoce do tratamento de suporte e o apoio multidisciplinar são essenciais para um bom prognóstico.
Palavras-chave: Exantema; Mucosite; Mycoplasma pneumoniae

INTRODUCTION

Reactive infectious mucocutaneous eruption (RIME) is a serious mucocutaneous adverse reaction predominantly affecting children and adolescents after respiratory infections.[1]

Epidemiologically, RIME predominantly affects male patients, with a mean age of around 12 years, and often occurs during the winter months.[1] Although *Mycoplasma pneumoniae* is considered the primary causal agent, other pathogens, including *Chlamydia pneumoniae* and various respiratory viruses, such as SARS-CoV-2, have also been implicated.[2-4]

This condition is characterized by pronounced mucositis, typically with minimal or absent cutaneous involvement, distinguishing it from conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are characterized by distinct pathophysiological mechanisms and clinical courses.[5] Oral mucosal involvement in RIME is nearly universal and bilateral conjunctivitis and urogenital lesions may be present. As histopathological findings are not pathognomonic, distinguishing this condition from other mucocutaneous conditions can be challenging.[6]

In 2015, the term 'mycoplasma pneumoniae-induced rash and mucositis' (MIRM) was introduced to differentiate mucocutaneous diseases linked to *Mycoplasma* from SJS/TEN.[7] However, due to the potential of other viral and bacterial agents to elicit similar mucocutaneous involvement, the broader classification of 'RIME' was proposed.[4]

CASE REPORT

A previously healthy nine-year-old boy presented with a 10-day history of fever accompanied by dry cough, followed by the appearance of oral mucosal lesions three days before admission. He was first evaluated in the emergency department one week after the onset of symptoms, where he was diagnosed with herpetic gingivostomatitis and discharged with oral acyclovir. As his condition deteriorated, with progressive difficulty in oral intake and a new erosive lesion on the glans, he was readmitted to the emergency department.

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On clinical examination, the patient exhibited numerous extensive aphthous and vesicular lesions in the oropharynx and a vesicular lesion on the urethral mucosa. There were no cutaneous exanthems nor other significant findings. Due to the extensive oral mucositis with urethritis and inability to tolerate oral intake, hospitalization was warranted.

The initial laboratory findings showed raised inflammatory markers (white blood cell count 12 450/mcL (reference range 3600 – 11 000/mcL), C-reactive protein 59.4 mg/L (reference range < 3 mg/L), with no other abnormal findings. The chest X-ray revealed non-specific bilateral interstitial infiltrates.

On the first day of hospitalization he developed vesicular, bullous, and target-like lesions on the face, trunk, abdomen, and lower limbs, accompanied by bilateral palpebral edema and conjunctival hyperemia, as well as photophobia (Figs. 1 and 2). Hemorrhagic crusting of the lips and erosions on the tongue and oral mucosa were also observed. Due to significant edema and lesions on the glans, the patient underwent bladder catheterization under anesthesia to prevent urinary tract obstruction.

Given the severity of the condition, SJS was initially suspected, leading to the administration of intravenous immunoglobulin on the second and third days of hospitalization. The patient was evaluated by Immunoallergology, and his prior medication history included paracetamol and antihistamines, resulting in an algorithm of drug causality for epidermal necrolysis (ALDEN) score of -1, (indicating that the suspected drug is considered an unlikely cause) which significantly reduced the likelihood of an SJS diagnosis.

Key diagnostic tests detected *Mycoplasma pneumoniae* in upper respiratory secretions by polymerase chain reaction (PCR) and a positive IgM and IgG serology. Other infectious agents, including herpes simplex, enterovirus, adenovirus, influenza, SARS-CoV-2, and *Chlamydia pneumonia* were not detected.

Considering the severe mucositis with minimal cutaneous involvement and evidence of recent *Mycoplasma pneumoniae* infection, the diagnosis of RIME was made. The patient received supportive care, including topical petrolatum jelly on skin lesions, ocular lubricants, daily hyaluronic acid-based solutions for mucosal lesions, saline compresses on the lips and oral mucosa, and oral rinses of aminocaproic acid twice daily. Due to severe pain related to the mucositis, enteral intake became unbearable, requiring the insertion of a central venous access and personalized parenteral nutrition. On day five of hospitalization, due to worsening blistering lesions and mucosal involvement with inability to tolerate oral feeding, methylprednisolone (1 mg/kg/day) was initiated for five days. Five days of azithromycin (10 mg/kg/day) were initially prescribed and on day seven of hospitalization, intravenous amoxicillin-clavulanate 150 mg/kg/day was added for seven days due to suspected superinfection of the cutaneous lesions. The patient was also assessed by the Physical Medicine and Rehabilitation team and the Psychology department.

New cutaneous and mucosal lesions were observed until day six, with limited involvement of both upper and lower extremities. Beginning in the second week, the patient showed gradual improvement in both mucositis and

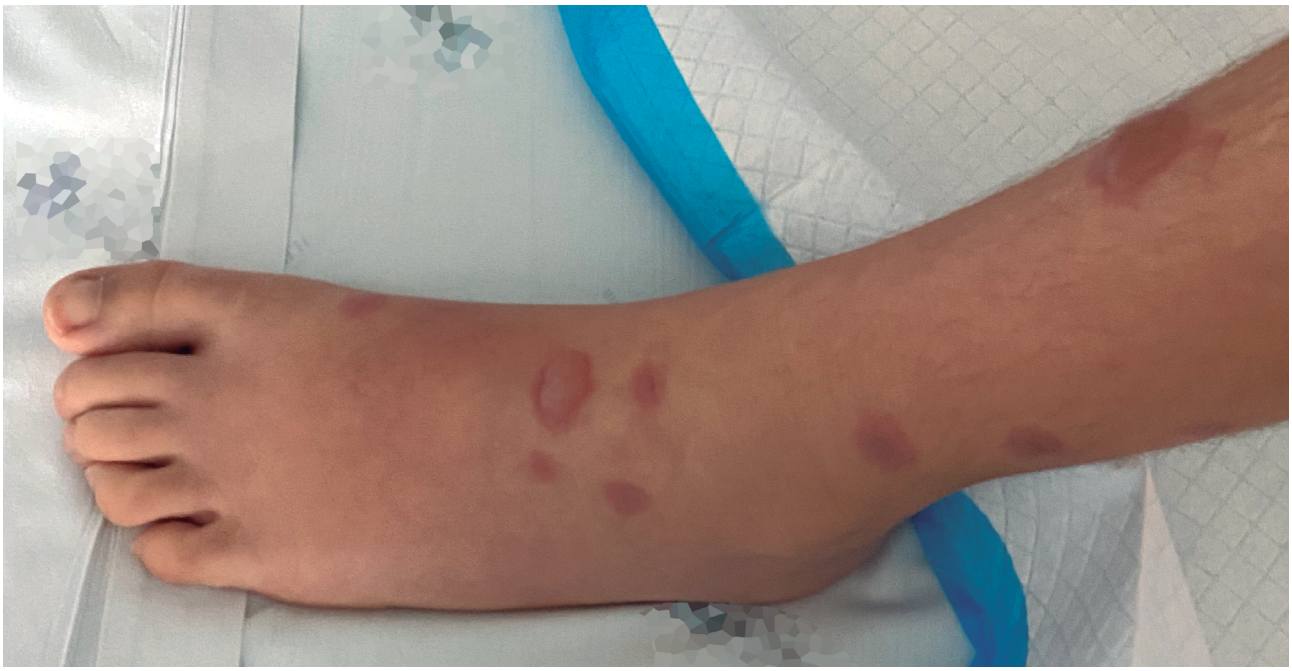

Figure 1 – Vesicular, bullous, and target-like lesions on the lower limb on the third day of hospitalization

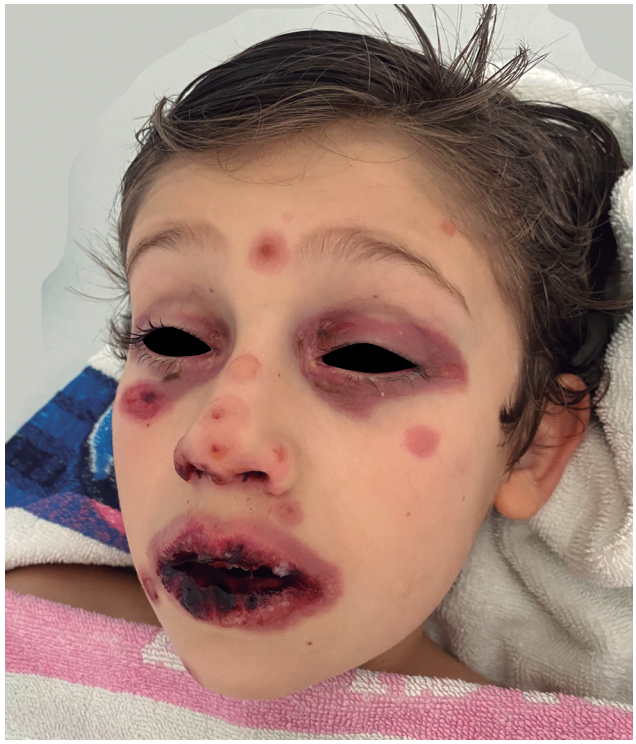

Figure 2 – Extensive mucositis with involvement of the palpebral, conjunctival, nasal and oral mucosa and vesicular and target-like lesions on the face on the fifth day of hospitalization

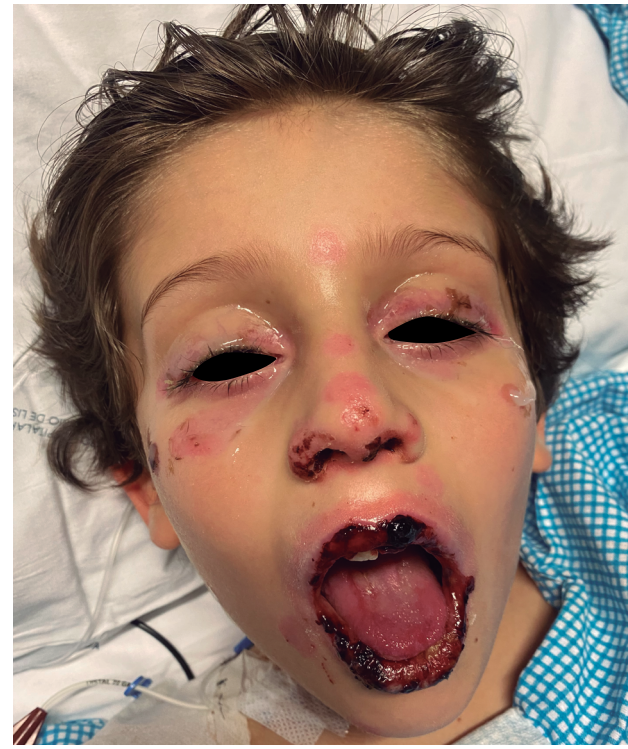

Figure 3 – Improvement of mucositis, characterized by resolution of conjunctival and palpebral hyperemia and significant improvement of lesions affecting the oral mucosa and facial regions on the thirteenth day of hospitalization

rash. (Fig. 3). Parenteral nutrition was suspended on the sixteenth day, and the patient was discharged on day eighteen of hospitalization for outpatient follow-up. The patient exhibited complete recovery, with no apparent sequelae.

