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A Medicina pela Paz: Imperativo Ético e Profissional

Medicine for Peace: An Ethical and Professional Imperative

Carlos CORTES✉[1]
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Palavras-chave: Conflitos Armados; Ética Médica; Médicos/ética; Prestação de Cuidados de Saúde; Responsabilidade Social; Saúde Global
Keywords: Armed Conflicts; Delivery of Health Care; Ethics, Medical; Global Health; Physicians/ethics; Social Responsibility

Nos últimos anos, e particularmente no atual contexto internacional, conflitos armados em várias regiões do mundo têm desafiado profundamente os limites éticos e humanitários. A comunidade médica global testemunhou uma crescente violação das normas internacionais, com ataques deliberados a civis, profissionais de saúde e hospitais, acompanhados por uma preocupante proliferação de armamentos, inclusive nucleares. Estas questões são, desde sempre, motivo de profunda preocupação para os médicos em Portugal.

Revistas científicas médicas internacionais de prestígio – como *The Lancet*, *The BMJ*, *The Journal of the American Medical Association* (JAMA) e *The New England Journal of Medicine* (NEJM) – têm liderado vozes contra esta barbárie, sublinhando que a paz é uma condição essencial para a saúde pública e o desenvolvimento humano sustentável.[1]

No terreno, profissionais de saúde têm sido reiteradamente alvos diretos da violência bélica. Ataques indiscriminados resultaram em milhares de mortes, incluindo crianças, idosos e profissionais de saúde, com danos deliberados a hospitais e ambulâncias. Além das mortes e ferimentos imediatos, o conflito desorganizou profundamente o sistema de saúde, comprometendo a vacinação, o tratamento de doenças crónicas e a saúde mental, com consequências devastadoras para várias gerações. Os impactos nas outras regiões do globo são igualmente alarmantes.

Estes ataques configuram crimes de guerra inequívocos e exigem uma resposta firme da comunidade internacional. Os profissionais de saúde, orientados por juramentos éticos e humanistas, desempenham um papel crucial como guardiões da dignidade humana, independentemente das partes envolvidas nos conflitos, devendo ser protegidos e nunca alvos militares. A neutralidade médica não deve ser interpretada como indiferença perante atrocidades, mas como um dever ético e moral de denunciar abusos e exigir responsabilização pelos atos praticados.

Publicações recentes da comunidade médica e científica demonstram claramente que os efeitos das guerras transcendem os combates imediatos. Crianças, idosos e outras pessoas especialmente vulneráveis são frequentemente as mais afetadas, sofrendo consequências devastadoras como doenças infeciosas, desnutrição grave, deterioração acentuada da saúde mental, destruição de serviços essenciais e traumas profundos que perduram ao longo da vida.[2,3] Estudos rigorosos alertam que cada conflito armado deixa marcas profundas na saúde coletiva, especialmente nestas populações fragilizadas, prolongando os danos por décadas após o término dos confrontos.[3] Assim, prevenir guerras significa proteger os mais vulneráveis, evitar doenças e garantir que o acesso universal à saúde seja sempre defendido como um direito humano fundamental.

Além disso, os conflitos armados têm resultado em deslocamentos forçados e crises humanitárias massivas, criando milhões de refugiados.[4] Nestes contextos, os médicos desempenham um papel crucial, não apenas garantindo apoio imediato nas zonas de conflito, mas também cuidando daqueles que foram obrigados a fugir. A solidariedade médica internacional e o acolhimento adequado, baseado em princípios éticos de justiça e equidade, são essenciais para proteger os direitos e a saúde dos refugiados.

Neste contexto, a comunidade médica portuguesa, através da Ordem dos Médicos, associações médicas, sindicatos médicos e sociedades científicas, junta-se ao apelo internacional em defesa da paz. Essas entidades médicas portuguesas reiteram a importância urgente de um cessar-fogo imediato e da proteção integral aos profissionais de saúde nas zonas de conflito, bem como do compromisso inequívoco com a neutralidade médica, a preservação da vida humana e o apoio médico efetivo aos refugiados e deslocados.[5]

É essencial que os médicos de Portugal e do mundo reforcem sua voz ativa e influente pela paz global. Os médicos detêm autoridade moral e profissional para combater a violência, assegurar a proteção médica e pressionar por políticas públicas que priorizem a vida e a dignidade humana acima de quaisquer interesses bélicos ou políticos.

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Que este compromisso com a paz seja assumido e renovado continuamente por todos os médicos, em todas as regiões do globo, recordando sempre que o primeiro dever da medicina é preservar a vida e aliviar o sofrimento humano de todas as pessoas, sem discriminação ou exceção. Os médicos portugueses assumem, neste contexto, o firme compromisso ético e profissional de defender a paz, a justiça e a dignidade humana em todas as circunstâncias.

REFERÊNCIAS

1. Abbasi K, Ali P, Barbour V, Bibbins-Domingo K, Olde Rikkert MG, Haines A, et al. Reducing the risks of nuclear war. BMJ. 2023;382:1682.
2. Bendavid E, Boerma T, Akseer N, Langer A, Malembaka EB, Okiro EA, et al. The effects of armed conflict on the health of women and children. Lancet. 2021;397:522-32.
3. Garry S, Checchi F. Armed conflict and public health: into the 21st century. J Public Health. 2020;42:e287-98. Erratum in: J Public Health. 2021;43:e110.
4. Martini M, Valchi L, Massaro E, Parrella R, Orsini D. War and health: the devastating impact of conflict on Wellbeing and Humanitarian Crises. J Prev Med Hyg. 2024;65:e464-8.
5. World Medical Association. WMA statement in times of armed conflict and other situations of violence. 2024. [consultado 2025 jul 25]. Disponível em: https://www.wma.net/policies-post/wma-regulations-in-times-of-armed-conflict-and-other-situations-of-violence.

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It Is Time to Recognize Family Medicine as a Specialty in Europe

É Tempo de Reconhecer a Medicina Geral e Familiar como uma Especialidade na Europa

Sara ARES-BLANCO✉[1,2,3], Tiago VILLANUEVA[4,5]
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Keywords: Europe; Family Practice; Physicians, Family
Palavras-chave: Europa; Medicina Geral e Familiar; Médicos de Família

In these uncertain times, marked by pandemics, conflicts, political polarization, and the erosion of social cohesion, family medicine has once again demonstrated its essential role within the community: listening, supporting, treating, and guiding patients through their lives and an increasingly complex healthcare system.[1] This is not a new role; we have been fulfilling this central function in patient care for decades (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23682/15723). But there comes a time when, as a profession, we must pause and reflect on where we are.

Surprisingly, the European Union (EU) still does not officially recognize general practice/family medicine as a medical specialty essential to the practice of the profession. This situation dates back to 2005. It is not a new demand – the European Union of General Practitioners/Family Physicians (UEMO) has been calling on the European Commission for over 20 years to put general practice/family medicine on par with all the other specialties, i.e., to become listed in the same Annex of the Professional Qualifications Directive.[2]

However, as of 2025, the landscape has changed. With a shortfall of nearly 20 000 family doctors across Europe, both society and decision-makers are finally acknowledging that family physicians play a pivotal role in addressing the health challenges of the population and are a key stakeholder in any public health crisis. General Practice/Family Medicine is now on the agenda of the World Health Organization (WHO), the Organization for Economic Co-Operation and Development (OECD), and numerous European governments. Yet, despite a broad consensus on the importance and need for family doctors, the necessary steps to formally recognize the specialty at the EU level have yet to be taken.

Why should the General Practice/Family Medicine specialty be officially recognized?

First, because it is a factual reality. Family doctors are specialists. General Practice/Family Medicine is recognized as a specialty in most European Union countries, and we undergo three to six years of structured postgraduate medical training,[3] fully regulated by national institutions within the EU. Moreover, we have the necessary competencies and skills to care for communities and, in doing so, we help improve life expectancy.[4] At the same time, we are the largest group of doctors and prescribers in the European Union and we see around 70% of European citizens each year. No other specialty reaches the whole population like us.

Second, because it is a matter of professional justice. Family physicians serve as the initial point of contact in patient care and remain engaged throughout the entirety of the diagnostic and therapeutic continuum, ensuring continuity and coordination of care. We follow patients throughout their lives, and it is only fair that our work be acknowledged, just as the contributions of other medical colleagues are. Moreover, the majority of patients during the COVID-19 pandemic were not treated in hospitals but in primary care. Family doctors not only cared for the majority of COVID-19 patients but also bore a disproportionate share of the burden – many fell ill, and some even lost their lives in the line of duty.[5] For this reason, it is only fair that our work be formally recognized, not just with applause, but with the legal recognition granted to other medical specialties.

Third, because of the misleading message it sends to the next generation of medical students. The lack of European recognition sends the wrong signal: that family medicine lacks prestige or importance because the EU does not value it. As a result, some may feel that completing the specialty training is not necessary, especially in countries

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where it is not a legal specialty requirement to practice. This not only undermines patient safety and health outcomes but also threatens the very foundation of generalist care, so essential to managing multimorbidity in an integrated, personalized, and compassionate way, grounded in long-term patient relationships.

And finally, recognition is necessary for scientific consistency. If European institutions truly support science and research, they cannot continue to ignore the substantial body of evidence supporting the effectiveness and development of family medicine. Denying it a place among the recognized medical specialties creates an unacceptable hierarchy, dividing science into 'first class' and 'second class'. That is neither ethical nor acceptable within today's scientific framework.

Recognizing family medicine as a specialty is not about proving a point – it is about doing what is right. We have more than enough reasons to raise our voice once again. This is not merely a collective demand; it is a call for action in defense of the health of 449 million Europeans, especially the 30 million who currently do not have access to family medicine. Because every citizen deserves to be cared for by a trained specialist in Family Medicine.

AUTHOR CONTRIBUTIONS

SA: Writing, review and editing of the paper.

TV: Review and editing of the paper.

Both authors agreed on the final version.

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SA: Received a PhD grant (Isabel Fernández) from semFYC in 2018, and further grants from EGPRN (European General Practice Research Network), 01/2022 and 10/2023, WONCA Europe, 07/2023. The collaborative research group Eurodata, of which she is a member, has received publication grants from the Deutsche Forschungsgemeinschaft, the Università di Modena e Reggio Emilia in Italy, and the Department of Primary Care Medicine, Center for Public Health, Medical University of Vienna, Austria.

TV: Received support from the Portuguese Medical Association, UEMO, Bulgarian Association of General Practitioners and North Macedonian Society of General Practitioners, Sociedad Española de Medicina General, European Medicines Agency, Spanish Medical Association and The BMJ to attend meetings and conferences. Is the President of the European Union of General Practitioners and Family Physicians (UEMO), unpaid.

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REFERENCES

1. Starfield B. Is primary care essential? Lancet. 1994;344:1129-33.
2. Official Journal of the European Union. Directive 2005/36/Ec of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications. L255 2005. [cited 2025 Jun 15]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005L0036.
3. Michels NR, Maagaard R, Buchanan J, Scherpbier N. Educational training requirements for general practice/family medicine specialty training: recommendations for trainees, trainers and training institutions. Educ Prim Care. 2018;29:322-6.
4. Sandvik H, Hetlevik Ø, Blinkenberg J, Hunskaar S. Continuity in general practice as predictor of mortality, acute hospitalisation, and use of out-of-hours care: a registry-based observational study in Norway. Br J Gen Pract. 2022;72:e84-90.
5. Yoshida I, Tanimoto T, Schiever N, Patelli F, Kami M. Characteristics of doctors' fatality due to COVID-19 in Western Europe and Asia-Pacific countries. QJM Mon J Assoc Physicians. 2020;113:713-4.

ACTA MÉDICA PORTUGUESA
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How to Unleash the Potential of the Portuguese Registry of Intensive Care Medicine?

Como Libertar o Potencial do Registo Nacional de Medicina Intensiva?

João João MENDES[1,2,3], Inês AMARAL[4], João GONÇALVES PEREIRA[3,5], José Artur PAIVA[6,7], Paulo FIGUEIREDO[8], Pedro PÓVOA[9,10,11], Teresa GUIMARÃES[12], Paulo MERGULHÃO[13,14]

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Palavras-chave: Cuidados Críticos; Portugal; Registos; Unidades Cuidados Intensivos

INTRODUCTION

Intensive Care Medicine has undergone profound transformations in recent years. Although reliable data specific to Portugal is unavailable, it is estimated that Intensive Care Departments (ICD) account for approximately 13.4% of total hospital costs, 4.1% of national healthcare spending, and nearly 0.6% of the gross national product globally.[1] Given the rapid pace of development in this field, ensuring safe, effective and equitable care depends on solid metrics and high-quality research as the cornerstones for continuous improvement.[2]

National registries, developed over 30 years ago as part of quality improvement programs, have become indispensable data sources globally, providing valuable insights into the epidemiology of critically ill patients.[3] The success of

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these pioneering initiatives, coupled with advancements in information technology and recognition of their potential to support a broad range of observational and interventional research, has driven their geographic expansion.[2]

The Portuguese Registry of Intensive Care Medicine (RNMI, Registo Nacional de Medicina Intensiva) was established within this global movement, with the goal of supporting research and quality improvement in national intensive care. By offering a robust, data-driven foundation, the RNMI enables meaningful national and international comparisons, fostering evidence-based practices and enhancing patient outcomes in intensive care settings. Furthermore, in 2012, Portugal had only 6.4 ICU beds per 100 000 inhabitants, and while the latest national census reports an increase to 9.5 active beds per 100 000 inhabitants, this figure remains significantly below the European average, highlighting the need for better resource planning.[4]

Project overview

The RNMI is based on an idea introduced over 20 years ago by Professor Rui Moreno to establish a National Center for Intensive Care Data Management. This initiative was formally implemented in 2022 through a consortium comprising the Portuguese Society of Intensive Care Medicine (SPCI), the College of Intensive Care Medicine of the Portuguese Medical Association (CEMIOM), and the Association of Intensive Care Medicine Trainees (AIMINT).

The primary goal of the RNMI is to improve the quality of intensive care by generating and advancing knowledge in this field and promoting its implementation and dissemination (Fig. 1).

The RNMI operates within a structured regulatory framework, accessible at https://www.spci.pt/rnmi.

Digital platform

Content structure

The content structure of RNMI was developed through a collaborative process led by a multiprofessional task force. This task force employed a modified Delphi methodology to reach a consensus, with all discussions conducted online.

The platform's design is based on a flexible modular system referred to as 'cassettes', with each cassette containing datasets specific to key aspects of intensive care (e.g., ventilation), thereby supporting a wide range of research studies within intensive care medicine. Furthermore, the platform was structured to automate calculations for essential clinical scores, including health-related quality-of-life metrics adapted for the Portuguese population.[5]

Technical specifications

Development and security guarantees

The digital platform was developed with rigorous standards to ensure data privacy and security. Hosted on European Microsoft Azure servers, the platform ensures data privacy and security through strict firewall policies, advanced encryption for data transfer and storage, and a multi-layered security approach to protect against external threats.

Anonymization and data security

The platform anonymizes patient data using a 'hash with salt' security technique (that transforms data into a fixed-length string using a unique random value) and assigns unique identifiers (UUIDs) to ensure data remains non-identifiable while enabling secure tracking and correlation throughout a study, even in the event of a breach.

Data management and research ethics principles

Compliance with General Data Protection Regulation

The RNMI ensures that data is collected and processed in strict compliance with data privacy laws, notably the General Data Protection Regulation (GDPR). The GDPR compliance for RNMI is further assured through oversight by a designated data protection officer, who is responsible for implementing the data protection strategy and ensuring adherence to regulatory standards.

Coordination with competent ethics committees

The RNMI's data collection and processing protocols adhere to high ethical standards, with data collection initiated only after approval from each institution's Ethics Committee. Data collected through the RNMI is anonymized, exempting it from informed consent requirements under the GDPR. However, the concept of anonymization is fluid, particularly in studies beyond the basic data package that handle a large volume of variables, where the data might be considered pseudo-anonymized. In such instances, informed consent may still be waived under national data protection regulations, as RNMI data is recognized as serving public interest by facilitating quality management and critical care coordination. Additionally, ethics committees may waive consent when it is impractical or impossible to obtain. For instance, in studies on cardiorespiratory arrest, excluding individuals unable to provide consent would undermine the research's validity.[6]

Data collection

The RNMI supports manual and automated data collection aligned with European interoperability standards (HL7). Currently, data is entered manually by supervised trainees, with automation requiring stakeholder agreements and application programming interface (API) development for hospital system integration.

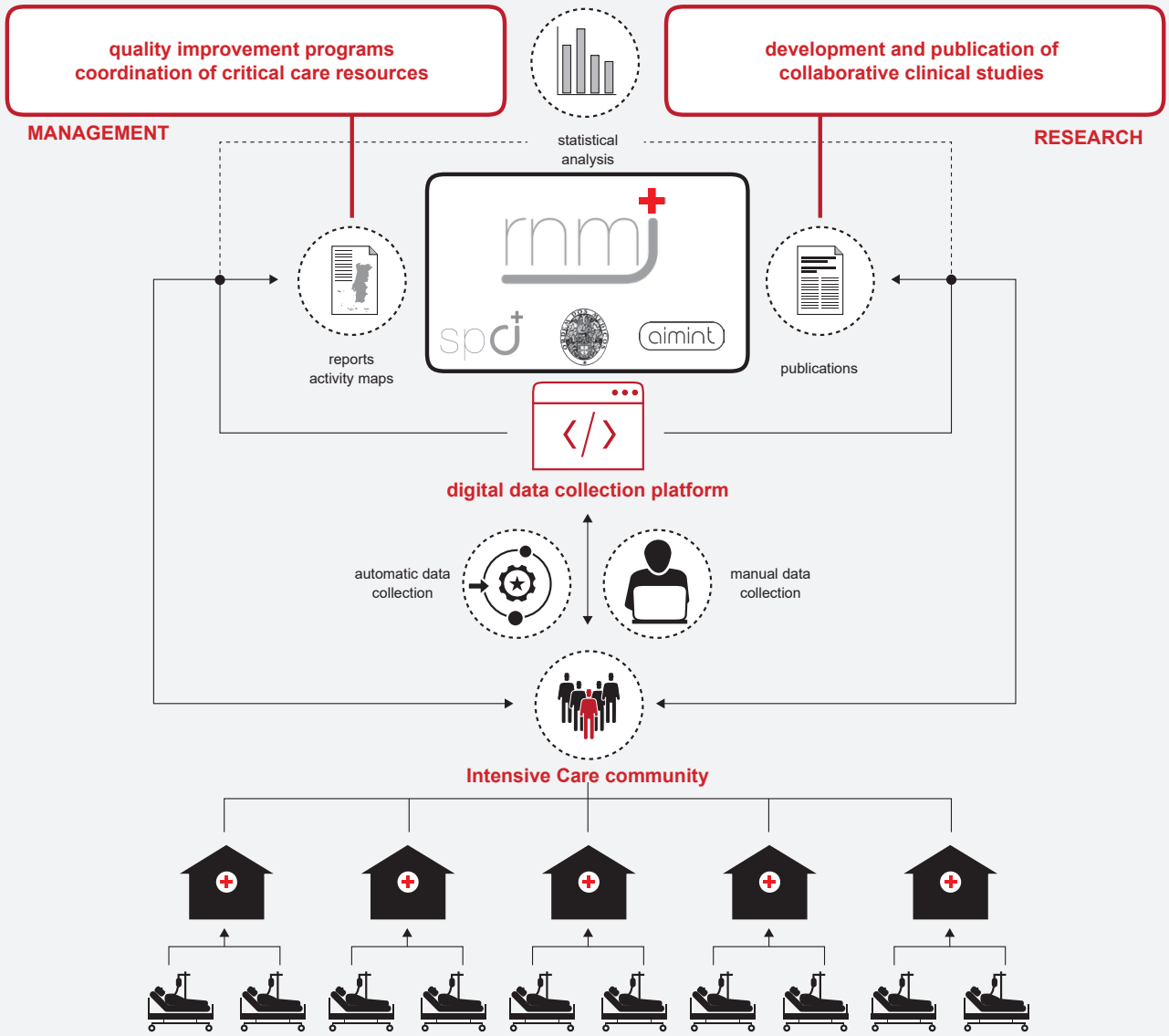

Figure 1 – Structure and functions of the Portuguese Registry of Intensive Care Medicine. The RNMI is built on a collaborative network linked to a digital data collection platform that supports both manual and automated data entry. This platform is designed to collect data for clinical research aimed at improving patient-centered outcomes. Additionally, it provides management tools at both local and national levels, enabling: (1) the creation of reports to support quality improvement initiatives and foster a collaborative quality improvement system, and (2) the development of activity maps to facilitate real-time and long-term coordination of critical care resources.

Seminal studies

RNMI-BACKEND, RNMI-TRAUMA and RNMI-PCR

To demonstrate the potential of the RNMI, three seminal studies were designed in key areas of Intensive Care Medicine: cardiac arrest (RNMI-PCR), trauma (RNMI-TRAUMA), and general supportive care (RNMI-BACKEND), each targeting essential areas for enhancing patient outcomes in intensive care.

RNMI-BACKEND studies the epidemiology of ICD patients and evaluates the prevalence and impact of supportive measures on patient outcomes, providing insight into general national intensive care practices. Both RNMI-TRAUMA and RNMI-PCR adopt standardized Utstein templates[7,8] (standardized reporting frameworks for collecting and comparing data on trauma and cardiac arrest) to ensure consistent, high-quality data collection, offering valuable insights into these two areas that currently lack comprehensive and up-to-date national data.

Dissemination of results

The findings from these seminal studies will be shared through publications in high-impact, peer-reviewed journals. Rigorous authorship standards that allow for large-scale contributions (e.g., CRediT system)[9] along with transparent data-sharing frameworks (e.g., FAIR principles),[10] will guide these efforts. On the other hand, by deepening the understanding of critical care in key areas in Portugal, these studies support quality improvement initiatives that drive data-informed protocols and eventually improve patient outcomes.

Participating intensive care units

As of the latest data, the RNMI has achieved an 80% participation rate across Portuguese ICDs, representing 90% of ICD beds in the country (Table 1). Such broad participation ensures the RNMI's capacity to generate high-quality, representative data, essential for scientific publications and for collaborative quality improvement programs at the national level.

Future prospects and conclusions

The RNMI has already achieved considerable success in developing a secure, scalable digital platform with a collaborative design, built around content created by intensivists. This initiative has launched seminal studies in critical areas of intensive care medicine and has gained participation from the vast majority of Portugal's ICDs, thereby creating a robust foundation for representative, large-scale data collection.

Despite these achievements, the RNMI still faces barriers to further development. These challenges include legislative and governance inconsistencies, particularly concerning data sharing and patient confidentiality, as well as technical issues related to system integration and interoperability.[2]

Strategically, the RNMI holds significant potential to evolve into a Center of Excellence for Intensive Care Medicine in Portugal. By fostering continuous high-quality data collection and maintaining an engaged professional network, the RNMI can position Portugal as a leader in intensive care research and quality improvement, enhancing resilience in healthcare and contributing meaningfully to international advancements in critical care. Moreover, the RNMI embraces interoperability at the European level, enabling connections to initiatives such as the European Health Data Space (https://www.european-health-data-space.com/). This integration underscores its commitment to international cooperation, fostering collaboration and innovation across borders while serving as a data-driven tool for optimal resource allocation.

Table 1 – Participation Rate of Intensive Care Units in the Portuguese Registry of Intensive Care Medicine

	Public system							Private system							National total						
	National		ICD		RNMI			National		ICD		RNMI			National		ICD		RNMI		
	ICD n	beds N	n	%	n	beds n	%	ICD n	beds n	n	%	n	beds n	%	ICD n	beds n	n	%	n	beds n	%
Northern Region	12	277	12	100%	277	100%		3	26	2	67%	20	77%		15	303	14	93%	297	98%	
Central Region	7	135	7	100%	135	100%		0	0	0	–	0	–		7	135	7	100%	135	100%	
Lisbon and Tagus Valley Region	13	299	11	85%	267	89%		5	59	2	40%	35	59%		18	358	13	72%	302	84%	
Alentejo and Algarve Region	5	84	4	80%	74	88%		0	0	0	–	0	–		5	84	4	80%	74	88%	
Autonomous Regions of the Azores and Madeira	4	47	2	50%	35	74%		1	7	0	0%	0	0%		5	54	2	40%	35	65%	
Total	41	842	36	88%	788	94%		9	92	4	44%	55	60%		50	934	40	80%	843	90%	

ICD: intensive care departments; RNMI: Portuguese Registry of Intensive Care Medicine (*Registo Nacional de Medicina Intensiva*)

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conceptualization, organization, writing, revision and approval of the final version of the manuscript.

COMPETING INTERESTS

JGP received honoraria for lectures from Biomerieux, Thermofisher, Gilead and MSD; is the president of Grupo de Infeção e Sépsis (unpaid role).

PM received an unrestricted research grant from AstraZeneca; received consulting fees from Chiesi; received payment or honoraria from AOP, MSD, Pfizer, Biomérieux, Shionoggi, Thermofisher, Cepheid, GSK and Chiesi; received support from MSD for attending the 2022 International Symposium on Intensive Care & Emergency Medicine (ISICEM); is the president of the Portuguese Society of Intensive Care.

PP received consulting fees from MSD, BioCodex and Gilead; received payment or honoraria from Gilead, Abionic and Mundipharma for lectures, presentations, speakers' bureaus, manuscript writing or educational events.

All other authors have declared that no competing interests exist.

