AMP

ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

ACTA MED PORT. ISSN 0870-399X e-ISSN 1646-0758

6-7 | 25

Número 6-7
Série II
Lisboa

Volume 38
Junho-Julho 2025
Publicação Mensal

AMP ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

Propriedade: Ordem dos Médicos (NIPC 500 984 492)

Sede do Editor / Redação: Av. Almirante Gago Coutinho, 151. 1749-084 Lisboa, Portugal. Tel: +351 21 151 71 00 E-mail: secretariado@actamedicaportuguesa.com

ISSN:0870-399X | e-ISSN: 1646-0758

Assinaturas: Nacional: 300 Euros; Internacional: 350 Euros.

AMP38(6-7) - Junho-Julho de 2025

Registo: Inscrito na Entidade Reguladora para a Comunicação Social com o Nº 106 369

Depósito legal: 20 957/88

Estatuto Editorial: http://www.actamedicaportuguesa.com/normas-de-publicacao

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Ending Nuclear Weapons, Before they End Us

Acabar com as Armas Nucleares, Antes que Acabem Connosco

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Acta Med Port 2025 Jun-Jul;38(6-7):357-359 ▪ https://doi.org/10.20344/amp.23271

Keywords: International Cooperation; Nuclear Weapons; Public Health
Palavras-chave: Armas Nucleares; Cooperação Internacional; Saúde Pública

This May, the World Health Assembly (WHA) will vote on re-establishing a mandate for the World Health Organization (WHO) to address the health consequences of nuclear weapons and war.[1] Health professionals and their associations should urge their governments to support such a mandate and support the new UN comprehensive study on the effects of nuclear war.

The first atomic bomb exploded in the New Mexico desert 80 years ago, in July 1945. Three weeks later, two relatively small (by today's standards), tactical-size nuclear weapons unleashed a cataclysm of radioactive incineration on Hiroshima and Nagasaki. By the end of 1945, about 213 000 people were dead.[2] Tens of thousands more have died from late effects of the bombings.

Last December, Nihon Hidankyo, a movement that brings together atomic bomb survivors, was awarded the Nobel Peace Prize for its "efforts to achieve a world free of nuclear weapons and for demonstrating through witness testimony that nuclear weapons must never be used again".[3] For the Norwegian Nobel Committee, the award validated the most fundamental human right: the right to live. The Committee warned that the menace of nuclear weapons is now more urgent than ever before. In the words of Committee Chair Jørgen Watne Frydnes, "it is naive to believe our civilisation can survive a world order in which global security depends on nuclear weapons. The world is not meant to be a prison in which we await collective annihilation".[4] He noted that our survival depended on keeping intact the "nuclear taboo" (which stigmatises the use of nuclear weapons as morally unacceptable).[5]

The nuclear taboo gains strength from recognition of compelling evidence of the catastrophic humanitarian consequences of nuclear war, its severe global climatic and famine consequences, and the impossibility of any effective humanitarian response. This evidence contributed significantly to ending the Cold War nuclear arms race.[6,7]

While the numbers of nuclear weapons are down to 12 331 now, from their 1986 peak of 70 300,[8] this is still equivalent to 146 605 Hiroshima bombs,[9] and does not mean humanity is any safer.[10] Even a fraction of the current arsenal could decimate the biosphere in a severe mass extinction event. The global climate disruption caused by the

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Recebido/*Received*: 01/04/2025 - **Aceite/*Accepted*:** 22/04/2025 - **Publicado/*Published*:** 02/06/2025

smoke pouring from cities ignited by just 2% of the current arsenal could result in over two billion people starving.[11]

A worldwide nuclear arms race is underway. Deployed nuclear weapons are increasing again, and China, India, North Korea, Pakistan, Russia and UK are all enlarging their arsenals. An estimated 2100 nuclear warheads in France, Russia, UK, US and, for the first time, also in China, are on high alert, ready for launch within minutes.[8] With disarmament in reverse, extensive nuclear modernisations underway, multiple arms control treaties abrogated without replacement, no disarmament negotiations in evidence, nuclear-armed Russia and Israel engaged in active wars involving repeated nuclear threats, Russia and the US deploying nuclear weapons to additional states, and widespread use of cyberwarfare, the risk of nuclear war is widely assessed to be greater than ever. This year the Doomsday Clock was moved the closest to midnight since the Clock's founding in 1947.[10]

Led by Ireland and New Zealand, in late 2024, the United Nations General Assembly (UNGA) voted overwhelmingly to establish a 21-member independent scientific panel to undertake a new comprehensive study on the effects of nuclear war,[12] with its final report due in 2027. Noting that "removing the threat of a nuclear war is the most acute and urgent task of the present day", the panel has been tasked with examining the physical effects and societal consequences of a nuclear war on a local, regional and planetary scale. It will examine the climatic, environmental and radiological effects of nuclear war, and their impact on public health, global socioeconomic systems, agriculture and ecosystems.

The resolution calls upon UN agencies, including WHO, to support the panel's work, including by "contributing expertise, commissioned studies, data and papers". All UN Member States are encouraged to provide relevant information, scientific data and analyses; facilitate and host panel meetings, including regional meetings; and make budgetary or in-kind contributions. Such an authoritative international assessment of evidence on the most acute existential threat to humankind and planetary health is long overdue. The last such report dates from 1989. It is shameful that France, UK and Russia opposed this resolution.[13]

In 1983 and 1987,[14] WHO convened an international committee of scientists and health experts to study the health effects of nuclear war. Its landmark, authoritative reports were influential and an excellent example of WHO fulfilling its constitutional mandate "to act as the directing and coordinating authority on international health work". In 1993, WHO produced an additional shorter report on the health and environmental effects of nuclear weapons, which included discussion of the production chain of nuclear weapons, including processing, testing and disposal.[15]

However, despite WHA having mandated WHO to report periodically on relevant developments, no further work was undertaken and in 2020 WHO's mandate on nuclear weapons and health lapsed.

The Marshall Islands, Samoa and Vanuatu, supported by seven co-sponsoring states and International Physicians for the Prevention of Nuclear War (IPPNW), are working to renew WHO's mandate. They are seeking wide support for a resolution on the health effects of nuclear weapons/war at this year's WHA in Geneva on 19-27 May.[1] WHO would then re-establish a programme of work on this most critical threat to health, and be able to lead strongly in providing the best health evidence to the UN panel.

Health professionals are well aware how crucial accurate and up-to-date evidence is to making good decisions. We and our organisations should support such a renewed mandate by urging our national WHA delegates to vote in support and commit the modest funds needed to re-establish WHO's work programme, especially now, as the organisation faces severe financial strain with the US decision to withdraw its membership.

Our joint editorial in 2023[16] on reducing the risks of nuclear war and the role of health professionals, published in over 150 health journals worldwide, urged three immediate steps by nuclear-armed states and their allies: adopt a "no first use" policy, take their nuclear weapons off hair-trigger alert, and pledge unequivocally that they will not use nuclear weapons in any current conflicts they are involved in. We also urged nuclear-armed states to work for a definitive end to the nuclear threat by urgently starting negotiations for a verifiable, timebound agreement to eliminate their nuclear arsenals, and called on all nations to join the Treaty on the Prohibition of Nuclear Weapons.[17]

It is an alarming failure of leadership that no progress has been made on these needed measures, nor on many other feasible steps away from the brink, acting on the obligation of all states to achieve nuclear disarmament. Nine states jeopardise all humanity and the biosphere by claiming an exclusive right to wield the most destructive and inhumane weapons ever created. The world desperately needs the leaders of these states to freeze their arsenals, end the modernisation and development of new, more dangerous nuclear weapons, and ensure that new technology such as artificial intelligence can never trigger the launch of nuclear weapons.

The UN scientific panel and a renewed mandate for WHO's work in this area can provide vital authoritative and up-to-date evidence for health and public education, evidence-based advocacy and policies, and the mobilised public concern needed to trigger decisive political leadership. This is a core health imperative for all of us.

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ACTA MÉDICA PORTUGUESA
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Infective Endocarditis in Children: Challenges and Evolving Profile in Portugal

Endocardite Infecciosa em Crianças: Desafios e Perfil em Mudança em Portugal

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Acta Med Port 2025 Jun-Jul;38(6-7):360-362 ▪ https://doi.org/10.20344/amp.23314

Keywords: Child; Endocarditis/epidemiology
Palavras-chave: Criança; Endocardite/epidemiologia

INTRODUCTION

Infective endocarditis (IE) is a rare but severe infectious and systemic clinical condition affecting the cardiac endocardium and implanted devices, associated with significant morbidity and mortality. Epidemiological data on IE show considerable variability and limited reproducibility, due to heterogeneity in case definitions, study populations, and geographical and sociodemographic factors, as well as the absence of large multicentric registries.

Recent population-based studies[1,2] have reported an increasing trend in the incidence of IE, a rise in complications, persistently high all-cause mortality, and lower-than-expected rates of surgical intervention. In Portugal, the incidence of IE in the pediatric population was quite low (0.3 - 0.6/100 000 inhabitants), revealing a non-significant rising trend between 2010 and 2018.[1] Nevertheless, data on pediatric IE remains limited, highlighting the need for further investigation in this subgroup.

The landscape of infective endocarditis in children in recent years and its lessons

The study conducted by Dias *et al*[3] provides an updated overview of the current epidemiological profile of IE in the pediatric population. This was a retrospective, single-center analysis carried out at a tertiary care hospital, encompassing all pediatric cases diagnosed with IE between 2008 and 2022. A total of 27 patients were included, with a mean age of 9.2 years. The majority (88.9%) had underlying structural heart disease, predominantly of congenital origin. Cardiac prosthetic material was present in 58.9% of the cohort, although only a minority of cases (25.9%) were attributable to healthcare-associated infections. Transthoracic echocardiography revealed identifiable vegetations in only one-third of the patients, underscoring the diagnostic challenges in this population. Curiously, transesophageal echocardiogram was only performed in 33% of patients. Nevertheless, computed tomography (CT) was performed in 44.4% of patients and PET-CT in 25.9%. This likely reflects a growing adoption of a multimodality imaging strategy, particularly given the inclusion of several patients diagnosed following the release of the 2015 European Society of Cardiology (ESC) guidelines on infective endocarditis. These guidelines emphasized the importance of integrating multiple imaging modalities and introduced updated diagnostic criteria to enhance the sensitivity and specificity of IE detection.

Interestingly, the surgical treatment rate for IE reported in this study is non inferior compared to the more recent single-center retrospective observational studies from adult cohorts in Portugal.[4]

Notably, the study reports a discernible upward trend in the annual incidence of IE from 2018 to 2022, suggesting an evolving clinical landscape. These findings are largely attributable to technical advances in surgical approaches and medical management of congenital heart disease (CHD), which have markedly improved survival rates. However, they have also contributed to a growing population of children at increased risk for IE and its associated complications, including significant morbidity and long-term functional impairment. This observation aligns with the existing literature, which estimates that only 8% - 10% of pediatric IE cases occur in children without CHD. Furthermore, the 25-year cumulative incidence of IE in patients with surgically corrected CHD is reported to range from 1.3% to 13%.

Given the well-established risk that CHD confers for the development of IE, preventive strategies should be increasingly emphasized and prioritized in this patient population. Key measures include appropriate use of antibiotic prophylaxis in high-risk scenarios, rigorous maintenance of oral health, and strict adherence to aseptic techniques during invasive procedures. These findings also underscore the need for standardized clinical protocols and well-established multidisciplinary referral networks to ensure timely diagnosis and management of a condition that appears to be increasing in incidence within this population.

In terms of microbiological profile, *Staphylococcus*

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Recebido/*Received*: 30/04/2025 - **Aceite/*Accepted*:** 05/05/2025 - **Publicado/*Published*:** 02/06/2025

aureus emerged as the most frequently isolated pathogen, followed by streptococcal species. This profile mirrors recent trends observed in adult IE registries,[5] in which *Staphylococci* have become the predominant causative agents. This shift is likely related to the increased use of intravascular devices and cardiac prostheses, including prosthetic valves and endovascular catheters, commonly employed in the management of congenital heart anomalies.

Limitations and external validity of findings

The study by Dias *et al*[3] presents several methodological and analytical limitations. Drawing population-level inferences from a single-center cohort comprising only 27 diagnosed cases inherently limits both the statistical power and external validity of the findings. Although the study was conducted at a national referral center for both infective endocarditis and congenital heart disease – thereby enabling the inclusion of a relatively higher number of cases and reflecting considerable clinical expertise – this setting introduces a notable selection bias.

From a methodological standpoint, one of the principal limitations of this study pertains to the case definition and the consistency in establishing a definitive diagnosis of IE. Notably, the authors acknowledge that the modified Duke criteria were not systematically applied, primarily due to logistical constraints. Furthermore, the use of imaging modalities lacked standardization, with no uniform diagnostic protocol in place. This variability introduces potential for diagnostic inconsistencies, including both underdiagnosis and overdiagnosis of IE cases.

It is also important to highlight the absence of data regarding patients' ethnic background, geographical origin, and migration status. This is particularly relevant in the context of ongoing demographic shifts in increasingly globalized societies. In Portugal, for instance, there has been a notable rise in migrant populations, many of whom originate from other Portuguese-speaking countries, particularly in Africa, sometimes with established healthcare protocols. As such, future epidemiological studies should incorporate sociodemographic variables to better characterize the affected populations and to inform tailored public health strategies.

A changing profile in Portugal for infective endocarditis in children

In the last 30 years, this is the fourth (retrospective) published analysis derived from pediatric single centers in Portugal (Table 1).

The first three series were published between 1996 and 2001.[6-8] This, once again, reflects the paucity of data in this field.

The recent work by Dias *et al* reveals a higher number of patients/year, a significant higher percentage of positive blood cultures and a significant lower all-cause mortality. Congenital heart disease constitutes a significant risk factor for IE in this specific subpopulation.

The rate of cardiac surgery was significantly higher in the study by Dias *et al*[3] when compared to the same institution in the series from Lira *et al*[8] in 2001.

Table 1 – Population characteristics of the pediatric cohorts of patients with infective endocarditis hospitalized in Portugal

Studies	Cunha *et al*,[6] 1996	Teixeira *et al*,[7] 1997	Lira *et al*,[8] 2001	Dias *et al*,[3] 2025
City	Coimbra	Porto	Porto	Porto
Period	1985 - 1995	1993 - 1997	1991 - 1998	2008 - 2022
Number of years	11	5	8	15
Sample size (n)	17	7	7	27
Patients/year	1.55	1.40	0.88	1.80
Mean age (years)	(range 10 days - 11 years old)	9	(range 4 months - 11 years old)	9.2
Male sex (%)	NA	43	43	40
Predominant sign (%)	Fever (88%), heart murmur (74%)	Fever (71.4%), heart murmur (57%)	Fever (100%)	Fever (88.9%)
Congenital heart disease (%)	65	86	86	85
Positive blood culture (%)	59	29	57	96
Heart failure (%)	53	NA	NA	NA
Uncontrolled infection (%)	0	NA	NA	NA
Embolization (%)	41	57	NA	44.4
Cardiac surgery (%)	0	43	0	29.6
Intrahospital mortality (%)	23.5	14	14	7.4

NA: not available

CONCLUSION

High-quality, evidence-based, and prospective data in infective endocarditis remain limited, especially in a pediatric population, with a notable absence of large-scale, multicentric studies capable of providing robust and generalizable conclusions. Nevertheless, investigations of this nature remain extremely valuable, particularly given the rarity of pediatric infective endocarditis. In such contexts, small-scale, single-center studies can provide crucial insights, especially within specific subpopulations. The profile of IE in this specific population is also evolving.

This highlights the need for IE registries that include the pediatric population that can capture the full picture.

AUTHOR CONTRIBUTIONS

JFP: Writing – original draft.

CS: Contents review as expert in the topic. Draft of the table comparing the results of this study with those of previous articles. Data curation.

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

JFP received honoraria for a medical lecture (fee paid directly to this author) from Boehringer Ingelheim Portugal. Travel and registration fees for this author to attend several medical meetings were also funded by Pfizer, MSD and AstraZeneca (fees paid to service providers).

CS reports that travel and registration fees for this author to attend several medical meetings were funded by Servier (fees paid to service providers).

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Artificial Intelligence in Healthcare Literacy: Promise, Gaps, and Guardrails

Inteligência Artificial na Literacia em Saúde: Potencial, Lacunas e Salvaguardas

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Acta Med Port 2025 Jun-Jul;38(6-7):363-365 ▪ https://doi.org/10.20344/amp.23286

Keywords: Artificial Intelligence; Generative Artificial Intelligence; Health Literacy; Medicine
Palavras-chave: Inteligência Artificial; Inteligência Artificial Generativa; Literacia em Saúde; Medicina

A timely inquiry into artificial intelligence for healthcare literacy

In this issue of Acta Médica Portuguesa, Ganicho *et al* present an exploratory study assessing ChatGPT's ability to respond to patient questions about HIV and pre-exposure prophylaxis (PrEP).[1] By submitting common queries to ChatGPT and scoring responses across clearly defined metrics, the authors provide structured evidence that artificial intelligence (AI) generated content may support health literacy efforts.[2] This is particularly relevant for strained healthcare systems, where clinicians have limited time for patient education.

The results appear promising: 80% of responses achieved a mean expert rating above four out of five, suggesting that, when deployed responsibly, AI could serve as a helpful adjunct in Portuguese patient education. The study identifies the potential of ChatGPT to offer real-time, private, and accessible information, especially to individuals with lower health literacy who face barriers in traditional healthcare communication. At the same time, equity considerations must not be overlooked, as the effectiveness of such tools may disproportionately favor already digitally literate individuals, exacerbating existing disparities in access to health information.

A fertile ground for application in clinical systems

Portugal's healthcare system may be especially fertile ground for the integration of such tools.[3] Portuguese clinicians often lack assistance from dedicated clinical support staff, making their time an especially scarce resource. Unlike the UK, where doctor's assistants support clinicians by taking notes during ward rounds, preparing clinical documentation, and coordinating follow-up appointments, no equivalent role exists in Portugal. Artificial intelligence tools that streamline communication and support patient understanding could improve care efficiency.

The implications extend beyond the individual to public health. In the context of infectious disease prevention programs, particularly for conditions like HIV and viral hepatitis, AI-assisted tools have demonstrated their ability in helping fine-tune screening algorithms.[4] By integrating diverse data sources – demographics, postal codes, prior infection history, and patterns of healthcare utilization – AI-powered electronic health record systems can identify individuals for screening when they present for urgent or routine care, creating a middle ground between costly universal approaches and narrowly risk-based strategies, which often result in missed opportunities for diagnosis. Whether one defines this as 'AI', 'machine learning', or simply 'big data' may be a matter of semantics, but the application is both practical and promising.

Looming ethical, legal, and systemic questions

While the study makes a very valuable contribution, it reflects a broader trend in early AI research penned by physicians, where policy implications are underexplored.[5] These dimensions, however, cannot be decoupled and are critical to address before such tools can be responsibly implemented at scale. While AI holds significant promise for health counseling and literacy, its integration into practice must abide by a modicum of appropriate ethical, legal, and operational frameworks.

First, the issue of ethical usage deserves close attention. Without clear guardrails, AI platforms risk perpetuating bias or disseminating misinformation, especially in sensitive areas such as HIV counseling.

Second, the question of medical liability remains unresolved. Should a patient suffer harm as a result of AI-generated advice, responsibility would be difficult to assign under current legal frameworks.

Third, although ChatGPT was used in its non-memory, anonymous version in the study, any future application in clinical environments must ensure compliance with patient and data protection laws, particularly the European Union's (EU) General Data Protection Regulation (GDPR). Artificial intelligence platform deployments must be designed to

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Recebido/*Received*: 30/04/2025 - **Aceite/*Accepted*:** 06/05/2025 - **Publicado/*Published*:** 02/06/2025

preserve patient confidentiality as rigorously as any other tool.

Fourth, reliance on proprietary, general-purpose platforms like ChatGPT, DeepSeek, Perplexity, and others presents structural challenges, as they may lack the sector-specific transparency and oversight necessary for healthcare. These tools are developed by private entities, often opaque in their data sources and potentially susceptible to internal and external pressures, as has been documented with Grok.[6] Responsible paths forward will require platform-agnostic guidelines with a minimum degree of public oversight. As an alternative to relying on general-purpose platforms, the development of patient-facing tools by dedicated healthcare software companies operating within the sector may offer a more viable route, as these entities are better equipped to navigate the regulatory intricacies of healthcare.

Lastly, governance remains a complex and unresolved issue. Under the EU AI Act, AI systems used for medical purposes must comply with specific requirements, including risk-mitigation protocols, human oversight, and quality data standards.[7] Oversight responsibilities are centralized within the newly established European AI Office, which supervises implementation and compliance. However, at the local level, it is still unclear who will approve and monitor the safety of these tools. The AI Act, together with the revised Product Liability Directive, clarifies that AI systems used in healthcare, including software, fall under the regulatory frameworks applied to medical devices and are subject to liability if defects cause harm.[8] Are national regulatory agencies currently equipped to undertake this role effectively, both in terms of resources and technical expertise?

Although full implementation and transposition of the AI Act will unfold progressively over the coming years, the practical impact of these frameworks remains uncertain, particularly as the pace of innovation in the field may outdo Europe's regulatory rollout. As a result, such technologies are likely to be adopted in practice across the continent before the EU's legal safeguards are fully operational – a pattern already evident in the cases of telehealth and healthcare professionals' use of social media, both of which hold significant potential to reduce health disparities but remain largely unregulated and unmonitored.

Future research and implementation priorities

The path ahead must include cross-disciplinary research involving not just clinicians, but also data scientists, implementation researchers, and legal experts. Studies comparing AI-generated counseling to human-delivered responses could help evaluate whether these tools enhance or hinder communication. This is especially important in areas such as empathy, nuance, and behavioral reinforcement – critical elements in counseling for conditions that carry stigma, like HIV.

Moreover, if AI tools are being used in medical publishing, as some journals are beginning to allow, clarity is needed around their role. While their capacity to edit language and reduce native-speaker acceptance bias is commendable, their current limitations in statistical reasoning and logic make them unreliable for biostatistical analyses.

More broadly, healthcare researchers using AI must resist the temptation to ignore implementation concerns. Historically, physicians have distanced themselves from management disciplines and discussions around healthcare cost, only to later realize its centrality to sustainable care. The same must not happen with AI. Understanding the systems into which AI will be deployed, and the laws that will govern its use, is essential. For this reason, collaboration with experts in health law and policy is not optional but necessary.

From *ad hoc* appraisal to methodological maturity

Ganicho *et al* lay important groundwork in a field where fewer than ten indexed studies currently address the use of AI in healthcare in Portugal. Their use of predefined quality criteria and expert scoring is a welcome departure from anecdotal assessments that have characterized early AI studies. Future efforts should build on this by adopting key tenets of qualitative research, including validated scoring systems, involving diverse evaluators, and incorporating patient feedback.

Indeed, if this line of research is to advance responsibly, clinicians must become more than end-users. They must engage with how systems are built, evaluated, and governed. Just as previous generations of doctors embraced healthcare management and economics, or health systems research at the turn of the century, today's practitioners must become literate in data science, artificial intelligence, and digital ethics.

ACKNOWLEDGEMENTS

The author has declared that ChatGPT was used to proofread the submitted manuscript.

COMPETING INTERESTS

The author has received consulting fees, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, and support for attending meetings and/or travel from Gilead Sciences.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Operacionalização do Tratamento Involuntário em Meio Prisional: Uma Perspetiva à Luz da Nova Lei de Saúde Mental em Portugal

Operationalization of Involuntary Treatment in a Prison Setting: A Perspective in Light of the New Mental Health Law in Portugal

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Acta Med Port 2025 Jun-Jul;38(6-7):366-368 ▪ https://doi.org/10.20344/amp.22684

Palavras-chave: Ética; Perturbações Mentais; Portugal; Tratamento Psiquiátrico Involuntário/ethics; Tratamento Psiquiátrico Involuntário/legislação e jurisprudência
Keywords: Ethics; Involuntary Treatment, Psychiatry/ethics; Involuntary Treatment, Psychiatry/legislation and jurisprudence; Mental Disorders; Portugal

TRATAMENTO INVOLUNTÁRIO NA NOVA LEI DA SAÚDE MENTAL

Vigorando desde 2023, a nova Lei da Saúde Mental (*n*LSM)[1] substituiu o anterior diploma regulador dos tratamentos involuntários (TI). Esta mudança legislativa, impelida pela necessidade de conformar a lei portuguesa à Convenção sobre os Direitos das Pessoas com Deficiência[2] e enformada por recomendações europeias[3] — entre elas, o protocolo a acrescentar à Convenção de Oviedo[4] —, inclui-se num esforço de uniformizar a aplicação dos TI em psiquiatria nos estados-membros da União Europeia, para prevenir abusos aos direitos das pessoas com doença mental. Fundada sobre estes documentos, a *n*LSM pretende ser um instrumento legal de assistência clínico-psiquiátrica que garanta o maior respeito pela autonomia e dignidade das pessoas que, pela sua doença mental, observem a sua liberdade cerceada, promovendo, igualmente, a sua não-discriminação.

A *n*LSM produz alterações significativas que se traduzem no modo como os agentes envolvidos a poderão aplicar. Algumas destas mudanças poderão ser problemáticas, como a substituição do conceito médico-legal de 'anomalia psíquica' pelo de 'doença mental', estritamente diagnóstico, nem sempre imediatamente realizável. Acresce que a *n*LSM parece enfocar os pressupostos do TI na noção de perigo. Esta aproximação generalista a um perigo, pode fazer olvidar o escopo do TI, caso os psiquiatras, por receio de litigância, se rejam por interpretações rígidas sobre os bens jurídicos em perigo, nomeadamente se apenas considerarem a vida ou a integridade física, quando, efetivamente, a própria saúde constitui um bem jurídico merecedor de proteção (ilustre-se aquela interpretação restritiva com o caso reportado[5] de TI não pela agudização de doença mental, mas pela presença concomitante de uma anemia grave, encontrada posteriormente, considerando-se esta última doença como perigo, numa aparente perversão do espírito da LSM e das recomendações europeias que a sustentam).[3,4] A *n*LSM poderá, pois, promover interpretações contrárias ao seu espírito, se não houver uma deliberação clínico-psiquiátrica multidimensional e responsável do ponto de vista técnico-científico, surgindo o risco de não haver lugar a TI, apenas por ausência de perigo para a vida ou integridade física, do próprio ou terceiros. Uma inibição deste tipo é particularmente relevante se pensarmos na comprovada incapacidade clínica para prever atos de violência, para o próprio doente e outros.[6]

Ainda na sua infância, a *n*LSM enfrenta os desafios da sua aplicabilidade e das hesitações que surgem da sua novidade. Interessa, então, manter um debate sobre como as alterações previstas serão efetivadas e que interpretações resultarão válidas. Nesta perspetiva, pretendemos começar esse debate pela aplicação da *n*LSM numa população vulnerável: os doentes mentais em reclusão.

UM NOVO ESPAÇO PARA O TRATAMENTO INVOLUNTÁRIO: O SISTEMA PRISIONAL

Ter cuidados adequados de saúde mental no sistema prisional é um direito da população privada de liberdade e uma oportunidade para o Estado prestar assistência a pessoas que, geralmente, são negligenciadas e não têm acesso direto ao sistema público de saúde.[7] Como referimos, uma das alterações significativas produzidas pela *n*LSM respeita à clareza com que se aplica no meio prisional. Esta clareza é ilustrada pela referência explícita "[à]s pessoas com necessidade de cuidados de saúde mental a quem seja aplicada pena, medida de segurança ou medida de coação" (n.º 2, art.º 7.º; n.º 2, art.º 8.º),[1] menção ausente na anterior LSM. Ademais, a *n*LSM (art.º 47.º)[1] altera o Código da Execução das Penas e Medidas Preventivas da Liberdade (CEPMPL), conferindo ao Tribunal de

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Recebido/*Received*: 02/12/2024 - **Aceite/*Accepted*:** 19/02/2025 - **Publicado *Online*/*Published Online*:** 04/04/2025 - **Publicado/*Published*:** 02/06/2025

Execução das Penas (TEP) a competência de "decidir sobre o [TI] do condenado com necessidade de cuidados de saúde mental". Por esta competência não estar atribuída ao TEP na anterior LSM, a população prisional com doença mental via-se discriminada, pelo que a *n*LSM traduz um evidente esforço pelo respeito pelo princípio da equivalência de cuidados entre as populações comunitária e prisional, esta última anteriormente, na prática, afastada da obtenção de um estatuto legal que possibilitasse quer o seu tratamento psiquiátrico involuntário quer a sua proteção durante esse tratamento.

Além da consagração formal do princípio da charneira dos cuidados prisionais — equivalência de cuidados —, qual a pertinência efetiva destas mudanças? Embora os dados de saúde mental prisional escasseiem em Portugal,[8] a verdade é que, internacionalmente, a evidência aponta para que a prevalência da maior parte das doenças mentais na população prisional seja mais do dobro do que a da comunidade, com particular nota para as perturbações psicóticas (4%) ou para a depressão (11%).[9] Face à elevada prevalência destas perturbações, com potencial de prejuízo do discernimento e juízo crítico, afigura-se clara a pertinência da entrada da *n*LSM no meio prisional, assim como a insuficiência e inadequação das medidas coercivas de tratamento previstas no CEPMPL (art.º 35.º),[10] cuja aplicação não parece ser sustentável fora de um contexto pontual e puramente contentor. Estas medidas são por isso incompatíveis com um tratamento apropriado de acordo com as *leges artis* psiquiátricas. A *n*LSM vem garantir aos reclusos com doença mental acesso a um estatuto legal assistencial psiquiátrico com os contrapesos imprescindíveis de recurso legal, diminuindo o espaço para abusos na aplicação de cuidados de saúde impostos de forma coerciva, conforme previsto no CEPMPL (art.º 35.º).[10]

Perante as mudanças operadas pela *n*LSM e justificada a sua pertinência, atendendo à prevalência de doença mental nos reclusos, torna-se imperioso que os psiquiatras possam atuar de modo a responder, de forma legal e ética, às novas exigências impostas no tratamento de doentes, com estados patológicos, umas vezes inaugurais, outras vezes crónicos, tendencialmente recrudescentes, num ambiente especialmente perturbador.

