AMP

ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

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

11 | 24

Número 11
Série II
Lisboa

Volume 37
Novembro 2024
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.

AMP37(11) - Novembro de 2024

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

Aumento de Infeções Sexualmente Transmissíveis: Uma Nova Realidade Inegável em Portugal

Increase In Sexually Transmitted Infections: A New Undeniable Reality in Portugal

Catarina CÔRTE-REAL✉[1], Manuel CASTRO PEREIRA[2], Mariana FLEMING TORRINHA[3], Maria MANUEL PINHO[1], Bernardo MATEIRO GOMES[4], Rita MACIEL BARBOSA[5]
Acta Med Port 2024 Nov;37(11):751-753 ▪ https://doi.org/10.20344/amp.21480

Palavras-chave: Doenças Sexualmente Transmissíveis/epidemiologia; Portugal
Keywords: Portugal; Sexually Transmitted Diseases/epidemiology

As infeções sexualmente transmissíveis (IST) constituem uma preocupação mundial no âmbito da saúde pública pelas repercussões diretas na saúde sexual e reprodutiva, pelo estigma associado, pelo risco de infertilidade, de cancro e de dor crónica, tendo impacto na morbimortalidade de uma população maioritariamente jovem, mas não só.

Segundo os dados do Centro Europeu de Prevenção e Controlo das Doenças relativos a 2022, houve um aumento expressivo, face ao ano anterior, das principais IST (48% nos casos de gonorreia, 34% para sífilis e 16% para clamídia). Dentro destas, a clamídia manteve-se como a infeção mais reportada. Portugal foi dos países com o maior aumento na taxa de incidência homóloga de notificação desta doença nos dois últimos anos analisados, com um aumento de 8,9 para 14,5 por 100 000 habitantes. Em 2022, 89,3% dos 28 países da União Europeia/Espaço Económico Europeu (UE/EEE) com dados reportados registaram aumentos na notificação de casos de gonorreia. Portugal registou uma subida de 80% face ao ano anterior, tendo uma taxa de incidência nacional superior à média da UE/EEE (21,8 *vs* 17,9 por 100 000 habitantes). Relativamente à sífilis, o número de casos aumentou mais de 25% em 14 países. Portugal descreveu um aumento importante em 2022 (14,8 *vs* 11,1 casos em 2021), um valor superior à taxa de notificação média dos países europeus (8,5 por 100 000 habitantes).[1]

A maioria das notificações foram em pessoas do sexo masculino. No caso da clamídia, a infeção verificou-se principalmente em relações sexuais heterossexuais, ao contrário da gonorreia e sífilis, em que se verificou uma maior incidência em pessoas homossexuais do sexo masculino (HSH).[1]

Na Europa, metade dos casos reportados de clamídia, gonorreia e sífilis, foram entre adolescentes e jovens adultos (15 - 24 anos).[2]

Estes números, conjuntamente com a perceção de aumento de casos por parte dos profissionais de saúde no terreno, devem-nos levar a questionar as estratégias de intervenção nesta área, com consequente necessidade de reformular medidas de prevenção a vários níveis.

É imperativo assegurar uma acessibilidade universal a cuidados de saúde sexual, promovendo a criação de uma infraestrutura abrangente para um aconselhamento eficaz na prevenção de comportamentos de risco. É essencial garantir a divulgação em larga escala de informação sobre as IST, alertando para o seu modo de transmissão, métodos de prevenção e sobre a importância do tratamento completo para evitar reinfeções.[3]

Sendo os cuidados de saúde primários o ponto de contacto inicial no sistema de saúde, é necessário proporcionar aconselhamento meticuloso aos utentes, particularmente na faixa etária mais suscetível às IST, como é o caso dos adolescentes e jovens adultos, devido a fatores comportamentais, biológicos e socioculturais.[3] Importa transmitir que uma das medidas mais eficazes de prevenção das IST é a prática de relações sexuais seguras, através da utilização correta de métodos de barreira. Deve promover-se uma comunicação aberta e livre de preconceitos com os utentes, para que o aconselhamento seja eficaz e ajustado às práticas sexuais de cada utente.[3]

No entanto, esta é uma abordagem complexa, dificultada pela intervenção comportamental e pelo estigma associado a estas patologias, o que constitui uma barreira na cascata de intervenção sobre as IST.[4]

Uma outra forma de prevenção que pode ser vantajosa é a vacinação contra estas infeções. O comité de vacinação e imunização do Reino Unido considera a vacinação contra o serogrupo B de *Neisseria meningitidis* uma medida

1. Unidade de Saúde Familiar São Martinho. Unidade Local de Saúde Tâmega e Sousa. Penafiel. Portugal.
2. Unidade de Saúde Familiar Navegantes. Unidade Local de Saúde Póvoa de Varzim/Vila do Conde. Vila do Conde. Portugal.
3. Unidade de Saúde Familiar Eça de Queirós. Unidade Local de Saúde Póvoa de Varzim/Vila do Conde. Póvoa de Varzim. Portugal.
4. Unidade Local de Saúde Entre Douro e Vouga. Santa Maria da Feira. Portugal.
5. Centro Integrado de Saúde Sexual (CISS). Unidade Local de Saúde Santo António. Porto. Portugal.
✉ **Autor correspondente:** Catarina Côrte-Real. catarinabcr@gmail.com
Recebido/*Received*: 08/03/2024 - **Aceite/*Accepted*:** 03/06/2024 - **Publicado *Online*/*Published Online*:** 14/08/2024 - **Publicado/*Published*:** 04/11/2024

custo-efetiva no controlo da infeção por gonorreia nos doentes de alto risco.[5] Do mesmo modo, está em investigação uma vacina que permita a prevenção da infeção por clamídia.[6]

Além da prevenção primária, é fundamental implementar estratégias de prevenção secundária e assegurar a disponibilidade universal de testes rápidos, acessíveis, sensíveis e específicos, de fácil utilização e com pontos de entrega convenientes.[7]

É necessário expandir os locais de testagem, favorecendo um rastreio oportunista, num contexto de proximidade e ajustado às necessidades dos grupos prioritários, nomeadamente através da possibilidade de realização de testes em farmácias, escolas, organizações de base comunitária ou através de recolha pelo doente.[3]

A adoção deste tipo de programas de rastreio numa base mais oportunista, por exemplo em Inglaterra, mostrou um impacto positivo, tendo tido a capacidade de alargar a cobertura populacional com a realização de cerca de 59% dos diagnósticos em jovens dos 15 aos 24 anos fora de serviços de saúde.[3]

Urge ainda desenvolver modelos de financiamento para minimização dos custos dos testes. De facto, os testes mais recentes de deteção das três principais infeções bacterianas ainda não estão disponibilizados em larga escala a nível mundial e têm um elevado custo, limitando o seu acesso.[7]

Em Portugal já foram introduzidas na tabela do setor convencionado as análises clínicas para pesquisa de clamídia e gonorreia.[8]

Contudo, em relação à testagem, importa referir que, apesar de carecer de melhor e maior investimento, esta tem sido mais frequente. Em Portugal, por exemplo, os utentes fazem rastreio trimestral das principais IST na consulta de profilaxia pré-exposição (PrEP), com diagnósticos de infeções por vezes ainda assintomáticas, motivando um aumento da sua notificação. A PrEP, considerada uma medida eficaz na diminuição da transmissão do VIH, tem, no entanto, sido sugerida como fator de aumento de comportamentos sexuais de risco e aumento de transmissão de IST. O consequente incremento do consumo de antibióticos contribui para o flagelo da resistência antimicrobiana, como se tem verificado no caso da *N. gonorrhoeae.* Uma possível estratégia contra esta situação, além da vacinação, é a utilização de novos antibióticos, atualmente em fase de ensaio.[7]

Recentemente foi divulgada uma nova forma de prevenção, a *doxyPEP*, que consiste na toma de doxiciclina após exposição ao risco. Esta medida demonstrou reduzir o risco de gonorreia, clamídia e sífilis em HSH e mulheres transgénero com história de IST no ano anterior, estando atualmente em aplicação nos Estados Unidos da América.[9] No entanto, esta abordagem merece uma reflexão crítica, não existindo ainda estudos sobre a sua efetividade a longo prazo, pelo que se deve analisar os seus efeitos comparativamente à intervenção comportamental.

É de salientar a importância da notificação de parceiros enquanto estratégia chave efetiva na abordagem às IST no âmbito da saúde pública. Esta garante a identificação, informação, notificação, testagem e/ou tratamento dos parceiros sexuais de risco, de forma a controlar a cadeia de transmissão.[10]

Por último, é importante incentivar relatórios nacionais abrangentes, que retratem a situação epidemiológica das IST, orientando a conceção e execução de programas de ação que sustentem uma abordagem holística e ambiciosa. É necessária uma intervenção integrada entre os diferentes níveis de atuação, de forma a ultrapassar barreiras individuais, estruturais, sociais e políticas quanto às IST. O plano nacional sueco contra a clamídia é um bom exemplo de uma abordagem estruturada, com uma resposta efetiva na diminuição dos casos desta infeção.

Em conclusão, destaca-se a incidência crescente de IST, sendo imperativo promover um acesso universal e gratuito a cuidados de saúde sexual, numa base oportunista e comunitária, segura e livre de estigma.

CONTRIBUTO DOS AUTORES

MCP, CCR: Concetualização, organização, aquisição e análise de dados, redação, revisão e aprovação da versão final do manuscrito.

MMP, MT, RMB: Aquisição e análise de dados, redação, revisão e aprovação da versão final do manuscrito.

BMG: Concetualização, aquisição e análise de dados, redação, revisão e aprovação final do manuscrito.

CONFLITOS DE INTERESSE

Os autores declaram 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.

REFERÊNCIAS

1. European Centre for Disease Prevention and Control. Annual epidemiological reports for 2022. [consultado 2024 mar 08]. Disponível em: https://www.ecdc.europa.eu/en/news-events/sti-cases-rise-across-europe.
2. Centers for Disease Control and Prevention. National Overview of STIs, 2022. Disparities in STIs. [consultado 2024 abr 06]. Disponível em: https://www.cdc.gov/std/statistics/2022/overview.htm.
3. Gravata A, Castro R, Borges-Costa J. Estudo dos fatores

sociodemográficos associados à aquisição de infeções sexualmente transmissíveis em estudantes estrangeiros em intercâmbio universitário em Portugal. Acta Med Port. 2016;29:360-6.
4. Lee AS, Cody SL. The stigma of sexually transmitted infections. Nurs Clin North Am. 2020;55:295-305.
5. GOV.UK. JCVI advice on the use of meningococcal B vaccination for the prevention of gonorrhoea, Independent Report. 2023. [consultado 2024 maio 07]. Disponível em: https://www.gov.uk/government/publications/meningococcal-b-vaccination-for-the-prevention-of-gonorrhoea-jcvi-advice-10-november/jcvi-advice-on-the-use-of-meningococcal-b-vaccination-for-the-prevention-of-gonorrhoea#jcvi-advice.
6. Gökengin D, Noori T, Alemany A, Bienkowski C, Liegon G, İnkaya AÇ, et al. Prevention strategies for sexually transmitted infections, HIV, and viral hepatitis in Europe. Lancet Reg Health Eur. 2023;34:100738.
7. Unemo M, Bradshaw CS, Hocking JS, de Vries HJ, Francis SC, Mabey D, et al. Sexually transmitted infections: challenges ahead. Lancet Infect Dis. 2017;17:e235-79.
8. Administração Central do Sistema de Saúde. Circular Normativa n.º 10/2024 - Introdução de novos MCDT na tabela do setor convencionado na área de Análises Clínicas – PReP Oral. 2024. [consultado 2024 maio 10]. Disponível em: https://www.acss.min-saude.pt/wp-content/uploads/2016/11/Circular_Normativa_10_2024.pdf.
9. Cannon CA, Celum CL. Doxycycline postexposure prophylaxis for prevention of sexually transmitted infections. Top Antivir Med. 2023;31:566-75.
10. Wayal S, Estcourt CS, Mercer CH, Saunders J, Low N, McKinnon T, et al. Optimising partner notification outcomes for bacterial sexually transmitted infections: a deliberative process and consensus, United Kingdom, 2019. Euro Surveill. 2022;27:2001895.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

European Alpha-1 Research Collaboration (EARCO) in Portugal: The Future Is Happening

European Alpha-1 Research Collaboration (EARCO) em Portugal: O Futuro Está a Acontecer

Maria SUCENA✉[1], Raquel MARÇÔA[2], Catarina GUIMARÃES[3]
Acta Med Port 2024 Nov;37(11):754-756 ▪ https://doi.org/10.20344/amp.20953

Keywords: alpha 1-Antitrypsin Deficiency; Portugal; Registries
Palavras-chave: Deficiência de alfa 1-Antitripsina; Portugal; Sistema de Registos

Alpha-1 antitrypsin deficiency (AATD), usually categorized as a rare disease,[1] is a common but under-recognized genetic condition that affects approximately one in 2000 - 5000 individuals of European descent and predisposes them to early-onset emphysema and liver disease. Understanding the clinical characteristics and the natural history of a rare disease may be challenging due to the lack of large cohorts.

Human alpha-1 antitrypsin (AAT) is codified by the *SERPINA1* gene, and the most prevalent deficiency alleles are Pi*S and Pi*Z. It is believed that the Pi*Z mutation has a relatively recent origin in northern Europe, having originated about 2000 years ago, and it has been proposed that the S variant emerged in the Iberian Peninsula about 10 000 – 15 000 years ago.[2]

Portugal has the highest estimated PI*SZ prevalence rate in the world (1:205),[2] with also a high PI*ZZ prevalence rate (1:2191).[1] Multiple rare alleles have been identified in Portugal, but their frequencies in the general population are still unknown.[3] The real burden of the disease is also unknown because there are very few studies on the epidemiology of AATD in Portugal[3,4] and a national registry does not exist.

To address the problem of the lack of prospective, standardized follow-up data, both healthcare professionals and patients have agreed to set up an international registry of patients with AATD. As an initiative of the Clinical Research Collaboration (CRC) of the European Respiratory Society (ERS), the European Alpha-1 antitrypsin Deficiency Research Collaboration (EARCO) international registry was created, with the objective of characterizing the different genotypes of AATD and investigating their natural history and the impact of different treatments, including augmentation therapy.[5,6] The core project of EARCO is the international AATD Registry, a collaboration which will offer longitudinal real-world data for patients with AATD. One of the key tasks of EARCO will be harmonizing the data collection and assessing the quality of the data included prospectively.[6] Although the EARCO registry was created as a European initiative, it has extended beyond European boundaries to become a global registry.

The EARCO international registry was launched in February 2020 and by May 2023 there were 80 recruiting centers in 24 countries. In the first publication describing the characteristics of the individuals included in the EARCO registry a total of 1044 individuals were analyzed. The most frequent genotype was PI*ZZ (60.2%), followed by PI*SZ (29.2%), PI*SS (3.9%) and rare variants (6.6%). Among PI*ZZ patients, emphysema was the most frequent lung disease (57.2%) followed by chronic obstructive pulmonary disease (COPD) (57.2%) and bronchiectasis (22%).[7]

Besides all the international initiatives, Portugal was still trailing some steps behind. In 2015 a Portuguese alpha-1 study group was created, as an initiative of the Portuguese Society of Pulmonology (Sociedade Portuguesa de Pneumologia - SPP), composed by dedicated AATD pulmonology specialists and fellows, who contributed to raising awareness of this disease in Portugal and were responsible for the publication and dissemination of the Portuguese consensus document for the management of AATD.[8] This alpha-1 study group also started planning a Portuguese AATD registry and, in 2018, all the legal aspects were solved and the database was prepared and ready for the registration of Portuguese patients. However, in 2018 the EARCO project was already approved and ongoing. Portuguese pulmonologists realized that moving forward on their own would compromise the ability to address and answer the questions associated with a rare disease and that being part of an international AATD registry, aimed at obtaining quality prospective information on the natural history of the

1. Pulmonology Department. Hospital de Santo António. Unidade Local de Saúde de Santo António. Porto. Portugal.
2. Pulmonology Department. Hospital Eduardo Santos Silva. Unidade Local de Saúde Gaia e Espinho. Vila Nova de Gaia. Portugal.
3. Pulmonology Department. Hospital da Senhora da Oliveira. Unidade Local de Saúde Alto Ave. Guimarães. Portugal.
✉ **Autor correspondente:** Maria Sucena. maria.sucena@hotmail.com
Recebido/*Received*: 15/11/2023 - **Aceite/*Accepted*:** 17/01/2024 - **Publicado/*Published*:** 04/11/2024

disease, would be much more profitable.

In October 2020 Portugal joined the EARCO International Registry and, since then, the Portuguese AATD registry consists of the Portuguese investigators, centers and participants included in the EARCO registry. The Portuguese registry has one national coordinator nominated by the SPP, and a steering committee formed by clinicians and researchers with expertise in the disease.

At the end of July 2023, the Portuguese AATD registry included 170 individuals with AATD from 12 centers distributed throughout the country [78 patients with the first follow-up (FU) visit completed and 22 with the second FU]. The distribution of genotypes was PI*ZZ in 65 patients (38%), PI*SZ in 53 patients (31%), PI*SS in 17 patients (10%) and rare or null variants in 35 patients (21%). Compared to EARCO data (7), Portugal seems to have a different distribution of AATD genotypes especially a higher percentage of Pi*SS (10% *vs* 3.9%) and rare variants (21% *vs* 6.6%). We need a higher number of patients included in the Portuguese AATD registry to confirm the possibility of a unique AATD population in Portugal.

The implementation of the EARCO in Portugal was presented in a previous editorial.[9] At that time, the EARCO registry and the Portuguese AATD registry were still preliminary projects without registered patients. But now they are both reality – the long awaited future was happening.

It was the persistence, hard work, enthusiasm, motivation, and resilience of some Portuguese clinicians and researchers dedicated to AATD and the support of our international colleagues that allowed us to overcome all the obstacles and bureaucracy and allowed the development of the Portuguese AATD registry. We did it – we finally have our own AATD registry. The Portuguese AATD registry will be an excellent opportunity to investigate the genetics, epidemiology, natural history, impact of different therapies, and prognosis of Portuguese AATD patients and identify their possible unique characteristics.

In addition to the development of the registry, there are other objectives of EARCO. All the EARCO information and projects can be consulted on the website www.earco.org.

Some EARCO projects have been finished and published with the participation of Portuguese clinicians. One of these projects, about the identification of the research priorities in AATD, concluded that the main research and management priorities identified by healthcare professionals and patients included understanding the natural history of AATD, improving information for physicians, access to specialized reference centers, personalizing the treatment, and having equal opportunities for access to existing therapies.[10] Another project analyzed the opinions and attitudes of pulmonologists about augmentation therapy and concluded that there is high variability in the criteria for augmentation prescribing among European experts that take into consideration several variables not included in the current recommendations described in the guidelines.[11]

Portugal is contributing to the different work packages of EARCO with some Portuguese projects that have been approved and are ongoing, such as 1) the impact of augmentation in patients with AATD with PI*SZ or with null or rare genotypes; 2) AATD associated with the Mmalton variant – characterization and prognosis; and 3) alpha-1 antitrypsin related disease risk for the PI*SS genotype.

The EARCO is working and has been supported by an enthusiastic community of researchers, clinical investigators, patients' representatives, and industry. It has attracted the attention of many young investigators, some of them Portuguese. This is an exciting, worthwhile project that is already generating new knowledge and will likely have a direct impact on patients' quality of life and clinical care,[5] including Portuguese patients. You are invited to be part of it.

ACKNOWLEDGEMENTS

The authors would like to thank the Portuguese EARCO study investigators.

List of Portuguese EARCO registry investigators: António Lopes, Bebiana Conde, Cristina Santos, Eunice Magalhães, Filipa Costa, Gabriela Santos, Isabel Ruivo dos Santos, Joana Amado, Joana Gomes, Rita Boaventura, Sónia Guerra, Teresa Martin.

AUTHOR CONTRIBUTIONS

MS: Conception, writing and critical review of the manuscript.

RM, CG: Conception and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

MS received payment or honoraria from Bial, CSL Behring, Grifols and Astra Zeneca for lectures, presentations, speakers' bureaus, manuscript writing or educational events; participated on a Data Safety Monitoring Board or

Advisory Board for Bial and CSL Behring.

CG received payment or honoraria from CSL Behring for lectures, presentations, speakers' bureaus, manuscript writing or educational events.

RM has 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.

REFERENCES

1. Cortes-Lopez R, Barjaktarevic I. Alpha-1 antitrypsin deficiency: a rare disease? Curr Allergy Asthma Rep. 2020;20:51.
2. Blanco IB, Diego I, Pérez -hS, Lara B, Maldonado F, Esquinas C, et al. Alpha-1 antitrypsin Pi*SZ genotype: estimated prevalence and number of SZ subjects worldwide. Int J Chron Obstruct Pulmon Dis. 2017;12:1683-94.
3. Meira L, Boaventura R, Seixas S, Sucena M. Alpha-1 antitrypsin deficiency detection in a Portuguese population. COPD. 2018;15:4-9.
4. Spínola C, Bruges-Armas J, Pereira C, Brehm A, Spínola H. Alpha-1-antitrypsin deficiency in Madeira (Portugal): the highest prevalence in the world. Respir Med. 2009;103:1498-502.
5. Miravitlles M, Chorostowska-Wynimko J, Ferrarotti I, McElvaney NG, O'Hara K, Stolk J, et al. The European Alpha-1 Research Collaboration (EARCO): a new ERS clinical research collaboration to promote research in alpha-1 antitrypsin deficiency. Eur Respir J. 2019;53:1900138.
6. Greulich T, Altraja A, Barrecheguren M, Bals R, Chlumsky J, Chorostowska-Wynimko J, et al. Protocol for the EARCO registry: a pan-European observational study in patients with α1-antitrypsin deficiency. ERJ Open Res. 2020;6:00181-2019.
7. Miravitlles M, Turner AM, Torres-Duran M, Tanash H, Rodríguez-García C, López-Campos JL, et al. Clinical and functional characteristics of individuals with alpha-1 antitrypsin deficiency: EARCO international registry. Respir Res. 2022;23:352.
8. Lopes AP, Mineiro MA, Costa F, Gomes J, Santos C, Antunes C, et al. Portuguese consensus document for the management of alpha-1-antitrypsin deficiency. Pulmonology. 2018;24:s1-21.
9. Sucena M, Gomes J, Guimarães C, Miravitlles M. Implementation of European Alpha-1 Research Collaboration (EARCO) in Portugal: the future starts now. Pulmonology. 2020;26:181-3.
10. Barrecheguren M, O'Hara K, Wilkens M, Boyd J, Kolda E, Lara B, et al. Research priorities in α1- antitrypsin deficiency: results of a patients' and healthcare providers' international survey from the EARCO Clinical Research Collaboration. ERJ Open Res 2020;6:00523-2020.
11. Greulich T, Albert A, Cassel W, Boeselt T, Peychev E, Klemmer A, et al. Opinions and attitudes of pulmonologists about augmentation therapy in patients with alpha-1 antitrypsin deficiency. a survey of the EARCO group. Int J Chron Obstruct Pulmon Dis. 2022;17:53-64.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Motivating Medical Students: Adaptation of the Academic Motivation Scale within the Framework of the Self-Determination Theory

Motivando Estudantes de Medicina: Adaptação da Escala de Motivação Académica no Âmbito da Teoria da Autodeterminação

Rita MATOS SOUSA✉[1], Nuno Gabriel SILVA GONÇALVES[1], Vítor Hugo PEREIRA[1], John NORCINI[1]
Acta Med Port 2024 Nov;37(11):757-766 ▪ https://doi.org/10.20344/amp.21926

ABSTRACT

Introduction: Motivation plays a crucial role in the academic success and professional development of medical students. Understanding the intricacies of motivation within the context of medical education is essential for designing effective interventions and support systems. The aim of this study was to explore the adaptation of the Academic Motivation Scale within the framework of the self-determination theory and of the self-efficacy theory to assess motivation among medical students.

Methods: The study adapted the Academic Motivation Scale to the Portuguese context, drawing upon insights from the self-determination theory. Two existing Portuguese scales, MATAMS and Ribeiro *et al*'s scale, served as foundational frameworks for the adaptation process. The study included qualitative interviews, which informed the creation of the Minho Medical Academic Motivation Scale – Minho-MEDAMS. This scale was applied to 281 medical students. To assess the scale's validity, we used the exploratory and confirmatory factor analyses, and the Cronbach's alpha to measure internal consistency.

Results: The exploratory factor analysis showed strong results with a KMO of 0.862, leading to five factors and the removal of two items. The initial confirmatory factor analysis indicated poor fit, prompting the removal of items with low R-squared values. The final Minho-MEDAMS includes 18 items: six for intrinsic motivation, nine for extrinsic motivation and three for amotivation. This refined scale demonstrates high internal consistency (α = 0.831), making it a reliable tool for assessing medical students' motivation.

Conclusion: The successful adaptation of the Academic Motivation Scale within the self-determination theory framework presents a valuable instrument for assessing motivation in medical students. The Minho-MEDAMS offers a comprehensive understanding of motivational dynamics, facilitating targeted interventions and support mechanisms to enhance student engagement and success. Its validity and reliability render it a practical tool for educators, administrators, and researchers in the field of medical education. Ultimately, the Minho-MEDAMS contributes to the advancement of strategies aimed at cultivating motivated and proficient healthcare professionals.

Keywords: Models, Psychological; Motivation; Personal Autonomy; Self Concept; Students, Medical/psychology

RESUMO

Introdução: A motivação desempenha um papel crucial no sucesso académico e no desenvolvimento profissional dos estudantes de medicina. Compreender as complexidades da motivação no contexto da educação médica é essencial para a construção de intervenções eficazes e sistemas de apoio. O objetivo deste estudo foi explorar a adaptação da Escala de Motivação Académica no âmbito da teoria da autodeterminação e da teoria da autoeficácia para avaliar a motivação entre os estudantes de medicina.

Métodos: O estudo utilizou uma metodologia rigorosa para adaptar a Escala de Motivação Académica ao contexto português, recorrendo à estrutura da teoria da autodeterminação. Duas escalas portuguesas existentes, a MATAMS e a escala de Ribeiro *et al*, serviram como as bases fundamentais para o processo de adaptação. O estudo incluiu entrevistas qualitativas que contribuíram para a criação da Escala de Motivação Académica para Estudantes de Medicina da Universidade do Minho – Minho-MEDAMS. Esta escala foi aplicada a 281 estudantes de medicina. Para avaliar a validade da escala, utilizámos análises fatoriais exploratória e confirmatória, e o alfa de Cronbach para medir a consistência interna.

Resultados: A análise fatorial exploratória apresentou resultados sólidos com um KMO de 0,862, resultando em cinco fatores e na remoção de dois itens. A análise fatorial confirmatória inicial indicou um ajuste inadequado, o que levou à remoção de itens com valores baixos de R-quadrado. A versão final do Minho-MEDAMS inclui 18 itens: seis para motivação intrínseca, nove para motivação extrínseca e três para desmotivação. Esta escala refinada demonstra uma elevada consistência interna (α = 0.831), tornando-se uma ferramenta fiável para avaliar a motivação dos estudantes de medicina.

Conclusão: A adaptação bem-sucedida da Escala de Motivação Académica dentro do quadro da teoria da autodeterminação apresenta um instrumento valioso para avaliar a motivação nos estudantes de medicina. A Minho-MEDAMS oferece uma compreensão abrangente das dinâmicas motivacionais, facilitando intervenções direcionadas e mecanismos de apoio para melhorar o envolvimento e o sucesso dos estudantes. A sua validade e confiabilidade tornam-na uma ferramenta prática para educadores, administradores e investigadores no campo da educação médica. No final, a Minho-MEDAMS contribui para o avanço de estratégias destinadas a cultivar profissionais de saúde motivados e proficientes.

Palavras-chave: Auto-Conceito; Autonomia Pessoal; Estudantes de Medicina/psicologia; Modelos Psicológicos; Motivação

1. Escola de Medicina. Universidade do Minho. Braga. Portugal.
✉ **Autor correspondente:** Rita Matos Sousa. rita.msousa5@gmail.com
Recebido/*Received*: 08/06/2024 - **Aceite/*Accepted*:** 09/09/2024 - **Publicado/*Published*:** 04/11/2024

KEY MESSAGES

- Motivation is an essential factor for the academic success and professional development of medical students.
- Understanding motivation within the context of medical education is crucial for developing effective interventions and support systems.
- The Minho-MEDAMS is composed of five dimensions of motivation: intrinsic motivation, identified regulation, external regulation, introjected regulation, and amotivation.
- Psychometric analysis has demonstrated that the Minho-MEDAMS possesses high reliability and validity, confirming its suitability for assessing the motivation of medical students in the Portuguese context.
- The Minho-MEDAMS can be a valuable tool for understanding the motivational dynamics of medical students.

INTRODUCTION

Motivation serves as the driving force that instills purpose and direction into behavior, operating at both conscious and unconscious levels. The study of motivation explores the processes linking individual needs to behavior, aiming to understand the fundamental reasons behind actions. Theories of motivation organize these findings to explain the 'why' of behavior.[1-3]

One pivotal theory in the domain of motivation is the self-determination theory (SDT), that offers a perspective on human motivation and personality.[2] Within the framework of SDT, intrinsic and extrinsic sources of motivation can be defined, elucidating the roles of intrinsic motivation (IM) and various types of extrinsic motivation (EM) in cognitive and social development and individual differences. This conceptualization has led to the creation of a framework illustrating the continuum between motivation types, their regulatory styles, perceived causes, and relevant regulatory processes.[4]

Another theory indirectly contributing to the construct of motivation is the theory of self-efficacy, that underscores the importance of an individual's perception of their personal capabilities as key determinants of successful outcomes.[5,6] This is crucial in understanding the students' confidence in their ability to succeed in the highly demanding environment of medical education. By integrating aspects of self-efficacy with the SDT, a framework emerges that allows a better understanding of students' motivations but also their belief in their capability to achieve desired outcomes.

Medical training is a context that demands high levels of motivation, stress resilience, and constant adaptation. Research on motivation in medical education has grown significantly, offering insights into how motivation affects learning experiences.[7-14] Studies show a positive correlation between medical students' motivation, learning quality, persistence, and performance.[10-15] These findings highlight the importance of educational strategies that enhance motivation of medical students.[16,17]

To understand and study motivation in medical students, the availability of suitable and contextually adapted scales is essential. The Academic Motivation Scale (AMS) was originally developed by Vallerand *et al* and comprises 28 items rated on a seven-point Likert scale, that are divided in seven subscales that respect the different dimensions of motivation described in the SDT: IM, EM and amotivation (AMOT).[18] Interestingly, while the original SDT defined the dimension of IM as a global construct, Vallerand *et al* divided this dimension into three subtypes and excluded the 'EM – integrated' subtype, explaining that this dimension of motivation only appears later in adult life with much less expression in the academic range.[19] With these concepts present, the AMS' items are distributed over the three dimensions defined by the SDT: four items for AMOT, 12 items for EM and 12 items for IM. The AMS assumes that stronger positive correlations should be present between adjacent dimensions as opposed to the dimensions that are further apart; and that the strongest negative correlation should appear between AMOT and IM items.[18,20-22] It is important to highlight that the AMS has been used in many studies to evaluate motivation and has demonstrated a robust internal and external reliability across diverse research studies and countries.[18,19,23-31]

The AMS has been widely used and validated across diverse studies and countries, making it a robust tool for evaluating motivation. However, given the unique demands of medical education, there is a need for a tailored scale that addresses the specific motivations of medical students. Thus, the aim of this study was to develop a simple, intuitive motivation scale for medical students, using the AMS as its foundation due to its comprehensive coverage of motivation types.

METHODS

Study design

We conducted an exploratory mixed-methods study to adapt the AMS based on a protocol for contextualized measurement scale adaptation.[32] We took two different perspectives of the validation process: a qualitative and a quantitative phase. The study took place at the School of Medicine of the University of Minho (EM-UM).

A comprehensive literature review on motivation scales

– with a primary focus on the AMS, including its variations, design, validation process, and impact assessment – was conducted through various databases.[7-18,23-25]

Qualitative phase

For the qualitative perspective, two distinct approaches were employed to address the research questions: Steps 1 and 2; where interviews were conducted following a semi-structured guideline. In Step 1, we used the grounded theory approach,[33] with a focus on the participant's understanding of motivation in medical education. Interviews continued until no additional information was acquired during the process. The participants were asked the following questions: (1) "What motivates medical students to study medicine?" (2) "What stimuli can increase the motivation of medical students?" (3) "What stimuli can decrease the motivation of medical students?" (4) "Can the environment in which medical students are placed alter their motivation levels? Why?" (5) "What intrinsic motivation factors can be identified in medical students?" (6) "What extrinsic motivation factors can be identified in medical students?" (7) "Why is motivation important for medical students?" The interviews lasted 30 - 80 min and were filled with open-ended questions; the interview outline was not strictly followed to obtain more information.

Based on the results of Step 1, we developed adapted items to measure motivation in medical students. In Step 2, we employed think-aloud methods to test the understanding of the measurement scale in the new context.[34]

In both interviews, no answer options were presented, as the focus was solely on respondents' reasoning.

Scale development and adaptation

Building upon the insights gained from the qualitative phases of Steps 1 and 2, a new adapted scale was crafted – the Minho Medical Academic Motivation Scale (Minho-MEDAMS). It is important to note that we used not only the original AMS, but also two already validated translations into Portuguese of the AMS, as the original framework.[18,20,35] The first version of Minho-MEDAMS was composed by 28 visual analogue scale (VAS) items and conceptually divided in seven subdimensions: IM to know, IM to accomplish, IM to stimulate, EM - Introjection, EM - Identification, EM - External Regulation and AMOT.

Quantitative phase

In this phase we assessed the psychometric properties and performance of the Minho-MEDAMS, adhering to criteria for scale construction.[36] The effectiveness of the quantitative measurement instrument in the new context was evaluated through several methods.

Participants

For the qualitative phase, we selected several groups including medical students, alumni, and faculty members. For Step 1, using the grounded theory approach, we conducted interviews with 13 participants, comprising six medical students, one alumnus, and six faculty members. For Step 2, we had a total of 10 medical students, two alumni and three faculty members. For this phase, the inclusion criteria were being a medical student/alumni/faculty member from the EM-UM. There were no exclusion criteria. All participants were contacted via the institutional e-mail.

To assess the validity of the scale, the inclusion criteria was being a medical student from the first to the sixth year of medical school at the EM-UM. There were no exclusion criteria. The sample size was calculated using a ratio of 10:1 (10 respondents for each scale item), with a minimum of 280 respondents for a total of 28 items.[36] The final sample size for the scale validation was 281 respondents. The participants were recruited via institutional e-mail and during seminars. The scale was shared on a website created for the purpose of this study.

Analysis

For Steps 1 and 2, qualitative content analysis was employed. The coding system for the interviews was discussed and validated amongst the authors. The results of the data analysis after three interview rounds showed that the community's acceptance, the choice of specialty and the notion of acquiring a good quality of life are essential for medical students, along with the feeling of personal accomplishment and social recognition. At that point, we achieved theoretical saturation, where additional data no longer generated new theoretical insights or uncovered new aspects of the existing theoretical categories.