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REFERENCES

1. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs. Crit Care Med. 2004;32:1254-9.
2. Salluh JI, Quintairos A, Dongelmans DA, Aryal D, Bagshaw S, Beane A, et al. National ICU registries as enablers of clinical research and quality improvement. Crit Care Med. 2024;52:125-35.
3. Stow PJ, Hart GK, Higlett T, George C, Herkes R, McWilliam D, et al. Development and implementation of a high-quality clinical database: the Australian and New Zealand intensive care society adult patient database. J Crit Care. 2006;21:133-41.
4. Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP. The variability of critical care bed numbers in Europe. Intensive Care Med. 2012;38:1647-53.
5. Ferreira PL, Pereira LN, Antunes P, Ferreira LN. EQ-5D-5L Portuguese population norms. Eur J Health Econ. 2023;24:1411-20.
6. Ross CE, Parker MJ, Mentzelopoulos SD, Scholefield BR, Berg RA. Emergency research without prior consent in the United States, Canada, European Union and United Kingdom: how regulatory differences affect study design and implementation in cardiac arrest trials. Resusc Plus. 2024;17:100565.
7. Bray JE, Grasner JT, Nolan JP, Iwami T, Ong ME, Finn J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: 2024 update of the Utstein out-of-hospital cardiac arrest registry template. Circulation. 2024;150:e203-23.
8. Ringdal KG, Coats TJ, Lefering R, Di Bartolomeo S, Steen PA, Roise O, et al. The Utstein template for uniform reporting of data following major trauma: a joint revision by SCANTEM, TARN, DGU-TR and RITG. Scand J Trauma Resusc Emerg Med. 2008;16:7.
9. Holcombe A. Farewell authors, hello contributors. Nature. 2019;571:147.
10. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR guiding principles for scientific data management and stewardship. Sci Data. 2016;3:160018.

AMP ACTA MÉDICA PORTUGUESA
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Antithrombotic Treatment After Valve-in-Valve, Valve-in-Ring, and Valve-in-MAC Procedures: A Systematic Review and Meta-Analysis

Tratamento Antitrombótico Após Procedimentos *Valve-in-Valve*, *Valve-in-Ring* e *Valve-in-MAC*: Uma Revisão Sistemática e Meta-Análise

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ABSTRACT

Introduction: While antithrombotic therapy following transcatheter valve implantation has been extensively studied in various clinical trials, there remains a notable gap in evidence regarding the optimal approach following valve-in-valve (ViV), valve-in-ring (ViR) and valve-in-mitral annular calcification (ViMAC) procedures, warranting further assessment. This gap is particularly concerning due to the apparent increased risk of thrombosis associated with ViV interventions. The aim of this systematic review was to explore the potential benefits of anticoagulation in ViV, ViR, and ViMAC procedures.

Methods: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials, as well as the grey literature, for observational and interventional studies published until December 2023. Trials were included if a comparative analysis between the two antithrombotic strategies was feasible and excluded if patients under 18 years old were analysed. The primary efficacy endpoints were incidence of clinical and total valve thrombosis (VT), major bleeding was the sole safety primary endpoint. Additional analyses were performed regarding valves in the mitral position and valve type. The risk of bias was evaluated using the Newcastle-Ottawa scale. Data was assessed using the Review Manager 5.4 software.

Results: A total of five observational and one case series were included (n = 614 on anticoagulation and n = 468 on antiplatelets), comprising a total of 1082 participants. Clinical VT rates were 4.2% for all procedures, and patients on anticoagulants were associated with a a lower risk of clinical VT (1.1% *vs* 8.3%; OR: 0.18; 95% CI: 0.07 - 0.42, I^2: 0%) and total VT (1.3% *vs* 8.5%; OR: 0.16; 95% CI: 0.07 - 0.37, I^2: 0%). Regarding bleeding events, the existing literature did not provide adequate information to enable a thorough analysis.

Conclusion: Our study suggests a potential benefit of anticoagulation regimens to decrease the high rates of VT following valve-in-valve, valve-in-ring and valve-in-mitral annular calcification procedures. However, the lack of randomized controlled trials and data on bleeding and mortality emphasises the necessity for further research.

Keywords: Anticoagulants/administration & dosage; Bioprosthesis; Cardiac Catheterization; Heart Valve Prosthesis; Heart Valve Prosthesis Implantation; Thrombosis/prevention & control

RESUMO

Introdução: Embora a terapêutica antitrombótica após a implantação de válvulas percutâneas tenha sido amplamente estudada em diversos ensaios clínicos, persiste uma lacuna significativa quanto à abordagem ideal após os procedimentos *valve-in-valve* (ViV), *valve-in-ring* (ViR) e *valve-in-mitral annular calcification* (ViMAC). Essa lacuna é particularmente relevante devido ao aparente aumento do risco trombótico associado aos procedimentos ViV. O objectivo desta revisão sistemática foi explorar os potenciais benefícios da anticoagulação em procedimentos ViV, ViR e ViMAC

Métodos: Foi feita uma pesquisa na PubMed, Embase, Cochrane Central Register of Controlled Trials, bem como da literatura cinzenta, para estudos observacionais e intervencionais publicados até dezembro de 2023. Foram incluídos estudos que realizaram uma análise comparativa entre uma estratégia anticoagulante e uma estratégia antiagregante, sendo excluídos aqueles que incluíram doentes com menos de 18 anos. O *outcome* primário de eficácia foi definido como a incidência de trombose valvular (TV) clínica e total. O *outcome* primário de segurança foi hemorragia *major*. Foram feitas análises adicionais relativamente à posição mitral e de acordo com o tipo de válvula utilizada. O risco de viés foi avaliado utilizando a escala de Newcastle-Ottawa. Os dados foram analisados com o *software* Review Manager 5.4.

Resultados: Foram incluídos cinco estudos observacionais e uma *case-series* (n = 614 sob anticoagulação e n = 468 sob antiagregantes), num total de 1082 participantes. A taxa de TV clínica foi de 4,2% para todos os procedimentos, e os doentes sob anticoagulação apresentaram uma redução significativa da TV clínica (1,1% *vs* 8,3%; OR: 0,18; IC 95%: 0,07 - 0,42; I^2: 0%) e da TV total (1,3% *vs* 8,5%; OR: 0,16; IC 95%: 0,07 - 0,37; I^2: 0%). Em relação aos eventos hemorrágicos, os dados disponíveis na literatura não permitiram uma análise adequada.

Conclusão: O nosso estudo sugere um potencial benefício potencial dos regimes anticoagulantes na redução das elevadas taxas de TV após os procedimentos *valve-in-valve*, *valve-in-ring* e *valve-in-mitral annular calcification*. No entanto, a ausência de ensaios clínicos randomizados e de dados sobre hemorragias e mortalidade reforça a necessidade de mais investigação.

Palavras-chave: Anticoagulantes/administração e dosagem; Bioprótese; Cateterismo Cardíaco; Implante de Prótese de Válvula Cardíaca; Trombose/prevenção e controlo

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KEY MESSAGES

- Anticoagulation was associated with significantly lower rates of clinical and total valve thrombosis after ViV, ViR, and ViMAC procedures, suggesting potential clinical benefit in this population.
- The findings were robust in the sensitivity analyses and showed no evidence of publication bias.
- Data on post-discharge bleeding and mortality are lacking, hindering assessment of net clinical benefit.
- Randomized controlled trials are urgently needed to establish the optimal antithrombotic strategy in this high-risk population.

INTRODUCTION

Annually, approximately 280 000 valve prostheses are implanted worldwide.[1,2] The majority are biological prostheses, which are mostly selected as they do not require antivitamin K anticoagulation, despite a shorter lifespan and susceptibility to degenerative damage.[3,4] The necessity of reintervention is a known surgical risk factor for open-heart surgery,[4-6] which led to the emergence of valve-in-valve (ViV) and valve-in-ring (ViR) procedures as alternatives for this subset of patients. While ViV involves implanting a bioprosthetic valve within the existing surgical prosthesis, benefiting from a defined and stable seating surface, ViR places the transcatheter valve inside a previously implanted annuloplasty ring (a device used to reshape and reinforce the mitral annulus), a procedure that is more technically challenging due to variability in ring design and rigidity and carries a higher risk of complications such as residual regurgitation and left ventricular outflow tract obstruction.These percutaneous procedures have shown better short- and mid-term outcomes than redo surgical valve replacements.[5,7-9] Nevertheless, the optimal antithrombotic management of these patients is unclear.

Several large-scale randomised controlled trials have evaluated antithrombotic therapies following transcatheter aortic valve implantation (TAVI), favouring antiplatelet therapy over anticoagulation in patients without an indication for anticoagulation.[10,11] Current guidelines reflect these findings.[12] However, for ViV, ViR, and valve-in-mitral annular calcification (ViMAC) procedures - the latter involving deployment of a balloon-expandable valve directly into a severely and variably calcified mitral annulus - the evidence remains limited. This is particularly relevant because patients undergoing aortic ViV appear to face a higher risk of clinical leaflet thrombosis and structural valve deterioration (SVD) than those undergoing conventional TAVI.I.[13,14] Moreover, there is a notable accumulation of reports of valve thrombosis (VT) following ViV procedures,[15-17] leading not merely to valve dysfunction and the need for reintervention,[15,16] but also posing a heightened risk of transient ischemic attacks and stroke,[18] sometimes resulting in death.[15,17]

Against this background we performed a systematic review and meta-analysis to further elucidate the potential role of anticoagulation in reducing the thrombotic risk associated with ViV, ViR, and ViMAC procedures.

METHODS

Protocol

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The systematic review and meta-analysis were registered in the PROSPERO database (CRD42023443581). No amendments to the protocol were deemed necessary.

Literature search

A systematic search was conducted in PubMed, Embase and the Cochrane Central Register of Controlled Trials from their inception to December 2023 for observational and interventional studies comparing individuals on anticoagulants and those not on anticoagulants following ViV, ViR, and ViMAC procedures. A similar search was conducted in the grey literature. No publication date limits were imposed on this latter search. The search was restricted by subject type (human), but not by language. The details of study selection are illustrated in Fig. 1.

Eligibility and exclusion criteria

We included observational studies comparing patients on anticoagulants and those not on anticoagulants at discharge, following ViV, ViR, and ViMAC procedures. Studies were excluded if no comparison between groups were conducted or not possible with available data or if patients under the age of 18 years were included.
Ethics committee approval was obtained in the context of each study.

Primary and secondary outcomes

The study's primary endpoints encompassed major bleeding, as per the criteria defined by the Bleeding Academic Research Consortium (BARC).[19] Major bleeding was defined as BARC 5, 3c, 3b or 3a. The other primary endpoint involved the assessment of clinical and total VT. Given the absence of a universally agreed-upon definition, the

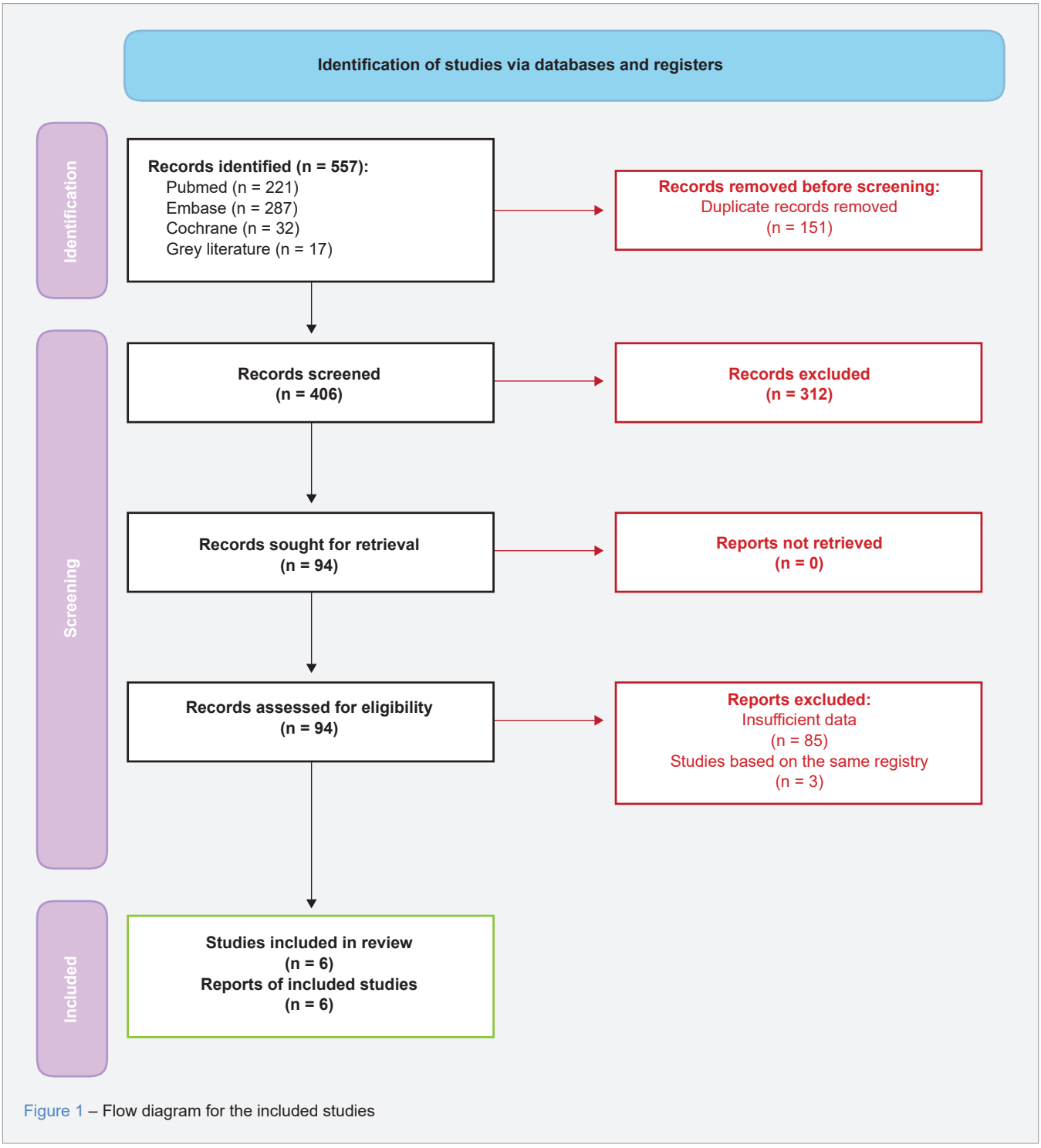


Figure 1 – Flow diagram for the included studies

study relied on the individual definitions provided by each participating study. In cases where only clinical history was described, clinical VT was determined if any of the following criteria were met: (1) manifestation of symptoms, (2) necessity of reintervention due to significant valve dysfunction or (3) documentation of notable increases in valve gradients. Cases of VT that did not meet any of these criteria, or situations where insufficient data was available, were categorized as subclinical valve thrombosis.

Additionally, the study considered all-cause mortality as

a secondary endpoint.

Secondary analysis regarding valve type was performed. Namely, comparisons between porcine and pericardial valves and porcine and other valve types were performed. A separate analysis regarding only valves in the mitral position was performed as well.

Results are presented as odds ratios (OR) with 95% confidence intervals.

Data collection and management

For each study, the following data were independently extracted: (i) general data (study design, year of publication), (ii) characteristics of trial participants [number, mean age, sex, coronary artery disease (CAD), peripheral artery disease, diabetes *mellitus*, hypertension, previous MI and previous stroke], (iii) type of valve, and (iv) number of patients with study outcomes in each treatment arm.

Risk of bias assessment

To explore the validity of eligible trials, the authors independently determined the appropriate generation of random allocation sequence, allocation concealment, blinding of patients and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other bias. Risk of bias was defined as 'high', 'medium' or 'low'. We resolved disagreements by discussion. The risk of bias was assessed by using the Newcastle-Ottawa scale. The quality assessment for each study is presented in the Risk of Bias Summary [Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22905/15700)].

To assess the robustness of the results, sensitivity analyses were conducted by excluding studies with a high risk of bias, applying alternative analytical models, and using different effect size measures. Egger's test was also performed to improve the analysis.

Statistical analysis

The statistical analysis was performed from January 25th, 2024, to February 12th, 2024, using the Mantel-Haenszel procedure in a random-effects model to calculate pooled OR with dichotomous non-adjusted data. Due to potential heterogeneity related to procedural aspects, the type of valve implanted, and the characteristics of the previously degenerated valve, a random-effects model was selected. The relatively small number of studies included in each analysis also contributed to the choice of this model. Study heterogeneity was evaluated by funnel plots. The mean effect was considered significant if its 95% confidence interval (CI) did not include one. Heterogeneity was assessed using the I^2 statistic and assumed to be relevant if it exceeded 50%.

RESULTS

Search results

A comprehensive search initially yielded a total of 557 articles for consideration. After eliminating duplicates, we were left with 406 publications for further evaluation, involving scrutiny of titles, abstracts, study types, and study populations. After screening, we identified six observational studies and one case series comparing antithrombotic strategies in ViV, ViR, and ViMAC patients. Upon closer examination, we identified two studies as updates of previously included research. In one instance, the updated version lacked discrimination between clinical and subclinical VT, limiting its inclusion to the analysis of clinical VT, for which only data from the initial publication was considered. In the other case, only the updated paper was included, resulting in a total of five observational studies and one case series included, involving 1082 patients.

It is noteworthy that, unfortunately, no published randomized controlled trials on this topic were available.

Detailed study characteristics are summarized in Table 1, while Fig. 1 represents study selection.

Table 1 – Baseline characteristics of the patients in each included study

Study	Patients (n)	Anticoagulated patients (%)	Age[a] (years)	Male (%)	PAD (%)	Diabetes (%)	HTN (%)	Previous MI (%)	Previous stroke (%)	STS score (%)
Eng 2021[29]	88	83[+]	76	43	12.0	26.0	NR	18.0	21.0	8.2
Yoon 2019[4]	521	72[#]	73	46	11.3	23.8	70.6	15.7	15.7	9.0
McElhinney 2019[30]	306	53[†]	40	NR	NR	NR	NR	NR	NR	NR
Abdel-Wahab 2018[31]	300	33*	80	59	24.4	25.8	NR	NR	18.8	7.8
Eng 2017[32]	13	77	75	38	15.0	38.0	NR	36.0	15.0	10.9
Whisenant 2015[33]	11	27	NR	NR	NR	NR	NR	NR	NR	NR

HTN: hypertension; MI: myocardial infarction; n: number; NR: not reported; PAD: peripheral artery disease; STS: Society of Thoracic Surgeons
a: Age is reported as mean for Eng[31] and Yoon,[4] and as median for the remaining studies.
+: A total of seven patients died before discharge and were excluded from our analysis
#: A total of 110 patients were excluded as antithrombotic strategy was unknown.
†: A total of 19 patients were excluded (9 because no therapy was initiated and 10 for lack of data available)
*: A total of eight patients were excluded (four because antithrombotic strategy was unknown and four as data regarding them was not provided).

Primary outcomes

In the pooled analysis, the incidence of clinical VT was 4.2% for all procedures (ViV, ViR, ViMAC) with significant differences between both groups. In fact, anticoagulation was associated with a lower risk of thrombosis in both clinical VT (1.1% *vs* 8.3%; OR: 0.18; 95% CI: 0.07 - 0.42; I^2 = 0%; p = 0.0001) and total VT (1.3% *vs* 8.5%; OR: 0.16; 95% CI: 0.07 - 0.37; I^2 = 0%; p < 0.0001).

This effect was accentuated when only considering ViV and ViR procedures, with clinical VT rates reaching 5.8% and slightly more pronounced differences between both groups (1.1% *vs* 9.4%; OR: 0.15; 95% CI: 0.05 - 0.46; I^2 = 0%; p = 0.0009).

Unfortunately, no analysis regarding post-discharge bleeding complications was feasible since each study reported only procedure-related bleeding or total bleeding, encompassing procedure-related events.

Forest plots of each analysis are represented in Figs. 2 and 3 and heterogeneity funnel plots are available in Appendix2(Appendix2:https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22905/15701).

To ensure the robustness of the findings, a sensitivity analysis was performed. No significant differences were observed when excluding studies with a higher risk of bias, nor when applying alternative analytical models or effect size measures. Egger's test was conducted for each analysis, with no statistically significant evidence of small-study effects or publication bias detected for clinical VT (p = 0.81), total VT (p = 0.52), and for ViV and ViR (p = 0.99).

The certainty of the evidence was assessed using the GRADE approach. All included studies were observational, which implies a starting rating of low certainty. However, the consistency of results (I^2 = 0%), the magnitude and statistical significance of the effect (OR 0.18; 95% CI: 0.07 - 0.42; OR: 0.16; 95% CI: 0.07 - 0.37), and the precision of estimates support an upgrade in confidence. Risk of bias was deemed serious due to the lack of adequate control for confounding in several studies, with Newcastle-Ottawa scores ranging from 5 to 7. Therefore, the overall certainty of the evidence was rated as moderate for the outcome of clinical valve thrombosis.

Secondary analysis

An additional analysis focused on mitral valves was performed. In this subset of patients, even though clinical VT rates only reached 2.8%, 71% of patients were on anticoagulants. Nonetheless, anticoagulation was also associated with a lower risk of VT (7.1% *vs* 1%; OR: 0.19; CI 95% CI: 0.06 -0.66, I^2: 0%) (Fig. 4).

Regarding valve type, our analysis found a non-significant association between previously implanted porcine valves and an increased risk of valve thrombosis in comparison to pericardial valves (OR: 1.72; CI: 0.66 - 4.48, CI 95%, I2: 0%) or to any other valve type (OR: 1.56; CI: 0.67 - 3.64, CI 95%, I2: 0%). Forest plots are available in Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22905/15701).

Regrettably, the available published data did not provide sufficient information to conduct analyses related to all-cause mortality or cardiovascular mortality.

DISCUSSION

Given the potential complications related to VT following TVI, extensive research on antithrombotic strategies for its prevention has been conducted, ultimately culminating in the development of randomized controlled trials (RCT). Specifically, two major RCTs compared an anticoagulant regimen with an antiplatelet regimen in TAVI patients: the ATLANTIS trial (apixaban *versus* single or dual antiplatelet strategy)[10] and the GALILEO trial (rivaroxaban and aspirin *versus* clopidogrel and aspirin).[11] In the GALILEO trial, patients on rivaroxaban faced, not only a higher risk of bleeding, but also a heightened risk of death or thromboembolic complications compared to those on an antiplatelet-based strategy. In an ATLANTIS substudy focused on VT,[20] patients receiving apixaban experienced an increase in non-cardiovascular deaths. Neither trial observed discernible clinical benefit in the anticoagulation arms.

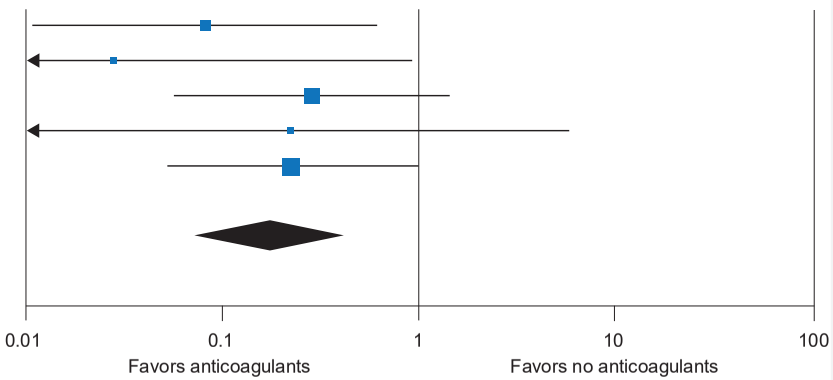
Based on this randomized controlled data, upon the release of the European Society of Cardiology (ESC) guidelines on valvular disease, recommendations for lifelong single antiplatelet therapy (SAPT) after TAVI and against anticoagulation in patients without other indication for its use, were published. As for transcatheter mitral valve implantation (TVMI), three months of VKA is suggested, but no formal recommendation was possible due to lack of data. Moreover, no specific recommendations were made for ViV, ViR or ViMAC procedures[21] as no substantial comparative data on the ideal antithrombotic treatment after discharge is available, creating a substantial evidence gap in this field.