DO ESPÍRITO À OPERACIONALIZAÇÃO PRISIONAL: PROBLEMAS E SOLUÇÕES

Embora existam discordâncias interpretativas da *n*LSM,[11] afirmaríamos que, na comunidade, o procedimento se afigura claro. Relativamente ao meio prisional, contudo, torna-se necessário averiguar a sua operacionalidade e debater o procedimento dos médicos em exercício nos estabelecimentos prisionais (EP). Acreditamos que deverão encarar esta *n*LSM não como um problema, mas como um instrumento promotor dos cuidados psiquiátricos, respeitando a ética e os direitos desta população, carente de cuidados de saúde mental e exposta a estigmas e crenças, entre os quais o de que os reclusos são menos merecedores de cuidados de saúde mental.[10] Efetivamente, na comunidade, "[o] médico que, no exercício das suas funções, conclua pela verificação de uma das situações de perigo previstas [...], pode comunicá-la à autoridade de saúde competente" (n.º2, art.º 16.º).[1] Verificada a situação, "as autoridades de saúde competentes devem requerer o [TI] sempre que tomem conhecimento de uma das situações de perigo". Na comunidade, portanto, o legislador tem em conta o segredo médico, fazendo articular entre clínicos a informação do doente. No sistema prisional, porém, a autoridade de saúde não se apresenta operacionalmente viável, pelo que a sinalização médica deverá chegar ao Ministério Público (MP), cujo conhecimento de uma situação de perigo também fará requerer o TI. Dado o MP não ser diretamente acessível ao médico sinalizador, o envolvimento do diretor do EP surge analogamente ao previsto no n.º 5 do art.º 35.º do CEPMPL[10] no que respeita aos cuidados de saúde coativamente impostos, sendo que, aqui, as intervenções e os tratamentos médico-cirúrgicos coativos são ordenados por despacho fundamentado (em informação médica) do diretor do EP e executados ou ministrados sob direção médica. Assim, caberá ao diretor do EP, após sinalização do médico, a remissão desta ao MP, que requererá a abertura do processo de TI junto do TEP competente. Um problema nesta atuação residiria numa violação do segredo médico, por transmissão de informação a terceiros — o diretor do EP e o MP. No entanto, e à semelhança do legislado no art.º 35.º do CEPMPL,[10] numa situação de perigo, com prejuízo do juízo crítico do doente e do alcance da recusa, não parece eticamente justificado suspender o envio de informação a entidades não-clínicas — respeitando, formalmente, o sigilo médico, mas limitando, efetivamente, o acesso do doente a tratamento —, uma vez que a própria autonomia do doente estará diminuída pela doença. Contudo, os dados veiculados devem conter apenas a informação estritamente necessária para indicar a presença do perigo e do nexo deste com a doença mental, prevenindo-se, assim, a divulgação de informação jurídico-penal relevante, que poderia trair os interesses do doente neste âmbito. É também fundamental entender que não cabe ao médico sinalizador provar a existência dos pressupostos para TI. Deverá haver tão-só uma forte suspeita clínica para que o TI possa ser requerido e o doente seja sujeito a avaliação clínico-psiquiátrica (art.º 20.º da *n*LSM). Esta hipótese de procedimento parece suster-se eticamente, mas também deontologicamente, uma vez que o Código Deontológico da Ordem dos Médicos, que, além de impedir o tratamento de presos ou detidos capazes de autonomia, no caso de

perigo para a vida ou grave perigo para a saúde, explica que o tratamento coercivo deverá ser confirmado por médico estranho à instituição (art.º 83.º).[12] O mesmo código ressalva que o médico deve denunciar à Ordem qualquer ato lesivo da saúde física ou psíquica dos detidos (art.º 81.º),[12] onde seria admissível incluir uma omissão do diretor que inibisse uma avaliação clínico-psiquiátrica, após sinalização médica.

CONTRIBUTO DOS AUTORES

Os autores contribuíram igualmente para o manuscrito e aprovaram a versão final a ser publicada.

CONFLITOS DE INTERESSE

SPA recebeu honorários pelo desempenho de funções de perita médica no Instituto de Medicina Legal e Ciências Forense, I.P.

SMM declara não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

A Perspetiva dos Médicos Portugueses sobre a Reestruturação da Carreira Médica: Um Estudo Transversal

The Portuguese Physicians' Perspective regarding the Restructuring of the Medical Career: A Cross-Sectional Study

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Acta Med Port 2025 Jun-Jul;38(6-7):369-376 ▪ https://doi.org/10.20344/amp.22971

RESUMO

Introdução: A carreira médica (CM) tem sido, em Portugal, um pilar e uma garantia de qualidade na organização e prestação de cuidados de saúde. Atualmente, é constituída por dois graus e três categorias, sendo a progressão possível mediante duas formas, ambas relacionadas com o sistema remuneratório. No entanto, assistimos hoje a uma preocupante estagnação da progressão na carreira dos médicos em Portugal. O presente estudo teve como objetivo principal avaliar a perceção, opinião, e desafios relacionados com a CM em Portugal.

Métodos: Foi aplicado um questionário aos médicos registados na Ordem dos Médicos de Portugal (n = 61 317), entre dezembro de 2024 e janeiro de 2025. Foram realizadas análises quantitativa e qualitativa.

Resultados: Foi obtida uma taxa de resposta de 9,36%. A maioria dos médicos apresentou idades compreendidas entre os 30 e 40 anos, era mulher, pertencia à categoria de assistente graduado, trabalhava no setor público e na área hospitalar. Foi consensual a relação entre a CM e a qualidade dos cuidados de saúde (91,45%), a necessidade de reestruturação da CM (87,57%), a integração do internato médico na CM (92,58%), a transversalidade da CM, independentemente do setor de atividade (78,1%) e a associação da progressão na CM à progressão remuneratória (95,86%). A maioria dos médicos considerou que a CM deveria ter mais graus (55,63%).

Conclusão: Os resultados suportam a perceção da importância da CM para a qualidade dos cuidados prestados. Destaca-se o consenso entre os médicos sobre a necessidade de reestruturação da CM, com propostas como a reintegração do internato médico e a criação de novos graus técnico-científicos. Embora a maioria dos médicos que responderam ao questionário trabalhe no setor público, o consenso sobre a transversalidade da CM entre os vários setores foi evidente. Contudo, a concretização desta transversalidade revela-se um desafio, especialmente quando combinada com a opinião consensual de que a progressão na carreira deve implicar sempre uma progressão remuneratória, crucial para o reconhecimento do trabalho médico.

Palavras-chave: Inquéritos e Questionários; Médicos; Motivação; Portugal; Programas Nacionais de Saúde; Satisfação Profissional

ABSTRACT

Introduction: The medical career (MC) has been, in Portugal, a pillar and a guarantee of quality in the organization and provision of healthcare. Currently, it consists of two levels and three categories, with progression possible by two ways, both related to the remuneration system. However, we are currently witnessing a concerning stagnation in the career progression of doctors in Portugal. The main aim of this study was to evaluate the perception, opinion, and challenges related to the MC in Portugal.

Methods: A questionnaire was applied to doctors registered in the Portuguese Medical Association (n = 61 317) between December 2024 and January 2025. Both quantitative and qualitative analyses were performed.

Results: A response rate of 9.36% was obtained. The majority of doctors were aged between 30 and 40 years, were women, held the category of senior attending physician, worked in the public sector, and in hospital-based specialties. There was consensus on the relationship between the MC and the quality of healthcare (91.45%), the need for restructuring the MC (87.57%), the integration of residency into the MC (92.58%), the cross-sector nature of the MC (78.1%), and the association of career progression with remuneration progression (95.86%). Most doctors felt that the MC should have more levels (55.63%).

Conclusion: The results support the perception of the importance of the MC for the quality of care provided. A consensus is evident among doctors regarding the need for restructuring the MC, with proposals such as the reintegration of the residency program and the creation of new technical-scientific levels. Although most doctors who responded to the questionnaire work in the public sector, there was a clear consensus about the cross-sector nature of the MC. However, the implementation of this cross-sector nature proves to be a challenge, especially when combined with the consensus that career progression should always involve a pay rise, which is crucial for the recognition of medical work.

Keywords: Job Satisfaction; Motivation; National Health Programs; Physicians; Portugal; Surveys and Questionnaires

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Recebido/*Received*: 02/02/2025 - **Aceite/*Accepted*:** 07/03/2025 - **Publicado/*Published*:** 02/06/2025

KEY MESSAGES

- A carreira médica (CM) contribui para a melhoria da qualidade da prestação de cuidados de saúde à população.
- É necessária a reestruturação da atual CM.
- O internato médico deve ser integrado na CM.
- A CM deve ser transversal, independentemente do setor de atividade (público/privado/social) do médico.
- A CM deve ter mais graus, além de 'especialista' e 'consultor'.
- A progressão na CM deve ser acompanhada de progressão remuneratória.

INTRODUÇÃO

Foi para preservar no ato médico as suas ancestrais características humanistas que, em 1961, um grupo de médicos publicou um manifesto intitulado "Relatório sobre as Carreiras Médicas".[1]

Desde então, a carreira médica (CM) tem sido, em Portugal, um pilar e uma garantia de qualidade essencial na organização e prestação de cuidados de saúde, refletindo uma evolução histórica marcada por reformas significativas e desafios contínuos.[1]

Em 1979, com a criação do Serviço Nacional de Saúde (SNS), ficou consagrado na Lei n.º 56/79, de 15 de setembro, que "ao pessoal do SNS que tenha a qualidade de funcionário é assegurado o regime de carreira".[2,3]

O Decreto-Lei (DL) 73/90, de 6 de março, veio "reformular o regime legal das carreiras médicas dos serviços e estabelecimentos do SNS", justificado como "objetivo prioritário do Governo de modernização da Administração Pública, através de um projeto de desenvolvimento e valorização dos seus profissionais, com vista à melhoria da rentabilidade e qualidade dos serviços a prestar". A CM passou a ser organizada em categorias hierarquizadas, às quais correspondiam funções da mesma natureza e que pressupunham a posse de graus como títulos de habilitação profissional.[4]

Em 2002, pela Lei n.º 27/2002, de 8 de novembro, definiu-se um novo modelo de gestão hospitalar, alargado em 2005 a todos os hospitais, transformados em Entidades Públicas Empresariais (EPE). Doravante, os médicos passaram a ser contratados em regime de contrato individual de trabalho (CIT), sujeitos à lei geral do trabalho.[5] Houve uma estagnação da CM e uma ameaça da extinção da mesma.

Foi só no ano de 2009, na sequência da negociação do governo com os sindicatos, que a CM foi resgatada mediante publicação de dois decretos, os DL 176/2009 e 177/2009, de 4 de agosto, consoante o regime de CIT ou contrato de trabalho em funções públicas (CTFP), respetivamente. Ambos os decretos foram publicados, posteriormente nos respetivos acordos coletivos de trabalho (ACT). Estes, iguais no articulado, enfatizam no preâmbulo a qualificação e desenvolvimento técnico-científico dos médicos como "um dos fatores críticos do sucesso do SNS" e referem que "tradicionalmente, as carreiras médicas têm sido um requisito e um estímulo para um percurso de diferenciação profissional, marcado por etapas exigentes, com avaliação interpares e reconhecimento institucional". É reconhecido pelo legislador que a CM tem "repercussões comprovadas na qualidade dos cuidados de saúde e nos resultados medidos por vários indicadores de saúde populacional".[6,7] Os ACT determinaram a vigência de dois graus ('especialista' e 'consultor'), como "títulos de habilitação profissional atribuídos pelo Ministérios da Saúde e reconhecidos pela Ordem dos Médicos (OM) em função da obtenção de níveis de competência diferenciados e sujeição a procedimento concursal", e três categorias ['assistente', 'assistente graduado' (AG) e 'assistente graduado sénior' (AGS)] e seus respetivos conteúdos funcionais e condições de admissão. A partir desta data, a CM é única e organizada por áreas de exercício profissional, nomeadamente hospitalar, medicina geral e familiar, saúde pública, medicina legal e medicina do trabalho.[6,7] Em 2012, com o DL n.º 266-D/2012, de 28 de dezembro, e na sequência da grave crise económica vivida em Portugal e intervenção da *troika* (Banco Central Europeu, Comissão Europeia e Fundo Monetário Internacional), ocorreram alterações no período normal de trabalho dos médicos, que passou para 40 horas semanais. No entanto, foi também uma oportunidade para a caracterização das áreas de exercício profissional e especificação do conteúdo funcional de cada categoria da CM.[8]

Assim, e desde o ano 2009, a CM em Portugal e no SNS estrutura-se de acordo com as categorias de 'assistente', que representa o início da CM especializada, com responsabilidades clínicas e formativas; AG, com experiência comprovada e avaliação favorável, desempenhando um papel mais autónomo e de maior responsabilidade na gestão de casos complexos; e AGS, reservada a profissionais com experiência consolidada, que lideram equipas e participam ativamente na formação de novos médicos e no desenvolvimento organizacional.[8] Esta hierarquia é essencial para o reconhecimento formal da experiência acumulada, o reconhecimento da idoneidade formativa das unidades de saúde, a motivação dos profissionais e para a garantia de uma prestação de cuidados de saúde de elevada qualidade.[9] A progressão na CM faz-se de duas formas, ambas

relacionadas com o sistema remuneratório: uma vertical, mediante a aquisição da categoria, e uma horizontal, através dos escalões remuneratórios, dependente do sistema de avaliação de desempenho da administração pública (SIADAP).[8]

No entanto, assistimos hoje a uma preocupante estagnação da progressão na carreira dos médicos em Portugal. São vários os fatores que concorrem para esta realidade. No caso dos concursos para habilitação do grau de consultor, com progressão para AG, estes estiveram suspensos durante o período de 2002 a 2012 a que se seguiu um reinício irregular e atribulado, muitas vezes aliado a um atraso na sua conclusão, que frequentemente se prolongou durante anos. No caso dos concursos para AGS, assistimos nos últimos anos a uma abertura, também irregular, de um número muito limitado de vagas, o que aliado ao número de médicos reformados nos últimos anos detentores desta categoria, determinou a ausência dos médicos mais graduados em vários serviços e, portanto, uma ameaça efetiva da capacidade formativa e de liderança organizacional das unidades de saúde.[9]

Noutros setores, como o social, forças armadas ou medicina legal, a CM apresenta-se residual e estagnada, apesar de negociada com os sindicatos médicos.

Deste modo, é muito importante compreender as especificidades da CM em Portugal, à luz das práticas e experiências nacionais e europeias, sendo essencial identificar barreiras e delinear estratégias de melhoria. A valorização da CM poderá contribuir para uma melhor organização dos recursos humanos em saúde, beneficiando tanto os profissionais como os utentes, criando valor para todo o sistema.

O presente estudo, baseado na aplicação de um questionário aos médicos a nível nacional, teve como objetivo principal avaliar a perceção, opinião, expectativa e desafios relacionados com a CM em Portugal.

MÉTODOS

População do estudo

A população incluiu todos os médicos registados na OM de Portugal com endereço de correio eletrónico válido (n = 61 317), num total de 64 941 médicos inscritos na OM.

Questionário

Foi construído um questionário específico para o estudo, por um painel de peritos, neste caso, os membros do Conselho Nacional Consultivo (CNC) para o SNS e CM da OM.[10] O questionário teve como principal objetivo recolher a perceção, opinião, expectativa e desafios no que respeita à CM em Portugal.

O questionário tem 12 questões, distribuídas da seguinte forma:

- Variáveis sociodemográficas: cinco questões, incluindo idade, género, categoria profissional, setor de atividade e área de exercício profissional;
- Questões diretamente relacionadas com a CM: sete questões (opções de resposta: 'sim'/'não'/'não respondo'), que incluíram os seguintes temas: contribuição da CM para a melhoria da qualidade da prestação de cuidados de saúde, necessidade de reestruturação da CM, possibilidade de integração do Internato Médico (IM) na CM, transversalidade da CM a todos os setores de atividade médica (público, privado, social), necessidade de mais graus técnico-científicos na CM, associação da progressão na CM à progressão remuneratória;
- Solicitação de comentários/sugestões acerca da CM: área de texto livre.

Todas as questões eram de carácter obrigatório, com a possibilidade de escolha de apenas uma opção.

Método de recolha de dados

O questionário foi elaborado na plataforma Google Forms, e foi enviado um *link* de acesso para os médicos registados na OM de Portugal com endereço eletrónico válido, pelos serviços centrais da OM, em nome do CNC para o SNS e CM. O questionário esteve disponível entre 17 de novembro a 12 de dezembro de 2024 e, neste período, foram enviados três 'lembretes' adicionais.

Considerações éticas

Este estudo respeitou os princípios éticos da investigação em saúde. Todos os participantes foram informados sobre os objetivos do estudo e garantiu-se o seu consentimento informado antes da submissão das respostas. A participação foi voluntária, não implicando qualquer tipo de compensação ou prejuízo para os inquiridos. Os dados foram recolhidos e analisados de forma anónima e confidencial, garantindo o cumprimento do Regulamento Geral de Proteção de Dados (RGPD) da União Europeia. Devido à natureza não interventiva do estudo, e à ausência de dados sensíveis ou clínicos, não foi necessária a submissão a uma Comissão de Ética.

Análise de dados

Foram realizadas duas análises dos dados, no período compreendido entre dezembro de 2024 e janeiro de 2025. Uma análise quantitativa, descritiva, com recurso ao programa informático Microsoft Excel, e uma análise qualitativa, do tipo análise de conteúdo, aos dados da questão que solicitou texto livre. A análise de conteúdo foi realizada por dois dos investigadores, teve como base a metodologia de Edwards (2016),[11] e seguiu os seguintes passos: 1. codificação independente em categorias; 2. análise da categorias e identificação de subcategorias (i.e., dimensões);

3. análise das dimensões e identificação de subdimensões; e 4. organização dos resultados.

RESULTADOS

Dos 61 317 questionários enviados, foi obtida uma taxa de resposta de 9,36% (5743 médicos).

A maioria dos médicos (45,16%) apresentou idades compreendidas entre as décadas de 30 (24,88%) e 40 (20,28%), e eram predominantemente do sexo feminino (57,79%). Relativamente à categoria, a maioria era AG (37,21%), e assistente (27,63%), trabalhando maioritariamente e exclusivamente no setor público (66,93%), e na área hospitalar (71,67%) (Tabela 1).

Quanto às questões sobre a CM (Tabela 2), 91,45% dos médicos concordou que a CM contribui para a melhoria da qualidade da prestação de cuidados de saúde à população, bem como com a necessidade de reestruturação da CM (87,57%) e a integração do IM na CM (92,58%). No que diz respeito à transversalidade da CM, 78,1% dos médicos considerou que deve ser transversal, independentemente do setor de atividade (público/privado/social). Quando questionados se a CM deveria ter mais graus, além de especialista e consultor, a percentagem de concordância diminuiu para 55,63%. A maioria dos médicos foi consensual (95,86%) quando se questionou se a progressão na CM, com os respetivos graus técnico-científicos, deveria ter sempre associada uma progressão remuneratória (Fig. 1).

Cerca de 1/5 dos médicos que responderam ao questionário fizeram comentários/sugestões sobre a CM (Tabela 3). Além dos temas diretamente ligadas à carreira (76,64%), foram notadas preocupações relacionadas com condições de trabalho (4,11%) e com o IM (2,52%). No que diz respeito aos temas relacionados diretamente com a CM, dois foram os mais predominantes: dificuldade de progressão na CM (48,41%), sendo o motivo apontado o atraso ou ausência de concursos (59,19%); e a necessidade de reestruturação da CM (25%), tendo sido dadas sugestões sobre a valorização da diferenciação teórica/investigação/gestão (26,43%), valorização da prática clínica (20,98%), e maior número de graus em relação ao atualmente existente (12,2%).

Tabela 1 – Variáveis sociodemográficas da população em estudo

Variável	n	%
Idade (anos)		
20 – 29	467	8,13
30 – 39	1429	24,88
40 – 49	1159	20,18
50 – 59	787	13,70
60 – 69	1253	21,82
70 – 79	587	10,22
80 – 89	56	0,98
Mais de 90	5	0,09
Sexo		
M	2415	42,05
F	3319	57,79
n/a	9	0,16
Categoria profissional		
Médico Interno da Formação Geral	197	3,43
Médico Interno da Formação Especializada	686	11,95
Médico Assistente	1587	27,63
Médico Assistente Graduado	2139	37,24
Médico Assistente Graduado Sénior	943	16,42
Sem categoria	191	3,33
Setor de atividade		
Público	3826	66,93
Privado	1003	17,55
Social	55	0,96
Público e privado	726	12,71
Público, privado e social	8	0,14
Privado e social	3	0,05
Forças Armadas	6	0,10
PPP	3	0,05
Academia	6	0,10
Aposentado	74	1,29
Estrangeiro	15	0,26
Indústria	3	0,05
Sem atividade	9	0,16
n/a*	6	0,10
Área de exercício profissional		
Hospitalar	4116	71,67
Medicina Geral e Familiar	1350	23,51
Saúde Pública	136	2,37
Medicina Legal	38	0,66
Medicina do Trabalho	103	1,79

*: inclui organizações governamentais/ONG; total de médicos que responderam ao questionário: 5743

DISCUSSÃO

Estudos feitos com questionários são desafiantes, especialmente no que diz respeito à construção do questionário em si e adesão da população-alvo.[10,12] Apesar da metodologia adotada para a construção do questionário[10], este pretendeu ser genérico e transversal à população médica o que, em si mesmo, pode ter condicionado a resposta, dada a variabilidade de situações individuais em cada área profissional em específico (por exemplo, área de medicina geral e familiar *versus* área hospitalar). Por outro lado, a

adesão da população-alvo foi baixa (9,36%), o que pode comprometer o tamanho e o poder da amostra, bem como a qualidade dos dados recolhidos, tal como a análise estatística realizada.[12] No entanto, este é o primeiro estudo realizado em Portugal, por médicos e para médicos, que tem como objetivo auscultar a opinião destes profissionais, avaliar os principais desafios da CM e colaborar em propostas para o futuro. Este estudo é revelador em relação à vontade dos médicos relativamente às principais questões que implicam uma mudança na CM e, tendo em conta a taxa de resposta em relação a algumas respostas, tornam-no inovador e uma ferramenta de apoio a uma eventual mudança na CM.

Constatou-se uma elevada participação de médicos mais jovens, maioritariamente nas categorias de assistente e AG, exercendo sobretudo em hospitais do setor público. Este perfil sugere a existência de necessidades específicas nesta área profissional, até pela extensa literatura, que tem como alvo os médicos mais jovens, e que estabelece uma forte relação entre *burnout*, número de horas de trabalho, diminuição da satisfação com o trabalho e vida pessoal, e da qualidade de vida.[13-15] A elevada taxa de resposta por parte de médicas mulheres reflete a feminização crescente das profissões relacionadas com a saúde.[16]

Os resultados revelam que os médicos consideram a CM um elemento essencial para assegurar a qualidade dos cuidados de saúde à população. Esta perceção está alinhada com as reformas implementadas ao longo das últimas décadas, que reforçaram a CM como um dos pilares fundamentais do SNS e da prestação de cuidados de excelência.[4,6,7] O novo Relatório sobre as Carreiras Médicas, que estabelece uma narrativa histórica da CM em Portugal e estabelece propostas de melhoria, também sublinha a importância da CM na estruturação e organização dos

Tabela 2 – Questões colocadas sobre a carreira médica

Questão n.º 6. Concorda que a organização/regulação da carreira médica contribui para a melhoria da qualidade da prestação de cuidados de saúde à população?		
Sim	5252	91,45
Não	344	5,99
Não respondo	147	2,56
Questão n.º 7. Concorda com a reestruturação da carreira médica?		
Sim	5029	87,57
Não	183	3,19
Não respondo	531	9,25
Questão n.º 8. Considera que o internato médico deve fazer parte da carreira médica?		
Sim	5317	92,58
Não	307	5,35
Não respondo	119	2,07
Questão n.º 9. Considera que a carreira médica deve ser transversal a todos os médicos, independentemente do setor de atividade (público/privado/social)?		
Sim	4485	78,1
Não	882	15,36
Não respondo	376	6,54
Questão n.º 10. Acha que a carreira médica deveria ter mais graus técnico-científicos (além de especialista e consultor)?		
Sim	3195	55,63
Não	1798	31,31
Não respondo	750	13,06
Questão n.º 11. A carreira médica, com os respetivos graus técnico-científicos, deve implicar sempre uma progressão remuneratória?		
Sim	5505	95,86
Não	127	2,21
Não respondo	111	1,93
Total de médicos que responderam ao questionário: 5743		

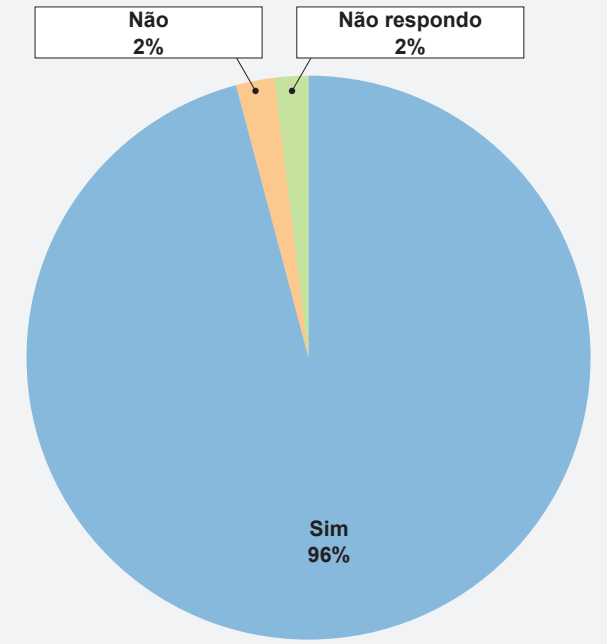

Figura 1 – Carreira médica e progressão remuneratória

próprios serviços de saúde.[17]

Destaca-se ainda o consenso entre os médicos sobre a necessidade de reestruturar a CM, com propostas como a reintegração do IM e a criação de novos graus técnico-científicos. No contexto europeu, observa-se que a organização da CM varia consoante os sistemas de saúde. Nos sistemas bismarckianos, como os dos Países Baixos e da Alemanha, financiados por seguros obrigatórios, existe uma forte ligação da CM às instituições hospitalares, com foco acentuado na prática clínica e na especialização.[18] Por outro lado, os sistemas beveridgianos, como os de Portugal, Reino Unido e países escandinavos, financiados predominantemente por impostos, oferecem uma integração mais ampla dos médicos no sistema público, com ênfase adicional em funções administrativas e de gestão.[19] Torna-se, assim, difícil a análise comparativa do nosso país com outros.

A análise qualitativa dos resultados evidencia duas sugestões importantes: a valorização da diferenciação teórica, investigação e gestão; e a valorização da prática clínica. Estes resultados refletem uma mudança no perfil dos médicos, cada vez mais orientados para a diferenciação teórica, através da realização de doutoramentos, e para a investigação, bem como para a aquisição de competências em gestão de serviços de saúde reconhecidas pela Ordem dos Médicos.[20] Tal mudança contrasta com outro grupo de médicos que se dedicam sobretudo à prática clínica, e que considera que esta vertente deve ser valorizada.

Embora a maioria dos médicos que responderam ao questionário trabalhe no setor público, onde a CM está regulamentada, o consenso sobre a transversalidade da CM entre os setores público, privado e social é evidente. Contudo, a concretização desta transversalidade revela-se um desafio, especialmente quando combinada com a opinião consensual de que a progressão na carreira deve implicar sempre uma progressão remuneratória. Estudos realizados em Portugal relacionam os níveis de satisfação dos médicos com as expectativas sobre o futuro profissional, particularmente as oportunidades de progressão.[21] A ausência de satisfação no setor público, frequentemente associada a questões remuneratórias, reforça que qualquer reestruturação da CM deve considerar a progressão salarial como uma valorização do desenvolvimento técnico-científico.

CONCLUSÃO

A CM desempenha um papel fundamental na garantia da qualidade dos cuidados de saúde prestados à população, refletindo o compromisso dos médicos com a excelência técnica e ética.

Este estudo suportou o consenso em torno da importância da CM como pilar essencial na organização do SNS e na motivação profissional.

Os resultados apontam para a necessidade urgente de reestruturação da CM, incluindo a integração do IM, a criação de novos graus técnico-científicos e uma transversalidade da mesma entre os setores público, privado e social. Adicionalmente, a progressão remuneratória vinculada à evolução na carreira foi destacada como crucial para o reconhecimento do desenvolvimento técnico-científico e para a valorização do trabalho médico.

Apesar das limitações inerentes à taxa de resposta, os resultados obtidos fornecem dados relevantes para o desenvolvimento de políticas de saúde que valorizem a CM, contribuindo para a sustentabilidade e qualidade dos sistemas de saúde em Portugal. A OM é chamada a desempenhar um papel central neste processo, articulando as demandas da classe médica com as necessidades dos utentes e do sistema de saúde.

AGRADECIMENTOS

Agradecemos ao Sr. Bastonário da Ordem dos Médicos de Portugal, Dr. Carlos Cortes.

CONTRIBUTO DOS AUTORES

GP: Conceção e organização do estudo, análise e interpretação dos dados, redação do manuscrito.

AMO: Conceção do estudo, interpretação dos dados,

Tabela 3 – Análise de conteúdo sobre a questão 12 ("Comentários/sugestões sobre a carreira médica")

Categorias	n	%	Dimensões	n	%	Subdimensões	n	%
Carreira	820	76,64	Progressão	397	48,41	Concursos	235	59,19
						Remuneração	91	22,92
						Valorização da diferenciação teórica/investigação/gestão	11	2,77
						Valorização da prática clínica	11	2,77
						n/a	46	11,59
			Reestruturação	205	25	Conteúdo funcional	3	1,46
						Designação dos graus	6	2,93
						Maior número de graus	25	12,2
						Menor número de graus	4	1,95
						Necessidade de maior diferenciação técnico-científica	13	6,34
						Valorização da diferenciação teórica/investigação/gestão	54	26,34
						Valorização da prática clínica	43	20,98
						n/a	57	27,80
			Qualidade dos cuidados	19	2,32			
			Valorização	72	8,78			
			IM	26	3,17			
			Academia	16	1,95			
			Transversalidade	68	8,29			
			SNS	15	1,83			
			n/a	2	0,24			
Qualidade dos cuidados	8	0,75						
Valorização dos médicos	11	1,03						
Condições trabalho	44	4,11						
Dedicação exclusiva	7	0,65						
IM	27	2,52						
Academia	2	0,19						
SNS	4	0,37						
n/a	147	13,74						
Total	1070							

IM: internato médico; SNS: Serviço Nacional de Saúde; n/a: não aplicável.

redação do manuscrito.

HS: Conceção do estudo, metodologia, redação do manuscrito.

JPA, JPF, LFS, JBP, JACC, HR: Revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

Todos os autores desempenham funções não remuneradas no Conselho Nacional Consultivo para o Serviço Nacional de Saúde e Carreira Médica da Ordem dos Médicos.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Hospitalizations for Infective Endocarditis in Children: 15-Year Analysis

Internamentos por Endocardite Infeciosa em Idade Pediátrica: Análise de 15 Anos

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Acta Med Port 2025 Jun-Jul;38(6-7):377-384 ▪ https://doi.org/10.20344/amp.22196

ABSTRACT

Introduction: Infective endocarditis (IE) is a challenging diagnosis with high morbidity and mortality. The aim of this study was to provide a comprehensive analysis of hospitalizations for infective endocarditis in pediatric population at a tertiary hospital.

Methods: A retrospective study examining hospitalizations for IE in pediatric population between 2008 and 2022 at Centro Hospitalar Universitário de São João - Unidade Local de Saúde São João, EPE was conducted. Clinical presentation, treatment, complications, and outcomes of IE, as well as underlying microorganisms were reviewed.

Results: During this period, there were 27 hospitalizations for IE in children. In recent years, an increase in hospitalizations due to infective endocarditis has been observed, with the number fluctuating between zero and two per year from 2008 to 2017, and between one and five per year from 2018 to 2022. The mean age was 9.2 years (± 5.8), the length of hospitalization had a mean duration of 44 days (± 25.4) with a maximum of 113 days, and two deaths occurred. Heart disease was present in 88.9% (n = 24) of patients, of which 95.8% (23/24) was congenital, 59.3% (16/27) of the patients had prosthetic material and, of these, 18.8% (3/16) had a mechanical valve. Regarding diagnosis, 33.3% of patients had no vegetation in imaging tests. In 25.9% of cases, positron emission tomography was performed. Complications occurred in 51.9% of patients, with 44.4% having cerebral or pulmonary emboli. Regarding underlying organisms, *Staphylococcus aureus* (48.1%), *Staphylococcus epidermidis* (14.8%), and *Streptococcus* (14.8%) were the most frequent. One patient had a culture-negative IE. The mean duration of antibiotic therapy was 6.8 weeks, and 29.6% (8/27) underwent surgery.