For the quantitative phase, to test the normality assumption, we used the following rules-of-thumb: absolute skewness (Sk) and kurtosis (K) values lower than 3.0 and 8.0, respectively, indicate normal distribution. Items with Sk and K over the limit were eliminated. To assess the construct validity of the Minho-MEDAMS, an exploratory factor analysis (EFA) was performed. To test the suitability of the scale for the factor analysis, we used the Kaiser-Meyer-Olkin (KMO) test, which measures sampling adequacy, ranging from 0 to 1, in which higher values mean higher suitability and a value of 0.6 is a suggested minimum; we also used the Bartlett's test of Sphericity, which tests the hypothesis that the correlation matrix is an identity matrix, and that would indicate that the variables are unrelated and therefore unsuitable for structure detection. We used the maximum likelihood analysis as the extraction method. To confirm the findings, a confirmatory factor analysis (CFA) was also performed, using the comparative index of fitness (CFI) with values greater

than 0.90 being considered a good fit. Finally, the root mean square error of approximation (RMSEA) was examined: values below 0.06 indicate a good fit, and values that are above 0.08 indicate reasonable approximation errors. We used the coefficient alpha (Cronbach's alpha) to estimate the internal consistency of the scale. Cronbach's alpha of at least 0.70 was considered to indicate adequate internal consistency.

Ethical considerations

The experimental protocol of this work was approved by the Ethics Committee of the University of Minho (CEICVS-121/2023). All participants signed an informed consent form and all the data regarding personal information of the participants was pseudoanonymized. Adherence to the Helsinki Declaration and the Convention on Human Rights of the Council of Europe was strictly observed. Written informed consent was obtained from each participant before data collection.

RESULTS

Is the motivation concept relevant and understood in a new context?

For Step 1, we used a predetermined coding system, which was derived from the SDT and the AMS. This system included seven primary codes corresponding to key motivational dimensions: IM to Know, IM to Accomplish, IM to Stimulate, EM - Identification, EM - Introjection, EM - External Regulation, and AMOT.

During the coding process, the transcripts of interviews were carefully reviewed, and segments of text were assigned to one of the seven predefined codes. The coding was both deductive, using the predefined categories based on SDT and AMS, and inductive, where new insights emerged from the data and were integrated into the existing framework.

The participants gave several perspectives regarding motivation, but all participants perceived that motivation is a major player for medical students' success, giving different justifications for this perception, such as "motivation allows you to overcome the most difficult moments" and also "[It is] the stimulus that makes people have the willingness and the volition to do and achieve their goals."

On the other hand, some participants talked about how an amotivated student can be problematic, saying, "I think that the student who is not motivated is not going to be the student that society needs."

Regarding IM, the participants were asked what factors might play a key role in intrinsically motivating medical students, and these factors appeared in several ways: "the social factor, the community factor of wanting to help, of wanting to evolve into society, of wanting to help people," and that drive to "always want to be better and always want to know a lot, which is also a direct or almost direct link between the more they study and the more they know, the better they will be able to help from a cognitive and technical point of view".

Other intrinsic dimensions were also noticed, such as the need for control of the situation: "the person feels that they have a role in that process, that they have some control over what is asked of them," which may contribute to the notion that they are "building a path [they]'re proud of."

Looking into 'IM to know', participants also talked about the excitement of learning and surpassing their own obstacles and difficulties. They count this as an important part of feeling intrinsically motivated because it gives them the drive to continuously pursue better results: "I'm learning something new and I'm starting to make new connections – it is starting to get interesting which is very stimulating." They also highlighted that "studying medicine is challenging but there is great satisfaction in learning things I'd never learned before."

When asking about EM, the answers of the participants were more fluid: "It is easier to think about what I want to obtain in return of my effort, than to think about what might drive me to start the effort from the beginning."

Regarding 'EM for identification', in which an external stimulus is perceived by the self as an individual choice or even when the external stimulus is the self, this specific type of motivation is one of the most frequently referred to during the interviews: "I believe that being a doctor is a noble profession, and I want that for myself." On the other hand, some said that while studying medicine they seem to have difficulty stopping the revision of the content for exams because they do not want to fail themselves and would feel embarrassed if they failed.

When accounting for the social effect, some behaviors are indeed driven by external stimuli that the student internalizes as a socially accepted behavior. Some of the participants said, "A lot of medical students chose to study medicine because when they finish high school, they have good grades, and everyone expects them to choose medicine." While others added that "a good medical student will always study because that is what they're supposed to do."

Reaching the last dimension of EM, the true external regulation, many participants focused on external stimuli that directly affect medical students' motivation. One of the biggest factors was the assessments they are put through. External validation in the form of a grade is perceived as being both a positive and negative stimulus for studying medicine. One participant mentioned that "most medical students are highly driven and competitive people, they compare themselves by their grades, but the system makes them that way." The 'system' referring to the several

selections that medical students go through in which they are selected by grade, mostly overlooking the remaining curricula. Other external stimuli are high salaries, social prestige, the possibility of having access to 'good quality of life'.

Finally, AMOT was regarded by most as a major problem when seen amongst medical students and perceived as being related to mental health issues such as depression, generalized anxiety, and burnout.

Are the motivation scale and its items understood?

In Step 2, we tested whether the items of the newly adapted scale were understood in the context of medical education. All the participants understood the purpose of the scale, while some had difficulties regarding the main question of the scale: "Why do I go to medical school?" When asked why, most participants pointed out that it seemed more adequate to specify "Why do I study medicine?" to be focused on the activity throughout the medical degree, while the first question seemed more appropriate for students starting medical school.

When thinking aloud while responding to the items, participants perceived that the questions were specific to medical students and focused on stimuli referring to different dimensions of motivation. Initially, the items were written in the third person, but participants raised concerns about whether medical students would truly relate to the question, making the items more easily understood if they were written in the first person.

Overall, the scale items were well understood and did not raise other significant concerns. Items in the negative form, which were specifically related to the AMOT dimension, were considered harder to understand for being generalist and abstract and were rephrased.

The adapted questionnaire was tested and understood by the participants. By changing the initial question and rephrasing the items, we adapted the scale minimally but still precisely for the new cultural context.

Is the scale valid and reliable in the new context?

The first version of the Minho-MEDAMS was composed of 28 items, scored with a VAS ranging from 1 to 10. Higher scores indicate a higher grade of correspondence of why the medical student studies medicine. The scale was tested on 281 students, with an average age of 20.7 years-old, the majority being in the first year (n = 99; 35.3%) and of the female sex (n = 224, 79.7%) (Table 1). This distribution is in line with the general sex distribution of the students in EM-UM as is the average age. There was a total of 281 answers and no missing values because every item was of mandatory response.

When testing the scale's items for its normality assumption, one item presented absolute skewness scores above 3 and kurtosis higher than 8, showing a deviation from the normal distribution; for that reason, item P19 was excluded from the scale.

Table 1 – Descriptive statistics regarding the medical students that answered the Minho-MEDAMS

	n	%
Sex		
Female	224	79.7%
Male	55	19.6%
Other	2	0.7%
Year		
1st year	99	35.2%
2nd year	36	12.8%
3rd year	37	13.2%
4th year	48	17.1%
5th year	32	11.4%
6th year	29	10.3%
Total	281	100.0%

The factor analysis was firstly assessed by an EFA on a 140 random sample of the results with maximum likelihood as the extraction method (Table 2). Test suitability was ensured by the KMO measure (KMO = 0.862) and the Bartlett's test of sphericity [χ^2 (281) = 2161.015; df = 351.0; $p < 0.001$]. Five factors were extracted, which are further detailed on Table 2 that presents the exploratory factor matrix regarding the 27 adapted items of the Minho-MEDAMS and their respective factor load, showing how variables are distributed into these five EFA ensuing factors. In this analysis, items P4 and P25 were not included in any factor, and after careful analysis, the authors decided to exclude both items from the final scale. Considering the original scale – the AMS – and the SDT already explained previously in this work, the authors classified the five factors as: IM, EM - Introjection, EM - Identification, AMOT and EM - External Regulation.

To confirm the EFA, we performed a CFA on a 141 random sample of the results and on a first model compiling five latent variables, as suggested by the EFA, revealing inadequate goodness of fit. The next step for the authors was to assess the R-squared value of each individual item. The R-squared of items refers to the proportion of variance in each observed item that is explained by its underlying latent construct or factor, measuring how well the latent factor accounts for the variability observed in each item. A higher R-squared value indicates that the latent factor explains a larger portion of the variance in the observed item, suggesting a stronger relationship between the item and

Table 2 – Exploratory factor analysis

Construct	Item	Factor				
		1	2	3	4	5
Intrinsic motivation	P2	0.435				
	P6	0.521				
	P9	0.623				
	P11	1.010				
	P13	0.574				
	P16	1.042				
	P23	0.738				
Extrinsic motivation - Introjection	P7		0.816			
	P18		0.431			
	P20		0.475			
	P21		0.764			
	P27		0.553			
	P28		0.581			
Extrinsic motivation - Identification	P3			0.460		
	P10			0.755		
	P17			0.446		
	P22			0.810		
	P24			0.606		
Amotivation	P5				0.855	
	P12				0.701	
	P26				0.988	
Extrinsic motivation - External Regulation	P1					0.525
	P8					0.405
	P14					0.500
	P15					0.874

the underlying construct, being interpreted as evidence of good construct validity, indicating that the item is a reliable and valid indicator of the intended construct. The post-hoc analysis of the model revealed low R-squared values for items P1, P10, P13, P18, P20, P22 and P27. When looking closely at these items, the authors concluded they were distributed between the different factors and considered there would not be significant changes to the overall construct if removed. For these reasons, those items were excluded from the final scale.

As such, the final model (Fig. 1) has good statistical results (χ^2 = 199.249, p < 0.001, df = 125, χ^2/df = 1.594, RMSEA = 0.065, SRMR = 0.079, GFI = 0.869, and CFI = 0.935). Also, the relationship between the dimensions of IM and AMOT showed a negatively correlation and, in the same way, the sub-dimensions of EM - Identification and AMOT showed a negative relationship between them. The sub-dimensions of EM - Introjection and EM - External Regulation did not show a negative correlation with AMOT, but the strength of the correlation was low. There was a positive relationship between the dimension of IM and the sub-dimensions of EM, with a special remark to the EM - Identification sub-dimension showing a very strong relationship with IM.

The evaluation of the internal consistency of the final version of the Minho-MEDAMS with 18-items was finally assessed by the Cronbach's Alpha revealing a value of 0.831, clearly higher than 0.70, which is considered the cut-off for good consistency. Considering that the five-factor structural model that was adopted, the internal consistency of the factors was as follows: IM (α = 0.876); EM - Introjection (α = 0.774); EM - Identification (α = 0.721); AMOT (α = 0.774), EM - External Regulation (α = 0.880).

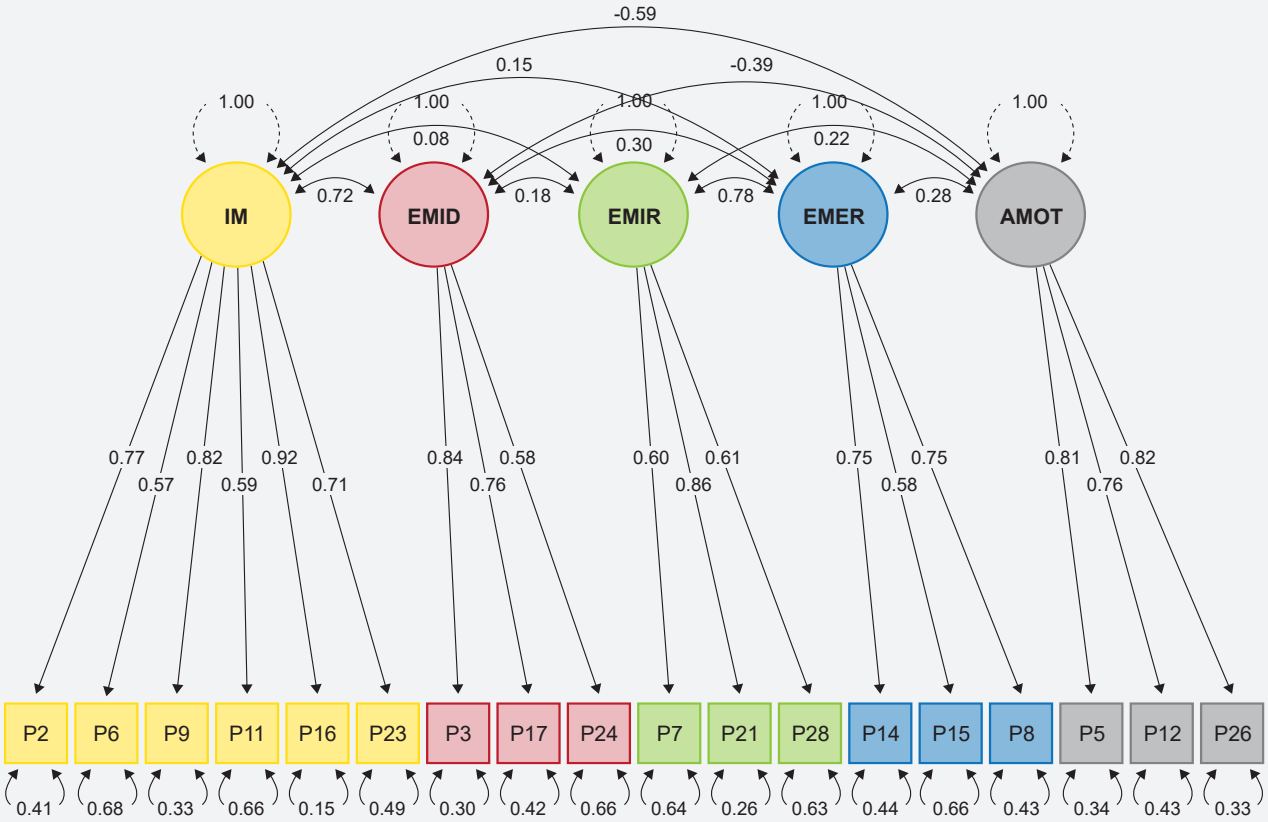


Figure 1 – Confirmatory factor analysis – Minho-MEDAMS final measurement model. The final model demonstrates strong statistical results. The relationships between IM and AMOT and between the EM - Identification and AMOT both show a negative correlation. While the sub-dimensions of EM - Introjection and EM - External Regulation do not show a negative correlation with AMOT, the correlation strength is low. There is a positive relationship between IM and the sub-dimensions of extrinsic motivation, particularly a strong relationship between IM and EM - Identification.

DISCUSSION

In this study we focused on the assessment of motivation levels in medical students in a Portuguese medical school, following a conceptual structure focused on the SDT and the theory of self-efficacy. One of the most important scales in this area that follows the SDT is the AMS, that is widely used to measure motivation in academic settings. However, we believe that the medical context deserves an adjusted perspective to fully understand what drives medical students' motivation. For this reason, we adapted the AMS to the medical students' context and submitted the new Minho-MEDAMS.

The process of adaptation and validation was performed in two different phases: a qualitative analysis of motivation in the context of a Portuguese medical school, and a quantitative analysis focused on the validation of a new adapted motivation scale for medical students – the Minho-MEDAMS. In the first phase, we understood that motivation for medical students follows the purposes of the SDT, and we identified several aspects that should be reinforced on a motivation scale for this population, such as the community's acceptance, the choice of specialty, and the prospect of acquiring a good quality of life. Through several interviews, we were able to formulate items that respected the dimensions of motivation identified in the original scale but were tailored for medical students. The items were then submitted to syntax and comprehensive analysis by medical students, faculty and alumni to ensure they were clear and easily understood. Through this process, a first sample of the Minho-MEDAMS was created.

During the quantitative analysis of the scale, one item (P19) was first removed from the scale to ensure a normal distribution of scores. In the factor analysis, the EFA results were satisfactory (KMO = 0.862), with the extraction of five factors and the exclusion of P4 and P25. However, the first model assessed by the CFA revealed inadequate

goodness of fit. To improve the model, we identified the items with lower R-squared values: P1, P10, P13, P18, P20, P22 and P27. These items showed distribution along the different identified factors but also along the different conceptual subtypes defined at the beginning of the process: IM, EM - Identification and EM - External Regulation, and were removed. The exclusion of items with low R-squared values ensured the model's fit and relevance. At this point, the Minho-MEDAMS's final version consisted of 18 items, six for IM, nine for EM (three for EM - Identification, three for EM – Introjection, and three for EM - External Regulation), and three for AMOT. It is important to note that we subsequently analyzed the reduction of the scale's items with the concern of maintaining the theoretical structure of the SDT while addressing the redundancy of some of the items within each dimension of the scale. We believe that the final version of the Minho-MEDAMS follows the principles of the SDT with significant representation of each dimension of motivation and the spectrum itself. Regarding internal consistency, Minho-MEDAMS reveals high consistency for all five dimensions and excellent results if all the items of the scale are considered, which reflects that Minho-MEDAMS is an appropriate instrument to measure motivation amongst medical students.

To develop this scale in Portuguese, we drew upon the AMS and two existing Portuguese scales that had already translated and validated the AMS.[20,35] The MATAMS focused solely on mathematics and extracted seven factors, aligning closely with the dimensions of motivation in the AMS.[20] Conversely, the scale by Ribeiro *et al* that directly translated the AMS to the Portuguese language was validated with only five factors that corresponded to the following dimensions of motivation: IM, AMOT, EM - Introjection, EM - External Regulation and EM - Integrated Regulation.[35] This is an interesting finding that goes in line with the results of this study, where only five factors were extracted with the difference lying in the inclusion of the EM -Identification and exclusion of the Integrated Regulation dimension in the Minho-MEDAMS. These two dimensions lie closely on the SDT spectrum and that might be a sufficient explanation of why these two subdimensions might even be presented as one given their proximity.[37] Another interesting topic of the Minho-MEDAMS is the lack of differentiation between the IM subdimensions. This follows the SDT that addresses IM as a whole and does not describe the subdimensions proposed on the AMS.[4,18] For this reason, we believe that the Minho-MEDAMS respects the SDT continuum and is a conceptually valid choice to remain only with the broader dimension of IM. Additionally, the emphasis on extrinsic motivation subtypes highlights the role of external expectations and professional standards, which are critical in the medical field.

In adapting the Minho-MEDAMS, the theory of self-efficacy also played a crucial role in shaping how we approached the formulation and validation of items. Self-efficacy theory emphasizes the importance of an individual's belief in their ability to succeed in specific situations, which directly correlates with their motivation levels.[5,6] During the qualitative phase of our research, we paid special attention to how medical students perceive their capabilities in relation to the challenges they face in their education. This influenced the design of items that aimed to capture not only their intrinsic and extrinsic motivations but also their confidence in successfully meeting academic and professional demands.

There are some limitations that should be considered when interpreting these results: i) the design of the study did not allow convergent and divergent validation mechanisms, which could be important to establish construct validity; ii) the number of participants, despite being adequate for validation, could still be improved in order to strengthen the results of this work; iii) students were recruited from a single medical school; and iv) students from the first year of medical school had a slightly bigger representation in this study, which may have influenced some of the results.

With these results, we propose that the implementation of the Minho-MEDAMS can help medical educators to get a better insight into the motivations of medical students in the Portuguese medical school's context. Looking ahead, the longitudinal application of the Minho-MEDAMS might be able to facilitate tracking and understanding of motivational shifts throughout the medical education journey. In the future, the scale might be adaptable to other contexts, such as residency training and continuing medical education.

CONCLUSION

In summary, by effectively capturing five essential dimensions of motivation with good psychometric properties, this scale may be a valuable tool for examining and comprehending the motivational dynamics among medical students. The comprehensive validation process underscores the reliability and validity of the Minho-MEDAMS, confirming its suitability for use within the Portuguese context. The scale highlights motivational factors such as professional identity and external expectations, offering educators insights into the intrinsic and extrinsic motivations specific to medical students. This understanding can inform curriculum development, enhancing student engagement and success.

The Minho-MEDAMS has broader implications for medical education, with potential adaptability to contexts such as residency training and continuing medical education. It serves as a valuable instrument in optimizing teaching strategies and learning outcomes, contributing to a deeper understanding of motivation in medical education.

AUTHOR CONTRIBUTIONS

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

NGSG: Data acquisition, analysis, and interpretation.

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

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

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

The work presented in this thesis was performed in the School of Medicine and in the Life and Health Sciences Research Institute, University of Minho. Financial support was provided by Grupo Fuste and 2CA Braga – Centro Clínico Académico, Braga.

REFERENCES

1. Pelaccia T, Viau R. Motivation in medical education. Med Teach. 2017;39:136-40.
2. Ryan RM, Kuhl J, Deci EL. Nature and autonomy: an organizational view of social and neurobiological aspects of self-regulation in behavior and development. Dev Psychopathol. 1997;9:701-28.
3. Morris LS, Grehl MM, Rutter SB, Mehta M, Westwater ML. On what motivates us: a detailed review of intrinsic v. extrinsic motivation. Psychol Med. 2022;52:1801-16.
4. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol. 2000;55:68-78.
5. Gallagher S. Multiple aspects in the sense of agency. New Ideas Psychol. 2012;30:15-31.
6. Schunk DH, DiBenedetto MK. Self-efficacy and human motivation. In Elliot AJ, editor. Advances in motivation science. Cambridge: Elsevier Academic Press; 2021. p.153-79.
7. Kusurkar RA, Ten Cate TJ, Vos CM, Westers P, Croiset G. How motivation affects academic performance: a structural equation modelling analysis. Adv Health Sci Educ Theory Pract. 2013;18:57-69.
8. Kusurkar RA, Croiset G, Mann KV, Custers E, Ten Cate O. Have motivation theories guided the development and reform of medical education curricula? A review of the literature. Acad Med. 2012;87:735-43.
9. Wu H, Li S, Zheng J, Guo J. Medical students' motivation and academic performance: the mediating roles of self-efficacy and learning engagement. Med Educ Online. 2020;25:1742964.
10. Assing Hvidt E, Søndergaard J, Wehberg S, Hvidt NC, Andersen CM. A cross-sectional study of student empathy across four medical schools in Denmark - associations between empathy level and age, sex, specialty preferences and motivation. BMC Med Educ. 2022;22:489.
11. Muntean LM, Nireștean A, Sima-Comaniciu A, Mărușteri M, Zăgan CA, Lukacs E. The relationship between personality, motivation and academic performance at medical students from romania. Int J Environ Res Public Health. 2022;19:8993.
12. Findyartini A, Felaza E, Setyorini D, Mustika R. Relationship between empathy and motivation in undergraduate medical students. GMS J Med Educ. 2020;37:Doc43.
13. Oláh B, Münnich Á, Kósa K. Identifying academic motivation profiles and their association with mental health in medical school. Med Educ Online. 2023;28:2242597.
14. Atalay KD, Can GF, Erdem SR, Muderrisoglu IH. Assessment of mental workload and academic motivation in medical students. J Pak Med Assoc. 2016;66:574-8.
15. Kunanitthaworn N, Wongpakaran T, Wongpakaran N, Paiboonsithiwong S, Songtrijuck N, Kuntawong P, et al. Factors associated with motivation in medical education: a path analysis. BMC Med Educ. 2018;18:140.
16. Viau R. La motivation en contexte scolaire. 5th ed. Pratiques pédagogiques. Paris: Deboeck Supérieur; 2009.
17. Eccles JS, Wigfield A, Schiefele U. Motivation to succeed. 5th ed. In Damon N, Eisenberg N, editors. Handbook of child psychology: social, emotional, and personality development. New York: John Wiley & Sons, Inc; 1998.
18. Vallerand RJ, Pelletier LG, Blais MR, Brière NM, Senécal CB, Vallières ÉF. Academic motivation scale (AMS, AMS-C 28, EME). Washington DC: APA PsycTests. 1992.
19. Stover JB, de la Iglesia G, Boubeta AR, Liporace MF. Academic motivation scale: adaptation and psychometric analyses for high school and college students. Psychol Res Behav Manag. 2012;5:71-83.
20. Sousa SP, Silva R. Validity and reliability of the portuguese version of mathematics academic motivation scale (MATAMS) among third cycle of basic school students. Mathematics. 2021;9:2049.
21. Fairchild AJ, Horst SJ, Finney SJ, Barron KE. Evaluating existing and new validity evidence for the academic motivation scale. Contemp Educ Psychol. 2005;30:331-58.
22. Can G. Turkish version of the academic motivation scale. Psychol Rep. 2015;116:388-408.
23. Al Ansari AM, Kumar AP, AlSaleh AF, Arekat MR, Deifalla A. Validation of academic motivation scale among medical students using factor analysis and structural equation modeling: middle eastern perspective. J Educ Health Promot. 2021;10:364.
24. Cadête Filho AA, Peixoto JM, Moura EP. Medical students' academic motivation: an analysis from the perspective of the theory of self-determination. Rev Bras Educ Med. 2021;45:e086.
25. Sobral DT. What kind of motivation drives medical students' learning quests? Med Educ. 2004;38:950-7.
26. Vallerand R, Pelletier L, Blais M, Brière N, Senécal C, Vallières E. On the assessment of intrinsic, extrinsic, and amotivation in education: evidence on the concurrent and construct validity of the academic motivation scale. Educ Psychol Meas. 1993;53:159-72.
27. Utvær BK, Haugan G. The academic motivation scale: dimensionality, reliability, and construct validity among vocational students. NJVET. 2016;6:17-45.
28. Guay F, Vallerand RJ, Blanchard C. On the assessment of situational intrinsic and extrinsic motivation: the situational motivation scale (SIMS). Motiv Emot. 2000;24:175-213.
29. Ayub N. Effect of intrinsic and extrinsic motivation on academic performance. PBR. 2010;12:363-72.
30. Alivernini F, Lucidi F. Relationship between social context, self-efficacy, motivation, academic achievement, and intention to drop out of high school: a longitudinal study. J Educ Res. 2011;104:241-52.
31. Barkoukis V, Tsorbatzoudis H, Grouios G, Sideridis G. The assessment of intrinsic and extrinsic motivation and amotivation: validity and reliability of the greek version of the academic motivation scale. Assess Educ Princ Policy Pract. 2008;15:39-55.

32. Ambuehl B, Inauen J. Contextualized measurement scale adaptation: a 4-step tutorial for health psychology research. Int J Environ Res Public Health. 2022;19:12775.
33. Belgrave LL, Seide K. Grounded theory methodology: principles and practices. In Handbook of research methods in health social sciences. Berlin: Springer; 2019. p.299-316.
34. Charters E. The use of think-aloud methods in qualitative research: an introduction to think-aloud methods. Brock Educ J. 2003;12:68-82.
35. Ribeiro MF, Saraiva V, Pereira P, Ribeiro C. Escala de motivação académica: validação no ensino superior público português. Rev Admin Contemp. 2019 23:288-310.
36. Anthoine E, Moret L, Regnault A, Sébille V, Hardouin JB. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. Health Qual Life Outcomes. 2014;12:176.
37. Smith KJ, Davy JA, Rosenberg DL. An empirical analysis of an alternative configuration of the academic motivation scale. Assess Educ: Princ Policy Pract. 2012;19:231-50.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Exposure to Second-Hand Tobacco Smoke in Portugal After the Implementation of the Smoking Ban: A Systematic Review

Exposição ao Fumo Ambiental do Tabaco em Portugal Após a Implementação da Proibição de Fumar: Uma Revisão Sistemática

Nerea MOURINO[1,2], Sofía RAVARA[3,4,5], Cristina CANDAL-PEDREIRA✉[1], Julia REY-BRANDARIZ[1], Leonor VARELA-LEMA[1,6,7], Alberto RUANO-RAVINA[1,6,7], Mónica PÉREZ-RÍOS[1,6,7]
Acta Med Port 2024 Nov;37(11):767-777 ▪ https://doi.org/10.20344/amp.21802

ABSTRACT

Introduction: Estimating the prevalence of second-hand tobacco smoke exposure is a public health priority while evaluating the population-attributable disease burden and impact of smoking bans. We conducted a systematic review to analyze how secondhand tobacco smoke exposure has been assessed, and how its prevalence has been estimated among the Portuguese population since the implementation of the partial smoking ban in 2008.

Methods: A literature search was conducted in the Web of Science, MEDLINE and Embase databases until November 2022, applying a pre-designed search strategy and following the PRISMA 2020 guidelines. The search was not restricted by study period, study design, sample size or language, and was complemented by a manual literature search. A modified Newcastle-Ottawa scale was used to assess the quality of the studies.

Results: Thirteen cross-sectional studies were included. The prevalence of second-hand tobacco smoke exposure among the three European studies ranged from 8.2% (adult population exposed at home in 2010) to 93.3% (adolescent/adult population exposed in bar/restaurant terraces in 2016). Three nationwide studies estimated children's exposure at home: ranging from 32.6% in 2010 - 2011 to 14.4% in 2016. According to the most recent studies, 49.8% of women living in Porto were exposed during the third trimester of pregnancy in 2010 - 2011; 32.6% and 38.4% of children were exposed at home, respectively in Lisbon and the Azores.

Conclusion: A significant proportion of the Portuguese population, especially children and pregnant women, remain exposed to secondhand tobacco smoke. A comprehensive smoke-free policy is needed, not only in outdoor public places, but also in indoor private settings.

Keywords: Environmental Exposure; Portugal; Smoke-Free Policy; Smoking/epidemiology; Tobacco Smoke Pollution/adverse effects

RESUMO

Introdução: Estimar a prevalência da exposição ao fumo ambiental de tabaco (FAT) é uma prioridade de saúde pública, permitindo avaliar a carga de doença atribuível na população e o impacto da lei de proibição de fumar. Realizou-se uma revisão sistemática para analisar como tem sido avaliada a exposição ao FAT; e como tem sido estimada a sua prevalência na população portuguesa, desde a implementação da proibição parcial de fumar em 2008.

Métodos: Foi feita uma pesquisa bibliográfica nas bases de dados Web of Science, MEDLINE e Embase até novembro de 2022, aplicando uma estratégia de pesquisa pré-concebida e seguindo as diretrizes PRISMA 2020. A pesquisa não foi restringida por período de estudo, desenho do estudo, tamanho da amostra ou idioma, e foi complementada por uma pesquisa manual da literatura. Foi utilizada a escala de Newcastle-Ottawa modificada para avaliar a qualidade dos estudos.

Resultados: Foram incluídos 13 estudos transversais. A prevalência da exposição ao FAT nos três estudos europeus variou entre 8,2% (população adulta exposta em casa em 2010) e 93,3% (população adolescente/adulta exposta em esplanadas de bares/restaurantes em 2016). Três estudos nacionais estimaram a exposição das crianças em casa: variando entre 32,6% em 2010 - 2011 e 14,4% em 2016. De acordo com os estudos mais recentes, 49,8% das mulheres residentes no Porto foram expostas ao FAT durante o terceiro trimestre de gravidez em 2010 - 2011; 32,6% e 38,4% das crianças foram expostas ao FAT em casa, respetivamente em Lisboa e nos Açores.

Conclusão: Uma percentagem significativa da população portuguesa, em particular as crianças e as mulheres grávidas, continua exposta ao fumo ambiental do tabaco. É necessária uma política abrangente de proibição de fumar, não só em locais públicos exteriores, mas também em locais interiores privados.

Palavras-chave: Exposição Ambiental; Portugal; Política Anti-Tabaco; Poluição pelo Fumo do Tabaco/efeitos adversos; Tabagismo/epidemiologia

INTRODUCTION

Exposure to second-hand tobacco smoke (SHS) is a global public health concern and there is no safe threshold of exposure.[1] Exposure to SHS (i.e., passive smoking) is defined as the involuntary inhalation of tobacco smoke produced by an active smoker. This includes both mainstream smoke (i.e., the smoke exhaled by a smoker when puffing off a cigarette) and sidestream smoke, (i.e., the combination of smoke from smoldering tobacco product between/during puffs and smoke components diffusing through cigarette paper).[1,2] In Portugal, 13 559 deaths were attributed to tobacco use in 2019, of which 1771 resulted from exposure to SHS.[3]

1. Department of Preventive Medicine and Public Health. Universidade de Santiago de Compostela. Santiago de Compostela. Spain.
2. College of Nursing. Campus de Oza. University of A Coruña. A Coruña. Spain.
3. Health Science Research Centre (CICS-UBI). Universidade da Beira Interior. Covilhã. Portugal.
4. Public Health Research Centre (CISP). National School of Public Health (ENSP). Universidade NOVA de Lisboa. Lisbon. Portugal.
5. Unidade de Cessação Tabágica. Serviço de Medicina Preventiva. Hospital Pêro da Covilhã. Unidade Local de Saúde Cova da Beira. Covilhã. Portugal.
6. Consortium for Biomedical Research in Epidemiology and Public health (CIBERESP). Madrid. Spain.
7. Health Research Institute of Santiago de Compostela (IDIS). Santiago de Compostela. Spain.
✉ **Autor correspondente:** Cristina Candal Pedreira. cristina.candal.pedreira@rai.usc.es

Recebido/*Received*: 22/06/2024 - **Aceite/*Accepted*:** 26/08/2024 - **Publicado *Online*/*Published Online*:** 20/09/2024 - **Publicado/*Published*:** 04/11/2024

Since the United States Surgeon General's report on involuntary smoking in 1986,[4] research focusing on SHS exposure and SHS health hazards, both in nonsmoking children and adults, evolved substantially. Children are particularly vulnerable to the effects of SHS exposure due to their specific anatomical, physiological, and behavioral features.[5] Data suggests that parental smoking is a major source of SHS exposure for nonsmoking children, with the home and cars remaining the most important target settings for reducing their exposure.[1]

Estimating the prevalence of SHS exposure in the population is crucial for understanding its public health impact. Accurate estimates are essential for assessing the disease burden associated with SHS, evaluating public awareness of its risks, and measuring the effectiveness of smoking bans and cessation interventions. Questionnaires have been widely used to estimate the prevalence of SHS exposure; however, their limitations must be taken into consideration: stemming not only from exposure recall, individual perceived susceptibility to SHS, but also, and particularly how the wording of different questions affects the assessment of SHS exposure. Underreporting is a problem when gathering information on children's SHS exposure from their parents.[6,7]

Comprehensive smoke-free laws are the most effective measures to eliminate SHS-related health hazards.[8] Portugal is among the few European countries that has not yet implemented a total ban on smoking in public places. Estimating the prevalence of SHS exposure in the population is crucial for understanding its public health impact. Accurate estimates are essential for assessing the disease burden associated with SHS, evaluating public awareness of its risks, and measuring the effectiveness of smoking bans and cessation interventions.[3] This law has suffered several amendments, the latest one in January 2023. However, exemptions and moratoria loopholes persist. Notably, to the best of our knowledge, no systematic review assessing the prevalence of SHS exposure among the Portuguese population and its trends over time has ever been conducted.

This systematic review aims to analyze how SHS exposure has been assessed, and how its prevalence has been estimated among the Portuguese population since the implementation of the partial smoking ban in 2008.

METHODS

A systematic review was conducted following the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[9] The systematic review protocol was registered in the PROSPERO database in February 2022 (registration no. CRD42022300201).