DISCUSSION

This case highlights the importance of recognizing RIME, particularly in children who present with severe mucositis following respiratory infections. The identification of RIME relies heavily on the clinical history, including prodromal respiratory symptoms followed by the emergence of mucocutaneous lesions, as demonstrated in our case.[8] Given the potential clinical overlap with conditions such as SJS/TEN, early identification is vital for guiding appropriate management and preventing complications.[7]

Recent reports from the Centers for Disease Control and Prevention (CDC) highlighting a rising incidence of *Mycoplasma pneumoniae* infections in the United States, alongside with similar trends observed across Europe, suggest that this increase may contribute to a corresponding rise in cases of RIME in the pediatric population.[9,10]

The management of RIME is primarily supportive, focusing on symptomatic relief, hydration, nutrition maintenance, and vigilant monitoring for potential complications. Antimicrobial agents, such as azithromycin, target the underlying infection, but their impact on disease duration is unclear. As such, treatment decisions should be individualized based on clinical severity, microbiological evidence, and potential risk of transmission. Similarly, evidence supporting the efficacy of intravenous immunoglobulin or systemic corticosteroids (used in cases of extensive mucosal involvement) is limited and requires careful consideration.[11,12] In our case, IVIG was administered early in the clinical course due to the initial suspicion of Stevens-Johnson syndrome, which prompted an aggressive treatment approach. Some authors suggest a potential immunomodulatory role, particularly in severe or refractory cases, yet no controlled studies have definitively demonstrated improved outcomes with its use in RIME. The overall prognosis of RIME is favorable, with high rates of complete recovery and a low incidence of long-term sequelae.[6] However, recurrence is not uncommon and may occur in 9% - 38% of cases, typically triggered by subsequent infections rather than reexposure to the initial pathogen.[11]

In conclusion, RIME represents a significant, yet often underrecognized, mucocutaneous reaction within pediatric populations. Heightened awareness and understanding

Table 1 – Diagnostic criteria for RIME[12]

Diagnostic criteria - RIME
1 – Mucocutaneous eruption involving one or more sites with less than 10% body surface area involvement.
2 – Presence of vesicular or target-like lesions that are atypical, sparse and dispersed.
3 – Non-suggestive medication history.
4 – Prodromal period (cough, fever, malaise) occurring 7 - 10 days before.
5 – Clinical, radiological or laboratory evidence of an infectious agent.

of its clinical features, diagnostic criteria (Table 1) and management strategies are essential for optimizing patient outcomes. Continued research into the underlying mechanisms, potential genetic predispositions, and effective treatment protocols for RIME is warranted to improve care for affected patients and to further clarify its relationship with other mucocutaneous diseases.

AUTHOR CONTRIBUTIONS

JVL: Literature review and writing of the manuscript.

APL, AMG, TMS: Writing and critical review of the manuscript.

CG: 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.

PARENTAL CONSENT

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Dorsal Hand Involvement in Porphyria Cutanea Tarda

Atingimento do Dorso das Mãos na Porfiria Cutânea Tarda

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Keywords: Alcoholism; Porphyria Cutanea Tarda
Palavras-chave: Alcoolismo; Porfiria Cutânea Tarda

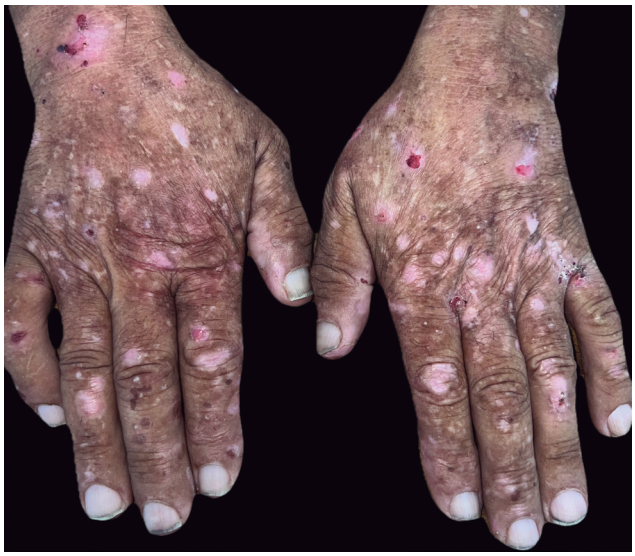

Figure 1 – Macular erythema, erosions, crusting, and hyper-/hypopigmented scarring present on the dorsum of the hands

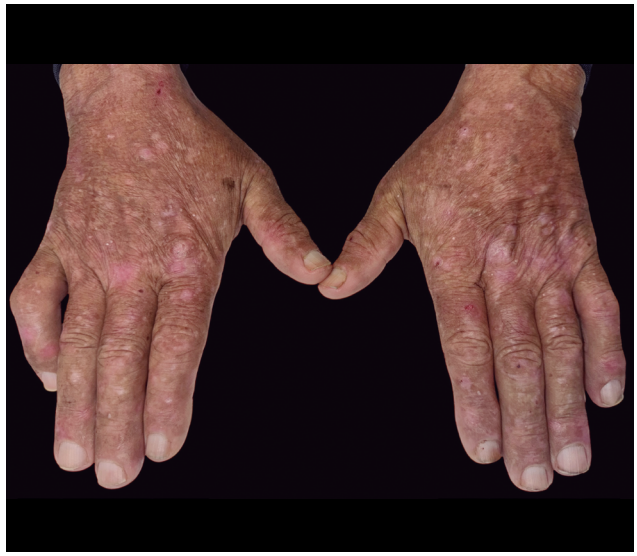

Figure 2 – Improvement of cutaneous lesions at 16-week follow-up

A 60-year-old male patient with a history of alcohol use disorder and smoking presented with skin fragility, hyper-/hypopigmented scars, macular erythema, and excoriated, ulcerated lesions on photo-exposed areas, particularly the backs of the hands (Fig. 1). Diagnostic work-up revealed elevated liver enzymes, ferritin level of 1600 ng/mL (reference range: 24 - 336 ng/mL) and increased levels of urinary uroporphyrin (871 µg/24h, reference range: < 60 µg/24h), supporting the diagnosis of porphyria cutanea tarda (PCT). Hepatitis C virus (HCV) serology and HFE mutation testing were negative. As the patient refused phlebotomy, treatment with hydroxychloroquine (200 mg twice weekly) and photoprotection was initiated, alongside alcohol cessation, leading to cutaneous improvement over the subsequent four months (Fig. 2). Porphyria cutanea tarda results from decreased uroporphyrinogen decarboxylase (UROD) activity, which can be acquired in the context of iron overload and susceptibility factors such as alcohol, smoking, HCV/human immunodeficiency viruses (HIV) infection, hemochromatosis, and UROD mutation.[1-3] It presents with photosensitivity, skin fragility and blistering in sun-exposed areas.[1-3] Management includes eliminating predisposing factors, phlebotomy or low-dose hydroxychloroquine.[4]

AUTHOR CONTRIBUTIONS

GPR, MBC: Study design, data interpretation, writing of the manuscript.

AM: Study design, data interpretation, 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.

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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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Diagnosis and Laboratory Follow-Up of Patients with Multiple Myeloma: Guidelines from the Portuguese Multiple Myeloma Group

Diagnóstico e Seguimento Laboratorial de Doentes com Mieloma Múltiplo: Recomendações do Grupo Português do Mieloma Múltiplo

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ABSTRACT

Multiple myeloma is a neoplasm of plasma cells that in most cases is associated with the secretion of monoclonal immunoglobulins and can involve multiple organs. Its timely diagnosis is essential to limit or avoid irreversible damage and dysfunction of target organs. Appropriate initial stratification of patients allows for optimization in the selection and sequence of therapy, as well as proper follow-up during treatment and monitoring, impacting survival. These laboratory guidelines from the Portuguese Multiple Myeloma Group provide recommendations for the diagnosis and laboratory follow-up of patients with multiple myeloma. The follow-up and diagnosis of patients with other clinically significant monoclonal gammopathies were not included in this text. This article was based on international guidelines, scientific publications, and the experience of a panel of specialists in clinical and laboratory fields dedicated to the study and treatment of multiple myeloma.

Keywords: Clinical Laboratory Techniques; Multiple Myeloma/blood; Multiple Myeloma/diagnosis; Portugal; Practice Guidelines as Topic

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RESUMO

O mieloma múltiplo é uma neoplasia de plasmócitos que, na maioria dos casos, se associa à secreção de imunoglobulinas monoclonais e que pode cursar com um atingimento multiorgânico. O diagnóstico atempado do mieloma múltiplo é essencial para evitar ou limitar danos irreversíveis e disfunção dos órgãos-alvo. A apropriada estratificação inicial dos doentes permite otimizar a seleção e a sequência da terapêutica, assim como o correto seguimento durante o tratamento, com impacto na sobrevivência. As presentes recomendações laboratoriais do Grupo Português do Mieloma Múltiplo oferecem orientações para o diagnóstico e seguimento laboratorial dos doentes com mieloma múltiplo. O seguimento e diagnóstico de doentes com outras gamapatias monoclonais de significado clínico não foram incluídos neste texto. A sua elaboração tem por base orientações internacionais, publicações científicas e experiência de um painel de especialistas nacionais das áreas clínicas e laboratoriais dedicados ao estudo e tratamento do mieloma múltiplo.

Palavras-chave: Guias de Prática Clínica; Mieloma Múltiplo/diagnóstico; Mieloma Múltiplo/sangue; Portugal; Técnicas de Laboratório Clínico

INTRODUCTION

Multiple myeloma (MM) is a hematologic neoplasm characterized by the proliferation of clonal plasma cells in the bone marrow (BM). It is often associated with the production of large quantities of monoclonal immunoglobulin (Ig), commonly referred to as monoclonal protein (MP), M-protein, or paraprotein. The MP can consist of intact Ig (the pair composed of both light and heavy chains) or, in some cases, only the Ig light chain. In rare cases (3% - 5%), MM may be non-secretory or oligo-secretory (it either does not produce, does not secrete, or secretes minimal amounts of MP). The diagnostic criteria for plasma cell dyscrasias are based on the guidelines from the International Myeloma Working Group (IMWG) (Table 1).[1]

Multiple myeloma is typically preceded by a pre-malignant stage called monoclonal gammopathy of undetermined significance (MGUS), followed by an intermediate, still asymptomatic stage known as smoldering MM (SMM), which is associated with a higher risk of progressing to symptomatic MM.[2-4] The term “monoclonal gammopathy of clinical significance” was introduced to describe monoclonal gammopathies with target organ involvement that do not meet MM or AL amyloidosis criteria. Its designation specifies the target organ affected, such as renal, cutaneous, or neurological monoclonal gammopathy.[5] Other plasma cell dyscrasias include solitary bone or extramedullary plasmacytoma, heavy or light chain deposition diseases, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), which are not covered in these recommendations. These guidelines specifically focus on the diagnosis and laboratory follow-up of MM.

The diagnosis of MM can be a lengthy and complex process, requiring the presence of clonal plasma cells in the bone marrow (≥ 10%) and the identification of disease markers that define myeloma-defining events (Table 1).[1] However, clinical symptoms often appear late and overlap with those of more common conditions, particularly in the elderly, such as bone pain, which can hinder early diagnosis and delay the start of MM treatment, negatively impacting prognosis and patient quality of life. Therefore, a well-targeted laboratory investigation is essential for an early and differential diagnosis of MM.

Due to the heterogeneous clinical course of MM, it is crucial to establish an algorithm for its diagnosis and staging, identify biomarkers for proper risk stratification, evaluate treatment response during different phases of the disease, and manage potential toxicities during or after treatment. While the laboratory plays a significant role in this process, the clinical information provided is equally important for selecting and optimizing the tests performed at each stage of disease evaluation.

Higher sensitivity and specificity may lead to quicker and more precise recognition of the disease, as well as to more individualized treatments regarding the patient and the MM subtype, while maximizing efficacy and minimizing adverse effects.

Despite the extensive information available on laboratory methods for the diagnosis and follow-up of MM, there is a lack of harmonization in the methodologies used, their interpretation, and the presentation of results.

In this article, the Portuguese Multiple Myeloma Group (PMMG) offers its recommendations for the laboratory diagnosis and follow-up of MM patients, providing a valuable tool to support timely and informed decision-making. These recommendations are based on international guidelines, scientific publications, and the expertise of clinical and laboratory specialists dedicated to the study and treatment of MM.

Most of the recommendations presented are grade C, based on level 4 evidence (evidence from expert committee reports and/or clinical experiences of respected authorities). When possible, level 1 - 3 evidence (based on randomized controlled trials, or well conducted non-randomized studies) was sought, with supporting references provided.

LABORATORY DIAGNOSIS

Significant advances in the understanding of MM biology have led to the development of various innovative therapies. Additionally, recently introduced methodologies enable more accurate evaluations, including the identification of prognostic factors that help recognize high-risk patients.