Conclusion: Throughout the study period, our hospital observed a trend towards an increase in hospitalizations for infective endocarditis in the pediatric population. *Streptococci* are still described as the most prevalent etiology, but *Staphylococci* are known to become more frequent, as shown in our sample. Awareness of IE in patients with heart disease and implanted prosthetic material is crucial.

Keywords: Child; Endocarditis, Bacterial/complications; Endocarditis, Bacterial/diagnosis; Endocarditis, Bacterial/epidemiology; Hospitalization

RESUMO

Introdução: A endocardite infeciosa (EI) é um diagnóstico desafiante, com alta morbilidade e mortalidade. Este estudo teve como objetivo fornecer uma análise dos internamentos por endocardite infeciosa em idade pediátrica num hospital terciário.

Métodos: Foi realizado um estudo retrospetivo, que analisou internamentos por EI em idade pediátrica entre 2008 e 2022 no Centro Hospitalar Universitário de São João - Unidade Local de Saúde São João, EPE. Foram revistos dados sobre a apresentação clínica, tratamento, complicações e evolução da EI, bem como os microrganismos envolvidos.

Resultados: Durante este período, ocorreram 27 internamentos por EI em crianças. Nos últimos anos, observou-se um aumento nos internamentos por EI, sendo que este número oscilou entre zero e dois por ano entre 2008 e 2017, e entre um e cinco internamentos por ano entre 2018 e 2022. A idade média foi de 9,2 anos (± 5,8), a duração média do internamento foi de 44 dias (± 25,4), com um máximo de 113 dias, e ocorreram duas mortes. A doença cardíaca esteve presente em 88,9% (n = 24) dos doentes, dos quais 95,8% (23/24) tinham doença cardíaca congénita. Dos doentes, 59,3% (16/27) tinham material de próteses cardíacas, sendo que 18,8% (3/16) possuíam válvula mecânica. Quanto ao diagnóstico, 33,3% dos doentes não apresentaram vegetações nos exames de imagem. Em 25,9% dos casos, foi realizada tomografia por emissão de positrões. Ocorreram complicações em 51,9% dos doentes, sendo que 44,4% apresentaram embolia cerebral ou pulmonar. Quanto aos microrganismos envolvidos, *Staphylococcus aureus* (48,1%), *Staphylococcus epidermidis* (14,8%) e *Streptococcus* (14,8%) foram os mais frequentes. Um doente teve EI com cultura negativa. A duração média da terapêutica antibiótica foi de 6,8 semanas, e 29,6% (8/27) dos doentes foram submetidos a cirurgia.

Conclusão: Verificou-se uma tendência para um aumento do número de internamentos por EI em idade pediátrica ao longo do período estudado no nosso hospital. Os estreptococos continuam a ser descritos como a etiologia mais prevalente, mas os estafilococos têm vindo a tornar-se cada vez mais frequentes, como demonstrado na nossa amostra. A consciencialização sobre a EI em doentes com doença cardíaca e material protésico implantado é fundamental.

Palavras-chave: Criança; Endocardite Bacteriana/complicações; Endocardite Bacteriana/diagnóstico; Endocardite Bacteriana/epidemiologia; Hospitalização

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Recebido/*Received*: 16/08/2024 - **Aceite/*Accepted*:** 20/03/2025 - **Publicado/*Published*:** 02/06/2025

KEY MESSAGES

- The study observed a trend towards an increase in hospitalizations for infective endocarditis (IE) in children at a tertiary hospital.
- A significant majority of the pediatric patients (almost 90%) had underlying heart disease, with most of those cases being congenital heart defects, highlighting the link between heart disease and increased risk of IE.
- Staphylococcus aureus was the most commonly identified microorganism in infective endocarditis cases, with Staphylococcus epidermidis and Streptococcus species also being frequent causes.
- Awareness and early diagnosis of infective endocarditis, particularly in patients with congenital heart disease or implanted prosthetic material, are critical, as timely intervention, including antibiotic therapy, significantly impacts patient outcomes.
- The main limitations of this study included the fact that our findings may not be generalizable to other populations at risk, since our hospital is a referral center for pediatric cardiology, and the fact that Duke's criteria were not used and not all patients underwent the same diagnostic imaging tests available.

INTRODUCTION

Infective endocarditis (IE) remains a challenging diagnosis with high morbidity and mortality.[1,2] Despite improvements in health care, the incidence of infective endocarditis has not decreased over the past decades. This apparent paradox is explained by a progressive evolution in risk factors.[3-5] Many factors affect the outcome of this serious disease, including the virulence of the microorganism, characteristics of the patients, presence of underlying disease, and delays in diagnosis and treatment.

The epidemiology of pediatric IE has changed in the modern era. Currently, IE is most likely to occur among young children with complex congenital heart disease. Life-saving medical interventions like the use of implanted prosthetic material led to a higher incidence of these infections.[6,7]

Regarding disease-causing pathogens, *Streptococci* are described as the most frequent agent, but the incidence of *Staphylococci* is increasing. Furthermore, IE caused by *Staphylococcus aureus* is typically an acute fulminant process with a high mortality rate, as compared with IE caused by most of other pathogens.[8-10]

To help the clinical practice of professionals who treat these patients, a large number of guidelines to diagnose and manage IE have been developed in recent years by the European Society of Cardiology[11-14] as well as by other societies and organizations.[15-18]

The aim of this study was to provide a comprehensive analysis of all hospitalizations for IE in the pediatric population at a tertiary hospital, focusing on both epidemiological and clinical data. The clinical variables assessed included symptoms and signs at presentation, laboratory findings, underlying microorganisms, imaging results, treatment approaches, complications, and the overall outcome of IE. By evaluating these factors, this study seeks to enhance understanding of the disease's clinical course, its diagnosis and management in this tertiary hospital.

METHODS

We conducted a retrospective study examining clinical medical files of hospitalizations for IE in pediatric population between 2008 and 2022 at a tertiary hospital and referral center for pediatric cardiology: Centro Hospitalar Universitário de São João - Unidade Local de Saúde São João, EPE. Patients' demographic information, such as date of birth and age at hospitalization for IE, was collected. The patients' past medical history was also recorded, including underlying congenital heart disease, medical and surgical interventional treatment, and the presence of prosthetic material.

Clinical variables, like symptoms and signs at presentation, laboratory findings, underlying microorganisms, imaging results, treatment, complications, and outcome (recovery or death) of IE, were reviewed. We excluded cases of suspected infective endocarditis that were not confirmed.

A line graph was created to illustrate the evolution of the number of hospitalizations for infective endocarditis over the past 15 years. The horizontal axis represents the years, while the vertical axis indicates the number of hospitalizations.

Continuous variables are reported as mean and standard deviation. Categorical variables are mentioned as frequencies and percentages of the specific group.

Clinical and epidemiological data were obtained using the SClínico® and JOne systems. Statistical analysis was performed using IBM® SPSS® Statistics.

The data used in this study were anonymized, ensuring patient confidentiality and privacy.

RESULTS

During the study period, there were 27 hospitalizations

for IE in children. Its distribution is presented in Fig. 1. The mean number of hospitalizations per year was two, but there were years with no hospitalized patients for IE (2010, 2012, and 2016). On the other hand, the years 2018 and 2020 had the maximum number of hospitalizations (five per year, each). From 2018 onwards, there was a notable increase, with numbers ranging from one to five per year from 2018 to 2022 (*versus* from zero to two per year from 2008 to 2017).

Demographic and clinical characteristics are described in Table 1.

The length of hospitalization had a mean duration of 44.4 days (± 25.4) with a maximum of 113 days. Regarding discharge follow-up, 24 (88.9%) patients were discharged to the outpatient clinic, one (3.7%) was transferred to another hospital and two (7.4%) died during hospitalization.

The mean age of the patients was 9.2 years (± 5.8), the youngest patient was one month old and the oldest one was 17. Sixty percent of patients were female.

Considering risk factors for IE, heart disease was present in 88.9% (n = 24) of patients; 95.8% (23/24) had congenital heart disease, 59.3% (16/27) had prosthetic material and of these, 18.8% (3/16) had mechanical valves. Of the four patients that had structurally normal hearts, all had *S. aureus* IE, one had periungual wounds and three had no risk factors. A central venous catheter was present in 22.2% of the patients. One patient had a previous dental procedure. One patient, who had two hospitalizations for IE during the study period, had a primary immunodeficiency (DiGeorge syndrome).

Hospital-acquired IE occurred in 25.9% of the hospitalizations and community-acquired IE in 74%.

Fever was present in 24 (88.9%) of the patients and petechial rash/lesions were present in 22.2% of the patients. Other clinical presentations included chest pain, fatigue, vomiting, food refusal, dyspnea, and headache.

The distribution of the underlying organisms is presented in Table 2.

Staphylococcus was identified in 66.7% of patient cultures. *Staphylococcus aureus* was the most common species, found in 48.1% of cases. Among these, Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in 18.5%, and Methicillin-sensitive *Staphylococcus aureus* (MSSA) in 29.6%. Additionally, *Staphylococcus epidermidis* was present in 14.8% of cases. *Streptococcus* species were found in 14.8% of cultures, including one case of *S. viridans* and three cases of *non-viridans* species. Other pathogens identified included *Listeria*, *Aspergillus*, *Candida*, *Klebsiella oxytoca*, *Granulicatella adiacens*, and *Cardiobacterium hominis*, among others. Four patients had isolation of more than one organism in culture: MRSA plus *S. epidermidis*, MRSA plus *Rothia mucilaginosa*, *S. epidermidis* plus *Candida parapsilosis*, and *S. hominis* plus *Klebsiella oxytoca* plus *Candida albicans*.

Diagnostic tests, treatment, complications, outcomes and follow-up are also described in Table 1.

Regarding diagnosis, blood cultures were positive in 96.3% of patients and four patients had a surgical fragment cultured (positive result in two). In the patient with negative cultures, the DNA of an *Aspergillus* was detected by reverse transcription polymerase chain reaction (RT-PCR) in blood samples/surgical fragment. Every patient did a transthoracic echocardiogram, nine (33.3%) did a transesophageal echocardiogram, 12 (44.4%) did computed

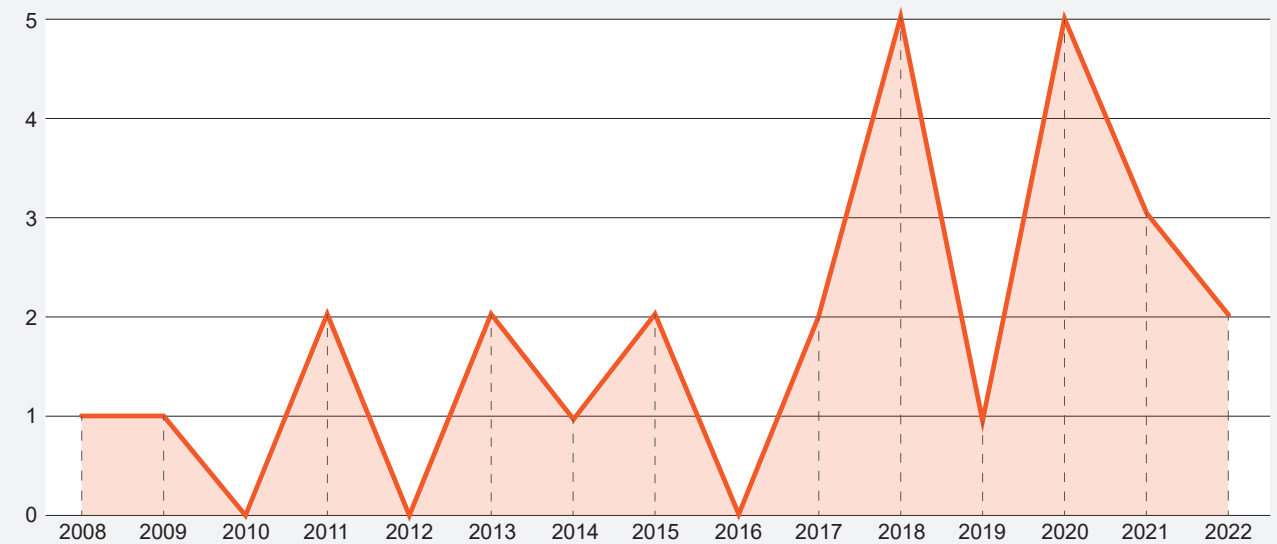

Figure 1 – Distribution of number of hospitalizations for Infective endocarditis per year (n = 27)

tomography (CT) and in seven (25.9%) cases positron emission tomography (PET) was performed. Almost half (42.8%) of the PET performed showed changes. In total, 33.3% (n = 9) of patients had no vegetation in imaging tests.

The mean duration of antibiotic therapy was 6.8 weeks, and 29.6% underwent surgery.

Complications occurred in 51.9% of patients, with 44.4% having cerebral or pulmonary emboli, 11.1% having brain abscesses, 8% having brain hemorrhage and 18.5% having liver, spleen, or kidney involvement. Among the cases with complications, in 64.3% of the patients, Staphylococci were isolated. On the other hand, in patients without complications, Staphylococci were isolated in nine (69.2%). Other agents isolated in cases with complications were *Aspergillus, Listeria, Cardiobacterium hominis, Candida albicans* and *Granulicatella adiacens*.

Table 1 – Demographic and clinical characteristics of hospitalizations for infective endocarditis (n = 27)

Age at hospitalization (mean, sd)	9.2 (5.8)
Sex (n, %)	
Male	11 (40)
Female	16 (60)
Length of hospitalization - days (mean, sd)	44.4 (25.4)
Clinical presentation[a] (n, %)	
Fever	24 (88.9)
Chest pain	2 (7.4)
Petechial rash/lesions	6 (22.2)
Risk factors[a] (n, %)	26 (96.3)
Heart disease	24 (88.9)
Prosthetic material	16 (59.3)
Mechanical valve	3 (11.1)
Central venous catheter	6 (22.2)
Wounds	6 (22.2)
Primary immunodeficiency	2 (7.4)
Dental procedure	1 (3.7)
Mode of acquisition of IE (n, %)	
Hospital-acquired IE	7 (25.9)
Community-acquired IE (n, %)	20 (74.0)
Medical complementary diagnostic tests[a] (n, %)	27 (100)
Blood culture	27 (100)
Positive blood culture	26 (96.3)
Transthoracic echocardiogram	27 (100)
Transesophageal echocardiogram	9 (33.3)
Computed Tomography	12 (44.4)
Positron Emission Tomography	7 (25.9)
Surgical fragment culture	4 (14.8)
Treatment[a] (n, %)	27 (100)
Antibiotherapy	27 (100)
Surgery	8 (29.6)
Mean duration of antibiotics in weeks (mean, sd)	6.8 (2.8)
Complications[a] (n, %)	14 (51.9)
Brain or pulmonary emboli	12 (44.4)
Brain abscess	3 (11.1)
Brain hemorrhage	2 (8.0)
Liver, spleen or kidney involvement	5 (18.5)
Arthritis	1 (4.0)
Discharge follow-up[b] (n, %)	
Outpatient consultation	24 (96)
Another hospital	1 (4)
Deaths (n, %)	2 (7.4)

IE: infective endocarditis; sd: standard deviation.
[a]: For clinical presentation, risk factors, diagnostic tests, treatment and complications, in the same variable, an individual may correspond to more than one category.
[b]: A total of 25 patients (with recovery) were included in this variable.

Table 2 – Infective endocarditis underlying organism (n = 27)

Organism	n (%)
MSSA	8 (29.6)
MRSA	5 (18.5)
Staphylococcus epidermidis	4 (14.8)
Staphylococcus hominis	1 (3.7)
Streptococcus viridans	1 (3.7)
Streptococcus sanguis	2 (7.4)
Streptococcus mitis	1 (3.7)
Haemophilus Parainfluenza	1 (3.7)
Listeria	1 (3.7)
Aspergillus spp	1 (3.7)
Granulicatella adiacens	1 (3.7)
Corynebacterium pseudodiphtheriticum	1 (3.7)
Rothia mucilaginosa	1 (3.7)
Candida parapsilosis	1 (3.7)
Candida albicans	1 (3.7)
Klebsiella oxytoca MS	1 (3.7)
Cardiobacterium hominis	1 (3.7)
Culture-negative IE	1 (3.7)

IE: infective endocarditis; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.
Four patients had isolation of more than one organism in culture: methicillin-resistant *Staphylococcus aureus* (MRSA) plus *Staphylococcus epidermidis*, MRSA plus *Rothia mucilaginosa*, *Staphylococcus epidermidis* plus *Candida parapsilosis*, and *Staphylococcus hominis* plus *Klebsiella oxytoca* plus *Candida albicans*. Therefore, the total number in this table may exceed 100%.

The two deaths occurred after 11 days and 52 days of hospitalization, and the causative agents were *Aspergillus* and *Listeria monocytogenes*, respectively. Both patients had congenital heart disease. The patient with IE for *Aspergillus* had Down syndrome and a congenital atrioventricular septal defect with patch correction, without prosthetic material.

DISCUSSION

A trend towards an increase in hospitalizations for infective endocarditis in the pediatric population was observed throughout the study period at our hospital. Few studies of endocarditis in children are available. However, the incidence rate seems to be increasing, mainly the proportion of device-related IE (such as the use of implanted prosthetic material) due to the improvement in survival of patients with complex congenital heart disease.[4,5,7,19,20]

Patients with the highest risk of IE are those with congenital heart disease, predominantly if a prosthetic valve or prosthetic material is present. In fact, the majority of our patients had congenital heart disease and half of them had prosthetic material. In our sample, one patient who came from a developing country had rheumatic heart disease. Although in developed countries rheumatic heart disease is an uncommon predisposing condition for IE in children, in resource-limited settings, rheumatic heart disease remains an important risk factor.[21-23]

In our sample, 14.8% of the patients did not have heart disease and all of them had a *S. aureus* endocarditis. This result concurs with the literature, which reports that 8% to 10% of pediatric cases of IE occur in structurally normal hearts, most frequently associated with *S. aureus*.[24-26]

Patients with previous IE are known to have a greater risk of new IE, higher mortality and higher incidence of complications than patients with a first episode of IE.[27] In our study, only one patient had a history of IE and required intensive care during the second episode.

Regarding clinical presentation, unsurprisingly, fever was the most frequent symptom. The clinical presentation of pediatric IE is variable and depends upon the extent of the local cardiac disease, the degree of involvement of other organs (e.g., embolization), and the causative agent. Apart from the infectious process linked to IE, the inflammatory and immune response frequently plays a role in the associated symptoms and clinical findings.[28] Immunologic presentations (i.e., Janeway lesions, and Osler nodes) are less common in children than they are in adults, but this manifestation was present in 22.2% of our patients.

Regarding evaluation, one-third of our patients did not show vegetations in the imaging tests. However, only four of these patients underwent CT or PET scans. Of the five patients who did not perform these tests, all had structural heart disease with good quality images in the transthoracic echocardiogram.

The sensitivity and specificity of the modified Duke criteria for native valve endocarditis are both suboptimal, with acceptable sensitivity reported in previous studies, along with high specificity.[29] Diagnostic accuracy for intracardiac prosthetic material-related infection is even lower.[30] The 2015 infective endocarditis guidelines added the new imaging modalities of computer tomography (CT) and PET-computer tomography (PET-CT) into the diagnostic criteria and endorsed the concept of safety of relatively early surgical treatment.[4] The recent published 2023 European Society of Cardiology Guidelines for the management of endocarditis[14] added new recommendations regarding imaging techniques (class I, level of evidence B), such as: “cardiac CT angiography (CTA) is recommended in patients with possible native valve endocarditis” (NVE); “^{18}F-fluorodeoxyglucose PET/CT {[^{18}F]FDG-PET/CT} and cardiac CTA are recommended in possible prosthetic valve endocarditis (PVE)”; “Cardiac CTA is recommended in NVE and PVE to diagnose paravalvular or periprosthetic complications if echocardiography is inconclusive.”; and “Brain and whole-body imaging {CT, [^{18}F]FDG-PET/ CT, and/or MRI} are

recommended in symptomatic patients with NVE and PVE to detect peripheral lesions or add minor diagnostic criteria." Non-invasive imaging modalities could potentially improve the diagnosis of infective endocarditis; however, their diagnostic accuracy is unclear.[12] A systematic review[31] of diagnostic accuracy of imaging in infective endocarditis consistently found positive albeit weak evidence for the diagnostic benefit of [^{18}F]FDG-PET/CT and electrocardiogram (ECG)-gated multidetector CT angiography (MDCTA) after carrying out standard evaluation with transthoracic echocardiography and transesophageal echocardiography. The authors concluded that additional imaging techniques should be considered if the suspicion of infective endocarditis remains, such as leucocyte scintigraphy with SPECT/CT or magnetic resonance.

In our sample there was one culture negative IE, in which *Aspergillus* was detected by RT-PCR. *Staphylococcus* was the most frequent agent, followed by *Streptococcus*. In fact, *Streptococci* are still described as the most prevalent etiology in the literature but some studies have shown that epidemiological changes were marked by an increase in IE due to *Staphylococcus* and healthcare-associated IE, thereby highlighting the importance of non-specific infection control measures.[32,33] Kelchtermans *et al*,[10] evaluated the microbial profile of IE in children (53 patients in the sample) and the causative organism was found in 49 (92%) cases: viridans group *Streptococci* were identified in 32% of the cases, *S. aureus* in 25% and coagulase-negative staphylococci in 20%. On the other hand, in the Day *et al* study,[22] *S. aureus* was the most common organism (57%) followed by the viridans group of Streptococci (20%).

Granulicatella is associated with large vegetations (10 mm), higher rates of complications, and valve replacement (around 50%).[34] Actually, the patient in our sample in which this agent was isolated had complications (pulmonary embolism and pleural effusion) and underwent conduit and valve replacement.

In our sample there were two deaths, both in patients with congenital heart disease, one with IE due to *Aspergillus* and another with IE due to *Listeria monocytogenes,* with the understanding that multiple factors may have contributed to the outcomes. *Aspergillus* endocarditis represents the second etiological cause of prosthetic endocarditis following *Candida* spp.[35,36] However, our patient with *Aspergillus* endocarditis did not have prosthetic material. Endocarditis due to *Listeria monocytogenes* is a rare but serious disease, often leading to valve dysfunction and heart failure with high mortality.[37,38]

In our sample, most of the cases with complications occurred in patients in which staphylococci were isolated. Other agents isolated in cases with complications were *Cardiobacterium hominis, Candida albicans and Granulicatella adiacens*.

Hill EE *et al*[39] conducted a study in adult patients with IE, showing that factors significantly associated with any embolism were the community-acquired IE and the etiologic microorganism, in particular *Staphylococci a*nd nonviridans *Streptococci*.

An 11-year study (2000 - 2010) carried out in the USA in pediatric patients showed that, despite the significant decrease in Staphylococcal IE during the study period, this agent was associated with the highest mortality.[9] Although *Staphylococcus* was the most prevalent agent in our sample, both in the group without complications and in the group with complications, no deaths were caused by this organism.

The mortality rate in our study was 7.4%. Reported mortality rates among children with IE are unknown, ranging from one to five percent in some studies[9,22,40] and around 10% in congenital heart disease-associated IE.[6] A study[39] conducted in Belgium that included 53 pediatric patients showed a mortality rate of 13%. A prospective multicenter study[41] performed in Spain included 5590 pediatric and adult patients, and showed a pediatric mortality rate of 16.3% *vs* 25.9% in adults (p = 0.126). These data suggest that IE is still associated with relevant morbidity and mortality.

Our study has some limitations since our hospital is a referral center for pediatric cardiology and a tertiary hospital, and, therefore, our findings may not be generalizable to other populations at risk, and we could not determine population-based rates for pediatric IE. Other methodological limitations included: Duke's criteria were not used, since the practice in our hospital is to collect only one blood culture instead of two; and not all patients underwent the same diagnostic imaging tests available.

Therefore, an evidence-based diagnostic work-up for infective endocarditis, including non-invasive techniques, should be performed if infectious endocarditis is suspected. Novel approaches to imaging of the heart and extracardiac complications are needed to improve and individualize the diagnostic work-up, treatment, prognosis, and financial expenses in patients with suspected infective endocarditis.

In conclusion, this study observed a rising trend in hospitalizations for infective endocarditis (IE) in the pediatric population at a tertiary hospital. Nearly 90% of the children had heart disease, with the majority having congenital defects, underscoring the critical link between heart conditions and susceptibility to IE. *Staphylococcus aureus* emerged as the most commonly identified microorganism in these cases. These findings emphasize the importance of early awareness and diagnosis of IE, particularly in children with heart disease and implanted prosthetic material. Unexplained and persistent fevers without a potential source in a patient who carries a high risk for IE should

be evaluated thoroughly. Nevertheless, children without risk factors are also an important part of this condition.

ACKNOWLEDGMENTS

The authors gratefully acknowledge all participants of the present study for making it possible.

AUTHOR CONTRIBUTIONS

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

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Use of ChatGPT in HIV Infection Counselling and Literacy

Utilização do ChatGPT para Aconselhamento e Literacia sobre a Infeção pelo VIH

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Acta Med Port 2025 Jun-Jul;38(6-7):385-392 ▪ https://doi.org/10.20344/amp.22805

ABSTRACT

Introduction: Artificial intelligence is an area that has been transforming various sectors of society. One of these tools is ChatGPT (chat generative pre-trained transformer), a large language model-based platform developed to understand language patterns and generate answers. The accessibility, answers in real-time, and privacy make ChatGPT a platform with enormous potential in health counseling. The aim of this study was to explore the potential of ChatGPT in health counseling and literacy regarding HIV infection and pre-exposure prophylaxis (PrEP).

Methods: A team of five experts in infectious diseases was consulted regarding the five most frequently asked questions by patients regarding initial HIV diagnosis and PrEP. The questions were submitted to the ChatGPT-4 version and the quality of the answers was reviewed based on a Likert scale from 1 to 5 (from 'strongly disagree' to 'strongly agree'). The evaluation of the expert's team followed a set of eight criteria: accuracy, clarity, relevance, depth, objectivity, conciseness, timeliness, and suitability for the target audience.

Results: The five most frequently asked questions by patients regarding HIV infection and the mean evaluation of the answers were: "What does it mean to have HIV? Will I die sooner?" (4.25), "Does HIV infection have a cure? Will I ever be able to stop taking medication?" (4.35), "Can I transmit my infection to other people? How to avoid it?" (4.03), "What are the adverse effects of the antiretroviral treatment?" (3.53), "Can I have unprotected sexual relationships? What are the risks?" (4.53). Regarding PrEP, the more frequently asked questions were: "I want to start pre-exposure prophylaxis. Is it safe?" (4.58), "What are the different regimens of pre-exposure prophylaxis?" (4.63), "After I start taking pre-exposure prophylaxis, do I have to take it forever?" (3.95), "What are the adverse effects of pre-exposure prophylaxis?" (4.63), "Does pre-exposure prophylaxis protect against other sexually transmitted infections or do I have to use condoms?" (4.60).

Conclusion: Only two answers received a rating below four on the 1 - 5 Likert scale, highlighting ChatGPT's potential as a promising tool for health counselling and literacy, provided ethical and legal concerns are effectively addressed.

Keywords: Artificial Intelligence; Health Literacy; HIV Infections/prevention & control; Pre-Exposure Prophylaxis

RESUMO

Introdução: A inteligência artificial é uma área que tem transformado todos os setores da nossa sociedade. Uma destas ferramentas é o ChatGPT (*chat generative pre-trained transformer*), uma plataforma baseada em *large language models*, desenvolvida para compreender padrões de linguagem e gerar respostas. As respostas em tempo real, a acessibilidade e a privacidade tornam o ChatGPT uma plataforma com um enorme potencial para o aconselhamento em saúde. Este estudo pretendeu explorar o potencial do ChatGPT no aconselhamento e literacia sobre a infeção por VIH e sobre a profilaxia de pré-exposição (PrEP).

Métodos: Uma equipa de 5 especialistas em doenças infeciosas foi consultada quanto às 5 questões mais frequentemente colocadas sobre o diagnóstico inaugural de infeção por VIH e sobre a PrEP. As questões foram colocadas à plataforma e a qualidade das respostas foram posteriormente avaliadas, numa escala de Likert de 1 a 5 (de 'discordo totalmente' a 'concordo totalmente') quanto à sua precisão, clareza, relevância, profundidade, objetividade, concisão, atualidade e adequação ao público-alvo.

Resultados: As perguntas mais frequentemente colocadas no âmbito do diagnóstico inaugural e a média das avaliações das respetivas respostas foram: "Qual o impacto da infeção por VIH na minha qualidade e esperança média de vida?" (4,25), "Terei de tomar medicação antirretrovírica para sempre ou a infeção por VIH tem cura?" (4,35), "Como evitar a transmissão da minha infeção (VIH) a outras pessoas?" (4,03), "Quais os efeitos adversos da terapêutica antirretrovírica?" (3,53) e "Posso ter relações sexuais desprotegidas (tendo infeção por VIH)?" (4,53). As questões colocadas no âmbito da PrEP foram: "A PrEP é uma medicação segura?" (4,58), "Quais as modalidades de PrEP?" (4,63), "Depois de começar a PrEP, tenho de fazer sempre?" (3,95), "Quais os efeitos adversos da PrEP?" (4,63/5) e "A PrEP protege contra outras infeções sexualmente transmissíveis ou tenho de usar preservativo?" (4,60).

Conclusão: Apenas duas respostas tiveram uma avaliação inferior a quatro pontos numa escala de Likert de 1 a 5, sendo isto um reconhecimento do potencial desta ferramenta no aconselhamento e literacia em saúde, desde que as preocupações éticas e legais sejam devidamente abordadas.

Palavras-chave: Inteligência Artificial; Infecções por VIH/prevenção e controlo; Literacia em Saúde; Profilaxia Pré-Exposição

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Recebido/*Received*: 01/01/2025 - **Aceite/*Accepted*:** 16/04/2025 - **Publicado/*Published*:** 02/06/2025

KEY MESSAGES

- Large language models can play a significant role in health literacy, given their ability to generate real-time answers, their accessibility, privacy, and intuitive interface.
- To explore their potential, this study assessed the quality of ChatGPT's answers to frequently asked questions about HIV and PrEP.
- On a Likert scale from 1 to 5, 80% of the answers received a mean rating above 4.
- The outputs depend on the sources these platforms are trained on, clear queries, and context, and may not capture linguistic or cultural nuances.
- Despite the positive evaluation, further studies must address confidentiality, legal implications, and patient acceptance of these technologies.

INTRODUCTION

Large language models in medicine

The use of artificial intelligence-based resources has transformed various sectors of society, including Medicine. One of these resources is chat generative pre-trained transformer (ChatGPT), a large language model (LLM) platform, introduced in 2018 by OpenAI[1] and made publicly available in 2022.[2,3] Large language models can recognize, interpret, understand language patterns and generate answers and outputs based on different sources, data, and literature. Therefore, they can have a wide range of applications, from text generation, translation or review[2] to chatbot-based technology in automated customer service systems.[4]

In Medicine, LLMs can serve multiple functions[3,5]: they can assist clinicians in therapeutic decision-making[6] processes, interpret electronic health records (EHRs)[7] and support clinicians in diagnostic processes.[8] Another field in which LLMs can have a significant role is health literacy, given their capability of generating answers in real-time, accessibility, privacy and intuitive interface with the user.[9-11] Despite the growing coverage regarding the use of this tool, it is important to evaluate its applicability, capabilities and safety,[11] particularly in Medicine.