In fact, the issue of VT following these procedures is of paramount importance given the apparent increased risk of thrombosis[13] and remarkably high VT rates in comparison to TAVI patients, as demonstrated in a previous observational study (11.6% *vs* 2.2%).[22]

Despite persistent research efforts, the exact factors contributing to this heightened risk remain elusive.[23-26] Nevertheless, some researchers have offered insightful perspectives on possible contributing factors. It has been suggested that the geometric constraints resulting from the encirclement of the valve's stent by a degenerated bioprosthesis may increase blood stagnation on the leaflets, potentially contributing to thrombosis.[23] Additionally, factors such as proximal valve implantation, under-expansion, and

Study or subgroup	Anticoagulant use Events	Total	No anticoagulant use Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Abdel-Wahab 2018[31]	1	97	22	195	19.1%	0.08 [0.01, 0.62]
Eng 2017[32]	0	10	2	3	6.4%	0.03 [0.00, 0.93]
McElhinney 2019[30]	2	152	6	135	29.8%	0.29 [0.06, 1.44]
Whisenant 2015[33]	0	3	3	8	7.4%	0.22 [0.01, 5.80]
Yoon 2019[4]	3	295	5	116	37.2%	0.23 [0.05, 0.97]
Total (95% CI)		557		457	100.0%	0.08 [0.01, 0.62]
Total events	6		38			

Heterogenelty: Tau² = 0.00; χ^2 = 2.17, df = 4 (p = 0.70); I² = 0%
Test for overall effect: Z = 3.86 (p = 0.0001)



Study or subgroup	Anticoagulant use Events	Total	No anticoagulant use Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Abdel-Wahab 2018[31]	1	97	22	195	16.3%	0.08 [0.01, 0.62]
Eng 2017[32]	2	67	4	14	20.1%	0.08 [0.01, 0.48]
McElhinney 2019[30]	2	152	6	135	25.5%	0.29 [0.06, 1.44]
Whisenant 2015[33]	0	3	3	8	63%	0.22 [0.01, 5.80]
Yoon 2019[4]	3	295	5	116	31.8%	0.23 [0.05, 0.97]
Total (95% CI)		614		468	100.0%	0.16 [0.07, 0.37]
Total events	8		40			

Heterogenelty: Tau² = 0.00; χ^2 = 1.84, df = 4 (p = 0.77); I² = 0%
Test for overall effect: Z = 4.34 (p < 0.0001)

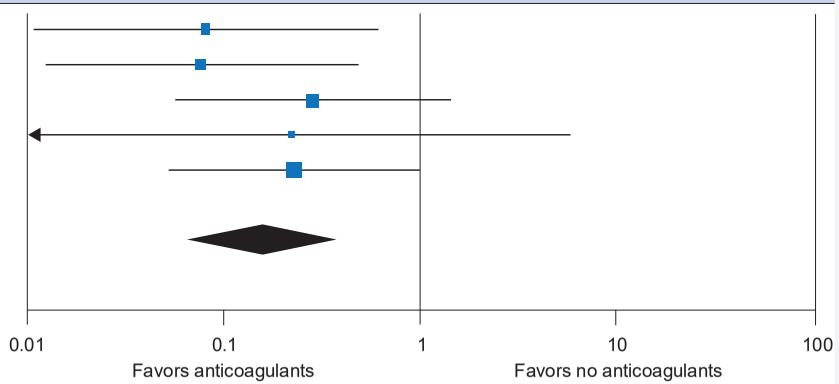


Figure 2 – Forest plot of meta-analysis for clinical VT (top) and total VT (bottom) following ViV, ViR and ViMAC
CI: confidence interval; M-H: Mantel–Haenszel

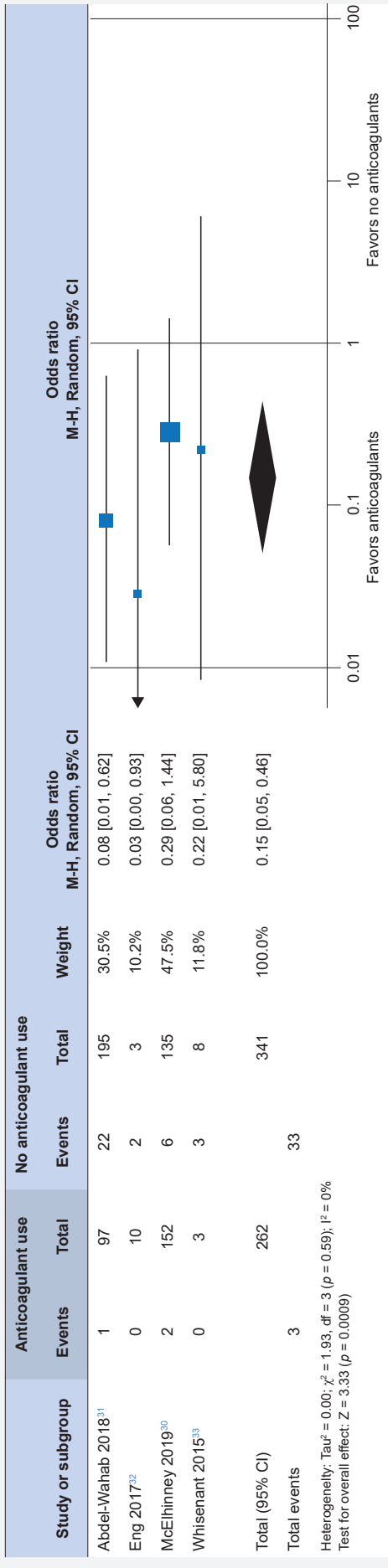


Figure 3 – Forest plot of metanalysis for clinical VT following ViV and ViR
CI: confidence interval; M-H: Mantel–Haenszel

device asymmetry have also been identified as possible contributors.[24]

Moreover, the potential severe complications of VT should not be undervalued.[15-17]

The influence of valve type on VT risk

There is no robust evidence on the relationship between valve type and VT in surgical cohorts, possibly due to the low incidence of events. In fact, in a large retrospective analysis of more than 4500 patients with surgically implanted bioprosthetic valves, early VT rates requiring reoperation in less than two years following implantation only reached 1.3%; however, every case occurred in porcine valves.[27] Whether porcine valves have increased thrombotic risk and, if so, the exact mechanisms for this risk remain to be explored.

Similar questions regarding the potential influence of valve type on VT risk arise in ViV patients. In fact, our study found that patients with previously implanted porcine stented valves tended to have higher VT rates compared to those with other valve types. However, this difference did not reach statistical significance. Notably, two additional studies were not included in our analysis due to insufficient data; nevertheless, these studies seem to align with that tendency. In one instance, five cases of ViV VT were reported, all of them in patients with porcine valves (Mosaic or Hancock II),[22] and in the other instance, ten cases of ViV VT were observed, with nine occurring in patients with previously implanted stented porcine valves.[28]

Further research to support or refute this tendency is needed.

Bleeding risk and death

Data regarding bleeding and death is severely lacking in this population. No published study reports such a comparison between anticoagulated and non-anticoagulated patients. This gap makes a net clinical gain analysis impossible, which would significantly increase the strength of our findings. Data regarding these two endpoints needs to be addressed by future research as it plays a pivotal role in the decision for the optimal antithrombotic strategy.

Exploring the role of anticoagulation after VIV, VIR and VIMAC procedures

Much like the historical debate surrounding antithrombotic treatment after TAVI, there is a contentious discourse concerning the role of anticoagulation following ViV, ViR and ViMAC. The challenge lies in evaluating the potential benefits of reducing thrombotic events in comparison to the associated risk of bleeding – a balance that has traditionally been unfavourable for TAVI patients.[10,11] However, for ViV patients, no such conclusion is possible.

Quantifying the bleeding risk remains unfeasible, given the absence of data. However, considering the significantly

increased thrombotic risk, the potential benefits of anticoagulation appear to be greater, especially given the remarkable efficacy of anticoagulation in decreasing clinical VT cases, which could yield substantial benefits for this population.

If the potential benefits outweigh the associated risks is still questionable and further studies are needed to address these unanswered questions.

Future approach: the BASILICA procedure

The BASILICA procedure is a technique designed to lacerate aortic valve leaflets, whether native or bioprosthetic, to prevent coronary artery occlusion in high-risk TAVI patients.[29] While initially developed for this specific high-risk situation, this procedure may assume a pivotal role in managing high-thrombotic risk patients, considering recent publications on the hemodynamic benefits of the procedure. Using computational simulations for two types of bioprosthetic transcatheter valves (SAPIEN 3 and Evolut Pro), BASILICA significantly decreased high-risk thrombotic areas, with laceration of two leaflets as the superior technique when compared to the laceration of one or three leaflets. This two-leaflet approach led to a significant reduction in thrombotic risk areas, decreasing from 27.06% to 15.42% with the SAPIEN valve and experiencing a remarkable decline from 22.31% to a 0.57% with the Evolut device.[30]

While real-world data on the BASILICA procedure remains scarce, despite its increasing popularity, these findings suggest the potential utility of this procedure in managing high-thrombotic risk patients.

Limitations

We identified several limitations in this study. Firstly, the absence of data comparing mortality and bleeding events between anticoagulated and non-anticoagulated groups hinders our ability to perform a comprehensive net clinical benefit analysis, which could have significantly enriched the depth of our research. Furthermore, the lack of randomized controlled trials within the selected studies decreases the robustness of our findings.

Moreover, due to the limited available body of evidence, no analysis divided by procedure (ViV, ViR, and ViMAC) or by valve position (aortic, mitral or tricuspid) was possible.

Additionally, the analysis conducted on the different valve types was constrained by the inclusion of only two studies. Expanding this aspect with more publications would undoubtedly strengthen the overall analysis.

As the field continues to evolve, we anticipate that future research will contribute with more evidence, potentially mitigating these limitations and allowing for a more comprehensive understanding of anticoagulation strategies in ViV, ViR, and ViMAC procedures.

CONCLUSION

While our understanding of anticoagulation in post-discharge

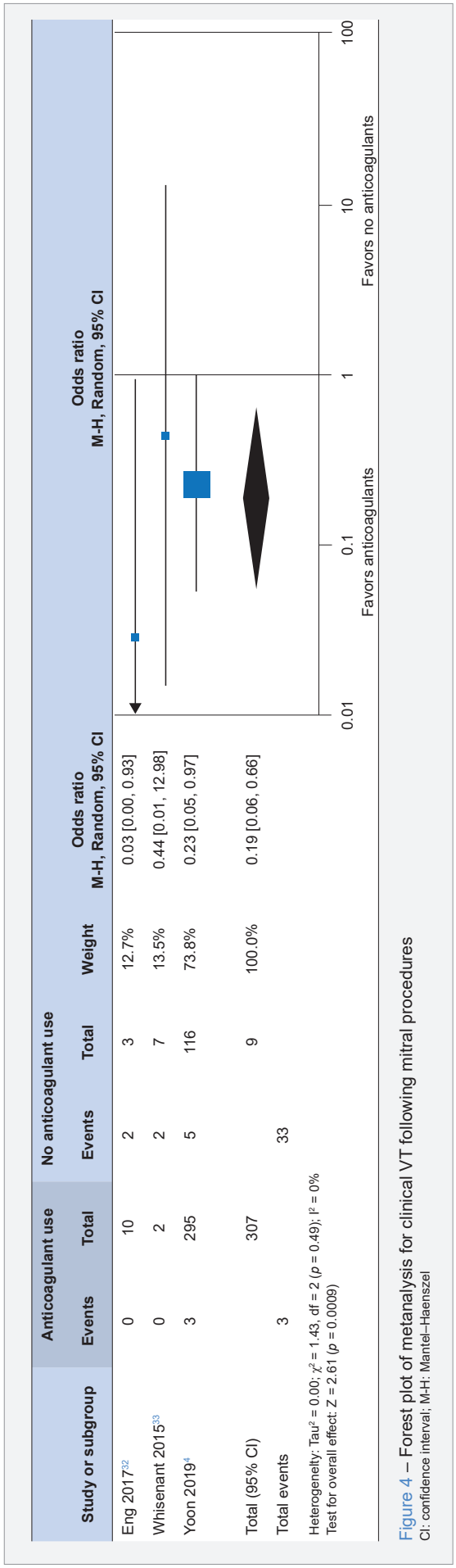


Figure 4 – Forest plot of metanalysis for clinical VT following mitral procedures
CI: confidence interval; M-H: Mantel–Haenszel

ViV, ViR, and ViMAC patients remains a work in progress, the thrombotic risk in these patients is higher and might benefit from a different antithrombotic strategy. Whether there is a significant benefit for any patients, or specifically for those at low bleeding risk and/or high thrombotic risk, remains to be explored.

Our work highlights the urgent need for further research to bridge the knowledge gaps in this area.

AUTHOR CONTRIBUTIONS

GTB, GFC: Literature search, writing of the manuscript.
JDS, LG: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. Kiyose AT, Suzumura EA, Laranjeira L, Buehler AM, Santo JA, Berwanger O, et al. Comparison of biological and mechanical prostheses for heart valve surgery: a systematic review of randomized controlled trials. Arq Bras Cardiol. 2019;112:292-301.
2. Bartus K, Sadowski J, Litwinowicz R, Filip G, Jasinski M, Deja M, et al. Changing trends in aortic valve procedures over the past ten years—from mechanical prosthesis via stented bioprosthesis to TAVI procedures—analysis of 50,846 aortic valve cases based on a Polish National Cardiac Surgery Database. J Thorac Dis. 2019;11:2340-9.
3. Rodriguez-Gabella T, Voisine P, Puri R, Pibarot P, Rodés-Cabau J. Aortic bioprosthetic valve durability. J Am Coll Cardiol. 2017;70:1013-28.
4. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J. 2019;40:441-51.
5. Bruno F, Elia E, D'Ascenzo F, Marengo G, Deharo P, Kaneko T, et al. Valve-in-valve transcatheter aortic valve replacement or re-surgical aortic valve replacement in degenerated bioprostheses: a systematic review and meta-analysis of short and midterm results. Catheter Cardiovasc Interv. 2022;100:122-30.
6. Kilic A, Acker MA, Gleason TG, Sultan I, Vemulapalli S, Thibault D, et al. Clinical outcomes of mitral valve reoperations in the United States: an analysis of the society of thoracic surgeons national database. Ann Thorac Surg. 2019;107:754-9.
7. Xu X, Liu H, Gu J, Li M, Shao Y. Valve-in-valve/valve-in-ring transcatheter mitral valve implantation vs. redo surgical mitral valve replacement for patients with failed bioprosthetic valves or annuloplasty rings: a systematic review and meta-analysis. Heliyon. 2023;9:e16078.
8. Sá MP, Eynde J Van den, Simonato M, Cavalcanti LR, Doulamis IP, Weixler V, et al. Valve-in-valve transcatheter aortic valve replacement versus redo surgical aortic valve replacement. JACC Cardiovasc Interv. 2021;14:211-20.
9. Ahmad D, Yousef S, Kliner D, Brown JA, Serna-Gallegos D, Toma C, et al. Outcomes of valve-in-valve transcatheter aortic valve replacement. Am J Cardiol. 2024;215:1-7.
10. Collet JP, Belle EV, Thiele H, Berti S, Lhermusier T, Manigold T, et al. Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial. Eur Heart J. 2022;43:2783-97.
11. Dangas GD, Tijssen JG, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. N Engl J Med. 2020;382:120-9.
12. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2022;43:561-632.
13. Mehilli J, Giannini C. Transcatheter valve-in-valve implantation for failed surgical bioprostheses – some answers and many unanswered questions. EuroIntervention. 2020;16:529-31.
14. Rheude T, Pellegrini C, Cassese S, Wiebe J, Wagner S, Trenkwalder T, et al. Predictors of haemodynamic structural valve deterioration following transcatheter aortic valve implantation with latest-generation balloon-expandable valves. EuroIntervention. 2020;15:1233-9.
15. Aktuerk D, Mirsadraee S, Quarto C, Davies S, Duncan A. Leaflet thrombosis after valve-in-valve transcatheter aortic valve implantation: a case series. Eur Heart J Case Rep. 2020;4:1-6.
16. Notaristefano F, Reccia MR, Notaristefano S, Annunziata R, Sclafani R, Ambrosio G, et al. Bailout surgical explantation of a transcatheter valve-in-valve for subacute thrombosis: when there is no time for anticoagulation. Cardiovasc Revasc Med. 2018;19:536-9.
17. Chu J, Nath N, Attanasio S. Thrombolysis for cardiogenic shock secondary to aortic bioprosthetic valve-in-valve thrombosis. Cureus. 2022;14:e33141.
18. Rosseel L, Backer OD, Søndergaard L. Clinical valve thrombosis and subclinical leaflet thrombosis following transcatheter aortic valve replacement: is there a need for a patient-tailored antithrombotic therapy? Front Cardiovasc Med. 2019;6:44.
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials. Circulation. 2011;123:2736-47.
20. Montalescot G, Redheuil A, Vincent F, Desch S, Benedictis M De, Eltchaninoff H, et al. Apixaban and valve thrombosis after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2022;15:1794-804.
21. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2022;43:561-632.
22. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2017;10:686-97.
23. Vahidkhah K, Javani S, Abbasi M, Azadani PN, Tandar A, Dvir D, et al. Blood stasis on transcatheter valve leaflets and implications for valve-in-valve leaflet thrombosis. Ann Thorac Surg. 2017;104:751-9.
24. Mangione FM, Jatene T, Gonçalves A, Fishbein GA, Mitchell RN, Pelletier MP, et al. Leaflet thrombosis in surgically explanted or post-mortem TAVR valves. JACC Cardiovasc Imaging. 2017;10:82-5.
25. Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. J Am Coll Cardiol. 2016;68:2670-89.
26. Brown ML, Park SJ, Sundt TM, Schaff HV. Early thrombosis risk in patients with biologic valves in the aortic position. J Thorac Cardiovasc Surg 2012;144:108-111.

27. Khan JM, Dvir D, Greenbaum AB, Babaliaros VC, Rogers T, Aldea G, et al. Transcatheter laceration of aortic leaflets to prevent coronary obstruction during transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2018;11:677-89.
28. Plitman Mayo R, Yaakobovich H, Finkelstein A, Shadden SC, Marom G. Impact of BASILICA on the thrombogenicity potential of valve-in-valve implantations. J Biomech. 2021;118:110309.
29. Eng MH, Kargoli F, Wang DD, Frisoli TM, Lee JC, Villablanca PS, et al. Short- and mid-term outcomes in percutaneous mitral valve replacement using balloon expandable valves. Catheter Cardiovasc Interv. 2021;98:1193-203.
30. McElhinney DB, Aboulhosn JA, Dvir D, Whisenant B, Zhang Y, Eicken A, et al. Mid-term valve-related outcomes after transcatheter tricuspid valve-in-valve or valve-in-ring replacement. J Am Coll Cardiol. 2019;73:148-57.
31. Abdel-Wahab M, Simonato M, Latib A, Goleski PJ, Allali A, Kaur J, et al. Clinical valve thrombosis after transcatheter aortic valve-in-valve implantation. Circ Cardiovasc Interv. 2018;11:e006730.
32. Eng MH, Greenbaum A, Wang DD, Wyman JD, Arjomand H, Yadav P, et al. Thrombotic valvular dysfunction with transcatheter mitral interventions for postsurgical failures. Catheter Cardiovasc Interv. 2017;90:321-8.
33. Whisenant B, Jones K, Miller D, Horton S, Miner E. Thrombosis following mitral and tricuspid valve-in-valve replacement. J Thorac Cardiovasc Surg. 2015;149:e269.

AMP ACTA MÉDICA PORTUGUESA
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Unmet Challenges in COVID-19 Prevention for Immunocompromised Individuals: A Consensus Analysis from Portugal

Desafios Não Atendidos na Prevenção da COVID-19 em Indivíduos Imunocomprometidos: Uma Análise de Consenso em Portugal

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ABSTRACT

Introduction: The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in significant disease burden and mortality. Despite vaccination successes, new virus variants persist, affecting unvaccinated and immunocompromised individuals (ICI) severely. These high-risk groups face elevated mortality and hospitalization rates. Vigilance and targeted health measures remain crucial post-pandemic. The aim of this study was to develop consensus on the unmet needs in COVID-19 prevention among ICI.

Methods: We performed a Delphi study involving 45 experts, including physicians, health managers, policymakers, public health experts, members of medical societies and patient organizations. Consensus was achieved at 65% for each identified strategy using a scale ranging from "strongly agree" to "strongly disagree." Three Delphi rounds were conducted to address four key questions: identifying unmet needs in COVID-19 prevention for ICI; identifying the characteristics that distinguish ICI as a susceptible group; determining the main outcomes of COVID-19 in ICI; and indicating action plans for protecting ICI. The first round involved voting on pre-identified indicators. The second and third rounds involved analyzing the gathered information and voting on each indicator to achieve consensus.

Results: A retention rate of 80% was achieved. Out of 89 valid indicators analyzed, 23 achieved consensus. These included: eight indicators highlighting the importance of raising awareness about COVID-19 and vaccination outcomes, ensuring safety and understanding, and developing targeted immunization strategies for ICI; five indicators identifying susceptible groups within ICI, such as individuals undergoing chemotherapy or radiotherapy, those with primary immunodeficiencies, solid organ transplant recipients, patients with chronic kidney disease, and bone marrow transplant recipients; two indicators showing improvements in clinical outcomes and reduced hospitalizations; and eight indicators recommending the development of effective therapies, more immunogenic vaccines, and treatments for viral infections in ICI.

Conclusion: The study emphasized the importance of targeted immunization strategies, monitoring, and tailored education to address diverse needs of ICI. These findings provide a foundation for future policies to effectively manage and protect ICI during and beyond the COVID-19 pandemic.

Keywords: COVID-19/prevention and control; Delphi Technique; Immunocompromised Host; Portugal; SARS-CoV-2

RESUMO

Introdução: A pandemia de COVID-19, causada pelo coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), resultou numa carga significativa de doenças e mortalidade. Apesar dos sucessos das vacinas, novas variantes do vírus persistem, afetando gravemente indivíduos não vacinados e imunocomprometidos (IIC). Estes grupos de alto risco enfrentam taxas elevadas de mortalidade e hospitalização. A vigilância e as medidas de saúde direcionadas permanecem cruciais após a pandemia. Este estudo teve como objetivo desenvolver um consenso sobre as necessidades não atendidas na prevenção da COVID-19 entre IIC.

Métodos: Realizámos um Delphi envolvendo 45 especialistas, incluindo médicos, gestores de saúde, decisores políticos, especialistas em saúde pública, membros de sociedades médicas e organizações de doentes. O consenso foi alcançado em 65% para cada estratégia identificada, utilizando uma escala que varia de "concordo totalmente" a "discordo totalmente". Foram realizadas três rondas Delphi para abordar quatro questões principais: identificar necessidades não atendidas na prevenção da COVID-19 para IIC; identificar as características que distinguem os IIC como um grupo suscetível; determinar os principais resultados da COVID-19 em IIC; e indicar planos de ação para proteger os IIC. A primeira ronda envolveu a votação de indicadores pré-identificados. As segunda e terceira rondas envolveram a análise das informações recolhidas e a votação de cada indicador para alcançar consenso.

Resultados: Foi alcançada uma taxa de retenção de 80%. Dos 89 indicadores válidos analisados, 23 alcançaram consenso. Estes incluíram: oito indicadores que destacaram a importância de aumentar a conscientização sobre a COVID-19 e os resultados da vacinação, garantindo segurança e compreensão, e desenvolvendo estratégias de vacinação direcionadas para IIC; cinco indicadores que identificaram grupos suscetíveis dentro dos IIC, como indivíduos em quimioterapia ou radioterapia, aqueles com imunodeficiências primárias, recetores de transplantes de órgãos sólidos, pacientes com doença renal crónica e recetores de transplantes de medula óssea; dois indicadores que mostraram melhorias nos resultados clínicos e redução das hospitalizações; e oito indicadores que recomendaram o desenvolvimento de terapias eficazes, vacinas mais imunogénicas e tratamentos para infeções virais em IIC.

Conclusão: O estudo enfatizou a importância de estratégias de vacinação direcionadas, monitorização e educação personalizada para abordar as diversas necessidades dos IIC. Estes resultados fornecem uma base para o desenvolvimento de políticas futuras que visem gerir e proteger eficazmente os IIC durante e após a pandemia de COVID-19.

Palavras-chave: COVID-19/prevenção e controlo; Hospedeiro Imunocomprometido; Portugal; SARS-CoV-2; Técnica Delphi

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KEY MESSAGES

- The study used the Delphi technique with a multidisciplinary panel of experts to identify gaps in COVID-19 prevention for ICI.
- Consensus was reached on the need for more effective vaccines, personalized vaccination strategies, and increased awareness of the disease and vaccination among ICI.
- Maintaining epidemiological surveillance and promoting health literacy were highlighted as essential prevention strategies.
- The diversity of expert opinions reflected the complexity of the topic and the need for more scientific evidence.

INTRODUCTION

The COVID-19 pandemic, resulting from the rapid global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was responsible, until July 7th, 2024, for approximately 775 673 955 cases of COVID-19 and 7 053 524 associated deaths worldwide.[1] During the same period, Portugal reported 5 657 579 cases and 28 556 associated deaths.[1]

The COVID-19 pandemic has had a profound impact on multiple sectors of society, disrupting healthcare, education, and the global economy.[2] The high morbidity and mortality rates overwhelmed healthcare systems, reduced workforce productivity, and triggered economic recessions due to lockdown measures aimed at controlling the virus's spread.[2,3] To meet the increasing demand for hospitalizations and intensive care, particularly for severe cases,[4] significant health resources were mobilized.[2] In response to this extraordinary challenge, unprecedented measures were implemented, primarily focusing on healthcare. Governments expanded ICU capacities, redeployed healthcare professionals, and allocated emergency resources to procure ventilators, personal protective equipment (PPE), and strengthen hospital infrastructure.[3,5] The effectiveness of vaccination has significantly transformed the course of the pandemic, reducing morbidity, mortality,[3,6-8] and the case-to-death ratio.[3] The success of vaccination efforts over the last almost four years reflects the positive impact of medical interventions in combating COVID-19.[1] Globally, as of December 31st, 2023, a total of 5.47 billion COVID-19 vaccine doses had been administered, including 9 822 021 in Portugal.[1]

However, despite these achievements, SARS-CoV-2 continues to infect individuals and cause severe illness and death.[9] Although the World Health Organization (WHO) has officially declared the end of the pandemic in May 2023, it has warned of the persistence of the virus, its transmission, and the risk of new mutations with the potential to escape vaccine protection and cause new waves of infections and deaths.[8] The WHO also emphasized that the official end of the pandemic period should not mean reducing vigilance in existing alert and response systems or minimizing the importance of precautions against COVID-19.[8]

Portugal still faces the repercussions of COVID-19.[1] According to data released by the Directorate-General of Health (DGS) in Portugal on July 24th, 2024, the virus continues to claim a considerable number of lives, with 787 deaths reported since January 1st, 2024.[10]

Among the populations with the highest risk of suffering more profound consequences of the infection are unvaccinated and immunocompromised individuals (ICI).[9,11,12] Unvaccinated individuals miss the immunological protection offered by vaccines, which typically guards against infection and its severe effects.[12] Moreover, they pose a challenge to public health efforts, being major contributors to viral transmission and evolution.[13] The widespread transmission of the virus creates opportunities for favorable mutations to emerge via natural selection.[14] This heightened risk presents a particular challenge for vulnerable populations, who face greater susceptibility to severe infection and increased mortality rates.[14]

In parallel, certain individuals with diverse immunocompromising health conditions or specific conditions experience varying levels of immunosuppression – persons with hematologic or solid organ cancers, hematopoietic stem cell or solid organ transplants, primary immunodeficiency disorders, advanced or untreated human immunodeficiency virus (HIV) infection, and those on chronic use of immunosuppressive medications, hindering their ability to generate an immune response to the COVID-19 vaccination.[15] Consequently, they may face heightened vulnerability to COVID-19, despite being fully vaccinated, increasing the risk of severe infections necessitating hospitalization and prolonged virus transmission.[15]

Within the diverse spectrum of ICI, various groups face heightened risks of severe COVID-19 outcomes. These include individuals with primary or secondary immunodeficiencies, such as cancer patients, especially those with hematologic neoplasms, transplant recipients, those on immunosuppressive medication, individuals with autoimmune diseases, those living with HIV/ acquired immunodeficiency syndrome (AIDS), and those with chronic kidney disease.[3,9,14] Immunocompromised

individuals are more likely to require Intensive Care Unit (ICU) hospitalization and experience in-hospital mortality, irrespective of vaccination status.[9] Intensive Care Unit data offers critical insights into the severe consequences of COVID-19, including individuals spanning the immune spectrum and facilitating more conclusive findings.[16] Notably, data from the United States in 2022 indicate that over 12% of hospitalized COVID-19 patients were immunocompromised, underscoring their heightened vulnerability.[9]

Despite the relevance of this evidence, there are still significant gaps in the literature regarding the unmet needs of ICI in the context of COVID-19 prevention. In this study we aimed to contribute to filling this gap by developing a consensus on the main vulnerabilities of ICI, understanding the main outcomes of COVID-19 in this population, and designing actionable strategies to safeguard their health.