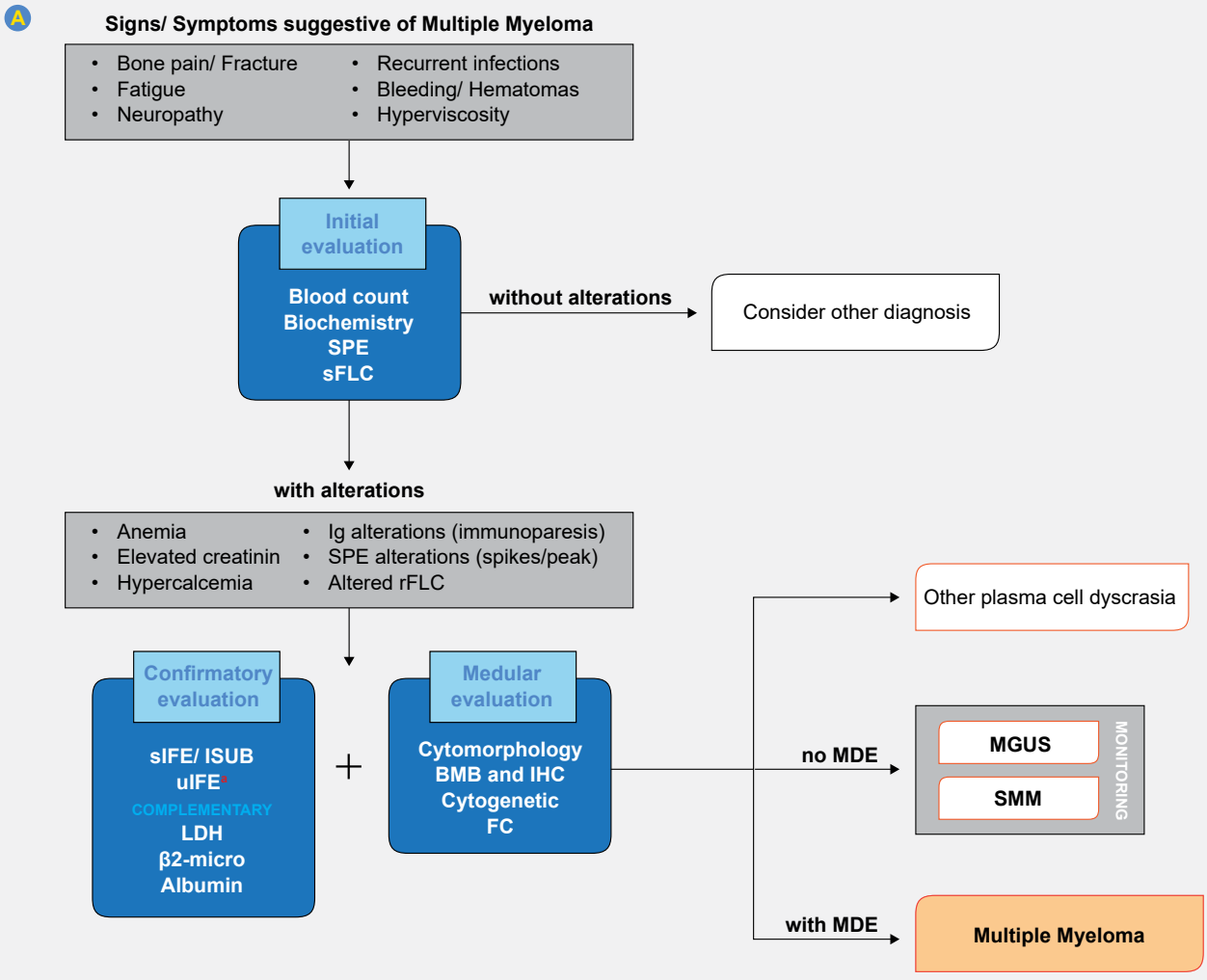
Clinical suspicion of MM serves as the starting point for its diagnostic algorithm (Fig. 1). This suspicion may be

Table 1 – Diagnostic criteria according to the International Myeloma Working Group (IMWG), adapted from Rajkumar *et al*, 2014.[1]

A	
Disorder	**Diagnostic criteria**
Monoclonal gammopathy of undetermined significance (MGUS)[a]	All criteria must be met: Non-IgM MGUS - Serum MP (non-IgM) < 30 g/L - Clonal BM plasma cells < 10% - Absence of myeloma defining events (MDE) Light chain MGUS - No Ig heavy chain expression on SIF - Abnormal FLC ratio (< 0.26 or > 1.65) - Urinary MP < 500 mg/24 hours - Clonal BM plasma cells < 10% - Absence of MDE IgM MGUS - Serum IgM MP < 30 g/L - BM lymphoplasmacytic infiltration < 10% - No evidence of LPD, AL amyloidosis or other lesions associated with light chains, heavy chains, or Ig
Smoldering multiple myeloma (SMM)	Both criteria: - Serum MP ≥ 30 g/L or urinary MP ≥ 500 mg/24 hours and/or clonal BM plasma cells 10% - 60% - Absence of MDE or amyloidosis
Multiple myeloma (MM)	Both criteria: - Clonal BM plasma cells ≥ 10% or BMB-proven bony or extramedullary plasmacytoma - Any of the MDE
Solitary plasmacytoma (SP)	All criteria must be met: - Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells - Absence of clonal BM plasma cells - No osteolytic lesions on skeletal radiography, CT or PET-CT - Absence of CRAB or amyloidosis
SP with minimal marrow involvement	Same as SP except: - BM clonal plasma cells < 10%
Non-secretory MM	- BM plasma cells ≥ 10% or biopsy-proven bone lesion - CRAB - Absence of serum or urinary MP
Plasma cell leukemia (PCL)	Diagnosis of MM and PB plasma cells ≥ 5%[b]

B		
Myeloma defining events (MDE)		
SLiM	(S) Clonal BM plasma cells ≥ 60%[c]	
	(Li) Involved/ uninvolved serum FLC ratio ≥ 100[d]	
	(M) > 1 focal lesion in MRI[e]	
CRAB	(C) Hypercalcemia	Serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
	(R) Renal failure	eGFR < 40 ml/min/1.73 m^2 or serum creatinin > 177 µmol/L (> 2 mg/dL)
	(A) Anemia	Hb < 10 g/dL or > 2 g/dL below the lower limit of normal
	(B) Bone lesions	One or more osteolytic lesions on skeletal radiography, CT or PET-CT

a: MGUS comprises three variants: non-IgM, Light chain, IgM.
b: Fernández de Larrea *et al*, 2021.[30]
c: Clonality established by light chain κ/λ restriction using flow cytometry, immunohistochemistry or immunofluorescence.
d: Involved FLC must be ≥ 100 mg/L.
e: Each focal lesion must be ≥ 5 mm. If BM clonal plasma cell < 10%, more than one lesion is necessary to distinguish solitary plasmacytoma from minimal marrow involvement.
BM: bone marrow; BMB: bone marrow biopsy; CT: computed tomography; eGFR: estimated glomerular filtration rate; FLC: free light chain; Hg: hemoglobin; Ig: immunoglobulin; LPD: lymphoproliferative disorders; MM: multiple myeloma; MP: M-protein; MRI: magnetic resonance imaging; PB: peripheral blood; PET-CT: positron emission tomography-computed tomography; SIF: serum immunofixation.



B

Tests \ Stage	Diagnosis	Follow-up[b]	Response evaluation	Relapse
SPE	x	x	x	x
sFLC	x	x	x	x
sIFE	x		x	
uIFE	x[c]		x[c]	x[c]
Morphology study (BM)	x	x[d]	x	x[d]
BMB	x			
Cytogenetic	x			x
FC	x	x[d]	x	x[d]
LDH	x			x
β2-micro	x			x

Figure 1 – Diagnostic algorithm for patients with suspected multiple myeloma (A) and summary table of tests/parameters to be conducted at different stages of patient evaluation (B)

a: Light chain MM and AL amyloidosis.
b: Any analysis that is not informative in the evaluation of MP can be excluded from the follow-up panel for that patient (example: SPE in the follow-up of a patient with light chain MM).
c: In the presence of proteinuria, confirmation of clonality may be necessary in light chain MM.
d: In patients with non-quantifiable MP, non-secretory/oligo-secretory MM.
BM: bone marrow; BMB: bone marrow biopsy; FC: flow cytometry; FISH: fluorescence in situ hybridization; Ig: immunoglobulins; IHC: immunohistochemistry; LDH: lactate dehydrogenase; MDE: myeloma-defining events; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; sFLC: serum free light chain; sIFE: serum immunofixation; SMM: smoldering MM; SPE: serum protein electrophoresis; rFLC: free light chain ratio; ISUB: immunosubtraction; uIFE: urine immunofixation

triggered by findings from 'routine' analytical studies (e.g., presence of MP, anemia, hypercalcemia, or renal dysfunction) and/or nonspecific but compatible clinical signs and symptoms (e.g., asthenia, recurrent infections, or back pain). The initial assessment includes identifying parameters to determine which patients need to begin therapy. This decision is guided by the presence of myeloma-defining events, known as the SLiM-CRAB criteria, as outlined in section B of Table 1.

Monoclonal protein is a highly specific and sensitive serum tumor marker for MM, offering a key advantage in differential diagnosis and patient follow-up. However, there are several forms of disease presentation, as well as different types and concentrations of MP, making its accurate identification challenging. Proper identification of MP depends on the sample quality, the clinical information provided, and the chosen analytical methods.

When MP is detected, either through changes in the serum protein electrophoresis (SPE) spectrum or an abnormal free light chain (FLC) ratio (which indicates an excess of one light chain type (κ or λ) *versus* the other), it is mandatory to characterize the Ig to confirm monoclonality by serum immunofixation (sIFE) or immunosubtraction. Immunosubtraction, a laboratory technique performed by capillary zone electrophoresis, may be used whenever sensitive. However, when in doubt, the reference method (sIFE) should be used.[6-8] Serum immunofixation screening is typically performed using antisera for IgG, IgA, IgM, κ, and λ. In cases where only a light chain is detected, testing with IgD and IgE antisera is recommended to exclude the rarer forms of IgD and IgE MM. If no changes are observed in the SPE spectrum but clinical suspicion of MM remains, sIFE should still be performed. This technique is more sensitive than SPE and can detect smaller amounts of MP.[9,10] Simultaneous assessment of SPE and FLC quantification (amount of free light chains produced by plasma cells) ensures effective screening for serum MP.[11] Moreover, FLC quantification is valuable in cases of suspected non-secretory/oligo-secretory MM and AL amyloidosis.

Testing for MP in a 24-hour urine sample (U24h) has traditionally been used for the characterization and follow-up of light chain MM and AL amyloidosis. However, recent studies suggest that serum FLC quantification can effectively replace U24h evaluation in most patients.[12-14] While renal function affects serum FLC concentration, there are adjusted reference intervals for the FLC ratio based on estimated glomerular filtration rate, which can be useful when applying this test to chronic kidney disease cases.[15,16] It is important to note that these intervals are assay-specific, and the patient's clinical status should be considered in each evaluation. As a result, U24h collection may be used more selectively. Although still referenced in IMWG recommendations, urine protein electrophoresis is a less sensitive method for detecting low MP concentrations, making it redundant in follow-up. In cases of discrepancies or diagnostic uncertainty, urine immunofixation (uIFE) is recommended.