Search strategy

A bibliographic search was performed until November 2022 in Web of Science, MEDLINE (PubMed), and EMBASE databases applying a pre-designed search strategy [Appendix, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21802/15513)] drawn up by three expert reviewers in the matter. The search terms included both MeSH and free terms: "tobacco smoke pollution", "secondhand smoke", "environmental tobacco smoke", "environment smoking", "passive smoking", "tobacco products", "household smoking", "pregnancy smoking", "occupational smoking", "outdoor smoking", "smoke free law" "smoke free legislation" "smoking ban" and "Portugal". A manual review of the bibliographic references was performed to ensure the inclusion of all possible studies. Study period, study design, sample size or language restrictions were not applied.

Inclusion and exclusion criteria

This review covered studies that estimated the prevalence of SHS exposure among the Portuguese population, including both general adult and vulnerable populations (newborns-adolescents, pregnant women, and the elderly), regardless of the exposure setting and the method used to assess SHS exposure (questionnaires and/or biomarkers). The PECOS question addressed in this review was: "Among the Portuguese population, what is the prevalence of SHS exposure?". We included all the studies that met the following PECOS criteria:

- Population: Studies involving the Portuguese population.
- Exposure: Exposure to SHS from surrounding active smokers in various settings.
- Comparator: Groups within the Portuguese population not exposed to SHS.
- Outcome: Prevalence of SHS exposure (%), measured either through self-declaration or biomarkers.
- Study design: Any study design that provided data on the prevalence of SHS (%) in Portugal.

The selected studies were limited to English, Spanish and Portuguese.

Studies with the following characteristics were excluded: neither their main objective was to estimate the prevalence of SHS, nor their outcome/dependent variable was SHS exposure; studies conducted before the implementation of Law no. 37/2007; those assessing exposure to secondhand aerosol from e-cigarette; and studies that did not estimate specific prevalence for Portugal. When different papers based on the same study were identified, we included the one with more recent data and the largest sample size.

Furthermore, we excluded conference communications, letters to the editor, opinion articles, preprints, reports,

narrative reviews, simulation studies or retracted publications.

Selection of articles and evidence synthesis

After eliminating duplicated papers, three researchers screened the titles and abstract of all papers yielded by the search. Each researcher evaluated eligibility separately on the basis of the title and abstract. In the case of papers considered potentially relevant, the full text was read to ensure that they fulfilled the inclusion/exclusion criteria. Any disagreements regarding article inclusion or exclusion of any given paper were settled by consensus of the three reviewers.

From each included study, the overall prevalence of SHS exposure was extracted, differentiating by exposure settings if data were available; however, in the case that the study did not provide an overall prevalence, we extracted the one corresponding to each subpopulation defined by age group (children vs. adults) or sex (women vs. men). When different prevalence data were provided, depending on the source or frequency of exposure, the highest value was extracted. For studies that provided prevalence, both at the national and subnational level, national data were extracted.

Data-extraction was performed using an *ad hoc* data extraction sheet in Microsoft Excel to capture all the relevant information from each selected paper. The data were manually extracted by two authors, and both files were then reviewed by a third. Discrepancies were discussed and settled by consensus. From each included study, data were extracted on: (1) Study characteristics: author, publication year, period of the study, geographical scope, and study

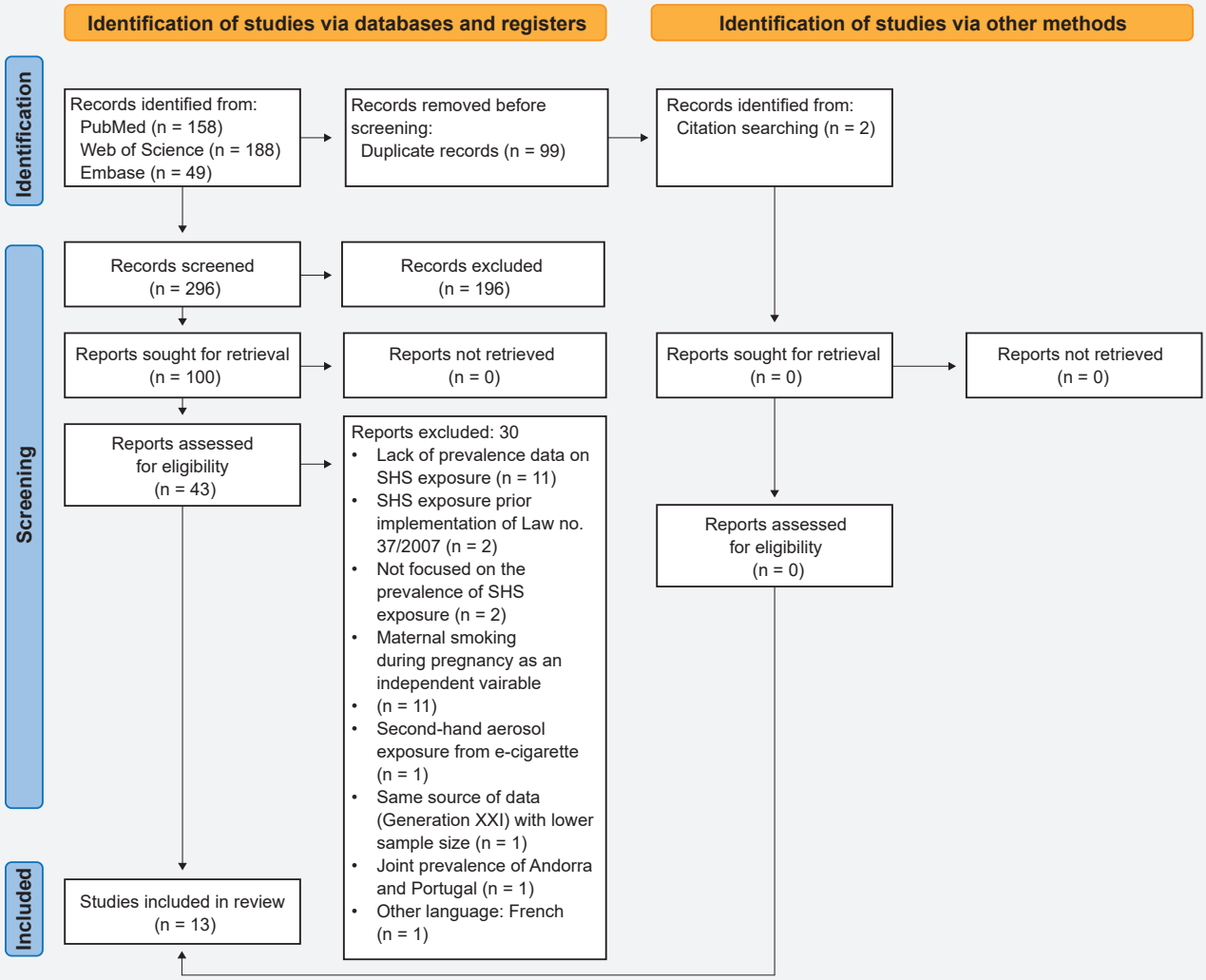


Figure 1 – Flowchart of studies selected for systematic review in accordance with the PRISMA 2020 guidelines

design; (2) Population characteristics: sample size, population group (pregnant women, newborns, children, adolescents and adults), age in years, and source of recruitment (hospital, health facilities, kindergartens, school or general population); (3) SHS exposure assessment data: definition of SHS exposure and method for assessment; and (4) Prevalence of SHS exposure (%) considering the geographical scope of the study (regional, national or European), population group, and exposure settings.

Assessment of quality and level of evidence

Study quality was evaluated using an adaptation of the Newcastle-Ottawa scale.[10] Two researchers screened each study separately evaluating sample selection/strategy (representativeness of the sample, comparability between respondents and non-respondents), assessment of the exposure (ascertainment and characterization of the exposure), and outcome (stratification of the prevalence data on SHS exposure, statistical test and assessment of potential biases/limitations) [Appendix, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21802/15513)]. Studies were scored from 0 to 8 by each researcher, with the final score being reached by agreement. In case of any difference of opinion, a third

Table 1 – Main characteristics of the studies included in the systematic review (n = 13)

Study characteristics				Population characteristics		
Author, year of publication	**Period of the study**	**Geographical scope**	**Study design**	**n**	**Population group**	**Age (years)**
Areias *et al*, 2009[18]	2008	Lisbon	Cross-sectional	96	Adults	18 - 44
Constant *et al*, 2011[19]	2010 - 11	Lisbon	Cross-sectional	313	Children and adolescents	5 - 13
Pereira *et al*, 2013[14]	2010	Portugal	Cross-sectional	6003	Children, adolescents and adults	< 15 - ≥ 65
Paradela *et al*, 2013[20]	2009 - 10	Chaves	Cross-sectional	287	Adults	19 - 86
Lupsa *et al*, 2015[11]	2010	Europe (includes Portugal)	Cross-sectional	120	Children and adults (mothers)	6 - 11
Vitória *et al*, 2015[15]	2010 - 11	Portugal	Cross-sectional	3187	Children and adolescents	8 - 13
Vitória *et al*, 2017[21]	2016 - 17	Lisbon	Cross-sectional	949	Children and adolescents	8 - 13
Mlinaric *et al*, 2019[12]	2016	Europe (Coimbra)	Cross-sectional	N/A*	Adolescents	14 - 17
Precioso *et al*, 2019[22]	2017	Azores	Cross-sectional	292	Children	9
Precioso *et al*, 2019[16]	2016	Portugal	Cross-sectional	2396	Newborns and Children	0 - 9
Alves *et al*, 2020[17]	2010 - 11	Portugal	Cross-sectional	3368	Adults (men)	25 - 79
Madureira *et al*, 2020[23]	2011 - 12	Porto	Cross-sectional	619	Pregnant women	18 - 46
Henderson *et al*, 2021[13]	2016	Europe (includes Portugal)	Cross-sectional	N/A*	Adolescents and adults	≥ 15

N/A*: not applicable

researcher was consulted. Studies with a score < 3 points were rated as poor-quality, those with a score of 3 - 4 points as moderate-quality, and those with a score of ≥ 5 points as high-quality. Regarding the quality evaluation, no studies were excluded.

RESULTS

Search results

The bibliographic search yielded a total of 296 papers; after examination of the titles and abstracts, 43 papers were deemed eligible for the full-text review; finally, 13 studies fulfilled the inclusion criteria (Fig. 1).

Characteristics of the studies

Table 1 and Fig. 2 show the main study characteristics. All the studies used a cross-sectional design; mostly were conducted between 2008 and 2013, estimating the prevalence of SHS exposure among the Portuguese population from newborns to adults aged 86 years (N = 19 823). Nine studies included children and/or adolescents. Of the 13 studies, three were performed at European level (one confined to Coimbra city),[11-13] four at the national level,[14-17] and six at the regional level (Porto, Chaves, and Lisbon cities, and the Azores region)[18-23] (Table 1 and Fig. 2).

	SHS exposure assessment data	
Source of recruitment	**Definition exposure to SHS**	**Method for assessment**
Hospitals	SHS exposure in closed public spaces and workplace two months after the implementation of the new legislative ban on smoking	One-on-one interviews using standardized pre-validated and anonymous questionnaires
Schools	Exposure at home and outside home to household smokers (mother/father or other members)	Proxy and self-administered questionnaire
General population	Exposure to at least one current smoker at home	Computer-assisted telephone interviews (CATI). The primary caregiver was responsible for answering the questions when the participant was under 15 years
Primary care facilities	Exposure from smokers during last week (daily or sometimes) at home/workplace/public spaces (bars, discos and restaurants) considering the duration of the exposure (hours per day/week)	Self-administered questionnaire by trained nurses
Schools	Exposure at home (daily or less than daily) and elsewhere than at home (frequent or sometimes)	Face-to-face interviews by trained staff. Proxy and self-administered (mothers) structured questionnaire
Schools	Exposure to SHS at home by family members or guests (daily/occasionally). Inclusion of questions regarding rules concerning smoking inside the house	Self-administered and child-responsive validated questionnaire (it does not mention if parental permission for participation was gathered)
Schools	Exposure at home (no-yes) based on paternal/maternal smoking	Self-administered and child-responsive questionnaire (after parental permission for participation)
Schools	Exposure in a car within the past seven days	Self-administered and adolescent-responsive questionnaire
Schools	Exposure at home (daily or sometimes) by at least one smoking household member (parental/siblings/visitors/others); exposure in the car by household members.	Self-administered and child-responsive validated questionnaire (CHETS) (after parental permission for participation)
Health centers, kindergartens and elementary schools	Exposure at home by at least one smoking household member (parental/siblings/others); exposure in the car by household members	Proxy and self-administered validated questionnaire (CHETS)
General population	Exposure in closed spaces by smokers	Self-administered questionnaire
Hospital	Exposure to SHS before and during pregnancy at home, leisure places or at work	Face-to-face interview
General population	Exposure in the last six months by people smoking regular cigarettes in outdoor areas (terraces of restaurants/bars, public transport stops, outdoor areas of hospitals and schools, parks, children's playgrounds, stadia and beaches)	Computer-assisted personal interviews (CAPI) by trained staff

Ten studies covered one or two settings when assessing SHS exposure (Fig. 2). The majority of the studies assessed SHS exposure by using non-standardized and proxy or self-administered questionnaires focusing on indoor SHS exposure (n = 12), and more specifically at home (n = 9). Four studies considered exposure duration (in the last six months; during the last week; before and during pregnancy;) and other four, the frequency of the exposure (daily *versus* less than daily; daily *versus* occasionally/sometimes; or frequent *versus* sometimes) (Table 1). One study measured the prevalence of SHS exposure via both questionnaires and biomarkers (urine cotinine).[11]

Table 2 shows the prevalence of exposure to SHS according to geographical scope, population group and different exposure settings. The prevalence of the exposure among studies conducted both at national (n = 10), and European level (n = 3), ranged respectively from 8.2% (adult population exposed at home in 2010) to 93.3% (adolescent and adult population exposed on bar/restaurant terraces in 2016). Among the nationwide studies, three estimated

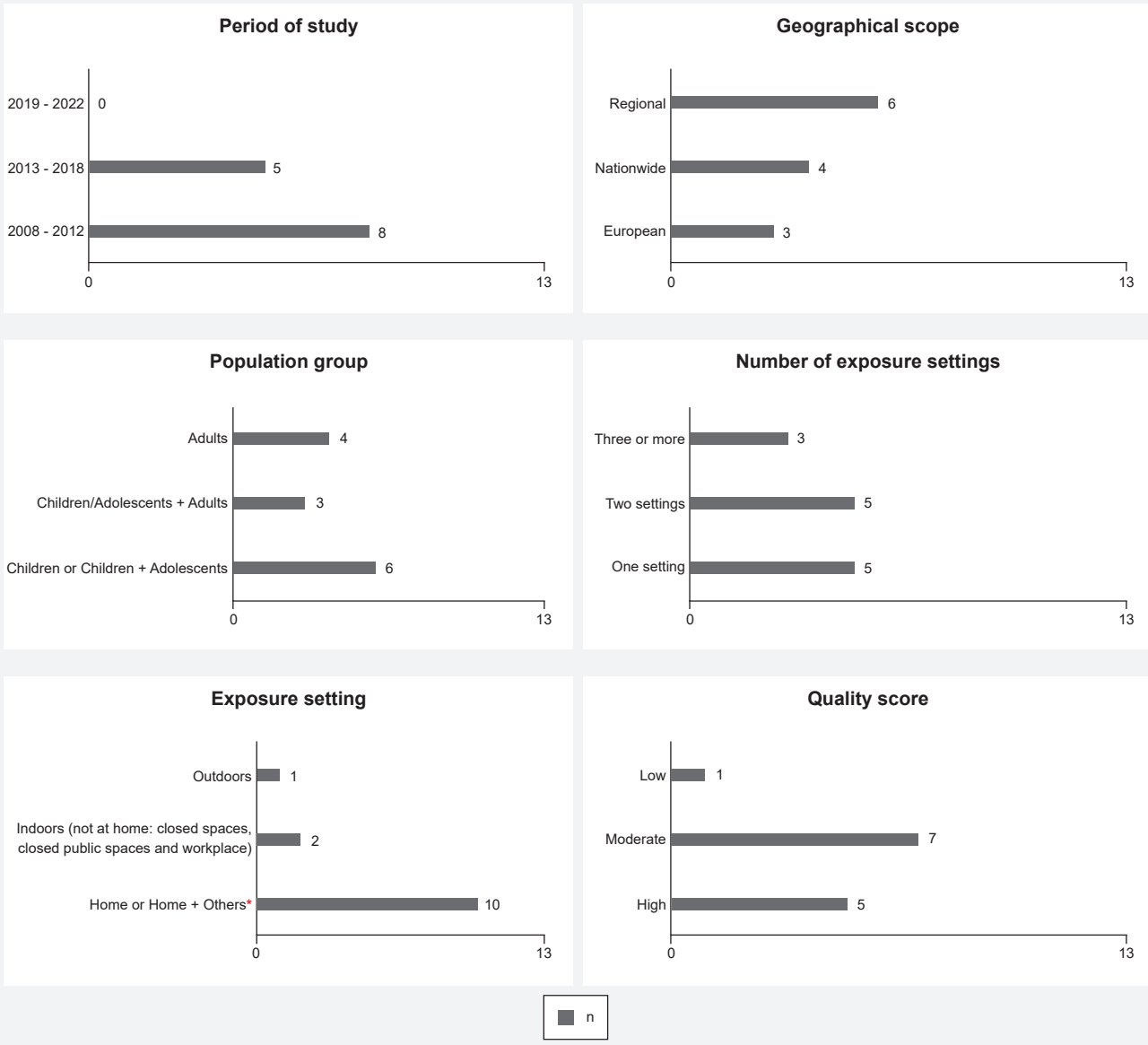


Figure 2 – Main characteristics of the studies included in the systematic review (n = 13) considering the period of the study, geographical scope, population group, SHS exposure settings, and the quality score based on the modified Newcastle-Ottawa scale

* Others: outside home, elsewhere than at home, car, workplace, public places/leisure places

children's exposure at home: ranging from 32.6% in 2010 - 2011 to 14.4% in 2016 (Table 2). At the regional level, SHS exposure has been measured mainly in Lisbon and among vulnerable populations (children/adolescents and pregnant women) (Tables 1 and 2). According to the most recent studies, 49.8% of pregnant women living in Porto were exposed

Table 2 – Prevalence of exposure to secondhand tobacco smoke in the studies included in the systematic review according to the geographical scope, population group and settings of exposure

Author, year of publication	Population group	Setting of exposure	Prevalence of self-reported SHS exposure (%)
European studies			
Lupsa *et al*, 2015	Adults	Home	8.2
Lupsa *et al*, 2015	Adults	Elsewhere than at home	46.6
Lupsa *et al*, 2015	Children	Home	15.0
Lupsa *et al*, 2015	Children	Elsewhere than at home	58.3
Mlinaric *et al*, 2019	Adolescents	Car	23.2
Henderson *et al*, 2021	Adolescents-adults	Children's playgrounds	53.0
Henderson *et al*, 2021	Adolescents-adults	Outdoor areas in schools	72.8
Henderson *et al*, 2021	Adolescents-adults	Stadia	81.5
Henderson *et al*, 2021	Adolescents-adults	Parks	83.3
Henderson *et al*, 2021	Adolescents-adults	Outdoor areas in hospitals	71.9
Henderson *et al*, 2021	Adolescents-adults	Public transport stops	87.3
Henderson *et al*, 2021	Adolescents-adults	Restaurant/bar terraces	93.3
Henderson *et al*, 2021	Adolescents-adults	Beaches	88.7
Nationwide studies			
Pereira *et al*, 2013	Children-adolescents-adults	Home	26.6
Vitória *et al*, 2015	Children-adolescents	Home	32.6
Precioso *et al*, 2019	Children	Home	14.4
Precioso *et al*, 2019	Children	Car	10
Precioso *et al*, 2019	Children	Home + Car	5.4
Alves *et al*, 2020	Adults (men)	Closed spaces	53.8
Alves *et al*, 2020	Adults (women)	Closed spaces	38.4
Regional studies			
Areias *et al*, 2009	Adults	Closed public places	3.1
Areias *et al*, 2009	Adults	Workplace	2.5
Constant *et al*, 2011	Children-adolescents	Home	34
Constant *et al*, 2011	Children-adolescents	Outside home	12
Paradela *et al*, 2013	Adults	Home	16.4
Paradela *et al*, 2013	Adults	Workplace	14.1
Paradela *et al*, 2013	Adults	Public spaces	32.7
Paradela *et al*, 2013	Adults	Home + Workplace + Public spaces	46.2
Vitória *et al*, 2017	Children-adolescents	Home	32.6
Precioso *et al*, 2019	Children	Home	38.4
Precioso *et al*, 2019	Children	Car	27.6
Precioso *et al*, 2019	Children	Home + Car	17.8
Madureira *et al*, 2020	Adults (pregnant women)	Before pregnancy	57.4
Madureira *et al*, 2020	Adults (pregnant women)	First trimester of pregnancy	51.2
Madureira *et al*, 2020	Adults (pregnant women)	Third trimester of pregnancy	49.8

to SHS during the third trimester in 2010 - 2011; in 2017, 32.6% and 38.4% of children in Lisbon and the Azores, respectively, were still exposed at home.

Study quality

When using a modified Newcastle-Ottawa scale to standardize study quality, five studies were rated as high-quality, seven as moderate, and one as low-quality [Fig. 2 and Appendix, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21802/15513)]. The low-quality score was due to lack of information on the definition of SHS exposure, poor statistical analysis, and potential limitations and biases. Most of the studies displayed information biases considering that the questions about SHS exposure were self-reported either by the children or parents.

DISCUSSION

Exposure to tobacco smoke in Portugal remains a significant concern, especially in vulnerable population groups such as children and pregnant women. The prevalence of SHS exposure derived from the 13 studies included in this systematic review might be an underestimation, since exposure was measured via proxy or self-reported questionnaires. The outdated (pre-2018) exposure data, the imprecise measurement of SHS exposure, and the heterogeneity in terms of geographical scope, target population, exposure settings, and sources of exposure preclude a precise estimate of the prevalence of SHS in Portugal. In addition, these limitations prevent an accurate assessment of the variation in SHS exposure over the last decade and a half.

The most recent data on SHS exposure in the Portuguese population aged 15 years and over–derives from a European study conducted in 2016.[13] This study places Portugal among the four countries with the highest prevalence of SHS exposure in outdoor public spaces. Thus, over 85% of Portuguese adolescents and adults were exposed on bars and restaurants terraces, beaches and public transport stops,[13] and over 50% in children's playgrounds. This exposure increases the visibility of negative role models and reinforces smoking normalization among children, adolescents, and the whole society.[24] Moreover, these data are consistent with Eurobarometer 2020 - 2021 findings, indication that Portugal is among the European countries with a highest prevalence of indoor SHS exposure in bars and restaurants above the European average.[25]

Data from the first National Health Survey with Physical Examination (INSEF) showed that the prevalence of daily exposure to SHS among the adult population in 2017 significantly varied by region and age group. The INSEF assessed SHS exposure across different settings, including home, workplaces, transports or other public spaces, and identified the highest prevalence in the Azores region (21.0%), and in the youngest age group, from 25 to 34 years (19.8%).[3] Analysis by region of the nationwide studies included in this systematic review reveals that the highest children's exposure to SHS at home was estimated in Lisbon and in the Azores, being higher than 21.1%.[14-16]

The Azores is ranked as the Portuguese region with the highest crude smoking prevalence and the highest daily consumption.[26] On the other hand, Lisbon is the region depicting the highest smoking rates among women.[26] In addition, the Azores is the region with the highest proportion of lung cancer cases and deaths attributable to smoking. The most recent study assessing SHS exposure in the Azores[22] showed that in 2017, 38.4% of nine-year-old children were exposed to SHS at home, driven by at least one smoker; this prevalence is 13.4 percentage points higher than a year earlier,[16] and it is similar to previous studies involving children from other countries.[27,28] Evidence shows that mass media awareness campaigns are effective in increasing public knowledge about the health risks associated with tobacco smoke, particularly among children and adolescents.[29,30] These campaigns enhance awareness, influence smoking behaviors, and support smoking cessation. Our results highlight the need for comprehensive tobacco control strategies, including targeted, sustained, and intensive public health campaigns, with a special focus on the Azores. Our findings show that an important percentage of Portuguese children are still exposed to SHS in their households and private vehicles. Precioso *et al*,[16] collected the most recent national data on childhood SHS exposure: in 2016, 18.4% of children aged 0 - 10 years were exposed to SHS at home or in the car driven by at least one smoking household member in 2016 (14.4% at home and 10.1% in the car).

According to the most recent Eurobarometer data on attitudes towards indoor home smoking, in 2010, 34% of Portuguese respondents allowed smoking at home but when smokers' responses were taken into account, this number rose to 69%.[31] One of the studies conducted by Vitória *et al* assessed Portuguese participants' rules concerning indoor smoking in their homes[15]: "smoking is not allowed in any part of the house"; "smoking is allowed in some parts/rooms of the house"; "smoking is allowed in any parts/rooms of the house" and "smoking is allowed only on special occasions". Results from this study[15] revealed that the rules were more easily ignored when the family received visitors, with smoking guests being the first source of exposure for children, followed by smoking parents (32.6% *versus* 29.5%, respectively); this could be explained by parental social stigma and/or poor awareness of the harmful effects of SHS on children's health, especially among parents with a low level of education.[16,19]

Despite the evidence that children's SHS exposure at home may have increased in recent years considering the impact of the COVID-19 pandemic lockdown on tobacco smoking behaviour,[32] we identified no studies evaluating possible variations in the prevalence of SHS exposure before and after the pandemic in Portugal. Moreover, it should be noted that none of the included studies differentiated between housing type despite the evidence that children living in multi-family dwellings may be more exposed to SHS than those living in single-family dwellings.[33] Beyond household interventions, policy approaches, such as smoke-free zones in multi-family dwellings, should be implemented worldwide to help protect children.

After the home, the car was the second most common private setting where SHS exposure was measured in Portuguese children. A study conducted in 2017 by Precioso *et al* showed that 27.6% of Azorean children were exposed to SHS in the car.[22] The most recent Eurobarometer on attitudes towards smoking in the car reported that, in 2010, 57% of Portuguese respondents allowed smoking in their private vehicles.[31] In 2018, the smoke-free car legislation was implemented in some European countries such as Cyprus, Greece, the United Kingdom, France, the Republic of Ireland and Italy.[12] In this context, a study found that California's 2007 smoke-free vehicle legislation resulted in a 37% reduction in the odds of children being exposed to SHS in vehicles during 2001 - 2011.[34] This finding supports the need to adopt and implement a general ban on car smoking in Portugal.

Pregnant women are another vulnerable group that should be a preferential target for interventions aimed at preventing SHS exposure, both for their and the fetus' well-being. A study by Madureira *et al,*[23] the first to assess SHS exposure in pregnant women in Portugal, observed a decrease in the prevalence of exposure during the third trimester compared to the first trimester (49.8% *versus* 51.2%), especially among women with high literacy levels. Pregnant women who are more educated may have greater willingness to avoid sources of exposure to tobacco smoke as a result of adequate health education on SHS-related health hazards.[23]

Our findings show that estimates of SHS exposure are based on non-standardized questionnaires completed and administered by the adult participant, and in the case of minors, by a proxy, or by the minors themselves after parental consent for participation. Although some studies measured exposure with validated questionnaires, most of them used broad definitions that do not allow for accurate quantification of the level, intensity and duration of SHS exposure. Furthermore, the questions did not include all possible settings where the population might be exposed; in fact, only two studies measured children's exposure both at home and outside home, but without specifying the outdoor settings.[11,19] Importantly, the use of questionnaires may have resulted in the inaccurate measurement of SHS exposure due to subjectivity (linked to differences in perception), ignorance of SHS exposures or recall, and social desirability biases.[6,7]

Over time, cotinine has become one of the most widely used biomarker of SHS exposure, particularly in the United States of America.[6,35] In Portugal, only the study conducted by Lupsa *et al*[11] measured SHS exposure using urine cotinine in conjunction with questionnaires; however, the same cotinine cut-point was used to differentiate between exposed and unexposed mothers and their children of different ages, without taking into account possible differences in their level of exposure, and in their cotinine metabolism/clearance.[36] Four of the 13 studies indicated that the non-measurement of cotinine exposure was due to budgetary constraints.[14-16,22] More studies measuring exposure to SHS with biomarkers are needed to accurately estimate the prevalence of SHS exposure, and thus update the impact of SHS exposure on different health outcomes.

Our findings underscore the need of a multifaceted approach to tobacco control and SHS exposure. A comprehensive strategy should include increasing tobacco excise taxes and allocating the revenue to strengthen tobacco control programs, public education, and cessation resources. A key component of this strategy involves regulating retail outlets and vending machines to limit tobacco access and prevent youth initiation. Enforcement of bans on tobacco advertising and promotion, along with prohibiting the sale, purchase, and consumption of tobacco products by individuals under 21 years of age is crucial for countering the normalization of smoking and reducing its consumption.[37] Effective smoke-free policies must extend to both public places (such as school campuses, childcare centers, parks, beaches, and government buildings) and private settings (such as homes and vehicles). By creating smoke-free environments at home, parents not only improve their own well-being but also contribute to a healthier, smoke-free setting that discourages their children from starting to smoke.[14,16,37] These measures are crucial for reducing smoking initiation, minimizing SHS exposure, supporting smoking cessation, and reinforcing the social unacceptability of smoking.[37] Public education campaigns should clearly communicate the health risks of smoking, including graphic warnings on cigarette packages, the benefits of quitting, and the importance of maintaining smoke-free environments.

Healthcare professionals play an important role in reducing tobacco use and SHS exposure by providing essential support and advocating for smoke-free policies and cessation efforts.[38] All frontline workers, including general practitioners / family physicians, nurses, hospital clinicians,

pharmacists, and dentists, should be trained to provide smoking cessation advice and support across various care settings. Furthermore, a national tobacco cessation campaign could be developed, incorporating telephone support services, online resources, social media outreach, and partnerships with community organizations and businesses to establish a comprehensive support network involving multiple stakeholders beyond healthcare professionals.[38]

To enhance the effectiveness of the strategies aimed at reducing tobacco consumption and SHS exposure, a coordinated national framework with a designated lead agency, standardized guidelines, and robust surveillance systems is essential. Establishing a national database and conducting ongoing research on tobacco use will help refine strategies and ensure their relevance. Regular evaluation of interventions and continuous training for healthcare professionals will ensure that strategies are evidence-based and have a significant impact.[38]

This review has both weaknesses and strengths. Firstly, we only used MEDLINE (PubMed), Web of Science, and EMBASE databases. However, we are reasonably confident not having missed any relevant studies, since we complemented the search with a manual reference review of the included studies. To the best of our knowledge, just one study was excluded due to language (written in French)[39]; however, it did not seem to meet the inclusion criteria based on the abstract data. As a major strength, this is, to the best of our knowledge, the first systematic review on the prevalence of SHS exposure among the Portuguese population. Our inclusion criteria were strict, and our results made it possible to examine the differences in the assessment of the prevalence of SHS exposure in Portugal, across almost one decade, considering the definitions of SHS exposure, exposure settings and target population, for a total of 19 823 children, adolescents, and adults exposed to this carcinogen. Finally, 12 out of 13 studies were judged to be of high or moderate quality when applying the modified Newcastle-Ottawa scale, which is a reliable tool for assessing the methodological quality of studies included in a systematic review.[40]

The results of this systematic review support the need for further research obtaining updated and accurate data on the prevalence of SHS among the Portuguese population.

Future research should address specific gaps, including evaluating the impact of COVID-19 on SHS exposure and conducting longitudinal and quasi-experimental studies to better understand how SHS exposure changes over time, and how specific tobacco control policies affect this exposure. In addition, more regular and standardized monitoring of SHS exposure, using consistent methods, is needed to accurately assess its prevalence, burden, and the effectiveness of existing tobacco control measures. Strengthening current tobacco control laws and policies in Portugal will be critical to addressing these issues and improving public health outcomes.

CONCLUSION

A significant proportion of the Portuguese population, especially vulnerable populations such as children and pregnant women, remains exposed to SHS. This may result from the limited protection of the partial smoking ban and its failure to change social norms. These findings also suggest poor awareness of SHS-related health hazards among the Portuguese population.

Notably, the highest level of children's SHS exposure occurs in public places not yet included in the current smoking ban. Portugal lacks a public health strategy to monitor SHS exposure in different settings and population subgroups. To address this shortcoming, it is essential to implement a multifaceted approach to tobacco control. This approach should include increasing excise taxes, regulating retail outlets, and raising the minimum age for tobacco consumption. Effective smoke-free policies must extend to both public and private settings, including a ban on smoking in vehicles where children are transported, as already implemented in some countries. These measures are critical for promoting smoke-free environments, reducing overall tobacco consumption, and consequently, minimizing SHS exposure. In addition, developing a national tobacco cessation campaign that integrates telephone support services, online resources, social media outreach, and partnerships with community organizations and businesses will provide a robust support network.

AUTHOR CONTRIBUTIONS

NM, MPR: Conception and design of the work; acquisition, analysis, and interpretation of data; drafting and critical review of the manuscript; final approval of the version to be published.

SR, CCP: Analysis, and interpretation of data; critical review the manuscript; final approval of the version to be published.

JRB, LVL, ARR: Critical review of the manuscript; final approval of the version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This work has been funded by the Instituto de Salud Carlos III (ISCIII) through the Project "PI22/00727" and co-funded by the European Union.