METHODS

Study design

To achieve the objectives of this study, we selected the Delphi technique, which is a consensus-building methodology that aims to reach consensus on a complex subject by a systematic forecasting process that draws on the combined knowledge of a group of specialists.[17,18] The technique involved the participation of specialists in the field of study, therefore guaranteeing informed insight and credibility.[18,19] This study convened a multidisciplinary panel of experts, encompassing physicians from different specialties (Infectious Diseases, Neurology, Immuno-Allergology, Nephrology, Internal Medicine, Rheumatology, Pulmonology and Hematology), as well as health managers, policy makers and consultants, public health specialists, members of medical societies and members of patient associations. These experts were selected through purposive sampling to ensure a comprehensive representation of perspectives and expertise relevant to the study, particularly from medical specialties with a fundamental role in this area, and ensuring a balanced representation across stakeholder groups, including considerations for geographic distribution. Participants were informed about the study methodology and objectives before providing informed consent for participation.

The questions formulated to perform the Delphi panel were informed primarily by literature review and experts' consultation.

The Delphi process comprised three successive rounds of data collection.[17,20] To begin the first round, the experts were asked four question, aimed at: 1) identifying unmet needs in COVID-19 prevention in ICI, based on their perceptions and clinical experience, inform and develop effective prevention measures for this population; 2) identifying the characteristics that distinguish ICI as a susceptible group in terms of COVID-19; 3) determining the main outcomes of COVID-19 in ICI; 4) developing the most effective action plans for protecting ICI in a COVID-19 prevention context.

Participants rated the following questions (Q) on a Likert scale ranging from "strongly agree", "agree", "neither agree nor disagree", "disagree", to "strongly disagree":

- Q1 –"In your perception, based on your clinical practice, management experience or contact with associates, what needs remain to be met in the prevention of COVID-19 in immunocompromised individuals (ICI)?"
- Q2 – "Who do you consider to be immunocompromised individuals (ICI), i.e. which ICI characteristics are related to COVID-19 susceptibility?"
- Q3 – "Currently, in your perception, what do you consider to be the main outcomes of COVID-19 in immunocompromised individuals (ICI)?"
- Q4 – "Regarding the need to prevent COVID-19 in immunocompromised individuals (ICI), what action strategies do you consider most effective to protect this population?"

The first round involved voting on several pre-identified indicators through an online form. Additionally, experts were given the opportunity to suggest new indicators they considered significant through a text box integrated into the questionnaire. These indicators were subsequently analyzed through thematic analysis.[21]

Three reviewers conducted the content analysis. Open-ended questions were organized by topic, allowing for a structured segmentation of responses. To minimize potential interpretation biases, participants were instructed in advance to provide open-ended responses in a bullet-point format. The extraction of emerging indicators followed an inductive approach, where indicators were identified based on the topics mentioned by the experts.

During the second round, the distribution of votes was graphically represented for the indicators that did not achieve previous consensus as well as for the new indicators previously generated. Experts had the opportunity to maintain or adjust their level of agreement regarding the indicators that lacked consensus and to vote on the new indicators.

The process of the second round was repeated in a third and final round, including the indicators recently added. The results of each round were consistently shared with the group anonymously to mitigate any potential biases stemming from experts' apprehension about their opinions being negatively perceived or influenced by personal factors.[20] The Delphi panel started on November 11th, 2023, and the response time ended on January 8th, 2024. The strategies used to minimize attrition rates between rounds included: (i) a clear communication, ensuring participants are well-informed about the study's purpose, procedures, and the

importance of their continued participation; (ii) regular reminders, sending timely reminders to participants about upcoming rounds and deadlines; (iii) feedback, providing participants with feedback on the results of each round to maintain engagement and interest; and (iv) flexibility, allowing flexible deadlines and accommodating participants' schedules to reduce dropout rates.

Data analysis

A consensus threshold of 65% agreement was established for each indicator and applied to the total sample, requiring at least 65% concurrence among responses.[22] This level of consensus can be achieved at any response level, including the options: "totally agree", "agree", "neither agree nor disagree", "disagree", and "totally disagree".

The software used for data analysis and graph generation was Microsoft Excel®.

RESULTS

Composition of the expert panel and response rate

The first round of the panel received 45 responses, meaning that 45 experts agreed to participate in the study. The panel consisted of 32 physicians, including 11 from Infectious Diseases, three from Neurology, one from Immuno-Allergology, seven from Nephrology, two from Internal Medicine, four from Rheumatology, two from Pulmonology, and two from Hematology. Additionally, the panel included two health managers, seven policymakers and consultants, one public health specialist, two members of medical societies, and one member of a patient association.

The second round received 37 responses, reflecting a response rate of 82.2% from the previous round. The third round received 36 responses, representing a 97.3% response rate from the second round.

Overall, a retention rate of 80% was achieved in all three rounds. This is a valid retention rate for studies of this nature, demonstrating the effectiveness of the strategies employed to minimize attrition.[22]

General results for analyzed indicators

Sixty indicators were identified for this Delphi panel based on the preceding qualitative phase. Following the first round of voting, a content analysis identified 29 additional indicators contributed by experts, resulting in a total of 89 indicators, as detailed in Table 1. The complete list of indicators analyzed by the experts can be found in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15716).

By the end of the third round, consensus was achieved for 23 out of the 89 indicators submitted for voting. The predominant level of agreement is in the "strongly agree" category. Of these 23 consensus indicators, eight pertain to Q1, five to Q2, two to Q3 and eight to Q4. Indicators for Q3 only reached consensus in the final round of voting, and specifically in the "agree" category (Figs. 1 to 4).

Unmet needs in COVID-19 prevention for ICI

Consensus was been reached on eight out of the 26 indicators related to unmet needs in COVID-19 prevention in ICI, always in the "strongly agree" category (Fig. 1). Consensus indicators were the following: (1) "raising awareness among ICI about COVID-19 and its consequences" (73% strongly agree), (2) "having more effective vaccines for ICI" (71% strongly agree), (3) "raising awareness among ICI about the results of vaccination" (69% strongly agree), (4) "to have vaccine regimens developed and evaluated specifically for immunosuppressed patients" (68% strongly agree), (5) "raising awareness among immunosuppressed patients to get vaccinated against COVID-19" (68% strongly agree), (6) "raising awareness among ICI about the COVID-19 immunization schedule and regimen" (68% strongly agree), (7) "identify ideal vaccination timings depending on the immunosuppressive/immunomodulatory medication taken, namely the need to temporarily suspend it and/or fit vaccination into its interval (in the case of non-daily medication)" (68% strongly agree) and (8) "to have vaccination regimens suitable for different

Table 1 – Indicators according to round, question, and total

		Indicators (n)	
		First round	Second round
Q.1.	To identify unmet needs in COVID-19 prevention in ICI, based on perceptions and clinical experience, to inform and develop effective prevention measures for this vulnerable population.	9	+17
Q.2.	To identify the characteristics that distinguish ICI as a susceptible group in terms of COVID-19.	13	+7
Q.3.	To determine the main outcomes of COVID-19 in ICI.	24	+1
Q.4.	To indicate the most effective action plans for protecting ICI.	13	+4
		60	29
		Total: 89	

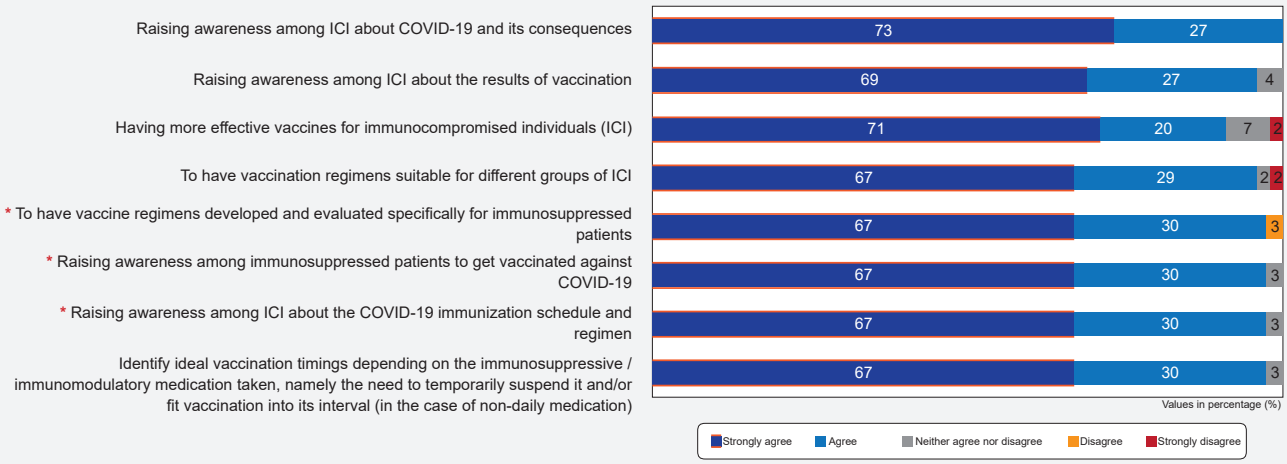

Figure 1 – Consensus regarding unmet needs in COVID-19 prevention for ICI. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding the unmet needs in COVID-19 prevention for ICI. Results correspond to answers to the question "In your perception, based on your clinical practice, management experience or contact with associates, what needs remain to be met in the prevention of COVID-19 in immunocompromised individuals (ICI)?"
* Indicators added by experts in the second round.

groups of ICI" (67% strongly agree) (Fig. 1). The indicators that did not reach consensus are shown in Appendix 2, Fig. A (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

ICI characteristics related to COVID-19 susceptibility

Considering the characteristics of ICI, 20 indicators were identified as being related to COVID-19 susceptibility. Among these, only five achieved consensus among the expert panel, reaching agreement at the following levels: (1) "individuals undergoing solid organ transplantation" (82% strongly agree), (2) "individuals with primary immunodeficiencies (PID)" (78% strongly agree), (3) "bone marrow transplant patients" (68% strongly agree), (4) "individuals undergoing chemotherapy (CT) and/or radiotherapy (RT)" (67% strongly agree) and (5) "individuals with chronic renal failure (CRF)" (65% agree) (Fig. 2). The indicators that did not reach consensus are shown in Appendix 2, Fig. B (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

Main outcomes of COVID-19 in ICI

Regarding the main outcomes of COVID-19 in the immunocompromised population, consensus was reached on only 2 of the 25 indicators. Consensus on this issue was not reached until the third round. The indicators with their

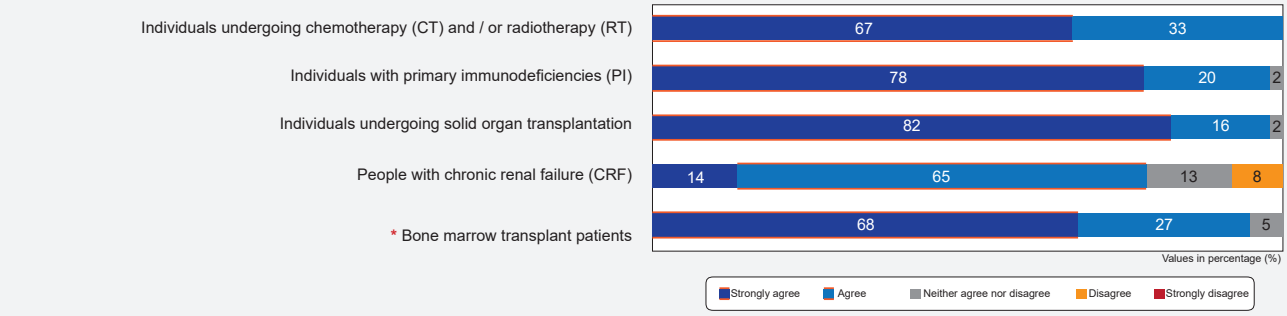

Figure 2 – Consensus regarding ICI characteristics related to COVID 19 susceptibility. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding ICI characteristics related to COVID-19 susceptibility. Results correspond to answers to the question "Who do you consider to be immunocompromised individuals (ICI), i.e. which ICI characteristics are related to COVID 19 susceptibility?"
* Indicators added by experts in the second round.

corresponding levels of agreement are as follows: (1) "existence of an improvement in the current situation compared to the past, regarding the clinical outcomes of COVID-19" (72% agree) and (2) "existence of an improvement in the current situation compared to the past regarding hospitalizations" (69% agree) (Fig. 3). The indicators that did not reach consensus are shown in Appendix 2, Fig. C (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

Action strategies for COVID-19 prevention in ICI

Concerning the most effective action strategies for COVID-19 prevention in ICI, 8 of the 17 indicators have reached consensus. All these indicators achieved the level of agreement in the "strongly agree" category, as follows: (1) "maintaining epidemiological surveillance of COVID-19" (80% strongly agree), (2) "promote health literacy on COVID-19 and vaccination among the immunocompromised population" (73% strongly agree), (3) "promote the use of measures to prevent the transmission of infection (hand washing) among ICI" (73% strongly agree), (4) "promote vaccination in ICI" (73% strongly agree), (5) "maintain investment (research) in vaccination: more effective and specific vaccines" (73% strongly agree), (6) "prioritize access for ICI to vaccination or drugs that provide greater protection" (70% strongly agree), (7) "facilitate the chain, from prescription to administration, of effective therapies for the prevention of infection (prophylaxis)" (69% strongly agree) and (8) "action strategies aimed at different sub-groups of ICI, groups that are more homogeneous (e.g. distinguishing different levels of severity; of need for intervention depending on this assessment of severity; of the pathology and the medication taken)" (67% strongly agree) (Fig. 4). The indicators that did not reach consensus are shown in Appendix 2, Fig. D (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717).

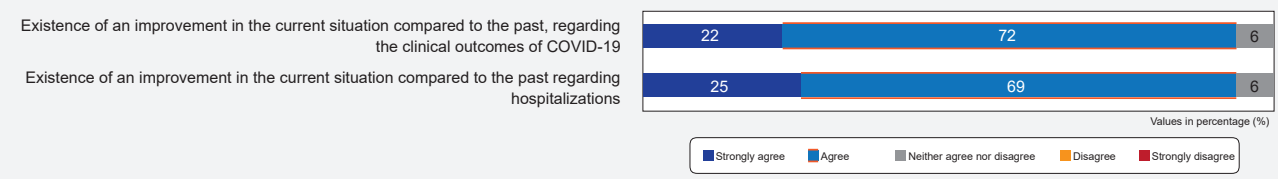

Figure 3 – Consensus regarding main outcomes of COVID-19 in ICI. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding the main outcomes of COVID-19 in ICI. Results correspond to answers to the question "Currently, in your perception, what do you consider to be the main outcomes of COVID-19 in immunocompromised individuals (ICI)?"
* Indicators added by experts in the second round.

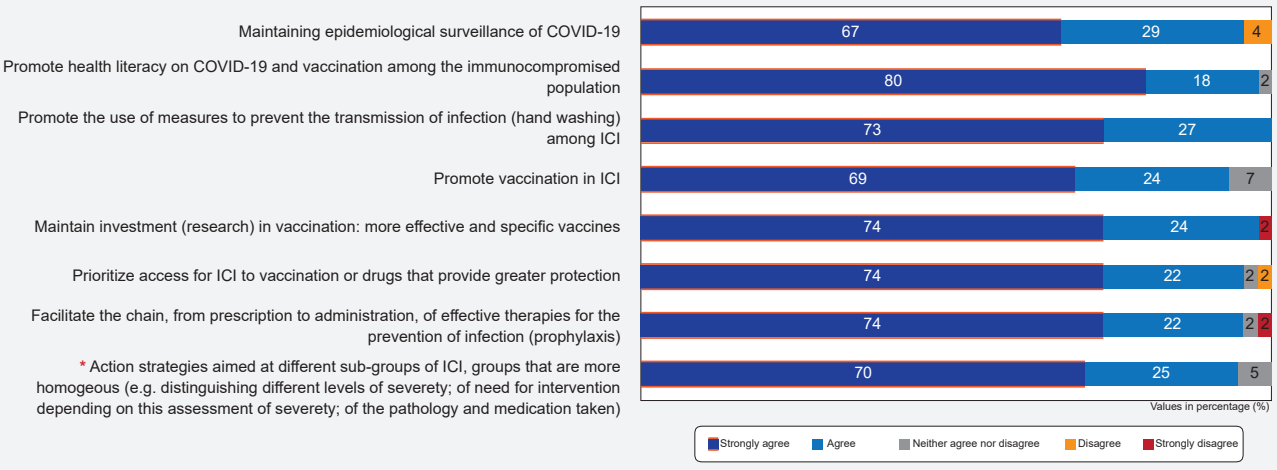

Figure 4 – Consensus regarding action strategies for COVID-19 prevention in ICI. Frequencies corresponding to the level of agreement among consensus indicators (highlighted borders) regarding the action strategies for COVID-19 prevention in ICI. Results correspond to answers to the question "Regarding the need to prevent COVID-19 in immunocompromised individuals (ICI), what action strategies do you consider most effective to protect this population?"
* Indicators added by experts in the second round.

DISCUSSION

This Delphi panel study comprehensively examined key indicators for preventing and managing COVID-19 in ICI using a broad and multidisciplinary panel of experts. In total, our expert panel identified 89 indicators in four different dimensions of the ICI and COVID-19 context. Though only 23 of such indicators reached consensus, which indicates a possible divergence in the experts' approaches or, in some cases, the need for more scientific evidence, the substantial agreement obtained in the "strongly agree" category underlines the experts' robust alignment on the consensus indicators.

Regarding the unmet needs in COVID-19 prevention for the immunocompromised population, the thematic prioritization of the consensualized results highlights several key areas needing attention. These include raising awareness about the disease and vaccination outcomes among ICI, ensuring their safety and understanding, and the urgent need for targeted vaccination strategies tailored to this population. This focus includes developing more effective vaccines and personalized immunization schedules that accommodate diverse health conditions and treatment regimens, as well as raising awareness of preventative measures to reduce vaccine hesitancy. These results align with existing scientific evidence,[23–27] emphasizing the need for optimized preventive strategies for ICI. To achieve the maximum level of protection, other authors also add that these strategies should consider the type of vaccine used, dosage regimens, and the possibility of additional doses or revaccinations.[3,28] Furthermore, other authors suggest additional measures to complement suboptimal vaccine response, such as the use of monoclonal antibodies,[3,6,24,29] which was an indicator that obtained 56 percent agreement in our panel (9% short of consensus on the "strongly agree" category) [Appendix 2, Fig. A (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/9949/15717)]. Hence, ICI face significant challenges in achieving adequate immune responses to COVID-19 vaccination, rendering them more susceptible to severe outcomes.[24,30,31] Addressing these challenges is considered essential to safeguarding ICI and mitigating the impact of COVID-19 on their health and healthcare systems.[25,29]

The identification of ICI characteristics related to COVID-19 susceptibility emerged as another significant point in this analysis. Although 20 indicators were identified, consensus was achieved on only five, highlighting the complexity of defining this population and respective subsets.[25,32] This expert divergence pinpoints the consequent challenges in developing universally applicable strategies for COVID-19 prevention and management, particularly in such diverse population subsets. According to our panel of experts, individuals undergoing chemotherapy or radiotherapy, those with primary immunodeficiencies, solid organ transplant recipients, individuals with chronic kidney disease, and bone marrow transplant recipients are identified as susceptible groups in terms of COVID-19. This characterization is corroborated by other authors, who have also identified these individuals as being at greater risk of developing serious complications and dying due to COVID-19.[9,33–35] Besides their immunocompromised status, these individuals often have advanced age and other comorbidities, further increasing their risk for poor outcomes.[9,36–40]

The clinical characteristics and outcomes of COVID-19 in ICI, who are believed to be at higher risk for severe disease but may also have reduced inflammatory responses, are not well defined.[33] Thus, more evidence is needed to determine the risk attributable to immunocompromising conditions and therapies for the prognosis of COVID-19.[34]

Regarding outcomes associated with COVID-19, experts found improvements in clinical results and a reduction in hospitalizations compared to the past (Fig. 3). These findings can be further contextualized in relation to the core outcome set (COS) for post-COVID-19 condition, as developed by Gorst *et al*.[41] This COS provides a standardized framework for assessing key health outcomes in post-COVID-19 patients, including fatigue, respiratory symptoms, cognitive dysfunction, and recovery measures.[41] Some of these indicators align with the vulnerabilities identified for ICI in our study, particularly the need for continuous monitoring and improved treatment accessibility.[41] However, while the COS broadly addresses post-COVID-19 outcomes, it does not fully capture the specific challenges faced by ICI, such as vaccine response limitations and a heightened risk of severe disease progression.[41] Future research should examine how these core outcomes can be adapted to better reflect the distinct health risks of ICI, ensuring that prevention strategies remain aligned with internationally recommended measures while addressing the unique vulnerabilities of this high-risk population. Although several experts emphasized the ongoing need to focus on reducing severe cases and subsequent hospitalizations, there was no consensus on this point. The limited agreement on COVID-19 outcome indicators – only two consensual out of 25 identified –suggests significant heterogeneity in expert opinions. While improvements in clinical conditions and reduced hospitalizations are positive signs, the lack of consensus on more indicators may reflect variations in clinical experience among experts or the need for more comprehensive scientific evidence.[42] This highlights the complexity of assessing COVID-19 outcomes in ICI and reinforces the need for targeted preventive measures.[43]

Furthermore, our results also emphasize the importance of disease monitoring and health literacy promotion in COVID-19 prevention strategies. The consensus reached

on the eight related indicators aligns with the unmet needs identified in this panel, highlighting the need to maintain epidemiological surveillance and drive forward health literacy initiatives among ICI and the wider public. Additionally, tailored educational strategies for specific subgroups of immunocompromised individuals, along with initiatives to enhance access to effective immunization strategies and therapies, were identified as crucial consensual strategies. These strategies are also consistent with existing evidence.[24,35,44,45]

Finally, experts have identified key research priorities, including the development of effective therapies, more immunization strategies, and treatments for viral infections in ICI. These research opportunities are crucial, as they aim to improve both health outcomes and quality of life of people with ICI.[9,45] As COVID-19 transitions from pandemic to endemic status, establishing effective health measures remains imperative to protect ICI from ongoing infectious threats.[24]

Strengths and limitations

One aspect of the study was the lack of consensus on many indicators. This outcome likely reflects the diversity of backgrounds, perspectives, and prioritizations among the experts involved, which led to differing opinions and interpretations of the pre-identified and generated indicators. Given the complexity of the topic and the inherent subjectivity in evaluating certain indicators, particularly those for which robust scientific evidence is still limited, some degree of divergence was expected. Rather than weakening the study, these differing perspectives contributed to a valuable discussion and helped identify areas where further research and clarification are necessary.

Although individual patients were not directly involved in the expert panel, the study incorporated specialists representing patient advocacy groups. This ensured that patient perspectives and priorities were considered in the evaluation of indicators, even if indirectly. The inclusion of these representatives strengthened the applicability of the findings by bridging clinical expertise with the lived experiences of the affected population.

The questions formulated to perform the Delphi panel were informed primarily by literature review and expert consultation, a widely accepted approach for developing indicators in consensus studies. These methods ensure that the questions reflect practical and field-relevant insights. While expert input alone may involve some inherent subjectivity, it remains a robust and appropriate method for this type of research.

Additionally, while the study did not explicitly control for regional representation or sex balance, the diversity of expertise within the panel ensured a broad and well-informed discussion. This approach strengthens the overall applicability of the findings.

Given that the response rate remained within the recommended range throughout the three Delphi panel rounds, it is also reasonable to conclude that the experts' responses were motivated by a genuine interest in the topic, thereby reducing potential bias. In addition, the inclusion of a significant number of specialists in this expert panel enriched the variability of perspectives, thereby strengthening the results.

To preserve confidentiality and anonymity, specific details regarding the identities and affiliations of the experts were intentionally excluded from the manuscript. Addressing these methodological considerations and maintaining transparency yielded valuable insights and actionable strategies from a diverse panel of experts. These findings offer crucial guidance for improving COVID-19 prevention strategies for ICI, highlighting gaps, and providing expert recommendations for safeguarding this vulnerable population.

CONCLUSION

In conclusion, this study highlights the critical need for tailored COVID-19 prevention and management strategies for ICI in Portugal. Through the Delphi panel methodology, 89 key indicators were identified, with consensus reached on 23 of them, revealing essential areas for intervention. The findings emphasize the importance of raising awareness among ICI about COVID-19 and vaccination, developing immunization strategies tailored to their specific conditions, and identifying optimal vaccination regimens for this population.