Total Ig quantification includes both monoclonal and polyclonal Ig and is therefore not recommended for identifying and quantifying MP.[9] Nevertheless, total Ig quantification can indicate which Ig is increased and provide insights into the patient's immunoparesis status (suppression of normal Ig production), which is important in MM patient evaluation. Quantifying Ig based on the heavy/light chain pair of Ig has become possible with the recent development of a specific immunoassay (Hevylite®) for the IgGκ/IgGλ, IgAκ/IgAλ, or IgMκ/IgMλ chain pairs. This tool offers advantages over traditional techniques by detecting MP that migrates in the beta fractions or several peaks of the same MP resulting from polymerization.[17] This tool also helps in assessing specific immunoparesis for specific Ig heavy/light chain pairs.[18-21]

Bone marrow morphological assessment, performed via bone marrow aspirate (BMA) and/or core needle bone marrow biopsy (BMB), allows for the identification and quantification of plasma cell infiltration. Simultaneous BMA and BMB are recommended at diagnosis,[22,23] and when there is a discrepancy in plasma cell counts between the two, the higher value should be considered.[1] Plasma cell clonality can be determined through immunophenotyping by flow cytometry (FC) on the BMA sample or by immunohistochemistry in the case of BMB.[24] In the minority of patients with non-secretory MM (with negative MP by SPE/sIFE, UPE/uIFE and sFLC), medullary plasmacytosis is the only measurable marker both at diagnosis and follow-up.

If the BMA is hemodiluted, unrepresentative, or shows plasma cell counts below 10%, but there is still a strong suspicion of MM, additional BM samples should be obtained from a different anatomical site, or a biopsy guided by imaging studies should be performed.[22,24,25] For a more comprehensive assessment and to resolve potential discrepancies, it is beneficial to integrate BMA and BMB results into a single report.[26] However, this is challenging due to differences in turnaround times, their execution in separate laboratories, and the involvement of different specialties.

The cell morphology findings in BMA, observed in at least 200 cells, range from morphologically normal plasma cells to those with varying degrees of cellular maturation or nuclear (sometimes multinucleated) and cytoplasmic alterations. The most common morphology findings in abnormal plasma cells include hyperbasophilic cytoplasm and a rounded nucleus with 'clock-face' or 'spoked-wheel' chromatin, eccentrically located, accompanied by marked perinuclear clearing.[22,24-27]

In peripheral blood smears, characteristic features of

MM can also be observed, such as erythrocyte stacking due to paraproteinemia (unbalanced production of a single type of MP), and the presence of abnormal plasma cells in circulation. If these plasma cells exceed 5% of the total leukocytes, it may indicate plasma cell leukemia, a rare and very aggressive entity.[28-30]

Flow cytometry plays a role in diagnosing MM by identifying and quantifying neoplastic plasma cells using specific antibodies (CD138, CD38), assessing phenotypic abnormalities (CD19, CD56, CD27, CD28, CD45, CD117, CD81, Beta2-microglobulin), and confirming clonality through intracellular κ and λ light chain restriction. Widely validated FC procedures and antibody panels, such as those developed by the Euroflow cooperative group, are widely used in clinical practice.[31]

It is worth noting that the quality of the BM sample can affect FC results, often leading to discrepancies with BMA findings due to sample hemodilution. Despite this limitation, FC remains an effective method for assessing plasma cell clonality and identifying phenotypic alterations associated with MM.[32]

Although cytogenetic abnormalities (CA) are not part of MM diagnostic criteria, their identification by fluorescence *in situ* hybridization (FISH) should be performed at diagnosis, given its prognostic impact, discussed later in these guidelines. This assessment should be conducted on BM samples with ≥ 10% plasma cells and/or whenever MM diagnosis is confirmed. To accurately detect CA, an analysis of at least 100 plasma cell nuclei is recommended, and for this, it is crucial first to isolate plasma cells using magnetic bead separation (antibody-coated magnetic beads specifically bind to plasma cells; by applying a magnetic field to the sample the magnetically labeled cells are retained while unlabeled cells are removed) or fluorescence-activated cell sorting (FACS) (a subtype of flow cytometry that allows plasma cells present in the sample to be separated by labeling them with specific fluorescence-conjugated antibodies; when passing through a laser beam the fluorochromes emit light captured by detectors; post-detection, the identified plasma cells are electronically charged and pass through an electromagnetic field that diverts them). This approach significantly increases sensitivity and ensures the identification of only MM-specific CA.[33]

Table 2 outlines the recommended tests and laboratory parameters to be evaluated at different stages for patients with suspected or confirmed MM.

STAGING AND RISK STRATIFICATION

The course of MM is highly heterogeneous among patients. Thus, it is essential to identify prognostic factors that can stratify patients into different risk groups, guiding therapeutic decisions. These factors should be evaluated during the initial process. The most used models in clinical practice are the International Staging System for Multiple Myeloma (ISS) and the Revised ISS (R-ISS) (Table 3). The R-ISS incorporates the traditional ISS markers (serum beta2-microglobulin and albumin), along with serum lactate dehydrogenase levels and CA with adverse prognostic value. The presence of these CA is associated with reduced overall survival (OS), with significantly lower survival rates in patients harboring two or more high-risk CA. These patients are classified as ultra-high-risk (≥ 2 high-risk CA), with a median OS of only nine months.[34]

While certain genetic mutations have been associated with poorer outcomes, routine screening for these mutations is not currently recommended in clinical practice.[34,35] Similarly, recent studies suggest that quantifying circulating tumor plasma cells in peripheral blood using Next Generation Flow (NGF) may also indicate a worse prognosis, but this method is not yet recommended for routine clinical assessment.[36]

FOLLOW-UP AND RESPONSE EVALUATION

The follow-up and evaluation of treatment response in patients with MM have evolved alongside significant advances in available therapeutic options.[37,38] After each treatment cycle, the patient's response should be assessed, considering both the diagnostic test results and current disease status, to ensure an accurate evaluation of the response (Table 2).[23]

The definition of treatment response includes the assessment of MP, BMA/BMB, and imaging studies (outside the scope of these recommendations), as well as parameters related to myeloma-defining events and potential treatment-related complications (Table 4).

Serum MP quantification remains a critical tool for monitoring changes in tumor burden during treatment. It is important to choose the biomarkers that best detect MP to ensure an accurate interpretation of the patient's condition. Serum immunofixation should only be performed when MP is not measurable and/or when new suspicious changes in the electrophoretic pattern emerge. Similarly, uIFE should only be performed if MP becomes undetectable or if there are doubts regarding clonality. Tests that do not add value to the known information, such as U24h, should be avoided to prevent unnecessary patient discomfort.

Bone marrow studies are valuable for confirming complete remission (following negative sIFE results), assessing measurable residual disease (MRD) in these patients, evaluating response in non-secretory MM, and investigating unexplained cytopenias.

In relapse/progression, a new BM evaluation may be beneficial for assessing CA via FISH, particularly if a complete cytogenetic study was not performed at diagnosis, or

Table 2 – Tests and laboratory parameters to investigate at different stages for patients with suspected or diagnosed multiple myeloma

	Sample	Collection tube/ container[a]	Tests	Observations
Diagnosis	PB	EDTA tube	Blood count	
		Dry tube with separation gel	Uremia, Creatinine, Calcium, Total Proteins, Albumin, LDH[b], β2m[b] and Ig	
			SPE	MP quantification
			sIFE/ISUB	Characterization of Ig isotype
			sFLC	
	BM aspirate	Slide	Cytomorphologic study	
		EDTA tube	Immunophenotype by FC	
		Lithium/sodium heparin tube	Cytogenetic study[b]	Analysis of AC by FISH
	BM biopsy	Flask with formaldehyde	Histological and immunohistochemical study	
	Urine (24h)	Dry flask	UTP	Assess the presence of glomerular proteinuria
			UPE	MP quantification
			uIFE	Characterization of Ig isotype
Monitoring (MGUS/SMM)	Repeat the tests performed at diagnosis in PB, without BM assessment or urine (24h)			
Follow-up/response evaluation[c]	PB	See diagnosis	Blood count	
			Creatinine Calcium and Ig	
			SPE	
			sIFE	If negative SPE
			sFLC	
	Urine		UPE	If positive MP (≥ 200 mg/24h) at diagnosis
			uIFE	If negative UPE
	BM aspirate[d]		Morphology and immunophenotypic study by FC	Confirmation of CR, study of cytopenias and MRD assessment[e]
Suspicion of relapse/ progresion	Repeat the tests performed at diagnosis. Consider performing a BM study (an increase in clonal plasma cells may help in deciding to start new treatment in patients where progression is uncertain, allows the identification of any new CA with an impact on therapeutic decisions, or establishes eligibility for clinical trials)			

a: The collection and container used are essential to ensure the quality of the sample and avoid interferences in the methodologies performed. Although there are alternatives to some of the collection tubes, the same characteristics should be maintained for the diagnosis and monitoring of the patient.
b: Prognostic value, see Table 3.
c: Response evaluation during treatment: before each cycle, post-induction/pre-transplant, and post-transplant (adapted to patient's characteristics, risk stratification and treatment – see observations).
d: In response evaluation post-induction/pre-transplant, and post-transplant/maintenance in patients in complete remission, to establish sustained MRD, see Table 4.
e: For MRD evaluation, see Table 4.
β2m: beta2 microglobulin; BM: bone marrow; CA: cytogenetic abnormalities; CR: complete response; EDTA: ethylenediaminetetraacetic acid; FC: flow cytometry; FISH: fluorescence in situ hybridization; FLC: free light chain; Ig: immunoglobulin(s); ISUB: immunosubtraction; LDH: lactate dehydrogenase; MP: M-Protein; MRD: measurable residual disease; PB: peripheral blood; sFLC: serum FLC; sIFE: serum Immunofixation; SPE: serum protein electrophoresis; uIFE: urine immunofixation; UPE: urine protein electrophoresis; UTP: urinary total protein.

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to detect newly emerging CA with therapeutic relevance.[39]

With the advent of more effective therapies that achieve deeper responses, the response criteria have been updated to include assessment of MRD (number of myeloma cells remaining after treatment) in the BM of patients in complete remission.[10] New-generation methodologies, such as NGF and next-generation sequencing (NGS), are now the reference methods due to their higher sensitivity (≤ 10^{-5}).[40] The NGF approach is validated and accessible in most clinical FC laboratories. The first BM aspirate sample (first pull) should be used [low sample quality and quantity (examples: coagulated, collected more than 48h, or hemodiluted) can lead to false negative results], specific populations whose absence/decreased values indicate hemodilution (mast cells, erythroblasts, myeloid and B lymphoid precursors) should be identified and comparison with reference values should be done (Table 4). Automated analysis with reference databases accelerates the process and avoids operator bias. Next-generation sequencing is more time-consuming, has a lower applicability rate than NGF, and is not widely available in most clinical laboratories. This methodology involves studying the specific rearrangement pattern of the *IgH* gene (*VDJ, DJ, Igκ*, and *Igλ*) present in each patient at diagnosis, although it can be performed on cryopreserved samples (Table 4).