Human immunodeficiency virus infection

Several studies highlight the link between low health literacy and worse health outcomes.[12-14] In fact, people with low health literacy are more likely to experience more adverse health conditions compared to the general population. The field of human immunodeficiency virus (HIV) is no exception and infection management and prevention are closely tied to health literacy levels. People living with HIV with low health literacy levels seem to face more disease-related complications, poorer medication adherence and more challenges in navigating healthcare services and understanding health-related information.[15-18] In fact, literacy remains a significant independent predictor of nonadherence,[18] emphasizing the need for initiatives and tools focused on improving patient health literacy.

The aim of the present study was to explore the potential of LLM platforms, specifically ChatGPT, in counseling and health literacy initiatives that focus on HIV diagnosis and pre-exposure prophylaxis (PrEP).

METHODS

To understand the potential of ChatGPT in counselling and health literacy related to HIV diagnosis and PrEP, an exploratory descriptive study was developed. A team of five infectious disease physicians also specialized in HIV prevention and management was questioned individually regarding the five most frequently asked questions by patients in the outpatient context regarding HIV inaugural diagnosis and PrEP. Questions related to logistics, such as appointment dates, laboratory results, and administrative information were excluded.

Each specialist independently submitted the five most frequently asked questions by patients regarding each topic, and the final 10 questions were selected by an independent investigator outside the experts' team based on the frequency with which they appeared across all submissions.

Each question was submitted individually and non-subsequently to the ChatGPT-4 version, without preamble, on August 8, 2024. No user preferences were set, nor was information regarding the querier provided to the platform beforehand. Furthermore, no memory functions were used in ChatGPT since the questions were submitted in non-paid, anonymous accounts. Since the expert team works in a clinical context involving Portuguese patients, the questions were submitted to the platform in Portuguese.

Afterwards, the answers were reviewed and rated based on a Likert scale from 1 to 5, independently by each expert, following a set of eight criteria: accuracy, clarity, relevance, depth, objectivity, conciseness, timeliness, and suitability for the target audience. The only statistical method used was a simple mathematical average of the ratings provided by the five experts.

Characterization of the team of experts

All physicians were native Portuguese speakers: four women and one man. They worked at the same hospital, having undergone a five-year residency program in infectious diseases, including in the field of HIV prevention and management, and had between two to twelve years of experience as experts (title acquired between 2012 and 2023).

Criteria definition

The experts had access to the criteria they would use to rate the answers, their definition and one example of applicability to clarify their meaning and significance in the context of HIV management. Table 1 presents the definition of each criterion, along with the sentence the experts were asked to rate based on their level of agreement with the statement.

Likert evaluation scale

The answers provided by the ChatGPT-4 version were rated by the initial team of five experts, using a Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree), based on their level of agreement with the statements in Table 1.

This study consisted of evaluating the quality of answers generated by an artificial intelligence platform (ChatGPT-4)

Table 1 – Criteria definition and applicability

Criteria	**Accuracy**
Definition	The measure by which the answer is correct and evidence based.
Example	The answer presents data that is confirmed by credible sources.
Statement	The answer is accurate.
Criteria	**Clarity**
Definition	The measure by which the answer can be easily understood.
Example	The answer uses simple and clear language, as well as a logical organization of ideas.
Statement	The answer is clear and easy to understand.
Criteria	**Relevance**
Definition	The measure by which the answer is directly related to the question asked.
Example	The answer avoids unnecessary information that is not related to the question.
Statement	The answer is relevant to the topic.
Criteria	**Depth**
Definition	The measure by which the answer explores the proportionate detail needed.
Example	The answer is explored in appropriate detail, taking into account nuances and implications.
Statement	The answer provides sufficient depth.
Criteria	**Objectivity**
Definition	The measure by which an answer is impartial, without bias or personal opinion.
Example	The answer is evidence-based and not subjective and personal opinions.
Statement	The answer is objective and unbiased.
Criteria	**Conciseness**
Definition	The measure by which an answer is direct, brief, and without redundancies.
Example	The answer avoids repetitive or irrelevant information.
Statement	The answer is concise and to the point.
Criteria	**Timeliness**
Definition	The measure by which an answer reflects updated and current information.
Example	The answer presents current information.
Statement	The answer is timely and up to date.
Criteria	**Suitability for the target audience**
Definition	The measure by which an answer is deemed appropriate for the target audience.
Example	The answer avoids complex language that is not appropriate for the target audience.
Statement	The answer is suitable for the intended audience.

to frequently asked questions by patients, as provided by healthcare professionals, concerning HIV infection and PrEP. The questions were submitted by infectious diseases specialists based on their clinical experience, and no personal, clinical, or identifiable patient data were used. There was no direct contact with patients, nor any intervention.

As this study relies exclusively on the analysis of the content generated by artificial intelligence, without involving human participants or the use of sociodemographic and/or clinical data, it was considered exempt from ethics committee approval. This approach is consistent with recognized ethical standards for research that does not involve risk to human subjects.

RESULTS

Evaluation by question

Table 2 presents the mean evaluation of the experts' assessment based on the eight criteria per question. Considering the eight criteria, 80% (8/10) of the answers had a mean evaluation by the experts higher than four (Likert scale 1-5).

Evaluation per criteria, per question, and group of questions

Table 2 also presents the mean evaluation of the experts' assessment based on each criterion, per question. It also highlights the mean evaluation of the answers to each group of questions, per criteria.

In the group of questions regarding the inaugural diagnosis of HIV, the two criteria with the worst evaluation were conciseness" and "suitability for the target audience", translating a length higher than desired and answers more complex or simple than required, considering the target audience. In comparison, the group of questions regarding PrEP received better evaluation across all criteria, except for "accuracy". However, it still had a mean evaluation higher than 4 (Likert scale 1-5) in this criteria.

DISCUSSION

This study was designed to explore the potential of LLM platforms, specifically ChatGPT, in counselling and health literacy initiatives focused on HIV diagnosis and PrEP. With that goal in mind, the study included a team of experts who manage HIV infection and individuals receiving PrEP and who, in their daily practice, welcome questions from patients on these topics.

Given the growing demand and challenges faced by healthcare systems and physicians, artificial intelligence tools may help in certain settings. Therefore, we aimed to test the platform's ability to produce quality outputs to ascertain its purpose, impact and relevance in clinical practice and health literacy initiatives.

In Table 2, 80% (8/10) of the answers provided had an evaluation higher than 4 (Likert scale 1 - 5). The two (20%) answers that presented an overall evaluation under 4 points (Likert scale 1 - 5), still had a positive assessment, over 3.5 points on the Likert scale.

Exploring the two answers with a lower evaluation, in the group of questions regarding the inaugural diagnosis of HIV, the answer to question Q4: "What are the adverse effects of the antiretroviral treatment?" had a rating of 3.53/5 and four criteria had an evaluation below this average: clarity, relevance, conciseness and suitability for the target audience. The experts considered that the answer was unclear, gave unnecessary and irrelevant information and was unsuitable for the target audience. Table 1 of the Appendix provides the answer to question Q4 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22805/15667).

In the group of questions regarding PrEP, the answer to question Q8 "After I start taking pre-exposure prophylaxis, do I have to take it forever?" had an evaluation of 3.95/5, with four criteria with an assessment below average: accuracy, clarity, relevance and conciseness. The experts considered that the answer had an accuracy below desired, was unclear and gave unnecessary and redundant information. Table 1 of the Appendix provides the answer to question Q8 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22805/15667).

Considering a total of ten answers evaluated based on eight criteria, we can explore a total of eighty evaluation markers. As shown in Table 2, considering both groups of questions, 80% (64) of these markers received a rating higher than 4 on the Likert scale (1 - 5). These results suggest that ChatGPT could be an interesting tool that can assist both physicians in their responsibility of health counselling and patients in clarifying their questions, thus contributing to raising health literacy.[10,17]

The impact of the source on the output generated

It is important to highlight the general limitations of ChatGPT-4, as well as those specific to this study and its application in the medical field.[3,6] Large language model platforms and ChatGPT are predominantly trained on data from the internet and as such they can present several biases, some of which are particularly sensitive in the context of the clinical practice, namely language, gender, racial, and cultural biases. In fact, the sources from which it gathers information can themselves be vulnerable to the previously mentioned biases, for example, they can express certain information regarding gender and race which may be inaccurate.[3,6]

Table 2 – Mean expert assessment of ChatGPT answers to questions regarding HIV inaugural diagnosis and PrEP

Rating criteria Likert scale 1 (strongly disagree) to 5 (strongly agree)	Mean expert assessment of ChatGPT answers to questions regarding HIV inaugural diagnosis **Q1: What does it mean to have HIV? Will I die sooner?** In Portuguese: *O que significa ter infeção por VIH para a minha vida? Vou morrer mais cedo?*	**Q2: Does HIV infection have a cure? Will I ever be able to stop taking medication?** In Portuguese: *A infecção por VIH tem cura? Alguma vez poderei deixar de tomar medicação?*	**Q3: Can I transmit my infection to other people? How to avoid it?** In Portuguese: *Posso transmitir a minha infecção a outras pessoas? Como evitar?*	**Q4: What are the adverse effects of the antiretroviral treatment?** In Portuguese: *Quais os efeitos adversos da terapêutica antirretrovírica?*	**Q5: Can I have unprotected sexual relationships? What are the risks?** In Portuguese: *Posso ter relações sexuais desprotegidas? Quais os riscos?*	**Total**
Accuracy	4.60	4.40	4.20	4.60	4.60	4.48
Clarity	4.40	4.20	4.00	3.00	4.60	4.04
Relevance	4.20	4.40	4.00	3.40	4.60	4.12
Depth	3.80	4.40	4.00	3.60	4.40	4.04
Objectivity	4.20	4.20	4.20	4.20	4.40	4.24
Conciseness	4.20	4.20	3.40	3.20	4.60	3.92
Timeliness	4.60	4.60	4.60	3.60	4.60	4.40
Suitability for the target audience	4.00	4.20	3.60	3.00	4.40	3.84
Total	4.25	4.35	4.03	3.53	4.53	

Rating criteria Likert scale 1 (strongly disagree) to 5 (strongly agree)	Mean expert assessment of ChatGPT answers to questions regarding PrEP **Q6: I want to start Pre-Exposure Prophylaxis. Is it safe?** In Portuguese: *Quero iniciar Profilaxia Pré-Exposição. É seguro?*	**Q7: What are the different regimens of Pre-Exposure Prophylaxis?** In Portuguese: *Quais as modalidades de Profilaxia Pré-Exposição?*	**Q8: After I start taking Pre-Exposure Prophylaxis, do I have to take it forever?** In Portuguese: *Depois de começar Profilaxia Pré-Exposição, tenho de fazer sempre?*	**Q9: What are the adverse effects of Pre-Exposure Prophylaxis?** In Portuguese: *Quais os efeitos adversos da Profilaxia Pré-Exposição?*	**Q10: Does Pre-Exposure Prophylaxis protect against other sexually transmitted infections (STIs) or do I have to use condoms?** In Portuguese: *A Profilaxia Pré-Exposição protege contra outras infecções sexualmente transmissíveis ou tenho de usar preservativo?*	**Total**
Accuracy	4.60	4.40	3.60	4.80	4.60	4.40
Clarity	4.60	4.60	3.40	4.60	4.80	4.40
Relevance	4.60	4.60	3.80	4.60	4.40	4.40
Depth	4.40	4.60	4.00	4.40	4.40	4.36
Objectivity	4.60	4.80	4.20	4.80	4.80	4.64
Conciseness	4.40	4.40	3.80	4.40	4.40	4.28
Timeliness	4.80	4.80	4.20	4.80	4.60	4.64
Suitability for the target audience	4.60	4.80	4.60	4.60	4.80	4.68
Total	4.58	4.63	3.95	4.63	4.60	

Input phrasing, language and context

Platforms such as ChatGPT are dependent on input phrasing, which means they rely on the way the user writes the prompts, which in turn impacts the quality of the generated content. Furthermore, if the user's queries are ambiguous or not sufficiently clear, taking into consideration the sources by which ChatGPT is trained, the platform may struggle to understand the context and the nuances needed to answer. This lack of understanding of the language and cultural nuances of how questions are made can produce superficial, inadequate or unsuitable answers to the target audience, defeating the purpose of using this type of platform for health literacy.[3] Also, it is important to highlight that platforms such as these, at least for now, have difficulties adapting their answer to the querier, namely their level of literacy, clinical context, and reasoning, limiting their capability of giving proper medical advice. With this in mind, it is important for AI-based models to clearly state that they cannot provide personalized medical counselling and that individuals should talk to a healthcare professional.

Individually and non-subsequently submitted questions

ChatGPT can provide better answers if context and background information are provided, since understanding the subject can improve the generated content.[3,6] Therefore, the accuracy and quality of the answers are dependent not only on the sources from which information is gathered but also on the context input. In this study, the questions were provided to ChatGPT-4 individually, non-subsequently, without preamble or memory functions which means that no context was provided to the platform. This was done to have a clear picture of the quality of the answers individually rather them being influenced by the previous context or answers provided. Since the experts served both as co-writers and evaluators, an independent investigator outside the team processed the data to mitigate potential investigator bias.

As shown in Table 2, 80% (8) of the answers provided had an evaluation higher than 4 (Likert scale 1 - 5), hence supporting their quality. It is expected that if more information was provided to ChatGPT-4, such as the target audience, the purpose of the questions, and the desired length of the answers, they would be more contextually aware, better suited to real-world situations, and overall, of higher quality.

Implementation, concerns and further areas of research

The implementation of AI-based technology such as ChatGPT depends on several factors that can be grouped into four sections: confidentiality, legal considerations, equity, and patient perspective. First, these platforms must ensure patient confidentiality, aligning with the General Data Protection Regulation and other data protection laws to preserve personal and medical information details. Second, the use of ChatGPT raises important legal questions such as the liability related to the answers provided in case they are incorrect, the dependence on a proprietary private platform and the lack of transparency on how the algorithms and data sources are integrated. Third, although it is an open-access tool, it requires a certain level of knowledge and proficiency, which may raise some equity-related questions, since not everyone may have the capability and resources needed to operate it. Finally, for the successful implementation of any tool, the patient's perspective is fundamental, so as to address their needs and challenges.

In this study, we focused on analyzing the potential of ChatGPT in health counseling and literacy regarding HIV infection and PrEP and, therefore, comparisons with similar studies in other medical fields or with answers provided by healthcare professionals were beyond the scope of this study. Nonetheless, both of these comparisons could be important to explore in future research to gain a deeper understanding of ChatGPT's potential in health literacy.

Finally, the aim of this study was to evaluate the quality of answers provided from a physician's perspective. However, to implement ChatGPT in a real-world clinical setting, further research is required. Beyond addressing the previously mentioned legal, ethical, and data protection concerns, it is important to conduct studies that actively assess patients' acceptance of these tools and their ability to understand and engage with them effectively.

CONCLUSION

People living with HIV with low health literacy levels seem to face more disease-related complications, poorer medication adherence and more challenges in understanding health-related information. Developing strategies that focus on expanding health literacy on HIV and PrEP is fundamental and LLM platforms, such as ChatGPT, can be a valuable tool for both physicians and patients.

The overall positive evaluation of every answer considering the eight criteria, testifies to the potential use of LLM platforms, specifically ChatGPT, in counselling and health literacy initiatives focusing on HIV diagnosis and PrEP. Nonetheless, when using artificial intelligence tools, particularly in Medicine, it is important to consider the platforms' bias, the input phrasing and context provided as well as how the prompts are written in order to have outputs and answers of higher quality.

DATA AVAILABILITY STATEMENT

Data regarding the evaluation of the experts' team is available upon request to the corresponding author.

AUTHOR CONTRIBUTIONS

JG: Study design, data interpretation, drafting of the manuscript.

MC, GC: Data interpretation, drafting of the manuscript.

CC, ML, DB, DS: Data interpretation, critical review of the manuscript.

ARG: Study design, data interpretation and discussion, drafting of the manuscript.

MJM: Critical review of the manuscript.

FM: Data interpretation and discussion, 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

JG received support for attending meetings and/or travel from ViiVHIV Healthcare, Pfizer, Merck Sharp & Dohme and Gilead Sciences.

MC received support for attending meetings and/or travel from Merck Sharp & Dohme and Gilead Sciences.

GC received support for attending meetings and/or travel from ViiVHIV Healthcare.

CC received consulting fees and payment for expert testimony from Merck Sharp & Dohme and Gilead Sciences; received support for attending meetings and/or travel from Janssen Cilag, ViiVHIV Healthcare, and Gilead Sciences; participated on Merck Sharp & Dohme and Gilead Sciences data safety monitoring boards or advisory boards.

ML received support for attending meetings and/or travel from ViiVHIV Healthcare, Pfizer, Merck Sharp & Dohme, and Gilead Sciences.

ARG received payment for expert testimony from ViiVHV Healthcare; received support for attending meetings and/or travel from ViiVHV Healthcare, Pfizer, Merck Sharp & Dohme, and Gilead Sciences; participated on a ViiVHIV Healthcare data safety monitoring board or advisory board.

DB received consulting fees and payment for expert testimony from Gilead Sciences; received support for attending meetings and/or travel from Gilead Sciences, AbbVie, ViiVHIV Healthcare, and Janssen Clag; participated on a Gilead Sciences data safety monitoring board or advisory board.

DS received consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Pfizer and Gilead Sciences; received payment for expert testimony from Pfizer and Giliead Sciences; received support for attending meetings and/or travel from Merck Sharp & Dohme, Pfizer, ViiVHIV Healthcare and Gilead Sciences; participated on Pfizer and Gilead Sciences data safety monitoring boards or advisory boards.

MJM received consulting fees, payment for expert testimony, support for attending meetings or travel and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from ViiVHIV Healthcare; participated on a ViiVHIV Healthcare data safety monitoring board or advisory board.

FM received consulting fees and payment for expert testimony from Exigo Consultores and Gilead Sciences; received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from ViiVHIV Healthcare and Gilead Sciences; received support for attending meetings or travel from Merck Sharp & Dohme, ViiVHIHV Healthcare, Gilead Sciences, and AbbVie.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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A Revista Científica da Ordem dos Médicos

Portuguese Public Attitudes Regarding Contact Between Healthcare Professionals and Patient's Relatives for Genetic Risk Disclosure: A Cross-Sectional Study

Atitudes do Público Português Relativas ao Contacto Direto entre Profissionais de Saúde e Familiares do Doente para Divulgar Risco Genético: Um Estudo Transversal

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Acta Med Port 2025 Jun-Jul;38(6-7):393-397 ▪ https://doi.org/10.20344/amp.22204

ABSTRACT

Hereditary diseases can affect patients and their biological relatives, who may be at risk of developing these conditions or transmitting them to their descendants. This study explores the attitudes of a sample of Portuguese people towards receiving information about genetic risks and policies on the disclosure of such risks. An online survey using 5-point Likert scale statements (from 1 – "totally disagree" to 5 – "totally agree") was distributed through social media and in public places, resulting in a sample of 1034 respondents with a mean (M) age of 38.58 (standard-deviation, SD = 14.91) years old; 75.4% were women, 74.4% had higher education, and 55.5% were childless. The main findings suggest that participants strongly prefer to be informed about genetic risks by a doctor rather than not being informed at all (M = 4.75; SD = 0.67), are less supportive of learning of genetic risks first by a close relative (M = 3.94; SD = 1.11), favor legislation allowing healthcare professionals to contact them even if their relatives do not wish to disclose the information (M = 4.47; SD = 0.87), and are less favorable towards laws requiring individuals to inform their direct family members of their genetic risks (M = 3.88; SD = 1.27). These findings could inform ongoing discussions about the roles and responsibilities of healthcare professionals in conveying relevant information to at-risk relatives.

Keywords: Communication; Confidentiality; Family; Genetic Counseling; Genetic Predisposition to Disease; Health Personnel/ethics; Professional-Patient Relations/ethics

RESUMO

As doenças hereditárias podem afetar os pacientes e seus familiares biológicos, que podem estar em risco de as desenvolver ou transmitir aos seus descendentes. Este estudo explora as atitudes de uma amostra da população portuguesa em relação à receção de informação sobre riscos genéticos e às políticas de divulgação desses riscos. Um questionário *online*, utilizando afirmações numa escala de Likert de 5 pontos (de 1 – "discordo totalmente" a 5 – "concordo totalmente") foi divulgado nas redes sociais e em locais públicos, resultando numa amostra de 1034 inquiridos, com uma média (M) de idades de 38,58 (desvio-padrão, DP = 14,91) anos, 75,4% mulheres, 74,4% com o ensino superior e 55,5% sem filhos. Os principais resultados sugerem que os participantes prefeririam ser informados sobre os riscos genéticos por um médico a não serem informados (M = 4,75; DP = 0,67), são menos favoráveis a serem informados sobre o seu risco genético primeiro por um familiar próximo (M = 3,94; DP = 1,11), apoiariam uma lei que permitisse serem informados através do contacto direto de profissionais de saúde, mesmo que os familiares não quisessem partilhar a informação (M = 4,47; DP = 0,87); e são menos favoráveis a uma lei que obrigue os pacientes a informar os seus familiares diretos sobre o seu risco genético (M = 3,88; DP = 1,27). Estes resultados poderão contribuir para as discussões em curso sobre os papéis e responsabilidades dos profissionais de saúde na transmissão de informação relevante aos familiares em risco.

Palavras-chave: Aconselhamento Genético; Comunicação; Confidencialidade; Família; Pessoal de Saúde; Predisposição Genética para Doença; Relações Profissional-Doente

Hereditary diseases can significantly affect both patients and their genetic relatives.[1] In Portugal, as in most countries, current practice encourages probands to inform relatives about increased genetic risks, particularly for conditions with effective surveillance, prevention and treatment. However, relatives may not always receive this information,[2] preventing them from taking preventive actions or mitigating future morbidity.

Portuguese legislation stipulates that physicians must inform patients about risks to their relatives while ensuring genetic information is handled in compliance with medical confidentiality.[3] However, no specific guidelines or laws regulate the disclosure of genetic information to patients' relatives. In contrast, some countries (e.g., the Netherlands,[4] France[5]) have implemented legal frameworks allowing healthcare professionals (HPs) to directly notify at-risk relatives, provided the patient consents. International studies on public attitudes toward genetic risk disclosure reveal mixed findings, ranging from strong support for direct contact by HPs[6,7] to a preference for family-mediated disclosure.[8] This study explores the attitudes of a sample of Portuguese people toward receiving genetic risk information and policies governing its disclosure.

This observational, cross-sectional study is part of a larger project approved by the i3S Committee for Ethical and Responsible Conduct of Research (Ref. N18/2023).

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Recebido/*Received*: 19/08/2024 - **Aceite/*Accepted*:** 23/01/2025 - **Publicado/*Published*:** 02/06/2025

Context and sample

A non-random convenience sample was used. The inclusion criteria were adults residing in Portugal. From a total of 1408 respondents, 374 were excluded (19 non-residents and 355 with incomplete questionnaire). The final sample comprised 1034 participants (response rate: 78.68%) (Table 1).

Instrument

Sociodemographic variables included gender, age, level

Table 1 – Sociodemographic characteristics of the sample (n = 1034)

Variables	n (%)
Gender	
Man	244 (23.6)
Woman	780 (75.4)
Non-binary	9 (0.9)
Other	1 (0.1)
Marital status	
Single	496 (48.0)
Married/cohabiting	446 (43.1)
Divorced/separated	79 (7.6)
Widowed	13 (1.3)
Area of residence	
Urban	840 (81.2)
Rural	194 (18.8)
Residential territorial unit	
North	479 (46.3)
Centre	236 (22.8)
Lisbon Metropolitan Area	226 (21.9)
Alentejo	35 (3.4)
Algarve	15 (1.5)
Azores Autonomous Region	23 (2.2)
Madeira Autonomous Region	20 (1.9)
Formal education	
None	1 (0.1)
5 to 6 years	19 (1.8)
7 to 9 years	17 (1.6)
Secondary (10 to 12 years)	228 (22.1)
Higher	769 (74.4)
Children	
Yes	460 (44.5)
No	574 (55.5)
Medical appointment for a hereditary disease	
Yes	210 (20.3)
No	709 (68.6)
I do not know	115 (11.1)
	M (SD; Min - Max)
Age (years)	38.58 (14.91; 18 - 81)
Number of children	0.78 (0.995; 0 - 5)

n: sample size; %: percentage; M: mean; SD: standard deviation; Min: observed minimum; Max: observed maximum.

of education, marital status, number of children, area of residence, and history of medical appointments related to a hereditary disease. A questionnaire was adapted from a previous study,[8] consisting of eight statements where participants indicated their level of agreement on a five-point Likert scale (from 1 = "completely disagree" to 5 = "completely agree"). It included questions on i) genetic testing, the receipt of information about genetic risks and the sharing of such information with family members, and ii) practice and policy approaches related to genetic risk disclosure. Here we focus on the latter.

Data collection

Data collection occurred from December 2023 to March 2024. The study was advertised through social media (via link, poster, and QR code) and in public places in Aveiro, Porto and Lisbon (flyers with QR code). The questionnaire was self-completed using the LimeSurvey platform. Access to the questionnaire was granted only after participants provided informed consent, following a review of study information, including research team contacts and a link to access the study results.

Data analysis

Frequencies and percentages describe categorical variables (gender, area of residence, education, marital status, number of children, and medical appointments for hereditary diseases). Means (M) and standard deviations (SD) describe age and number of children (discrete variables). Since normality was not confirmed by the Kolmogorov-Smirnov test, non-parametric tests (Mann-Whitney and Kruskal-Wallis) were used. Correlations between variables were tested using Spearman's correlation coefficient. Data were analyzed using SPSS statistical software 28.0 (SPSS Inc., USA).

Participants

The 1034 participants had a mean age of 38.58 (SD = 14.91) years (range: 18 - 81 years); 75.4% were women, 48% were single, and 43.1% were married or cohabiting. The majority resided in urban areas (81.2%), had completed higher education (74.4%), and were childless (55.5%). Respondents lived mainly in the North (46.3%), Centre (22.8%) or in the Lisbon Metropolitan Area (21.9%) (Table 1).

Receiving information about genetic risk

The highest mean preference was for being informed by a doctor rather than not being informed (M = 4.75; SD = 0.67), followed by a preference for being informed by a distant relative rather than not being told (M = 4.31; SD = 1.06), and for being informed first by a doctor rather than by a distant relative (M = 4.21; SD = 1.06). The lowest mean preference was for being informed first by a close relative (M = 3.94; SD = 1.11) (Table 2). No significant differences or associations were observed across sociodemographic variables.

Policies on genetic risk disclosure

The highest mean preference was for supporting a law allowing HPs to contact patients' relatives directly, even if relatives choose not to inform them (M = 4.47; SD = 0.87). This was followed by support for authorizing HPs to access personal data from population registers (M = 4.40; SD = 0.90) and contact details (M = 4.28; SD = 1.01) to inform individuals of genetic risks (Table 2). The lowest mean preference was for supporting a law obligating patients to inform their direct relatives of their risk (M = 3.88; SD = 1.27).

Significant differences were observed based on gender, marital status, formal education, and having had a medical appointment for a hereditary disease. Specifically, the preference for authorizing HPs to obtain personal data from population registers was significantly higher among women than men (U = 87,649.0; $p = 0.032$), divorced participants compared to singles [Mann-Whitney test with Bonferroni correction, H(2) = 6.899; $p = 0.032$; $\varepsilon^2 = 0.005$], participants with less than nine years of formal education compared to those with secondary and higher education [Mann-Whitney test with Bonferroni correction, H(2) = 9.450; $p = 0.009$; $\varepsilon^2 = 0.010$], and those with children compared to those without (U = 120,181.5; $p = 0.004$).

Women also showed significantly higher support than men for authorizing HPs to access personal contact details to inform them of genetic risks (U = 85,446.0; p = 0.007). Support for a law obligating patients to inform direct relatives was significantly higher among divorced participants compared to singles [Mann-Whitney test with Bonferroni correction, H(2) = 6.120; $p = 0.047$; $\varepsilon^2 = 0.040$]. Participants who had not had a medical appointment for a hereditary disease showed significantly higher preferences than those who answered "I do not know" [Mann-Whitney test with Bonferroni correction, H(2) = 10.045; $p = 0.007$; $\varepsilon^2 = 0.007$] (Table 2).

This study is the first to explore public attitudes toward genetic risk disclosure in Portugal. The main findings suggest that the sample of Portuguese people prefers being informed of genetic risks directly by a HP rather than by a family member, support policies that facilitate dissemination of genetic risk information by HPs, and is less supportive of policies that legally require patients to inform relatives of increased genetic risk. A previous study with people living with hereditary diseases in Portugal similarly reported widespread acceptance of HP-mediated direct approaches.[9] These findings are consistent with

Table 2 – Receiving information about genetic risk and policies on genetic risk disclosure, and sociodemographic variables (significant differences only)

	M (SD)	Statistical result	M (SD)	Statistical result	M (SD)	Statistical result	M (SD)	Statistical result
I would prefer:								
	To be informed by a doctor rather than not be informed.		To be informed by a distant relative rather than not be told.		The first communication to be made by a close relative.		The first communication to be made by a doctor rather than a distant relative.	
	4.75 (0.67)		**4.31 (1.06)**		**3.94 (1.11)**		**4.21 (1.06)**	
I would support/authorize:								
	Healthcare professionals to access my data from population registers to inform me.		Sharing my personal contact details to enable me to be informed		A law that would allow health professionals to contact me, even if my relatives didn't wish to inform me.		A law that would require patients to inform their direct family members.	
	4.40 (0.90)		**4.28 (1.01)**		**4.47 (0.87)**		**3.88 (1.27)**	
Gender[a]								
Men (244)	4.32 (0.91)	U = 87649 p = 0.032	4.14 (1.08)	U = 85446.0 p = 0.007				
Women (780)	4.42 (0.90)		4.33 (0.98)					
Marital status[b]								
Single (496)	4.40 (0.83)	$H(2)$ = 6.899 p = 0.032					3.87 (1.23)	$H(2)$ = 6.12 p = 0.047
Married (446)	4.37 (0.97)						3.82 (1.32)	
Divorced (79)	4.56 (0.93)						4.20 (1.23)	
Formal education[c]								
Up to 9 (36)	4.83 (0.46)	$H(2)$ = 9.45 p = 0.009						
Secondary (228)	4.64 (0.85)							
Superior (769)	4.38 (0.91)							
Children								
Yes (460)	4.45 (0.92)	U = 120181.5 p = 0.004						
No (574)	4.36 (0.88)							
Have had a medical appointment about a hereditary disease								
Yes (210)							3.90 (1.23)	$H(2)$ = 10.045 p = 0.007
No (709)							3.91 (1.30)	
I do not know (115)							3.72 (1.28)	

[a]: non-binary gender not considered, n = 9;
[b]: Widowers not considered, n = 13;
[c]: No schooling not considered, n = 1;
M: mean; SD: standard-deviation; U: Mann-Whitney test; H: Kruskal-Wallis test.
Spearman's correlation between all the statements and age and number of children were all weak (r_s < 0.1), and statistically significant (p < 0.05). In all the statements, the minimum and maximum observed values were 1 and 5.

international public opinion.[6-8] The limitations of this study include the use of a convenience sample, leading to an overrepresentation of women, individuals with higher education, and those living in urban areas. The recruitment method also introduced a bias towards individuals more engaged with online platforms and social media. Future research should include additional questions and aim to collect a representative sample. Our findings suggest that the Portuguese public favors a more proactive approach from the healthcare system in notifying patient's relatives of genetic risks, compared to current practice. Broader discussions are needed on how to appropriately cascade genetic risk information, involving all relevant stakeholders.[1,9,10]

PREVIOUS AWARDS AND PRESENTATIONS

Ribeiro I, Tavares J, Freixo JP, Sousa L, Mendes A. Disclosure of genetic risk in the family: Attitudes of the general Portuguese population. Hybrid poster presentation from the 56th European Society of Human Genetics (ESHG) Conference; 2024 Jun 1 - 4; Berlin, Germany.