The study also underscores the necessity of strengthening epidemiological surveillance and promoting health literacy to enhance preventive measures. Experts reached consensus on the importance of maintaining continuous monitoring of COVID-19, ensuring access to accurate information, and implementing targeted educational strategies to reduce vaccine hesitancy and increase adherence to protective measures. Additionally, investment in research remains essential to develop more effective vaccines and therapeutic options specifically suited for ICI.

Regarding the outcomes of COVID-19 in ICI, consensus was reached on the perception that there have been improvements in clinical outcomes and hospitalization rates compared to the past. However, the lack of consensus on several other indicators suggests a need for further research to better define the risks and prognosis of COVID-19 in this population.

Furthermore, experts strongly agreed on the need for a structured approach to COVID-19 prevention in ICI, which includes maintaining access to vaccination and prophylactic treatments, prioritizing ICI in public health strategies, and

tailoring prevention measures based on different immunosuppressive conditions. The study reinforces the importance of collaboration between healthcare professionals, policymakers, and patient associations to effectively implement these strategies.

Given the persistent presence of SARS-CoV-2 and the risk of new variants, continuous efforts to safeguard immuno-compromised individuals remain crucial. The insights obtained in this study provide a foundation for future discussions and policy development, aiming to optimize COVID-19 prevention strategies for ICI in Portugal and address existing gaps in their protection and care.

AUTHOR CONTRIBUTIONS

ASC, BR, ARP: Study conception and design; study conduction, the analysis and interpretation of the results; first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript.

JVC: First draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript.

MJM: Study conception and design; final version of the manuscript revision, with important contributions to the discussion.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

MJM is employed by AstraZeneca.

All other authors have declared that no competing interests exist.

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REFERENCES

1. World Health Organization. COVID-19 cases. WHO COVID-19 dashboard. [cited 2024 Jul 24]. Available from: https://data.who.int/dashboards/covid19/cases?n=c.
2. Mekkawi R, Elkattan BA, Shablak A, Bakr M, Yassin MA, Omar NE. COVID-19 vaccination in cancer patients: a review article. Cancer Control. 2022;29:107327482211062.
3. Tan TT, Ng HJ, Young B, Khan BA, Shetty V, Azmi N, et al. Effectiveness of vaccination against SARS-CoV-2 and the need for alternative preventative approaches in immunocompromised individuals: a narrative review of systematic reviews. Expert Rev Vaccines. 2023;22:341-65.
4. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy. 2021;76:428-55.
5. Kant S, Kronbichler A, Salas A, Bruchfeld A, Geetha D. Timing of COVID-19 vaccine in the setting of anti-cd20 therapy: a primer for nephrologists. Kidney Int Rep. 2021;6:1197-9.
6. Gentile I, Schiano Moriello N. COVID-19 prophylaxis in immunosuppressed patients: beyond vaccination. PLoS Med. 2022;19:e1003917.
7. Dioverti V, Salto-Alejandre S, Haidar G. Immunocompromised patients with protracted COVID-19: a review of "long persisters". Curr Transplant Rep. 2022;9:209-18.
8. Jena A, James D, Singh AK, Dutta U, Sebastian S, Sharma V. Effectiveness and durability of COVID-19 vaccination in 9447 patients with IBD: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2022;20:1456-79.e18.
9. Singson JR, Kirley PD, Pham H, Rothrock G, Arminstead I, Meek J, et al. Factors associated with severe outcomes among immunocompromised adults hospitalized for COVID-19 — COVID-NET, 10 States, March 2020–February 2022. MMWR Morb Mortal Wkly Rep. 2022;71:878-84.
10. Portugal. Directorate-General of Health. Number of new cases and deaths per day, last updated on July 24. [cited 2024 Jul 24]. Available from: https://covid19.min-saude.pt/numero-de-novos-casos-e-obitos-por-dia/.
11. Wise J. Covid-19: WHO declares end of global health emergency. BMJ. 2023;381:1041.
12. Centers for Disease Control and Prevention. Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare professionals. 2024. [cited 2024 May 03]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.
13. Rzymski P, Camargo CA, Fal A, Flisiak R, Gwenzi W, Kelishadi R, et al. COVID-19 vaccine boosters: the good, the bad, and the ugly. Vaccines. 2021;9:1299.
14. Mohamed K, Rzymski P, Islam MS, Makuku R, Mushtaq A, Khan A, et al. COVID-19 vaccinations: the unknowns, challenges, and hopes. J Med Virol. 2022;94:1336-49.
15. Sun J, Zheng Q, Madhira V, Olex AL, Anzalone AJ, Vinson A, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. JAMA Intern Med. 2022;182:153-62.
16. Primorac D, Vrdoljak K, Brlek P, Pavelic E, Molnar V, Matišić V, et al. Adaptive immune responses and immunity to SARS-CoV-2. Front Immunol. 2022;13:848582.
17. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: how to decide its appropriateness. World J Methodol. 2021;11:116-29.
18. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm. 2016;38:655-62.
19. Delbecq A, Van de Ven A, Gustafson D. Group techniques for program planning: a guide to nominal group and Delphi processes. Group Organ Stud. 1976;1.
20. Barrett D, Heale R. What are Delphi studies? Evid Based Nurs. 2020;23:68-9.
21. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3:77-101.
22. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32:1008-15.
23. Shoham S, Batista C, Ben Amor Y, Ergonul O, Hassanain M, Hotez P,

et al. Vaccines and therapeutics for immunocompromised patients with COVID-19. EClinicalMedicine. 2023;59:101965.
24. Razonable RR. Protecting the vulnerable: addressing the COVID-19 care needs of people with compromised immunity. Front Immunol. 2024;15:1397040.
25. Antinori A, Bausch-Jurken M. The burden of COVID-19 in the immunocompromised patient: implications for vaccination and needs for the future. J Infect Dis. 2023;228:S4-12.
26. Bonanni P, Ceddia F, Dawson R. A call to action: current challenges and considerations for COVID-19 vaccination in immunocompromised populations. J Infect Dis. 2023;228:S70-6.
27. Negahdaripour M, Shafiekhani M, Moezzi SM, Amiri S, Rasekh S, Bagheri A, et al. Administration of COVID-19 vaccines in immunocompromised patients. Int Immunopharmacol. 2021;99:108021.
28. Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, et al. Triple combination therapy with 2 antivirals and monoclonal antibodies for persistent or relapsed severe acute respiratory syndrome coronavirus 2 infection in immunocompromised patients. Clin Infect Dis. 2023;77:280-6.
29. Morawska M. Reasons and consequences of COVID-19 vaccine failure in patients with chronic lymphocytic leukemia. Eur J Haematol. 2022;108:91-8.
30. Galmiche S, Luong Nguyen LB, Tartour E, de Lamballerie X, Wittkop L, Loubet P, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. Clin Microbiol Infect. 2022;28:163-77.
31. Lee AR, Wong SY, Chai LYA, Lee SC, Lee MX, Muthiah MD, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. BMJ. 2022;376:e068632.
32. Agrati C, Bartolini B, Bordoni V, Locatelli F, Capobianchi MR, Di Caro A, et al. Emerging viral infections in immunocompromised patients: A great challenge to better define the role of immune response. Front Immunol. 2023;14:1147871.
33. Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. Clin Infect Dis. 2021;72:340-50.
34. Bytyci J, Ying Y, Lee LYW. Immunocompromised individuals are at increased risk of COVID-19 breakthrough infection, hospitalization, and death in the post-vaccination era: a systematic review. Immun Inflamm Dis. 2024;12:e1259.
35. National Institutes of Health. Immunocompromised. COVID-19 treatment guidelines. 2024. [cited 2024 Jul 03]. Available from: https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised/.
36. Evans RA, Dube S, Lu Y, Yates M, Arnetorp S, Barnes E, et al. Impact of COVID-19 on immunocompromised populations during the omicron era: insights from the observational population-based INFORM study. Lancet Reg Health Eur. 2023;35:100747.
37. Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell. 2020;183:996-1012.e19.
38. Grifoni A, Alonzi T, Alter G, Noonan DM, Landay AL, Albini A, et al. Impact of aging on immunity in the context of COVID-19, HIV, and tuberculosis. Front Immunol. 2023;14:1146704.
39. Jakharia N, Subramanian AK, Shapiro AE. COVID-19 in the immunocompromised host, including people with human immunodeficiency virus. Infect Dis Clin North Am. 2022;36:397-421.
40. Danwang C, Noubiap JJ, Robert A, Yombi JC. Outcomes of patients with HIV and COVID-19 co-infection: a systematic review and meta-analysis. AIDS Res Ther. 2022;19:3.
41. Gorst SL, Seylanova N, Dodd SR, Harman NL, O'Hara M, Terwee CB, et al. Core outcome measurement instruments for use in clinical and research settings for adults with post-COVID-19 condition: an international Delphi consensus study. Lancet Respir Med. 2023;11:1101-14.
42. Rowe G, Wright G, McColl A. Judgment change during Delphi-like procedures: the role of majority influence, expertise, and confidence. Technol Forecast Soc Change. 2005;72:377-99.
43. Turtle L, Thorpe M, Drake TM, Knight SR, Harrison EM, Docherty AB, et al. Outcome of COVID-19 in hospitalised immunocompromised patients: an analysis of the WHO ISARIC CCP-UK prospective cohort study. PLoS Med. 2023;20:e1004086.
44. Saleem SM, Jan SS. Navigating the infodemic: strategies and policies for promoting health literacy and effective communication. Front Public Health. 2024;11:1324330.
45. Whitaker JA. Immunization strategies to span the spectrum of immunocompromised adults. Mayo Clin Proc. 2020;95:1530-48.

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Communication in Neonatal Intensive Care: Translation and Validation of the "Parents' Experiences of Communication in Neonatal Care" Questionnaire for the Portuguese Population

Comunicação em Cuidados Intensivos Neonatais: Tradução e Validação do Questionário "Parents' Experiences of Communication in Neonatal Care" para a População Portuguesa

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ABSTRACT

Introduction: Communication is a fundamental aspect in healthcare, more so in fragile environments such as Neonatology. To optimize communication strategies with parents, it is essential to assess its quality. The aim of this study was to validate, for the Portuguese population, an instrument for assessing the quality of communication between healthcare professionals and parents in neonatal care units.

Methods: The Parents' Experiences of Communication in Neonatal Care questionnaire was developed in the United Kingdom to evaluate communication with parents specifically. The 28-question instrument was adapted and translated to European Portuguese following a three-step protocol: translation, review, and back-translation. Subsequently, the validation process was conducted in three stages: (1) face validity through cognitive interviews; (2) content validity through external panel evaluation; and (3) performance assessment through a four-month pilot study in a tertiary neonatal intensive care unit.

Results: Cultural adaptation resulted in the removal of two questions. The remaining questions were translated to Portuguese. Cognitive interviews were conducted with a convenience sample of ten parents, leading to important revisions in two questions. Five external professionals evaluated the item's relevance in a 4-point Likert scale. Four questions presented an item content validity index value below the threshold of 0.78. Two questions were adjusted and two were eliminated at this stage. The questionnaire was delivered to 31 parents, with a total of 60 questionnaires completed. Five questions were reviewed due to a non-response rate greater than 5%, and one for exceeding 95% uniform responses. No question had a dropout rate greater than 5%, nor did any have a rate of non-informative answers exceeding 5%. A significant correlation (Kendall's Tau > 0.7) was found between three sets of questions.

Conclusion: The European Portuguese version of Parents' Experiences of Communication in Neonatal Care survey contains 24 questions. This is the first comprehensive and valid instrument at national level to objectively measure satisfaction with communication of parents of children admitted to the neonatal intensive care units. Its use will enable monitoring of interventions aimed at improving communication, which is crucial for enhancing family-centered care.

Keywords: Communication; Intensive Care Units, Neonatal; Parents/psychology; Portugal; Surveys and Questionnaires; Translations

RESUMO

Introdução: A comunicação é um aspeto fundamental na prestação de cuidados de saúde, especialmente em ambientes de maior fragilidade como a Neonatologia. Para a otimização de estratégias de comunicação com os pais é essencial avaliar a sua qualidade. Este estudo teve como objetivo a validação de um instrumento de avaliação da qualidade da comunicação dos profissionais de saúde com os pais em unidades de cuidados neonatais para a população portuguesa.

Métodos: O questionário *Parents' Experiences of Communication in Neonatal Care* foi desenvolvido no Reino Unido para avaliação específica da comunicação com os pais. O instrumento com 28 questões foi adaptado e traduzido para português Europeu em três etapas protocoladas: tradução, revisão e tradução reversa. Posteriormente, o processo de validação realizou-se em três fases: 1) validade de face através de entrevistas cognitivas; 2) validade de conteúdo através da avaliação por um painel externo; 3) avaliação de desempenho através de um estudo piloto de quatro meses numa unidade de apoio perinatal diferenciado.

Resultados: O processo de adaptação cultural resultou na remoção de duas questões. As restantes questões foram traduzidas para a língua portuguesa. Realizaram-se entrevistas cognitivas a uma amostra de conveniência de 10 pais, conduzindo à revisão de duas questões. Um painel de cinco profissionais externos avaliou a relevância de cada item numa escala de Likert de quatro pontos. Quatro questões apresentaram um índice de validade de conteúdo inferior a 0,78. Nesta fase, duas questões foram ajustadas e duas foram removidas. O questionário foi entregue a 31 pais, num total de 60 questionários preenchidos. Nesta avaliação cinco questões foram revistas por ausência de resposta em > 5% dos questionários e uma por > 95% de respostas uniformes. Foi encontrada uma correlação significativa, com Tau de Kendall superior a 0,7, entre três conjuntos de questões.

Conclusão: A versão portuguesa do questionário *Parents' Experiences of Communication in Neonatal Care* contém 24 questões. Este é o primeiro instrumento nacional validado para avaliar objetivamente a satisfação dos pais com a comunicação durante o internamento em cuidados intensivos neonatais. A sua utilização permitirá monitorizar intervenções que visam melhorar a comunicação, fundamentais para a melhoria dos cuidados centrados na família.

Palavras-chave: Comunicação; Inquéritos e Questionários; Pais/psicologia; Portugal; Traduções; Unidades de Cuidados Intensivos Neonatais

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KEY MESSAGES

Strengths:

- Communication plays a central role in family-centered care, and its evaluation is essential for improving the quality of care.
- The European Portuguese version of the "Parents' Experiences of Communication in Neonatal Care" (PEC) questionnaire enables real-time assessment of communication with parents, driving improvement strategies that can be continuously monitored.
- The translation and cultural adaptation of the PEC questionnaire involved parent participation and an external evaluation of content validity.

Limitations:

- The translated version was evaluated in a single center, which may not be fully representative.
- This study did not include parents who do not fluently speak European Portuguese, a group that may be particularly vulnerable to communication issues.

INTRODUCTION

Communication is a fundamental aspect of quality in health care, playing a critical role in several aspects such as promoting healthy habits and primary prevention, establishing a therapeutic relationship between healthcare professionals and patients, effectively guiding diagnostic investigations, and defining and ensuring adherence to a treatment plan.[1,2]

The communication process is strategically important as it can significantly influence the families' perceptions of the quality of care, psychological adaptation to the clinical situation, and behaviors of therapeutic compliance.[1,2]

The main challenges in communication between healthcare professionals and families relate to four key aspects: the transmission of information; interpersonal styles and attitudes of both professionals and families toward communication; non-verbal communication; and the cultural, linguistic, and social factors specific to each family. To ensure effective communication it is essential to consider the dynamic needs of the family including the clinical, affective, social, and cultural aspects.[2]

In Neonatology, effective communication serves several purposes: to inform and clarify the parents of the newborn's clinical condition, to encourage their participation in everyday care as well as their involvement in the decision processes. It is also an important tool for emotional support to the families.[3] The quality of communication with parents during Neonatal Intensive Care Unit (NICU) admission can have a significant impact. Ineffective communication has been shown to negatively affect parental stress and anxiety, which can hinder the parent-newborn bonding process. Conversely, effective communication can positively influence family satisfaction and their autonomy in care, while also benefiting the well-being and satisfaction of the staff.[4-7]

The NICU's specific features influence communication between parents and healthcare professionals. The quality of communication is affected by the complex NICU environment, which is highly technological and often lacks privacy. Additionally, working dynamics characterized by periods of agitation, the need to prioritize urgent tasks, and staff turnover can impair interactions with parents. Beyond these constraints, it is crucial to consider the vulnerability of the newborn and the inherent risks of complications that impact both short- and long-term prognosis. The emotional needs and expectations of families must also be taken into account.[5,8]

To improve the quality of care, it is essential to evaluate parents' experiences and perceptions regarding the quality of communication. This assessment is challenging and often relies on unvalidated instruments that retrospectively evaluate communication alongside other aspects of parental satisfaction.[9]

In this regard, a new instrument was recently developed in the United Kingdom (UK) to evaluate parental satisfaction in neonatal care, specifically focusing on communication of clinical information and parental involvement in care. This new survey, entitled "Parents' Experiences of Communication in Neonatal Care" (PEC) was assessed for the United Kingdom population and enables real-time evaluation of parental experiences, as well as monitoring of interventions aimed at improving communication.[10]

In Portugal there are few publications about communication in neonatology. The existing literature primarily addresses the importance of this topic and suggests strategies for evaluating and improving healthcare professionals' communication skills.[8,11] However, in the literature review conducted by the authors, no tools specifically designed to evaluate aspects of communication with families in neonatal care were identified that are validated for the Portuguese population.

The evaluation of communication using an objective tool that measures parents' perceptions is a crucial step toward implementing targeted strategies to improve

communication between parents and healthcare professionals in Portuguese NICUs, facilitating shared decision-making and enhancing parental involvement in care. Interventions can be tailored to each NICU and may include staff training, the development of protocols and communication strategies, care planning meetings, and improved access to written and audiovisual information.[3,6] A tool that can assess the effectiveness of these measures, such as the PEC questionnaire, is particularly valuable.

Our main objective was to validate an instrument for assessing the communication of healthcare professionals with parents during NICU admissions for the Portuguese population.

METHODS

Stage 1: Translation and adaptation to the Portuguese language

The translation of the original PEC survey into Portuguese followed a structured method and adhered to the survey adaptation recommendations of the Picker Institute. The authors initially reviewed the questionnaire to ensure that the questions were relevant to the Portuguese context. The survey was then translated using a three-step process: 1) forward translation by an independent translator, 2) revision by an expert panel composed by the independent translator, one neonatologist, and one statistician, 3) backward translation conducted by a second independent translator, which was subsequently assessed by the Picker Institute to ensure consistency with the original version.

Stage 2: Face validity and cognitive testing

The translated version of the survey was used in cognitive interviews. A sample of ten parents was selected from those whose newborns were admitted to the NICU in a differentiated perinatal support unit. The cognitive interviews were conducted individually by a member of the research team, following the model described by Tourangeau.[12] Participants were asked to respond to each question orally, and their answers were compared to the responses they had provided on a previously completed printed version of the questionnaire. To establish face validity, the response process, level of comprehension, and cultural appropriateness of each question were evaluated. The structure, flow and length of the questionnaire were also assessed. Upon revision of the issues raised during the interviews, the final version of the translated questionnaire was established.[13]

Stage 3: Content validity

To establish content validity, the final translated version was evaluated by a panel of five external neonatology professionals. This panel comprised three neonatologists and two specialized neonatal nurses, with between ten and twenty years of clinical experience. The experts were selected from a range of neonatal care settings in Portugal, including intensive care (differentiated perinatal support) and intermediate care (perinatal support) units, and a unit in a private hospital. The panel broadly assessed the scope and comprehensiveness of the questionnaire. Each question was individually graded in terms of relevance on a 4-point Likert scale (1 = non-relevant, 2 = mildly relevant, 3 = relevant, 4 = very relevant). The item content validity index (I-CVI) was calculated for each question, and the average content validity index (A-CVI) was calculated for the questionnaire. An I-CVI below 0.78 indicates that the question should be reviewed or considered for removal. An A-CVI above 0.8 - 0.9 is considered sufficient to establish content validity, depending on the reference.[14]

Stage 4: Survey evaluation

To formally evaluate the survey, we conducted an observational prospective study in a Portuguese NICU over a period of four months. Study participants included parents or legal representatives of newborns admitted to the NICU for longer than 48 hours. Parents who could not speak Portuguese fluently were excluded. The translated version of the PEC survey was distributed weekly to all parents present who met the inclusion criteria. Demographic variables of the participants were registered.

The evaluation of the questionnaire included the following components:

- Non-response rate: an absence of answers exceeding 5% for each question was considered significant.
- Dropout rate: determined by the last question answered by each participant.
- Rate of non-informative answers: a rate of uninformative responses (e.g., “don’t know”) greater than 5% for any question was deemed significant.
- Rate of uniform answers: a rate of uniform responses greater than 95% for any question was considered significant.
- Correlation between questions: Kendall’s tau correlation coefficient was calculated for questions with numerical answers, correlations greater than 0.7 were considered relevant. For parents who completed more than one questionnaire, responses were aggregated by calculating the mean value for each question, which was then used to compute the Kendall’s tau coefficient.

Statistical analysis was performed with the software R®.[15]

Ethical and legal considerations

The use of the Parents’ Experiences of Communication in Neonatal Care survey was licensed by the Picker Institute

for translation and adaptation into Portuguese. The study received approval from the ethics committee of Hospital Garcia de Orta. All participants provided written informed consent, and their responses were kept anonymous.

RESULTS

Stage 1: Translation and adaptation to the Portuguese language

The adaptation and translation process were conducted as outlined. An initial review by the research team led to the removal of two questions (B3 and B8 from the original version). These questions addressed parental presence during medical rounds and access to medical records, two aspects that do not apply to the reality of the clinical practice of NICU's in Portugal. Information regarding ethnicity was also excluded due to ethical concerns.

The survey was subsequently translated using the previously described three-step process. The back-translation review by the Picker Institute resulted in minor grammatical changes to the translated version.

Stage 2: Face validity and cognitive testing

Cognitive interviews were conducted in March 2024. Ten parents of newborns admitted to the NICU were selected through convenience sampling. Participant demographics are presented in Table 1. Most participants were female (n = 8), with a predominant age range of 30 - 34 years (n = 4), though all age groups were represented. Gestational ages ranged from 24 to 39 weeks, with the majority being less than 32 weeks. The length of stay varied from under one week to over six months, with most stays being under two weeks. The parents who participated in the cognitive interviews represented a range of educational levels (basic, secondary, and tertiary education) and diverse socioeconomic backgrounds (including lower- and middle-income households, as well as Portuguese-speaking immigrant families), reflecting the profile of the population typically admitted to this NICU.

Doubts regarding wording throughout the questionnaire, identified during the interviews, were corrected in the final version, along with formatting issues. Inconsistencies between written and verbal responses revealed comprehension issues, leading to wording adjustments in questions A4 and A8. No questions were removed or added at this stage.

The interviews confirmed that this sample of parents understood the questionnaire's purpose, the meaning of each question, and were able to provide accurate responses, thereby establishing the face validity of the translated version.

Stage 3: Content validity

Overall, the questionnaire received positive evaluations, with all external professionals considering it an important, easy-to-understand, and sufficiently comprehensive tool. However, three of the five professionals found the questionnaire to be too long. Each panel member rated the questions based on their relevance, and the I-CVI was calculated. Table 2 displays questions with an I-CVI of less than 1 in the translated PEC questionnaire. All other questions were unanimously rated as relevant or very relevant.

Questions with an I-CVI below 0.78 were reviewed. The questions with the lowest I-CVI (0.4), B6 and B9 from the original version, were removed, as both addressed the frequency of communication with doctors and nurses, a topic covered by other questions. The other two questions, B5 and B7, were retained to avoid narrowing the scope of the survey.

Based on a suggestion during the content validity evaluation, an open-response field was added to question C4, allowing parents to explain why they feel insufficiently involved in their baby's care.

With the removal of these questions, the a-CVI was calculated at 0.91, confirming the content validity of the translated version of the PEC questionnaire.

Stage 4: Survey evaluation

A prospective study was conducted between June and September 2024 in a differentiated perinatal support unit at Hospital Garcia de Orta in Portugal. During the study period, 60 questionnaires were completed by 31 parents, with

Table 1 – Demographics for cognitive interview participants

Sex	n	Age (years)	n	Gestational age	n	Time since admission	n
Male	2	18 - 24	1	24 - 27 weeks	3	< 1 week	4
Female	8	25 - 29	2	28 - 31 weeks	4	1 - 2 weeks	2
		30 - 34	4	32 - 36 weeks	2	1 - 2 months	3
		> 35	3	36 - 40 weeks	1	> 6 months	1

Table 2 – Item content validity index values < 1 (original version numbering)

Question	A2	A8	B2	B4	B5	B6	B7	B9	B10	B11	D1
I-CVI	0.8	0.8	0.8	0.8	0.6	0.4	0.6	0.4	0.8	0.8	0.8

Table 3 – Demographic details for questionnaire responses in the prospective study

Sex	n (%)	Age (years)	n (%)	Gestational age	n (%)	Time since admission	n (%)
Male	16 (27)	< 18	2 (3)	24 - 27 weeks	16 (27)	< 1 week	11 (18)
Female	44 (73)	18 - 24	1 (2)	28 - 31 weeks	28 (47)	1 - 2 weeks	15 (25)
		25 - 29	20 (33)	32 - 36 weeks	9 (15)	2 - 4 weeks	8 (13)
		30 - 34	9 (15)	36 - 39 weeks	4 (7)	1 - 2 months	18 (30)
		≥ 35	28 (47)	≥ 40 weeks	2 (3)	2 - 4 months	3 (5)
						≥ 6 months	5 (8)

the number of questionnaires per parent ranging from 1 (18 parents) to 8 (1 parent), averaging 1.94 per parent. Each response corresponded to a specific time point during the newborn's admission.

Demographic details for each response are presented in Table 3. Most respondents were female (73%) and over 25 years of age (95%). Gestational ages ranged from 24 to 41 weeks, with most under 32 weeks. The length of stay corresponding to each response is also included.