Achieving MRD negativity is associated with improved overall survival (OS),[41] making this level of depth of response an important treatment goal. Correct identification of patients achieving MRD negativity is essential, as their responses are both deeper and more durable.[42] In addition to being a surrogate marker for OS, MRD negativity has also been approved by the Food and Drug Administration as a valid endpoint in MM clinical trials, further emphasizing its significance in patient management.[43]

PRESENTATION OF RESULTS/REPORT

Harmonizing laboratory activities is essential to ensure that each patient receives the maximum benefit from the information provided. Results generated by different laboratories must be comparable in terms of terminology, units of measurement, reference ranges, decision limits, and report formats, in addition to the accuracy of analytical results.[44]

Table 3 – Recommended laboratory evaluation for risk stratification in multiple myeloma

Variables	Laboratory parameters	Stages	References
ISS	Serum β2m Serum albumin	I: serum β2m < 3.5 mg/L, serum albumin ≥ 3.5 g/dL II: neither I nor III III: serum β2m > 5.5 mg/L	Greipp *et al*, 2005
CA[a]	del 17p13 (TP53) t(4;14)(p16;q32) (IGH::FGFR3/NSD2) t(14;16)(q32;q23) (IGH::MAF) t(11;14)(q13;q32) (IGH::CCND1) 1p32/1q21 alterations (1q21 amp/gain: *MCL1, CKS1B, ANP32E, BCL9*[b]; del(1p): *CDKN2C, MTF2, FAM46C*)[c]	Adverse risk: del 17p13 (TP53), t(4;14)(p16;q32) (IGH::FGFR3/NSD2), t(14;16)(q32;q23) (IGH::MAF), 1p32/1q21 alterations (1q21 amp/gain: *MCL1, CKS1B, ANP32E, BCL9*[b]; del(1p): *CDKN2C, MTF2, FAM46C*)	Fonseca *et al*, 2009
LDH	LDH levels	High: Serum LDH > upper normal limit	Terpos *et al*, 2010
R-ISS	In risk stratification, the three previous prognostic factors are included (ISS stage, CA, and LDH)	I: ISS I and no high-risk CA and normal LDH II: neither I nor III III: ISS III and high-risk CA or abnormal LDH	Palumbo *et al*, 2015
R2-ISS	1q+ (0.5 points) ISS II (1 points) ISS III (1.5 points) del(17p) (1 points) Abnormal LDH (1 point) t(4;14) (1 point)	Low: R2-ISS I (0 points) Low-intermediate: R2-ISS II (0.5 - 1 points) High-intermediate: R2-ISS III (1.5 - 2.5 points) High: R2-ISS IV (3 - 5 points)	D'Agostino *et al*, 2022

a: Cytogenetic study performed in purified plasma cells from bone marrow aspirate [CD38+ cells magnetically separated (*beads*) or by FACS].
b: Gain of 1q represents an extra copy of the long arm of chromosome 1 (three copies of 1q), while amplification of 1q is defined as the presence of two or more additional copies (≥ 4 copies of 1q).
c: Additional CA that can be identified are t(14;20)(q32;q12) (IGH::MAFB) (present in 2% - 3%; adverse risk) and t(6;14)(p21;132) (IGH::CCND3) (present in 5%; adverse risk) (Sonneveld *et al*, 2016; Walker *et al*, 2019).[16,50]
1q+: 1q gain/amplification; β2m: beta2 microglobulin; CA: cytogenetic abnormalities; del: deletion; FACS: fluorescence-activated cell sorting; FISH: fluorescence in situ hybridization; ISS: international staging system; LDH: lactate dehydrogenase; R-ISS: 1st revision of ISS; R2-ISS: 2nd revision of ISS; t: translocation.

Table 4 – Response criteria in multiple myeloma, adapted from Kumar *et al*, 2016[10] (section 1 of 2)

Response	Criteria	Additional recommendations
Sustained MRD negative	MRD negativity in bone marrow (by NGF, NGS, or both) and by imaging confirmed with a minimum of one year between assessments (subsequent evaluations can be used to define the duration of response negativity)	The method used to define the response (sustained MRD negativity by NGF; sustained MRD negativity by NGS) must be specified
Imaging MRD negative[a]	Absence of bone lesions by PET-CT	
Sequencing MRD negative	Absence of clonal plasma cells by NGS in BM aspirates using a validated methodology with a sensitivity of ≥ 10^{-5}	The presence of a clone is defined as < 2 identical DNA sequences
Flow MRD negative	Absence of phenotypically aberrant clonal plasma cells by NGF in BM aspirates following the EuroFlow methodology (or equivalent validated methodology) with a sensitivity of ≥ 10^{-5}	The reference NGF method consists of 2 tubes of 8 colors with the evaluation of at least 5 million cells[51]
S*tringent* complete Response (sCR)	CR, normal FLC ratio, absence of clonal plasma cells in BM	Presence/absence of clonal plasma cells on BM based on a count of ≥ 100 plasma cells (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients respectively)
Complete response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow (non-secretary MM)	In patients without detectable MP in serum or urine, a normal FLC ratio is required
Very good partial response (VGPR)	Serum and urine MP detectable by immunofixation but not on electrophoresis or > 90% reduction in serum MP plus urine MP level < 100 mg/24h	
Partial response (PR)	≥ 50% reduction in serum MP, > 90% reduction in urine < 200 mg/24h	In patients without quantifiable MP in serum or urine, ≥ 50% reduction in the difference between involved FLC and uninvolved FLC is required. In patients without quantifiable MP in serum or urine and not evaluable by sFLC, but with > 30% clonal plasma cells in BM at diagnosis, a ≥ 50% reduction in plasma cells in BM is required. In patients with plasmacytomas at diagnosis, a reduction of ≥ 50% in size is also necessary.
Minimal response	≥ 25% but ≤ 49% reduction in serum MP, 50% - 89% reduction in urinary MP (24h)	In patients with plasmacytomas at diagnosis, a reduction of ≥ 50% in size is also necessary
Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease	

a: Outside the scope of these recommendations.
BM: bone marrow; CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions; CR: complete response; DNA: deoxyribonucleic acid; FLC: free light chain(s); IHC: immunohistochemistry; MP: M-protein; MRD: measurable residual disease; NGF: next generation flow; NGS: next generation sequencing; PET-TC: positron emission tomography-computerized tomography.

While the IMWG has developed recommendations for classification, diagnosis, and response evaluation, it does not provide guidance on standardizing reporting in this area. However, some groups have been working towards this goal.[45-48]

Diagnosis and response evaluations for patients in follow-up should be conducted in the same laboratory using the same methodology. Additionally, reports should contain the same amount of information and be presented in a uniform format, regardless of who produces them. Specifying the methodologies used is crucial, given the variety of available options and the inherent sensitivity differences between them.

Given the potential severity of MM, especially in the diagnostic context, it is vital to ensure the timely delivery of samples to the laboratory, their rapid processing, and acceptable turnaround times tailored to each laboratory methodologies used.

Table 5 compiles suggestions for the presentation of results/report.

Table 4 – Response criteria in multiple myeloma, adapted from Kumar *et al*, 2016[10] (section 2 of 2)

Response	Criteria	Additional recommendations
Progressive disease	Increase of > 25% from the lowest response value in any one or more of the following:	
	- Serum MP (absolute increase ≥ 0.5 g/dL)	Serum MP increases of > 1 gm/dL are sufficient to define relapse if starting MP is > 5 g/dL.
	- Urinary MP (absolute increase ≥ 200 mg/24h)	
	- Difference between involved and uninvolved FLC levels (absolute increase > 10 mg/dL)	Only in patients without measurable serum and urine MP levels
	- BM plasma cell percentage (absolute percentage > 10%)	In patients without quantifiable serum or urinary MP and not evaluable by FLC
	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas (≥ 50% in size of > 1 lesion or in the diameter of a pre-existing lesion with > 1cm of smaller axis	
	Increase of ≥ 50% of circulating plasma cells (≥ 200/uL)	When this is the only way to assess tumor burden
	Development of hypercalcemia (corrected calcium > 11.5 mg/dL or 2.65 mmol/L)	Attributed solely to the plasma cell proliferative disorder
Relapse	Requires ≥ 1:	
	- Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)	
	- New soft tissue plasmacytomas or bone lesions	
	- Definite increase in the size of existing plasmacytomas or bone lesions (≥ 50% and ≥ 1 cm, respectively)	
	- Hypercalcemia (corrected calcium > 11.5 mg/dL or 2.65 mmol/L)	
	- Decrease in haemoglobin of > 2 g/dL or 1.25 mmol/L) attributed to the disease	
	- Rise in serum creatinine by ≥ 2 mg/dL or ≥ 177 mmol/L	
	- Hyperviscosity symptoms secundary to MP	

a: Outside the scope of these recommendations.
BM: bone marrow; CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions; CR: complete response; DNA: deoxyribonucleic acid; FLC: free light chain(s); IHC: immunohistochemistry; MP: M-protein; MRD: measurable residual disease; NGF: next generation flow; NGS: next generation sequencing; PET-TC: positron emission tomography-computerized tomography.

FINAL REMARKS

Recent advancements in the treatment and management of MM have led to the development of more precise and specific laboratory tests, requiring careful consideration regarding their integration into routine diagnostic processes. In addition to the methodologies currently available, others such as the detection and characterization of monoclonal proteins using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) and liquid chromatography mass spectrometry (LC-MS), as well as the identification of circulating tumor components through liquid biopsy techniques, such as the detection of circulating pathological plasma cells, nucleic acids (circulating tumor DNA or microRNA), and extracellular vesicles may have the potential to become part of standard laboratory testing in the future.

It is important to note that diagnosing MM requires additional diagnostic tests, including imaging studies, which fall outside the scope of these laboratory recommendations. Given that this diagnosis involves various clinical and laboratory areas, it should be reviewed and discussed in a multidisciplinary meeting.

These recommendations from the PMMG provide key guidance for the diagnosis and follow-up of patients with MM, emphasizing the importance of using the most appropriate laboratory tests at each stage of evaluation.

Table 5 – Recommendation on information to include in a laboratory report in the context of multiple myeloma (section 1 of 2)

Test	Important information to include in the report	Comments
SPE	Methodology used	
	Electrophoresis profile	• Include all determined fractions, their concentration, and respective reference values. Presenting the percentage values of the fractions is optional.
	MP when present, quantified in g/L or g/dL (with one decimal place) and reported separately from other fractions	• Characterize the isotype of the MP in the first sample where it is identified. • If it is not possible to identify the isotype of the MP, mention the need for a confirmatory test and identification of monoclonal Ig isotype. • In the electrophoresis profile, shade the area corresponding to the MP migration, obtained by the perpendicular drop method. • If more than one monoclonal isotype is present, identify and quantify each one independently, indicating their respective mobilities in the profile. • If the quantification is below the limit of detection (LoD) of the technique, report the value as "< LoD g/L." • In cases of Ig polymerization, characteristic of IgA, the MP quantification corresponds to the sum of the peaks present in the profile. • The presence of small peaks may be transient and should therefore be evaluated in the clinical and therapeutic context, especially after bone marrow transplant or the start of monoclonal antibody treatment. • Clarify any type of interference that could affect the interpretation of the results in the comments section.
	Total serum protein value	• Present this value, which is necessary for calculating the concentration of the fractions, and specify the determination method.
UPE	Methodology used	
	Total protein value in 24-hour urine	• Present values in g/24h or mg/24h, along with the respective determination method; note that the test may not be informative in the absence of proteinuria.
	Electrophoresis profile, if relevant	• If the profile is included, quantify the fractions found and the M-protein, if present, in g/L; the M-protein should be identified.
sIFE/ ISUB/ uIFE	Methodology used	
	Presence or absence of MP	• When MP is present, identify the isotype(s) and their respective mobility zones.
sFLC	Methodology used	
	Results for both light chains and their ratio	• If the Freelite® assay is used, it is possible to indicate the existence of a reference range for patients with impaired renal function (reduced eGFR).[15,16]
Bone marrow aspirate	Anatomical site and difficulty of the aspiration	
	Adequacy and cellularity of the aspirate	
	Differential count of nucleated cells, total number of cells counted, and erythroid:myeloid ratio	• Include quantitative and qualitative comments regarding all cell lineages and any abnormal cells. For example, quantification and description of the plasma cells found.
	Iron deposition staining and cytochemical studies, if performed	
	A conclusion	

CG: cytogenetics; FC: flow cytometry; FISH: fluorescence in situ hybridization; FLC: free light chains; ICD: international classification of diseases; ISCN: The International System for Human Cytogenomic Nomenclature; ISUB: immunosubtraction; LoD: limit of detection; LQ: limit of quantification; eGFR: estimated glomerular filtration rate; MG: molecular genetics; MoAb: monoclonal antibodies; MP: M-protein; MRD: measurable residual disease; Ig: immunoglobulin; SNOMED CT: systematized nomenclature of medicine; SPE: serum protein electrophoresis; sIFE: serum immunofixation; uIFE: urinary immunofixation; UPE: urinary protein electrophoresis

Table 5 – Recommendation on information to include in a laboratory report in the context of multiple myeloma (section 2 of 2)

Test	Important information to include in the report	Comments
Bone marrow biopsy	Adequacy, macroscopic appearance, and length of the core biopsy	
	Percentages and pattern of cellularity	
	Bone architecture and reticulin staining	
	Characterization of different cell lineages	• Include location, number, morphology, and differentiation pattern.
	Characterization of abnormal cells and/or infiltrates	
	Immunohistochemistry results	
	A conclusion	• Include disease classification/differential diagnosis and its SNOMED CT or ICD coding.
FC	The identified populations and their respective percentages in the total cellularity	• In response evaluation (MRD), include erythroblasts, B lymphoid precursors, and mast cells (indicators of sample hemodilution in bone marrow).
	Percentage of plasma cells	• Indicate the total value of analyzed plasma cells and neoplastic plasma cells (in the total cellularity and total plasma cell population).
	Description of the neoplastic plasma cell phenotype	• Include clonality.
	LoD and LQ (sensitivity)	• Include in response evaluation (MRD), calculated based on the total number of acquired events and the number of neoplastic plasma cells, with a minimum of 30 cells for LoD and 50 for LQ, respectively[52]
	A conclusion	• Indicate the cellularity pattern and sample adequacy (e.g., hypocellular, hemodiluted sample).
CG	Methodology and probes used	
	Clear description of the results obtained	• Following the latest version of the International System for Human Cytogenomic Nomenclature (ISCN) – http//iscn.karger.com/
	Interpretation of the results	• Indicate the clinical significance of the results, including prognosis.
MG	Methodology used	
	Interpretation of the results	• Indicate the clinical significance of the results

CG: cytogenetics; FC: flow cytometry; FISH: fluorescence in situ hybridization; FLC: free light chains; ICD: international classification of diseases; ISCN: The International System for Human Cytogenomic Nomenclature; ISUB: immunosubtraction; LoD: limit of detection; LQ: limit of quantification; eGFR: estimated glomerular filtration rate; MG: molecular genetics; MoAb: monoclonal antibodies; MP: M-protein; MRD: measurable residual disease; Ig: immunoglobulin; SNOMED CT: systematized nomenclature of medicine; SPE: serum protein electrophoresis; sIFE: serum immunofixation; uIFE: urinary immunofixation; UPE: urinary protein electrophoresis

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AUTHOR CONTRIBUTIONS

AMP, JPB, JC: Study design, writing and critical review of the manuscript.