Ribeiro I, Tavares J, Sousa L, Mendes A. Portuguese public attitudes towards genetic risk disclosure support

direct contact by healthcare professionals with family members. Poster presentation from the 28th Portuguese Society of Human Genetics (SPGH) Meeting; 2024 Dec 5 - 7; Porto, Portugal.

AUTHOR CONTRIBUTIONS

IR: Data collection, writing of the manuscript.
JT: Data analysis.
LS, AM: Study design, 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

AM acknowledges support from FCT through the research contract CEECIND/02615/2017.

All the other authors declare no competing interests.

FUNDING SOURCES

This work was supported by the Portuguese Foundation for Science and Technology. I.P. (FCT) in the scope of the project DECIDE, within the CINTESIS R&D Unit (UIDB/4255/2020 and UIDP/4255/2020) and within the scope of the project RISE (LA/P/0053/2020) (https://sciproj.ptcris.pt/en/175847PRJ). Part of this work has also been financed by European Fund for Economic and Regional Development (FEDER) (COMPETE 2020 - POCI, Portugal 2020) and by FCT in the framework of the project "Instituto de Investigação e Inovação em Saúde" (POCI-01-0145-FEDER-007274).

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A Revista Científica da Ordem dos Médicos

A Perturbação por Uso de Substâncias como Comorbilidade em Doentes com Perturbação de Hiperatividade e Défice de Atenção

Substance Use Disorder as a Comorbidity in Patients with Attention Deficit Hyperactivity Disorder

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Acta Med Port 2025 Jun-Jul;38(6-7):398-407 ▪ https://doi.org/10.20344/amp.21937

RESUMO

A perturbação de hiperatividade e défice de atenção (PHDA) é uma perturbação do neurodesenvolvimento que se manifesta por desatenção e/ou hiperatividade e impulsividade. É uma perturbação com início na infância, mas que pode persistir na vida adulta. Está associada ao surgimento de várias comorbilidades, entre elas, muito frequentemente, o desenvolvimento de perturbação por uso de substâncias (PUS). Esta comorbilidade confere uma maior gravidade ao quadro clínico, e torna o tratamento mais complexo e desafiante. Apesar de serem patologias diferentes, apresentam algumas características etiológicas comuns. Esta revisão narrativa pretendeu estudar a associação entre a PHDA e a PUS, nomeadamente no que concerne à prevalência desta associação, etiologia e quais as melhores estratégias de diagnóstico e tratamento. Conclui-se que a PUS corresponde a uma das comorbilidades mais comuns entre os doentes com PHDA, com fatores genéticos, alterações neuroanatómicas e neurofisiológicas a correlacionarem ambas as patologias. Os doentes com PHDA, com PUS em comorbilidade, apresentam um início mais precoce da PUS, com um consumo mais intenso, e piores resultados terapêuticos. Assim, deve ser recomendada uma atenção especial a esta comorbilidade em doentes com PHDA, bem como uma pesquisa ativa de sintomas de PHDA em doentes com PUS. Esta pesquisa pode ser realizada primeiramente, através de escalas de *screening* de autopreenchimento. O tratamento adequado pode incluir uma combinação de tratamento farmacológico e não farmacológico, com estratégias dirigidas para ambas as patologias.
Palavras-chave: Comorbilidade; Diagnóstico Duplo; Perturbação de Hiperatividade e Défice de Atenção/complicações; Perturbação por Uso de Substâncias; Prevalência; Terapia Combinada

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder manifested by inattention and/or hyperactivity and impulsivity. It is a disorder that begins in childhood but can persist into adulthood. It is associated with the emergence of various comorbidities, including, very often, the development of substance use disorders (SUD). When present simultaneously, they contribute to more severe presentations of both conditions and makes treatment more complex and challenging. Despite being different conditions, they have potentially common etiological pathways. The main aims of this article were to study the correlation between ADHD and SUD, particularly concerning the prevalence of this association, etiology and what are the best diagnostic and treatment strategies. We conclude that SUD is one of the most common comorbidities among ADHD patients, with genetic factors, neuroanatomical and neurophysiological impairments correlating both conditions. Patients with ADHD and SUD have an earlier onset of SUD, heavier abuse and worse outcomes. Special attention to this disorder is recommended in patients with ADHD. Furthermore, an active search for ADHD in patients with SUD is highly recommended, which can be carried out in the first place with self-reported scales. The appropriate treatment seems to involve a combination of pharmacological and non-pharmacological approaches, with strategies targeting both conditions.
Keywords: Attention Deficit Disorder with Hyperactivity/complications; Combined Modality Therapy; Comorbidity; Diagnosis, Dual (Psychiatry); Prevalence; Substance-Related Disorders

INTRODUÇÃO

A perturbação de hiperatividade e défice de atenção (PHDA) é uma perturbação do neurodesenvolvimento que cursa com um padrão persistente de desatenção e/ou hiperatividade e impulsividade que interfere no funcionamento psicossocial do individuo.[1] Apesar de ser uma perturbação caracteristicamente associada à infância esta pode persistir ao longo dos anos e continuar para a idade adulta.[1–3] A perturbação por uso de substâncias (PUS) é uma perturbação mental caracterizada pelo uso repetido de substâncias. A característica essencial consiste na presença de um conjunto de sintomas cognitivos, comportamentais e fisiológicos indicando o uso contínuo pelo indivíduo, apesar de problemas significativos relacionados com a substância.[1] A PUS é uma comorbilidade comum entre os doentes com PHDA. Fatores como a apetência por estímulos novos, e a hipótese de automedicação de sintomas nucleares de PHDA podem ajudar a explicar esta comorbilidade.[4–6] Os doentes que apresentam esta comorbilidade tendem a começar o consumo de substâncias numa idade mais precoce, e a realizarem um consumo de maiores quantidades.[7] A PHDA e PUS, apesar de constituírem síndromes clínicas aparentemente distintas, apresentam origens etiológicas e um substrato neurobiológico comum, ocorrendo frequentemente juntas e contribuindo para o desenvolvimento e manutenção uma da outra e, desta forma, podem também hipoteticamente beneficiar de estratégias de tratamento comuns.[6,8,9] Este artigo pretende realizar uma revisão bibliográfica para estudar a associação entre a

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Recebido/*Received*: 12/06/2024 - **Aceite/*Accepted*:** 28/03/2025 - **Publicado *Online*/*Published Online*:** 28/04/2025 - **Publicado/*Published*:** 02/06/2025

PUS e a PHDA, com um foco particular na prevalência desta associação, na avaliação das substâncias mais commumente utlizadas, e na avaliação das melhores estratégias terapêuticas nos doentes que apresentam esta comorbilidade.

Metodologia

O presente estudo enquadra-se na tipologia de revisão narrativa da literatura. Iniciámos a exploração bibliográfica pela análise das bases de dados Google Scholar e PubMed, entre setembro e dezembro de 2023, utilizando os descritores: "attention deficit hyperactivity disorder", "substance use disorder", "comorbid", "prevalence", "dual diagnosis", individualmente ou em associação. Foram definidos os seguintes critérios de inclusão: artigo científico, em língua inglesa. A seleção dos mesmos foi realizada com base na leitura do título e *abstract*, seguida da sua leitura integral. Não foram feitas restrições relativas à metodologia ou à data de publicação dos estudos.

Perturbação de hiperatividade e défice de atenção

A PHDA é uma perturbação do neurodesenvolvimento caracterizada por sintomas em três domínios: desatenção, impulsividade e hiperatividade. A classificação da quarta edição do Manual Diagnóstico e Estatístico de Distúrbios, DSM-IV agrupava os sintomas em três subtipos: predominantemente desatento, predominantemente hiperativo-impulsivo ou combinado. Contudo esta terminologia foi substituída por apresentações na classificação DSM-V, o que reflete que os sintomas não são estanques e a apresentação pode variar ao longo do tempo.[1,2]

O diagnóstico da PHDA é clínico e, de acordo com o DSM-V, implica a presença de seis ou mais critérios A1, critérios de desatenção e/ou seis ou mais critérios A2, critérios de hiperatividade e impulsividade, com impacto negativo nas atividades sociais, académicas e educacionais. Além disso, é necessário que vários sintomas estejam presentes antes dos 12 anos, que se manifestem em mais do que um ambiente ou contexto, que exista evidência de disfunção clinicamente significativa no funcionamento social, académico ou ocupacional e que os sintomas não sejam explicados por outras doenças mentais.[1] Do DSM-IV para o DSM-V foram realizadas algumas mudanças ao nível dos critérios diagnóstico, como a idade de início e o número de sintomas necessários para realizar o diagnóstico, em adolescentes mais velhos e adultos, passando a ser necessária a presença de pelo menos cinco sintomas.[1] A nova versão do DSM-V-TR mantém os critérios de diagnóstico, acrescentando apenas dados sobre a prevalência da PHDA (Tabela 1).[10]

O tratamento preconizado consiste numa abordagem multimodal que combina medidas não farmacológicas e farmacológicas. Nas crianças, as medidas não farmacológicas incluem treino parental, reforço positivo, treino comportamental e medidas escolares. Nos adultos, estas englobam a psicoeducação, intervenções comportamentais e sociais, e psicoterapia. O tratamento farmacológico de primeira linha são os psicoestimulantes, destacando-se os de longa duração.[11] As opções incluem formulações de metilfenidato e anfetaminas. Como segunda linha, os fármacos não estimulantes incluem inibidores da recaptação de noradrenalina, como a atomoxetina e a viloxazina, bem como agonistas α2-adrenérgicos, como a clonidina e a guanfacina. Alguns doentes podem beneficiar de combinações de estimulantes de curta e longa duração ou de estimulantes com não estimulantes. Entre os efeitos adversos mais comuns estão a redução do apetite e, no caso dos estimulantes, a insónia. Pequenos aumentos transitórios na frequência cardíaca e pressão arterial são comuns, mas geralmente sem relevância clínica. Existe um risco pequeno de hipertensão e doença arterial em adultos com uso prolongado de doses elevadas. O tratamento ideal requer um processo de tentativa e erro. Em suma, as diretrizes recomendam, em primeiro lugar o uso de metilfenidato, seguido da lisdexanfetamina ou de outras anfetaminas e depois de não estimulantes.[12] Apesar da eficácia da terapia farmacológica, apenas uma minoria das pessoas recebe o tratamento adequado, sendo esta percentagem ainda menor quando nos referimos a países menos desenvolvidos.[13]

História natural da doença

A PHDA afeta cerca de 5% das crianças e cerca de 2% a 3% dos adultos.[1,14,15] É uma perturbação do neurodesenvolvimento da criança, mas que pode, em cerca de 50% a 70% dos casos, persistir na idade adulta.[1–3] A persistência da PHDA na idade adulta está diretamente associada ao surgimento de outras comorbilidades, com cerca de 80% dos adultos com PHDA a exibirem outra doença psiquiátrica. Entre as principais comorbilidades temos perturbações de ansiedade, perturbação por uso de substâncias, perturbações da personalidade, perturbações depressivas e perturbações específicas da aprendizagem. Esta emergência de comorbilidades leva a que, em muitos casos, os doentes recorram aos cuidados de saúde e recebam tratamento pelas comorbilidades e não para a PHDA.[11]

Novos estudos sobre a PHDA sugerem que pode ser possível haver um início da mesma apenas na idade adulta, PHDA de início tardio. Vários adultos cumprem todos os critérios de PHDA, exceto a presença de sintomas antes dos 12 anos, sugerindo um possível surgimento de novo da doença.[8,11] No entanto, é preciso cautela no que concerne à PHDA de início tardio. Um estudo recente sugere que vários casos primeiramente classificados como PHDA de início tardio, quando sujeitos a uma avaliação clínica

Tabela 1 – Diferenças nos critérios de diagnóstico da PHDA nas diferentes versões do Manual de Diagnóstico e Estatístico de Transtornos Mentais (parte 1 de 2)

	DSM-IV	DSM-V	DSM-V-TR
Nome do capítulo	Perturbações habitualmente diagnosticadas na primeira e na segunda infâncias e na adolescência	Perturbações do neurodesenvolvimento	Perturbações do neurodesenvolvimento
Critérios de Diagnóstico	**A -** Presença de **seis** ou mais sintomas	**A** - Para adolescentes mais velhos e adultos (17 anos ou mais), pelo menos **cinco** sintomas são necessários.	Sem alterações
	B - Vários sintomas de desatenção ou hiperatividade-impulsividade que causam défice surgem **antes dos 7 anos** de idade.	**B -** Vários sintomas de desatenção ou hiperatividade-impulsividade estavam presentes **antes dos 12 anos** de idade.	Sem alterações
	C - Alguns **défices** provocados pelos sintomas estão presentes em dois ou mais contextos [p.e., escola (ou trabalho) e em casa]	**C -** Vários **sintomas** de desatenção ou hiperatividade-impulsividade estão presentes em dois ou mais ambientes (p.e., em casa, na escola, no trabalho; com amigos ou parentes; em outras atividades).	Sem alterações
	D - Devem existir provas claras de um **défice clinicamente significativo** do funcionamento social, académico ou laboral	**D -** Há evidências claras de que os sintomas interferem no funcionamento social, académico ou profissional ou de que **reduzem a sua qualidade.**	Sem alterações
	E - Os sintomas não ocorrem exclusivamente durante uma **Perturbação Global do Desenvolvimento**, Esquizofrenia ou outra Perturbação Psicótica e não são mais bem explicados por outra perturbação mental (por exemplo, perturbação do humor, perturbação de ansiedade, perturbação dissociativa ou perturbação da personalidade)	**E -** Os sintomas não ocorrem exclusivamente durante o curso de esquizofrenia ou outro transtorno psicótico e não são mais bem explicados por outra perturbação mental (por exemplo, perturbação do humor, perturbação de ansiedade, perturbação dissociativa ou perturbação da personalidade, **intoxicação ou abstinência de substâncias**).	Sem alterações
Tipos	**Subtipos:** tipo combinado, tipo predominantemente desatento, tipo predominantemente hiperativo-impulsivo. **Nota de codificação:** Para sujeitos (especialmente adolescentes e adultos) que atualmente tenham sintomas e que já não preencham todos os critérios, deve especificar-se **"em remissão parcial".**	**Apresentações:** apresentação combinada, apresentação predominantemente desatenta, apresentação predominantemente hiperativa/impulsiva. **Em remissão parcial:** Quando todos os critérios foram preenchidos no passado, nem todos os critérios foram preenchidos nos últimos 6 meses, e os sintomas ainda resultam em prejuízo no funcionamento social, académico ou profissional. **Gravidade**: leve, moderada, grave.	Sem alterações

Tabela 1 – Diferenças nos critérios de diagnóstico da PHDA nas diferentes versões do Manual de Diagnóstico e Estatístico de Transtornos Mentais (parte 2 de 2)

	DSM-IV	DSM-V	DSM-V-TR
Prevalência	A prevalência da perturbação de défice de atenção/hiperatividade está estimada em 3%-5% nas crianças em idade escolar. Os dados sobre a prevalência na adolescência e na idade adulta são limitados.	Levantamentos populacionais sugerem que a PHDA ocorre na maioria das culturas em cerca de 5% das crianças e 2,5% dos adultos.	Levantamentos populacionais sugerem que a PHDA ocorre mundialmente em cerca de 7,2% das crianças; No entanto, a prevalência a nível transnacional varia muito, de 0,1% a 10,2% das crianças e adolescentes. **A prevalência é mais elevada em populações especiais, como crianças de acolhimento ou em ambientes correcionais**. Numa meta-análise transnacional, a PHDA ocorreu em 2,5% dos adultos.
Questões diagnósticas	- Questões diagnósticas relativas à cultura, idade e ao género	- Questões diagnósticas relativas ao género - Questões diagnósticas relativas à cultura	- Questões diagnósticas relativas ao sexo e ao género - Questões diagnósticas relativas à cultura

mais cuidada, apresentavam uma sintomatologia mais bem explicada por PUS ou por outra perturbação mental. Por outro lado, também vários doentes podem ter sintomas *subthreshold* em criança (ou pouca memória sobre estes), acabando por não ter critérios para um diagnóstico formal de PHDA em crianças e serem classificados como um diagnóstico de PHDA de início tardio.[16]

Perturbação por uso de substâncias

A PUS refere-se a padrões de uso de substâncias com impacto negativo na saúde física e mental e na vida do indivíduo. Está presente em cerca de 30% dos adultos e 9% dos adolescentes.[15] Todas estas substâncias provocam uma ativação direta do sistema de recompensa cerebral. A PUS e todas as fases envolvidas nesta, como intoxicação, abstinência e tolerância, são mais frequentes em homens do que em mulheres.[17,18]

O início precoce da PUS, durante a adolescência, está diretamente correlacionado com um pior prognóstico. Nestes casos, existe um consumo mais frequente, uma escalada mais rápida no uso de substâncias, menos procura de tratamento e uma duração mais prolongada da doença.[15,19]

O diagnóstico da PUS segundo o DSM-V é feito com critérios que avaliam o controlo sobre o uso de substâncias (critérios 1 a 4), disfunção social (critérios 5 a 7), o risco do uso de substâncias (critérios 8 e 9) e critérios farmacológicos (critérios 10 e 11), mais concretamente a tolerância (critério 10) e abstinência (critério 11). A PUS pode ser classificada quanto à sua gravidade em ligeira (dois a três sintomas), moderada (quatro a cinco sintomas) ou grave (mais do que seis sintomas).[1] De forma geral, o tratamento é baseado em psicoterapia, tratamento das complicações e reabilitação.

Relativamente ao contexto português da perturbação por uso de substâncias, a canábis é a droga mais consumida, com um agravamento significativo no consumo de risco elevado entre os jovens de 15 - 24 anos, que quase duplicou em cinco anos e sextuplicou em dez. Dados do Inquérito Nacional ao Consumo de Substâncias Psicoativas (INPG 2022) indicam que 11% da população de 15 - 74 anos consumiu alguma droga ao longo da vida, sendo a canábis a mais prevalente. O consumo intensivo e diário/quase diário de canábis foi reportado por uma fração significativa de consumidores, com 0,7% da população geral apresentando consumo de risco elevado ou moderado, subindo para 1,3% na faixa dos 15 - 34 anos.[20]

No inquérito anual de 2022, "Comportamentos Aditivos aos 18 anos: inquérito aos jovens participantes no Dia da Defesa Nacional",[20] as prevalências de consumo de qualquer droga entre jovens de 18 anos foram de 34% ao longo da vida, 27% nos últimos 12 meses e 16% nos últimos 30 dias. A canábis apresentou prevalências semelhantes às de qualquer droga, enquanto 11%, 8% e 4% dos inquiridos tinham consumido outra droga ao longo da vida nos últimos 12 meses e 30 dias, respetivamente. Entre estas substâncias destacaram-se as anfetaminas/metanfetaminas (incluindo *ecstasy*), com prevalências de 6% ao longo da vida, 5% nos últimos 12 meses e 2% nos últimos 30 dias, seguidas pela cocaína, alucinogénios, novas substâncias psicoativas (NSP) e opiáceos. Os consumos continuam a ser mais expressivos nos rapazes.[20]

Relativamente ao álcool, observa-se um panorama de agravamento nos consumos de risco elevado e dependência, apesar do aumento da abstinência na população geral

entre 2017 e 2022. Registou-se uma diminuição na idade média de início do consumo e aumentos no consumo recente e atual, na embriaguez severa e na dependência, que quase quadruplicou em dez anos. Estes agravamentos foram mais expressivos nos homens e em grupos etários específicos, como os jovens de 15 - 24 e 25 - 34 anos e os adultos de 35 - 54 anos. Entre jovens de 18 anos, apesar da estabilidade do consumo recente, verificou-se um aumento do consumo *binge* e da embriaguez, especialmente no grupo feminino. Adicionalmente, o número de pessoas a iniciar tratamento por problemas relacionados com o álcool atingiu valores recorde, tal como os internamentos hospitalares e os óbitos por doenças atribuíveis ao álcool.[21]

Relação entre a perturbação de hiperatividade e défice de atenção e a perturbação por uso de substâncias

A PUS é uma das comorbilidades mais comuns presente nos doentes com PHDA. Esta associação é mais prevalente nos homens do que nas mulheres e apresenta vários desafios.[14,22,23] Os doentes com PHDA representam uma população sensível, com uma tendência a um início mais precoce de PUS, uma escalada rápida desde o primeiro contacto com a substância até ao desenvolvimento de dependência e uma maior tendência para o abuso de mais do que uma substância. Para além disso, o tratamento é também um desafio, apresentando estes doentes um curso mais crónico da PUS, maior número de hospitalizações e uma menor adesão terapêutica (Fig. 1).[2,15,18,19,24,25]

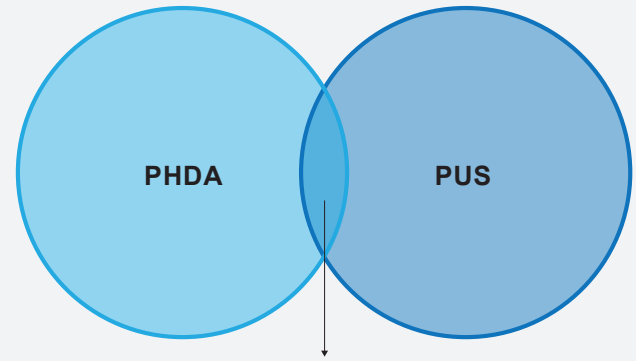
Cerca de um terço dos doentes com PHDA desenvolve PUS, sendo esta probabilidade de desenvolver PUS o dobro da probabilidade presente na população geral.[3,11,23,25] Por outro lado, a prevalência de PHDA nos doentes que procuram tratamento para PUS varia entre os 20% e os 25%.[8,24,26,27] Vários fatores contribuem para a emergência de PUS nos doentes com PHDA, entre eles temos as características inerentes ao diagnóstico de PHDA, como a impulsividade, a procura de novas sensações e disfunção no pensamento executivo, que são fatores de risco estabelecidos para a PUS.[7] Outra hipótese para explicar a emergência de PUS é a teoria de automedicação, que defende que os pacientes com PHDA usam substâncias com o intuito de aliviar os seus sintomas. Esta hipótese é sustentada pelo efeito de algumas substâncias nos níveis de dopamina.[28] Além disto, os indivíduos com PHDA são expostos, mais frequentemente, a situações de risco psicossociais, em resultado de insucesso académico e influências negativas dos pares, que podem levar a uma exposição precoce a substâncias (Fig. 2).[7]

Nos doentes com PHDA o álcool é a substância primária de abuso mais comum, com uma prevalência de cerca de 54%, seguida pela nicotina (20% - 40%), estimulantes (15%), cannabis (10,8%) e opioides (10,8%).[29] Os doentes com PHDA apresentam frequentemente policonsumos. Capusan *et al*[18] concluíram que os doentes com PHDA não tinham preferência por nenhuma substância em específico, o que pode ser explicado pelo uso das substâncias para alívio sintomático com recurso aquela que estiver mais facilmente disponível ou a preferências culturais.[18]

Neurofisiologia e genética

A PHDA e a PUS relacionam-se através de predisposições genéticas, alterações neuroanatómicas e neurofisiológicas.

Alterações no sistema dopaminérgico ocupam um papel central em ambas as patologias. Na PHDA existem sistemas dopaminérgicos e noradrenérgicos hipoativos, com défice da via mesolímbica e da via inibitória córtex pré-frontal. A ligação ao transportador da dopamina (DAT) e aos recetores da dopamina D2 e D3 estão diminuídas em doentes com PHDA, quando comparados com a população normal.[6,8] O consumo de substâncias provoca um aumento da dopamina a nível do estriado ventral e conduz a adaptações neurológicas na via mesolímbica (via de recompensa dopaminérgica). Desta forma, a presença de um sistema dopaminérgico deficiente, torna os indivíduos com PHDA mais sensíveis aos efeitos do uso de substâncias. Para



Predisposições genéticas;
Alterações neuoanatómicas;
Alterações neurofisiológicas.

Início mais precoce de PUS;
Escalada mais rápida desde o primeiro contacto com a substância até ao desenvolvimento de dependência;
Abuso mais frequente e tendência para o abuso de mais do que uma substância;
Curso mais crónico da PUS;
Maior número de hospitalizações;
Menor adesão terapêutica.

Figura 1 – Relação comórbida entre a perturbação de hiperatividade e défice de atenção e a perturbação por uso de substâncias

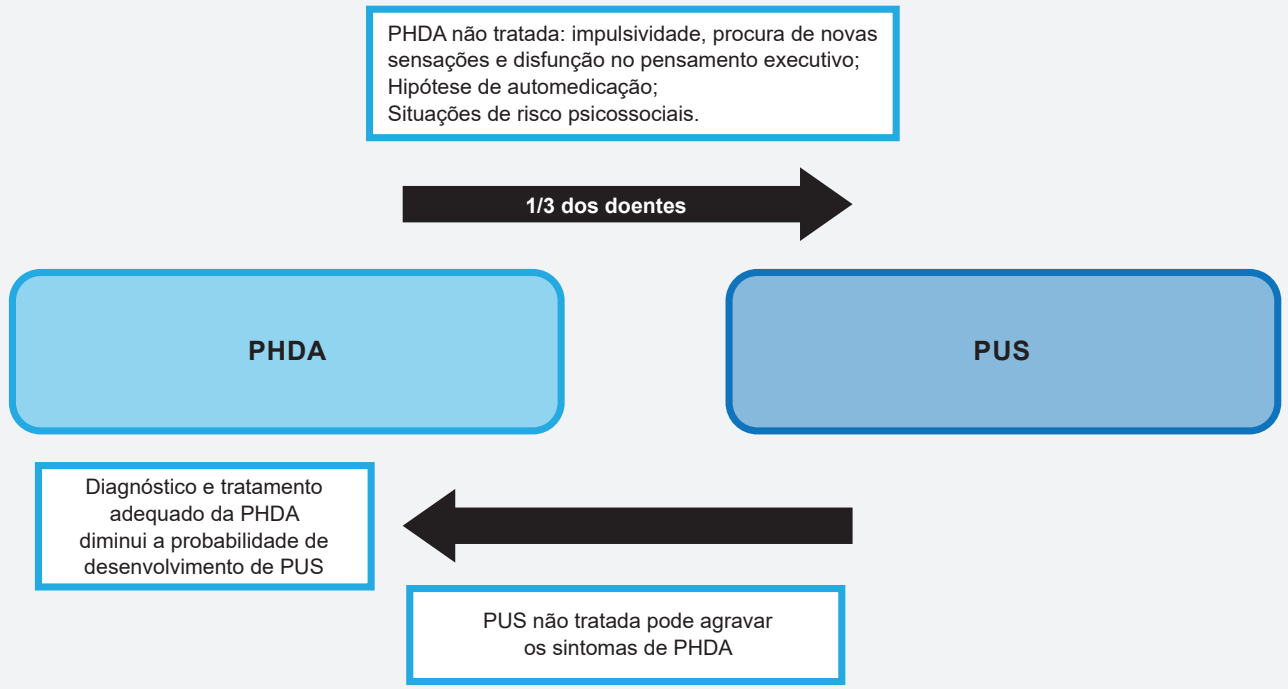


Figura 2 – Associação entre a perturbação de hiperatividade e défice de atenção e a perturbação por uso de substâncias

além de disfunção dopaminérgica, existe também disfunção serotoninérgica nos doentes com PHDA. O álcool e a nicotina provocam um aumento da função serotoninérgica, mais uma vez explicando a maior sensibilidade a estes por parte dos doentes com PHDA.[9,30]

Tanto a PHDA como a PUS são perturbações com um componente genético. A herdabilidade da PHDA é de cerca de 71% a 73% e a da PUS cerca de 40% a 55%.[9] Cerca de 50% do abuso de álcool em doentes com PHDA é explicado por fatores genéticos.[30,31] Com base nas alterações dos sistemas dopaminérgico e serotoninérgico, Groenman *et al*[9] criaram *scores* de risco genético e apesar de ser expectável que tanto o *score* de risco genético dopaminérgico como o serotoninérgico fossem capazes de prever o risco de PUS nos doentes com PHDA, apenas o *score* de risco genético serotoninérgico mostrou correlação e apenas para o abuso de álcool.[9]

Algumas alterações neuroanatómicas foram objetivadas neste grupo de doentes, mais concretamente em doentes com PHDA e abuso de cocaína. Estes apresentam uma maior redução de substância cinzenta na região occipital e no putâmen.[32]

Diagnóstico

Como os doentes com PHDA e PUS apresentam um prognóstico mais desfavorável, é importante um diagnóstico precoce de PUS nos doentes com PHDA e uma procura ativa de PHDA nos doentes que se apresentam para tratamento de PUS. Este diagnóstico apresenta vários desafios, entre os quais a sobreposição de sintomas entre ambas as patologias e a subnotificação dos mesmos. Apesar de menos frequente, pode haver um exagero dos sintomas por parte dos doentes com o objetivo de obter prescrição para medicação estimulante.[26,33–35]

O uso de *Continuous Performance Tests* (CPT) é atualmente uma ferramenta de avaliação neuropsicológica complementar ao diagnóstico de PHDA. Este teste permite avaliar a atenção seletiva, a atenção sustentada e a impulsividade. Entre os parâmetros avaliados estão os erros de comissão, que ocorrem quando o indivíduo responde incorretamente a um estímulo não-alvo, refletindo impulsividade ou dificuldade em inibir respostas automáticas. A possibilidade de ser utilizada como ferramenta auxiliar de diagnóstico em doentes que apresentam PHDA e PUS foi estudada, tendo por base a hipótese de que, como ambas as doenças estão associadas a alterações na atenção, seria esperado um CPT com défices mais severos na comorbilidade entre PHDA e PUS do que na PHDA isolada. Os resultados foram contraditórios, apesar de alguns estudos terem relatado um maior número de erros de comissão,[36–39] outros não encontraram a mesma associação.[40–43] Desta forma conclui-se que não existem diferenças significativas

nos resultados que permitam que este seja utilizado como ferramenta de diagnóstico.[33]

Outras ferramentas auxiliares de diagnóstico incluem a escala *Conners' Adult ADHD Rating Scale Screening Self--Rating* (CAARS-S-SR), *Adult ADHD Rating Scale* (ASRS), *Wender Utah Rating Scale* (WURS), *Attention Deficit Scales for Adults* (ADSA), escalas de autorrelato e ainda a entrevista *Mini International Neuropsychiatric Interview-Plus* (MINI-Plus) e a *DIVA 2.0* (Entrevista de Diagnóstico de PHDA em Adultos). Todos estes instrumentos foram considerados válidos para o rastreio de PHDA em doentes com PUS, mas para que o diagnóstico de PHDA possa ser realizado é necessária avaliação clínica especializada daqueles que testem positivo no rastreio. A ASRS, quando usado o *cut-off* de quatro pontos, apresentou uma sensibilidade de 87,5% e uma especificidade de 68,8%.[34] Contudo Luderer *et al*[26] sugerem o uso de *cut-offs* mais baixos, pois ao diminuir os mesmos a sensibilidade melhorava, apesar de haver um aumento do número de falsos positivos. Os melhores resultados foram obtidos com o uso da combinação da ASRS com a CAARS-S-RS.[26]