The following aspects were analyzed:

- Non-response rate: five questions had a missing response rate greater than 5%. One question was removed during the content validity evaluation, while the remaining four questions were retained and reformulated to preserve the survey's scope.
- Dropout rate: apart from the final open question, which was previously reviewed in the later parameter, no other question exhibited a dropout rate exceeding 5%.
- Uniform response rate: one question had 100% uniform responses. This question was retained.
- Uninformative responses rate: no question had an uninformative response rate greater than 5%. The reviewed questions and subsequent alterations are presented in Table 4.
- Correlation between questions: Three sets of questions from the Portuguese (PT) version revealed a significant correlation (Fig. 1). B5 and B8a (PT) (Kendall's tau = 0.74, $p < 0.0001$), indicating that parents who were more satisfied with the frequency of information provided by nurses were also more satisfied with how verbal information was delivered. B8a is also correlated with B8b (Kendall's tau = 0.81, $p < 0.0001$) and B8d (Kendall's tau = 0.76, $p < 0.0001$) indicating that parents who were more satisfied with how verbal information was delivered were also more satisfied with information conveyed by telephone and overall form of information delivery. Although the

Table 4 – Questions reviewed and subsequent changes to the questionnaire (original version numbering)

Question	Missing responses > 5%	%	Decision and changes to the questionnaire
A7	*"Qual a principal razão pela qual não tem conseguido falar com o médico as vezes que gostaria?"*	15	Retained. Clarification on how to respond this question was added in question A6: (*ir para questão A7/A8*)
A8	*"Têm-lhe sido transmitidas informações contraditórias, pelos profissionais, sobre o estado de saúde ou cuidados ao seu bebé?"*	6.7	Retained. The word contradictory was clarified: different professionals transmitting opposite information (*profissionais diferentes transmitem informações opostas*).
B6	"*Nas últimas 24h, quantas vezes pediu presencialmente, ao/à enfermeiro/a, uma atualização sobre o seu bebé?"*	11	Removed. The question performed poorly on both the content validity evaluation and the prospective study.
B12c	*"Numa escala de 1 a 10, quão satisfeito está com a forma como recebe informação sobre o seu bebé na Unidade?"*	8.3	Both retained. The questions highlight important sources of information. This result is significantly improved compared to the original survey, following the addition of the 'not applicable' option. The formatting was altered.
B12b		15	
E1	*"Se existe mais alguma coisa que gostasse de nos dizer sobre a sua experiência dos cuidados na Unidade de Neonatologia, por favor faça-o aqui."*	71.7	Retained. It is the only open-ended question in the survey, allowing parents to express concerns that may not be addressed elsewhere.
	> 95% uniform responses	**%**	**Decision and changes to the questionnaire**
A3	*"Foram-lhe explicadas as práticas de controlo de infeção, nomeadamente a lavagem das mãos e os procedimentos para visitas?"*	100	Retained. The question addresses an important topic for evaluating quality in NICUs.

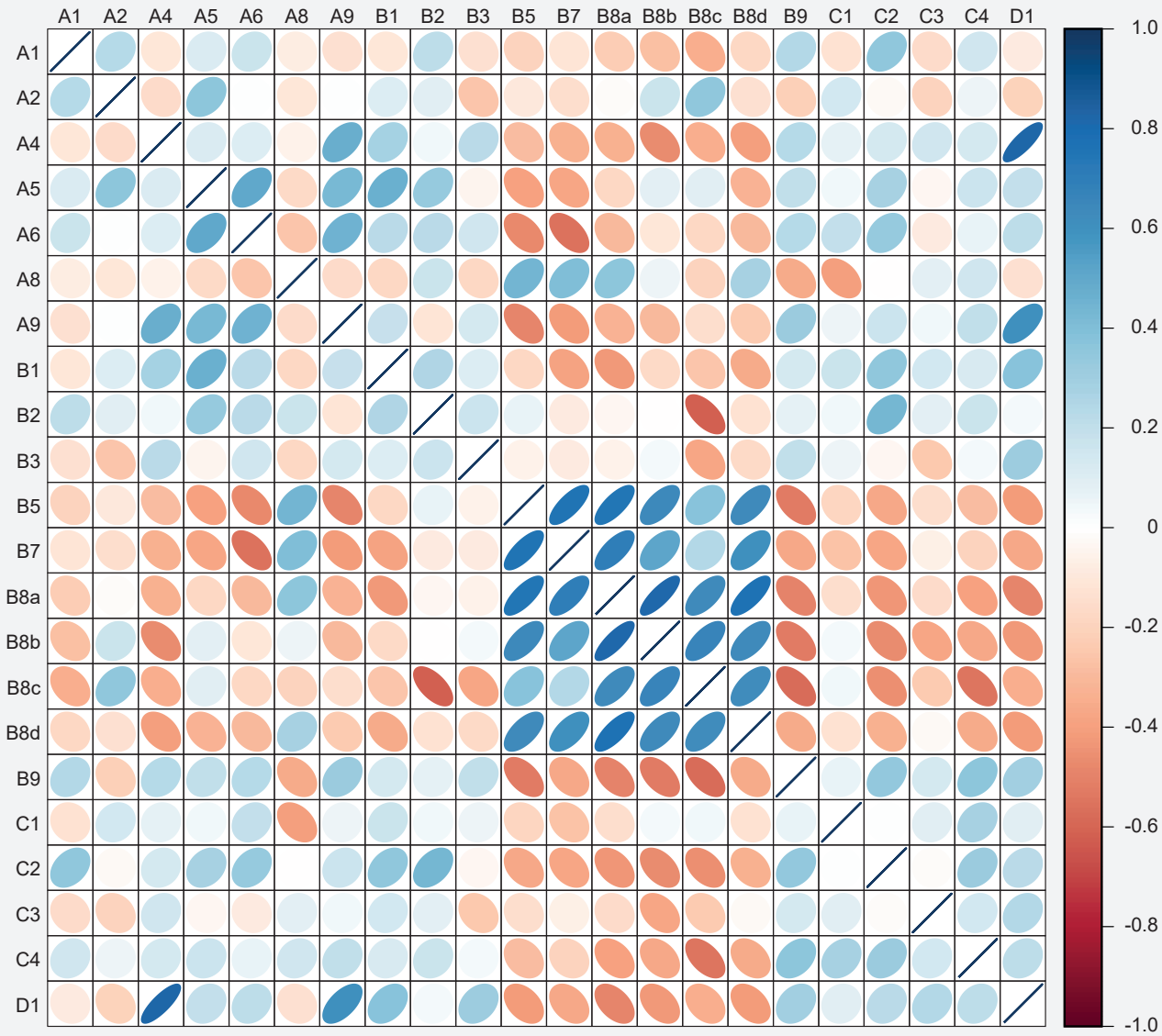

Figure 1 – Correlation matrix between questions in the Portuguese version, Kendall's tau values. The remaining graphical aspects, although redundant in relation to the correlation value, are useful as they allow for the rapid identification of groups of questions with similar correlations between them (flattening/compression of the ellipses: the higher the compression, the higher the absolute value of the correlation; orientation of the longest axis of the ellipse: positive for positive correlation, negative for negative correlation).

set A4 and D1 also presented an adequate Kendall's tau value, we did not consider this correlation significant due to the low variability in answers in both questions after the aggregated answer per parent. All questions were retained, as they measure different aspects of communication, and the correlations highlight important factors for improving parents' satisfaction with communication.

The final version of the Portuguese PEC questionnaire has 24 questions. It can be directly compared with the English version (Table 5).

Table 5 – Numbering equivalence between the English (EN) and Portuguese (PT) versions of the PEC questionnaire.

EN	A1	A2	A3	A4	A5	A6	A7	A8	A9	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	C1	C2	C3	C4	D1	E1
PT	A1	A2	A3	A4	A5	A6	A7	A8	A9	B1	B2	X	B3	B4	X	B5	X	X	B6	B7	B8	B9	C1	C2	C3	C4	D1	E1

DISCUSSION

We adapted, translated and validated the Parents' Experiences of Communication in Neonatal Care questionnaire to the Portuguese population, a tool to assess the level of satisfaction of parents with communication during NICU admission.

The assessment of communication practices in neonatal care is challenging yet essential for advancing the field. Using surveys to measure parental satisfaction is a valuable resource in neonatal care. The development of surveys focused on communication can help to evaluate quality and enable parents to voice concerns about specific aspects, allowing targeted strategies to enhance both communication and care.[16,17]

We have identified previously developed and validated tools specifically designed to evaluate communication in NICU settings. The Perceptions of Parent-Staff Communication questionnaire was developed to assess communication quality at two different points during the first two weeks of admission. While it is a reliable instrument, its applicability to other periods remains unknown.[4] The EMpowerment of PArents in the Intensive Care-Neonatology (EMPATHIC-N) is another valid and reliable instrument for measuring parental satisfaction and has been translated into several languages, including European and Brazilian Portuguese. This tool evaluates both communication and parental involvement in care, although it also includes additional aspects of parental satisfaction and is administered to parents only after discharge.[18-20]

The Parents' Experiences of Communication in Neonatal Care (PEC) questionnaire is adapted from a broader, previously developed survey. This former tool, the Parents' Experiences of Neonatal Care questionnaire, was created by the Picker Institute Europe in 2010 and assesses parents' perceptions of care quality across seven distinct domains. Developed in collaboration with parents, this questionnaire was later used in two large-scale surveys in England, in 2010 and 2014, providing valuable data to guide targeted improvement measures in neonatal units.[21,22] To develop the PEC survey, researchers from the Picker Institute and Imperial College London adapted questions from the Parents' Experiences of Neonatal Care survey that focused on communication and parental involvement in care. The new survey was designed to capture real-time feedback, allowing for continuous performance assessment and monitoring improvement interventions. Cognitive interviews and a performance evaluation confirmed its effectiveness in assessing communication in the neonatal parent population.[10]

The translation of the PEC questionnaire to European Portuguese adhered to a rigorous methodology focused on concept and cultural adequacy to achieve a conceptual equivalence rather than a literal translation. A structured, stepwise approach in collaboration with the original developers ensured the Portuguese version retained the fundamental aspects of the original instrument.

Cognitive interviews confirmed that this instrument is clear, comprehensible and easy to complete. Parental collaboration was essential to maintaining the tool's focus on capturing the parent perspective accurately. Content validity assessment plays a critical role in the development of new instruments, as well as in the translation and adaptation of existing tools. In our study this step ensured representativeness and appropriateness of the content of the questionnaire. The calculation of the I-CVI confirmed the relevance of each included item, and the removal of two items raised the a-CVI to 0.91, a universally accepted value indicating strong content validity.[14]

Performance evaluation demonstrated that this tool is feasible for routine application in everyday practice. Parents adhered to the survey and were willing to repeat it several times if needed to monitor ongoing interventions while still admitted, maintaining a good response rate.

Our study has some limitations. The translated survey was evaluated at a single center which may not fully represent Portuguese hospitals. However, the tool used has been previously tested in a European country, and the sample analyzed is representative of the target population, including mothers and fathers of all ages, at various stages of admission, and requiring different levels of neonatal care. Additionally, the content validity evaluation conducted by professionals from other Portuguese neonatal units helped to address this limitation. In both the cognitive interviews and performance evaluation, an increased number of mothers participated, as they were more frequently present in the unit for several and complex reasons, making it more challenging to enroll additional fathers. Given the limited sample size in our study factor analysis and reliability assessment were not possible. The application of this instrument in larger samples and other units will allow these studies, thus helping to strengthen our validation data.

Lastly, this study and the resulting questionnaire did not include parents who are not fluent in Portuguese, a group that currently represents a significant percentage of admissions. Communication with parents who do not speak the primary language is particularly challenging, and many of these parents feel that the language barrier limits their understanding of their child's condition and hinders their ability to express doubts and concerns.[23] This, in turn, negatively impacts outcomes, as previously noted. Addressing this issue is beyond the scope of this study since the main objective is the validation of the European Portuguese language. However, it is essential to consider this population when designing procedures to measure and improve communication in the NICU, which should address their difficulties.

This can include the translation of this tool into other languages.

The PEC survey and European Portuguese translation are available under license through *Picker Institute*. It is the authors' intention to apply the survey in the differentiated perinatal support unit where it was tested, aiming to specifically identify weaknesses and develop strategies to improve communication with parents. This validated tool will enable the measurement of communication quality and reassessment after implementing the proposed strategies. Additionally, the results may be correlated with parental stress and anxiety scores to provide further information on these outcomes.

Administering the survey in neonatal units across Portugal will support further research involving larger and more diverse populations. Direct comparisons with data gathered using the original version are straightforward (Table 5), facilitating international studies.

CONCLUSION

The validation of the PEC questionnaire in Portuguese established the first tool at a national level for objectively assessing the quality of communication with parents in neonatal units. The survey will allow the monitoring of interventions to improve communication, a central feature of family-centered care. Its wider application may also contribute to the development of communication studies nationwide in larger samples and comparison with objective international data.

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AUTHOR CONTRIBUTIONS

RMP: Study design, data collection and interpretation, writing of the manuscript.

RG: Study design, data collection and interpretation, critical review of the manuscript.

LG, RG: Data collection, critical review of the manuscript.

BS: Study design, critical review of the manuscript.

MCR, AC: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

AC participated on a data safety monitoring board or advisory board for Chiesi.

All other authors have declared that no competing interests exist.

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REFERENCES

1. Teixeira JA. Comunicação em saúde: Relação Técnicos de Saúde – Utentes. Análise Psicológica. 2004;22:615-20.
2. Levetown M. Communicating with children and families: from everyday interactions to skill in conveying distressing information. Pediatrics. 2008;121:e1441-60.
3. Wreesmann WW, Lorié ES, van Veenendaal NR, van Kempen AA, Ket JC, Labrie NH. The functions of adequate communication in the neonatal care unit: a systematic review and meta-synthesis of qualitative research. Patient Educ Couns. 2021;104:1505-17.
4. Reid T, Bramwell R, Booth N, Weindling M. Perceptions of parent–staff communication in Neonatal Intensive Care: the development of a rating scale. J Neonatal Nurs. 2007;13:24-35.
5. Wigert H, Dellenmark MB, Bry K. Strengths and weaknesses of parent–staff communication in the NICU: a survey assessment. BMC Pediatr. 2013;13:71.
6. Labrie NH, van Veenendaal NR, Ludolph RA, Ket JC, van der Schoor SR, van Kempen AA. Effects of parent-provider communication during infant hospitalization in the NICU on parents: a systematic review with meta-synthesis and narrative synthesis. Patient Educ Couns 2021;104:1526-52.
7. van de Vijver M, Evans M. A tool to improve communication in the neonatal unit. BMJ Qual Improv Rep. 2015;4:u203180-w3084.
8. Germana C, Miranda F, Carvalho C. Communication in a neonatal intensive care setting: 10-step approach. Acta Med Port. 2022;35:316-9.
9. Guttmann KF, Orfali K, Kelley AS. Measuring communication quality in the neonatal intensive care unit. Pediatr Res. 2022;91:816-9.
10. Sakonidou S, Kotzamanis S, Tallett A, Poots AJ, Modi N, Bell D, et al. Parents' experiences of communication in neonatal care (PEC): a neonatal survey refined for real-time parent feedback. Arch Dis Child Fetal Neonatal Ed. 2023;108:416-20.
11. Carvalho C, Vale A, Magalhães S. Communication and decision making in neonatal intensive care: why narrative medicine matters. New Trends Qual Res. 2020;1:104-21.
12. Tourangeau R. Cognitive Sciences and survey methods. Cognitive aspects of survey methodology: building a bridge between disciplines. 1984.
13. Boateng GO, Neilands TB, Frongillo EA, Melgar-Quiñonez HR, Young SL. Best practices for developing and validating scales for health, social, and behavioral research: a primer. Front Public Health. 2018;6:149.
14. Almanasreh E, Moles R, Chen TF. Evaluation of methods used for estimating content validity. Res Social Adm Pharm. 2019;15:214-21.
15. R Core Team. R: a language and environment for statistical computing.

R Foundation for Statistical Computing. 2024. [cited 2024 Dec 01]. Available from: https://cran.r-project.org/doc/manuals/r-release/fullrefman.pdf.
16. Latour JM, Hazelzet JA, van der Heijden AJ. Parent satisfaction in pediatric intensive care: a critical appraisal of the literature. Pediatr Crit Care Med. 2005;6:578-84.
17. Dall'Oglio I, Fiori M, Tiozzo E, Mascolo R, Portanova A, Gawronski O, et al. Italian Empathic-N Study Group. Neonatal intensive care parent satisfaction: a multicenter study translating and validating the Italian EMPATHIC-N questionnaire. Ital J Pediatr. 2018;44:5.
18. Latour JM, Duivenvoorden HJ, Hazelzet JA, van Goudoever JB. Development and validation of a neonatal intensive care parent satisfaction instrument. Pediatr Crit Care Med. 2012;13:554-9.
19. Peixoto, AC. EMpowerment of PArents in THe Intensive Care Neonatology (EMPATHIC-N) questionnaire: tradução e validação para português. Coimbra: Universidade de Coimbra;2024. [cited 2024 Dec 01]. Available from: https://hdl.handle.net/10316/115975.
20. Gomez DB, Vidal SA, Lima LC. Brazilian adaptation and validation of the empowerment of parents in the intensive care-neonatology (EMPATHIC-N) questionnaire. J Pediatr. 2017;93:156-64.
21. Esther H, Graham C. Parents' experiences of neonatal care - a report on findings from a national survey. Picker Institute Europe. 2011. [cited 2024 Dec 01]. Available from: https://picker.org/wp-content/uploads/2022/01/Parents-experiences-of-neonatal-care....pdf.
22. Burger S, King J, Tallett A. Parents' experiences of neonatal care in England. Patient Exp J. 2015;2:45-52.
23. Batton E, Hurst S, Ramos C, Catalan L, Freeman M, Marc-Aurele K. Communication in the neonatal ICU for Spanish speaking parents: a qualitative interview study. BMC Pediatr. 2023;23:481.

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Translation, Cultural Adaptation, and Preliminary Validation of the "Palliative Care and Rapid Emergency Screening Tool" into European Portuguese

Tradução, Adaptação Cultural e Validação Preliminar da "Palliative Care and Rapid Emergency Screening Tool" para o Português Europeu

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ABSTRACT

The aim of this study was to translate, culturally adapt, and conduct a preliminary validation of the "Palliative Care and Rapid Emergency Screening Tool" into European Portuguese for use in the emergency department. The tool was developed to assist healthcare professionals in identifying patients with palliative needs, ensuring timely referrals for palliative care consultation. The translation and adaptation process followed established guidelines for cross-cultural adaptation. Content validity was assessed by eight experts in palliative care, who confirmed that the tool was clear, relevant, and easy to understand. Face validity was evaluated by ten emergency department professionals, who rated the tool highly in terms of clarity and applicability to the target population. The study found that the tool effectively addresses key domains in palliative care, offering a simple and practical approach for use in the emergency care setting. These findings suggest that the "*Instrumento de Triagem Rápida para Cuidados Paliativos no Serviço de Urgência*" (PALinSU) can potentially enhance the identification of palliative care needs, leading to improved patient care and timely referrals.
Keywords: Cross-Cultural Comparison; Emergency Service, Hospital; Palliative Care; Portugal; Psychometrics; Surveys and Questionnaires; Translations

RESUMO

Este estudo teve como objetivo traduzir, adaptar culturalmente e realizar a validação preliminar da "*Palliative Care and Rapid Emergency Screening Tool*" para o português europeu, com aplicação no serviço de urgência. A ferramenta foi desenvolvida para ajudar os profissionais de saúde a identificar doentes com necessidades paliativas, garantindo referenciações precoces para a consulta de cuidados paliativos. O processo de tradução e adaptação seguiu as diretrizes estabelecidas para a adaptação transcultural. A validade de conteúdo foi determinada por oito especialistas em cuidados paliativos, que confirmaram que a ferramenta era clara, relevante e fácil de compreender. A validade facial foi realizada por dez profissionais do serviço de urgência, que classificaram a ferramenta positivamente em termos de clareza e aplicação à população alvo. O estudo concluiu que o instrumento trata de forma eficaz os domínios-chave dos cuidados paliativos, oferecendo uma abordagem simples e prática para utilização no contexto de urgência. Estes resultados sugerem que o "Instrumento de Triagem Rápida para Cuidados Paliativos no Serviço de Urgência" (PALinSU) pode potencialmente melhorar a identificação das necessidades paliativas dos doentes, levando a uma melhor prestação de cuidados de saúde e a referenciações mais precoces para cuidados paliativos.
Palavras-chave: Comparação Transcultural; Cuidados Paliativos; Inquéritos e Questionários; Portugal; Psicometria; Serviço Hospitalar de Emergência; Traduções

In 2013, the American College of Emergency Physicians (ACEP) emphasized the importance of promptly involving available palliative and hospice care services in the emergency department (ED) for patients who could benefit from such support.[1]

The "Palliative Care and Rapid Emergency Screening Tool" (P-CaRES) was developed with input from palliative care (PC) experts and a review of ED-specific challenges.[2] Designed to be concise and practical for the fast-paced ED environment, it assists healthcare professionals in identifying patients with palliative needs and facilitating appropriate PC referrals.[2] Recent findings suggest that P-CaRES is a valuable tool for predicting the six-month survival of older adults admitted from the ED.[3]

The objective of this study was the translation, cultural adaptation, and preliminary validation of the P-CaRES into European Portuguese.

This study was methodological, quantitative, descriptive, and observational. It adhered to the "Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures",[4] and was conducted with the approval of the Ethics Committee of the Lisbon Academic Medical Centre (Reference 157/24). The study was conducted at the Unidade Local de Saúde Santa Maria (Lisbon, Portugal) during the second half of 2024.

Phase 1

With the author's consent, the "P-CaRES" scale was translated and culturally adapted from English to European Portuguese. Two independent translations were created by certified translators, followed by a reconciled Portuguese version by the authors. This was back translated into English by two additional translators unfamiliar with the original instrument.

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Following the author's retirement, a member of the original research team made two minor revisions to the final version, which was then approved. The Portuguese version, titled "*Instrumento de Triagem Rápida para Cuidados Paliativos no Serviço de Urgência*" (PALinSU), consists of 13 items: eight in the first part and five in the second (Fig. 1).

Phase 2

Content validity was assessed by eight doctors recognized as Palliative Medicine experts by the Portuguese Medical Association. These experts, working in hospital-based PC teams and consulting for the ED, reviewed the PALinSU for consistency with its conceptual framework. They evaluated each of the 13 items on four dimensions: "item consistency with the content area," "item wording clarity," "item perceived easiness," and "item inclusion in the questionnaire," using a dichotomous scale ("yes" = 1, "no" = 0). The maximum score for content validity was 416 (13 items × four dimensions × eight experts). The average content validity index (CVI) was calculated by dividing the total score by the maximum, with a CVI of ≥ 0.75 deemed acceptable.[5] Experts could also provide comments on each item.

Phase 3

In September 2024, with permission from the ED director, face validity was assessed by ten ED nurses and doctors.[6] Using a dichotomous scale ("yes" = 1, "no" = 0), they evaluated the PALinSU for clarity, ease of understanding, and relevance. The maximum face validity score was 390 (13 items × three dimensions × 10 professionals). Participants could also provide comments on each item.

For content validity, the PALinSU achieved a score of 403 out of 416, corresponding to an average CVI of 0.97, indicating that the items were consistent, clear, and easy to complete, with no exclusions. In the face validity assessment by ten professionals, the PALinSU scored 377 out of 390, with all items receiving high scores, confirming the tool's clarity, ease of understanding, and relevance to the target population.

This study presents the translation, cultural adaptation, and preliminary validation of a rapid triage tool for PC patients in the ED. Experts confirmed the PALinSU's strong content validity, with items deemed clear, easy to understand, and relevant. Face validity also received high ratings, suggesting that the tool is comprehensible and suitable for its target population. These findings indicate that the PALinSU effectively addresses key domains with relevant and well-constructed items.

The cross-cultural adaptation of the PALinSU has significant implications for clinical practice in the ED. By helping healthcare professionals identify patients with PC needs more effectively, the tool could lead to more timely referrals, improving care delivery, patient triage, and access to PC in emergency settings. This objective aligns with the ACEP's "Choosing Wisely" initiative, which has not yet been fully implemented in Portugal regarding palliative care.[7]

The ED plays a vital role in identifying unmet PC needs and delivering timely care to seriously ill patients experiencing rapid decline.[8] Implementing PC screening earlier in the ED, rather than post-admission, could help reduce medical interventions and overall healthcare costs.[8]

Palliative care in the ED can enhance symptom management, streamline access to essential services, shorten hospital stays, improve end-of-life care, support families through bereavement and post-bereavement, and boost ED staff confidence in providing PC.[9]

This study has several strengths. To our knowledge, it is the first to publish a non-English version of this American instrument. Moreover, it was conducted in one of the main public hospitals of the Portuguese National Health Service, with input from recognized experts in the field.

A key limitation is that it focuses only on preliminary content and face validity. To further strengthen PALinSU, future research should assess its construct validity and test-retest reliability, which is why data collection is ongoing. Notably, the original authors also evaluated the acceptability and reliability of P-CaRES.[10]

Future studies should investigate the tool's effectiveness across diverse clinical settings, including non-academic hospitals, district hospitals, and private institutions. Additionally, its impact on patient outcomes and healthcare efficiency warrants further evaluation.

The PALinSU demonstrated strong content and face validity, which suggests it has potential for effectively assessing the implementation of PC principles by ED professionals. With robust preliminary validation, health authorities could consider promoting the tool to guide policies and interventions aimed at identifying palliative needs in the ED.

Further research is required to verify the construct validity, test-retest reliability, and broader applicability of the PALinSU across various clinical settings. These steps will help assess its impact on patient care, healthcare efficiency, and its overall effectiveness in improving access to PC.