REFERENCES

1. Office on Smoking and Health. The health consequences of involuntary exposure to tobacco smoke: a report of the surgeon general. Atlanta: Centers for Disease Control and Prevention; 2006.
2. Jaakkola MS, Jaakkola JJ. Assessment of exposure to environmental tobacco smoke. Eur Respir J. 1997;10:2384-97.
3. Instituto Nacional de Saúde Doutor Ricardo Jorge. 1.º inquérito nacional de saúde com exame físico (INSEF 2015): Determinantes de Saúde. Lisboa: INSA, IP; 2017.
4. Centers for Disease Control (CDC). 1986 Surgeon General's report: the health consequences of involuntary smoking. MMWR Morb Mortal Wkly Rep. 1986;35:769-70.
5. Hang B, Wang P, Zhao Y, Sarker A, Chenna A, Xia Y, et al. Adverse health effects of thirdhand smoke: from cell to animal models. Int J Mol Sci. 2017;18:932.
6. Florescu A, Ferrence R, Einarson T, Selby P, Soldin O, Koren G. Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: focus on developmental toxicology. Ther Drug Monit. 2009;31:14-30.
7. Aurrekoetxea JJ, Murcia M, Rebagliato M, Guxens M, Fernández-Somoano A, López MJ, et al. Second-hand smoke exposure in 4-year-old children in Spain: sources, associated factors and urinary cotinine. Environ Res. 2016;145:116-25.
8. World Health Organization. WHO report on the global tobacco epidemic, 2019 offer help to quit tobacco use. Geneva: WHO; 2019.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10:89.
10. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-5.
11. Lupsa IR, Nunes B, Ligocka D, Gurzau AE, Jakubowski M, Casteleyn L, et al. Urinary cotinine levels and environmental tobacco smoke in mothers and children of Romania, Portugal and Poland within the European human biomonitoring pilot study. Environ Res. 2015;141:106-17.
12. Mlinarić M, Schreuders M, Mons U, Kunst AE. Exposure to car smoking among youth in seven cities across the European Union. Drug Alcohol Depend. 2019;204:107561.
13. Henderson E, Lugo A, Liu X, Continente X, Fernández E, López MJ, et al. Secondhand smoke presence in outdoor areas in 12 European countries. Environ Res. 2021;199:111337.
14. Pereira AM, Morais-Almeida M, Sá e Sousa A, Jacinto T, Azevedo LF, Robalo Cordeiro C, et al. Environmental tobacco smoke exposure at home and smoking prevalence in the general Portuguese population--the INAsma study. Rev Port Pneumol. 2013;19:114-24.
15. Vitória PD, Machado JC, Araújo AC, Ravara SB, Samorinha C, Antunes H, et al. Children's exposure to second hand smoke at home: a cross-sectional study in Portugal. Rev Port Pneumol. 2015;21:178-84.
16. Precioso J, Rocha V, Sousa I, Araújo AC, Machado JC, Antunes H. Prevalence of Portuguese children exposed to secondhand smoke at home and in the car. Acta Med Port. 2019;32:499-504.
17. Alves J, Filipe R, Machado J, Nunes B, Perelman J. Change in the prevalence and social patterning of first-and second-hand smoking in PORTUGAL: a repeated cross-sectional study (2005 and 2014). Int J Environ Res Public Health. 2020;17:3594.
18. Areias A, Duarte J, Figueiredo J, Lucas R, Matos I, Pires J, et al. Asthma and the new anti -smoking legislation. What has changed? Rev Port Pneumol. 2009;15:27-42.
19. Constant C, Sampaio I, Negreiro F, Aguiar P, Silva A, Salgueiro M, et al. Environmental tobacco smoke (ETS) exposure and respiratory morbidity in school age children. Rev Port Pneumol. 2011;17:20-6.
20. Paradela C, Pérez-Ríos M, Ruano-Ravina A, Barros-Dios JM. Exposure to environmental tobacco smoke in Chaves after the implementation of the law 37/2007. A cross-sectional study in two healthcare settings. Rev Port Pneumol. 2013;19:168-74.
21. Vitória PD, Nunes C, Precioso J. Parents' educational level and second-hand tobacco smoke exposure at home in a sample of Portuguese children. Rev Port Pneumol. 2017;23:221-4.
22. Precioso J, Frias S, Silva CN, Rocha V, Cunha-Machado J, Gonçalves F, et al. Prevalence of children exposed to secondhand smoke at home and in the car in Azores (Portugal). Pulmonology. 2019;25:283-8.
23. Madureira J, Camelo A, Silva AI, Reis AT, Esteves F, Ribeiro AI, et al. The importance of socioeconomic position in smoking, cessation and environmental tobacco smoke exposure during pregnancy. Sci Rep. 2020;10:15584.
24. Alesci NL, Forster JL, Blaine T. Smoking visibility, perceived acceptability, and frequency in various locations among youth and adults. Prev Med. 2003;36:272-81.
25. European Commission. Attitudes of Europeans towards tobacco and electronic cigarettes: Special Eurobarometer 506. – Tobacco. Brussels: TNS Opinion & Social; 2021.
26. Direção-Geral da Saúde. Programa nacional para a prevenção e controlo do tabagismo 2020. Lisboa: DGS; 2021.
27. Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. 2011;377:139-46.
28. Brody DJ, Lu Z, Tsai J. Secondhand smoke exposure among nonsmoking youth: United States, 2013-2016. NCHS Data Brief. 2019;348:1-8.
29. Brinn MP, Carson KV, Esterman AJ, Chang AB, Smith BJ. Mass media interventions for preventing smoking in young people. Cochrane Database Syst Rev. 2010;11:CD001006.
30. Stead M, Angus K, Langley T, Katikireddi SV, Hinds K, Hilton S, et al. Mass media to communicate public health messages in six health topic areas: a systematic review and other reviews of the evidence. Southampton: NIHR Journals Library; 2019.
31. European Commission. Tobacco: special eurobarometer 332. – tobacco. Brussels: TNS Opinion & Social; 2010. [cited 2023 Feb 20]. Available from: https://data.europa.eu/data/datasets/s790_72_3_ebs332?locale=en.
32. Sarich P, Cabasag CJ, Liebermann E, Vaneckova P, Carle C, Hughes S, et al. Tobacco smoking changes during the first pre-vaccination phases of the COVID-19 pandemic: a systematic review and meta-analysis. EClinicalMedicine. 2022;47:101375.
33. Wilson KM, Klein JD, Blumkin AK, Gottlieb M, Winickoff JP. Tobacco-smoke exposure in children who live in multiunit housing. Pediatrics. 2011;127:85-92.
34. Patel M, Thai CL, Meng YY, Kuo T, Zheng H, Dietsch B, et al. Smoke-free car legislation and student exposure to smoking. Pediatrics. 2018;141:S40-50.
35. Mourino N, Ruano-Raviña A, Varela Lema L, Fernández E, López MJ, Santiago-Pérez MI, et al. Serum cotinine cut-points for secondhand smoke exposure assessment in children under 5 years: a systemic review. PLoS One. 2022;17:e0267319.
36. Mourino N, Pérez-Ríos M, Santiago-Pérez MI, Lanphear B, Yolton K, Braun JM. Secondhand tobacco smoke exposure among children under 5 years old: questionnaires versus cotinine biomarkers: a cohort study. BMJ Open. 2021;11:e044829.
37. Pérez-Ríos M, Ahluwalia J, Guerra-Tort C, García G, Rey-Brandariz J, Mourino-Castro N, et al. Towards stronger tobacco control policies to curb the smoking epidemic in Spain. Clin Transl Oncol. 2024;26:1561-9.
38. Health Service Executive. Tobacco free ireland. Report of the Tobacco Policy Review Group. Dublin: HSE; 2013.
39. Wanner P, Khlat M, Bouchardy C. Habitudes de vie et comportements en matière de santé des immigrés de l'Europe du sud et du Maghreb en France. Rev Epidemiol Sante Publique. 1995;43:548-59.
40. Cook DA, Reed DA. Appraising the quality of medical education research methods: the Medical Education Research Study Quality Instrument and the Newcastle-Ottawa Scale-Education. Acad Med. 2015;90:1067-76.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Insights from Portuguese Nephrologists and Rheumatologists Concerning the Treatment of ANCA Vasculitis

Perspetivas dos Nefrologistas e Reumatologistas Portugueses Sobre o Tratamento das Vasculites Associadas aos ANCA

Inês FERREIRA[1,2], Ana ÁGUEDA[3], Carolina BELINO[3], Bruno SCHAU[4], João ROVISCO[5], Carina FERREIRA[6,7]
Acta Med Port 2024 Nov;37(11):778-786 ▪ https://doi.org/10.20344/amp.21635

ABSTRACT

Introduction: Antineutrophilic cytoplasmic antibodies-associated vasculitis (AAV) encompasses granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. These rare diseases are characterized by an exaggerated immune response in blood vessels, leading to inflammation, vascular injury, ischemia, and necrosis of affected tissues and organs. Despite the existence of European recommendations for treating AAV, their implementation in Portugal remains unclear.

Methods: To address this gap, an online Delphi panel was conducted involving 55 Portuguese nephrologists and rheumatologists, representing the main specialties involved in the management of AAV. The primary objective was to assess the level of consensus regarding the treatment of AAV in Portugal and the application of European recommendations in daily clinical practice. The specialists evaluated 29 statements formulated by a group of Portuguese experts with extensive experience in AAV, addressing key aspects of AAV management, rated on a 4-point Likert scale. Consensus was defined as > 70% of responses either strongly agreeing or strongly disagreeing with a statement, while the majority level required > 70% agreement or disagreement.

Results: After one round, no statement reached consensus globally, and eight out of the 29 statements did not achieve a qualified majority. Nonetheless, this study demonstrates a high level of agreement within each medical specialty, due to the distinct characteristics of the patient populations treated by each specialty. While the results suggest partial adherence to European recommendations, they also highlight the need to standardize clinical practices for AAV treatment in Portugal.

Conclusion: This study underscores the importance of aligning national practices with established European recommendations to ensure the best outcomes for patients with AAV.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/drug therapy; Nephrologists; Practice Patterns, Physicians; Rheumatologists

RESUMO

Introdução: As vasculites associadas a anticorpos citoplasmáticos antineutrófilos (AAV) engloba a granulomatose com poliangiite, a poliangiite microscópica e a granulomatose eosinofílica com poliangiite. Estas doenças raras caracterizam-se por uma resposta imunológica exacerbada nos vasos sanguíneos, levando a inflamação, lesão vascular, isquemia e necrose dos tecidos e órgãos afetados. Apesar de existirem recomendações europeias para o tratamento da AAV, a sua implementação em Portugal permanece desconhecida.

Métodos: Para abordar esta lacuna, foi realizado um painel *online* do tipo Delphi envolvendo 55 nefrologistas e reumatologistas portugueses, representando as principais especialidades envolvidas na gestão da AAV. O principal objetivo foi avaliar o nível de consenso em relação ao tratamento da AAV em Portugal e aplicação das recomendações europeias na prática clínica diária. Os especialistas avaliaram 29 afirmações formuladas por um grupo de peritos portugueses com vasta experiência em AAV, abordando aspetos-chave da gestão da AAV, classificadas numa escala Likert de 4 pontos. O consenso foi definido como > 70% das respostas a concordar totalmente ou a discordar totalmente com uma declaração, enquanto o nível de maioria exigia > 70% de concordância ou discordância.

Resultados: Após uma ronda, nenhuma declaração alcançou consenso de forma global, e oito das 29 declarações não atingiram uma maioria qualificada. Contudo, este estudo demonstra um elevado nível de concordância em cada especialidade médica, devido às características distintas das populações de doentes tratadas por cada especialidade. Embora os resultados sugiram uma adesão parcial às recomendações europeias, também destacam a necessidade de padronizar as práticas clínicas de tratamento da AAV em Portugal.

Conclusão: Este estudo sublinha a importância de alinhar as práticas nacionais com as recomendações europeias estabelecidas para garantir os melhores resultados para os doentes com AAV.

Palavras-chave: Nefrologistas; Padrões de Prática Médica; Reumatologistas; Vasculite Associada a Anticorpo Anticitoplasma de Neutrófilos

INTRODUCTION

Antineutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of rare diseases consisting of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1,2] Its estimated incidence is 10 to 20 new cases per million individuals per year in Europe and a prevalence rate of 46 to 184 per million individuals.[3,4]

The pathogenic role of ANCA results from the induction of an exacerbated immune response in blood vessels, leading to inflammation, vascular injury, ischemia, and necrosis

1. Department of Medicine. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
2. Departament of Nephrology. Hospital de São João. Unidade Local de Saúde de São João. Porto. Portugal.
3. Department of Rheumatology. Hospital Pêro da Covilhã. Unidade Local de Saúde da Cova da Beira. Covilhã. Portugal.
4. CSL Vifor. Lisboa. Portugal.
5. Department of Rheumatology. Hospitais da Universidade de Coimbra. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.
6. Department of Nephrology. Hospital Curry Cabral. Unidade Local de Saúde de São José. Lisbon. Portugal.
7. NOVA Medical School. Universidade NOVA de Lisboa. Lisbon. Portugal.

✉ **Autor correspondente:** Inês Ferreira. ines.passos@ulssjoao.min-saude.pt

Recebido/*Received*: 08/04/2024 - **Aceite/*Accepted*:** 24/09/2024 - **Publicado/*Published*:** 04/11/2024

of the affected tissues and organs.[5,6] Vasculitis management, namely disease activity status, and cumulative impact on patient's health can be performed using the Birmingham Vasculitis Activity Score (BVAS) and the Vascular Damage Index (VDI), respectively.[7-11] Following AAV diagnosis, the immunosuppressive regimen used to treat this condition should be promptly initiated, as a delay in treatment initiation leads to a worse prognosis.[12] Recently, the European League Against Rheumatism/ European Renal Association-European Dialysis and Transplant Association (EULAR/ ERA-EDTA) published guidelines for the two phases of AAV treatment[12-15]: The remission induction phase (a more aggressive immunosuppression phase to achieve remission in three months, defined by the complete absence of signs

Table 1 – Defined statements for the Delphi-like panel

A. Therapeutic scheme	
1	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is cyclophosphamide, associated with corticotherapy.
2	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is rituximab, associated with corticotherapy.
3	I prescribe a rapid weaning scheme for oral corticotherapy according to the PEXIVAS scheme.
4	The treatment of ANCA vasculitis is independent of the type of antibody.
5	The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy.
6	The immunosuppressant I most often prescribe in maintenance therapy is methotrexate and corticotherapy.
7	The immunosuppressant I most often prescribe in maintenance therapy is rituximab and corticotherapy.
8	In severe disease in remission, I suspend maintenance therapy after 18 months.
9	In severe disease in remission, I do not suspend corticotherapy.
10	The use of avacopan in ANCA vasculitis minimizes the use of corticotherapy.
11	The use of avacopan in ANCA vasculitis has been tested and can be used in induction schemes.
12	Avacopan may be helpful in corticodependent cases and may be considered for maintenance of remission in combination with another immunosuppressant.
13	Avacopan is equally effective in granulomatous as in non-granulomatous manifestations.
14	Avacopan is a therapeutic alternative to corticosteroids in the treatment of ANCA vasculitis.
B. Refractory and/or relapsing disease	
15	I change the induction immunosuppressive regimen when treating relapse.
16	I repeat the renal biopsy on suspicion of renal recurrence.
17	IVIg can be used in refractory cases and when the risk of infection is high.
C. Renal disease	
18	I perform renal biopsy whenever renal involvement by ANCA vasculitis is suspected.
19	Renal failure usually precludes the use of methotrexate.
20	Plasmapheresis still has a place in the treatment of ANCA vasculitis with renal involvement.
D. Other manifestations of illness and/or comorbidities	
21	Immunosuppression, namely high-dose corticotherapy, is the first-line treatment for orbital pseudotumor.
E. Safety	
22	Low-dose corticotherapy has a good long-term safety profile and is virtually risk-free.
F. Prophylaxis	
23	I do prophylaxis for *Pneumocystis jirovecii* with cotrimoxazole.
24	I do prophylaxis for fungal infections.
25	I do prophylaxis for osteoporosis.
26	I screen for tuberculosis before starting immunosuppression.
27	I assess the risk of reactivation of Hepatitis B in patients treated with RTX.
G. Monitoring and follow-up	
28	I use the BVAS/VDI for therapeutic decisions and/or disease activity monitoring.
29	I use FFS for therapeutic decisions.

of active disease),[16] and the maintenance phase (less intense phase, aimed at maintaining remission and minimizing medication-related adverse effects).[6,13,17] In patients with generalized or severe-stage disease (renal failure with creatinine > 5.65 mg/dL or significant organ changes, such as pulmonary hemorrhage), the first-line therapy is based preferably on rituximab (RTX), or on cyclophosphamide (CYC).[12]

Considering the inherent toxicity of corticosteroid-based regimens, other effective alternatives have been under evaluation, such as avacopan.[6] Avacopan is an oral inhibitor of the C5a complement receptor, which prevents complement-mediated activation and migration of pro-inflammatory leukocytes.[18,19] This new compound showed superiority in maintaining remission at 52 weeks and reduced the relapse rate from 21% to 10% compared to a prednisone regimen in gradual dose reduction for 20 weeks (phase III ADVOCATE study).[19] Avacopan effectively contributed to remission in relapses and severe disease, while breaking through steroid dependency and allowing corticosteroid tapering.[20,21] Given its high potential as a therapeutic alternative to corticosteroids, the use of avacopan in the treatment of AAV has been added to the official 2023 EULAR revision and Canadian recommendations.[14,22,23]

Although knowledge about these diseases is constantly evolving, the recommendations of specialists should be the mainstay of medical decision-making, always framed by the specific context of each patient and their circumstances. Despite the existence of European recommendations for treating AAV,[12,13,15,24] their implementation in the Portuguese reality is not known. Therefore, this Delphi-like panel assessed the positioning of national nephrology and rheumatology specialists regarding the treatment of AAV in Portugal, in order to raise awareness on the need to standardize clinical procedures across the Portuguese healthcare context.

METHODS

This study assessed the agreement of nephrology and rheumatology specialists on clinical practice methodologies regarding AAV treatment.

To accomplish it, five Portuguese experts in ANCA vasculitis joined a focus group and formulated 29 statements based both on evidence-based clinical practice and on the EULAR recommendations for the management of ANCA-associated vasculitis.[14] The topics covered included the therapeutic scheme, refractory and/ or relapsing disease, renal disease, other manifestations of illness and/ or comorbidities, safety, prophylaxis and monitoring, and follow-up (Table 1). Following the focus group, a Delphi-like panel of only one round was conducted (Fig. 1). A group of 113 national nephrologists and rheumatologists was invited to anonymously answer the questionnaire, and to categorize the previously defined 29 statements using a 4-point Likert scale: “fully disagree”, “disagree”, “agree”, and “fully agree”. The consensus agreement level was set according to the definitions described in Fig. 1. The responses were analyzed by the frequency distribution through the presented 4-point Likert scale.

RESULTS

This one-round Delphi-like panel included 34 nephrologists and 21 rheumatologists (a total of 55 individuals), from a universe of 113 invited clinicians, who were requested to categorize the 29 statements elaborated by the focus group using a 4-point Likert scale. The results were analyzed considering all the responses and according to the medical specialty (Table 2).

No statement was categorized as consensual regarding the total number of responses (Table 2). A qualified majority was obtained in 21 statements, with more than 70% of the collective agreement (“fully agree” and “agree”) in 16 statements, and more than 70% of the collective disagreement (“fully disagree” and “disagree”) in the five remaining ones (Table 2). The lasting eight statements attained heterogeneous answers (Table 2 and Fig. 2). The highest level of discrepancies was obtained for the following statements: “The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy” (therapeutic scheme), “I do prophylaxis for fungal infections” (prophylaxis), and “I use (Five Factor Score) FFS for therapeutic decisions” (monitoring and follow-up).

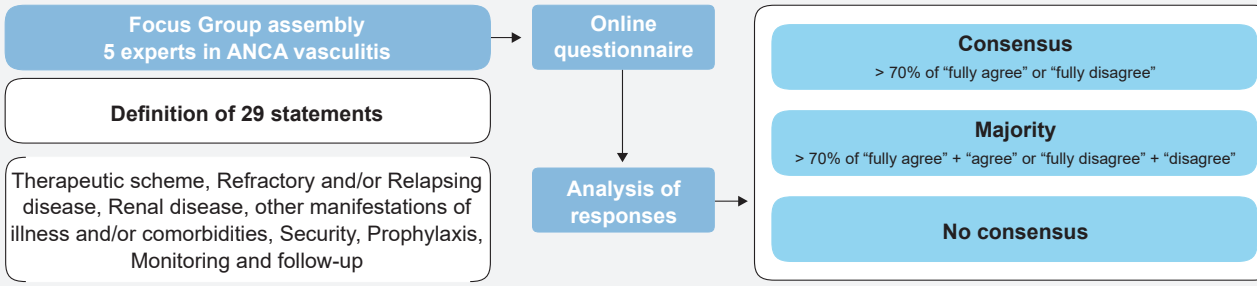


Figure 1 – Methodology of the Delphi-like panel (one round only)

Table 2 – Statements defined for the Delphi panel. In light green, the statements where a majority was obtained among all experts (> 70% of "fully agree" + "agree" = "Agreed"); in orange, the statements where a majority was obtained among all experts (> 70% of "fully disagree" + "disagree" = "Disagreed"); in dark green/red, the statements where consensus was identified (agree/disagree); in grey, statements were no consensus or qualified majority was gathered.

	A. Therapeutic scheme	Total	N	R
1	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is cyclophosphamide, associated with corticotherapy.	74%	85%	
2	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is rituximab, associated with corticotherapy.			100%
3	I prescribe a quick weaning scheme for oral corticotherapy according to the PEXIVAS scheme.	86%	97%	
4	The treatment of ANCA vasculitis is independent of the type of antibody.	71%	74%	
5	The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy.			
6	The immunosuppressant I most often prescribe in maintenance therapy is methotrexate and corticotherapy.	87%	C	
7	The immunosuppressant I most often prescribe in maintenance therapy is rituximab and corticotherapy.			71%
8	In severe disease in remission, I suspend maintenance therapy after 18 months.	71%		86%
9	In severe disease in remission, I do not suspend corticotherapy.	82%	76%	91%
10	The use of avacopan in ANCA vasculitis minimizes the use of corticotherapy.	100%	100%	100%
11	The use of avacopan in ANCA vasculitis has been tested and can be used in induction schemes.	76%	71%	86%
12	Avacopan may be helpful in corticodependent cases and may be considered for maintenance of remission in combination with another immunosuppressant.	95%	94%	95%
13	Avacopan is equally effective in granulomatous as in non-granulomatous manifestations.	76%	74%	81%
14	Avacopan is a therapeutic alternative to corticosteroids in the treatment of ANCA vasculitis.	89%	91%	86%
	B. Refractory and/or relapsing disease			
15	I change the induction immunosuppressive regimen when treating relapse.	75%	74%	76%
16	I repeat the renal biopsy on suspicion of renal recurrence.			
17	IVIg can be used in refractory cases and when the risk of infection is high.	83%	74%	100%
	C. Renal disease			
18	I perform renal biopsy whenever renal involvement by ANCA vasculitis is suspected.	84%	85%	81%
19	Renal failure usually precludes the use of methotrexate.	78%	94%	
20	Plasmapheresis still has a place in the treatment of ANCA vasculitis with renal involvement.			76%
	D. Other manifestations of illness and/or comorbidities			
21	Immunosuppression, namely high-dose corticotherapy, is the first-line treatment for orbital pseudotumor.	84%	88%	76%
	E. Safety			
22	Low-dose corticotherapy has a good long-term safety profile and is virtually risk-free.	93%	94%	90%
	F. Prophylaxis			
23	I do prophylaxis for *Pneumocystis jirovecii* with cotrimoxazole.	96%	100%	91%
24	I do prophylaxis for fungal infections.		73%	76%
25	I do prophylaxis for osteoporosis.	98%	97%	C
26	I screen for tuberculosis before starting immunosuppression.	91%	91%	91%
27	I assess the risk of reactivation of Hepatitis B in patients treated with RTX.	98%	97%	C
	G. Monitoring and follow-up			
28	I use the BVAS/VDI for therapeutic decisions and/or disease activity monitoring.			86%
29	I use FFS for therapeutic decisions.			

Total: combined responses (%) in terms of agreement/disagreement, considering all specialties (n = 55); N: combined responses (%) in terms of agreement/disagreement, considering only nephrology (n = 34); R: combined responses (%) in terms of agreement/disagreement, considering only rheumatology (n = 21).
ANCA: antineutrophilic cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; C: consensus; FFS: five factor score; IVIg: intravenous immunoglobulins; RTX: rituximab; VDI: vascular damage index.

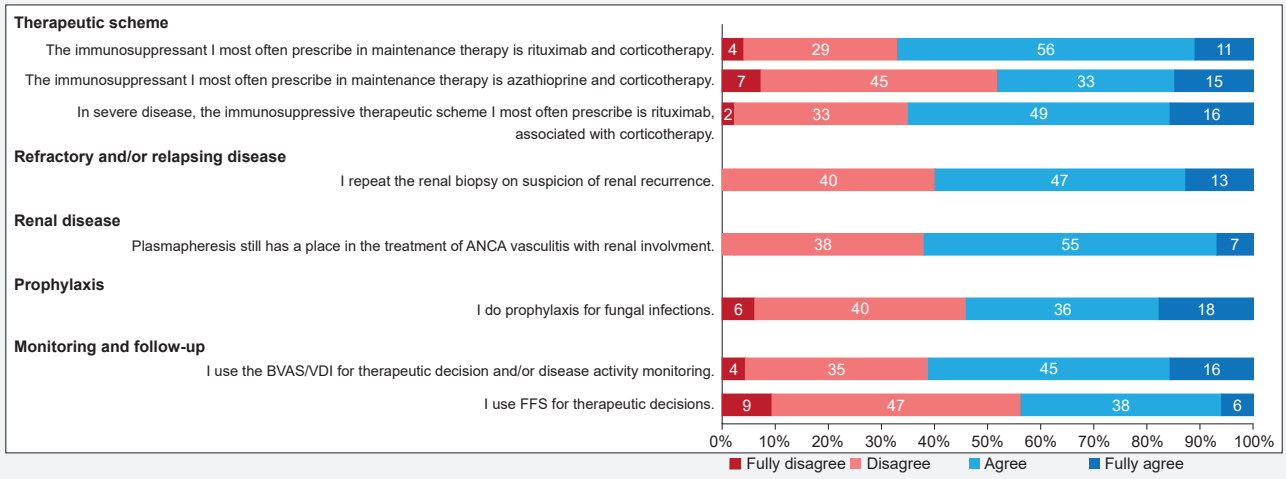


Figure 2 – Characterization of the statements (per %) that failed to achieve a qualified majority after the Delphi-like panel

The analysis of the results per specialty disclosed a marginally increased agreement compared to the overall analysis. Regarding nephrology, a consensus was obtained in one statement from the 'therapeutic scheme' section, specifically the full disagreement with the sentence "The immunosuppressant that I most often prescribe in maintenance therapy is methotrexate and corticotherapy" (statement six, Table 2). A qualified majority was obtained in 20 statements (17 expressing agreement and three stating disagreement, Table 2), and in the remaining eight, the answers received were heterogeneous (Table 2 and Fig. 3). Among these, in the 'therapeutic scheme' section, the two statements with higher response variability were "The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy" and "The immunosuppressant I most often prescribe in maintenance therapy is rituximab and corticotherapy"; and in the Monitoring and Follow-up section were "I use the BVAS/VDI for therapeutic decision and/or disease activity monitoring" and "I use FFS for therapeutic decisions". Interestingly, in the 'renal disease' section, the statement "Plasmapheresis still has a place in the treatment of ANCA vasculitis with renal involvement" divided the experts' opinions almost evenly (nearly 50% agreed and 50% disagreed).

The highest level of agreement registered in this Delphi-like panel was obtained in the rheumatology panel. Specifically, a consensus was obtained in two statements from the 'prophylaxis' section, specifically, "I perform osteoporosis prophylaxis" (statement 25) and "I evaluate the risk of reactivation of hepatitis B in patients treated with RTX" (statement 27, Table 2). A qualified majority was obtained in 19 statements (15 expressing agreement and 4 stating

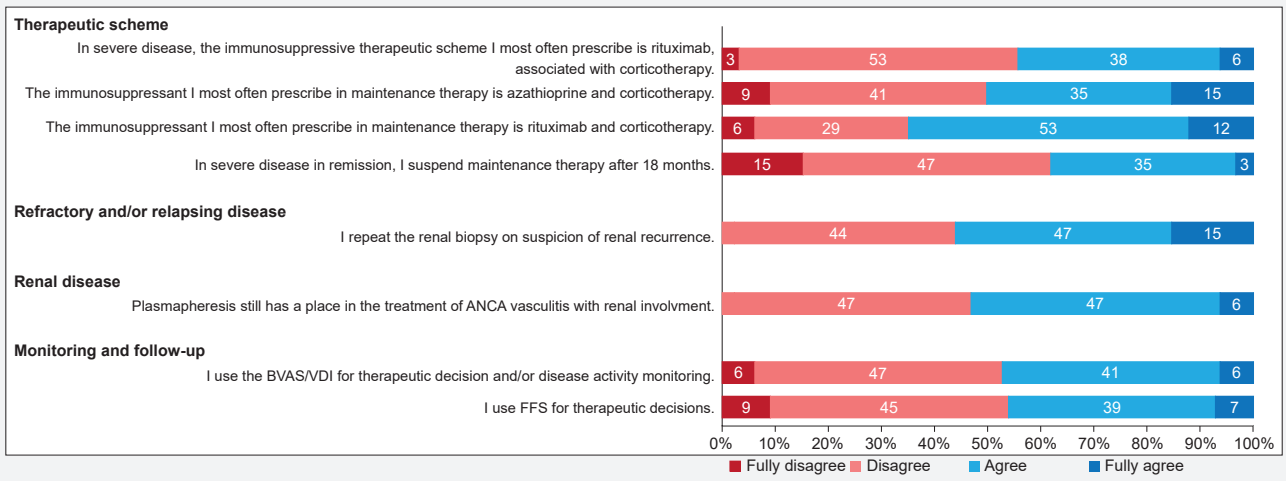


Figure 3 – Characterization of the statements (per %) that failed to achieve a qualified majority after the Delphi-like panel among the nephrologists

disagreement, Table 2). In the remaining eight, the answers were heterogeneous (Table 2 and Fig. 4). Specifically, the statements "In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is cyclophosphamide, associated with corticotherapy" (therapeutic scheme) and "Renal failure usually precludes the use of methotrexate" (renal disease) are those that obtained more pronounced divergence.

DISCUSSION

This Delphi-like panel assessed the positioning of national nephrology and rheumatology specialists regarding the treatment of AAV in Portugal. Despite the existence of various international recommendations for the therapeutic management of AAV, these might not be feasible to use in clinical practice, affecting the patients' proper diagnosis, treatment, and prognosis. Therefore, generating knowledge and unifying opinions is essential to come up with the most suitable and personalized therapeutic scenario to improve these patients' QoL. The outcome of this panel of experts was in adequate compliance with European recommendations for managing these diseases. Still, the overall analysis revealed a high lack of consensus regarding the treatment of AAV patients among different specialties.

In the 'therapeutic scheme' section, explicitly referring to the most prescribed immunosuppressive therapeutic scheme in severe disease, most experts advocate for a combination of CYC and corticosteroids. Notably, this recommendation is more aligned with nephrologists, whereas rheumatologists seem to prefer RTX with corticosteroids. This divergence in approach may stem from the distinctive medical responsibilities, with nephrologists typically managing cases involving significant renal complications. Moreover, the available data regarding the use of RTX and corticosteroids in induction therapy for patients with notably reduced or rapidly declining glomerular filtration rates (GFR), especially those with a serum creatinine level exceeding 4 mg/dL (354 µmol/L), is limited, thus favoring CYC as the preferred agent for inducing remission in cases of severe kidney disease. Despite the association of CYC with infertility, due to young patients' exposure to gonadal toxicity and an elevated risk of cancer development, its combined use with corticosteroids has been the only available option for many years, and it is recognized as a valuable therapeutic strategy.[12,25,26] Following remission, most rheumatologists agreed to use RTX combined with corticosteroids for maintenance therapy,[27-29] a practice endorsed by the EULAR/EDTA guidelines,[12,14] instead of MTX or AZA. Nephrologists also consensually disagreed with MTX due to its nephrotoxic potential, dose adjustments needed due to chronic kidney disease (CKD), and lack of indication during dialysis, thus favoring alternative maintenance regimens. Specifically, there is evidence that suggests that RTX may offer advantages, particularly for patients with a history of relapsing disease, proteinase 3-ANCA (PR3)-positive AAV, AZA intolerance and following RTX induction. Still, it is essential to exercise caution, as long-term data on the effects of RTX maintenance therapy are limited, with potential concerns regarding the development of secondary immunodeficiency in this patient population.

Concerning the tapering of oral corticosteroids, the consensus among experts leans towards adopting the PEXIVAS trial protocol.[30] The analysis according to medical specialty shows that this inclination is primarily driven by nephrologists, with 33% of rheumatologists expressing disagreement with its adoption. The PEXIVAS scheme was

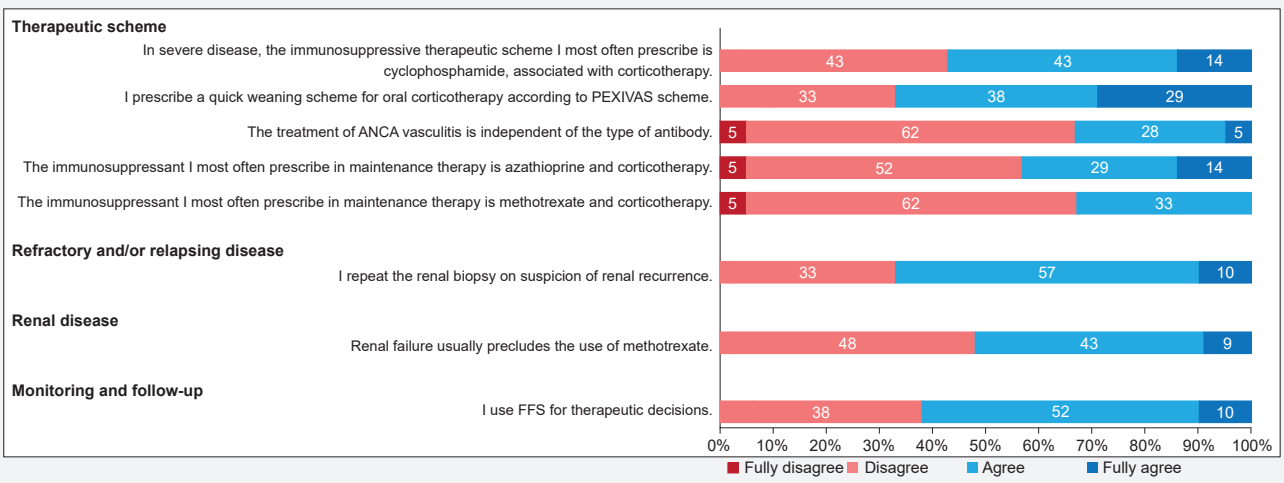


Figure 4 – Characterization of the statements (per %) that failed to achieve a qualified majority after the Delphi-like panel among the rheumatologists

evaluated in a recent randomized clinical trial, specifically assessing the role of PLEX (plasma exchange) and two corticosteroid regimens (standard and reduced dose) in patients with severe AAV [estimated GFR < 50 mL/min/1.73 m^2 of body-surface area, or diffuse alveolar hemorrhage (DAH)]. This study found that the reduced-corticosteroid regimen was non-inferior to a standard dose concerning death and end-stage renal disease (ESRD) outcomes, while it significantly reduced the risk of severe infections within the first year of treatment.[30]

Notably, efforts are being made to reduce the toxicity associated with high-dose, prolonged corticosteroid regimens, particularly in frail patients, due to toxicity and side effects.[31] Accordingly, most experts disagreed on not suspending corticosteroids in severe disease in remission. The recent appraisal of pathogenetic mechanisms, including complement activation pathways, has introduced the concept of an alternative to corticosteroids, such as avacopan.[32] Therefore, the final topic of this section focused on avacopan, and most experts agreed that its usage could be adopted in induction schemes, allowing the reduction of corticosteroids and being equally effective in granulomatous and non-granulomatous manifestations. Most experts agree that avacopan is a suitable therapeutic alternative to corticosteroids in treating ANCA vasculitis, which aligns with the EULAR recommendations for managing AAV.[14]

In the 'refractory and/or relapsed disease' section, the overall analysis of the responses reflects those from each specialty. Most experts agree that the immunosuppression regimen should be altered when treating a relapse. In fact, alternative approaches beyond a temporary corticosteroid dosage increase should be used, not only because disease activity is often less severe at relapse than at initial diagnosis but also considering patients with frequent relapses.[33] One available option for refractory or relapsing disease endorsed by most experts, and when the risk of infection is high, is intravenous immunoglobulins (IVIg). This option is usually considered in patients with hypogammaglobulinemia, especially with recurrent infections, either as Ig replacement therapy or in addition to ongoing immunosuppression.[34,35] A recent meta-analysis explored the role of IVIg in active AAV and disclosed that BVAS significantly decreased after the administration.[36]

There was no agreement on the prospect of repeating renal biopsy in cases where renal recurrence is suspected, primarily due to the invasiveness of the procedure and associated risks, with some experts arguing that clinical and immunological assessments may suffice for diagnosing recurrence. Still, the EULAR task force recommends biopsies to evaluate further patients suspected of relapsing vasculitis.[14]

In the 'renal disease' section, most experts agreed to perform a renal biopsy whenever renal involvement by AAV is suspected. Renal involvement usually leads to ESRD and increases mortality. Prompt diagnosis and initiation of adequate immunosuppressive therapy are critical to ensure the best patient and kidney outcomes.[37] Most nephrologists agreed that MTX is contraindicated in renal failure, emphasizing their primary role in treating patients with severe renal involvement. On the other hand, rheumatologists frequently employed MTX as an immunosuppressive agent in their practice. Still, caution is warranted, particularly in cases of ANCA vasculitis, as there is a recognized risk of adverse events, and dose adjustments are recommended for patients with renal impairment.