Na prática clínica, o diagnóstico de PHDA em doentes com PUS é frequentemente adiado para quando é alcançado um período de abstinência, resultando num atraso do início de um tratamento integrado para ambas as patologias. Um estudo demonstrou que é possível realizar o diagnóstico de PHDA durante a fase ativa de consumo de substâncias, apresentando uma estabilidade do diagnóstico de PHDA de 95,3% entre a fase ativa e uma fase de diminuição de consumo ou abstinência.[44]

No que concerne o despiste de PUS em doentes já diagnosticados com PHDA a abordagem torna-se mais simples. Existem várias ferramentas que podem ser utilizadas nos cuidados de saúde primários, de forma simples e rápida, entre as quais o acrónimo CRAFFT (acrónimo com as perguntas "Já andou de carro conduzido por alguém que tivesse consumido álcool?", "Já consumiu para relaxar?", "Já consumiu sozinho?", "Já se esqueceu do que fez enquanto consumia álcool?", "Os amigos ou família alguma vez disseram que devia reduzir o consumo?", "Alguma vez teve problemas enquanto consumia?") e CAGE (um acrónimo com as perguntas chave "Já tentou reduzir o consumo de álcool?", "Fica irritado com as críticas sobre o consumo?", "Sente-se culpado pelo consumo de álcool?", "Sente necessidade de beber logo pela manhã?").[45]

Tratamento da perturbação por hiperatividade e défice de atenção com estimulantes e as suas consequências na perturbação por uso de substâncias

O tratamento farmacológico de primeira linha preconizado para a PHDA é o uso de fármacos estimulantes, tais como o metilfenidato. Contudo algumas dúvidas quanto à relação entre este tratamento e o surgimento e curso de PUS surgem na literatura. A preocupação face à possível relação do tratamento estimulante com o surgimento de PUS assenta na hipótese de este causar uma sensibilização. Esta hipótese postula que a exposição a estimulantes provoca alterações no sistema dopaminérgico, nomeadamente aumentando as concentrações de dopamina no núcleo *accumbens*, levando a um aumento da sensibilidade ao efeito de drogas.[46,47] Em oposição a esta hipótese, é sugerido pela literatura um possível efeito protetor com o tratamento estimulante. O fármaco estimulante, ao tratar os sintomas cardinais da PHDA, leva a uma diminuição da PUS.[47]

Vários estudos demonstraram que o início de um tratamento farmacológico adequado para a PHDA durante a infância está associado a uma diminuição do risco de desenvolvimento de PUS na idade adulta.[47–49] Um estudo recente concluiu que os participantes que tinham história de PHDA medicada apresentavam menos alterações em todos os domínios funcionais e um menor consumo de álcool, canábis e outras drogas ilegais, quando comparados com doentes com PHDA não medicada.[49] Em concordância com estes resultados, Groenman *et al*[47] concluíram que os doentes com PHDA a realizar tratamento estimulante apresentavam o mesmo risco de desenvolver PUS que o grupo controlo com indivíduos saudáveis. Contudo este efeito protetor diminuiu com a idade, o que suporta os benefícios de um início precoce do tratamento.[47] Também os estudos em adultos demonstraram benefícios no uso de estimulantes no tratamento da PHDA e PUS.[50,51]

Tratamento

A abordagem do doente com PHDA e PUS comórbida é complexa. Estes doentes apresentam uma fraca adesão ao tratamento e uma resposta insatisfatória aos tratamentos habitualmente utilizados. Tendo em conta a interligação de ambas as patologias, o tratamento adequado dos sintomas da PHDA é o fator chave para o sucesso do tratamento da PUS.[8]

No que concerne ao tratamento farmacológico, os estudos sugerem que os doentes com PUS e PHDA podem necessitar de doses superiores de metilfenidato para atingir um bom controlo dos sintomas da PHDA. A necessidade de doses crescentes estabiliza nos primeiros dois anos de tratamento, o que pode ser justificado pela utilização de doses insuficientes inicialmente devido à falta de normas estabelecidas para a abordagem destes doentes. A estabilização da dose necessária contraria a possibilidade de uma tolerância crescente aos estimulantes ao longo do tratamento.[52] Os doentes tratados com doses mais elevadas de metilfenidato mostraram ter uma maior adesão ao tratamento, superior em cerca de 15%, do que aqueles que

utilizavam doses mais baixas.[53]

Apesar de existir pouca evidência na literatura acerca da terapia não farmacológica neste grupo de doentes, esta parece apresentar um papel promissor. Um estudo recente comparou doentes a realizar terapia cognitivo-comportamental apenas direcionada ao tratamento da PUS, com doentes que recebiam terapia cognitivo-comportamental integrada, com estratégias direcionadas tanto para a PUS como para a PHDA. Na terapia integrada, durante uma primeira fase do tratamento esta foi direcionada apenas para a PUS e baseada no manual *Motivational Enhancement Therapy manual and Cognitive Behavioral Coping skills training.* Numa segunda fase a terapia foi direcionada para ambas as patologias, sendo a abordagem da PHDA baseada no programa de terapia cognitivo-comportamental *Mastering your adult ADHD.* Os doentes que receberam uma terapia integrada mostraram uma melhoria mais significativa nos sintomas de PHDA, demonstrando que esta adição simples e fácil de implementar pode resultar em melhorias.[54]

O grupo *International Collaboration on ADHD and Substance Abuse* (ICASA) publicou um consenso internacional para a abordagem dos doentes com PHDA e PUS. Neste consenso é sugerida uma abordagem que combine farmacoterapia com terapêuticas não farmacológicas direcionadas para ambas as doenças. A terapia farmacológica preferida consiste em doses elevadas de estimulantes de libertação prolongada ou, no caso dos doentes com abuso alcoólico, a atomoxetina, que demonstrou alguma evidência de superioridade.[35] Outro consenso foi recentemente publicado, baseado na combinação de dados resultantes de investigação científica com a experiência obtida na prática clínica. Para a obtenção deste consenso um grupo de 55 peritos de 17 países classificou 37 afirmações, subdivididas em seis categorias (generalidades sobre a PHDA e PUS, risco de desenvolvimento de PUS, rastreio e diagnóstico, tratamento psicossocial da PHDA e PUS comórbida, tratamento farmacológico da PHDA e PUS comórbida e tratamento complementar), construídas com base na literatura disponível. Este grupo concordou com uma abordagem multimodal destas patologias, incluindo a disponibilização de tratamento farmacológico, preferencialmente estimulantes de libertação prolongada, e não farmacológico, com psicoeducação e terapia cognitivo-comportamental. A única afirmação que não reuniu consenso foi a necessidade de abstinência ou, pelo menos, uma redução e estabilização do abuso de substância antes do tratamento farmacológico da PHDA.[55]

CONCLUSÃO

A relação entre a PHDA e a PUS é inequívoca. Os indivíduos com PHDA representam uma população suscetível ao desenvolvimento de comorbilidades psiquiátricas, sendo uma das mais comuns a PUS. Nestes doentes, a PUS tem início em idades mais jovens, existe uma evolução mais rápida da perturbação, um abuso mais grave e uma maior prevalência de policonsumos. Estas duas patologias partilham influências genéticas e alterações neurofisiológicas e neuroanatómicas. Um dos mecanismos centrais na relação da PHDA e da PUS é a disfunção do sistema dopaminérgico. Tendo em conta que muitos doentes recorrem aos cuidados de saúde pelos sintomas da PUS, ainda sem o diagnóstico de PHDA, e tendo em conta a relação inequívoca entre estas duas patologias, é recomendado um rastreio de PHDA nos doentes com PUS. O tratamento destes doentes é complexo e ainda necessita de mais investigação, contudo uma abordagem multimodal parece apresentar vantagens. Os estimulantes de libertação prolongada apresentam bons resultados em doses mais elevadas. Utilizar uma terapia não farmacológica com estratégias para a gestão de ambas as perturbações parece ser também um passo importante.

CONTRIBUTO DOS AUTORES

MIR: Conceção e elaboração do manuscrito.

GF: Revisão crítica do manuscrito.

Ambos os autores aprovaram a versão final a ser publicada.

CONFLITOS DE INTERESSE

GF recebeu honorários de consultoria e apoio para participar no *9th World Congress of ADHD 2023* da BIAL; recebeu honorários de consultoria da Jaba Recordati.

MIR declara não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Spinocerebellar Ataxia Type 27B (SCA27B): A Hereditary Ataxia in Portugal

Ataxia Espinocerebelosa Tipo 27B (SCA27B): Uma Ataxia Hereditária em Portugal

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Acta Med Port 2025 Jun-Jul;38(6-7):408-411 ▪ https://doi.org/10.20344/amp.22232

ABSTRACT

Spinocerebellar ataxia type 27B (SCA27B) is a recently discovered hereditary disease caused by $(GAA)_{\geq 250}$ repeat expansion in the fibroblast growth factor 14 (*FGF14*) gene, and multiple studies have recognized it as one of the most common causes of autosomal dominant ataxia in the European population. We present the case of a 62-year-old Portuguese patient who developed a slowly progressive gait impairment associated with wide-base ataxic gait, dysarthria, left upper limb dysmetria, and dysdiadochokinesia. This pure cerebellar phenotype had an episodic worsening induced by intense physical activity and alcohol intake. The patient had an older brother with a late-onset cerebellar ataxia of unknown cause. Genetic testing detected a heterozygotic intronic *FGF14* repeat expansion with complete penetrance (> 360 repeats), confirming the diagnosis of SCA27B. To our knowledge, we present the first reported case of SCA27B in the Portuguese population.
Keywords: Spinocerebellar Ataxias/diagnosis; Spinocerebellar Ataxias/genetics; Portugal

RESUMO

A ataxia espinocerebelosa tipo 27B (SCA27B) é uma doença hereditária descoberta recentemente, provocada por expansões $(GAA)_{\geq 250}$ no gene do fator de crescimento de fibroblastos 14 (*FGF14*), e vários estudos sugerem ser uma das causas mais comuns de ataxia de transmissão autossómica dominante na população europeia. Apresentamos o caso de um doente português de 62 anos que iniciou um quadro de desequilíbrio da marcha lentamente progressivo, associado a marcha atáxica, disartria, dismetria e disdiadococinesia do membro superior esquerdo, que apresentava um agravamento paroxístico induzido pela atividade física intensa e consumo de álcool. O doente tinha um irmão mais velho diagnosticado com ataxia cerebelosa de início no adulto de causa indeterminada. A pesquisa de expansões patogénicas no gene *FGF14* detetou uma expansão intrónica em heterozigotia com penetrância completa (> 360 repetições), confirmando o diagnóstico de SCA27B. Tanto quanto sabemos, apresentamos o primeiro caso reportado de SCA27B na população portuguesa.
Palavras-chave: Ataxias Espinocerebelosas/diagnóstico; Ataxias Espinocerebelosas/genética; Portugal

INTRODUCTION

Late-onset cerebellar ataxias (LOCA) are a group of heterogeneous neurodegenerative diseases characterized by progressive cerebellar dysfunction after the age of 30.[1] In recent decades, advances in molecular and genetic techniques have allowed the detection of new causative genes and genetic variants. Nonetheless, more than half of patients with LOCA remain without a diagnosis.[1-3] Recently, a new cerebellar autosomal dominant (AD) ataxia caused by $(GAA)_{\geq 250}$ repeat expansion in intron 1 of the fibroblast growth factor 14 (*FGF14*) gene was identified as a cause of slowly progressive cerebellar ataxia, designated spinocerebellar ataxia type 27B (SCA27B).[1] The *FGF14-SCA27B* repeat locus has highly variable lengths, with the level of pathogenicity classified as follows: $(GAA)_{<200}$ repeats – normal; $(GAA)_{200-249}$ repeats – uncertain pathogenicity; $(GAA)_{250-300}$ repeats – pathogenic with incomplete penetrance, so a diagnosis should only be made in patients with a compatible phenotype and AD transmission; $(GAA)_{>300}$ repeats – pathogenic with complete penetrance.[1,2] Multiple population studies across Europe showed that SCA27B is a common cause of AD ataxia in this population. To our knowledge, we present the first reported case of SCA27B in the Portuguese population.

CASE REPORT

A 62-year-old male patient of European ancestry presented with a five-year history of slowly progressive gait and balance impairment. The patient reported a paroxysmal worsening induced by intense physical activity and alcohol ingestion, even in small quantities. Medical history was, otherwise, unremarkable.

The neurological examination revealed impaired smooth ocular pursuit without nystagmus, wide-base ataxic gait with tandem gait impairment, mild dysarthria, mild left upper limb dysmetria, and dysdiadochokinesia – Scale for the Assessment and Rating of Ataxia (SARA) of 5.5 points (maximum score of 40 points, with higher scores indicating more severe ataxia). There were no pyramidal, extrapyramidal, or sensory signs. Extensive blood work including auto-immune, paraneoplastic, and toxic causes of ataxia was unremarkable. Brain magnetic resonance imaging (MRI) revealed mild atrophy of the cerebellar vermis (Fig. 1).

A therapeutical trial with riluzole resulted in a worsening of the cerebellar symptoms, that resolved after drug interruption. During the three-year follow-up, the patient remained clinically stable, without significant progression of the cerebellar syndrome (SARA 5.5 points at three years of follow-up). However, he reported paroxysmal episodes of

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Recebido/*Received*: 25/08/2024 - **Aceite/*Accepted*:** 07/10/2024 - **Publicado *Online*/*Published Online*:** 11/10/2024 - **Publicado/*Published*:** 02/06/2025

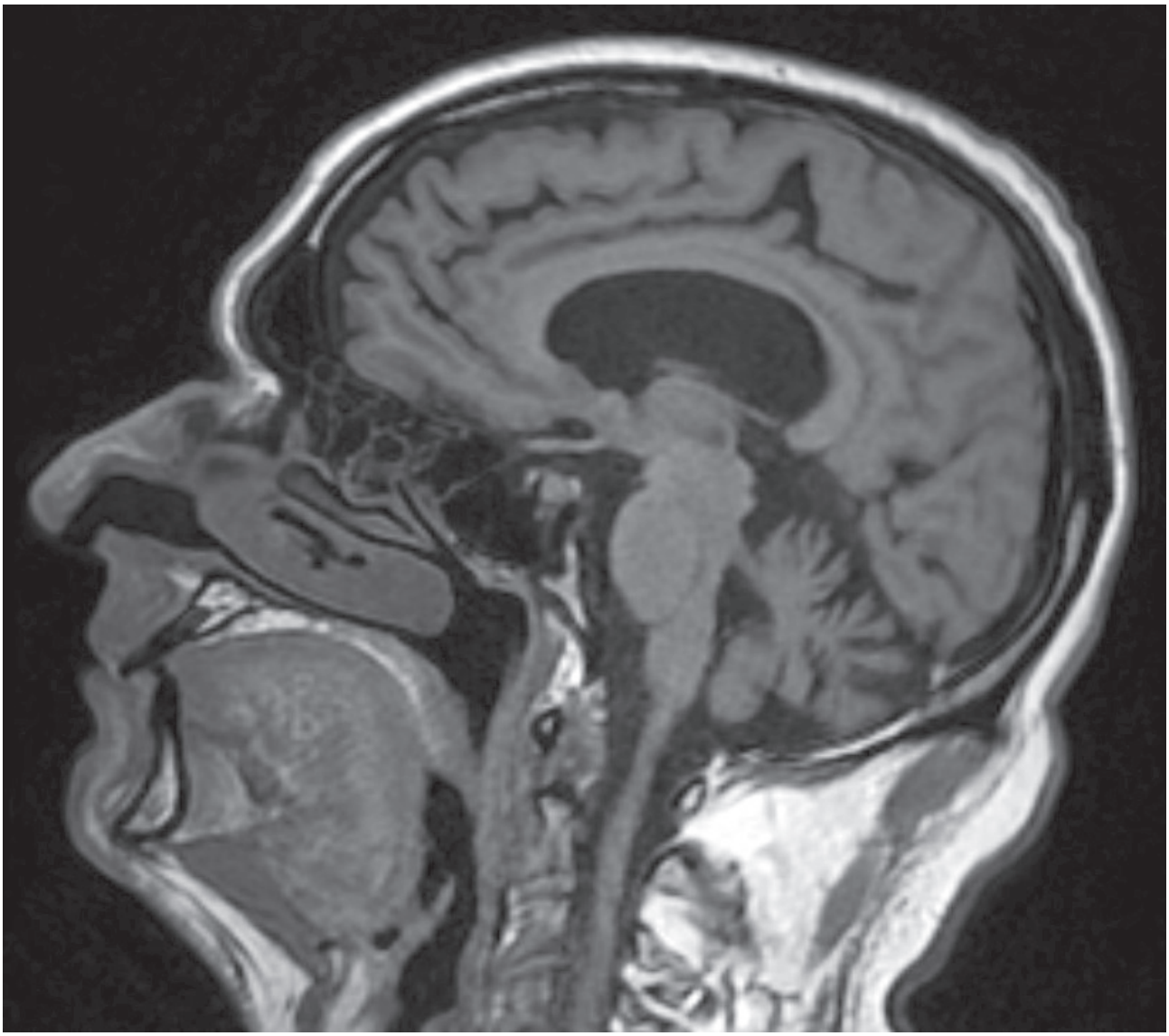

Figure 1 – Mild cerebellar atrophy most pronounced in the cerebellar vermis

oscillopsia and dizziness.

Regarding family history, his older brother had been diagnosed with late-onset pure cerebellar ataxia of unknown cause at the age of 70, characterized by slowly progressive gait impairment with wide-base gait, accompanied by episodic dysarthria and diplopia. Brain MRI revealed mild chronic ischemic microangiopathy with mild diffuse cerebral atrophy. Genetic evaluation, including common causes of hereditary ataxias (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *ATXN8*, *ATN1*, *TBP*, *FXN*, *PGN* genes) was unremarkable. A more extensive exome sequencing ataxia genetic panel revealed two heterozygotic variants of uncertain significance (VUS) in *CAMTA1* and *KIF5A* genes. The patient's brother died of medical complications at 77 years old. Assuming a common etiology between both siblings, our patient initially performed a *CAMTA1* and *KIF5A* genetic testing that was negative, without the previously mentioned VUS. Subsequently, *FMR1* and *RFC1* gene pathogenic expansions were also excluded. Due to paroxysmal symptoms and slow disease progression, *FGF14* intronic expansion testing was performed and detected a heterozygotic repeat expansion with complete penetrance (> 360 repeats), confirming the diagnosis of SCA27B.

DISCUSSION

Spinocerebellar ataxia type 27B is a recently discovered AD hereditary ataxia, and as such, its epidemiologic data and phenotypic spectrum are yet to be fully clarified.[1] The current literature suggests that this diagnosis should be considered in patients with a pure late-onset cerebellar

ataxia, typically presenting in the fifth to seventh decade of life with a slowly progressive course and a pan-cerebellar phenotype.[2,3]

The presence of episodic symptoms, either at disease onset or throughout disease progression, appears to be one of the main distinguishing factors from other hereditary ataxias.[1-3] Up to now, alcohol consumption, intense physical exercise, and caffeine intake have been identified as the most common triggers.[2] The most common clinical features by range of frequency are gait ataxia (95% - 100%); cerebellar oculomotor signs, including pursuit impairment, dysmetric saccades, and nystagmus (80% - 96%); episodic symptoms (13% - 80%); cerebellar dysarthria (12% - 74%); upper limb ataxia (44% - 71%); diplopia, oscillopsia, and visual blurring (40% - 68%); vertigo and dizziness (21% - 67%); postural tremor of upper limbs (10% - 27%).[3-7] Dysautonomic symptoms are classically absent, an important feature for distinguishing this condition from multiple system atrophy type C (MSA-C), another common form of LOCA.[8] We present a case of SCA27B with onset in the fifth decade that presented with a slowly progressive gait and balance impairment. In our patient, the disease had a slowly progressive clinical course of pure cerebellar ataxia as it has been previously described. In our case, although cerebellar oculomotor signs are one of the most common findings in SCA27B, with downbeat nystagmus being particularly mentioned in previous cohorts, we only identified impaired ocular pursuit. We did not identify pyramidal signs, extrapyramidal signs, sensory signs, or dystonia, which seem to be uncommon in SCA27B. The cerebellar symptoms were exacerbated by physical exertion and alcohol intake, but not caffeine (another common trigger).[3-7] Brain MRI revealed cerebellar atrophy that was more evident in the cerebellar vermis without brainstem atrophy, which concurs with what is documented in the literature, in which 60% - 97% of SCA27B patients have mild to moderate cerebellar atrophy, more pronounced in the cerebellar vermis.[3]

Riluzole has been used off-label for the treatment of hereditary cerebellar ataxias, with several trials showing clinical improvement.[9] In our literature review, we did not find any reports of riluzole use in SCA27B patients. However, in our case this drug led to a worsening of the cerebellar symptoms, which the patient described as exacerbated dysarthria, gait imbalance, and upper limb ataxia, comparable to what was observed with the previously mentioned triggers. This led to the early discontinuation of the drug. The knockdown of *FGF14* in cerebellar granule cells has been demonstrated to reduce calcium currents and vesicular recycling, suggesting that SCA27B may, at least in part, stem from dysregulation of calcium channel function.[10] Additionally, riluzole inhibits N-type and P/Q-type calcium channels, resulting in decreased calcium influx at presynaptic terminals, which may account for the exacerbation of symptoms observed with riluzole treatment in our patient.[10,11] On the other hand, initial findings from observational case series suggest that 4-aminopyridine (also known as fampridine) may be beneficial for SCA27B patients, reducing the severity and frequency of cerebellar symptoms. Even though randomized placebo-controlled trials are needed to validate these findings, it seems to be an effective symptomatic therapy.[2]

To our knowledge, this is the first reported case of SCA27B in Portugal, and this report should encourage not only neurologists but also ophthalmologists and otolaryngologists to consider this new entity when approaching cases of adult-onset cerebellar ataxia, as it appears to be a common cause of LOCA in the European population. Furthermore, and given its high prevalence and potential treatment, it should be considered as one of the main causes of genetic ataxias to investigate during the initial evaluation of these patients.

AUTHOR CONTRIBUTIONS

VMF: Study design, writing of the manuscript.

MM, BM, RB: 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 2013.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

RB has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boston Scientific; received support for attending meetings and/or travel from Medtronic.

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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Ileocolic Intussusception in Adults: A Rare Presentation of an Underlying Malignancy

Invaginação Ileocólica em Adultos: Uma Apresentação Rara de uma Neoplasia Subjacente

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Acta Med Port 2025 Jun-Jul;38(6-7):412-413 ▪ https://doi.org/10.20344/amp.23111

Keywords: Ileal Diseases; Intestinal Neoplasms; Intussusception/diagnosis
Palavras-chave: Doenças do Íleo; Invaginação/diagnóstico; Neoplasias Intestinais

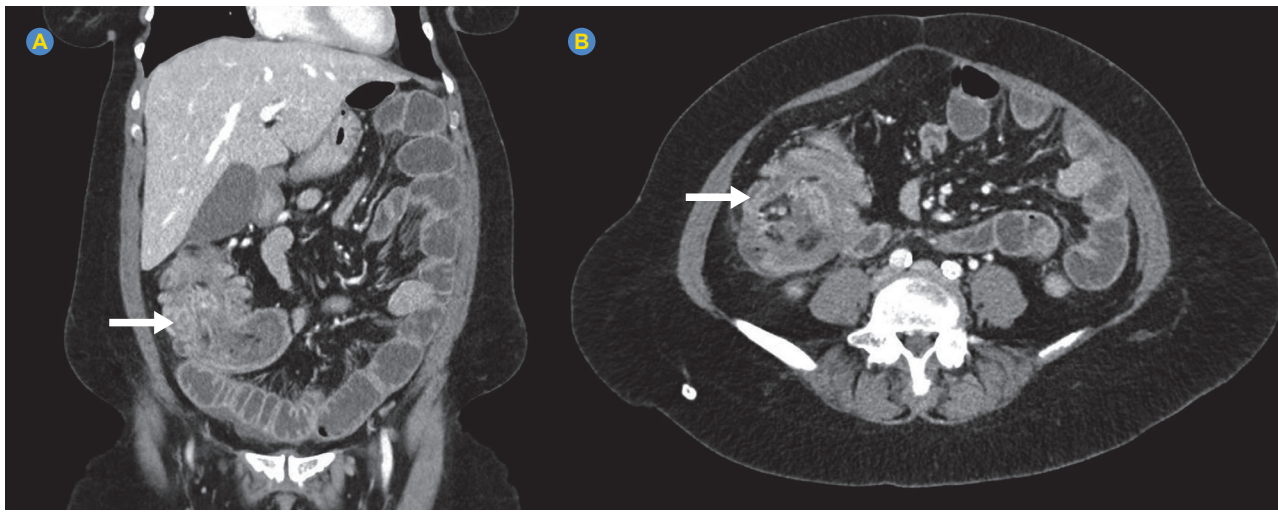

Figure 1 – Abdominal computed tomography revealing ileocolic intussusception (arrows): (A) – coronal view; (B) – axial view.

A 62-year-old melanodermic woman with type 2 diabetes *mellitus* and human immunodeficiency virus (HIV) presented to the emergency department with one day of nausea and vomiting. The patient also reported months of epigastric pain, heartburn, and belching. Abdominal computed tomography revealed ileocecal intussusception (Fig. 1A, Fig. 1B). She underwent a right hemicolectomy (Fig. 2), and histopathology confirmed mucinous adenocarcinoma (pT3 pN1b G2).

Ileocolic intussusception in adults is rare and often signals an underlying malignancy. Unlike pediatric cases, adult intussusception typically presents with chronic or intermittent abdominal pain, nausea, vomiting, and bowel obstruction. Computed tomography is the diagnostic method of choice.[1,2]

Surgical resection is the preferred treatment in adults, especially in emergencies requiring oncologic evaluation.[3,4] Most adult cases are caused by a pathological lead point – an abnormal lesion that initiates the telescoping of the bowel. Due to this underlying cause, definitive surgical intervention is generally required.[5,6]

AUTHOR CONTRIBUTIONS

CRS: Writing of the manuscript.
FN, AMC: 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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Recebido/*Received*: 13/03/2025 - **Aceite/*Accepted*:** 17/04/2025 - **Publicado/*Published*:** 02/06/2025

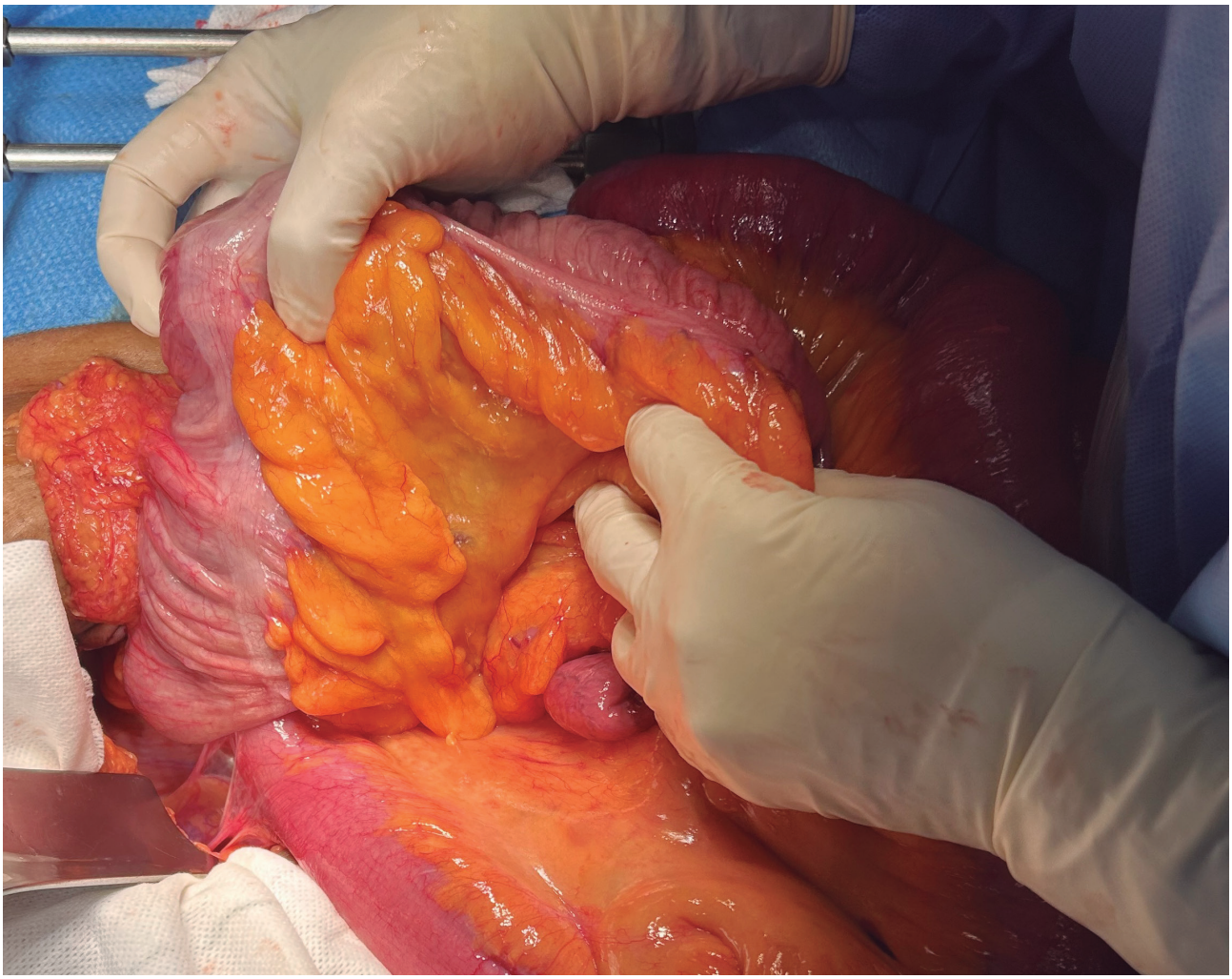

Figure 2 – Intraoperative view of ileocolic intussusception prior to right hemicolectomy

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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Multiple Sclerosis Disease-Modifying Treatment Algorithms: 2025 Positioning of the Portuguese Multiple Sclerosis Study Group

Algoritmos das Terapêuticas Modificadoras da Esclerose Múltipla: Posicionamento do Grupo de Estudos de Esclerose Múltipla em 2025

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Acta Med Port 2025 Jun-Jul;38(6-7):414-426 ▪ https://doi.org/10.20344/amp.22380

ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune-mediated neurodegenerative disease characterized by inflammation, demyelination, and axonal/neuronal damage in the central nervous system. In Portugal, the prevalence of MS is approximately 64.4 per 100 000 individuals. It is typically diagnosed in young adults aged 30 to 40, with a higher incidence in women, although it can also affect children/adolescents and the elderly. Recent advances in MS treatment include the development and approval of several new disease-modifying therapies (DMTs) such as ocrelizumab, cladribine, siponimod, and others, thus expanding options for relapsing-remitting MS (RRMS). However, the options for progressive forms of MS remain limited. In Portugal, MS management strategies, guided by the 2015 recommendations of the Directorate-General of Health and the Portuguese medicines agency, need updating to incorporate recent scientific evidence and clinical expertise. The aim of this manuscript is to highlight gaps in current Portuguese MS treatment algorithms and propose enhancements aligned with global standards, thus improving treatment selection and patient outcomes in the Portuguese healthcare system. Developed by nine Portuguese neurology experts from the Portuguese Multiple Sclerosis Study Group, this document not only provides evidence and clinical practice-based recommendations but also includes DMT algorithms tailored for various MS subtypes, including radiologically and clinically isolated syndromes, RRMS, progressive MS, and specific situations in MS treatment such as pediatric-onset MS, late-onset MS, pregnancy and breastfeeding. This document provides evidence- and clinical practice-based recommendations to optimize decision-making during MS management in Portuguese centers. The experts aim to prompt the urgent revision of national MS treatment frameworks, incorporating the latest advancements in MS research and international guidelines, to reduce the socio-economic burden on the national healthcare system and improve the long-term health outcomes of MS patients.
Keywords: Age of Onset; Multiple Sclerosis/drug therapy; Multiple Sclerosis, Relapsing-Remitting/drug therapy

RESUMO

A esclerose múltipla (EM) é uma doença neurodegenerativa crónica mediada por autoimunidade, caracterizada por inflamação, desmielinização e lesões axonais/neuronais no sistema nervoso central. Em Portugal, a prevalência da EM é de aproximadamente 64,4 por 100 000 indivíduos. A EM é geralmente diagnosticada em adultos jovens entre 30 e 40 anos, com maior incidência nas mulheres, embora também possa ocorrer em crianças/adolescentes e idosos. Avanços recentes no tratamento da EM incluem o desenvolvimento e aprovação de várias novas terapêuticas modificadoras da doença (TMD), como ocrelizumab, cladribina, siponimod e outras, ampliando assim as opções para a EM surto-remissão (EMSR). Contudo, as opções para as formas progressivas de EM permanecem limitadas. Em Portugal, as estratégias de gestão da EM, orientadas pelas recomendações de 2015 da Direção-Geral da Saúde e do Infarmed, carecem de urgente atualização para incorporar evidências científicas recentes e perícia clínica. Este manuscrito tem como objetivo destacar lacunas nos atuais algoritmos de tratamento da EM em Portugal e propor melhorias alinhadas com os padrões globais, melhorando a seleção de terapêuticas e os resultados dos doentes no sistema de saúde português. Desenvolvido por nove especialistas portugueses em neurologia do Grupo de Estudos de Esclerose Múltipla, este documento fornece recomendações baseadas na evidência e na prática clínica, incluindo algoritmos de tratamento com TMD adaptados para vários subtipos de EM, incluindo síndromes clinicamente e radiologicamente isoladas, EMSR, EM progressiva e situações específicas no tratamento da EM, como EM pediátrica, EM de início tardio, e a gestão na gravidez e amamentação. Este documento oferece recomendações baseadas em evidências e práticas clínicas para otimizar a tomada de decisão durante a gestão da EM em centros

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Recebido/*Received*: 01/10/2024 - **Aceite/*Accepted*:** 24/01/2025 - **Publicado *Online*/*Published Online*:** 06/05/2025 - **Publicado/*Published*:** 02/06/2025

portugueses. Os especialistas pretendem incentivar a revisão urgente das normas de tratamento da EM, incorporando os avanços mais recentes na pesquisa sobre a EM e nas diretrizes internacionais, com o intuito de reduzir o impacto socioeconómico no sistema de saúde nacional e melhorar os resultados de saúde de longo prazo dos doentes com EM.
Palavras-chave: Esclerose Múltipla/tratamento farmacológico; Esclerose Múltipla Recidivante-Remitente/tratamento farmacológico; Idade de Início

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune-mediated neurodegenerative disease, characterized by inflammation, demyelination, and axonal/neuronal damage on the central nervous system.[1] In Portugal, it is estimated that 64.4 per 100 000 individuals are affected by MS.[2] This disease is usually diagnosed in young adults of 30 to 40 years of age, has a higher incidence in women than men (3:1), and can be observed during childhood/adolescence (< 18y) or in the senior population (≥ 50y).[3-5]

Diagnosis of MS is based on the McDonald criteria (last revision in 2017),[6] which involves a combination of clinical evaluation, imaging studies [magnetic resonance imaging (MRI)], and laboratory tests [cerebrospinal fluid (CSF)]. Its phenotypes can be categorized as relapsing or progressive in the context of current medical status and history (Table 1), but these categories do not provide temporal information about the ongoing disease process. On this note, the 2013 phenotypic classification update by the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials in Multiple Sclerosis introduced "disease activity" [detected by clinical relapses and/or lesion formation on MRI (T1 gadolinium-enhancing lesions and/or new or enlarging T2 lesions) on an annual timeframe] and "disease progression" (clinical evidence of disease progression, independent of relapses, assessed annually in patients who have a progressive disease course) as meaningful descriptors of relapsing or progressive MS.[7]

Disease progression can manifest as disability dependent on relapses, known as "relapse-associated worsening" (RAW), and/or as disability progression largely independent of relapses, termed "progression independent of relapse activity" (PIRA). Briefly, RAW occurs when relapses directly contribute to the accumulation of disability, while PIRA represents a gradual worsening of disability that occurs without associated relapses, driving the progression of progressive MS.[8] Understanding these concepts is crucial for tailoring treatment strategies to effectively manage both aspects of disease progression in MS.