AUTHOR CONTRIBUTIONS

CR: Conceptualization, methodology, investigation, data curation, visualization, writing - original draft preparation.

PRP: Conceptualization, methodology, supervision, validation, writing - reviewing and editing.

All authors approved the final version to be published.

INSTRUMENTO DE TRIAGEM RÁPIDA PARA CUIDADOS PALIATIVOS NO SERVIÇO DE URGÊNCIA (PALinSU)

1. O doente tem uma doença que condiciona a sua vida?
(Verifique todos os itens e assinale)

- ☐ **Demência avançada ou Doença do Sistema Nervoso Central** (Por ex.: história de Acidente Vascular Cerebral, Esclerose Lateral Amiotrófica, Doença de Parkinson): Necessita de ajuda para a maior parte dos cuidados pessoais (por ex., marcha, higiene) **e/ou** com expressão verbal mínima
- ☐ **Cancro em fase avançada:** Metastizado **ou** doença localmente agressiva
- ☐ **Nefropatia em estadio terminal:** Em diálise **ou** creatinina > 6 mg/dl
- ☐ **Doença Pulmonar Obstrutiva Crónica avançada:** Oxigénio contínuo no domicílio **ou** dispneia crónica em repouso.
- ☐ **Insuficiência cardíaca avançada:** Dispneia crónica, dor no peito **ou** fadiga para atividades mínimas ou em repouso
- ☐ **Doença Hepática terminal:** História de ascite recorrente, hemorragia gastrointestinal **ou** encefalopatia hepática
- ☐ **Choque séptico (ou seja, sinais de falência orgânica por infeção):** Requer admissão na Unidade de Cuidados Intensivos **e** tem doença concomitante significativa pré-existente
- ☐ **Critério do Cuidador – probabilidade elevada de morte acelerada:** Exemplos: fratura da anca > 80 anos; traumatismos major nos idosos (fraturas múltiplas nas costelas, hemorragia intracraniana); Síndrome da Imunodeficiência Adquirida em fase avançada, etc.

Não há itens assinalados? PARAR. O questionário está concluído.	**UM** ou mais itens assinalados? CONTINUAR o questionário!

2. O doente tem DUAS ou mais necessidades de cuidados paliativos não satisfeitas?
(Verifique todos os itens e assinale)

- ☐ **Visitas frequentes:** 2 ou mais consultas no serviço de urgência ou internamentos nos últimos 6 meses.
- ☐ **Sintomas não controlados:** Consulta motivada por sintoma(s) descontrolado(s): por ex.: dor, dispneia, depressão, fadiga, etc.
- ☐ **Declínio funcional:** Por ex.: perda da mobilidade, quedas frequentes, via oral instável, lesões da pele por pressão, etc.
- ☐ **Incerteza quanto aos objetivos do cuidado e/ou angústia do cuidador:** O cuidador não consegue satisfazer as necessidades a longo prazo; incerteza/angústia quanto aos objetivos dos cuidados?
- ☐ **Pergunta surpresa:** Ficaria surpreendido se este doente morresse nos próximos 12 meses?

Menos que DOIS itens assinalados? PARAR! O questionário é negativo.	**DOIS ou mais itens assinalados?** Recomenda-se referenciação a Consulta de Cuidados Paliativos.

Figure 1 – *Instrumento de triagem rápida para cuidados paliativos no serviço de urgência* (PALinSU)

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. American College of Emergency Physicians. ACEP announces list of tests as part of choosing wisely campaign. 2013. [cited 2025 Jan 31]. Available from: https://www.acep.org/administration/quality/acep-announces-list-of-tests-as-part-of-choosing-wisely-campaign.
2. George N, Barrett N, McPeake L, Goett R, Anderson K, Baird J. Content validation of a novel screening tool to identify emergency department patients with significant palliative care needs. Acad Emerg Med. 2015;22:823-37.
3. Paske JR, DeWitt S, Hicks R, Semmens S, Vaughan L. Palliative care and rapid emergency screening tool and the palliative performance scale to predict survival of older adults admitted to the hospital from the emergency department. Am J Hosp Palliat Care. 2021;38:800-6.
4. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine. 2000;25:3186-91.
5. Yaghmaie F. Content validity and its estimation. J Med Education. 2003;3:25-7.
6. Allen MS, Robson DA, Iliescu D. Face validity: a critical but ignored component of scale construction in psychological assessment. Eur J Psychol Assess. 2023;39:153-6.
7. Rolão C, Reis-Pina P. Palliative care in Portugal: are we "choosing wisely"? Acta Med Port. 2024;37:671-2.
8. Prachanukool T, George N, Bowman J, Ito K, Ouchi K. Best practices in end of life and palliative care in the emergency department. Clin Geriatr Med. 2023;39:575-97.
9. Bayuo J, Agbeko AE, Acheampong EK, Abu-Odah H, Davids J. Palliative care interventions for adults in the emergency department: a review of components, delivery models, and outcomes. Acad Emerg Med. 2022;29:1357-78.
10. Bowman J, George N, Barrett N, Anderson K, Dove-Maguire K, Baird J. Acceptability and reliability of a novel palliative care screening tool among emergency department providers. Acad Emerg Med. 2016;23:694-702.

ACTA MÉDICA PORTUGUESA
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Selective Digestive Decontamination in Hemato-Oncological Patients Colonized with Carbapenem-Resistant Enterobacterales

Descontaminação Digestiva Seletiva em Doentes Hemato-Oncológicos Colonizados por Enterobacterales Resistentes aos Carbapenemos

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ABSTRACT

Infections caused by multidrug-resistant Gram-negative bacteria, including carbapenem-resistant Enterobacterales, are a global threat and their gradual increase is alarming. They represent a major challenge to public health because of limited therapeutic options and high case-fatality rates. Hemato-oncological patients represent a high-risk subpopulation for these types of infections, more specifically in previous carbapenem-resistant Enterobacterales colonized patients, because of severe immunosuppression not only due to the disease itself but also due to treatment like intensive chemotherapy or allogeneic hematopoietic stem cell transplant. Selective digestive decontamination is a prophylactic intervention with the purpose of reducing or eliminating gut colonization by pathogenic agents, preserving beneficial endogenous flora but its application remains controversial due to great heterogeneity amongst studies. However, in this review we intend to examine the role of selective digestive decontamination in context of high-risk patients such as hemato-oncological carbapenem-resistant Enterobacterales carriers who will receive highly immunosuppressive treatments, as it appears to be an appealing short-term strategy for the prevention of difficult-to-treat infections.
Keywords: Carbapenems; Decontamination; Drug Resistance, Bacterial; Enterobacteriaceae; Enterobacteriaceae Infections; Gastrointestinal Tract; Hematologic Neoplasms

RESUMO

As infeções causadas por bactérias Gram-negativo multirresistentes, entre os quais se incluem Enterobacterales resistentes aos carbapenemos, são uma preocupação global e o seu aparecimento crescente tem sido alarmante. Representam, assim, um grande desafio em termos de saúde pública devido à limitação de opções terapêuticas e elevadas taxas de mortalidade. Os doentes hemato-oncológicos representam uma subpopulação de elevado risco para este tipo de infeções, mais especificamente em doentes previamente colonizados por Enterobacterales resistentes aos carbapenemos, uma vez que apresentam frequentemente imunossupressão grave, não só pela doença em si como também devido aos tratamentos a que são submetidos, como quimioterapia intensiva ou alotransplante de células estaminais hematopoiéticas. A descontaminação digestiva seletiva surge como uma intervenção profilática destinada a reduzir ou eliminar a colonização por agentes patogénicos ao nível do aparelho gastrointestinal, preservando a flora endógena benéfica, embora a sua aplicabilidade se mantenha controversa principalmente pela elevada heterogeneidade entre estudos. Contudo, pretende-se com esta revisão avaliar o papel de descontaminação digestiva seletiva no contexto de doentes de elevado risco, como doentes hemato-oncológicos colonizados por Enterobacterales resistentes aos carbapenemos e que vão ser submetidos a tratamentos associados a imunossupressão grave, uma vez que desperta interesse como uma estratégia a curto prazo para prevenir infeções por esses mesmos agentes.
Palavras-chave: Carbapenemos; Descontaminação; Enterobacteriaceae; Infecções por Enterobacteriaceae; Neoplasias Hematológicas; Resistência Bacteriana a Medicamentos; Trato Gastrointestinal

INTRODUCTION

The global rise of multidrug-resistant bacteria, such as carbapenem-resistant Enterobacterales (CRE), has been alarming and according to the 2024 World Health Organization priority list of pathogenic bacteria, CRE remain in the critical priority category, highlighting the urgent need for research and development of prevention, control, and treatment options in this field.[1] Amongst CRE colonized patients, there are high-risk populations such as hematological patients who are highly vulnerable to subsequent CRE infections due to their underlying disease and immune-suppressing treatments such as chemotherapy (with cytotoxic effects that lead to gastrointestinal mucositis and/or chemotherapy-induced neutropenia), immunotherapy, and hematopoietic stem cell transplantation (HSCT). Bloodstream infections are amongst the most common infectious complications in these patients, accounting for 20% - 30% of febrile neutropenia episodes in adult cancer patients, with mortality rates between 34% and 50%, which can rise to 80% in cases associated with CRE infections.[2-5]

Selective digestive decontamination (SDD) is a prophylactic intervention with the purpose of reducing or eliminating the CRE carriage state which in turn reduces the likelihood of infection by these multidrug resistant strains. Although SDD remains controversial as a strategy for the prevention of CRE infections, in this narrative review we aim to describe the current evidence of SDD in CRE carriers with a focus on the hemato-oncological population.

METHODS

In terms of literature search strategy, the PubMed database was used to identify articles of interest. The search terms used were as follows: “decolonization”,

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"selective digestive decontamination", "carbapenem-resistant Enterobacterales", "CRE carriers", "hematology", "hemato-oncological patients" and "hematological patients". The search was restricted to full-text articles published in English without restriction of publication year. Literature search was carried out between October 2024 and January 2025. Articles that did not focus on CRE carriers or decolonization strategies with oral antibiotics were excluded. The main articles discussed in this study were organized and summarized in supplementary material [Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23139/15714)].

CARBAPENEM-RESISTANT ENTEROBACTERALES: A GLOBAL THREAT

Enterobacterales are an order of Gram-negative bacteria that include common microorganisms such as *Escherichia coli*, *Klebsiella* spp., *Serratia* spp., and *Enterobacter* spp. Although these bacteria are part of the normal intestinal microbiota of humans, under certain circumstances, can cause infections acquired both in the community and in healthcare settings.[6]

These microorganisms have the ability to easily acquire antimicrobial resistance genes and in the beginning posed as a public health threat due to the production of extended-spectrum β-lactamases, which conferred resistance to penicillins and cephalosporins.[6,7] Consequently, the medical community turned to carbapenems as the first-line empirical treatment in such situations, which subsequently led to the development of various resistance mechanisms against these antibiotics.[8]

Carbapenem-resistant Enterobacterales can be divided into two main groups according to their resistance mechanisms: carbapenemase-producing CRE, the most prevalent group, and non-carbapenemase-producing CRE, which include mechanisms such as efflux pumps and porin mutations.[8,9] A wide variety of carbapenemases have been identified (i.e., enzymes capable of hydrolyzing carbapenems) being *Klebsiella pneumoniae* carbapenemase the most prevalent and globally disseminated.[8,10]

In one study it was demonstrated that carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) represented the fastest-growing antibiotic resistance threat in Europe in terms of morbidity and mortality.[11] These bacteria cause severe infections such as bloodstream infections, pneumonia, urinary tract infections, and intra-abdominal infections. They pose a major public health challenge due to limited therapeutic options, requiring the use of reserve antibiotics (according to the WHO AWaRe classification[12]) and high mortality rates, resulting in a significant economic burden related to disinfection procedures and dissemination control.[8,13]

According to the European Centre for Disease Prevention and Control (ECDC) 2023 annual epidemiological report on antimicrobial resistance in the European Union, the incidence of bloodstream infections by CR-*Kp* was 57.5% higher than in 2019, far from the 5.0% reduction target set for 2030. In Portugal, the same report highlighted alarming CRE rates, with 13.1% of resistant isolates in 2023 (Fig. 1). Compared to 2019, there was a 43% increase in CR-*Kp* infection incidence and a staggering 700% increase in carbapenem-resistant *Escherichia coli*, the latter significantly contradicting the overall European trend.[14]

Additionally, according to the latest ECDC data, Portugal showed a 2.0% increase in total antibiotic consumption between 2019 and 2023, being the only country to demonstrate a statistically significant increase in hospital antibiotic consumption. Of these, 43.7% corresponded to broad-spectrum antibiotics, including carbapenems. Notably, the data from Portugal were exclusively derived from public hospitals in the mainland.[15]

To characterize the epidemiology of carbapenemase-producing CRE in Portugal, a retrospective study was conducted in 2012, based on data from the North Lisbon University Hospital Center. The study revealed carbapenemase-producing CRE dissemination across different wards,

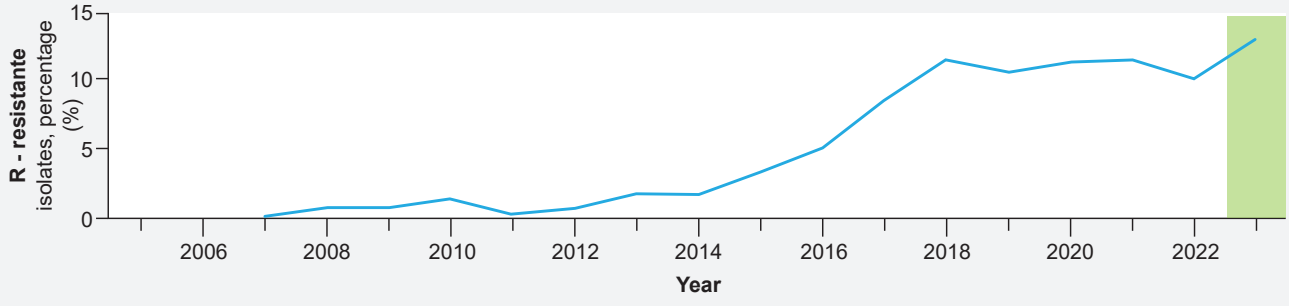

Figure 1 – Evolution of carbapenem resistance rates in *K. pneumoniae* in Portugal between 2007 and 2023 (public data from the ECDC Surveillance Atlas of Infectious Diseases)

with *Klebsiella pneumoniae* being the most frequently detected species (83%), and the Hematology department accounting for the highest number of cases (22%).[16]

HEMATO-ONCOLOGICAL PATIENTS: A HIGH-RISK POPULATION

Hemato-oncological patients are considered a high-risk population for multidrug-resistant Enterobacterales infections, as they frequently present multiple risk factors for colonization, including prior antibiotic use and frequent and prolonged hospitalizations.[17,18] A recent systematic review and meta-analysis found an intestinal CRE colonization prevalence rate of 21.7% in hematological patients, which is comparable to other high-risk populations. Prior exposure to antibiotics (carbapenems, tigecycline, or penicillins), acute myeloid leukemia, neutropenia, and chemotherapy were identified as risk factors for CRE colonization in this population.[19]

Previous intestinal multidrug-resistant Enterobacterales colonization in hematological patients was found to be a risk factor for subsequent infections[20,21] and more than 30% of multidrug-resistant Enterobacterales colonized transplant recipients developed infections caused by the same colonizing agent.[22] A prospective multicenter study in Italy identified the following independent risk factors for CR-*Kp* bloodstream infections in carriers: intensive care unit admission, invasive abdominal procedures, undergoing chemotherapy/radiotherapy, and the number of additional colonized sites, besides rectal colonization.[23] Moreover, immunosuppression status was independently associated with mortality among CRE carriers in a prospective study by Bar-Yoseph *et al*,[24] where the majority of the study population consisted of hemato-oncological patients.

In 2013, European recommendations were developed for targeted antibiotic therapy against CRE in febrile neutropenic patients.[25] An appropriate CR-*Kp* targeted antibiotic therapy was defined as a combination including at least two among colistin/polymyxin B, tigecycline and gentamicin, preferably with the addition of meropenem, and eventually also fosfomycin. However, an Italian bone marrow transplant group (GITMO) study found that half of the patients who received a first line CR-*Kp* targeted antibiotic therapy still died due to the infection.[3,26] Similarly, Patel *et al*,[27] demonstrated that CR-*Kp* infections treated with combinations of susceptible non-β-lactam antibiotics were not associated with improved clinical outcomes. This led to the controversial questioning of whether HSCT, especially allo-HSCT, should be considered in CR-*Kp* carriers with prior infection, given the high associated mortality risk (64.4% in allo-HSCT *vs* 16% in autologous HSCT).[26]

Recently, new antibiotics have been developed, including β-lactam/β-lactamase inhibitor combinations (e.g., ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, aztreonam/avibactam), which have shown to be associated with improved clinical outcomes and reduced toxicity compared to regimens previously used, which, as was mentioned, were often polymyxin and aminoglycoside-based.[28] Nevertheless, in a more recent review, infections caused by multidrug-resistant Gram-negative bacteria (MDR-GNB) remain a prevalent problem in high-risk hematological patients, with high mortality rates, especially when the initial empirical antibiotic treatment is inappropriate.[29] In a retrospective study, timely rectal swab screening, especially before the onset of carbapenem-resistant organism bloodstream infections, and preemptively adjusting an antibiotic regimen based on the results, significantly reduced 30-day mortality in hematological patients.[2]

SELECTIVE DIGESTIVE DECONTAMINATION: A PREVENTION STRATEGY

Given the previously outlined scenario, both regarding the alarming global situation of CRE and the susceptibility of hematologic patients to these hard-to-treat infections, it makes sense to explore options that anticipate the occurrence of infection, particularly through the identification of asymptomatic carriers to implement prevention and control measures. The eradication of intestinal CRE in asymptomatic carriers not only serves as a solution for infection prevention but also has the potential to limit bacterial dissemination to other patients.[18,30]

This introduces the concept of decolonization, which can be defined as a preventive infection method aimed at reducing or eliminating the burden of one or more pathogens through the administration or application of antimicrobial or antiseptic agents.[31] Various decolonization strategies exist, including selective digestive decontamination.[32]

According to the literature, the concept of SDD emerged in a study by Sleijfer *et al*[33] precisely from the understanding that antibiotic prophylaxis in patients susceptible to infections by intestinal Gram-negative bacteria should be performed selectively, as opposed to 'total intestinal sterilization'. The goal is to reduce or eliminate potentially pathogenic agents without affecting the anaerobic flora, which includes various species that naturally prevent colonization and overgrowth of those same contaminating agents.[33] This natural barrier concept was named colonization resistance, proposed by van der Waaij *et al*.[34] Thus, in general terms, the premise of the SDD strategy is, as the name suggests, to selectively decolonize the gastrointestinal tract, focusing on aerobic Gram-negative bacteria.

However, even after almost 40 years of studies in the field, particularly in intensive care units, the use of SDD remains highly controversial. This is mainly due to the heterogeneity of applied regimens – in terms of types and doses of

agents used, universal versus targeted strategy and target population – leading to the absence of robust scientific evidence on SDD efficacy.[35,36]

Focusing on SDD as a strategy for preventing CRE infections, in 2019, a multidisciplinary group of experts selected by the European Committee on Infection Control (EUCIC) conducted a systematic review[35] of existing studies on decolonization interventions specifically in carriers of MDR-GNB across all settings, with the aim of providing clinical recommendations on decolonization regimens for these cases. Unfortunately, due to several limitations, such as study heterogeneity, which precluded performing a meta-analysis, the panel considered the evidence insufficient to provide recommendations for any regimen and even did not recommend routine decolonization of MDR-GNB carriers. However, based on the results of SDD effects specifically in CRE carriers, the panel highlighted the need for high-quality research on the use of regimens with oral colistin sulfate, with or without oral gentamicin sulfate, in both hematologic and solid organ transplant patients, as they are a subpopulation at high risk of developing infections. It is noteworthy that, of the eleven studies with focus on CRE, only one was a randomized clinical trial and only three studies were on the hematological population, of which all were case series.

In the study by Saidel-Odes *et al*,[36] the application of both an oral gel and an oral solution formulated with a combination of gentamicin (80 mg) and colistin (1 million IU), given four times daily for seven days, was investigated in 20 CR-*Kp* carriers. They observed a significant reduction in CR-*Kp* colonization after two weeks compared to the placebo control group (61.1% *vs* 16.1%, respectively; $p < 0.0016$), but no significant difference at six weeks (58.5% *vs* 33.3%, respectively; $p \geq 0.05$). In another study, Oren *et al*[37] investigated three different SDD regimens (gentamicin 80 mg, colistin 100 mg, or both with same doses already mentioned), with the duration dependent on achieving eradication (defined as three consecutive negative cultures and a negative PCR in the last sample). The SDD application limit was 60 days, after which patients were considered persistent carriers. They observed a significantly higher eradication rate in the SDD group compared to the spontaneous eradication control group (44% *vs* 7%, respectively; $p < 0.001$). Additionally, they found a significantly lower mortality rate in the eradicated group compared to the persistently colonized group (17% *vs* 49%, respectively; $p = 0.002$). Machuca *et al*[38] evaluated the effects of two SDD regimens (gentamicin 80 mg or streptomycin 80 mg + neomycin 40 mg) applied for 14 days in high-risk patients carrying colistin-resistant CR-*Kp*. The results were compared to a control group after 180 days, and they found that the oral gentamicin regimen was associated with a lower risk of all-cause mortality, lower risk of CR-*Kp* infections, and greater microbiological response (i.e., at least two negative rectal swabs > 48 h after completing the SDD regimen).

More recently, a randomized clinical trial[39] specifically in hemato-oncological patients emerged, which was not included in the EUCIC systematic review. The aim of the study was to evaluate the efficacy of an SDD regimen with 2 million IU of colistin in the intestinal eradication of MDR-GNB carriers. They observed a significant positive effect at the end of the 14-day SDD period (61.3% vs. 32.3%; OR 3.32; 95% CI 1.17–9.44; p=0.0241), but the difference was not maintained at 21 days. Additionally, a lower incidence of bacteremia was observed 30 days after SDD.

Interestingly, despite the significant variability between applied regimens, the authors of the various described studies reached similar conclusions. Although no long-term benefits of SDD were observed, the primary interest of decolonization, more than eradication to contain bacterial transmission, is the hypothesis that SDD may be sufficient to reduce the pathogenic intestinal burden in the short term, representing a viable solution for preventing infection and death in high-risk patients.[36,37,39]

Another perspective to consider is the presence of concomitant systemic antibiotic treatment (CSAT). Tascini *et al*,[40] in an uncontrolled study of a SDD regimen with 80 mg of oral gentamicin in 50 patients colonized with CR-*Kp*, observed a significant difference in the decontamination rate between the group receiving only oral gentamicin compared to the group receiving CSAT (96% *vs* 44%, respectively; $p < 0.001$). Supported by other studies,[26,41-43] which reported systemic antibiotic exposure as a risk factor for CR-*Kp* acquisition and persistent colonization, they hypothesize that CSAT seems to favor the persistence of colonization through selective pressure on the intestinal microbiome, contributing to lower eradication rates compared to SDD alone. However, they do not exclude the possibility that CSAT could be a marker of more fragile patients with more severe disease. Lambelet *et al*,[44] in a small observational study, obtained similar results and reinforced the potential negative role that CSAT may have on the effect of SDD.

On the contrary, in a retrospective cohort[45] of 14 ICU CP-*Kp* carriers treated for seven days, four times daily, with colistin sulphate (1 million IU) and gentamicin sulphate (80 mg), no significant difference in the decolonization rate was found in comparison to non-decolonized patients. Also, there was no significant effect of decolonization treatment on mortality during hospitalization or on length of hospital stay between the two groups. The authors considered that the unsuccessful SDD treatment could be explained by the relatively short course applied, in addition to the low dosage of colistin, as other SDD protocols used up to 3 million IU. Additionally, a more recent study in Spain,[46] in a population of CR-*Kp* carriers, applying a regimen four times daily of

colistin (100 mg), amikacin (80 mg), and nystatin (300 mg) for 10 days, compared to a non-intervention group, did not show significant differences in eradication rates after one month of follow-up, nor did they observe any effect on clinical infection rates. However, the authors considered that the clinical infection risk of the study population was not high, which may explain why it was not significantly influenced by the intervention. This supports the recommendation that decolonization strategies should only be considered in patients with a well-defined high infectious risk.

One of the main concerns regarding SDD is the subsequent development of resistance to the antimicrobials used, especially since colistin and gentamicin are currently last-resort antibiotics for treating CR-*Kp*. According to a recent review[30] on SDD, the authors considered that the results, particularly in intensive care units, provided some reassurance on this matter. However, they emphasized that many of the studies were conducted in low multidrug resistance pressure environments and have limited follow-up times. In fact, based on the studies analyzed in this article, there were divergent results on this issue. However, among the studies reporting the emergence of resistance,[37,38,45] it is noted that two of them applied SDD regimes in monotherapy rather than combination therapy. Lubbert *et al*[45] observed rapid emergence of resistance, even with a double combination SDD protocol but it is important to highlight, with respect to colistin, that 45% of the isolates in SDD treated patients were initially resistant. As Lubbert *et al*[45] had mentioned, the use of suboptimal doses regarding colistin, Oren *et al*[37] also mentioned this possibility, particularly concerning gentamicin. However, other studies using a monotherapy regimen with gentamicin at the same dosage (80 mg, 4 x/day), with follow-up ranging from three to nine months, did not observe the emergence of resistance to this agent.[44,47] Moreover, these studies were conducted in areas considered endemic for CR-*Kp*. Finally, considering the two randomized clinical trials mentioned earlier, they did not observe the occurrence of resistance to the agents used in the SDD regimens.[36,39]

CONCLUSION

In the 2019 systematic review,[35] a lack of robust scientific evidence was identified regarding the various decolonization strategies directed at MDR-GNB carriers, mainly due to the significant heterogeneity between studies. However, given the major threat these pathogens currently represent, it is imperative to continue research to identify the best possible strategy for infection control, prevention, and treatment.