MJS, CG, BF, MC, SC, HC, CC, APC, MC, MRC, NC, PF, JGF, RH, SL, PL, AP, CP, IR, ABS, PS, JS, MJRS, SS, TS, MT, FT, RB, AR, CJ: 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.

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Mother-Baby Day Hospitals: An Effective Option for Perinatal Mental Health Care?

Hospitais de Dia Mãe-Bebé: Uma Alternativa Eficaz em Saúde Mental Perinatal?

Keywords: Hospitals; Mental Health; Mother-Child Relations/psychology; Mothers/psychology; Postpartum Period
Palavras-chave: Hospitais; Mães/psicologia; Período Pós-Parto; Relações Mãe-Filho/psicologia; Saúde Mental

Dear Editor,

In recent years, it has become well recognized that the perinatal period carries a high risk for the onset and recurrence of maternal mental health disorders, with an estimated one in five women developing a mental health condition postpartum, some of which are serious, requiring hospitalization. Psychiatric hospitalizations in the postpartum period often result in discontinuation of maternal care. This mother-baby separation has consequences for the mother, infant and family, negatively impacting the attachment relationship and increasing stress, which can lead to a higher risk of maladaptive coping skills, and emotional, social, and cognitive problems for all.[1,2] The gold standard for treating mental illness in the perinatal period is mother-baby units (MBU), in which mothers are co-admitted with their infants.[3] Some countries (United Kingdom, France, Australia, and Spain) have already implemented these units.[2] However, in Portugal there are no MBUs, even though some hospitals offer perinatal consultations. There are two possible modalities for dyad-based interventions: MBUs with inpatient treatment, and mother-baby day hospitals (MBDH) with partial hospitalization; few studies focus on MBDH, but those show good results.[2,4,5] Both function as specialized units, with similar multidisciplinary teams, ideally comprising adult and child psychiatrists, pediatricians, psychologists, nurses, occupational therapists, and social workers. They aim to support the mother's psychiatric recovery while helping navigate motherhood, including guidance in breastfeeding, social skills, and baby care, involving family members, through individual and group interventions, and psychopharmacological treatment. When the condition is severe (e.g. psychosis, suicidal ideation, risk of dual-harm, or substance use) the mother should be guided towards an in-patient ward rather than an MBDH.[5] Structured discharge plans are important and should involve carers and healthcare providers ensuring follow-up for the dyad to prevent relapses, emphasizing the importance of perinatal-community psychiatric teams, which provide continuous clinical surveillance and psychosocial support.

In conclusion, mother-baby admissions enable early intervention in the mother's mental disorder, ensuring continuity of dyad-focused care and mitigating the impact of maternal illness on child development. We recognize barriers to implementing MBDHs, namely the diversity of clinical presentations and the need for highly specialized multidisciplinary teams and appropriate settings. Nevertheless, we argue that MBDHs, which have been shown to improve patient outcomes, may offer a less restrictive option by reducing the need for full hospitalization, which often distances patients from their homes, and a cost-effective alternative making them a feasible solution within the Portuguese healthcare system, while still acknowledging the importance of inpatient care for severe cases.

AUTHOR CONTRIBUTIONS

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LCC: Critical review of the manuscript.
All authors approved the final version to be published.

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Tratamento de Escabiose com Ivermectina em Crianças com Menos de 15 kg: Uma Opção Segura e Eficaz

Treatment of Scabies Using Ivermectin in Children Under 15 kg: A Safe and Effective Option

Palavras-chave: Criança; Escabiose/tratamento farmacológico; Ivermectina/uso terapêutico
Keywords: Child; Ivermectin/therapeutic use; Scabies/drug therapy

Caro Editor,

Lemos atentamente o artigo recentemente publicado na Acta Médica Portuguesa, intitulado "Abordagem da Escabiose em Idade Pediátrica: Uma Atualização",[1] uma revisão narrativa de qualidade sobre esta patologia que apresenta uma prevalência significativa em consultas de Dermatologia, Pediatria e de Cuidados de Saúde Primários.

Parece-nos, no entanto, ser importante fazer uma nota sobre o uso de ivermectina em idade pediátrica, e expandir a referência que os autores fazem sobre a segurança do seu uso em crianças com menos de 15 kg, por representar uma opção terapêutica altamente eficaz, particularmente quando há dúvidas sobre a adesão terapêutica, quando existe perda da integridade cutânea ou em surtos.[2]

A ivermectina está aprovada para tratamento da escabiose em crianças com peso superior a 15 kg. Apesar de na literatura constar comummente a limitação a crianças com idade acima de dois anos, no resumo das características do medicamento (RCM), não consta qualquer indicação de idade.[3] O limite de peso presente no RCM deve-se à indisponibilidade de estudos de segurança específicos nesta faixa etária no momento da aprovação inicial, e não por existir evidência que demonstrasse um risco acrescido ou efeitos adversos significativos nesta população.[4]

Evidência recente tem, no entanto, mostrado que este fármaco é seguro inclusive em crianças com menos de 15 kg.[4,5] Numa meta-análise de 2021,[4] foram avaliados 1088 casos em que foi administrada ivermectina a crianças com menos de 15 kg, dos quais 94,3% para tratamento de escabiose. Foram relatados 18 casos de efeitos adversos (1,4%), todos de gravidade ligeira, sendo os mais frequentes eczema (0,5%) e diarreia (0,4%). Apesar de a vasta maioria dos casos de administração de ivermectina ter sido para tratamento de escabiose, 50% dos efeitos adversos ocorreram durante o tratamento de outras patologias (tricuríase e estrongiloidíase). Os autores concluíram que o uso de ivermectina em crianças com menos de 15 kg é seguro e bem tolerado. Num outro ensaio de 2024, que avaliou uma dose fixa de 3 mg em 100 crianças entre os dois e os quatro anos, verificou-se uma taxa de cura de 91% e efeitos adversos ligeiros em 7% dos casos, reforçando a segurança da ivermectina nesta faixa etária.[6]

Com efeito, as recomendações da Sociedade Francesa de Dermatologia sobre o tratamento de escabiose em crianças com menos de 15 kg e mulheres grávidas, ou a amamentar, publicadas em 2024[2] aconselham o uso de ivermectina em segunda linha a partir dos dois meses de idade quando existe falência dos tratamentos tópicos, e em primeira linha em crianças com mais de dois anos (mesmo que com menos de 15 kg), especialmente se houver dúvidas sobre a adesão terapêutica, perda da integridade cutânea ou em surtos. A dose recomendada é a mesma dos restantes grupos: 200 mcg/kg no dia 0 e dia 7.[4,5]

Apesar de *off-label*, parece-nos importante ter em conta esta opção terapêutica inclusive em crianças com menos de 15 kg, conforme as recomendações acima. Não estando disponível para dispensa em farmácia comunitária, poderá ser obtido através de farmácia hospitalar ou como fármaco manipulado (cápsulas ou solução oral).

CONTRIBUTO DOS AUTORES

AMS: Revisão da literatura, elaboração do manuscrito.
JAR, HL, JMR, RP: Revisão crítica do manuscrito.
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Mieloneuropatia Tóxica a Óxido Nitroso: Ilustração de um Caso em Idade Pediátrica

Nitrous Oxide–Induced Toxic Myeloneuropathy: Illustration of a Pediatric Case

Palavras-chave: Doenças da Medula Espinal/induzidas quimicamente; Óxido Nitroso/toxicidade; Distúrbios Relacionados com Substâncias
Keywords: Nitrous Oxide/toxicity; Spinal Cord Diseases/chemically induced; Substance-Related Disorders

O consumo recreativo de óxido nitroso (N_2O) aumentou significativamente entre jovens, pela facilidade de acesso, baixo custo, efeitos psicotrópicos, difícil deteção e por ser considerado seguro.[1,2] Reportamos um caso de mieloneuropatia tóxica por N_2O em idade pediátrica, visando alertar para a sua elevada morbilidade neurológica.

Um rapaz de 17 anos, consumidor regular de N_2O desde há nove meses, com frequência diária nas últimas três semanas, foi trazido ao serviço de urgência por apresentar parestesias e diminuição da força muscular dos membros inferiores (MI), com caráter ascendente, associadas a instabilidade da marcha, de agravamento progressivo na última semana, sem história de traumatismo ou contexto infecioso. Objetivamente, destacava-se diminuição simétrica da força e arreflexia osteotendinosa dos MI e hipoestesia táctil dos dedos dos pés, tal como diminuição das sensibilidades propriocetivas e vibratórias dos quatro membros. Tinha ataxia truncal na posição de sentado e instabilidade da marcha, só possível com apoio, e prova de Romberg positiva. Analiticamente, destacava-se vitamina B12 134 pg/mL (VR 197 - 771 pg/mL) e homocisteína 123,20 µmol/L (VR < 15 µmol/L). Iniciou terapêutica intramuscular diária com hidroxicobalamina 1 mg e reabilitação motora em internamento. Realizou ressonância magnética (RM) medular que revelou sinal hiperintenso bilateral e simétrico dos cordões posteriores da medula cervico-dorsal, compatível com degeneração combinada subaguda da medula espinhal (DCSM) (Fig. 1). A eletromiografia mostrou redução da amplitude dos potenciais motores e sensitivos dos MI. Teve alta aos oito dias, com vitamina B12 e homocisteína normais, e melhoria parcial dos défices neurológicos. Foi referenciado para centro de reabilitação motora, com adesão irregular.