The revised disease classification, incorporating disease activity (relapses and MRI), has updated the previous terms "progressive relapsing MS" (PRMS) and "secondary progressive MS with relapses" (SPMSr) to "active primary progressive MS" (aPPMS) and "active secondary progressive MS" (aSPMS), respectively. Consequently, the terms "PRMS" and "SPMSr" should be discontinued. Of note, the term "relapsing MS" should not be confused with "RRMS", as it also includes "aSPMS".

The 2013 classification considers disease progression only in progressive forms (PPMS and SPMS), but it is currently consensual that MS is progressive from the onset and, therefore, the axis of progression should also be considered as well in relapsing forms of the disease. While not considered *per se* as a phenotype of MS, radiologically isolated syndrome (RIS) describes asymptomatic individuals exhibiting suggestive MRI clinical features, thus posing an elevated risk of developing MS.[9,10] Identifying the MS phenotype is crucial to guide treatment decisions and understand the disease course and prognosis for each individual/patient.

Although the course of MS can be extremely heterogeneous and difficult to predict, several prognostic factors have been identified as indicating a higher probability of poor disease outcomes,[11-14] thus being crucial for treatment decisions and for decisions related to various aspects of the patients' life (e.g., family planning, pregnancy, relationships, and work life). The presence of poor prognostic factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], especially when multiple co-existing factors are present, is more likely to result in higher and more frequent disease activity and earlier disability.

The goal of MS disease-modifying therapy (DMTs) is to reduce early clinical and subclinical disease activity, attenuating the accrual of long-term disability.[15-17] To improve long-term patient outcomes and preserve quality of life, it is critical to achieve a sustained state of "no evidence of disease activity-3" (NEDA-3), which encompasses the prevention of

Table 1 – Current MS phenotype classification

Clinically Isolated Syndrome (CIS) **Relapsing-Remitting MS (RRMS)**	Active or Not active
Secondary Progressive MS (SPMS) **Primary Progressive MS (PPMS)**	Active with/without progression or Not active with/without progression

MS: multiple sclerosis

relapses, the halting of disability progression, and the minimization of new/enlarging T2 lesions and/or T1 gadolinium-enhancing lesions on MRI scans.[18]

The armamentarium for MS treatment, summarized in [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], has expanded very rapidly for RRMS, but remains limited for progressive MS. Over the past 10 years, notable developments have occurred in the field, including the approval of several new DMTs such as ocrelizumab, cladribine, siponimod, ozanimod, ponesimod, ofatumumab and ublituximab. Noteworthy, recent evidence suggests the potential effectiveness of pharmacotherapy in RIS.[19-22] Considering the 2024 McDonald criteria, which had not yet been published at the time of writing this manuscript but were presented at the 2024 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) conference, RIS may fulfill the criteria for RRMS, and, therefore, may become a potential target for DMTs already approved for RRMS. New molecules are currently under development and have shown promising clinical benefits in MS treatment, such as Bruton's tyrosine kinase (BTK) inhibitors [e.g., tolebrutinib for inactive secondary progressive MS – HERCULES study (NCT04411641)] and CD40L inhibitors (e.g., frexalimab for relapsing MS).[23,24] Additionally, there have been updates to diagnostic criteria, emerging evidence supporting early treatment with high-efficacy DMTs (HE-DMTs), a heightened emphasis on tools for assessing patients' perception of the disease through patient-reported outcomes (PROs), and endeavors to integrate remote monitoring tools used in clinical trials into routine clinical practice. Mitoxantrone, a chemotherapeutic agent previously used in the treatment of aggressive MS, has seen its use significantly restricted due to concerns regarding its potential for severe cardiotoxicity.[25]

In Portugal, current MS management strategies have been guided a decade ago by the 2015 recommendations of Direção-Geral da Saúde (DGS) and by the National Medicines Agency (Infarmed)'s guidance documents – which lack the consideration of the patient's poor prognosis factors in the choice of the treatment algorithm.[26,27]

As the diagnostic criteria for MS continue to evolve and new therapeutic strategies emerge it is evident that the existing treatment recommendations followed by Portuguese centers require revision and updating, drawn upon up-to-date scientific evidence and clinical expertise. This manuscript endeavors to analyze the gaps in the current Portuguese MS treatment algorithms compared to global standards, highlighting the urgency for an updated decision-making framework in Portugal. Drawing from contemporary MS research and the clinical insights of Portuguese experts, this initiative seeks to enhance treatment guidelines tailored to diverse subsets of MS patients within the Portuguese healthcare system, to ultimately provide safe and efficient selection of MS therapies and optimization of patient outcomes.

MATERIAL AND METHODS

Acknowledging the developments and needs on the field, nine Portuguese neurologists with extensive expertise on MS, members of the Portuguese Multiple Sclerosis Study Group (GEEM), endorsed a series of expert meetings to draw a consensus document advocating for revision of the current MS treatment framework in Portuguese centers. The goal of this document is to aid decision-making for MS specialists, to help reduce excessive variation in practice, and ensure safe and effective prescribing. The proposed MS treatment algorithms presented herein reflect the consensus opinions of all authors based on their clinical experience, and are built upon the currently available guidelines from the ECTRIMS/European Academy of Neurology (EAN) guidelines for Europe, the Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) for the Middle East/North Africa, the American Academy of Neurology (AAN) for North America, and the individual initiatives of the Multiple Sclerosis Therapy Consensus Group (MSTCG), the National Institute for Health and Care Excellence (NICE) and the Spanish Society of Neurology.[28-33]

The experts' recommendations for the management of MS in Portugal

The panel of expert neurologists from GEEM convened to develop various algorithms to guide the therapeutic strategies for MS, including specific situations such as pediatric onset MS, MS management during pregnancy and breastfeeding, and late-onset MS, based on the available scientific evidence, approved indication labels, and expert opinion.

Choosing the best treatment strategy: escalation or early initiation of HE-DMTs

The classification of DMTs based on efficacy lacks uniformity in the literature, particularly regarding the inconsistent positioning of S1P receptor modulators and cladribine. Given this, the GEEM experts collectively decided to introduce a third efficacy category, "low efficacy," to complement the commonly used "moderate efficacy" and "high efficacy" classifications. Accordingly: i) low efficacy DMTs include IFNβ formulations, glatiramer acetate, teriflunomide, and dimethyl fumarate; ii) moderate efficacy DMTs include S1P receptor modulators (fingolimod, ozanimod, ponesimod, siponimod) and cladribine; and iii) high efficacy DMTs comprise monoclonal antibodies, specifically natalizumab, alemtuzumab, and anti-CD20 therapies (ocrelizumab,

ofatumumab, and ublituximab).

The decision to initiate DMTs for MS is based on several factors, which include the patient's disease characteristics (e.g., clinical presentation, frequency of relapses, MRI findings, and disability progression), prognostic factors, and patient-neurologist shared decision making. Immunomodulatory/immunossupressive DMTs should be offered as soon as possible to control disease activity and progression to i) patients with RIS with persistent imaging activity; ii) patients with CIS and risk of progression to MS; iii) RRMS; iv) aSPMS; v) aPPMS; vi) younger patients (≤ 50) with inactive SPMS (iSPMS) and PPMS (iPPMS) with progression.

The prevailing guidelines in Portugal endorse an escalation approach, initiating patients with low- and moderate-efficacy DMTs (LE-/ME-DMTs, respectively) and transitioning to HE-DMTs, if increased disease activity, poor compliance or side effects are observed.[26,34] Opting for such a conservative management approach may have limitations in terms of disease control and long-term outcomes. The rationale for initiating early HE-DMTs to mitigate disease progression in the initial stages of MS is supported by an increasing body of evidence consistently demonstrating that early start of HE-DMTs, as opposed to LE-/ME-DMTs or early transitioning to HE-DMTs, may yield optimal benefits in managing the evolution of MS.[35-42] This is attributed to their heightened capacity to curtail the accumulation of irreversible clinical disability, the onset of secondary progressive MS, and the advancement of brain atrophy more effectively. This approach is particularly relevant for patients with aggressive forms of MS or those who have failed to respond adequately to LE-/ME-DMTs. However, one should keep in mind that this approach requires careful monitoring and management.

Controlled trials directly comparing escalation treatment and early onset of HE-DMTs are lacking. However, observational studies and subgroup analyses from clinical trials consistently suggest that patients receiving early HE-DMTs treatment exhibit less disease activity, reduced disability, and a lower risk of progressing to SPMS within the first five years compared to those receiving these treatments later.[37,39,43,44] Real-life studies indicate that patients treated early with HE-DMTs are approximately twice as likely to achieve NEDA-3 compared to those treated with LE-/ME-DMTs.[45] Considering that persistent clinical or subclinical activity may lead to irreversible neurological damage, it is reasonable to consider HE-DMTs as the initial option after weighing the risks and benefits of treatment.

Proposed treatment algorithms for MS

The initial treatment decision in MS should be based on shared decision-making between the clinician and patient, taking into account both patient-related factors and drug-related factors. Choosing a specific drug involves considering not only patient prognostic factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], and drug-related factors, but also individual patient factors such as age, sex, literacy, occupation, family planning, comorbidities, disease phenotype, type of deficits, progression of disability, disease activity, autonomy/dependence, presence of cognitive deficits, comfort, expectations, concerns, and motivation for effective adherence to prescribed medication.[11] This comprehensive approach ensures that the chosen therapy aligns with the patient's unique circumstances, leading to more effective and satisfactory outcomes.

Radiologically isolated syndrome

Patients diagnosed with radiologically isolated syndrome (RIS) should be promptly referred to a specialized MS center for monitoring. If multiple risk factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] are present and follow-up MRI reveals evidence of new lesions, treatment should be initiated (teriflunomide or dimethyl fumarate) (Fig. 1).[21,22] Under the updated 2024 McDonald diagnostic criteria (not yet published at the time of manuscript preparation), RIS may meet the criteria for relapsing-remitting multiple sclerosis (RRMS), making it eligible for DMTs approved for RRMS.

Clinically isolated syndrome

Clinically isolated syndrome (CIS) patients who do not fulfill the criteria for MS and present abnormal MRI findings (≧ 2 T2 lesions), thus being considered high-risk,[46] should be treated with IFNβ formulations, glatiramer acetate, teriflunomide or cladribine (Fig. 1). In the presence of one or two poor prognostic factors, cladribine should be considered.[47,48]

Relapsing-remitting multiple sclerosis

Upon disease activity detection on treatment-naïve patients with i) zero unfavorable prognostic factors, one should consider LE-DMTs as IFNβ, glatiramer acetate, teriflunomide or dimethyl fumarate; ii) one to two unfavorable prognostic factors, one should consider ME-DMTs as S1P receptor modulators and cladribine; or iii) more than two unfavorable prognostic factors, one should consider HE-DMTs as natalizumab, anti-CD20/B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, ublituximab), and alemtuzumab (Fig. 1). Patient-related factors should also be considered for the choice of DMT [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)].

The treatment strategy for patients on DMTs should be

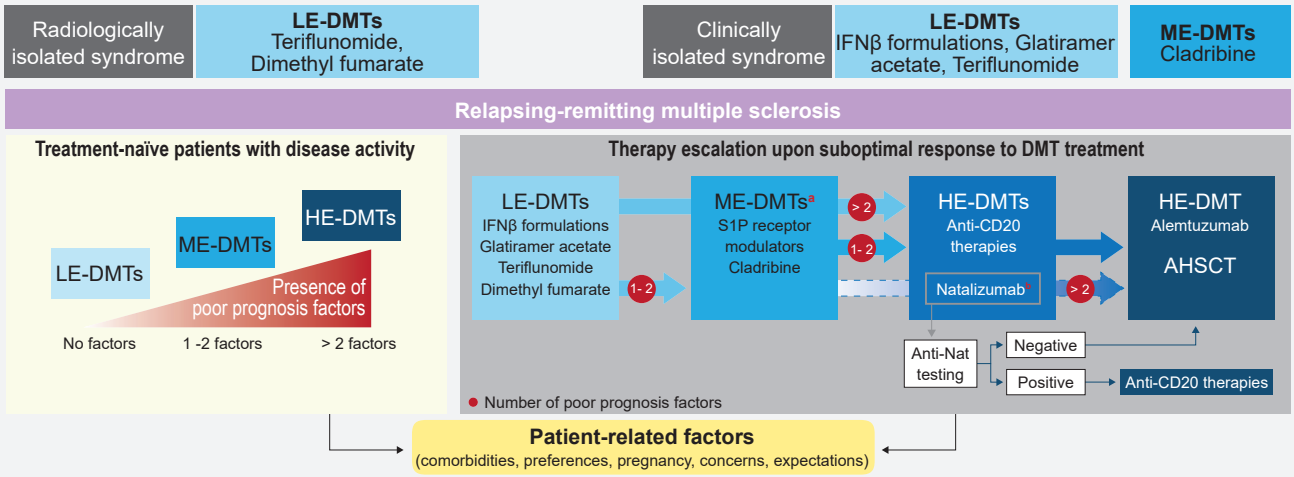

Figure 1 – 2025 algorithm for the management of RIS, CIS and RRMS

Disease activity or suboptimal response is generally defined as "presence of relapses, new/enlarged T2 lesions, gadolinium-enhancing T1 lesions, or confirmed disability progression over one year (≥ 1.5 if EDSS 0; 1.0 if EDSS 1.0 - 5.5; or 0.5 if EDSS ≥ 6.0, sustained across ≥ 2 consecutive visits separated by ≥ 6 months). In both treatment-naïve patients and those with a suboptimal response to DMTs, therapeutic switching should take into account the presence of prognostic factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] and patient-related factors.

a: In case of suboptimal response to ME-DMTs, escalation to HE-DMTs (anti-CD20 therapies or natalizumab) is recommended prior to considering alemtuzumab or AHSCT.

b: In case of suboptimal response to ME-DMTs, natalizumab should be used preferentially in patients with negative JC virus serology. In cases of suboptimal response or infusion reactions before subsequent infusions, the presence of persistent anti-natalizumab antibodies should be confirmed. If positive, a switch to anti-CD20 therapies can be considered. If negative, alemtuzumab or AHSCT may be considered.

AHSCT: autologous hematopoietic stem-cell transplantation; CIS: clinically isolated syndrome; DMTs: disease-modifying therapies; HE-DMTs: high efficacy DMTs; IFNβ: interferon β; LE-DMTs: low efficacy DMTs; ME-DMTs: medium efficacy DMTs; RIS: radiologically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis

carefully reassessed if suboptimal response is detected (Fig. 1). Disease activity or suboptimal response is generally defined as "presence of relapses, new/enlarged T2 lesions, gadolinium-enhancing T1 lesions, or confirmed disability progression over one year (≥ 1.5 if EDSS 0; 1.0 if EDSS 1.0 - 5.5; or 0.5 if EDSS ≥ 6.0, sustained across ≥ 2 consecutive visits separated by ≥ 6 months).[29] Such scenario should prompt a therapeutic switch, in a form of DMT treatment escalation, guided by the presence of poor prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] and patient-related factors. In cases where only increased disability is observed during a one-year period of DMT use, DMTs with a stronger impact on this component (PIRA), such as anti-CD20 therapies, should be prioritized.

For patients with suboptimal responses to LE-DMTs (Fig. 1), escalation to ME- or HE-DMTs with an acceptable safety profile should be considered. Suitable options include cladribine, S1P receptor modulators, anti-CD20 therapies or natalizumab for John Cunningham virus (JCV) seronegative patients. Escalation to ME-DMTs is recommended in the presence of one to two poor prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], whereas escalation to HE-DMTs is advised when more than two poor prognosis factors are present. In such cases, HE-DMTs such as anti-CD20 therapies or natalizumab should be prioritized before considering alemtuzumab or AHSCT.

If suboptimal response/disease activity is observed with ME-DMTs (Fig. 1), escalation to HE-DMTs is recommended. In the presence of one to two poor prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], preferred options include anti-CD20 therapies or natalizumab for JCV seronegative patients. Alemtuzumab may be considered, particularly when more than two poor prognosis factors are present.[48-50] Autologous hematopoietic stem-cell transplantation (AHSCT) is also a viable strategy for managing MS refractory to DMT treatment, but should be carefully considered due to the risks of immunosuppression and potential side effects.[51]

For patients with suboptimal responses to HE-DMTs (such as natalizumab, anti-CD20 therapies, including off-label use of rituximab) (Fig. 1), alemtuzumab or AHSCT should be considered. Additionally, in these cases, natalizumab antibody testing should be performed and confirmed in patients who experience infusion reactions or breakthrough disease activity while using natalizumab. If positive, a lateral switch to an anti-CD20 therapy may be appropriate; if negative, a vertical switch to alemtuzumab or AHSCT can be considered.

Active secondary progressive MS and active primary progressive MS

For the treatment of aSPMS (Fig. 2), the following DMTs

can be considered: IFNβ formulations, glatiramer acetate, cladribine, siponimod, ponesimod, ocrelizumab, ofatumumab, and ublituximab. However, the DMTs with the most documented clinical benefit for this form of MS are siponimod and B-cell depleting therapies.[49,50] Since the treatment target is disease activity (inflammation), the same considerations for RRMS should be applied in aSPMS, including the presence of poor prognostic factors and previously employed DMTs.

Ocrelizumab is the only approved therapeutic agent for aPPMS.[50] Ocrelizumab serum levels have been associated with a greater reduction in the risk of disability progression, forming the basis for the ongoing GAVOTTE (NCT04548999; in aPPMS patients) and MUSETTE (NCT04544436; in aSPMS patients) trials.[52] In this context, and given the limited therapeutic options for aPPMS, in cases of disease progression under the standard 600 mg dose of ocrelizumab, higher doses of 1.200 mg in patients < 75 kg or 1.800 mg in patients ≥ 75 kg, every 24 weeks, may be considered (Fig. 2).

Results of a randomized double-blind placebo-controlled multicenter trial (OLYMPUS) suggest that off-label use of rituximab may be also effective in PPMS patients.[51]

Inactive secondary progressive MS (iSPMS) and inactive primary progressive MS (iPPMS)

For the treatment of iSPMS and iPPMS (Fig. 2), specific therapeutic options are considered based on patient age and disease progression. In younger patients (≤ 50 years old) with iSPMS characterized solely by progression, siponimod and anti-CD20 therapies, such as ocrelizumab and ofatumumab, can be considered. Similarly, for ≤ 50 year old patients with iPPMS showing only progression, ocrelizumab, potentially at higher doses, is a viable treatment option. These treatments focus on managing disease progression in the absence of active inflammation.

Therapeutic switch

Upon the decision to switch DMTs (Figs. 1, 2), a washout period is typically implemented before starting the second DMT, to mitigate the potential risks associated with cumulative effects (Table 2). Therefore, the switching process poses challenges for patients that should be considered: i) a brief washout period between DMTs heightens the likelihood of adverse events (e.g., opportunistic infections due to DMT-induced immunosuppression), and ii) an extended washout period raises the risk of reactivation/rebound disease activity, including relapses, worsening disability, and/or increased MRI activity. Therapeutic switch should be performed under the following principles:

- If discontinuing LE-DMTs, another LE-DMTs or ME/HE-DMTs or an induction therapy may be initiated without a washout period, provided the patient's biological test results are normal.
- In both treatment-naïve patients and those with a suboptimal response to DMTs (Fig. 1), therapeutic switching should take into account the presence of prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] and patient-related factors.
- Clinicians should consider the transition to non-injectable or less frequently injectable DMTs if patients report discomfort with injections or exhibit signs of

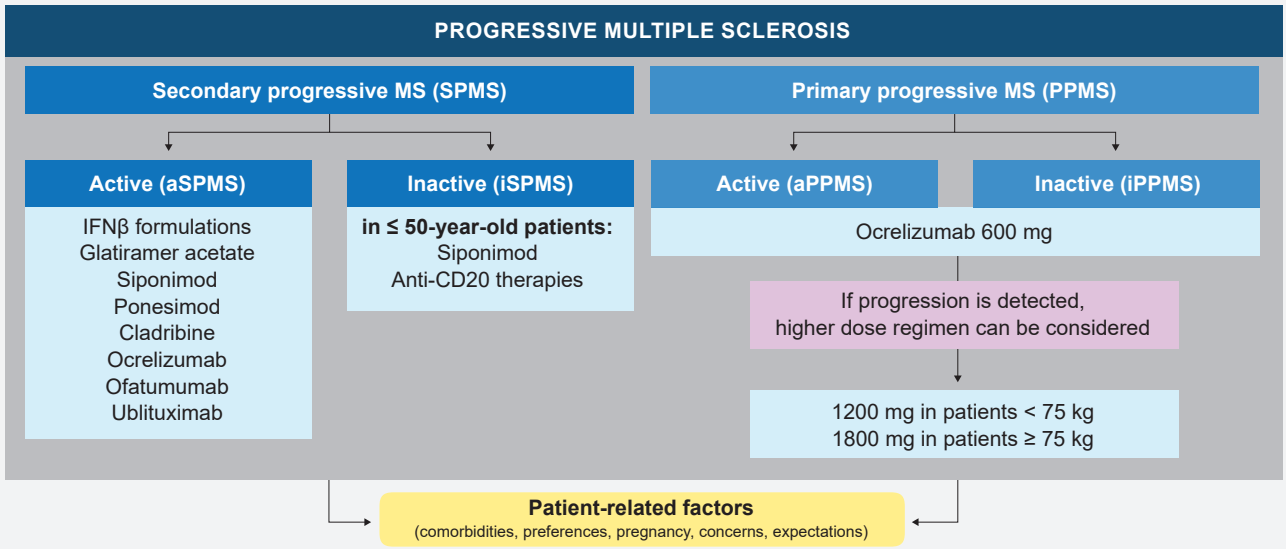

Figure 2 – 2025 algorithm for the management of progressive MS
IFNβ: interferon β; MS: multiple sclerosis; PPMS: primary progressive MS; SPMS: secondary progressive MS

Table 2 – Recommended washout periods after disease-modifying therapies switch

Discontinued DMT	Washout time before starting LE-DMT	Washout time before starting ME/HE-DMT or induction therapy
IFNβ	No washout	No washout
Glatiramer acetate	No washout	No washout
Teriflunomide	No washout	No washout
Dimethyl fumarate	No washout (if lymphocyte count > 800/mm^3)	No washout (if lymphocyte count > 800/mm^3)
Fingolimod		One month
Siponimod		10 days
Ozanimod		One month
Ponesimod		One week
Natalizumab		One month
Alemtuzumab		If disease activity (clinical or imaging)
Ocrelizumab		Six months (or until B-cell repletion)*
Ofatumumab		One month (or until B-cell repletion)*
Ublituximab		Six months (or until B-cell repletion)*
Cladribine		If disease activity (clinical or imaging)

*: The therapeutic switch can coincide with the scheduled infusion (ocrelizumab and ublituximab: every six-months infusion; ofatumumab: every one-month infusion).
DMT: disease-modifying therapy; HE-DMT: high efficacy DMT; IFN: interferon; LE-DMT: low efficacy DMT; ME-DMT: medium efficacy DMT.

injection fatigue.

- Clinicians should discuss a switch to a DMT with a lower risk of progressive multifocal leukoencephalopathy (PML) in patients under natalizumab and anti-JCV seropositive (particularly if their anti-JCV antibody index rises above 0.9 while on therapy).
- A one-month washout period is typically recommended when switching from S1P receptor modulators to anti-CD20 therapies and natalizumab, although this may vary depending on the specific S1P receptor modulator used. However, disease reactivation is common after discontinuing S1P receptor modulators, requiring close monitoring. The preference for anti-CD20 agents after S1P receptor modulators is due to their rapid B-cell depleting effect, with onset times ranging from 24 hours for ublituximab to 14 days for ocrelizumab and ofatumumab.
- In cases of switching to cladribine, caution is required due to its delayed onset of action, which may increase the risk of disease reactivation or rebound.[53] Therefore, a bridging strategy with an anti-CD20 agent should be considered. Given this, particularly in the context of switching from S1P receptor modulators during pregnancy, cladribine should be avoided in favor of natalizumab or anti-CD20 therapies, which are more appropriate options in this setting.
- When determining the required washout period from anti-CD20 therapies for a therapeutic switch in MS treatment, the duration depends on the speed of B-cell reconstitution, which varies among anti-CD20 therapies. For example, median time to B-cell repletion for ocrelizumab is 72 weeks, 24.6 weeks for ofatumumab, and 70 weeks for ublituximab.

Specific situations in MS treatment

Pediatric onset MS

Pediatric onset MS (POMS) is generally defined as MS with onset before the age of 18 years, and 3% - 10% of all MS patients have their first demyelinating attack before the age of 16 years.[54] In agreement, two studies conducted in Portugal found that 9.2% of MS patients had symptoms starting at a young age, and the average age of initial symptom onset was 14 years.[55,56] The 2017 revised McDonald criteria for adult-onset MS are widely used as diagnostic criteria for the pediatric population.

Early intervention is crucial in POMS, as these patients reach irreversible disability at a younger age than patients with adult-onset MS,[57] and 98% of the pediatric patients present a relapsing-remitting course.[58] Given the relatively high relapse rate and accumulation of disability at younger age, early initiation of DMTs is recommended to reduce the intense inflammatory process early in the disease.[59] Several DMTs are currently used for the management of POMS, which have proved useful and safe approaches due to their high tolerance and effective reduction of relapse rate and disease activity, as well as long market experience (Table 3). These include injectable therapies, such as IFNβ-1a/-1b and glatiramer acetate.[60-65] Oral therapies such as teriflunomide, fingolimod, dimethyl fumarate or monoclonal

Table 3 – Overview of the disease-modifying therapies for POMS. The information is based on the EMA Summary of Product Characteristics (SmPC) for each medication

DMTs	EMA approved indication (SmPC)
IFN-βa*	Children > 10 years: • IFN-β-1a: IM 30 mcg, once weekly • IFN-β-1a: SC 22 mcg or 44 mcg, three times weekly • IFN-β-1b: SC 8250 mcg, every other day
Glatiramer acetate*	Children > 10 years: • SC 20 mg daily • SC 40 mg three times per week
Fingolimod	• ≤ 40 kg bodyweight: oral 0.25 mg, daily • > 40 kg bodyweight: oral 0.5 mg, daily
Teriflunomide	• ≤ 40 kg bodyweight: oral 7 mg, daily • > 40 kg bodyweight: oral 14 mg, daily
Azathioprine*	Oral 2 - 3 mg/kg daily
Cyclophosphamide*	600 to 1.000 mg/m^2 per dose - Induction regimen of 5 doses provided over 8 days followed by monthly pulse treatments or single induction course of 5 doses over 8 days or monthly without induction
Dimethyl fumarate	Oral 120 mg BID for 7 days, then 240 mg BID
Rituximab*	IV 750 mg/m^2 (500 – 1.000 mg) every 6 months, induction with 2 doses separated by 2 weeks
Natalizumab*	IV 300 mg, every 4 weeks

*: off-label use
BID: bidaily; EMA: European Medicines Agency; IFN: interferon; IM: intramuscular; IV: intravenous; POMS: pediatric onset multiple sclerosis; SC: subcutaneous.

antibodies have also shown promise in POMS, offering dosing convenience and a better adherence.[66-70] Of these, only fingolimod (for patients aged 10 years or older), teriflunomide (for patients aged 10 - 17 years) and dimethyl fumarate (for patients aged 13 - 17 years) have formal approval from the European Medicines Agency. The use of azathioprine and cyclophosphamide in POMS is both off-label and highly exceptional, reserved only for cases of extreme clinical or radiological aggressiveness where no response to other treatments is observed, or when other drugs are contraindicated. Rituximab, although also off-label in POMS, may present a more practical option and is currently under investigation alongside ocrelizumab and ofatumumab, whose efficacy and safety are being actively studied in the pediatric MS population.[71] Natalizumab was also shown to have consistent effectiveness in reducing disease activity in pediatric patients, including children with aggressive disease onset.[72,73] To safeguard the risk-benefit of natalizumab use on pediatric patients, given the associated risk of PML, regular serologic testing for anti-JCV antibodies and MRI screening are crucial.[73-75]

Clinicians managing pediatric patients with MS face the challenging decision of whether to commence treatment with a safer, yet potentially less effective, injectable therapy and escalate if insufficient response is observed, or to initiate a more potent treatment despite its less favorable safety profile, underscoring the need for personalized treatment strategies. Close monitoring is essential to detect potential complications or treatment ineffectiveness, ensuring optimal outcomes for children with MS. Although a significant portion of the DMTs employed in this population remains off-label, ongoing clinical trials are exploring additional options, such as siponimod (NCT04926818), ofatumumab (NCT04926818) and ocrelizumab (NCT04075266, NCT05123703) and, in the short-term, ponesimod and ozanimod. Globally, these studies are expected to catalyze further research and, eventually, faster approval by regulatory bodies.