Regarding plasmapheresis, most rheumatologists consider that this intervention still has a place in treating ANCA vasculitis. In contrast, while acknowledging its utility in severe cases, nephrologists are influenced by the PEXIVAS trial findings, which demonstrated limited benefits in moderate circumstances. Specifically, it failed to establish a significant delay in kidney failure or mortality with plasma exchange in patients with AAV, particularly those with reduced kidney function or alveolar hemorrhage, over a median follow-up period of 2.9 years.[30]

In the 'other manifestations of illness and/ or comorbidities' section, most experts agreed that immunosuppression is the first-line treatment for orbital pseudotumor, probably related to their availability and efficacy in inducing disease remission.[38] Unsurprisingly, most experts disagreed that low dose corticosteroids have a good long-term safety profile, being virtually risk-free, concerning the 'safety' section.

In the 'prophylaxis' section, most experts from both medical specialties agreed to perform prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) with cotrimoxazole and osteoporosis scenarios (consensus in rheumatology), which aligns with the EULAR recommendations. Notably, while most nephrologists agreed to perform prophylaxis for fungal infections, rheumatologists advocated the opposite, which stems from their distinct patient populations. Nephrologists typically manage severely ill and highly immunosuppressed patients, often dealing with CKD cases. Therefore, they commonly recommend prophylaxis for fungal infections using agents like nystatin, akin to post-renal transplantation care. This approach acknowledges the added immunosuppressive impact of CKD and azotemia. Conversely, rheumatologists adopt a different approach, refraining from advocating for fungal infection prophylaxis, mainly because invasive fungal infections are infrequent in AAV patients.[39] The experts also agreed to screen for tuberculosis before starting immunosuppression and to assess the risk of reactivation of hepatitis B in patients treated with RTX (consensus in rheumatology), considering that infection is the most significant contributor to morbidity and mortality in the first

year of treatment.[39]

Finally, in the 'monitoring and follow-up' section, the answers reflected a more heterogeneous practice. Most rheumatologists agreed to adopt the BVAS/VDI for therapeutic decisions and/or disease activity monitoring, and no agreement was reached when considering the FFS for the therapeutic decision, possibly due to the challenging assessment of its utility in clinical practice. Nonetheless, it is advisable to do a comprehensive clinical evaluation during follow-up examinations at regular intervals, as AAV impacts several organs and relapses are common. The BVAS can be helpful in methodically documenting treatment responses in clinical practice. To prevent unnecessary intensified treatment, it is essential to distinguish between damage caused by AAV or its treatment and actual disease.

This study has several limitations that warrant consideration. One significant limitation is the representativeness of the panel, which comprised 34 nephrologists and 21 rheumatologists. While this panel included experts from two relevant specialties, the imbalance in the number of nephrologists compared to rheumatologists may have influenced the consensus, potentially skewing the results towards nephrological perspectives on AAV treatment. Moreover, the severity of AAV patients followed by nephrologists and rheumatologists differs intrinsically. Expert participation in the Delphi survey was by invitation and voluntary, potentially attracting those with a particular interest in AAV. The inclusion of immunologists or general internists would have also provided a more holistic view of AAV management, due to their role in the management of these patients. Furthermore, geographic and practice setting diversity within the panel can also impact the generalizability of the findings across different patient populations within the Portuguese healthcare scenario. Further research is essential to confirm the findings. A Portuguese multicenter trial would be crucial to better understand the patient population, treatment protocols, and clinical outcomes. Additionally, it would provide clear differentiation of results across various procedures.

CONCLUSION

This study represents, to the best of our knowledge, the first assessment of consensus levels concerning the treatment of AAV in Portugal and the integration of European recommendations into daily clinical practice. This study demonstrates a high level of agreement within each medical specialty (nephrology and rheumatology), attributable to the unique characteristics of the patient populations they manage. Concerns regarding the safety implications of long-term corticosteroids are shared by both rheumatologists and nephrologists. There was also a noteworthy consensus on the prophylactic treatment for opportunistic infections and unanimous support for the use of avacopan. These findings underscore the critical need for initiatives aimed at enhancing awareness and education among Portuguese physicians regarding disease monitoring scores. Lastly, this study underscores the importance of aligning national practices with established European recommendations to ensure the best outcomes for patients with AAV.

ACKNOWLEDGMENTS

The authors acknowledge CSL Vifor's financial support for medical writing assistance, provided by Evidenze Portugal, Lda.

AUTHOR CONTRIBUTIONS

IF, AA; CB, JR, CF: Study design, writing and critical review of the manuscript, approval of the final version of the paper.

BS: Approval of the final version of the paper.

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.

COMPETING INTERESTS

IF received honoraria for lectures from CSL Vifor and GlaxonSmithKline, and support for attending congresses from CSL Vifor.

AA received honoraria for lectures from CSL Vifor and Amgen.

CB received honoraria for lectures from CSL Vifor.

BS is an employee of CSL Vifor.

JR received honoraria for advisory boards from CSL Vifor.

CF received honoraria for lectures and support for attending congresses from CSL Vifor and AstraZeneca.

FUNDING SOURCES

This research received CSL Vifor's financial support for medical writing assistance. The sponsor did not influence the opinions expressed here, which are those of the authors.

REFERENCES

1. Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL, Homburger HA, et al. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med. 2007;120:643 e9-14.
2. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37:187-92.
3. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suarez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015;30:i14-22.
4. Ntatsaki E, Watts RA, Scott DG. Epidemiology of ANCA-associated vasculitis. Rheum Dis Clin North Am. 2010;36:447-61.
5. Jennette JC, Falk RJ. Small-vessel vasculitis. review-article. N Engl J Med. 1997;337:1512-23.
6. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. ReviewPaper. Nat Rev Dis Primers. 2020;6:71.
7. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM. 1994;87:671-8.
8. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009;68:1827-32.
9. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997;40:371-80.
10. Flossmann O, Bacon P, de Groot K, Jayne D, Rasmussen N, Seo P, et al. Development of comprehensive disease assessment in systemic vasculitis. Ann Rheum Dis. 2007;66:283-92.
11. Miller A, Basu N, Luqmani R. Assessment of systemic vasculitis. Autoimmun Rev. 2008;8:170-5.
12. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75:1583-94.
13. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310-7.
14. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2024;83:30-47.
15. Geetha D, Jin Q, Scott J, Hruskova Z, Hanouneh M, Little MA, et al. Comparisons of guidelines and recommendations on managing antineutrophil cytoplasmic antibody-associated vasculitis. Kidney Int Rep. 2018;3:1039-49.
16. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007;66:605-17.
17. Sharma P, Sharma S, Baltaro R, Hurley J. Systemic vasculitis. Am Fam Physician. 2011;83:556-65.
18. Bekker P, Dairaghi D, Seitz L, Leleti M, Wang Y, Ertl L, et al. Characterization of pharmacologic and pharmacokinetic properties of ccx168, a potent and selective orally administered complement 5a receptor inhibitor, based on preclinical evaluation and randomized phase 1 clinical study. PLoS One. 2016;11:e0164646.
19. Jayne DR, Merkel PA, Schall TJ, Bekker P, Group AS. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med. 2021;384:599-609.
20. Gabilan C, Pfirmann P, Ribes D, Rigothier C, Chauveau D, Casemayou A, et al. Avacopan as first-line treatment in antineutrophil cytoplasmic antibody-associated vasculitis: a steroid-sparing option. Kidney Int Rep. 2022;7:1115-8.
21. van Leeuwen JR, Bredewold OW, van Dam LS, Werkman SL, Jonker JT, Geelhoed M, et al. Compassionate use of avacopan in difficult-to-treat antineutrophil cytoplasmic antibody-associated vasculitis. Kidney Int Rep. 2022;7:624-8.
22. Schirmer J, Sanchez-Alamo B, Monti S, Hellmich B, Jayne D. Pos0830 Systematic literature review informing the 2022 update of the eular recommendations for the management of anca-associated vasculitis: focus on treatment strategies. Ann Rheum Dis. 2022;81:s706.1-706.
23. Turgeon D, Bakowsky V, Baldwin C, Cabral DA, Clements-Baker M, Clifford A, et al. CanVasc consensus recommendations for the use of avacopan in antineutrophil cytoplasm antibody-associated vasculitis: 2022 addendum. Rheumatology. 2023;62:2646-51.
24. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology. 2014;53:2306-9.
25. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150:670-80.
26. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221-32.
27. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. research-article. N Engl J Med. 2014;371:1771-80.
28. Charles P, Terrier B, Perrodeau E, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77:1143-9.
29. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Aljayyousi R, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis. 2020;79:1243-9.
30. Morris A, Geetha D. PEXIVAS challenges current ANCA-associated vasculitis therapy. Nat Rev Nephrol. 2020;16:373-4.
31. McGovern D, Williams SP, Parsons K, Farrah TE, Gallacher PJ, Miller-Hodges E, et al. Long-term outcomes in elderly patients with ANCA-associated vasculitis. Rheumatology. 2020;59:1076-83.
32. Quintana LF, Kronbichler A, Blasco M, Zhao MH, Jayne D. ANCA associated vasculitis: the journey to complement-targeted therapies. Mol Immunol. 2019;112:394-8.
33. McClure M, Jones RB. Treatment of relapses in ANCA-associated vasculitis. Clin J Am Soc Nephrol. 2019;14:967-9.
34. Kant S, Azar A, Gapud EJ, Antiochos B, Manno R, Seo P, et al. Subcutaneous Immunoglobulin for antibody deficiency in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Cureus. 2019;11:e6367.
35. Crickx E, Machelart I, Lazaro E, Kahn JE, Cohen-Aubart F, Martin T, et al. Intravenous immunoglobulin as an immunomodulating agent in antineutrophil cytoplasmic antibody-associated vasculitides: a french nationwide study of ninety-two patients. Arthritis Rheumatol. 2016;68:702-12.
36. Shimizu T, Morita T, Kumanogoh A. The therapeutic efficacy of intravenous immunoglobulin in anti-neutrophilic cytoplasmic antibody-associated vasculitis: a meta-analysis. Rheumatology. 2020;59:959-67.
37. Molnar A, Studinger P, Ledo N. Diagnostic and therapeutic approach in ANCA-associated glomerulonephritis: a review on management strategies. Front Med. 2022;9:884188.
38. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: distribution, clinical features, and treatment outcome. Arch Ophthalmol. 2003;121:491-9.
39. King C, Harper L. Avoidance of harm from treatment for ANCA-associated vasculitis. Curr Treatm Opt Rheumatol. 2017;3:230-43.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Avaliação do Efeito da Implementação de um Centro de Responsabilidade Integrado de Obesidade no Desempenho Hospitalar em Portugal

Assessment of the Effect of Implementing an Obesity Center of Integrated Responsibility on Hospital Performance in Portugal

Jorge CARVALHO✉[1,2], Adalberto CAMPOS FERNANDES[2]
Acta Med Port 2024 Nov;37(11):787-791 ▪ https://doi.org/10.20344/amp.22103

RESUMO

O aumento contínuo na prevalência da obesidade é um desafio ao nível global, em termos económicos e de saúde pública. Em Portugal, o tratamento da obesidade apresenta problemas acentuados no acesso aos serviços de saúde. Neste contexto, surge a necessidade de implementar e avaliar novos modelos de gestão que ofereçam respostas mais eficazes, como os centros de responsabilidade integrados. Este estudo tem como objetivo principal avaliar o impacto da implementação de um centro de responsabilidade integrado de obesidade no desempenho hospitalar. A pesquisa foi conduzida por meio de um estudo de caso múltiplo, predominantemente descritivo, mas com elementos também explanatórios. A abordagem metodológica é mista, combinando análises quantitativas e qualitativas. São avaliados indicadores de desempenho hospitalar, incluídos na dimensão do acesso, produção, eficiência, qualidade e económico-financeira, antes e após a implementação do novo modelo. Em termos globais a implementação de um centro de responsabilidade integrado de obesidade conduziu a melhorias no desempenho hospitalar nas dimensões avaliadas, sobretudo ao nível do acesso, produção e eficiência. Apesar de promissor, este novo modelo poderá beneficiar de um conjunto de melhorias em termos organizacionais, funcionais e jurídico-legais, como por exemplo no método de concessão de incentivos e no processo de financiamento. Nos casos analisados, este novo modelo de organização demonstrou ser uma solução para incrementar o desempenho hospitalar. Estas unidades podem desempenhar um papel estratégico fundamental no Sistema Nacional de Saúde, contribuindo para o acesso a tratamentos especializados, retenção de profissionais e sustentabilidade financeira.
Palavras-chave: Acesso aos Serviços de Saúde; Avaliação de Resultados em Cuidados de Saúde; Departamentos Hospitalares/organização e administração; Governança Clínica; Obesidade; Portugal

ABSTRACT

The continuous increase in the prevalence of obesity has generated growing concern, having become an important challenge at a global level in economic and public health terms. In Portugal, the treatment of obesity presents significant problems in access to health services. In this context, there is a need to implement new management models that offer more effective responses. Centers of integrated responsibility, already implemented in this area, are a cutting-edge approach, and it is important to evaluate their performance and identify recommendations for improving the model. The main objective of this study is to assess the impact of implementing an obesity center of integrated responsibility on hospital performance. This study was conducted using a comprehensive multiple-case study approach, which was predominantly descriptive but also included explanatory elements. The methodological approach is a well-balanced mix of quantitative and qualitative analyses. The study evaluates various hospital performance indicators, encompassing the dimensions of access, production, efficiency, quality, and economic-financial, both before and after the implementation of the new model. The overall results indicate that the implementation of an obesity center of integrated responsibility led to improvements in hospital performance, particularly in the dimensions of access, production, and efficiency. While these findings are promising, the study also identifies areas for potential improvement in the model, such as organizational, functional, and legal aspects, including the method of granting incentives and the funding process. In the analyzed cases, this new organizational model proved to be a solution for improving hospital performance, particularly around obesity. These units can play a fundamental strategic role in the National Health System, contributing to access to specialized treatments, retention of professionals and financial sustainability.
Keywords: Clinical Governance; Health Management; Health Services Accessibility; Hospital Departments/organization and administration; Obesity; Outcome Assessment, Health Care

INTRODUÇÃO

O aumento global da obesidade representa uma preocupação crescente, com impacto na economia e na saúde pública.[1] Esta condição, considerada uma doença crónica multifatorial,[2] está associada a diversas doenças graves[3] e sua prevalência continua a aumentar, sem indícios de declínio.[4] Em Portugal, mais de metade da população adulta é afetada pelo excesso de peso,[5] refletindo uma tendência semelhante na Europa.[6] O impacto económico direto da obesidade e do excesso de peso é substancial, com custos crescentes associados ao tratamento e à perda de produtividade.[7] O Programa de Tratamento Cirúrgico da Obesidade (PTCO) do Serviço Nacional de Saúde (SNS) procurou abordar esta questão de forma multidisciplinar. O tratamento da obesidade enfatiza a adoção de um estilo de vida saudável, podendo incluir terapia medicamentosa ou cirurgia, esta última considerada uma das opções mais custo-efetivas.[8]

Num setor como o da saúde, onde os desafios atuais são exigentes,[9] é fundamental desenvolver e implementar modelos de governação que melhorem o acesso, a qualidade e a eficiência dos cuidados de saúde. Nesse sentido, os centros de responsabilidade integrados (CRI) emergem

1. Unidade Local de Saúde de Santo António. Porto. Portugal.
2. Escola Nacional de Saúde Pública. Lisboa Portugal.
✉ **Autor correspondente:** Jorge Carvalho. jorgemiguelcarvalho@gmail.com
Recebido/*Received*: 23/07/2024 - **Aceite/*Accepted*:** 08/08/2024 - **Publicado *Online*/*Published Online*:** 30/08/2024 - **Publicado/*Published*:** 04/11/2024

como uma abordagem que pretende alavancar esses princípios, assentes no incremento da autonomia com responsabilização[10] e atribuição de incentivos pelo desempenho.

Este estudo procura avaliar o impacto da implementação de um CRI de obesidade (CRI-O) no desempenho hospitalar, nas suas diferentes dimensões, e ainda identificar recomendações para a melhoria do modelo.

MÉTODOS

Como fontes de dados utilizamos dados de gestão fornecidos pelos conselhos de gestão, juntamente com os relatórios de atividades. Considerando que não foi possível obter um conjunto alargado de dados de gestão em todas as unidades, foi selecionado um leque de indicadores comuns ao nível do acesso, produção, eficiência, qualidade e económico-financeiros, detalhados nos resultados. Realizaram-se ainda entrevistas aos membros do conselho de gestão de cada unidade, para complementar os dados.

Foi desenvolvido um estudo de caso múltiplo,[11] descritivo e explanatório, combinando abordagens quantitativas e qualitativas. Analisamos três casos (que serão denominados como Unidade A, B e C, de forma a preservar o anonimato) para permitir uma descrição alargada e conceptualizações detalhadas. A utilização de múltiplas fontes de evidência reforça a validade do estudo.[12]

A população em estudo consistiu nos CRI-O. A amostra incluiu as unidades A, B e C, selecionadas por conveniência, pelo facto de existirem dados pré e pós implementação do CRI-O e um mínimo de um ano completo de atividade em CRI.

A recolha de dados proveio de diferentes fontes,[11] como a análise documental; documentos internos do CRI-O, contendo dados de gestão; e entrevistas semiestruturadas, no sentido de permitir a confrontação de dados, com recurso à triangulação. Recorreu-se à estatística univariada com Microsoft Excel® para a análise de dados quantitativos, e análise de conteúdo, segundo Bardin[13] para os dados qualitativos. O estudo respeitou rigorosamente todos os protocolos de investigação e obteve a aprovação de todas as comissões de ética das instituições em estudo.

RESULTADOS

De seguida, apresentam-se os indicadores de desempenho nos triénios (2016 - 2018, pré-CRI) e (2019 - 2021, em CRI), das Unidades A (centro hospitalar e universitário do grupo III[14] – Tabela 1) e B (centro hospitalar do grupo I[14] – Tabela 2); e dos anos de 2019 (pré-CRI) e 2022 (em CRI), da Unidade C (hospital do grupo I[14] – Tabela 3). Em simultâneo, da análise e entrevistas efetuadas foram identificadas diversas recomendações para melhorar o modelo CRI, quer no tratamento da obesidade, quer em termos globais.

Tabela 1 – Indicadores de desempenho Unidade A

Unidade A									
Dimensão	Indicador	2016	2017	2018	2019	2020	2021	Variação (%) entre triénios (média)
Acesso	% Cumprimento TMRG LEC	26,66%	17,18%	14,09%	28,99%	85,22%	94,45%	260,18%
	Mediana TE em LEC (dias)	299	417	551	272	98	66	-65,59%
	Mediana TE em LIC (dias)	84	126	238	134	72	89	-34,15%
	% Cumprimento TMRG LIC	97,41%	80,57%	33,20%	60,47%	83,48%	100,0%	15,53%
Produção	N.º consultas total	5138	5718	5849	9123	12 877	15 959	127,23%
	N.º cirurgias total	566	497	274	582	535	607	28,95%
	N.º doentes saídos	575	564	309	603	508	580	76,15%
Eficiência	N.º doentes operados fora	0	3	27	0	0	0	-100%
	Demora média internamento	3,92	3,4	3,51	2,47	2,49	2,69	-29,36%
Qualidade	% Reinternamentos < 30 dias	0,70%	3,01%	2,27%	0,34%	0,00%	0,17%	-91,46%
Económico-financeiro	Resultado rendimentos-gastos	-259 053,07€	-522 693,64€	-243 900,79€	-180 376,76€	8510,40€	920,00€	83,33%

TMRG: tempos máximos de resposta garantidos; LEC: lista espera consulta; TE: tempo espera; LIC: lista inscritos cirurgia

Tabela 2 – Indicadores de desempenho Unidade B

Unidade B								
Dimensão	Indicador	2016	2017	2018	2019	2020	2021	Variação (%) entre triénios (média)
Acesso	% Cumprimento TMRG LEC	100%	90,1%	100%	90,2%	99,3%	84,8%	-5,45%
	Mediana TE em LEC (dias)	46	68	31	65,5	66	70	38,98%
	Mediana TE em LIC (dias)	220	291	176	77	79	73	-66,67%
	% Cumprimento TMRG LIC	40,0%	45,2%	55,9%	80,1%	88,5%	89,7%	83,07%
Produção	N.º consultas total	4688	4935	5899	8943	8441	10 408	79,05%
	N.º cirurgias total	206	175	210	408	292	683	134,01%
	N.º doentes saídos	166	168	262	490	337	469	117,45%
Eficiência	N.º doentes operados fora	9	15	43	1	0	3	-94,04%
	Demora média internamento	3,6	3,2	3,3	3,8	3,1	2,7	-5,04%
Qualidade	% Reinternamentos < 30 dias	3,95%	2,08%	3,93%	5,86%	4,59%	2,70%	31,93%
Económico-financeiro	Resultado rendimentos-gastos	n.d.	n.d.	n.d.	336 287,94€	249 787,54€	575 555,91€	n.d.

TMRG: tempos máximos de resposta garantidos; LEC: lista espera consulta; TE: tempo espera; LIC: lista inscritos cirurgia

Recomendações identificadas para a melhoria do modelo

- Incentivos: enquadrar e detalhar juridicamente a distribuição de incentivos, evitando que sejam exclusivamente provenientes da produção adicional. Incluir indicadores de qualidade e resultados clínicos para atribuição de incentivos, sobretudo em áreas não cirúrgicas;
- Financiamento: rever o financiamento das consultas de nutrição e psicologia fora do PTCO. Ajustar as tabelas de financiamento à produção, para refletir as necessidades atuais. Criar linhas específicas de financiamento por patologia tratada, baseadas em indicadores de qualidade e resultados clínicos;
- Gestão: introduzir instrumentos de gestão para apurar rendimentos e gastos. Promover a compra centralizada de consumíveis para reduzir custos. Promover *accountability* através do desenvolvimento de mecanismos transversais de monitorização e avaliação;
- Critérios: estabelecer critérios claros para a abertura e encerramento de CRI, baseados em objetivos estratégicos e resultados;
- Sistemas de informação: otimizar os sistemas administrativos e clínicos centralmente, para melhorar a gestão e monitorização do desempenho;
- Planeamento: garantir a aprovação atempada dos planos de atividades e orçamento para uma gestão eficiente e autónoma. Promover redes de referenciação específicas por patologia e incentivar os centros de referência, como incubadoras para novos CRI;
- Alargamento do modelo: criar uma *task-force* para formar novas equipas em CRI. Maximizar a cirurgia de ambulatório e robótica.

DISCUSSÃO

Este estudo compara o desempenho das três unidades antes e depois da implementação do CRI, focando o impacto deste novo modelo de gestão. A análise incluiu indicadores de desempenho e aspetos da atividade assistencial, considerando eventos como a greve cirúrgica de 2019 e a pandemia de COVID-19.

Observou-se uma tendência de melhoria no acesso ao tratamento cirúrgico da obesidade, com maior conformidade nos tempos máximos de resposta garantidos (TMRG) e redução do tempo de espera para consultas e cirurgias. Embora a Unidade B tenha demostrado um ligeiro declínio nos indicadores de acesso devido à elevada procura, o acesso global melhorou e os resultados superaram a média nacional dos centros de tratamento cirúrgico de obesidade.[15]

Tabela 3 – Indicadores de desempenho Unidade C

Unidade C				
Dimensão	Indicador	2019	2022	Variação (%)
Acesso	% Cumprimento TMRG LEC	26,17%	98,06%	274,70%
	Mediana TE em LEC (dias)	217	42	-80,65%
	Mediana TE em LIC (dias)	39	38	-2,56%
	% Cumprimento TMRG LIC	100%	100%	0%
Produção	N.º consultas total	4764	8768	84,05%
	N.º cirurgias total	251	406	61,75%
	N.º doentes saídos	257	427	66,15%
Eficiência	N.º doentes operados fora	0	0	0%
	Demora média internamento	2,33	3,19	26,96%
Qualidade	% Reinternamentos < 30 dias	4,67%	2,11%	-54,82%
Económico-financeiro	Resultado rendimentos-gastos	n.d.	6730 €	n.d.

TMRG: tempos máximos de resposta garantidos; LEC: lista espera consulta; TE: tempo espera; LIC: lista inscritos cirurgia.

O número de consultas e cirurgias aumentou significativamente em todas as unidades, com um aumento correspondente na atividade assistencial. Os recursos humanos permaneceram estáveis, facilitando a avaliação do impacto do CRI.

Em termos de eficiência, houve uma diminuição global na demora média, exceto na Unidade C, que tratou alguns doentes complexos, já sujeitos a cirurgia prévia. A redução do número de doentes operados fora das instituições concorreu para garantir a sustentabilidade financeira ao evitar altos custos com vales cirurgia.

A taxa de reinternamentos diminuiu, refletindo melhorias na assistência pós-operatória, embora a Unidade B tenha apresentado um aumento associado à troca de material cirúrgico, que requereu alguma adaptação. Ressalva-se a necessidade de avaliar outros indicadores de qualidade relacionados com a obesidade, não disponíveis.

Na vertente económico-financeira, os dados disponíveis sugerem melhorias nos resultados após a implementação do CRI, antevendo maior sustentabilidade, mas exigindo também uma análise mais aprofundada dos rendimentos e custos, no sentido de melhor compreender a forma como a instituição gera e cria valor.[16]

O modelo CRI foi descrito como facilitador na reorganização dos serviços de saúde, centrado nas necessidades dos doentes, promovendo a colaboração entre a equipa multidisciplinar e a diferenciação clínica. Apesar dos desafios, os resultados sugerem que podem ser geradas melhorias no acesso, produção, eficiência, qualidade e resultados económico-financeiros, destacando-se a necessidade de uma avaliação contínua e ajustes no modelo para garantir a sua eficácia e expansão a breve prazo. Estudos futuros poderão ser muito úteis para confirmar e/ou generalizar os nossos resultados.

Considerações finais

Considerando os dados disponíveis, a implementação de um CRI-O teve um impacto globalmente positivo nas unidades estudadas. O estudo efetuado aponta algumas considerações relevantes, como: a necessidade de uma abordagem holística para a obesidade; um CRI-O pode melhorar o acesso ao tratamento cirúrgico da obesidade, reduzir listas de espera e cumprir os TMRG, especialmente se integrado num programa bem estabelecido (PTCO); as lideranças e uma equipa dedicada são cruciais para o sucesso; os incentivos baseados no desempenho criam motivação e promovem a retenção de profissionais; o CRI pode aumentar a competitividade interna e ser replicado em outras áreas clínicas; o modelo pode ser aprimorado com a inclusão de indicadores de resultado reportados pelos doentes, com foco na qualidade e nos resultados clínicos.

AGRADECIMENTOS

Os autores agradecem a Xavier Barreto, Eduardo Lima da Costa, Filipe Conceição, Mário Nora, José Adão, Rui Pinto e Carla Lopes pela profícua colaboração na disponibilização de dados e entrevistas.

CONTRIBUTO DOS AUTORES

JC: Conceptualização e desenho do artigo, recolha e análise de dados, elaboração e revisão crítica do manuscrito.

ACF: Conceptualização do artigo, revisão crítica do manuscrito.

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 2013.

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

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

REFERÊNCIAS

1. Mohajan D, Mohajan HK. Obesity and Its Related Diseases: A New Escalating Alarming in Global Health. J Innovat Med Res. 2023;2:12-23.
2. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6-10.
3. Organisation for Economic Cooperation and Development /European Union: Overweight and obesity among adults. In Health at a Glance: Europe 2022: State of Health in the EU Cycle. Paris: OECD Health Publishing; 2022. [consultado 2023 maio 18]. Disponível em: https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe-2022_26e2160a-en.
4. World Obesity Federation. World Obesity Atlas 2023. London: WOF; 2023. [consultado 2023 maio 30]. Disponível em: https://www.who.int/europe/publications/i/item/WHO-EURO-2021-2574-42330-58595.
5. Oliveira A, Araújo J, Severo M, Correia D, Ramos E, Torres D, et al. Prevalence of general and abdominal obesity in Portugal: comprehensive results from the National Food, nutrition and physical activity survey 2015-2016. BMC Public Health. 2018;18:614.
6. Marques A, Peralta M, Naia A, Loureiro N, de Matos MG. Prevalence of adult overweight and obesity in 20 European countries, 2014. Eur J Public Health. 2018;28:295-300.
7. Páscoa R, Teixeira A, Henriques TS, Monteiro H, Monteiro R, Martins C. Characterization of an obese population: a retrospective longitudinal study from real-world data in northern Portugal. BMC Prim Care. 2023;24:99.
8. Borisenko O, Adam D, Funch-Jensen P, Ahmed AR, Zhang R, Colpan Z, et al. Bariatric surgery can lead to net cost savings to health care systems: results from a comprehensive European decision analytic model. Obes Surg. 2015;25:1559-68.
9. Bernardino M. Gestão em Saúde: organização interna dos serviços. Coimbra: Almedina; 2017.
10. Portugal. Portaria N.º 330/2017. Diário da República, I série, n.º 210 (31/10/2017). p.5848-52.
11. Yin RK. Case study research and applications: design and methods. 6ª ed. Los Angeles: SAGE; 2018.
12. Brito MJ, Rezende DA, Ávila GS, Lima Cardoso CM. O estudo de caso como método de investigação na pesquisa qualitativa em Enfermagem. In Atas do 8º Congresso Ibero-Americano em Investigação Qualitativa. Aveiro: Ludomedia; 2019. p.444-53.
13. Bardin L. Análise de Conteúdo. São Paulo: Edições 70; 2016.
14. Portugal. Portaria N.º 82/2014. Diário da República. I série, n.º 71 (10/04/2014). p.2364-6.
15. Entidade Reguladora da Saúde. Cuidados de saúde prestados no SNS na área da obesidade. Porto: Entidade Reguladora da Saúde; 2019. [consultado 2023 maio 05]. Disponível em: https://www.ers.pt/uploads/writer_file/document/2448/ERS_-_Cuidados_obesidade_SNS.pdf.
16. Porter M. Competitive advantage: creating and sustaining superior performance. New York: Free Press; 1985.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Principles of the Orthogeriatric Model of Care: A Primer

Fundamentos dos Modelos Assistenciais de Ortogeriatria: Uma Introdução

Cameron STEPHEN[1], Yashar MASHAYEKHI[1], Mohamed H. AHMED[2,3,4], Lia MARQUES[5], Maria P. PANOURGIA✉[3,4]
Acta Med Port 2024 Nov;37(11):792-801 ▪ https://doi.org/10.20344/amp.20768

ABSTRACT

It is well known that over the last few decades, there has been significant growth of the aging population worldwide and especially in Europe, with an increase of more than two years per decade since the 1960's. Currently, in Europe, people aged over 65 years old represent 20% of the population, creating many new and complex challenges for national healthcare systems. In many countries, geriatric medicine is an established medical specialty, integrated into the primary and secondary care of the older population. In some countries, such as Portugal, specialist training in geriatric medicine is not available, even though the life-expectancy in Portugal is currently 81 years due to a decrease in fertility and mortality, and people aged over 60 currently represent nearly a third of the population. There is strong evidence in the medical literature that a fracture following a fall, and especially a neck of femur fracture, is one of the most serious events that can happen in an older person's lifetime. These fractures have been associated with increased morbidity, loss of independence, a high rate of institutionalization, and mortality. Rates of mortality after a year from femoral fractures have been proven to be three to four times higher than the expected in the general population, ranging between 15% to 36%. This emphasizes the importance of developing well-organized care pathways for these patients, which combine specialized geriatric care (also known as orthogeriatric care). This narrative review will focus on the core principles of orthogeriatric care and how medical professionals, including those who are not specialized in geriatric care, can effectively use them.
Keywords: Geriatric Assessment; Geriatrics; Health Services for the Aged; Femoral Neck Fractures; Orthopedics

RESUMO

O envelhecimento da população mundial tem sido exponencial nas últimas décadas, em particular na Europa, onde os adultos com mais de 65 anos representam 20% da população, o que tem criado novos e complexos desafios aos sistemas de saúde. Na maior parte dos países da Europa, a medicina geriátrica é uma especialidade médica bem estabelecida, integrada nos cuidados de saúde primários e secundários. Noutros países, como em Portugal, não existe ainda um internato de formação especifica em medicina geriátrica, apesar de um terço da população portuguesa ter mais de 60 anos. A ocorrência de quedas com fraturas, em particular fraturas da extremidade proximal do fémur, é um marcador de mau prognóstico nas fases mais avançadas da vida. Estas fraturas associam-se a um aumento da morbilidade, perda de autonomia funcional, aumento da necessidade de admissão em estruturas residenciais para idosos e aumento da mortalidade. A taxa de mortalidade no ano seguinte à ocorrência de uma fratura da extremidade proximal do fémur é três a quatro vezes superior à esperada para a população geral, e varia entre os 15% e os 36%. A necessidade de implementar modelos de cuidados específicos para este grupo de doentes baseados nos princípios da medicina geriátrica levou ao desenvolvimento da Ortogeriatria. Esta revisão narrativa centra-se nos princípios dos modelos de cuidados de Ortogeriatria e em estratégias para que os clínicos, mesmo num país em que não existe a especialidade de Medicina Geriátrica, possam aplicar estes princípios e implementar estes modelos.
Palavras-chave: Avaliação Geriátrica; Geriatria; Fracturas do Colo do Fémur; Ortopedia; Serviços de Saúde para Idosos

INTRODUCTION

According to the United Nations World Population Prospects 2022, the older population (aged 65 or over) is increasing worldwide and in Europe it is projected to reach 29% of the total population by 2050, from the current 19%.[1] This growth burdens healthcare systems because of the volume of care required for the aged population. Portugal has seen a rise in life expectancy to 81 years, with 23% of the population aged 65 and over as per 2022 statistics.[2,3] Management of older patients with fractures, particularly neck of femur fractures (NOF), poses a significant challenge within healthcare frameworks, given the high prevalence and associated morbidity and mortality.[4-6]