As manifestações neurológicas são as mais comuns nos consumidores de N_2O,[3] associadas ao défice funcional de vitamina B12, fundamental para as funções de mielinização.[4] O consumo regular de N_2O, com défice de vitamina B12 e hiperhomocisteinémia, ajudaram a corroborar o diagnóstico diferencial, nomeadamente com etiologias inflamatórias/autoimunes, como a síndrome de Guillain-Barré. Os exames complementares confirmaram a mieloneuropatia – RM com sinais sugestivos de DCSM (Fig. 1) e eletromiografia sugerindo neuropatia axonal.[4]

O diagnóstico e terapêutica precoces são determinantes para o prognóstico desta entidade, havendo risco de lesões irreversíveis.[5] O tratamento consiste na cessação do consumo de N_2O e suplementação com vitamina B12.[3]

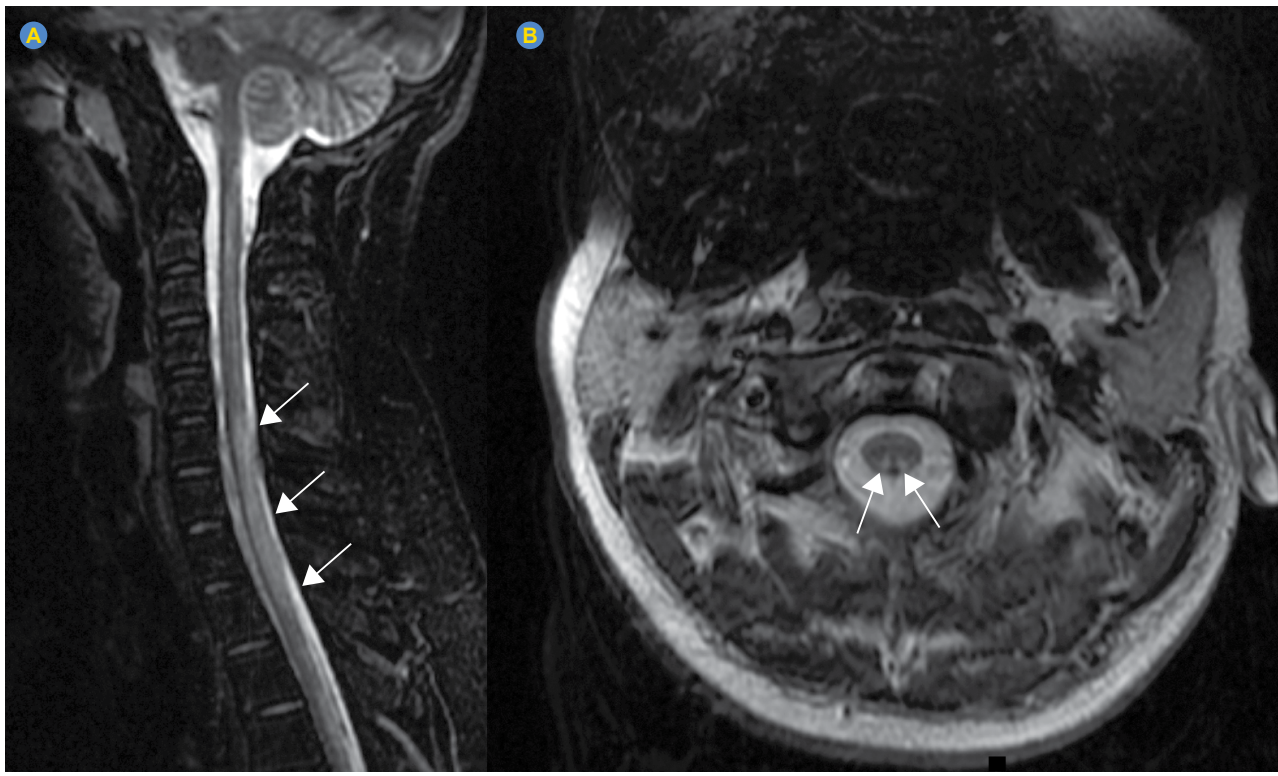

Figure 1 – STIR sagital RM: lesões com hipersinal longitudinalmente extensas do parênquima medular, extensão crânio-caudal entre C6 e D2 (A); T2 axial RM: lesões com hipersinal dos cordões posteriores da medula bilaterais e simétricos entre C1-C2 (B).

As alterações comportamentais e da força muscular resolvem mais precocemente, em oposição à ataxia sensitiva.[3] A reabilitação motora e apoio psicológico são essenciais, podendo ser um desafio sobretudo neste grupo etário.

Pretendemos alertar para o consumo crescente de N_2O em Portugal[2] e seus riscos, e para a necessidade de impor medidas de sensibilização na comunidade sobre os seus riscos.

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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

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The Potential of a New Population Screening: Preventing Osteoporotic Fractures

O Potencial de um Novo Rastreio Populacional: Prevenção de Fraturas Osteoporóticas

Keywords: Osteoporotic Fractures/prevention & control
Palavras-chave: Fraturas Osteoporóticas/prevenção e controlo

Dear Editor,

We read with interest the publication from Quintal & Antunes,[1] which analyzed participation levels and income-related inequalities in all population-based cancer screening programs implemented in Portugal, using 2019 data. While the overall results are encouraging, the notable regional and socioeconomic disparities are concerning. We commend the authors while reflecting on the broader value of population-based screening.

In Portugal, population-based screening programs have been implemented since 1990 for breast and cervical cancer, and since 2008 for colorectal cancer (CRC).[2] According to a European review published in 2015,[3] cancer population-based screening – among other factors – has contributed to a reduction in mortality rates of approximately 30%, 80%, and 20% for breast, cervical, and CRC, respectively, across the late 20th and early 21st centuries.

The most recent available data on the performance of cancer screening programs in Portugal refers to 2023,[2] indicating geographic coverage rates by primary healthcare units ranging from 89.5% to 100%, and population-based screening rates between 17.2% and 55.5% (Table 1).

Although cancer screening may be considered a successful example in Portuguese population-based programs, could there be additional opportunities? Aren't other diseases justifying the urgent development of systematic and organized screening? We consider that osteoporotic fractures (OF), though fundamentally distinct from oncological diseases, represent a clear example of a condition with significant individual, societal, and economic burden – including mortality – that remains insufficiently recognized.

In Portugal, OF – particularly hip fractures – are associated with mortality rates comparable to or even exceeding those of certain cancers. The annual standardized mortality rate following a fracture in individuals aged ≥ 50 is estimated at 89 per 100 000 (data from 2019).[4] This contrasts with 27.7 per 100 000 women for breast cancer, 3.4 per 100 000 women for cervical cancer, and 32.1 per 100 000 for CRC.[2] Moreover, around 21% of patients die within the first year after a hip fracture,[5] a strikingly high rate, especially when considering that cancer-related deaths often occur over longer timeframes.

Internationally recognized as a public health problem, the incidence of OF in Portugal was 15.8/1000 in 2019 and is expected to increase 28.9% by 2034.[4]

Current evidence supports the implementation of osteoporotic fracture (OF) risk screening through predictive tools such as FRAX®, combined with traditional bone densitometry. This integrated approach is widely regarded as a relevant and critically important intervention strategy for addressing the issue.[6] Portuguese multidisciplinary guidelines recommend regular assessment and management of fracture risk in all women and men aged 50 and above,[7] preferably using the FRAX®Port algorithm. To change this paradigm, there are already ongoing Portuguese initiatives, such as the OPTIMIST-OP® project, which is aimed at implementing systematic screening programs for OF risk in primary healthcare.[8] We reiterate the need for urgent discussion and coordinated public health action, including input from key stakeholders (citizens, healthcare professionals, managers, among others).

AUTHOR CONTRIBUTIONS

TS: Drafting and critical review of the manuscript.

AC: Critical review of the manuscript.

RJOF: Conceptualization and critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Table 1 – Data referring to population-based oncological screening performance indicators in Portugal (2023)[2]

Population-based screening	Population coverage rate (%)	Geographic coverage rate/primary healthcare functional unit (%)	Population screening rate (%)	Participation rate (%)
Breast cancer	98.7	100	55.5	56.2
Cervical cancer	59.2	91.0	55.3	93.5
Colorectal cancer	32.2	89.5	17.2	53.5

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Pyogenic Granuloma of the Upper Eyelid during Pregnancy

Granuloma Piogénico da Pálpebra Superior na Gravidez

Keywords: Eye Hemorrhage; Granuloma, Pyogenic; Pregnancy; Pregnancy Complications
Palavras-chave: Complicações na Gravidez; Gravidez; Granuloma Piogénico; Hemorragia Ocular

Pyogenic granuloma (PG), or lobular capillary hemangioma, is a benign fibrovascular lesion affecting up to 5% of pregnancies, typically arising from the second trimester onward.[1] It commonly presents as a solitary, red to purple, sessile or pedunculated mass that grows rapidly. The lesion often has a friable surface, prone to ulceration and bleeding, yet typically remains painless.[2] Even though the gingiva and buccal mucosa are the most common locations, other sites in the head, neck, trunk, and extremities may also be affected.[2] Eyelid involvement is rare.[3]

We present the case of a 26-year-old nulliparous woman (G5A4) with mild left hemiplegic cerebral palsy. Gestation was uneventful until 23 weeks, when she reported a painless, reddish lesion on her right upper eyelid that progressively enlarged, becoming friable. The lesion was non-tender and showed no signs of infection or systemic involvement.

Due to functional impairment, surgical excision was performed at 29 weeks following ophthalmological evaluation. Histopathology confirmed a pyogenic granuloma. Despite initial improvement, the lesion recurred and reached 2 cm by 38 weeks. Given the persistent functional limitation and maternal distress, labor was induced at 39 weeks (Fig. 1A) – earlier than the hospital's standard protocol of inducing labor at 41 weeks for low-risk pregnancies. Delivery was complicated by arrest of labor, leading to an urgent cesarean section and the birth of a healthy newborn weighing 3285 g, with Apgar scores of 9/10/10.

At five weeks postpartum, spontaneous regression to nearly half its size was observed (Fig. 1B). The patient was discharged from obstetrics follow-up and remained under ophthalmological surveillance until five months postpartum, with no further intervention required.

The pathogenesis of PG remains unclear.[2] It has been associated with chronic irritation, traumatic injury, hormonal imbalances, and certain medications. Although angiogenic factors and signal transduction pathways have been studied, no single mechanism for lesion development has been conclusively identified. During pregnancy, elevated estrogen and progesterone levels are thought to amplify the inflammatory response, thereby contributing to lesion growth.[1,2]

Diagnosis is primarily clinical and histopathology may be useful to exclude similar conditions.[2] Spontaneous postpartum regression is common, and conservative management may be appropriate in selected cases.[1] However, significant symptoms or functional impairment often warrant treatment during pregnancy. Although surgical excision – widely regarded as the standard treatment due to low recurrence – was ultimately chosen in this case, other options could have been considered.[1,4] Laser therapy (CO_2 and pulsed dye) and cryotherapy have been associated with similarly low recurrence rates and may offer less invasive alternatives with potentially superior cosmetic outcomes.[4] Topical agents like timolol may not lead to complete resolution but can promote partial regression and help control symptoms during pregnancy.[5] Lesions treated during pregnancy have a higher recurrence risk, likely due to persistent hormonal stimulation, with rates up to 16%.[1]

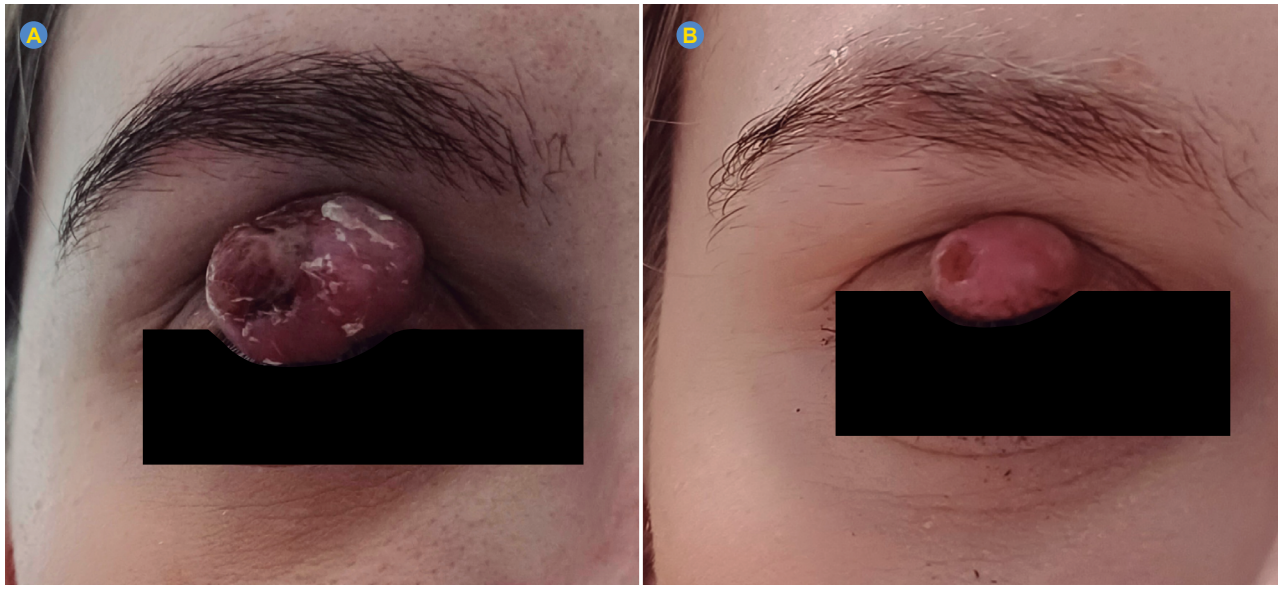

Figure 1 – Pyogenic granuloma of the upper eyelid at 39 weeks of gestation (A). Pyogenic granuloma of the upper eyelid 5 weeks postpartum (B).