Late-onset MS

Late-onset MS (LOMS) is conventionally defined when MS manifests at ≥ 50 years, with a prevalence rate ranging from 0.6% to 12%.[76,77] Accounting for ≈5% of total MS cases, LOMS has motor involvement as the most common clinical phenotype, in contrast to early onset-MS.[78] Moreover, LOMS is associated with higher EDSS when considering the same disease duration, translating into increased disability.[79] The prevalence of progressive forms in LOMS poses challenges in terms of selecting appropriate treatments, and age is considered an essential modifier of DMTs efficacy in MS patients.[80] Despite these limitations, DMTs are often prescribed to LOMS patients, although evidence regarding their safety and efficacy is scarce.[49,81-86]

Pregnancy and breastfeeding

Managing MS during pregnancy and breastfeeding poses unique challenges for women of childbearing age. The fluctuating hormonal levels during pregnancy may influence

the course of the disease, leading to symptom improvement or worsening. Nonetheless, MS does not appear to carry a significant risk for an adverse pregnancy outcome compared with women without MS.[87,88]

While all DMTs carry the potential for adverse effects on the fetus, the universal recommendation is to cease treatment prior to attempting conception. Nevertheless, this strategy heightens the risk of relapse, particularly if conception is delayed. Moreover, there are concerns regarding the potential hazards associated with discontinuing beneficial DMTs during pregnancy, especially in women with highly active disease.

Guidelines for the management and treatment of MS during pregnancy and breastfeeding (Table 4) have been delineated in a previous publication by experts from GEEM.[89] Overall, we recommend:

- A thorough analysis of the DMTs risk profile (including risks of fetal exposure pre-conception and during pregnancy), and factors associated with a high risk of postpartum activity (severity of the disease in previous years, number of relapses, accumulated disability, or lesion burden) should be performed.
- Disease activity should be determined through regular clinical assessment, at least every three months.
- Routine MRI monitoring for lesion burden should be avoided during pregnancy, thus being reserved only if essential for therapeutic decision-making and gadolinium should not be administered.
- Glatiramer acetate and IFNβ are currently accepted as safe therapies during pregnancy.
- Natalizumab treatment should be continued until 34 weeks of gestation for women, expanding interval

Table 4 – Guidance for use of approved DMTs for MS during pregnancy and breastfeeding[97]

DMTs	Preconception washout	During pregnancy	During breastfeeding
IFNβ	Not necessary	Acceptable	Acceptable (evaluate risk-benefit)
Glatiramer acetate	Not necessary	Acceptable	Possibly acceptable (evaluate risk-benefit)
Teriflunomide	Discontinuation before conception (accelerated elimination procedure and maintain contraception until plasma levels of teriflunomide are < 0.02 mg/L)	Contraindicated*	Contraindicated
Dimethyl fumarate	Stop when pregnancy confirmed	Not recommended	Not recommended
Natalizumab	Maintain during conception	Maintain during pregnancy up to 34 weeks; resume 1-2 weeks post-partum	Acceptable
Alemtuzumab	Discontinuation before conception; maintain contraception for four months	Not recommended	Acceptable
Ofatumumab	Stop when pregnancy confirmed (time monthly injection with menses to decrease chance of exposure in pregnancy)	Not recommended	Acceptable
Ocrelizumab	Discontinuation before conception; maintain contraception for two months	Not recommended	Acceptable
Rituximab	Discontinuation before conception; maintain contraception for two months	Not recommended	Acceptable
Ublituximab	Discontinuation before conception; maintain contraception for four months	Not recommended	Acceptable
Cladribine	Discontinuation before conception; maintain contraception for six months	Not recommended	Contraindicated
Fingolimod	Discontinuation before conception; maintain contraception for two months	Not recommended	Not recommended
Ozanimod	Discontinuation before conception; maintain contraception for three months	Not recommended	Contraindicated
Siponimod	Discontinuation before conception; maintain contraception for 10 days	Not recommended	Contraindicated
Ponesimod	Discontinuation before conception; maintain contraception for one week	Not recommended	Contraindicated

*: due to possible teratogenicity.
DMTs: disease-modifying therapy; IFN: interferon; MS: multiple sclerosis.

dosing to six weeks, and to resume the treatment one to two weeks postpartum.[90-92]

- Fingolimod, siponimod, ozanimod, ponesimod, teriflunomide, cladribine, ocrelizumab, ofatumumab, ublituximab, and alemtuzumab should not be used during pregnancy, and should be discontinued before conception, with washout periods adapted according to their respective half-lives.
- Regarding S1P receptor modulator discontinuation, due to the risk of disease reactivation and rebound, a switch to natalizumab or anti-CD20 agent is recommended before pregnancy.
- Only IFNβ, glatiramer acetate, ofatumumab and ublituximab are approved for use during breastfeeding.
- Breastfeeding should be avoided in patients on teriflunomide, S1P receptor modulators, dimethyl fumarate and cladribine. In general, monoclonal antibodies (alemtuzumab, natalizumab, rituximab, ocrelizumab, ofatumumab, ublituximab) are secreted in negligible amounts in breastmilk two-weeks postdelivery (skipping the initial secretion of colostrum), due to its large molecular weight. Therefore, all aforementioned medicines can be considered safe for use during breastfeeding.

Monitoring of treatment effectiveness and follow-up

The effectiveness of DMTs should be regularly evaluated through periodical clinical assessments as well as MRI scans to detect new or enlarging brain lesions, which are a sign of active inflammation and disease activity. For monitoring and follow-up, we recommend following the Spanish Society of Neurology guidelines[33]:

- Follow-up consultations should occur every three months following the initiation of the first DMTs. However, visit frequency should be tailored to individual patient characteristics and treatment responses.
- Regardless of the chosen DMTs (LE, ME or HE), follow-up consultations should be conducted at least every six months for patients who are clinically and radiologically stable, and every three months for unstable patients whenever feasible. If progression to SPMS is suspected, follow-up consultations should be scheduled at least every six months.
- MRI study should be performed three to six months after DMTs onset to serve as a new reference point (re-baseline) and annually thereafter.

Patient-reported outcome measures (PROM) and patient-reported experience measures (PREM) are also valuable tools to assess the impact of DMTs' on activities of daily living, to guide treatment decisions and monitor long-term treatment [e.g., Multiple Sclerosis Impact Scale (MSIS-29), Modified Fatigue Impact Scale, Multiple Sclerosis International Quality of Life questionnaire (MSQOL)].[93] Biomarkers (e.g., loss of brain or spinal cord volume on MRI or CSF-specific biomarkers as IgG and/or IgM oligoclonal bands, serum biomarkers as glial fibrillary acid protein (GFAP) and NfL levels) are also promising tools for prediction of disease progression and evaluation of treatment response.[94-96]

CONCLUSION

This document developed by Portuguese neurology experts from GEEM provides evidence and clinical practice-based recommendations intended to optimize the management of MS in Portuguese centers. With this effort, the experts aim to prompt the urgent revision of national MS treatment frameworks, reflecting the latest advancements in MS research and international guidelines, thus reducing the socioeconomical burden on the national healthcare system and improving the long-term health outcomes of MS patients.

ACKNOWLEDGMENTS

Editorial support in the form of medical writing and editing assistance for manuscript preparation was provided by Evidenze Portugal.

AUTHOR CONTRIBUTIONS

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This article was fully supported by the Portuguese Multiple Sclerosis Study Group (GEEM), without any additional external funding.

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Purpura Fulminans and *Rickettsia Conorii* Israeli Tick Typhus Infection

Púrpura Fulminante e Infeção por Tifo da Carraça Israelita *Rickettsia Conorii*

Keywords: Purpura Fulminans; Rickettsia conorii; Rickettsia Infections; Spotted Fever Group Rickettsiosis
Palavras-chave: Infecções por Rickettsia; Purpura Fulminante; Rickettsia conorii; Rickettsiose do Grupo da Febre Maculosa

Purpura fulminans (PF) is a rare, life-threatening thrombotic disorder marked by sudden cutaneous hemorrhage, skin necrosis, and disseminated intravascular coagulation.[1] It is commonly associated with severe bacterial infections, especially *Neisseria meningitidis* and *Streptococcus pneumoniae*, and can also result from rickettsial diseases.[2] Spotted fever, caused by *Rickettsia* species, is endemic in Mediterranean countries, including Portugal, and presents with fever, rash, and an inoculation eschar. If untreated, it can lead to PF, multi-organ failure, and septic shock. These conditions are due to failure of the anticoagulant protein C pathway and uncontrolled microvascular clotting.[3] Early diagnosis and treatment are essential, even though PF often has high morbidity and mortality rates up to 32.3% in hospitalized patients, despite therapy.[1,2]

We describe the case of a 67-year-old male presenting with hypertension, dyslipidemia, and obesity, with fever (40°C), abdominal pain, and myalgias lasting for eight days. He lived in an urban apartment, with no recent travel or animal contact, except for his domestic dog and cat. Physical examination revealed hypotension and non-blanching erythematous-violaceous macules lasting 24 hours, compatible with PF, and a necrotic plaque on the left thigh, consistent with a *tache noire* (Fig. 1). This raised suspicion for Mediterranean spotted fever, acute infectious PF by other infectious agent and idiopathic or acquired PF. Lab results showed thrombocytopenia, acute kidney injury and rhabdomyolysis. Empirical treatment with doxycycline, piperacillin-tazobactam, and vasopressors was started. Despite improvement from septic shock after treatment for 21 days with doxycycline, the thrombotic nature of PF, combined with vasoconstriction induced by the vasopressor therapy, caused extensive cutaneous necrosis on the lower limbs and scrotum, bullae formation and secondary bacterial infections, resulting in bilateral below-knee amputations and scrotal reconstruction. Skin biopsy confirmed the initial hypotheses, revealing thrombotic vasculopathy. Furthermore, polymerase chain reaction on the skin biopsy confirmed *Rickettsia conorii* Israeli tick typhus.

This case demonstrates a rare yet severe complication of Mediterranean spotted fever, resulting in PF and multi-organ failure due to endothelial injury, disseminated intravascular coagulation and tissue necrosis.[3] The patient's progression from nonspecific symptoms to septic shock and PF emphasizes the challenge of diagnosing rickettsial infections, particularly in non-endemic urban areas. The presence of a *tache noire* is a critical diagnostic clue in febrile patients with a rash.[4] Despite prompt treatment with doxycycline, rapid deterioration can occur once endothelial damage and coagulation are widespread. This case underscores the importance of an early diagnosis and a multidisciplinary care in managing PF's complications.[5]

AUTHOR CONTRIBUTIONS

FM, MA, PF: Study design, data acquisition and analysis, writing and critical review of the manuscript.

ITA, PV: Data acquisition, writing and critical review of the manuscript.

All authors approved the final version to be published.

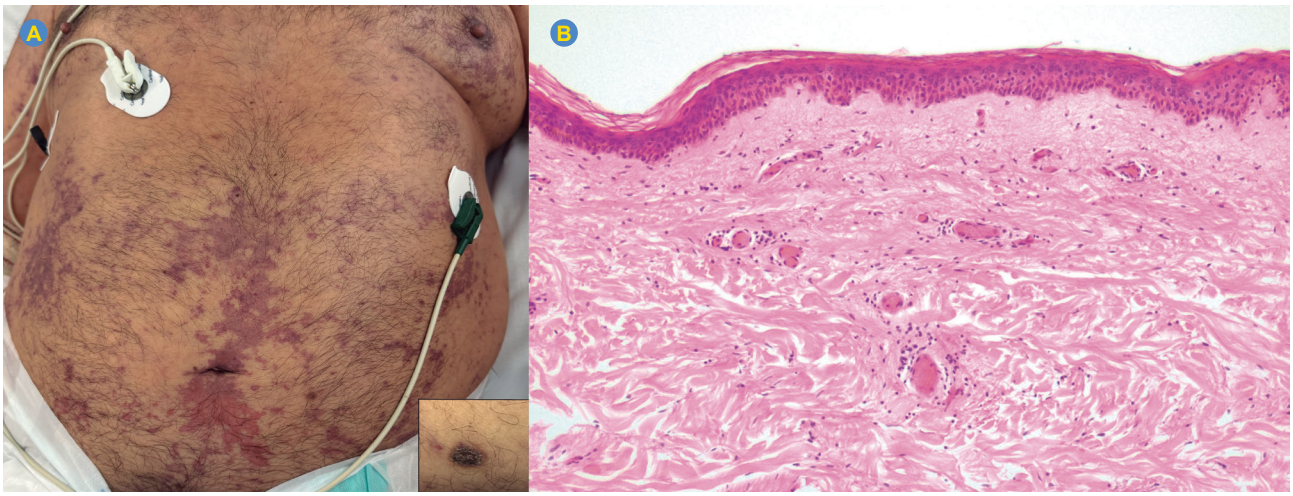

Figure 1 – Physical examination revealing non-blanching erythematous-violaceous macules and patches distributed on the abdomen and chest, and a black eschar on the medial region of the left thigh compatible with a *tache noire* (inset) (A). Intravascular hyaline thrombi in the dermis, accompanied by a sparse perivascular neutrophilic infiltrate and no epidermal changes on histopathological exam (B).

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 01/03/2025 - **Aceite/*Accepted*:** 17/04/2025 - **Publicado/*Published*:** 02/06/2025

https://doi.org/10.20344/amp.23068

Successful Management of Extensive Rhino-Orbito-Cerebral Mucormycosis: Prompt Neuroimaging-Supported Diagnosis and Aggressive Antifungal and Surgical Treatment

Abordagem Bem-Sucedida de Mucormicose Rino-Orbito-Cerebral Extensa: Diagnóstico Radiológico Célere, Terapêutica Antifúngica e Cirúrgica Agresssiva

Keywords: Mucormycosis/diagnosis; Mucormycosis/diagnostic imaging; Mucormycosis/drug therapy
Palavras-chave: Mucormicose/diagnóstico; Mucormicose/diagnóstico por imagem; Mucormicose/tratamento formacológico

Mucormycosis is a life-threatening fungal infection caused by fungi from the zygomycetes class, often affecting immunocompromised individuals. It is a rare infection in Europe, with an estimated incidence of 0.04 – 0.12 cases/100 000 people annually.[1-3] Worldwide, rhino-orbital-cerebral mucormycosis is the most common presentation and has a poor prognosis.[1,3,4] Extensive disease is associated with high mortality rates (40% - 80%). In these cases, early aggressive antifungal and surgical treatment can be lifesaving.[5] Since the confirmation of diagnosis can be delayed (involving histopathological analysis and/or culture of samples), imaging studies can be key to reach a diagnosis.

We present a case of rhino-orbital-cerebral mucormycosis in a 61-year-old woman with well-controlled diabetes, sarcoidosis treated with prednisolone 40 mg/day in the last month, and a history of breast cancer (treated, without recurrence). The patient developed a fever, cough with purulent sputum, nasal obstruction, sinus pain, hematic rhinorrhea, periocular inflammation, and a persistent headache over the previous two weeks. She was found unconscious and admitted with a Glasgow Coma Scale score of 13, total right ophthalmoplegia, periocular edema, and purulent discharge. Imaging studies revealed severe sinus and orbital involvement, as well as signs of cerebral ischemia and a pseudoaneurysm. Given her immunosuppressed state, invasive fungal infection was suspected, and she was transferred to a tertiary center for a multidisciplinary surgical approach. Corticosteroid therapy was discontinued, and within 48 hours she was promptly started on liposomal amphotericin B. She underwent three extensive surgeries, including right orbital exenteration and neurosurgical debridement.

An ethmoidal sinus biopsy was performed, followed promptly by a polymerase chain reaction assay, which tested positive for order *Mucorales*. Histological analysis confirmed the presence of *Mucor* zygomycetes, confirming the diagnosis. Unfortunately, fungal cultures from this sample were non-viable. The patient was kept on liposomal

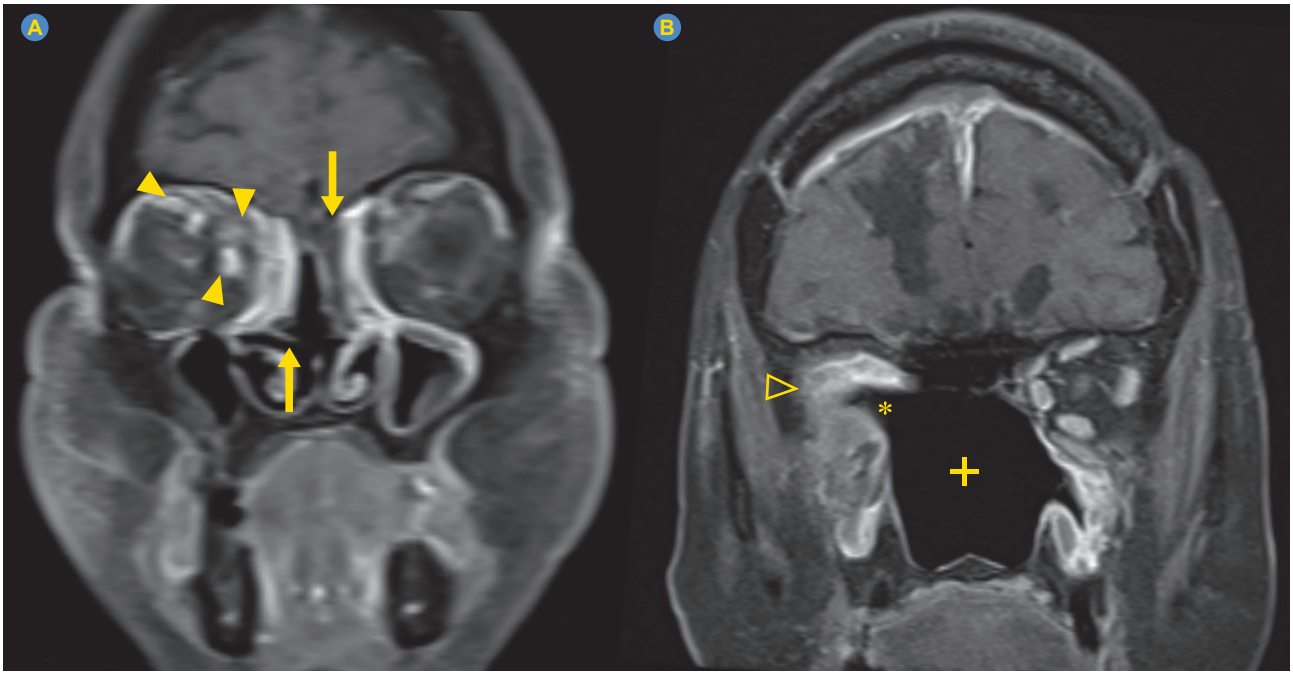

Figure 1 – Magnetic resonance imaging (MRI) at diagnosis, coronal post-contrast T1 Dixon Water-Only (A). Extensive inflammatory/infectious filling of the ethmoidal air cells and the superior parts of the nasal cavities, and maxillary sinus mucosal thickening. Notably, there is minimal or no contrast enhancement of the nasal mucosa, as well as the middle turbinates, known as the 'black turbinate sign' (indicated by arrows), in regions of low signal on T2 STIR (not shown) which is suggestive of acute invasive fungal rhinosinusitis. Right orbital involvement is seen reflected by signal abnormalities of the intraorbital fat alongside edema (on T2 STIR, not shown), thickening and increased contrast uptake of the medial and superior rectus and superior oblique muscles (indicated by arrowheads). Additionally, there is evidence of slow flow of the superior ophthalmic vein. Follow-up MRI (1 year later), coronal post-contrast T1 Dixon Water-Only (B), reveals the extent of surgical interventions: right orbital exenteration (indicated by asterisk), total and bilateral ethmoid-maxillo-sphenoidectomy, turbinate and nasal septum resection (indicated by plus sign), and bilateral resection of the gyrus rectus with bifrontal cranioplasty. Residual inflammation is noted in the right orbital compartment (indicated by open arrowhead) and fronto-basal region, but there are no signs of an active infectious process.

amphotericin 5 to 10 mg/kg for 52 days, followed by isavuconazole 200 mg. She was discharged on oral isavuconazole, maintained for two years and stopped due to sustained imagiological and clinical improvement. The patient has adapted well to the sequelae of her extensive surgery. She has preserved eyesight in her remaining eye and performs her daily activities autonomously with good support from her family.

This case emphasizes the importance of rapid recognition of mucormycosis from clinical and imagological findings and prompt surgical and medical treatment. Imaging plays a crucial role in evaluating disease extent, particularly with rhino-orbital-cerebral involvement, and follow-up evaluation during treatment.[5] Aggressive management, including antifungal therapy, surgical debridement, and control of underlying conditions, can lead to favorable outcomes, even in the presence of extensive disease.[4,5]

ACKNOWLEDGEMENTS

The authors would like to thank Francisco Almeida, Lurdes Santos, and Carina Reis, from the Infectious Diseases Department and Neuroradiology Department of Unidade Local de Saúde São João.

AUTHOR CONTRIBUTIONS

ECS: Study design, writing and critical review of the manuscript.
ACM: Writing and critical review of the manuscript.
SC: Image collection, 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

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 01/02/2025 - **Aceite/*Accepted*:** 24/04/2025 - **Publicado/*Published*:** 02/06/2025

https://doi.org/10.20344/amp.22967

Nonfatal *Strongyloides Stercoralis* Hyperinfection Secondary to Pemphigus Vulgaris Immunosuppressant Treatment: Case Report and Brief Literature Review

Hiper-infeção Não-Fatal por *Strongyloides Stercoralis* Secundária a Tratamento Imunossupressor para Pênfigo Vulgar: Relato de Caso e Breve Revisão da Literatura

Keywords: Immunosuppressive Agents/adverse effects; Pemphigus/drug therapy; Strongyloides stercoralis; Strongyloidiasis/chemically induced; Strongyloidiasis/diagnosis; Strongyloidiasis/drug therapy; Superinfection
Palavras-chave: Estrongiloidíase/diagnóstico; Estrongiloidíase/induzida quimicamente; Estrongiloidíase/tratamento farmacológico; Imunossupressores/efeitos adversos; Pênfigo/tratamento farmacológico; Strongyloides stercoralis; Superinfecção

A 36-year-old Afro-Brazilian man presented with widespread flat cutaneous blisters and erosions as well as oral and genital erosions for four months. His medical history was unremarkable. A skin biopsy revealed an intraepidermal blister, direct immunofluorescence showed intercellular IgG and complement deposits, and a Tzanck smear demonstrated round epithelial cells suggestive of acantholytic pemphigus cells, confirming the diagnosis of pemphigus vulgaris. Intermittent eosinophilia was noted. The patient was started on prednisolone 1 mg/kg, followed by mofetil mycophenolate (1500 mg/day) as a steroid-sparing agent. However, his condition worsened, requiring intravenous immunoglobulin cycles (2 mg/kg divided into four doses), which proved ineffective. The patient was then treated with rituximab. Following the second infusion, an intense flare of pemphigus blisters occurred. Salvage therapy with intravenous methylprednisolone pulses led to initial improvement, but intense recurrence of blisters and mucosal erosions occurred three weeks later. Another methylprednisolone cycle was administered and, after its end, the patient developed intestinal obstruction, with abdominal distention, nausea, vomiting, fever, tachycardia, hypotension, and an altered mental status. Upper endoscopy revealed mucosal erosions in the esophagus, stomach, and duodenum. The mucosal biopsies revealed numerous *Strongyloides stercoralis* forms (Fig. 1). Successive blood cultures isolated *Escherichia coli*, *Enterococcus faecium* and *Pseudomonas aeruginosa.* These findings led to the diagnosis of *S. stercoralis* hyperinfection with secondary sepsis. The patient was treated with albendazole (400 mg twice a day for seven days), ivermectin (200 µg/kg) and intravenous broad-spectrum antibiotics. Despite the high mortality rate associated with *S. stercoralis* hyperinfection, the patient survived without active pemphigus lesions but with severe wasting.

Strongyloides stercoralis is an intestinal nematode predominantly acquired in tropical and subtropical regions, with an estimated global prevalence of 100 million individuals. The diagnosis of *Strongyloides* infection can be established through serial stool examinations or with serologic tests.[1] Chronic infection is frequently asymptomatic in immunocompetent individuals, although up to 75% of patients have peripheral eosinophilia or elevated total IgE levels.[1] Hyperinfection syndrome implies the presence of signs and symptoms attributable to increased larval migration. If untreated, the mortality rate is high (75%).[2] Ivermectin is the drug of

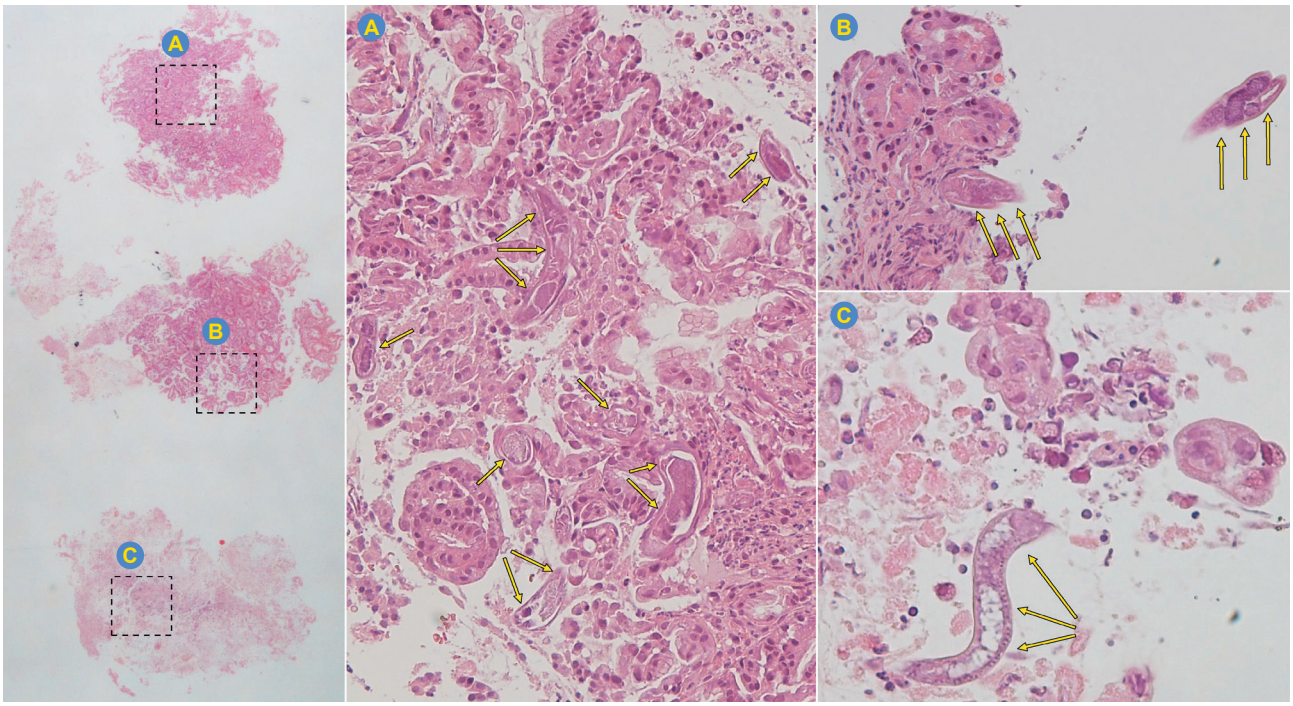

Figure 1 – Fibrin, granulocytic exudate and two fragments of pyloric gastric mucosa with marked activity; in (A) and (B) are identified numerous parasite ova, larvae and adult worms (arrows) surrounding the foveolar and glandular epithelium, with intense granulocytic and histiocytic infiltration; in (C) is observed, in more detail, the structure of the Strongyloides stercoralis (arrows).

choice for hyperinfection syndrome.[1] This case reminds us that immigrants from endemic areas may have chronic asymptomatic intestinal colonization with *S. stercoralis*, which may progress to hyperinfection and dissemination under immunosuppression therapy.[3] Patients with conditions that require long-term immunosuppressive treatment or chemotherapy are at increased risk of this serious complication.[4,5] Examination of a stool sample from all patients, particularly from endemic areas, on long-term immunosuppressive therapy should be mandatory to prevent the occurrence of *S. stercoralis* hyperinfection and avoid morbidity and mortality associated with it.[1,5] Given the low sensitivity of parasitological examination of stool samples, therapy with ivermectin should always be considered in individuals from endemic areas.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to Miguel Reis for his valuable contribution to this work, particularly in writing and revising the manuscript. His contributions, characterised by his unwavering commitment, perpetual accessibility, and exacting recommendations, proved instrumental in the project's evolution and enhancement.

AUTHOR CONTRIBUTIONS

ITA: Study design, data collection, writing of the manuscript.

PV: Study design, data collection, critical review of the manuscript.

MDR, PF: Critical review of the manuscript.

LSA: Data collection, critical review of the manuscript.

All authors approved the final version to be published.

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The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 30/01/2025 - **Aceite/*Accepted*:** 29/04/2025 - **Publicado/*Published*:** 02/06/2025

https://doi.org/10.20344/amp.22948

Correction to the Article "PRIMARY-HF: Heart Failure Screening in Primary Care using Point-of-Care".

Errata ao Artigo "PRIMARY-HF: Diagnóstico de Insuficiência Cardíaca em Cuidados de Saúde Primários com Point-of-Care".

On page 243, in the '**COMPETING INTERESTS**' section, the sentence "JS received financial payments from Roche for advising." should be disregarded.

On the same page, in the '**FUNDING SOURCES**' section, where it reads:
Roche provided NT-proBNP test kits. There was no direct financial support.

It should read:
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Article published with errors:
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Na página 243, na secção '***COMPETING INTERESTS***', a frase "*JS received financial payments from Roche for advising.*" deverá ser ignorada.

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Artigo publicado com erros:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22463

https://doi.org/10.20344/amp.23337

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