Orthogeriatric care is a medical-surgical model involving a multidisciplinary team (MDT). The MDT is an interprofessional and interdisciplinary team that includes medical professionals such as orthopedic surgeons, geriatricians, nurses, physical and occupational therapists, social workers, nutritionists, pharmacists and, most importantly, the patient and their next of kin. The role of the MDT is to optimize the management of surgical and medical complications surrounding NOF fractures.[7,8]

The Fragility Fracture Network (FFN) was established in 2011 to address the growing challenges of the care of fragility fracture patients.[9] The FFN provides support and training to relevant medical professionals, disseminating research and clinical practice improvement across pillars of care for fragility fracture patients that include perioperative care, surgical treatment, rehabilitation, secondary prevention, and policy change. The FFN Four Pillars of Orthogeriatric Care are summarized in Fig. 1.[9]

1. Medical School. University of Buckingham. Buckingham. United Kingdom.
2. Department of Medicine and HIV Metabolic Clinic. Milton Keynes University Hospital. National Health Service Foundation Trust. Milton Keynes. United Kingdom.
3. Department of Geriatric Medicine. Milton Keynes University Hospital. National Health Service Foundation Trust. Milton Keynes. United Kingdom.
4. Faculty of Medicine and Health Sciences. University of Buckingham. Buckingham. United Kingdom.
5. Department of Medicine. Hospital CUF Tejo. Lisbon. Portugal.
✉ **Autor correspondente:** Maria P. Panourgia. maria.panourgia@mkuh.nhs.uk
Recebido/*Received*: 02/10/2023 - **Aceite/*Accepted*:** 25/07/2024 - **Publicado/*Published*:** 04/11/2024

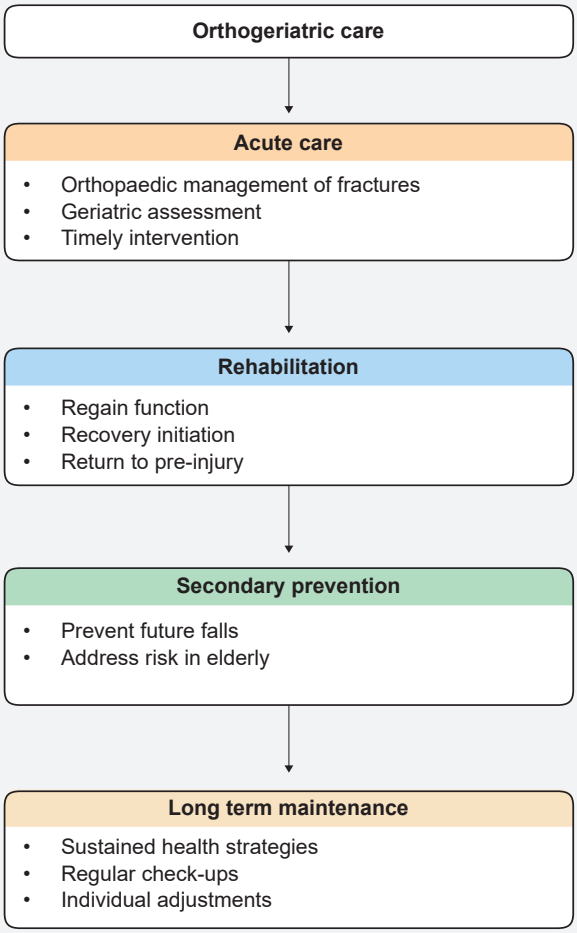


Figure 1 – The Fragility Fracture Network's four pillars of orthogeriatric care

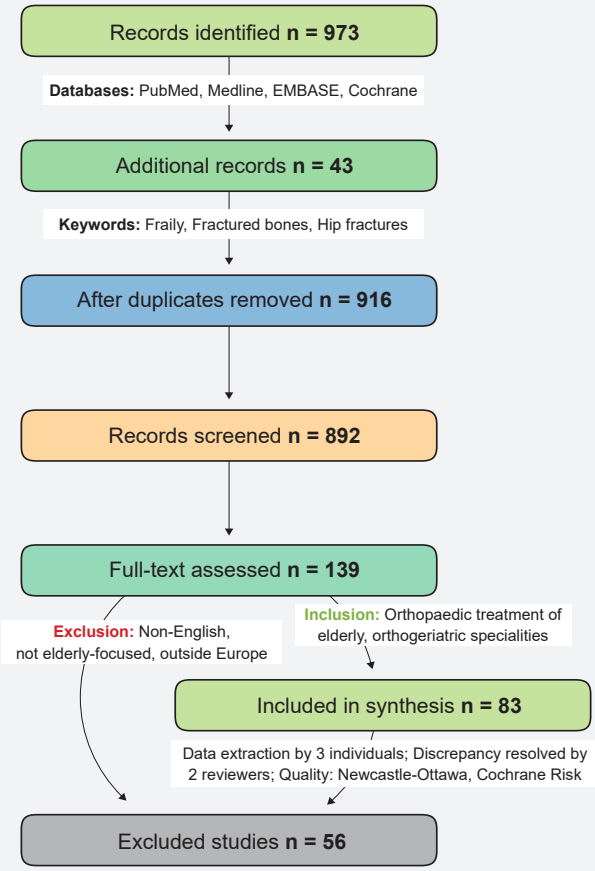


Figure 2 – PRISMA diagram as described in methodology

This review provides an overview of the principles of geriatric medicine and how geriatric care is essential to improve patients' outcomes following a major fragility fracture such as a femoral one.

Methodology

A comprehensive literature search on geriatric care in patients with neck of femur and fragility fractures was undertaken across databases including PubMed, Medline, EMBASE, and the Cochrane Library, spanning the period from January 1990 to December 2022. The following keywords which represent the essence of geriatric medicine and geriatric care in femoral fractured old people were used for the search: "geriatric care", "orthogeriatric", "hip fracture", "frailty", "delirium", "outcome" and "orthopedic care". For inclusion, the studies focused on orthopedic treatment of the older person in Europe, the origins of orthogeriatric specialties, and clinical trials related to orthogeriatric therapies. Non-English articles, those that included data of participants younger than 60 years old or outside of Europe, and those with insufficient data or weak methodology, were excluded. Fig. 2 illustrates the review process in a PRISMA diagram.

Ethical considerations

Since this was a review article, no primary data were gathered, hence there was no need for ethical approval. However, the ethical implications of each study that was reviewed as well as the permission received for the original research were evaluated. The authors did not receive any financial support from third parties.

PRINCIPLES OF GERIATRIC MEDICINE

Geriatric medicine is a recognized independent medical specialty in 17 of 31 European countries, a recognized subspecialty in 10 countries, and in two countries (Germany and France), both models (independent specialty and subspecialty) exist. Only five countries (Cyprus, Estonia, Greece, Portugal, and Slovenia) do not have a recognized

postgraduate medical degree in geriatric medicine (medical specialty) as of 2016.[10]

Geriatric medicine is a specialty concerned with physical, mental, functional, and social conditions in acute, chronic, rehabilitative, preventive, and end-of-life care in older patients. This group of patients are considered to have a high degree of frailty and active comorbidities, requiring a holistic approach. Diseases may present differently in old age, are often very difficult to diagnose, the response to treatment is often delayed, and there is frequently a need for social support. Geriatric medicine therefore exceeds organ-oriented medicine offering additional therapy in a multidisciplinary team setting, the main aim of which is to optimize the functional status of the older person and improve the quality of life and autonomy.[11]

Geriatric syndromes

Geriatric syndromes are distinct conditions occurring in older patients that do not stem from identifiable diseases but rather occur due to the accumulation of impairments across multiple systems affecting multiple domains. They are often the consequence of multiple underlying factors and include frailty, urinary incontinence, falls, delirium, polypharmacy, and pressure ulcers. It is well known that in the general geriatric population, geriatric syndromes are predictors of hospitalization, increased healthcare costs, and increased overall mortality.[12-17] The most common geriatric syndromes and screening tools are listed in Fig. 3.

The use of the comprehensive geriatric assessment (CGA) is of utmost importance in the identification of geriatric syndromes, encompassing complex illnesses which frequently result in adverse health outcomes among older individuals.[18,19]

Frailty

Frailty can be described as "a biological syndrome characterized by a reduction in physiological reserve and resistance to stresses".[20]

This condition arises from the cumulative deterioration across several physiological systems, ultimately rendering individuals more susceptible to negative health outcomes.[21,22] In the evaluation of frailty, it is customary to employ instruments such as the Clinical Frailty Scale (CFS), which classifies individuals into nine distinct stages ranging from highly robust to terminally ill, considering factors such as mobility, energy levels, physical activity, and overall functional capacity.[23] The validity of this scale has been established for diverse populations, including the Portuguese population.[24] Based on our experience, the CFS is more advantageous than other scales for NOF patients as it eliminates the need for mobilization to measure muscle strength.

Sarcopenia

Sarcopenia, as described by the European Working Group on Sarcopenia in Older People's (EWGSOP) second meeting, in 2018, is "a progressive and generalized skeletal muscle condition linked with an elevated risk of undesirable consequences such as physical disability, poor quality of life, and mortality".[25]

According to a recent metanalysis, sarcopenia is associated with a high risk of osteoporosis, falls, fracture, functional decline, hospitalization, cognitive impairment, metabolic syndrome, diabetes, non-alcoholic liver disease, liver fibrosis, hypertension, depression, dysphagia, and increased mortality.[26] The prevalence of sarcopenia ranges from 5% to 13% in people aged 60 to 70, rising to 11% to 50% in people over 80 years old.[27,28]

The EWGSOP consensus meeting in 2018 defines sarcopenia as a condition characterized by low muscle strength (criterion 1) and low muscle quantity or quality (criterion 2). If low physical performance is also present (criterion 3), then the sarcopenia is considered severe.[25]

Considering the adverse physical outcomes and the economic cost of sarcopenia to the national healthcare systems, the "International Clinical Practice Guidelines for Sarcopenia" produced by the task force of the International Conference on Sarcopenia and Frailty Research (ICSFR) and the EWGSOP recommend annual screening of everyone older than 65 in general practice or outpatient clinics using a tool such as SARC-F questionnaire.[25,29] There are five SARC-F components: strength, assistance with walking, rise from a chair, climb stairs and falls. The scores range from 0 to 10, with 0 to 2 points for each component; a score equal to or greater than 4 is predictive of sarcopenia and poor outcomes.[30]

Once patients have been screened via the SARC-F and identified as likely affected by sarcopenia, then their muscle strength (criterion 1) should be assessed. Muscle strength can be measured with the grip strength or the chair stand test. If the patient has low muscle strength, then the presence of sarcopenia is probable. To confirm the presence of sarcopenia, muscle quantity or quality should be measured (criterion 2), but this can be challenging in most clinical settings as it requires access to radiological examinations like dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), or computed tomography (CT) scans; hence, the EWGSOP group recommends searching for the causes and implementing interventions in patients that have been identified as likely sarcopenic using the criterion 1.[25]

Once sarcopenia is confirmed by the presence of criterions 1 and 2, then the physical performance (criterion 3) should be assessed using tests like the gait speed, the 'Timed Up and Go' (TUG), a short physical performance battery, and a 400-meter walk.[25]

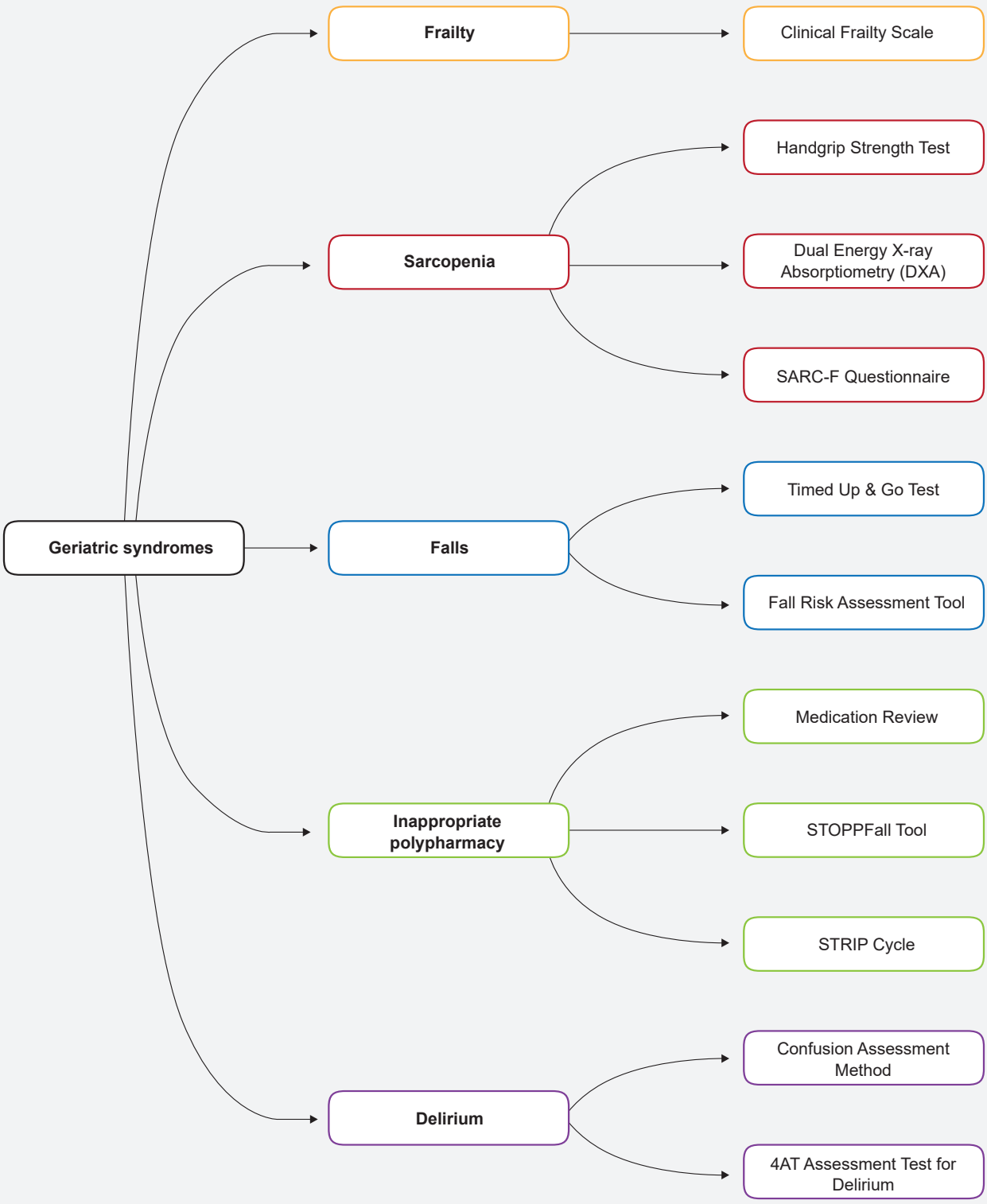


Figure 3 – Geriatric syndromes and screening tools
SARC-F: strength, assistance in walking, rise from a chair, climb stairs – falls; STOPPFall: screening tool of older persons prescriptions in older adults with high fall risk; STRIP cycle: systematic tool to reduce inappropriate prescribing cycle; 4AT: assessment test for delirium and cognitive impairment

Falls

It is well known that falls are the main cause of hip fractures in the aging population.[31] Falls occur in 30% of adults over 65 years old[32] and they have well known consequences and negative health outcomes such as personal distress and loss of confidence, increased disability, hospital admissions, and mortality.[33-35]

In September 2022 the "World Guidelines for Falls Prevention and Management for Older Adults: A Global Initiative" were published.[36] The guidelines recommend "a multiprofessional and multifactorial assessment to community-dwelling older adults identified to be at high risk of falling, to guide tailored interventions".[36] Part of the recommendation on falls assessment includes consideration of factors such as the patient's environment (e.g., lighting, cluttered rooms, etc.), footwear, fall history, eyesight and balance issues, daily activities, and medication side effects.[36,37] The guidelines also recommend the use of three key questions to identify individuals at risk of falls: A) "has the person fallen in the past year?"; B) "do they feel unsteady when standing or walking?"; C) "do they worry about falling?".[36] The patient is considered being at high risk of falling if the answer is positive for one of the three key questions and there is the presence of at least one of the following five events that determine the fall severity: a) injury following the fall; b) two or more falls in a year; c) frailty; d) lying on the floor or unable to get up after a fall; e) loss of consciousness or suspected syncope; and individually tailored interventions should be put in place.

In case there are no fall severity events, then the gait and balance of the patient should be assessed with the TUG test or the gait speed (cut off > 15 sec and < 0.8 m/s, respectively). If the gait and balance are impaired, then the patient is considered at intermediate risk of falls, and they should be offered tailored exercises on balance, strength, and gait, and education on fall prevention.[36]

Recognizing individuals through these metrics allows for timely and effective interventions that can significantly lower the likelihood of falls. Prioritizing fall assessments and focused interventions can provide immediate and noticeable benefits in reducing hip fractures and related morbidities in the older population.

Inappropriate polypharmacy

Inappropriate polypharmacy is rather prevalent in the population concerned and has the potential to cause a myriad of complications, such as falls.[21,38,39]

In the context of post-operative care, the completion of a medication review allows for the optimization of patient care. Not only does this have the potential to decrease the pharmaceutical burden on the patient or their carer, but also reaps benefits for the healthcare system at-large, decreasing the dispensing of unnecessary or unwanted medications hence decreasing costs in this area.[40,41] Carrying out such a review should be done on any admission, ensuring medications are genuinely indicated and at optimal dose if so.

The European Geriatric Society used an expert Delphi consensus process to produce the STOPPFall tool, defined as Screening Tool of Older Persons Prescriptions in older adults with high fall risk.[42] This tool allows clinicians to identify the fall-risk-increasing drugs and offers a practical deprescribing tool for medical optimization.

This can be thought of as "right drug, right patient, right dose, right time."

Many groups have formulated methods of decreasing polypharmacy, one of which being Systematic Tool to Reduce Inappropriate Prescribing (STRIP).[43] This works on the premise of five steps, which aim to identify and resolve incidents of polypharmacy and reduce inappropriate prescribing, which can be reviewed and cycled regularly for optimization of care, summarized in Table 1.[43]

Delirium

Delirium has been defined by the Royal College of Psychiatrists UK as "a state of mental confusion that starts suddenly and is caused by a physical condition".[44]

Post-operative delirium is one of the most serious complications following NOF surgery. Post-operative delirium can occur in up to 50% of NOF surgery patients, especially older patients with pre-existing cognitive deficits.[45] This delirium has serious consequences, including an increased risk of mortality following surgery, with some studies indicating a threefold increase in the chance of death within the first year.[45] Furthermore, the occurrence of delirium in the context of orthopedic procedures, particularly those involving NOF fractures, remains a major issue due to the associated lengthy hospital stays, healthcare expenses, and rehabilitation challenges.[46,47] It can be detrimental to physiotherapy, extending the rehabilitation period.[48] In addition, delirium increases the risk of falls, leads to long-term cognitive impairment,[49] and admission to long term care.[50-52]

Contributing factors can be summarized using the acronym 'PINCH ME' (Table 2), which is a useful tool to identify

Table 1 – Summary of Systematic Tool to Reduce Inappropriate Prescribing (STRIP) cycle

Step	Summary
Step 1	Drug history
Step 2	Analysis of drugs
Step 3	Treatment plan
Step 4	Patient preferences
Step 5	Follow-up and monitoring

Table 2 – The 'PINCH ME' acronym (pain, infection, nutrition, constipation, hydration, medication/metabolic, environment) helps to identify causes of delirium and possible interventions

Letter	Cause of delirium	Clinical tips and considerations
P	Pain	Undertake a thorough pain assessment. Check for urinary retention.
I	Infection or intoxication	Urinary tract infections can present atypically in the older adult. Review medication and intoxicants.
N	Nutrition (malnutrition)	Check nutritional status, electrolytes, B12, and folate levels.
C	Constipation or central nervous system pathology	Bowel movements history is crucial. Consider imaging for central nervous system pathology if indicated.
H	Hydration (dehydration) or hypoxia	Monitor fluid balance and urine output. Check oxygen saturation and arterial blood gas if needed.
M	Metabolic/medications	Thyroid, liver, and kidney function tests. Review all medications for anticholinergic load or other side effects.
E	Environment (new surroundings) or endocrine	Assess for unfamiliar surroundings leading to disorientation. Thyroid dysfunction, hypo/hyperglycaemia.

the possible cause for delirium and plan an intervention.

For optimal post-operative management in senior patients, it is important that healthcare professionals are trained in delirium prevention, early diagnosis, and therapeutic intervention.[44]

Some commonly used tools for detection of delirium are the 4AT, a quick method that does not require specific training that uses four domains (alertness, abbreviated mental and attention testing, and observation of an acute change in mental state)[53]; and the Confusion Assessment Method.[54]

The comprehensive geriatric assessment

The CGA is a collaborative and interdisciplinary approach that incorporates an inclusive perspective of the health of older individuals, frequently integrating insights from many healthcare professionals such as geriatricians, nurses, social workers, physiotherapists, and occupational therapists.[55]

The CGA is used to identify the presence of geriatric syndromes and following the CGA the MDT will provide an individualized plan to manage patient needs.[56,57]

The assessment typically encompasses multiple fundamental domains:

- Medical evaluation: to assess and address chronic diseases and the use of many medicines, which are frequently encountered in the senior population.
- Functional status: to obtain insight of the patient's ability to engage in self-care activities and move independently.[58]
- Mental health evaluation: involves screening for cognitive impairment and emotional well-being.[59]
- Nutritional status: conducted through the use of validated screening instruments to identify and effectively manage instances of malnutrition or the potential for malnutrition.[59]
- Socio-environmental aspects: comprise the living conditions and social support systems accessible to the individual.[57]

SPECIFIC CONDITIONS MANAGED BY ORTHOGERIATRICIANS

One of the subspecialties of geriatric medicine is orthogeriatrics. The orthogeriatricians are specialists in the care of the geriatric population and work in collaboration with the orthopedic surgeons to provide the best possible care to the patients admitted with fragility fractures, particularly, but not only, femoral fractures.[60]

Infections

Infections are one of the most common post-operative complications, following surgery for a fractured NOF[61] and may be considered an ongoing battle in the war of perioperative care. A Danish study[62] collating the data of over 74 000 hip fracture patients found that mortality was significantly higher in those with infection "irrespective of patients' age, sex and comorbidity".

Older patients admitted to orthopedic wards following hip fractures are often frail and susceptible to infection, most common chest or urinary. Additionally, the procedure itself poses a potential source of infection.[62,63]

The orthogeriatrician with the experience and knowledge in the field of geriatric care and internal medicine can promptly recognize and manage post-operative complications, including infections.[64]

Pain management

The use of efficient pain management strategies following fractures in senior individuals is crucial, as it serves the dual purpose of mitigating discomfort and facilitating prompt mobilization, which reduces the likelihood of adverse

outcomes such as delirium and extended hospital stays. Nevertheless, the management of pain in older adults is a complex matter as it is influenced by age-related changes in drug metabolism, the existence of multiple simultaneous medical diseases and the heightened susceptibility to potential drug interactions.[65]

Paracetamol is frequently regarded as the primary choice for pain management in older individuals owing to its comparatively favorable safety profile. However, it is imperative for doctors to maintain a state of constant awareness regarding the possibility of hepatotoxicity, particularly in those with pre-existing liver conditions or those who are administered high doses of medication.[66]

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs often used to treat a variety of medical ailments, including pain relief and inflammation reduction. Despite this, a major implication of NSAID use is that of impaired bone healing. There are contrasting literature findings including several meta-nalyses suggesting an impairment of osteogenesis and increased chances of delayed or non-union, so the regular use of NSAIDs is not recommended.[67-71]

Opioids, despite being beneficial, carry side effects including constipation, respiratory depression, and risk of falls. Opioids should only be used temporarily, starting with the lowest dose and up-titrating, if necessary, frequently assessing for toxicity.[68]

Peripheral nerve blocks can be particularly beneficial for pain or specific pain syndromes.[69] Nerve blocks can be used as an alternative to, or in conjunction with, systemic analgesics. In comparison to NSAIDs or opioids, they frequently have fewer systemic side effects and provide localized pain relief.[70] In the United Kingdom (UK), the National Institute for Care and Health Excellence, in recent guidelines (2023), recommends the fascia iliac block to be offered in the emergency department.[71]

Bone health

In the countries where orthogeriatric care is available, orthogeriatricians are the promoters of secondary prevention for fragility fractures using the local and national guidelines for osteoporosis.[72] The prevention and treatment of osteoporosis is a vast argument and beyond the scope of this review. However, it is important to point out that in a meta-analysis, Van Camp *et al*[73] demonstrate that "orthogeriatric care is associated with higher rates of diagnosing osteoporosis, initiation of calcium and vitamin D supplements and anti-osteoporosis medication".

The benefits of orthogeriatric care

It has been proven, across multiple national healthcare systems, that the established collaboration between orthopedic surgeons and geriatricians improves patient outcomes.

Studies regarding the benefits surrounding reductions of postoperative complications when orthogeriatric care was involved showed the risk of delirium drop by 19%, as well as a decrease in risk of in-hospital and one-year mortality by 14% and 28%, respectively.[74,75] A further review collated and analyzed data on length-of-stay as well as in-hospital and long-term mortality for orthogeriatric models and hip fracture patients, whilst another study found use of nerve blocks prior to admission also reduced time spent in hospital [OR 1.07 (1.03, 1.11)].[64,75] This showed that orthogeriatric care, particularly that of the shared-care model (where the care of the patient is equally shared between the orthopedic surgeon and the orthogeriatrician), had a significant impact on the reduction of each of these factors.[76] Shared-care models saw a significant reduction in length of stay, from 27.5 to 21 days and 22% in 30-day mortality, following control for factors such as age, sex, American Society for Anesthesiology grade, and Abbreviated Mental Test score.[76]

A review of patients on the Danish Multidisciplinary Hip Fracture Registry[77] pooled data of over 11 000 patients aged 65 or over, assessing six process performance measures, 30-day mortality, length of stay, and time to surgery across orthogeriatric and standard orthopedic wards. It found that those cared for by orthogeriatric specialists experienced a reduction in 30-day mortality (adjusted odds ratio 0.69; 95% CI 0.54 - 0.88) while the length of stay and time to surgery remained similar (adjusted relative time of 1.18 and 1.06, respectively).

The national hip fracture database has shown great improvements in mortality across the UK, from 10.9% to 6.7% between 2007 to 2016 respectively.[78,79] This is related to the presence of geriatricians in the orthopedic wards and the promotion of time to theatre within 36 hours from the admission. From this, it can be concluded that there is strong evidence to support the role of orthogeriatric care, particularly the shared-care model.[80-82]

It could be argued that the overall reduction in postoperative complications decreases strain on healthcare services, reducing costs incurred with prolonged stays and medicines to treat complications. This would also serve to reduce stress and pressures placed on staff members, as a multidisciplinary approach encourages collaborative and well-supported care.[76-78] Regarding costs, direct medical expenses associated with hospitalization, surgical procedures, drugs, and rehabilitation services are extremely burdensome. The yearly cost for hip fractures in the UK was estimated at approximately £2 billion.[83] Financial Aspects of Orthogeriatric Post-Fracture Care are summarized in Table 3.

Table 3 – Summarising the financial aspects of orthogeriatric post-fracture care

Aspect	Details
Direct costs	Encompasses hospitalization, surgical procedures, medications, and rehabilitation.
Indirect costs	Covers lost productivity, caregiver time and resources, and potential home modifications or long-term care facilities.
Potential savings	Proactive geriatric assessments and interventions can reduce hospital readmissions and subsequent costs.
Financial challenges and solutions	Balancing quality of care with rising costs. Collaborative models and preventive measures like fall prevention can improve outcomes and reduce costs.

The use of collaborative shared-care models, which involve the joint management of patients by orthopedic surgeons and geriatricians, has demonstrated potential in enhancing patient outcomes and achieving cost savings.

Research has demonstrated that the use of early intervention strategies and complete geriatric evaluations can effectively decrease the rates of hospital readmissions, resulting in significant financial savings.[56,64]

CONCLUSION

Neck of femur fractures represent a dramatic moment for all patients. However, their subsequent management can be very challenging in the older population. There are proven associations with increased postoperative morbidity, the need for long-term care, and mortality. The care provided by an orthogeriatrician aims to prevent clinical complications such as infections and delirium and to assist with pain management, thus improving the overall care. As discussed, there is evidence that the outcomes for NOF patient drastically improve in the presence of an MDT including an orthogeriatrician.

Orthogeriatricians have the expertise to identify and manage geriatric syndromes as well as other clinical complications that may occur during the admission of a frail patient with a fracture. In countries where geriatric medicine is an integrated part of the healthcare, the collaboration between orthopedic doctors and geriatricians has produced an outstanding improvement in overall patient outcomes. We believe the presence of a geriatrician or a medical physician with expertise in the care of older adults is not only beneficial but should be considered the gold-standard.

Importantly, orthogeriatricians play a pivotal role in the prevention of falls and fragility fractures, whilst promoting appropriate rehabilitation, reducing multidisciplinary stress through providing thorough and ongoing medical support, and reducing the chances of multiple admissions, all whilst ultimately improving outcomes for the patient and their loved ones.

AUTHOR CONTRIBUTIONS

CS, YM: Writing and critical review of the article.

MHA, LM, MPP: Study conception and design, writing and critical review of the article.

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.

COMPETING INTERESTS

MP is a member of the executive board of Fragility Fracture Network, Greece.

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.

REFERENCES

1. United Nations. United Nations world population prospects 2022. [cited 2024 Jan 30]. Available from: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf.
2. Instituto Nacional de Estatística. Tábuas de mortalidade em Portugal. [cited 2024 Jan 30]. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_destaques&DESTAQUESdest_boui=594474380&DESTAQUESmodo=2.
3. The World Bank Data. Population ages 65 and above (% of total population) – Portugal. [cited 2024 Jan 30]. Available from: https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS?locations=PT.
4. Mundi S, Pindiprolu B, Simunovic N, Bhandari M. Similar mortality rates in hip fracture patients over the past 31 years: a systematic review of RCTs. Acta Orthop. 2014;85:54-9.
5. Katsoulis M, Benetou V, Karapetyan T, Feskanich D, Grodstein F, Pettersson U, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. J Intern Med. 2017;281:300-10.