A multidisciplinary approach – balancing obstetric and therapeutic considerations – is essential for achieving optimal maternal care and fetal safety.

AUTHOR CONTRIBUTIONS

MF: Literature review, data analysis, writing of the manuscript.

MPV: Study design, literature review, 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.

PATIENT CONSENT

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The Eyes Never Lie: A Rare Cutaneous Manifestation of Hematological Malignancy

Os Olhos Não Mentem: Uma Manifestação Cutânea Rara de Neoplasia Hematológica

Keywords: Multiple Myeloma; Necrobiotic Xanthogranuloma
Palavras-chave: Mieloma Múltiplo; Xantogranuloma Necrobiótico

A 92-year-old female patient was referred to our Dermatology department for symmetrical yellow plaques around the eyes, which were asymptomatic but had grown for over a decade (Fig. 1A). Her medical history was relevant for monoclonal gammopathy of undetermined significance, diagnosed approximately a decade before the cutaneous eruption first developed. A skin biopsy was performed that showed numerous foamy histiocytes occupying the dermis, as well as giant multinucleated Touton cells (Fig. 1B). This is consistent with the diagnosis of xanthogranuloma *necrobioticum* (NXG), a non-Langerhans cell histiocytosis, belonging to the mucocutaneous group. It manifests as yellowish indurated plaques or nodules (that can ulcerate), usually around the eyes, although they can also arise on the torso and limbs. It is notably associated with underlying systemic disorders, especially monoclonal gammopathies (up to 80% of cases).[1-4] Clinically, NXG should be distinguished from xanthelasma, which presents as multiple soft, flat, yellow papules and plaques, symmetrically located on the medial eyelids of adults, which differ from the bigger confluent lesions of NXG. The characteristic yellow colour of NXG occurs due to cholesterol deposition in macrophages, as a result of a complex interaction between immunoglobulins and lipoproteins.[5] The histopathological features of NXG include foamy macrophages, multinucleated giant cells (Touton cells) and necrobiotic collagen degeneration (the latter two features are absent in xanthelasma).[4,6] The diagnosis of NXG requires two major criteria: 1) yellow/orange cutaneous papules, plaques or nodules; 2) suggestive histopathology and one of two minor criteria; 3) paraproteinemia/lymphoproliferative disease; 4) periorbital distribution of lesions – all four are present in our case.[7]

AUTHOR CONTRIBUTIONS

GAS: Conception and writing of the manuscript.
LS: Literature review, writing of the manuscript.
JA: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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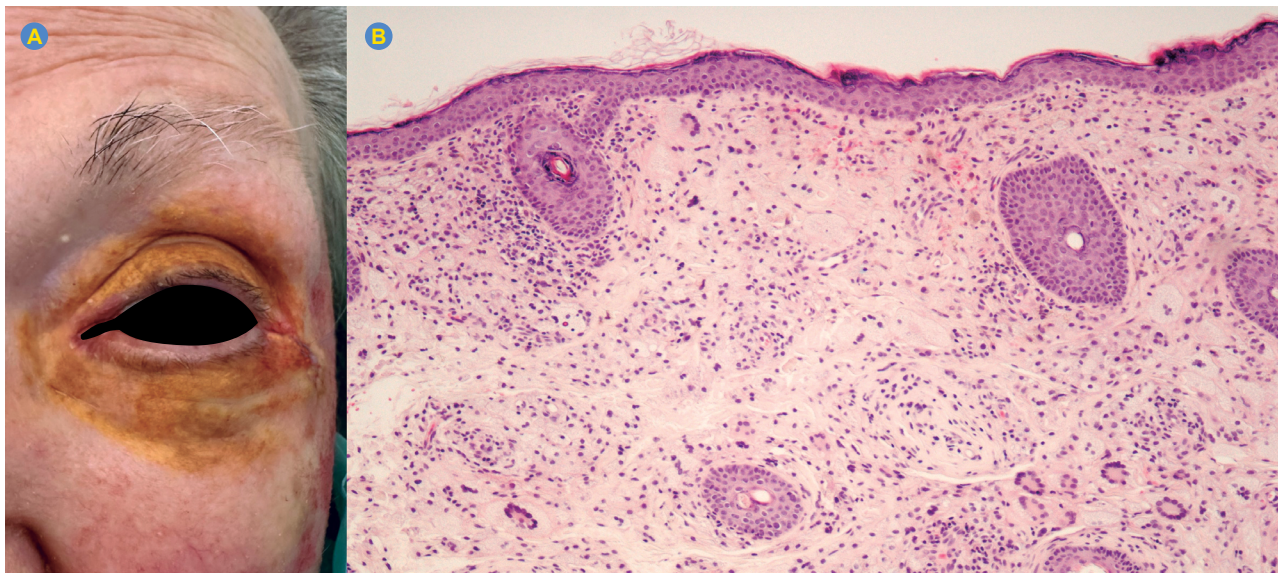

Figure 1 – Assymptomatic yellow plaques on the peri-orbital area (A). Foamy histiocytes occupying the dermis, as well as giant multinucleated Touton cells (B).

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Intentional Use of Known Allergens for Self-Harm Behavior

Uso Intencional de Alergénios Conhecidos para Comportamentos Autolesivos

Keywords: Adolescent; Drug Hypersensitivity/complications; Ibuprofen/adverse effects; Self-Injurious Behavior
Palavras-chave: Adolescente; Comportamento Autolesivo; Hipersensibilidade a Medicamentos/complicações; Ibuprofeno/efeitos adversos

Intentional self-harm represents a challenge for healthcare professionals.[1] Non-suicidal self-injury includes behaviors such as skin scratching, cutting, burning and hitting oneself.[1] Contributing factors include genetics, psychiatric conditions, and social influences.[1] About 18% of United States high school students engage in non-suicidal self-injury, rising to 24% among female adolescents.[2] In Portugal, evidence suggests a rising prevalence of self-harm among adolescents.[3]

Deliberate use of allergens for self-harm is remarkably rare in the literature. Reported cases include suicide attempts using penicillin, peanut butter, canned fish or peach juice ingestion.[4,5] No cases of self-harm lacking suicidal intent with known allergens were found.

Non-steroidal anti-inflammatory drugs (NSAIDs) hypersensitivity affects 0.6% - 5.7% of the population,[6] and they are widely available without a medical prescription. We report the case of an adolescent with ibuprofen hypersensitivity, who intentionally used this drug for self-harm.

We present a 13-year-old female with an intellectual developmental disorder, regularly assessed in child and adolescent psychiatry (CAP) appointments and under regular psychotherapy. She had a dysfunctional family environment, recurrent conflicts, and poor school performance, suffering from bullying along with difficulties integrating with peers.

She was referred to the allergology clinic for suspected ibuprofen hypersensitivity, following three reproducible episodes of generalized urticaria and palpebral angioedema immediately after ibuprofen intake. To confirm the diagnosis, we performed an open (both the patient and the clinician know what substance is being administered) oral provocation test (OPT) with ibuprofen, positive after a cumulative dose of 370 mg, with eyelid/retroauricular urticaria and labial angioedema within 90 minutes. Total NSAIDs avoidance was recommended, except for paracetamol (posteriorly tolerated) and nimesulide, following a negative open OPT.

Subsequent CAP evaluations revealed she had been developing intentional self-harm behaviors, specifically forearm self-mutilation, without suicidal ideation, due to anxiety. Four months after hypersensitivity confirmation, she presented twice to the emergency department with generalized urticaria and angioedema, without any apparent precipitating factor. Later on, the intentional intake of ibuprofen in those episodes was admitted by the patient, as a reaction to family disfunction. Assessment by social services led to patient institutionalization.

This case highlights an adolescent with a psychiatric background who used a known allergen for non-suicidal self-harm, rarely reported but a potentially overlooked behavior. Its true prevalence is unknown due to under-recognition or mislabeling as accidental exposure. Preventive measures are crucial, including early identification of self-injurious tendencies in allergic patients, particularly those with risk factors for severe reactions, monitoring of psychiatric comorbidities, patient education and personalized emergency plans. Collaboration between allergists, psychiatrists, and other healthcare providers is essential for proper management.

PREVIOUS AWARDS AND PRESENTATIONS

This case was previously presented as a poster at the 5th National Congress of Immunoallergology of Hospital da Luz, organized by the Allergy and Immunology Department of Hospital da Luz Lisboa, held on May 24th, 2024.

AUTHOR CONTRIBUTIONS

AA, ARP: investigation, writing – original draft preparation.

JG, ERG: conceptualization, investigation, writing – review & editing.

All authors approved the final version to be published.

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DATA CONFIDENTIALITY

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LEGAL GUARDIAN CONSENT

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Carta ao Editor Referente ao Artigo "Que Competências Devem ser Adquiridas na Educação Pré-Escolar?"

Letter to the Editor Concerning the Article "What Skills Should be Acquired in Pre-School Education?"

Palavras-chave: Desenvolvimento da Criança; Leitura; Pré-Escolar/educação
Keywords: Child Development; Child, Preschool/education; Reading

Caro Editor,

O artigo "Que Competências Devem ser Adquiridas na Educação Pré-Escolar?", de Branca Cunha *et al*,[1] publicado em fevereiro de 2025 na Acta Médica Portuguesa, aborda de forma pertinente a importância da prontidão escolar e da deteção precoce de dificuldades no desenvolvimento infantil. No entanto, gostaria de aprofundar algumas dimensões complementares que julgo essenciais.

É crucial considerar o impacto das desigualdades socioeconómicas no desenvolvimento infantil. Dados do estudo Geração XXI demonstram que crianças em contextos desfavorecidos apresentam maior risco de atrasos no desenvolvimento cognitivo e linguístico, afetando a sua preparação escolar.[2] Assim, políticas educativas eficazes devem integrar estratégias que mitiguem essas desigualdades desde a educação pré-escolar.

Quanto à avaliação do desenvolvimento, além da Escala Mary Sheridan, o uso de instrumentos validados para o contexto nacional como o ASQ-PT (*Ages and Stages Questionnaires* – versão portuguesa) tem mostrado elevada sensibilidade e especificidade (≥ 85% e ≥ 90%, respetivamente), com base nos dados da validação portuguesa.[3]

No entanto, a implementação ampla do ASQ-PT enfrenta barreiras, como a necessidade de formação específica e de articulação interinstitucional,[4] que devem ser consideradas no desenho de políticas públicas.

Neste sentido, a colaboração entre os setores da saúde e da educação deve ser operacionalizada de forma concreta. Programas como o "A PAR – Aprender em Parceria",[5] implementado em Lisboa com famílias em contextos vulneráveis, demonstraram resultados positivos no desenvolvimento cognitivo e emocional das crianças, bem como na capacitação parental. Contudo, estudos apontam a ausência de protocolos nacionais e lacunas na formação dos docentes como obstáculos persistentes.[6]

Assim, propõe-se a criação de mecanismos formais de articulação intersetorial, com protocolos comuns, formação partilhada e metas conjuntas, visando garantir uma resposta integrada e equitativa às necessidades das crianças.

A participação ativa das famílias e o acompanhamento holístico e contínuo do desenvolvimento são, igualmente, pilares fundamentais para o sucesso destas estratégias.

CONFLITOS DE INTERESSE

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