6. de Joode SG, Kalmet PH, Fiddelers AA, Poeze M, Blokhuis TJ. Long-term functional outcome after a low-energy hip fracture in elderly patients. J Orthop Traumatol. 2019;20:20.
7. Lamb LC, Montgomery SC, Wong Won B, Harder S, Meter J, Feeney JM. A multidisciplinary approach to improve the quality of care for patients with fragility fractures. J Orthop. 2017;14:247-51.
8. Tarazona-Santabalbina FJ, Belenguer-Varea Á, Rovira E, Cuesta-Peredó D. Orthogeriatric care: improving patient outcomes. Clin Interv Aging. 2016;11:843-56.
9. Fragility Fracture Network. Fragility Fracture Network FFN. [cited 2023 Sep 09]. Available from: https://fragilityfracturenetwork.org/.
10. European Union of Medical Specialists. Geriatric Medicine - Section of UEMS. [cited 2024 Jan 30]. Available from: https://uemsgeriatricmedicine.org/www/index.asp.
11. European Union of Medical Specialists Geriatrics Section. Definition of Geriatrics (English Version, original version). [cited 2024 Jan 30]. Available from: https://uemsgeriatricmedicine.org/www/land/definition/english.asp.
12. World Health Organization. Ageing and health. 2022. [cited 2024 Jan 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
13. Huang HH, Lin PY, Chen TY, Wang TY, Chang JC, Peng LN, et al. Geriatric syndromes predict mortality of people aged 75+ years in the observation room of emergency department: towards function-centric emergency medicine. Arch Gerontol Geriatr. 2022:100:104662.
14. Magnuson A, Schroder S, Nightingale G, Saracino R, Skonecki E, Trevino K. A practical guide to geriatric syndromes in older adults with cancer: a focus on falls, cognition, polypharmacy, and depression. Am Soc Clin Oncol Educ Book. 2019;39:e96-109.
15. Evans SJ, Sayers M, Mitnitski A, Rockwood K. The risk of adverse outcomes in hospitalized older patients in relation to a frailty index based on a comprehensive geriatric assessment. Age Ageing. 2014;43:127-32.
16. Chang SF, Lin PL. Frail phenotype and mortality prediction: a systematic review and meta-analysis of prospective cohort studies. Int J Nurs Stud. 2015;52:1362-74.
17. Kamwa V, Seccombe A, Sapey E. The evidence for assessing frailty and sarcopenia in an acute medical unit: a systematic review. Acute Med. 2021;20:48-67.
18. Eamer G, Taheri A, Chen SS, Daviduck Q, Chambers T, Shi X, et al. Comprehensive geriatric assessment for older people admitted to a surgical service. Cochrane Database Syst Rev. 2018;1:CD012485.
19. British Geriatrics Society. Comprehensive geriatric assessment toolkit for primary care practitioners. [cited 2023 Jun 12]. Available from: https://www.bgs.org.uk/.
20. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173:489-95.
21. Fried L, Tangen C, Walston J, Newman A, Hirsch C, Gottdiener J, et al. Frailty in older adults evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56.
22. van Ka GA, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc. 2008;9:71-2.
23. Falaschi P, Marsh D, editors. Orthogeriatrics: the management of older patients with fragility fractures. 2nd ed. Cham: Springer; 2021.
24. Pereira Pinto M, Martins S, Mesquita E, Fernandes L. European Portuguese version of the clinical frailty scale: translation, cultural adaptation and validation study. Acta Med Port. 2021;34:749-60.
25. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16-31. Erratum in: Age Ageing. 201;48:601.
26. Yuan S, Larsson SC. Epidemiology of sarcopenia: prevalence, risk factors, and consequences. Metabolism. 2023;144:155533.
27. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. J Cachexia Sarcopenia Muscle. 2014;5:253-9. Erratum in: J Cachexia Sarcopenia Muscle. 2015;6:192.
28. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: a systematic review and meta-analysis of general population studies. J Diabetes Metab Disord. 2017;16:21.
29. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging. 2018;22:1148-61.
30. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14:531-2.
31. Marks R, Allegrante JP, Ronald MacKenzie C, Lane JM. Hip fractures among the elderly: causes, consequences and control. Ageing Res Rev. 2003;2:57-93.
32. Ganz DA, Latham NK. Prevention of falls in community-dwelling older adults. N Engl J Med. 2020;382:734-43.
33. Blain H, Masud T, Dargent-Molina P, Martin FC, Rosendahl E, van der Velde N, et al. EUGMS Falls and Fracture Interest Group; European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), Osteoporosis Research and Information Group (GRIO), and International Osteoporosis Foundation (IOF). A comprehensive fracture prevention strategy in older adults: The European Union Geriatric Medicine Society (EUGMS) Statement. J Nutr Health Aging. 2016;20:647-52.
34. James SL, Lucchesi LR, Bisignano C, Castle CD, Dingels ZV, Fox JT, et al. The global burden of falls: global, regional and national estimates of morbidity and mortality from the Global Burden of Disease Study 2017. Inj Prev. 2020;26:Si3-11.
35. Kwan MM, Close JC, Wong AK, Lord SR. Falls incidence, risk factors, and consequences in Chinese older people: a systematic review. J Am Geriatr Soc. 2011;59:536-43.
36. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51:afac205.
37. National Institute for Health and Care Excellence. Falls in older people: assessing risk and prevention. 2013. [cited 2023 Aug 19]. Available from: https://www.nice.org.uk/guidance/cg161.
38. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13:57-65.
39. Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging. 2009;26:1039-48.
40. Kojima G, Bell C, Tamura B, Inaba M, Lubimir K, Blanchette PL, et al. Reducing cost by reducing polypharmacy: the polypharmacy outcomes project. J Am Med Dir Assoc. 2012;13:818.e11-5.
41. Morgan SG, Hunt J, Rioux J, Proulx J, Weymann D, Tannenbaum C. Frequency and cost of potentially inappropriate prescribing for older adults: a cross-sectional study. CMAJ Open. 2016;4:E346-51.
42. Seppala LJ, Petrovic M, Ryg J, Bahat G, Topinkova E, Szczerbińska K, et al. STOPPFall (screening tool of older persons prescriptions in older adults with high fall risk): a delphi study by the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Age Ageing. 2021;50:1189-99.
43. Drenth-van Maanen AC, Leendertse AJ, Jansen PA, Knol W, Keijsers CJ, Meulendijk MC, et al. The systematic tool to reduce inappropriate prescribing (STRIP): combining implicit and explicit prescribing tools to improve appropriate prescribing. Thematic. J Eval Clin Pract. 2018;24:317-22.
44. Royal College of Psychiatrists. RCPsych: delirium. 2019. [cited 2023 Aug 19]. Available from: https://www.rcpsych.ac.uk/mental-health/mental-illnesses-and-mental-health-problems/delirium.
45. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: a meta-analytic review. Int Psychogeriatr. 2007;19:197-214.
46. Juliebø V, Bjøro K, Krogseth M, Skovlund E, Ranhoff AH, Wyller TB. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. J Am Geriatr Soc. 2009;57:1354-61.
47. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008;168:27-32.
48. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367:30-9.
49. MacLullich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long-

term cognitive impairment. Int Rev Psychiatry. 2009;21:30-42.
50. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304:443-51.
51. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354:1157-65. Erratum in: N Engl J Med. 2006;354:1655.
52. Chen Y, Liang S, Wu H, Deng S, Wang F, Lunzhu C, et al. Postoperative delirium in geriatric patients with hip fractures. Front Aging Neurosci. 2022;14:1068278.
53. MacLullich A. The 4AT. 2010. [cited 2023 Aug 19]. Available from: https://www.the4at.com/.
54. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941-8.
55. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet. 1993;342:1032-6.
56. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2011;7:CD006211.
57. Pilotto A, Cella A, Pilotto A, Daragjati J, Veronese N, Musacchio C, et al. Three decades of comprehensive geriatric assessment: evidence coming from different healthcare settings and specific clinical conditions. J Am Med Dir Assoc. 2017;18:192.e1-e11.
58. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49:M85-94.
59. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. J Am Geriatr Soc. 1991;39:S8-16.
60. Aw D, Sahota O. Orthogeriatrics moving forward. Age Ageing. 2014;43:301-5.
61. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study BMJ. 2005;331:1374.
62. Kjørholt KE, Kristensen NR, Prieto-Alhambra D, Johnsen SP, Pedersen AB. Increased risk of mortality after postoperative infection in hip fracture patients. Bone. 2019;127:563-70.
63. Pincus D, Ravi B, Wasserstein D, Huang A, Paterson JM, Nathens AB, et al. Association between wait time and 30-day mortality in adults undergoing hip fracture surgery. JAMA. 2017;318:1994-2003.
64. Van Heghe A, Mordant G, Dupont J, Dejaeger M, Laurent MR, Gielen E. Effects of orthogeriatric care models on outcomes of hip fracture patients: a systematic review and meta-analysis. Calcif Tissue Int. 2022;110:162-84.
65. Borsheski R, Johnson QL. Pain management in the geriatric population. Mo Med. 2014;111:508-11.
66. Dixon J, Ashton F, Baker P, Charlton K, Bates C, Eardley W. Assessment and early management of pain in hip fractures: the impact of paracetamol. Geriatr Orthop Surg Rehabil. 2018;9:2151459318806443.
67. Wheatley BM, Nappo KE, Christensen DL, Holman AM, Brooks DI, Potter BK. Effect of NSAIDs on bone healing rates: a meta-analysis. J Am Acad Orthop Surg. 2019;27:e330-6.
68. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-United States. JAMA. 2016;315:1624-45.
69. Kim CH, Yang JY, Min CH, Shon HC, Kim JW, Lim EJ. The effect of regional nerve block on perioperative delirium in hip fracture surgery for the elderly: a systematic review and meta-analysis of randomized controlled trials. Orthop Traumatol Surg Res. 2022;108:103151.
70. Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. Anesth Analg. 2017;124:308-35.
71. National Institute for Health and Care Excellence. Hip fracture: management. Clinical guideline [CG124]. 2023. [cited 2024 Jan 30]. Available from: https://www.nice.org.uk/guidance/cg124/resources/cg124-hip-fracture-full-guideline.
72. Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. Lancet. 2022;399:1080-92. Erratum in: Lancet. 2022;400:732.
73. Van Camp L, Dejaeger M, Tournoy J, Gielen E, Laurent MR. Association of orthogeriatric care models with evaluation and treatment of osteoporosis: a systematic review and meta-analysis. Osteoporos Int. 2020;31:2083-92.
74. Office for National Statistics. Profile of the older population living in England and Wales in 2021 and changes since 2011. 2023. [cited 2023 Jul 12]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/profileoftheolderpopulationlivinginenglandandwalesin2021anddchangessince2011/2023-04-03#:~:text=The%20number%20of%20people%20aged,from%2016.4%25%20to%2018.6%25.
75. Hawley S, Inman D, Gregson CL, Whitehouse M, Johansen A, Judge A. Predictors of returning home after hip fracture: a prospective cohort study using the UK National Hip Fracture Database (NHFD). Age Ageing. 2022;51:afac131.
76. Middleton M, Wan B, da Assunção R. Improving hip fracture outcomes with integrated orthogeriatric care: a comparison between two accepted orthogeriatric models. Age Ageing. 2017;46:465-70.
77. Kristensen PK, Thillemann TM, Søballe K, Johnsen SP. Can improved quality of care explain the success of orthogeriatric units? A population-based cohort study. Age Ageing. 2016;45:66-71.
78. Middleton M. Orthogeriatrics and hip fracture care in the UK: factors driving change to more integrated models of care. Geriatrics. 2018;3:55.
79. Neuburger J, Currie C, Wakeman R, Johansen A, Tsang C, Plant F, et al. Increased orthogeriatrician involvement in hip fracture care and its impact on mortality in England. Age Ageing. 2017;46:187-92.
80. Patel R, Judge A, Johansen A, Marques EM, Chesser T, Griffin XL, et al. Patients' recovery of mobility and return to original residence after hip fracture are associated with multiple modifiable components of hospital service organisation: the REDUCE record-linkage cohort study in England and Wales. BMC Geriatr. 2023;23:459.
81. Zhang J, Yang M, Zhang X, He J, Wen L, Wang X, et al. The effectiveness of a co-management care model on older hip fracture patients in China - a multicentre non-randomised controlled study. Lancet Reg Health West Pac. 2021;19:100348.
82. Tarazona-Santabalbina FJ, Ojeda-Thies C, Figueroa Rodríguez J, Cassinello-Ogea C, Caeiro JR. Orthogeriatric management: improvements in outcomes during hospital admission due to hip fracture. Int J Environ Res Public Health. 2021;18:3049.
83. Office for Health Improvement & Disparities. Guidance falls: applying all our health. 2022. [cited 2024 Apr 07]. Available from: https://www.gov.uk/government/publications/falls-applying-all-our-health/falls-applying-all-our-health.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Idiopathic Systemic Capillary Leak Syndrome: Report of a Pediatric Case

Síndrome de Extravasamento Capilar Sistémico Idiopático: Relato de um Caso Pediátrico

João VASCO✉[1], Francisca ALBUQUERQUE[2], Francisca COSTA[3], Ana DIAS CURADO[4], Carlos ESCOBAR[3]
Acta Med Port 2024 Nov;37(11):802-804 ▪ https://doi.org/10.20344/amp.21531

ABSTRACT

The idiopathic systemic capillary leak syndrome is characterized by recurrent episodes of hypovolemia, with an unknown cause, presenting as a distributive and hypovolemic shock, due to fluid loss to the extravascular space. We describe a case of a previously healthy seven-year-old boy, who started with prodromal symptoms (abdominal pain, fatigue, nausea), followed by a fluid extravasation phase, with hemoconcentration, hypoproteinemia, and muscular edema in the abdominal wall and lower limbs, accompanied by pain – compartment syndrome. After a couple of days, spontaneous and fast recovery was noted, with clinical and analytic improvement. The inflammatory markers were always normal, and the blood cultures were negative. In this case, it is possible to distinguish the three idiopathic systemic capillary leak syndromes phases, as described in the literature. Although rare, this syndrome can be fatal, and the differential diagnosis with other causes of shock represents a challenge.
Keywords: Capillary Leak Syndrome; Child; Shock

RESUMO

A síndrome de extravasamento capilar sistémico idiopático é caracterizada por episódios recorrentes de hipovolemia, apresentando-se como um choque distributivo e hipovolémico, pela perda de líquido para o espaço extravascular, sendo a sua fisiopatologia desconhecida. Descrevemos o caso de um rapaz de sete anos, previamente saudável, que iniciou um quadro clínico de sintomatologia inespecífica, com evolução para uma fase de extravasamento de líquidos, com hemoconcentração, hipoproteinemia e edema intermuscular abdominal, progredindo para os membros inferiores, com queixas álgicas – síndrome compartimental. Posteriormente, evoluiu favoravelmente com recuperação espontânea após recrutamento do líquido extravascular, com melhoria clínica e analítica. Os parâmetros inflamatórios permaneceram negativos e não foi isolado nenhum microrganismo. Perante esta evolução característica, com as três fases descritas na literatura, admitimos uma síndrome de extravasamento capilar sistémico que, apesar de rara, pode ser fatal, fazendo diagnóstico diferencial com outras causas de choque, com tratamento urgente, demonstrando a importância do diagnóstico precoce.
Palavras-chave: Choque; Criança; Síndrome de Vazamento Capilar

INTRODUCTION

Idiopathic systemic capillary leak syndrome (ISCLS) was first described in 1960 by Clarkson *et al.*[1] Characterized by recurrent episodes of increased vascular permeability, with loss of protein rich fluid to the extravascular space, it can result in a distributive and hypovolemic shock, mimicking serious conditions, such as septic shock or anaphylaxis.[2-5] Idiopathic systemic capillary leak syndrome is a rare disorder, with around 500 adult cases reported in the literature, and is even less common in children, with around 30 cases described.[2]

The etiology and pathophysiology are unknown, although several theories of pathogenesis have been proposed.[4] In adults it has been associated with monoclonal gammopathy,[2-5] but this correlation is not present in the pediatric population.[2-4] Another distinctive factor is that in children, almost every episode is triggered by an acute infection.[2,3] Intense physical exercise may also trigger attacks.[6]

The syndrome progresses in three distinct phases, starting with a prodromal phase consisting of symptoms like fatigue, nausea/vomiting, abdominal pain, edema and myalgias. After one to four days the second phase takes place, presenting as a hypovolemic shock, with hypotension, hypoalbuminemia, and hemoconcentration due to fluid extravasation.[2-4] In this phase, acute kidney injury, compartment syndrome of the extremities, and cerebral edema can occur.[2-5] The last stage is the recovery phase, with fluids recruited back to the vascular bed, and normalization of blood tests and clinical condition.[2-4] Therapy is mostly supportive in the various stages, according to needs. In patients with ISCLS already diagnosed, prophylactic immunoglobulin seems to reduce the number of acute episodes and improve morbidity and mortality.[2,4]

Here we present the case of a seven-year-old with an acute episode of ISCLS, describing the clinical manifestations and evolution, and addressing this rare condition and the importance of an early diagnosis.

CASE REPORT

A seven-year-old boy, previously healthy, presented with a three-day history of fatigue, arthralgias, muscle soreness,

1. Serviço de Pediatria. Hospital do Divino Espírito Santo. Ponta Delgada. Portugal.
2. Serviço de Pediatria. Unidade Local de Saúde do Alentejo Central. Évora. Portugal.
3. Unidade de Cuidados Intensivos e Especiais Pediátricos. Unidade Local de Saúde Amadora/Sintra. Amadora. Portugal.
4. Unidade de Infeciologia e Imunodeficiências. Serviço de Pediatria. Hospital de Santa Maria. Unidade Local de Saúde de Santa Maria. Lisboa. Portugal.
✉ **Autor correspondente:** João Vasco. jgoncalvesvasco@gmail.com
Recebido/*Received*: 18/03/2024 - **Aceite/*Accepted*:** 08/07/2024 - **Publicado *Online*/*Published Online*:** 23/08/2024 - **Publicado/*Published*:** 04/11/2024

abdominal pain, dysuria and periorbital edema. A week before he had a self-limited viral infection and sustained physical exercise. After the first observation in the emergency room, he started vomiting and abdominal pain intensified. Lab results showed hemoconcentration (Hb 18.1 g/dL; Htc 54.7%) due to fluid loss. Fluid therapy was initiated, with a first bolus, but persistent tachycardia and oliguria were noted. Analytic reevaluation revealed an abnormal renal function (serum creatinine 1.09 mg/dL; GFR 49 mL/min/1.73 m^2) and worsening of hemoconcentration (Hb 21.4 g/dL; 66.3%). Urinalysis, thorax x-ray and cardiac tests (echocardiogram and biomarkers) were normal. Due to clinical progression with hypotension, a second fluid bolus was administered. There was no need for vasoactive drugs. Ceftriaxone was started and blood cultures collected. The patient was transferred to an intensive care unit.

In the pediatric intensive care unit (PICU) he remained tachycardic (150 bpm), without hypotension, and with abdominal pain. At admission blood gases revealed pH 7.35, $HCO3^-$ 16.8 mEq/L, base deficiency 14.1 mEq/L and lactate 4.3 mmol/L (max. 8 mmol/L). Hemoconcentration (Hb 22.7 g/dL, Htc 68%) persisted and hypoalbuminemia (2.48 g/dL) was revealed. An abdominal computed tomography (CT)-scan revealed intermuscular edema in the abdominal wall and thighs. A few hours later, the renal function worsened (maximum creatinine 1.48 mg/dL), with progression to anuria, and hypoproteinemia. For that reason, albumin 20% 1 g/kg was administered, and a furosemide infusion was started with improvement in the urine output. The patient complained about non-specific pain in the lower limbs.

In the next day, the clinical condition began to improve, with normal urine output and a reduction in heart rate. Inflammatory blood markers, serologic testing and blood cultures were negative, excluding infectious shock causes. Antibiotic therapy was stopped after three days. At the end of the day, lower limb edema suddenly became noticeable, with pale skin and reduced dorsalis pedis pulse, accompanied by worsening of the pain. Compartment syndrome of the extremities was confirmed, with measured tissue pressure around 30 mmHg and diastolic blood pressure of 60 mmHg, and presence of rhabdomyolysis with elevation of creatinine phosphokinase (CK) – max 4340 U/L. After surgical evaluation, fasciotomy was not needed. Ultrasound excluded deep venous thrombosis.

Two days later, the child began to improve, with regression of periorbital and lower limb edema. A second furosemide perfusion was required during the recovery phase. When discharged from the intensive care unit, analytic evaluation showed a normal renal function and complete blood count. The patient fully recovered one week after hospital admission, diagnosis of ISCLS was assumed and prophylactic treatment was started with monthly intravenous immunoglobulin therapy (IVIG) 1 g/kg. Outpatient follow-up was maintained, with no new episodes until the present day.

DISCUSSION

According to the literature, the median age at presentation of pediatric ISCLS is 4.5 years-old, but it has been described in all ages from newborns to adolescence.[2] Around 75% of children affected by this disease, as in our case, had an acute illness preceding the episode.[2,3] Patients typically present with tachycardia, hypotension, hemoconcentration and hypoalbuminemia.[2-5] Differential diagnosis with common causes of distributive shock can be challenging. The most common complications of the acute extravasation phase are uncompensated circulatory shock and rhabdomyolysis – with or without compartment syndrome –, and, in the recovery phase, pulmonary edema.[2,3] Other analytic changes have been described as rise of IL-8, TNF- a and CCL2.[3]

The treatment is not well established, consisting of supportive care during the extravasation and recovery phase.[2-4] In most of the described cases, multiple crystalloid bolus and albumin administrations were used,[3] as in our patient. More specific and successful treatments in the acute phase are described with aminophylline plus terbutaline[2-4] and IVIG.[3,4] In one pediatric case, infliximab appeared effective in reverting symptoms.[4] Prophylactic therapy is well-documented in adults, with IVIG being the treatment of choice,[3,4] and in most recent series it has been equally successful in children.[3] As recurrent episodes can be severe or fatal, even with prompt recognition, we decided to start prophylactic IVIG in our patient.

With this report we aim to raise awareness of a rare but life-threatening disease that mimics other serious conditions such as septic shock, toxic shock syndrome or anaphylaxis. The characteristic triad of hypotension, hypoalbuminemia, and hemoconcentration, along with negative inflammatory markers, helps with the diagnosis. After excluding the previously described conditions, ISCLS should be considered and treated to give support and prevent complications.

AUTHOR CONTRIBUTIONS

JV: Literature review and writing of the manuscript.

FA, FC, ADC: Writing and critical review of the manuscript.

CE: 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.

PARENTAL 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.

REFERENCES

1. Clarkson B, Thompson D, Horwith M, Luckey EH. Cyclical edema and shock due to increased capillary permeability. Am J Med. 1960;29:193-216.
2. Bozzini MA, Milani GP, Bianchetti MG, Fossali EF, Lava SA. Idiopathic systemic capillary leak syndrome (Clarkson syndrome) in childhood: systematic literature review. Eur J Ped. 2018;177:1149-54.
3. Hsu P, Xie Z, Frith K, Wong M, Kakakios A, Stone KD, et al. Idiopathic systemic capillary leak syndrome in children. Pediatrics. 2015;135:e730-5.
4. Bichon A, Bourenne J, Gainnier M, Carvelli J. Capillary leak syndrome: state of the art in 2021. Rev Méd Interne. 2021;42:789-96.
5. Lee H, Shin J, Kim S, Hwang JH. Idiopathic systemic capillary leak syndrome: a case report. BMC Nephrology. 2023;24:72.
6. Gousseff M, Arnaud L, Lambert M, Hot A, Hamidou M, Duhaut P, et al. The systemic capillary leak syndrome: a case series of 28 patients from a European registry. Ann Intern Med. 2011;154:464-71.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

When Eyes Speak Louder: Uncontrolled Hypothyroidism Revealed Through Madarosis and Eyelid Edema

Quando os Olhos Falam Mais Alto: Madarose e Edema Palpebral como Sinais de Hipotiroidismo Não Controlado

Nuno ROCHA JESUS✉[1], Juliana SILVA[2], Patrícia TAVARES[1]
Acta Med Port 2024 Nov;37(11):805-806 ▪ https://doi.org/10.20344/amp.21720

Keywords: Coma; Myxedema; Hypothyroidism
Palavras-chave: Coma; Mixedema; Hipotiroidismo

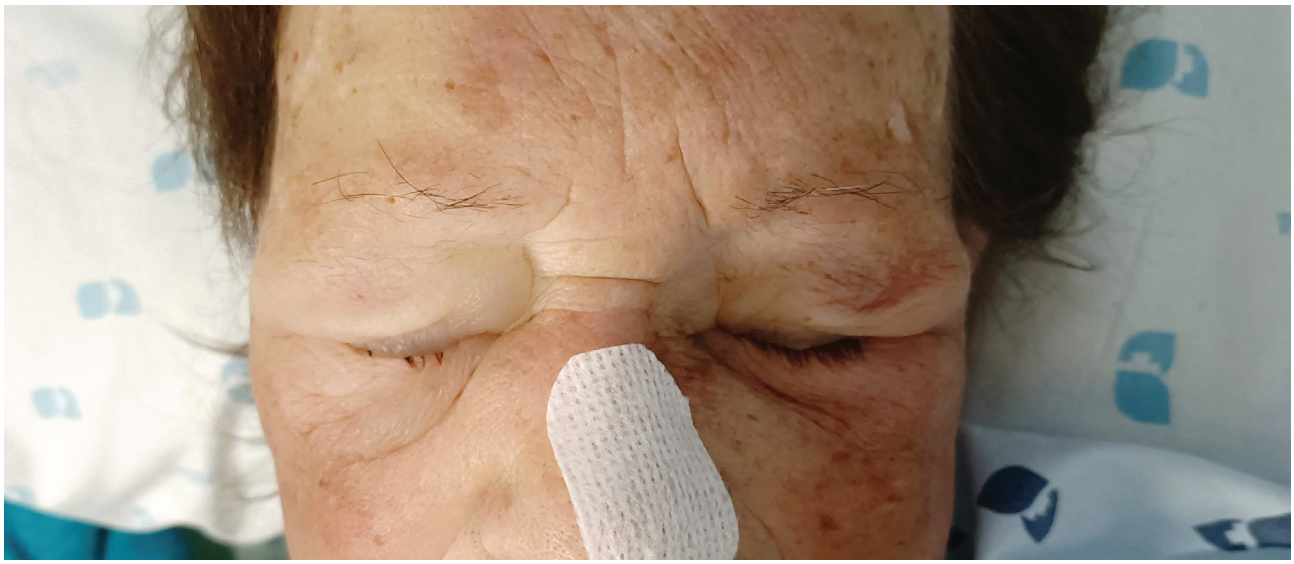


Figure 1 – Marked eyelid edema and madarosis (loss of the distal third of the eyebrows) in a 79-year-old woman with decompensated hypothyroidism

A 79-year-old woman, with dependence on daily activities, and history of moderate-stage dementia and hypothyroidism due to total thyroidectomy for multinodular goiter, was hospitalized for prostration, arterial hypotension (78/45 mmHg), hypoglycemia (47 mg/dL), anorexia, and urinary tract infection, scoring 65 points on the Diagnostic Scoring System for Myxedema Coma (≥ 60 points is highly suggestive/diagnostic of myxedema coma).[1] Despite the correction of hypoglycemia and the start of antibiotic therapy with decreasing inflammatory markers, the patient did not improve her consciousness level in the following two days. Physical examination revealed marked eyelid edema, madarosis (loss of eyebrows or eyelashes), and pitting edema in the upper and lower limbs. Laboratory studies revealed TSH 135 µU/mL (reference range: 0.27 – 4.20 µU/mL) and T4L < 0.039 ng/dL (reference range: 0.93 – 1.70 ng/dL). The patient was referred to the Endocrinology clinic and was started on hydrocortisone 100 mg every eight hours, received a single dose of levothyroxine 200 mcg IV, and kept levothyroxine on 100 mcg once a day. The next day, her arousal level, the eyelid edema, and the pitting edema in the limbs had significantly improved. The patient was discharged five days later.

The mortality rate of myxedema coma ranges from 30% - 60%, mainly due to delayed diagnosis and treatment.[2] Diagnosis is clinical and should be suspected, especially in elderly patients with altered mental status and a history of hypothyroidism. Early replacement therapy with hydrocortisone and levothyroxine is crucial, even before analytical confirmation.[3] Clinicians should be aware of less common

1. Serviço de Endocrinologia. Unidade Local de Saúde Gaia e Espinho. Vila Nova de Gaia. Portugal.
2. Serviço de Medicina Interna. Unidade Local de Saúde Gaia e Espinho. Vila Nova de Gaia. Portugal.
✉ **Autor correspondente:** Nuno Rocha Jesus. nrjesus@live.com.pt
Recebido/*Received*: 19/05/2024 - **Aceite/*Accepted*:** 02/09/2024 - **Publicado/*Published*:** 04/11/2024

signs of hypothyroidism, such as eyelid edema and madarosis. However, these signs are nonspecific, so other systemic diseases should be considered.

AUTHOR CONTRIBUTIONS

NRJ: Data acquisition, analysis and interpretation, writing and critical review of the manuscript.

JS, PT: Data acquisition, analysis and interpretation, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

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.

REFERENCES

1. Popoveniuc G, Chandra T, Sud A, Sharma M, Blackman MR, Burman KD, et al. A diagnostic scoring system for myxedema coma. Endocr Pract. 2014;20:808-17.
2. Bridwell RE, Willis GC, Gottlieb M, Koyfman A, Long B. Decompensated hypothyroidism: a review for the emergency clinician. Am J Emerg Med. 2021;39:207-12.
3. Ylli D, Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. Pol Arch Intern Med. 29 2019;129:526-34.

A Rare Case of Pulmonary Lymphoepithelial-Like Carcinoma

Um Caso Raro de Carcinoma Pulmonar Linfoepitelial

Keywords: Carcinoma, Non-Small-Cell Lung; Lymphoid Tissue
Palavras-chave: Carcinoma Pulmonar de Células não Pequenas; Tecido Linfoide

Dear Editor,

Pulmonary lymphoepithelial-like carcinoma (PLELC) is a rare subtype of non-small cell lung cancer (NSCLC), representing < 1% of all lung cancers. Epstein-Barr virus (EBV) infection is the most common cause.[1] It is generally diagnosed in middle-aged, non-smoking women of Asian descent.[2]

The authors present the case of a 71-year-old woman, born in Macau, non-smoker, who was admitted to the emergency department due to productive cough, fever, and an episode of hemoptoic sputum in the previous three weeks. Chest computed tomography (CT) with contrast, excluded active hemorrhage and identified a spiculated lingular nodule. In the oncology clinic, 18F-FDG PET/CT confirmed the presence of a solid lingular nodule, measuring 12.5 X 9 mm, hypermetabolic (SUV max: 1.4) consistent with a malignant neoplastic lesion. A contrast-enhanced magnetic resonance imaging (DCE-MRI) excluded secondary lesions. Therefore, a clinical stage IA (cT1N0M0) was defined, according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual.

Given the inaccessibility of the lesion by bronchoscopy or transbronchial lung biopsy, an extemporaneous biopsy was performed, as well as lingulectomy and mediastinal lymphadenectomy using uniportal video-assisted thoracoscopic surgery. The examination of the wedge resection surgical specimen identified a PLELC with invasion of the visceral pleura and, therefore, a pathological stage IB (pT2aN0M0), according to the 8th edition of the AJCC staging manual. Immunohistochemistry revealed positivity for CK5/6, p40, TTF1 and EBV encoded RNA; PD-L1 40%. Plasma EBV-DNA was negative and next generation sequencing had no target molecular mutations. Adjuvant chemotherapy with platinum doublet was started, having completed four cycles. During chemotherapy, the patient presented with anemia grade 1 (mild symptoms), according to the definition issued by the Common Terminology Criteria for Adverse Events version 5.0. The patient is currently under surveillance.

Although PLELC is a rare malignant tumor, it has a better prognosis than that of other NSCLC. Most patients tend to present at early and resectable stages and surgical resection is a common primary approach with a curative intent. Therefore, in the case of a patient of Asian descent, non-smoker, with non-specific respiratory symptoms and chest CT evidence of a solitary mass/nodule,[3] it is important to consider PLELC in the list of differential diagnoses, since it is a subtype of NSCLC that, if diagnosed and treated in a timely manner, has a high survival rate.[4,5]

AUTHOR CONTRIBUTIONS

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

MG, GS, LF: Writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

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.

REFERENCES

1. Wei J, Liu Q, Wang C, Yu S. Lymphoepithelioma-like hepatocellular carcinoma without Epstein-Barr virus infection: A case report and a review of the literature. Indian J Pathol Microbiol. 2015;58:550-3.
2. Liang Y, Wang L, Zhu Y, Lin Y, Liu H, Rao H, et al. Primary pulmonary lymphoepithelioma-like carcinoma: fifty-two patients with long-term follow-up. Cancer. 2012;118:4748-58.
3. Zhou L, Liu XY, He Y, Li LT, Zhang SJ. Pulmonary lymphoepithelioma-like carcinoma: a case report with emphasis on computed tomography findings. Medicine. 2021;100:e24453.
4. He J, Shen J, Pan H, Huang J, Liang W, He J. Pulmonary lymphoepithelioma-like carcinoma: a surveillance, epidemiology, and end results database analysis. J Thorac Dis. 2015;7:2330-8.
5. Lin L, Lin T, Zeng B. Primary lymphoepithelioma-like carcinoma of the lung: an unusual cancer and clinical outcomes of 14 patients. Oncol Lett. 2017;14:3110-6.

Mariana TAVARES✉[1], Marcos OLIVEIRA[1,2], Gonçalo SAMOUCO[1], Luís FERREIRA[1,2]
1. Department of Pulmonology. Hospital Sousa Martins. Unidade Local de Saúde da Guarda. Guarda. Portugal.
2. Faculdade de Ciências da Saúde. Universidade da Beira Interior. Covilhã. Portugal.
✉ **Autor correspondente:** Mariana Tavares. mari.tavares.cardoso@gmail.com
Recebido/*Received*: 17/06/2024 - **Aceite/*Accepted*:** 02/09/2024 - **Publicado *Online*/*Published Online*:** 27/09/2024 - **Publicado/*Published*:** 04/11/2024

https://doi.org/10.20344/amp.21951

A Rare Cause of Common Pain: Herpes Zoster-Induced Sciatica

Uma Causa Rara de Dor Comum: Ciática Induzida por Herpes Zoster

Keywords: Herpes Zoster/complications; Sciatic Nerve; Sciatica/etiology
Palavras-chave: Ciática/etiologia; Herpes Zoster/complicações; Nervo Ciático

Dear Editor,

Lumbosacral radiculopathy, presenting as dysesthetic (abnormal and often uncomfortable sensations such as burning, tingling, or sharp pain) lower back pain radiating to the legs, results from compression or irritation of the nerve roots in the lumbosacral spine. A common form is sciatic nerve radiculopathy, where pain extends below the knee, mostly affecting individuals in their 40s and 50s, with a lifetime incidence of up to 40%.[1] While mainly caused by emerging nerve root compression, it can also result from various diseases, including infections like varicella-zoster virus (VZV).[1-3]

We report the case of a previously healthy 43-year-old man presenting with a one-week history of left lower limb persistent dysesthetic pain, extending from the plantar foot surface (L4/L5 dermatome) to the posterior calf and thigh (S1/S2 dermatome), with a 4/10 intensity in the numerical rating scale. After being questioned, he reported a two-day history of fever and a painful rash on the left internal malleolus (L4 dermatome). He self-medicated with non-steroidal anti-inflammatory drugs, and obtained moderate relief. Physical examination revealed a positive straight leg raise test on the left and painful gait limitation on tiptoes, with preserved muscle strength and deep tendon reflexes. Cutaneous inspection showed multiple grouped vesicles on an erythematous base mainly along the L4 sensory dermatome (Fig. 1). Laboratory tests revealed positive IgG and IgM serology for VZV, without other abnormalities including a negative HIV test. The diagnosis of herpes zoster-induced sciatica was established. The patient was treated with valacyclovir 1000 mg thrice a day for seven days and paracetamol as needed for pain. At the one-month follow-up, he had fully recovered without complications.

The sciatic nerve, formed by the anterior rami of spinal nerves L4-S3,[1,4] innervates the dermatomes affected in this patient. Nerve compromise is mainly due to musculoskeletal causes, such as disc herniation or spinal stenosis, but non-musculoskeletal causes – including neoplastic, vascular, inflammatory and infectious diseases – can also be involved.[1-3] Varicella-zoster virus's primary infection typically occurs during childhood, resulting in varicella, which allows the virus to remain latent in sensory ganglia. Reactivation due to immunosuppression may cause herpes zoster,[5] characterized by prodromal pain often misinterpreted, followed by cutaneous lesions two to three days later, usually restricted to single or multiple contiguous dermatomes, evolving from erythematous papules to grouped vesicles or bullae within days, and possibly becoming pustular or hemorrhagic in severely immunosuppressed individuals.[5] Correct etiological diagnosis of VZV affecting the sciatic nerve allows for targeted and effective treatment, thus reducing future complications.

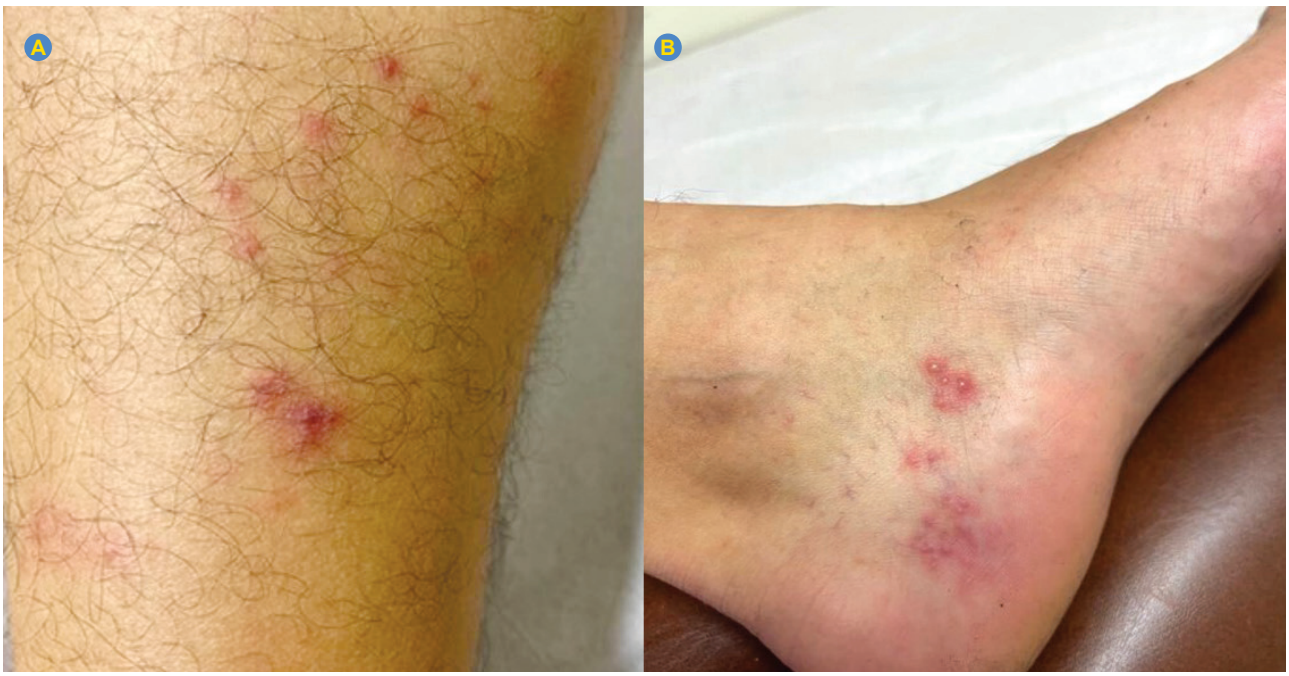


Figure 1 – Photographs of the posterior left leg (A) and medial side of the left foot (B). Multiple small, grouped vesicles on an erythematous base, with distribution along the L4, S1 and S2 sensory dermatomes.

We highlight the importance of considering non-musculoskeletal causes in the differential diagnosis of radiculopathy and emphasize the need for a meticulous examination, including the skin. The VZV, typically presenting with characteristic cutaneous findings, is an infrequent cause of sciatica that warrants targeted treatment.

AUTHOR CONTRIBUTIONS

MJC: Conception and writing of the manuscript.

JO, JT, CD: Data analysis and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

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.

REFERENCES

1. Ropper AH, Zafonte RD. Sciatica. N Engl J Med. 2015;372:1240-8.
2. Chad DA. Disorders of nerve roots and plexuses. In: Bradley WG, Daroff RB, Fenichel GM, editors. Neurology in clinical practice. 4th ed. Philadelphia: Elsevier; 2004. p. 2267.
3. Wei FL, Li T, Song Y, Bai LY, Yuan Y, Zhou C, et al. Sciatic herpes zoster suspected of lumbar disc herniation: an infrequent case report and literature review. Front Surg. 2021;8:66374.
4. Standring S. Gray's anatomy: the anatomical basis of clinical practice. 42nd ed. Amsterdam: Elsevier; 2020.
5. Howley PM, Knipe DM. Fields virology: emerging viruses. 7th ed. Philadelphia: Wolters Kluwer Health; 2020.

Maria João CADÓRIO✉[1], João OLIVEIRA[1], João TEIXEIRA[2], Cátia DUARTE[1]
1. Serviço de Reumatologia. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.
2. Serviço de Dermatologia e Venereologia. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.
✉ **Autor correspondente:** Maria João Cadório. 17741@ulscoimbra.min-saude.pt
Recebido/*Received*: 08/07/2024 - **Aceite/*Accepted*:** 05/09/2024 - **Publicado *Online*/*Published Online*:** 25/09/2024 - **Publicado/*Published*:** 04/11/2024

https://doi.org/10.20344/amp.22038

Diagnostic Accuracy of Computed Tomography in Lymphangioleiomyomatosis

Valor Diagnóstico da Tomografia Computadorizada na Linfangioleiomiomatose

Keywords: Lung Neoplasms/diagnostic imaging; Lymphangioleiomyomatosis/diagnostic imaging; Tomography, X-Ray Computed
Palavras-chave: Linfangioleiomiomatose/diagnóstico por imagem; Neoplasias do Pulmão/diagnóstico por imagem; Tomografia Computorizada

Dear Editor,

Lymphangioleiomyomatosis (LAM) is a rare disease classified by the World Health Organization (WHO) as a low-grade perivascular epithelioid tumor. It involves the development of multiple cysts in the epithelial layers due to the proliferation of abnormal smooth muscle cells, known as LAM cells.[1] This disease primarily affects women, typically around the age of 35, and while it is mostly idiopathic, it is associated with tuberous sclerosis in approximately 15% of cases.[2] Early symptoms are often mild, but the disease progresses and is characterized by dyspnea, with a strong association with spontaneous pneumothorax.[3] Additionally, about 1% of patients with scleroderma exhibit LAM-like changes in their lungs.[3]

We present the case of a 28-year-old woman with a 20-year history of systemic scleroderma who presented with shortness of breath lasting for two hours. Her medical history included reflux, gastritis, Raynaud's phenomenon, scoliosis, hands arthritis (interphalangeal), and nephrolithiasis. At the time, the patient was on daily omeprazole and amlodipine and received annual zoledronic acid treatment. She had no history of surgeries or other major diseases and had not experienced previous respiratory symptoms, despite being a long-term smoker. Muscle weakness was her initial symptom of systemic scleroderma. A thoracic computed tomography (CT) scan revealed multiple round, thin-walled cysts distorting her lung architecture (Fig. 1A). The CT also identified a pneumothorax, which was subsequently drained, as well as renal angiomyolipomas and nephrolithiasis (Fig. 1B). These CT findings led to a suspected diagnosis of lymphangioleiomyomatosis, which was confirmed through histopathological analysis of a transthoracic lung biopsy. The biopsy detected LAM cells, and immunohistochemical staining showed a positive reaction with the HMB-45 antibody. Unfortunately, the vascular endothelial growth factor-D (VEGF-D) test was not performed, as it was unavailable in the patient's city. The patient began treatment with sirolimus (2 mg/day), and due to significant lung function deterioration over the following month, she was placed on the lung transplant waiting list.

The diagnosis of LAM typically starts with non-invasive investigations, guided by clinical suspicion and characteristic findings on chest CT. To confirm the diagnosis, patients must also present at least one of the following: tuberous sclerosis complex, renal angiomyolipomas on CT or magnetic resonance imaging (MRI), lymphangioleiomyomas on abdominal or pelvic CT or MRI, chylous effusions, positive cytology for LAM cells in effusions or lymph nodes, or histopathological confirmation from a lung biopsy if needed. Elevated levels of VEGF-D, particularly in cases with lymphatic involvement, further support the diagnosis.[4]

Lymphangioleiomyomatosis is initially suspected based on chest CT scans, which typically reveal multiple cysts, usually 2 to 5 mm in diameter with thin walls. In severe cases, cysts may reach up to 12 mm and are usually distributed bilaterally.[2] A definitive diagnosis requires immunohistochemical staining and histopathological analysis,[3] which identify LAM cells by their spindle-shaped appearance, eosinophilic cytoplasm, and variable structures, ranging from nodules to small clusters. The nuclei are oval and contain fine chromatin.[2]

Treatment for LAM includes the use of bronchodilators to alleviate symptoms, which is effective in about a quarter of patients. Smoking cessation is also essential to delay disease progression.[5] Additionally, sirolimus has been shown to improve lung function and quality of life, as well as slow the progression of LAM.[2]

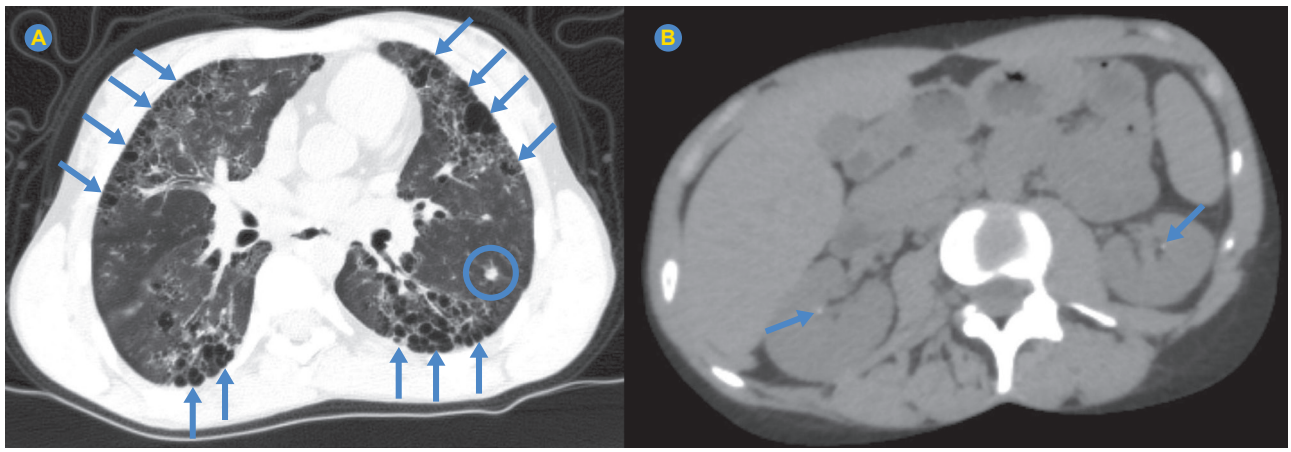


Figure 1 – Axial section of the patient's computed tomography (lung window), revealing multiple pulmonary cysts (arrows) and a nodule in the left lung (circle) (A). Abdominal computed tomography of the patient, demonstrating nephrolithiasis in both kidneys (arrows) (B).

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

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

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.

REFERENCES

1. Sekimoto Y, Suzuki K, Okura M, Hayashi T, Ebana H, Kumasaka T, et al. Uncommon radiologic computed tomography appearances of the chest in patients with lymphangioleiomyomatosis. Sci Rep. 2021;11:7170.
2. Sathirareuangchai S, Shimizu D, Vierkoetter KR. Pulmonary lymphangioleiomyomatosis: a case report and literature review. Hawaii J Health Soc Welf. 2020;79:224-9.
3. Cong CV, Anh TT, Ly TT, Duc NM. Pulmonary lymphangioleiomyomatosis (LAM): a literature overview and case report. Radiol Case Rep. 2022;17:1646-55.
4. Gupta N, Finlay GA, Kotloff RM, Strange C, Wilson KC, Young LR, et al. Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. an official American Thoracic Society/Japanese Respiratory Society clinical practice guideline. Am J Respir Crit Care Med. 2017;196:1337-48.
5. Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J. 2010;35:14-26.

Pedro Henrique SEGATT[1], Marcelo DE QUEIROZ PEREIRA DA SILVA[2], Thaís NOGUEIRA DANTAS GASTALDI[3], Márcio Luís DUARTE✉[1,3]

1. Universidade de Ribeirão Preto (UNAERP) - Campus Guarujá. Guarujá. Brazil.
2. WEBIMAGEM Telerradiologia. São Paulo. Brazil.
3. Diagnósticos da América S.A. (DASA). São Paulo. Brazil.

✉ **Autor correspondente:** Márcio Luís Duarte. marcioluisduarte@gmail.com

Recebido/*Received*: 25/07/2024 - **Aceite/*Accepted*:** 09/09/2024 - **Publicado *Online*/*Published Online*:** 23/09/2024 - **Publicado/*Published*:** 04/11/2024

https://doi.org/10.20344/amp.22116

Epilepsy Secondary to Occipital Cobblestone Malformation in an Adult Patient with Merosin-Deficient Congenital Muscular Dystrophy Type 1A

Epilepsia Secundária a Malformações do Desenvolvimento Cortical num Doente Adulto com Distrofia Muscular Congénita do Tipo 1A

Keywords: Epilepsy/etiology; Laminin/genetics; Muscular Dystrophies/congenital; Nervous System Malformations/genetics
Palavras-chave: Distrofias Musculares/congénitas; Epilepsia/etiologia; Laminina/genética; Malformações do sistema nervoso/genética

Dear Editor,

We report the case of a 41-year-old male, whose first symptoms appeared at the age of four and consisted of impairment while walking on toes due to contractures of both Achilles tendons. At 11 years old, he began experiencing brief episodes of sudden loss of awareness, lasting less than a minute, with post-ictal amnesia. Carbamazepine 400 mg daily was initiated and maintained over three decades without seizure recurrence. During adolescence, he developed a severe rigid spine and multiple contractures of the elbows, knees, and interphalangeal joints. Later, at 40 years old, he mentioned the onset of transient episodes of flashing lights in his visual field, lasting a few seconds, without loss of awareness or associated headache.

At the age of 41, the neurological examination disclosed symmetric proximal muscle weakness and atrophy in the upper (4/5 on MRC scale) and lower limbs (4/5 on MRC scale). Biceps and Achilles reflexes were absent. He had an unaided waddling/myopathic gait ("duck-like" walk).

Creatine kinase levels were mildly elevated (922 IU/L – reference 26-192 U/L). Cardiopulmonary functions were unaffected. Right deltoid muscle biopsy revealed a severe dystrophic pattern with extensive fatty tissue replacement and fibrosis. Next-generation sequencing gene panel customized for congenital muscular dystrophies revealed a previously reported compound heterozygous mutation in the *LAMA2* gene. Brain magnetic resonance imaging (MRI) showed a cortical malformation pattern, described as cobblestone lissencephaly (Fig. 1A). Electroencephalogram recording showed periodic epileptiform discharges in the left posterior temporal area (Fig. 1B).

Following an increase in seizure frequency, the patient's carbamazepine dosage was incrementally raised to 800 mg daily, resulting in a two-year seizure-free period.

This case underscores the association between merosin-deficient congenital muscular dystrophy type 1A (MDC1A) and epilepsy secondary to cortical malformations. The onset of seizures in adolescence aligns with previous observations in MDC1A patients with an epilepsy phenotype, typically presenting with middle childhood-onset focal seizures.[1] The change in seizure presentation after several years in our case was also observed in some patients from the largest cohort of patients with epilepsy.[1] Although our patient exhibited interictal epileptiform activity and cortical malformations consistent with previous reports, their response to low-dose monotherapy contrasts with the typically refractory epilepsy described in this phenotype.[1-3] The benign evolution observed in this case may be attributed to the reduced extent of cortical malformations compared to previous cohorts.[1] Some case reports suggest that the severity of central nervous system (CNS) involvement and muscular phenotypes do not necessarily correlate. It remains to be elucidated which seizure-free patients should be screened for central nervous system abnormalities.

AUTHOR CONTRIBUTIONS

MS: Literature review and writing of the manuscript.

CB, CM, MOS: Literature review, writing and critical review of the manuscript.

All authors approved the final version to be published.

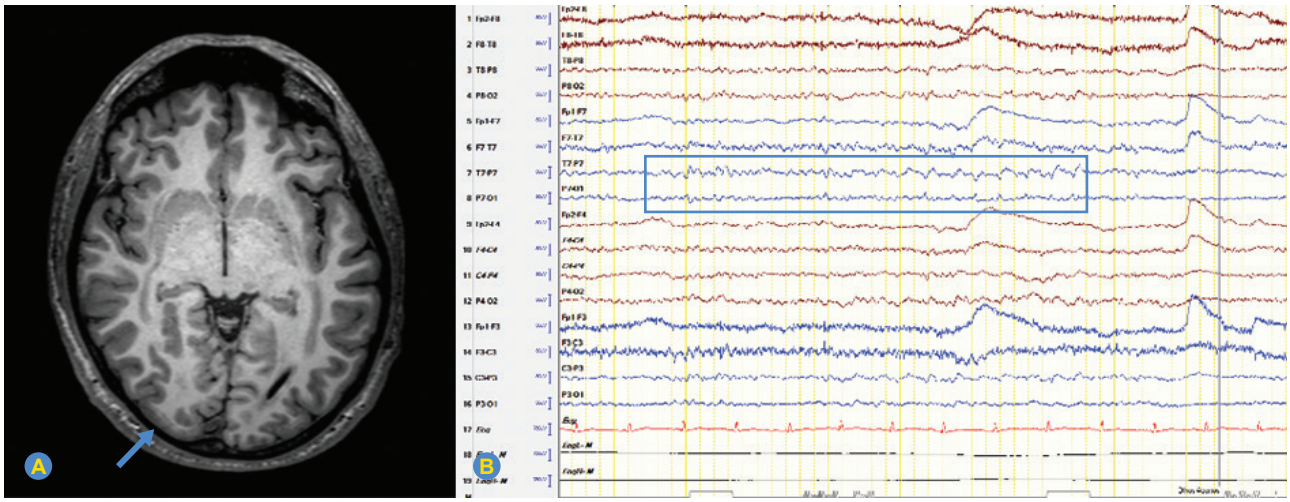


Figure 1 – Axial T1-weighted brain MRI of our patient illustrating bilateral occipital cobblestone malformation, characterized by reduction in normal sulcation, associated with a bumpy or pebbly cortical surface and streaks of discontinuous subcortical heterotopia just beneath the occipital cortex (arrow) (A). Routine EEG: slow activity in the left temporal and posterior regions. Periodic activity (sharp waves at 2 - 3 Hz) in the left posterior temporal region (rectangle).(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 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

CB has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Angelini and Eisae; received support for attending meetings and/or travel from Angelini and Eisae; participated in a Data Safety Monitoring Board or Advisory Board for Angelini; is the president of Liga Portuguesa Contra a Epilepsia.

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.

REFERENCES

1. Natera-de Benito D, Muchart J, Itzep D, Ortez C, González-Quereda L, Gallano P, et al. Epilepsy in LAMA2-related muscular dystrophy: an electro-clinico-radiological characterization. Epilepsia. 2020;61:971-83.
2. Jayakody H, Zarei S, Nguyen H, Dalton J, Chen K, Hudgins L, et al. Cobblestone malformation in LAMA2 congenital muscular dystrophy (MDC1A). J Neuropathol Exp Neurol. 2020;79:998-1010.
3. Salvati A, Bonaventura E, Sesso G, Pasquariello R, Sicca F. Epilepsy in LAMA2-related muscular dystrophy: a systematic review of the literature. Seizure, 2021;91:425-36.

Miguel SCHÖN✉[1], Carla BENTES[1,2,3], Carlos MORGADO[4,5], Miguel OLIVEIRA SANTOS[1,3]
1. Department of Neurosciences and Mental Health (Neurology). Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
2. EEG/Sleep Laboratory/Stroke Unit Department of Neurosciences and Mental Health. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
3. Centro de Estudos Egas Moniz. Faculty of Medicine. Universidade de Lisboa. Lisbon. Portugal.
4. Department of Neuroradiology. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
5. Faculty of Medicine. Universidade de Lisboa. Lisbon. Portugal.
✉ **Autor correspondente:** Miguel Schön. miguelcbschon@gmail.com
Recebido/*Received*: 09/06/2024 - **Aceite/*Accepted*:** 09/09/2024 - **Publicado *Online*/*Published Online*:** 04/10/2024 - **Publicado/*Published*:** 04/11/2024

https://doi.org/10.20344/amp.21928

Parenchymal-subcutaneous Fistula without Pneumothorax: A Rare Complication of Chest Drain Placement

Fístula Parênquimo-subcutânea sem Pneumotórax: Uma Complicação Rara da Colocação de Dreno Torácico

Keywords: Bronchial Fistula/complications; Chest Tubes/adverse effects; Cutaneous Fistula/complications; Drainage/adverse effects
Palavras-chave: Drenagem/efeitos adversos; Fístula Brônquica/complicações; Fístula Cutânea/complicações; Tubos torácicos/efeitos adversos

Dear Editor,

A fistula is a pathological communication between two structures, usually deriving from iatrogenic causes, infections, or trauma. In the thorax, bronchopleural or alveolar-pleural fistulas are probably the most common,[1] leading to pneumothorax due to the establishment of air flow between the bronchus or parenchyma (respectively) and the pleural space. They can originate a persistent air leak that lasts for five to seven days.[2] A bronchocutaneous fistula, with only a small number of cases reported in the literature,[3-5] represents a communication between a bronchus and the cutaneous tissue, usually resulting from chest drain placement.

Considering this, one could conceptualize a fistula between the lung parenchyma and the subcutaneous tissue, which would lead to subcutaneous emphysema but no pneumothorax. To the best of our knowledge, such a process has never been described.

A 56-year-old female patient with stage IV lung adenocarcinoma was admitted for sudden dyspnea. A chest computed tomography (CT) scan revealed a right secondary spontaneous pneumothorax, and an 18 French chest tube was inserted by the emergency room team, with partial lung re-expansion but continuous air leak. Four days later, the patient developed subcutaneous emphysema. Due to a suspected de-positioning of the chest tube, a new 22 French chest tube was placed in the same location, despite no subsequent improvement.

Bronchoscopy excluded bronchial fistulas or lacerations, prompting video-assisted thoracoscopic surgery that found and repaired a pulmonary laceration on the right upper lobe. Talc poudradge (spraying of talc on the pleural surface during thoracoscopy in order to induce pleurodesis) was performed, and two new chest tubes (28 French and 24 French) were placed. Initial improvement was observed until the third postoperative day, when severe subcutaneous emphysema recurred, spreading to the thorax, abdomen, inguinal region, and face, despite no oscillation or bubbling in the chest tubes.

A new chest CT revealed a fistulous tract between the lung parenchyma and the subcutaneous tissue on the first chest tube location, with no pneumothorax. The patient underwent rethoracothomy to seal the fistulous tract with Tisseel® (a fibrin tissue adhesive) and placement of two new chest tubes (28 French). Total resolution of subcutaneous emphysema ensued, and the chest tubes were removed after five days.

This case reflects the possibility of parenchymatous fistulas to the subcutaneous tissue as a complication of chest tube placement. It underscores the importance of the multidisciplinary approach, involving intensivists, bronchologists, thoracic surgeons, and radiologists. The chest CT was pivotal in allowing the development of a pathophysiological model to understand the cause of the subcutaneous emphysema and the planning of an effective intervention with a favorable outcome.

AUTHOR CONTRIBUTIONS

AN, FFr: Study design, data acquisition and analysis, writing and critical review of the manuscript.

DC, FS, FFe: Study design, data analysis, critical review of the manuscript.

All authors approved the final version to be published.

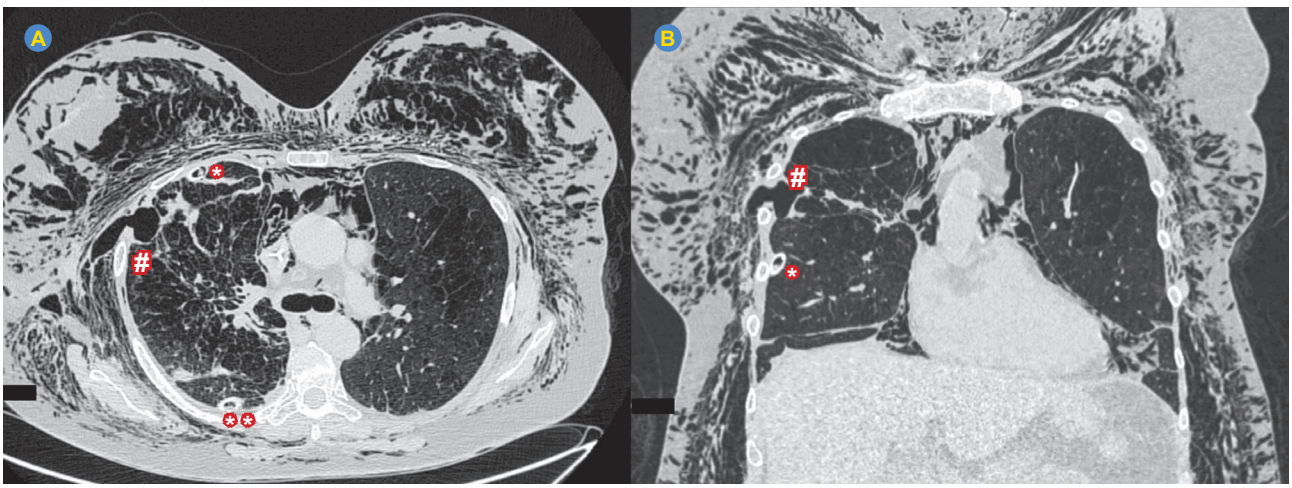


Figure 1 – Chest CT revealing the two chest tubes placed during the first surgical intervention (* and **) as well as a fistulous tract between the lung parenchyma and the subcutaneous tissue (#)

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

FFr received grants or contracts from MSD; received consulting fees from MSD, Sanofi, AstraZeneca and GSK; received payment for lectures from MSD, Sanofi, AstraZeneca, GSK, Gilead and Bial; participated on Data Safety Monitoring Boards or Advisory Boards for MSD, AstraZeneca and GSK.

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.

REFERENCES

1. Lazarus DR, Casal RF. Persistent air leaks: a review with an emphasis on bronchoscopic management. J Thorac Dis. 2017;9:4660-70.
2. Dugan KC, Laxmanan B, Murgu S, Hogarth DK. Management of persistent air leaks. Chest. 2017;152:417-23.
3. Roberts RM, Dhesi B, Amerasekera S, Johnston AM. Bronchocutaneous fistula without pneumothorax after intercostal chest drain placement. Am J Respir Crit Care Med. 2016;194:765-6.
4. Mallat M, Diab A, Bleibel J, Olaywan L. Extensive subcutaneous emphysema post-traumatic tube thoracostomy. Cureus. 2023;15:e34428.
5. John SK, Jacob S, Piskorowski T. Bronchocutaneous fistula after chest-tube placement: a rare complication of tube thoracostomy. Heart Lung. 2005;34:279-81.

André NUNES✉[1,2], Daniel CABRAL[3], Fernanda SANTOS[2], Francisco FÉLIX[3], Filipe FROES[2]
1. Integrated Responsibility Center for Pulmonology. Hospital de Torres Vedras. Unidade Local de Saúde do Oeste. Torres Vedras. Portugal.
2. Medical-Surgical Intensive Care Unit. Thorax Department. Hospital Pulido Valente. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
3. Thoracic Surgery Service. Thorax Department. Hospital Pulido Valente. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
✉ **Autor correspondente:** André Filipe Santos Nunes. andre.nunes@ulso.min-saude.pt
Recebido/*Received*: 03/06/2024 - **Aceite/*Accepted*:** 27/09/2024 - **Publicado/*Published*:** 04/11/2024

https://doi.org/10.20344/amp.21899

Errata ao Artigo "Recomendações para a Redução do Impacto Ambiental dos Inaladores em Portugal: Documento de Consenso", Publicado em Acta Med Port 2024 Sep;37(9):654-661, https://doi.org/10.20344/amp.22062.

Correction to the Article "Recommendations for Reducing the Environmental Impact of Inhalers in Portugal: Consensus Document ", Published on Acta Med Port 2024 Sep;37(9):654-661, https://doi.org/10.20344/amp.22062.

Na página 659, Tabela 1, onde se assinalou 'Nível de pegada' a amarelo:

RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	

Deverá entender-se assinalado 'Nível de pegada' a **verde** (ver páginas seguintes para tabela completa).

RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	

Artigo publicado com erros:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22062

On page 659, '*Tabela 1'* (Table 1), '*Nível de pegada'* (Footprint level) cells colored in yellow:

RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	

It should be '*Nível de pegada*' (Footprint level) colored in **green** (see next pages for full table).

RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	

Article published with errors:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22062

https://doi.org/10.20344/amp.22395

Tabela 1 – Nível da pegada ambiental dos diferentes tipos de inaladores em Portugal

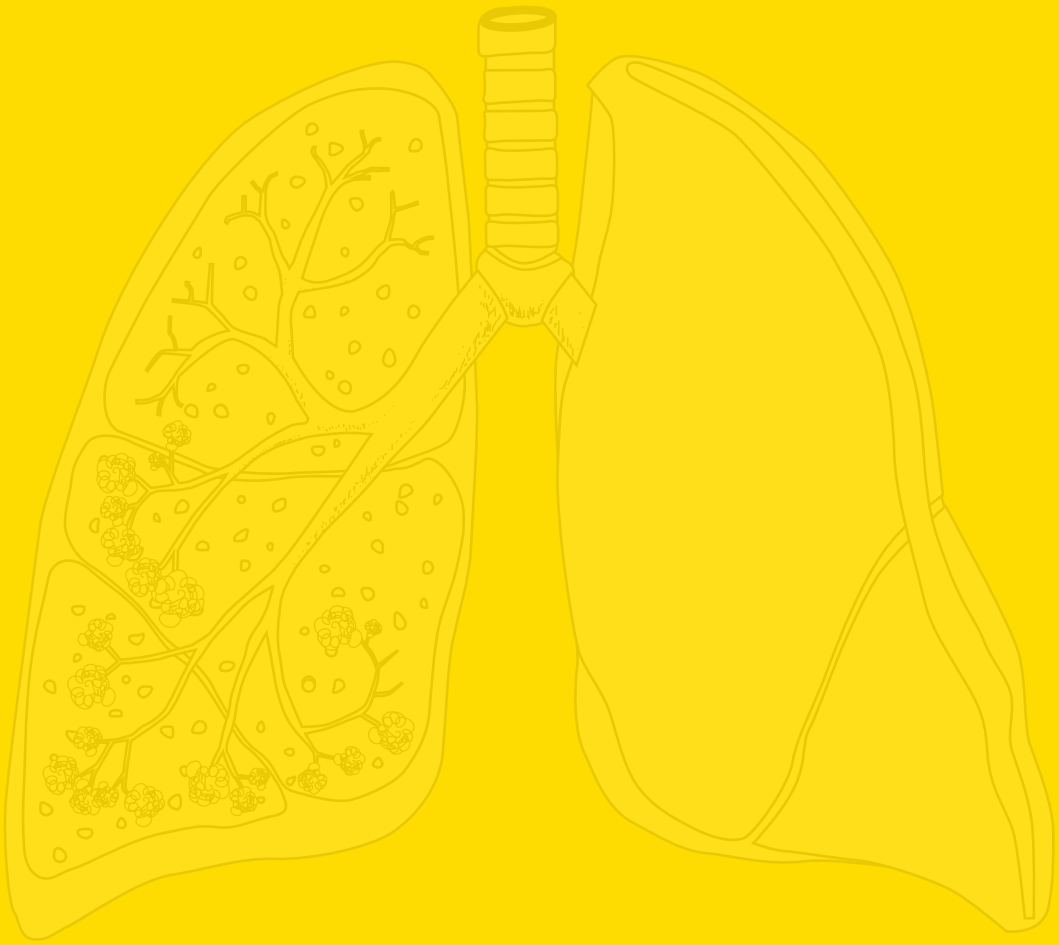
Nome	Tipo de inalador	Tipo de terapêutica	Nível de pegada
AIRFLUSAL FORSPIRO	DPI	Manutenção	
ANORO ELLIPTA	DPI	Manutenção	
ASMANEX TWISTHALER	DPI	Manutenção	
ASMATIL	DPI	Manutenção	
ASMO-LAVI	DPI	Manutenção	
ASSIEME TURBOHALER	DPI	Manutenção	
ATROVENT	MDI	Alívio	
BECLOTAIDE	MDI	Manutenção	
BEVESPI AEROSPHERE	MDI	Manutenção	
BIRESP SPIROMAX	DPI	Manutenção	
BR IPRATROPIO BUP	MDI	Alívio	
BRETARIS GENUAIR	DPI	Manutenção	
BRICANYL	DPI	Alívio	
BRIMICA GENUAIR	DPI	Manutenção	
BRISOMAX	DPI	Manutenção	
BRISOVENT DISKUS	DPI	Manutenção	
BRISOVENT INALADOR	MDI	Manutenção	
BROPAIR SPIROMAX	DPI	Manutenção	
BUFOMIX EASYHALER	DPI	Manutenção	
DUAKLIR GENUAIR	DPI	Manutenção	
DUORESP SPIROMAX	DPI	Manutenção	
EKLIRA GENUAIR	DPI	Manutenção	
ELEBRATO ELLIPTA	DPI	Manutenção	
FLIXOTAIDE DISKUS	DPI	Manutenção	
FLIXOTAIDE (AEROSSOL)	MDI	Manutenção	
FLUTIC+SALMET CCL	MDI	Manutenção	
FLUTIC+SALMET GES	DPI	Manutenção	
GIBITER EASYHALER	DPI	Manutenção	
INCRUSE ELLIPTA	DPI	Manutenção	
INHALOK AIRMASTER	DPI	Manutenção	
LAVENTAIR ELLIPTA	DPI	Manutenção	
MAIZAR	DPI	Manutenção	
QVAR	MDI	Manutenção	
RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	
SALBUTAMOL MG GPO	MDI	Alívio	
SALBUTAMOL MG SDZ	MDI	Alívio	
SALFLUMIX EASYHALE	DPI	Manutenção	
SEEBRI BREEZHALER	DPI	Manutenção	
SEFFALAIR SPIROMAX	DPI	Manutenção	
SERATAIDE DISKUS	DPI	Manutenção	
SERATAIDE INALADOR	MDI	Manutenção	
SERKEP	MDI	Manutenção	
SYMBICORT TURBOHALER	DPI	Manutenção	
SYMBICORT	MDI	Manutenção	
TOVANOR BREEZHALER	DPI	Manutenção	
TRELEGY ELLIPTA	DPI	Manutenção	
ULTIBRO BREEZHALER	DPI	Manutenção	
VENTILAN	MDI	Alívio	
VERASPIR	DPI	Manutenção	
XOTERNA BREEZHAL	DPI	Manutenção	

Verde: nível baixo ou menos que 2 $kgCO_2$ e por inalador; Amarelo: nível alto ou menos de 20 $kgCO_2$ e por inalador; Vermelho: nível muito alto ou mais de 20 $kgCO_2$ e por inalador.

Tabela 1 – Nível da pegada ambiental dos diferentes tipos de inaladores em Portugal

Nome	Tipo de inalador	Tipo de terapêutica	Nível de pegada
AIRFLUSAL FORSPIRO	DPI	Manutenção	
ANORO ELLIPTA	DPI	Manutenção	
ASMANEX TWISTHALER	DPI	Manutenção	
ASMATIL	DPI	Manutenção	
ASMO-LAVI	DPI	Manutenção	
ASSIEME TURBOHALER	DPI	Manutenção	
ATROVENT	MDI	Alívio	
BECLOTAIDE	MDI	Manutenção	
BEVESPI AEROSPHERE	MDI	Manutenção	
BIRESP SPIROMAX	DPI	Manutenção	
BR IPRATROPIO BUP	MDI	Alívio	
BRETARIS GENUAIR	DPI	Manutenção	
BRICANYL	DPI	Alívio	
BRIMICA GENUAIR	DPI	Manutenção	
BRISOMAX	DPI	Manutenção	
BRISOVENT DISKUS	DPI	Manutenção	
BRISOVENT INALADOR	MDI	Manutenção	
BROPAIR SPIROMAX	DPI	Manutenção	
BUFOMIX EASYHALER	DPI	Manutenção	
DUAKLIR GENUAIR	DPI	Manutenção	
DUORESP SPIROMAX	DPI	Manutenção	
EKLIRA GENUAIR	DPI	Manutenção	
ELEBRATO ELLIPTA	DPI	Manutenção	
FLIXOTAIDE DISKUS	DPI	Manutenção	
FLIXOTAIDE (AEROSSOL)	MDI	Manutenção	
FLUTIC+SALMET CCL	MDI	Manutenção	
FLUTIC+SALMET GES	DPI	Manutenção	
GIBITER EASYHALER	DPI	Manutenção	
INCRUSE ELLIPTA	DPI	Manutenção	
INHALOK AIRMASTER	DPI	Manutenção	
LAVENTAIR ELLIPTA	DPI	Manutenção	
MAIZAR	DPI	Manutenção	
QVAR	MDI	Manutenção	
RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	
SALBUTAMOL MG GPO	MDI	Alívio	
SALBUTAMOL MG SDZ	MDI	Alívio	
SALFLUMIX EASYHALE	DPI	Manutenção	
SEEBRI BREEZHALER	DPI	Manutenção	
SEFFALAIR SPIROMAX	DPI	Manutenção	
SERATAIDE DISKUS	DPI	Manutenção	
SERATAIDE INALADOR	MDI	Manutenção	
SERKEP	MDI	Manutenção	
SYMBICORT TURBOHALER	DPI	Manutenção	
SYMBICORT	MDI	Manutenção	
TOVANOR BREEZHALER	DPI	Manutenção	
TRELEGY ELLIPTA	DPI	Manutenção	
ULTIBRO BREEZHALER	DPI	Manutenção	
VENTILAN	MDI	Alívio	
VERASPIR	DPI	Manutenção	
XOTERNA BREEZHAL	DPI	Manutenção	

Verde: nível baixo ou menos que 2 $kgCO_2$ e por inalador; Amarelo: nível alto ou menos de 20 $kgCO_2$ e por inalador; Vermelho: nível muito alto ou mais de 20 $kgCO_2$ e por inalador.



www.actamedicaportuguesa.com