Although there are no solid recommendations and the general stance is against the routine use of decolonization in carriers, the literature reviewed in this work suggests that SDD can be a very promising measure, particularly in preventing infections during critical high-risk periods, such as those that occur in CRE colonized hemato-oncological patients undergoing immunosuppressive treatments like intensive chemotherapy or allogeneic hematopoietic stem cell transplantation. Selective digestive decontamination could be considered more as a short-term strategy aimed at temporarily reducing colonization burden, rather than achieving long-term total eradication.

It is important to note that several other types of decolonization strategies not relying on antibiotics are being studied. Some involve natural components such as fecal microbiota transplantation (FMT), prebiotics and probiotics, while others explore alternative therapies like tea tree oil, photodynamic therapy, *omiganan pentahydrochloride*, and the use of bacteriophages. Focusing on combined treatments, such as SDD followed by FMT or probiotics, should also be taken into account as an effort to develop well-defined and effective strategies against the multidrug resistance phenomenon.

AUTHOR CONTRIBUTIONS

SAL: Study conception and design, data collection and analysis, writing and critical review of the manuscript.

CMS: Study design, data analysis, critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: WHO; 2024.
2. Gao S, Yan R, Zhang S, Li L, Zhang R, Fan J, et al. Rectal culture could predict carbapenem-resistant organism bloodstream infection and reduce the mortality in haematological patients: a retrospective cohort study. J Global Antimicrob Resist. 2024;36:96-104.
3. Girmenia C, Rossolini GM, Piciocchi A, Bertaina A, Pisapia G, Pastore D, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant. 2015;50:282-8.
4. Amanati A, Sajedianfard S, Khajeh S, Ghasempour S, Mehrangiz S, Nematolahi S, et al. Bloodstream infections in adult patients with malignancy, epidemiology, microbiology, and risk factors associated with mortality and multi-drug resistance. BMC Infect Dis. 2021;21:636.

5. Wang S, Song Y, Shi N, Yin D, Kang J, Cai W, et al. Characteristics, outcomes, and clinical indicators of bloodstream infections in neutropenic patients with hematological malignancies: a 7-year retrospective study. Infect Drug Resist. 2023;16:4471-87.
6. European Centre for Disease Prevention and Control. Carbapenem-resistant Enterobacteriaceae, second update. Stockholm: ECDC. 2019.
7. Pana ZD, Zaoutis T. Treatment of extended-spectrum β-lactamase-producing enterobacteriaceae (ESBLs) infections: what have we learned until now? F1000Res. 2018;7:F1000 Faculty Rev-1347.
8. Suay-García B, Pérez-Gracia MT. Present and future of carbapenem-resistant enterobacteriaceae (CRE) Infections. Antibiotics. 2019;8:122.
9. Lutgring JD, Limbago BM. The problem of carbapenemase-producing-carbapenem-resistant-enterobacteriaceae detection. J Clin Microbiol. 2016;54:529-34.
10. Porreca AM, Sullivan KV, Gallagher JC. The epidemiology, evolution, and treatment of KPC-producing organisms. Curr Infect Dis Rep. 2018;20:13.
11. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19:56-66.
12. Web Annex C. WHO AWaRe (access, watch, reserve) classification of antibiotics for evaluation and monitoring of use, 2023. In: The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines, 24 – 28 April 2023. Geneva: World Health Organization; 2023.
13. Jean S-S, Harnod D, Hsueh P-R. Global threat of carbapenem-resistant gram-negative bacteria. Front Cell Infect Microbiol. 2022;12:823684.
14. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - annual epidemiological report 2023. Stockholm: ECDC; 2024.
15. European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA (ESAC-Net) - annual epidemiological report 2023. Stockholm: ECDC; 2024.
16. Pires D, Zagalo A, Santos C, Cota de Medeiros F, Duarte A, Lito L, et al. Evolving epidemiology of carbapenemase-producing enterobacteriaceae in Portugal: 2012 retrospective cohort at a tertiary hospital in Lisbon. J Hosp Infect. 2016;92:82-5.
17. Cattaneo C, Di Blasi R, Skert C, Candoni A, Martino B, Di Renzo N, et al. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. Ann Hematol. 2018;97:1717-26.
18. Campos-Madueno EI, Moradi M, Eddoubaji Y, Shahi F, Moradi S, Bernasconi OJ, et al. Intestinal colonization with multidrug-resistant enterobacterales: screening, epidemiology, clinical impact, and strategies to decolonize carriers. Eur J Clin Microbiol Infect Dis. 2023;42:229-54.
19. Luo H, Chen X, Jiang Z, Yan Q. Prevalence of and risk factors for intestinal colonisation by multidrug-resistant gram-negative bacteria in patients with haematological malignancies: a systematic review and meta-analysis. Int J Antimicrob Agents. 2024;63:107043.
20. Vehreschild MJ, Hamprecht A, Peterson L, Schubert S, Hantschel M, Peter S, et al. A multicentre cohort study on colonization and infection with ESBL-producing enterobacteriaceae in high-risk patients with haematological malignancies. J Antimicrob Chemother. 2014;69:3387-92.
21. Scheich S, Reinheimer C, Brandt C, Wichelhaus TA, Hogardt M, Kempf VAJ, et al. Clinical impact of colonization with multidrug-resistant organisms on outcome after autologous stem cell transplantation: a retrospective single-center study. Biol Blood Marrow Transplant. 2017;23:1455-62.
22. Girmenia C, Bertaina A, Piciocchi A, Perruccio K, Algarotti A, Busca A, et al. Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an italian prospective multicenter survey. Clin Infect Dis. 2017;65:1884-96.
23. Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, et al. Risk factors for carbapenem-resistant Klebsiella pneumoniae bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect. 2014;20:13507-62.
24. Bar-Yoseph H, Cohen N, Korytny A, Andrawus ER, Even Dar R, Geffen Y, et al. Risk factors for mortality among carbapenem-resistant enterobacteriaceae carriers with focus on immunosuppression. J Infect. 2019;78:101-5.
25. Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica. 2013;98:1836-47.
26. Girmenia C, Viscoli C, Piciocchi A, Cudillo L, Botti S, Errico A, et al. Management of carbapenem resistant Klebsiella pneumoniae infections in stem cell transplant recipients: an Italian multidisciplinary consensus statement. Haematologica. 2015;100:e373-6.
27. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol. 2008;29:1099-106.
28. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis. 2024;ciae403.
29. Garcia-Vidal C, Stern A, Gudiol C. Multidrug-resistant, gram-negative infections in high-risk haematologic patients: an update on epidemiology, diagnosis and treatment. Curr Opin Infect Dis. 2021;34:314-22.
30. Catho G, Huttner BD. Strategies for the eradication of extended-spectrum beta-lactamase or carbapenemase-producing enterobacteriaceae intestinal carriage. Expert Rev Anti Infect Ther. 2019;17:557-69.
31. Goldman L, Schafer AI, editors. Goldman-Cecil medicine. 25th ed. Philadelphia: Elsevier/Saunders; 2016.
32. Septimus EJ, Schweizer ML. Decolonization in prevention of health care-associated infections. Clin Microbiol Rev. 2016;29:201-22.
33. Sleijfer DTh, Mulder NH, De Vries-Hospers HG, Fidler V, Nieweg HO, van Der Waaij D, et al. Infection prevention in granulocytopenic patients by selective decontamination of the digestive tract. Eur J Cancer. 1980;16:859-69.
34. van der Waaij D, Berghuis-de Vries JM, Lekkerkerk Lekkerkerk-v null. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. J Hyg. 1971;69:405-11.
35. Tacconelli E, Mazzaferri F, De Smet AM, Bragantini D, Eggimann P, Huttner BD, et al. ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers. Clin Microbiol Infect. 2019;25:807-17.
36. Saidel-Odes L, Polachek H, Peled N, Riesenberg K, Schlaeffer F, Trabelsi Y, et al. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination using oral gentamicin and oral polymyxin e for eradication of carbapenem-resistant klebsiella pneumoniae carriage. Infect Control Hosp Epidemiol. 2012;33:14-9.
37. Oren I, Sprecher H, Finkelstein R, Hadad S, Neuberger A, Hussein K, et al. Eradication of carbapenem-resistant enterobacteriaceae gastrointestinal colonization with nonabsorbable oral antibiotic treatment: a prospective controlled trial. Am J Infect Control. 2013;41:1167-72.
38. Machuca I, Gutiérrez-Gutiérrez B, Pérez Cortés S, Gracia-Ahufinger I, Serrano J, Madrigal MD, et al. Oral decontamination with aminoglycosides is associated with lower risk of mortality and infections in high-risk patients colonized with colistin-resistant, KPC-producing Klebsiella pneumoniae. J Antimicrob Chemother. 2016;71:3242-9.
39. Stoma I, Karpov I, Iskrov I, Krivenko S, Uss A, Vlasenkova S, et al. Decolonization of intestinal carriage of mdr/xdr gram-negative bacteria with oral colistin in patients with hematological malignancies: results of a randomized controlled trial. Mediterr J Hematol Infect Dis. 2018;10:2018030.
40. Tascini C, Sbrana F, Flammini S, Tagliaferri E, Arena F, Leonildi A, et al. Oral gentamicin gut decontamination for prevention of KPC-producing Klebsiella pneumoniae infections: relevance of concomitant systemic antibiotic therapy. Antimicrob Agents Chemother. 2014;58:1972-6.
41. Ben-David D, Masarwa S, Navon-Venezia S, Mishali H, Fridental I, Rubinovitch B, et al. Carbapenem-resistant klebsiella pneumoniae in post-acute-care facilities in israel. Infect Control Hosp Epidemiol. 2011;32:845-53.

42. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant enterobacteriaceae: epidemiology and prevention. Clin Infect Dis. 2011;53:60-7.
43. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother. 2008;52:1028-33.
44. Lambelet P, Tascini C, Fortunato S, Stefanelli A, Simonetti F, Vettori C, et al. Oral gentamicin therapy for carbapenem-resistant klebsiella pneumoniae gut colonization in hematologic patients: a single center experience. New Microbiol. 2017;40:161-4.
45. Lübbert C, Faucheux S, Becker-Rux D, Laudi S, Dürrbeck A, Busch T, et al. Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing klebsiella pneumoniae: a single-centre experience. Int J Antimicrob Agents. 2013;42:565-70.
46. Pellicé M, Rodríguez-Núñez O, Rico V, Agüero D, Morata L, Cardozo C, et al. Factors associated with short-term eradication of rectal colonization by KPC-2 producing klebsiella pneumoniae in an outbreak setting. Front Microbiol. 2021;12:630826.
47. Zuckerman T, Benyamini N, Sprecher H, Fineman R, Finkelstein R, Rowe JM, et al. SCT in patients with carbapenem resistant Klebsiella pneumoniae: a single center experience with oral gentamicin for the eradication of carrier state. Bone Marrow Transplant. 2011;46:1226-30.

ACTA MÉDICA PORTUGUESA
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Osimertinib: A Game-Changer in Stage IV EGFR-Driven Lung Cancer

Osimertinib: Um Ponto de Viragem no Cancro do Pulmão EGFR Positivo em Estádio IV

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ABSTRACT

Lung cancer has a high mortality rate; however, treatment with tyrosine kinase inhibitors targeting specific molecular alterations has significantly improved the survival of patients with advanced or metastatic non-small cell lung carcinoma (NSCLC). EGFR mutations are present in approximately 15% of NSCLC cases. Osimertinib was approved in Portugal by Infarmed (Portuguese Medicines Agency) in 2021 as a first-line therapy for advanced NSCLC with EGFR sensitizing mutations. A 55-year-old man, a former smoker, presented to the Emergency Department with a six-month history of dry cough and dyspnea that had worsened and was now accompanied by fever. Chest CT revealed multifocal pulmonary consolidations that were already present in a scan performed three months earlier. Bronchial biopsies confirmed a diagnosis of lung adenocarcinoma with an EGFR exon 19 deletion. Staging tests revealed stage IV-A disease (pulmonary metastasis and, later, right adrenal metastasis identified on PET-FDG). The patient was started on osimertinib. He was discharged and progressively recovered his baseline general condition, achieving a performance status of 0 and resuming physical activity. Despite the extensive thoracic disease, the patient achieved a complete metabolic response documented on PET-CT five months after initiating therapy, along with significant clinical improvement. Osimertinib effectively inhibits the EGFR signaling pathway and has been established as the first-line treatment for patients with stage IV disease since the FLAURA trial. However, such complete responses are rare and raise further questions about the factors influencing these responses, the optimal duration of therapy in these cases, and the role of circulating tumor DNA in therapy monitoring and discontinuation decisions.
Keywords: Carcinoma, Non-Small-Cell Lung/drug therapy; ErbB Receptors; Lung Neoplasms/drug therapy; Osimertinib

RESUMO

Apesar de o cancro do pulmão apresentar uma elevada taxa de mortalidade, o tratamento com inibidores de tirosina-cinase dirigidos a determinadas alterações moleculares, tem melhorado a sobrevivência dos doentes com carcinomas de não-pequenas células (CPNPC) avançado ou metastático. As mutações do EGFR estão presentes em cerca de 15% dos CPNPC. Em Portugal, o osimertinib foi aprovado pelo Infarmed em 2021 como primeira linha terapêutica no CPNPC avançado com mutações sensibilizadoras do EGFR. Um homem de 55 anos, ex-fumador, com sintomas tosse seca e dispneia com seis meses de evolução, recorreu ao Serviço de Urgência por agravamento das queixas e febre. A tomografia computorizada torácica revelou consolidações pulmonares multifocais, já presentes no exame realizado três meses antes. Foram realizadas biópsias brônquicas compatíveis com adenocarcinoma do pulmão com deleção do exão 19 do EGFR. Os exames de estadiamento revelaram estádio IV-A (metastização pulmonar e, posteriormente em PET-FDG, suprarrenal direita) e foi iniciado osimertinib. O doente teve alta e progressivamente recuperou o seu estado geral prévio. Apesar de doença torácica extensa, o doente atingiu resposta metabólica completa, documentada em PET-TC após cinco meses do início da terapêutica, com melhoria clínica significativa. O osimertinib bloqueia eficazmente a via de sinalização do EGFR, sendo o tratamento de primeira linha nos doentes com CPNPC EGFR positivo avançado ou metastático desde o estudo FLAURA. Contudo, este tipo de resposta completa é raro e levanta-nos outras questões que realçam a necessidade de mais investigação sobre os fatores que influenciam este tipo de resposta, a duração da terapêutica nestes casos e o papel do DNA tumoral circulante na monitorização da terapêutica e decisão de suspensão.
Palavras-chave: Carcinoma Pulmonar de Células não Pequenas/tratamento farmacológico; Neoplasias do Pulmão/tratamento farmacológico; Osimertinib; Receptor ErbB-2

INTRODUCTION

Lung cancer is the third most prevalent cancer in Portugal, yet it remains the leading cause of death from oncological diseases.[1,2] Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of cases, with adenocarcinoma being the most prevalent subtype. Biomarkers increasingly guide treatment decisions, leading to improvement in response rates, survival outcomes, and quality of life. Epidermal growth factor receptor (EGFR) mutations are the most common oncogenic drivers in NSCLC, occurring in approximately 15% of lung adenocarcinomas in Europe.[2] Osimertinib has been approved in Portugal as a first-line treatment for locally advanced or metastatic EGFR-positive lung carcinomas since 2021, following the results of the FLAURA clinical trial.[3] In this trial, the efficacy of osimertinib was compared to gefitinib or erlotinib (first-generation tyrosine kinase inhibitors) as first-line therapy for EGFR+N SCLC. The majority of patients achieved a partial response (77%), with only seven patients exhibiting a complete response, as assessed by RECIST criteria.[4]

CASE-REPORT

A 55-year-old man with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 (symptomatic but fully ambulatory), history of dyslipidemia and a former light smoker (five pack-years), presented at the Emergency Department (ED). He had a six-month history of progressive

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dry cough and exertional dyspnea, classified as grade 2 (walks slower than people of the same age because of dyspnea) on the modified Medical Research Council (mMRC) scale, with considerable worsening over the prior week, accompanied by fever and, in the previous three days, yellowish sputum. A chest computed tomography (CT) performed approximately three months after symptom onset revealed an extensive multilobe consolidation with air-bronchogram in the left lung. The patient's condition remained unresolved after two antibiotic courses, and he awaited further evaluation. He presented at the ED with a Glasgow Coma Scale of 15, a respiratory rate of 28 cycles per minute, and was unable to complete sentences. Cardiac auscultation revealed rhythmic heart sounds without murmurs, while lung auscultation showed diminished vesicular murmur in the left lower third, with crackles. Arterial blood gas analysis on room air (FiO_2 21%) demonstrated severe type 1 respiratory failure, with a paO_2 of 49 mmHg (RV > 70 mmHg). Blood tests revealed mild leukocytosis (10 230 cells/µL) and a CRP of 5.8 mg/dL. Progressive increases in oxygen supplementation were required during the first hours of admission, with a paO_2 of 67 mmHg on FiO_2 60%, which led to admission to the intensive care unit. A bacterial superinfection was assumed, and the patient started empirical antibiotic therapy with amoxicillin/clavulanate and azithromycin.

The patient tested positive for respiratory syncytial virus, and a new chest CT showed extensive multifocal consolidation and numerous bilateral ground-glass opacities (Fig. 1). Despite starting high-flow oxygen, the patient quickly deteriorated and was placed on invasive mechanical ventilation. After stabilization of the clinical status, a flexible bronchoscopy was performed for further investigation. Since the patient had been experiencing symptoms for six months and, for at least three months, had an extensive persistent pulmonary consolidation on CT scan, in addition to the collection of material for microbiological analysis, transbronchial lung biopsies in the left lower lobe and lingula were performed. These revealed papillary lung adenocarcinoma with PD-L1 expression of 0% and cultural studies were negative. An EGFR exon 19 deletion (19del) was detected by Idylla® (a fully automated PCR-based system that enables rapid detection of genetic mutations), providing a faster diagnosis later confirmed by next-generation sequencing (glu746_Ala750del).

Staging tests with contrast-enhanced brain and upper abdominal CT scans, did not show extrathoracic metastasis. The case was discussed in a multidisciplinary tumor board, and the staging was determined as cT4NxM1a (IV-A) due to lesions in the contralateral lung already shown in the previously performed CT scan. Staging fluorodeoxyglucose (FDG) positron emission tomography (PET-FDG) was postponed due to the current infectious context. The patient

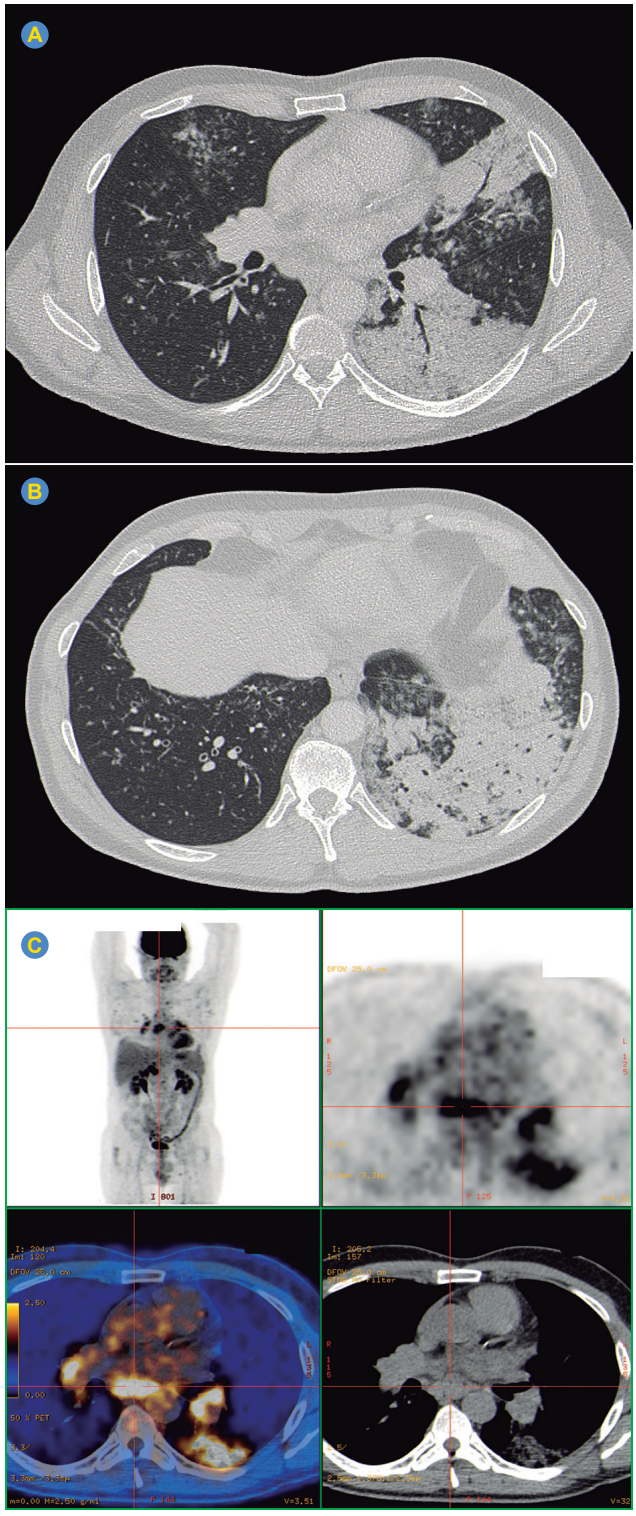

Figure 1 – Chest CT showing multifocal consolidation involving almost the entire left lower lobe and lingula, comprising approximately 50% of the left lung, as well as numerous bilateral ground-glass opacities (A) (B). PET-CT showing increased metabolic uptake in the left upper and lower lobes, right middle lobe, and bilateral lymph stations (10L, 7, 4L, 10R) (C).

was extubated after 48 hours. Given the extensive consolidation, thought to be neoplastic, and the respiratory failure, despite not completing staging, the patient started osimertinib 80 mg once daily and was discharged a few days later. Four weeks later, PET-FDG revealed increased metabolic uptake in the left upper and lower lobes (SUV 4.4 and 4.0, respectively), right middle lobe (SUV 1.8), bilateral lymph node stations (4L, 7, 10L, 10R with maximum SUV of 4.9) and in the right adrenal gland (SUV 8.0) (cT4N3M1b; IV-A; TNM 8th edition) (Fig. 1).

Five months after the onset of treatment, a chest CT revealed a significant improvement in the previously identified consolidation, with only a few bronchiolectasis and ground-glass opacities remaining in the left upper lobe and lingula. Additionally, a sparse fibrotic-cicatricial subpleural reticulation was observed. A subsequent FDG PET-CT confirmed a complete treatment response (Fig. 2).

The patient regained his previous overall health status, experienced gradual improvement in symptoms and eventually became asymptomatic. He resumed regular work and physical activities, exhibiting a PS 0 at the time of this report. The continued use of osimertinib has been well tolerated, with only grade 1 (mild and localized) cutaneous toxicity, assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), and treated with topical corticosteroids.

DISCUSSION

Osimertinib is a potent irreversible third-generation EGFR tyrosine kinase inhibitor. It binds covalently to the cysteine residue within the ATP-binding site of the EGFR kinase domain, preventing its autophosphorylation and downstream signaling pathways. By disrupting these crucial signaling cascades, osimertinib effectively stops EGFR's aberrant activation, leading to apoptosis of tumor cells.[4]

Currently, it is the standard first-line therapy for stage IV NSCLC patients carrying EGFR 19del.[5] In the FLAURA trial, although a high rate of patients exhibited stable disease or partial response, only 3% achieved complete response, highlighting the rarity of such outcomes.[4]

Takeyasu Y *et al* showed that patients with 19del had significantly higher response rates than patients with exon 21 *L858R* mutations. When comparing the distinct efficacy of first-line osimertinib according to mutation subtypes, patients with 19del had more often complete central nervous system (CNS) response (42% *vs* 25%) and a higher clinical benefit (97% *vs* 79%). Among 229 evaluated patients, only three exhibited complete systemic response (two with del19 and one with L858R).[6]

We present a rare case of a significant clinical response and complete treatment response to osimertinib as first-line therapy in a stage IVA NSCLC patient, despite initially documented extensive tumor lesions. The absence of CNS, pleural or hepatic metastases, along with the patient's favorable PS, may have contributed to the favorable prognosis. This case emphasizes the need for continued investigation on individual variations in treatment response, encouraging further research into factors contributing to complete remission. Treatment with osimertinib is recommended until disease progression or unacceptable toxicity. If the patient maintains this response pattern over time, it raises questions regarding the optimal duration of treatment and the absence of recommendations regarding the role of PET in these cases. Circulating tumor DNA (ctDNA) is already being used for EGFR mutation testing; however, it lacks sensitivity, particularly in cases with a low disease burden. As such, a tissue biopsy remains necessary if cfDNA results are negative. Nevertheless, its role in monitoring therapeutic response, predicting treatment outcomes, and enabling early detection of relapse or disease progression has gained increasing interest.[5,7] Could ctDNA play a role in monitoring response or in determining whether therapy could be suspended in these patients? There are clinical trials ongoing to determine the role of ctDNA in disease monitoring.[7] With the increasing accessibility of molecular testing and an increase in diagnosed EGFR-driven tumors, these sustained complete response patterns may become increasingly documented, which underscores the need for recommendations on how to manage these patients over time.

Ultimately, this case highlights the critical role of a precise diagnosis and comprehensive investigation, including mutational status, especially when facing high clinical suspicion scenarios and when patients present with critical illness, to promptly initiate therapy and improve patient outcomes.

AUTHOR CONTRIBUTIONS

SS: Literature review, writing of the manuscript.
JD: Writing of the manuscript.
CS, MF: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

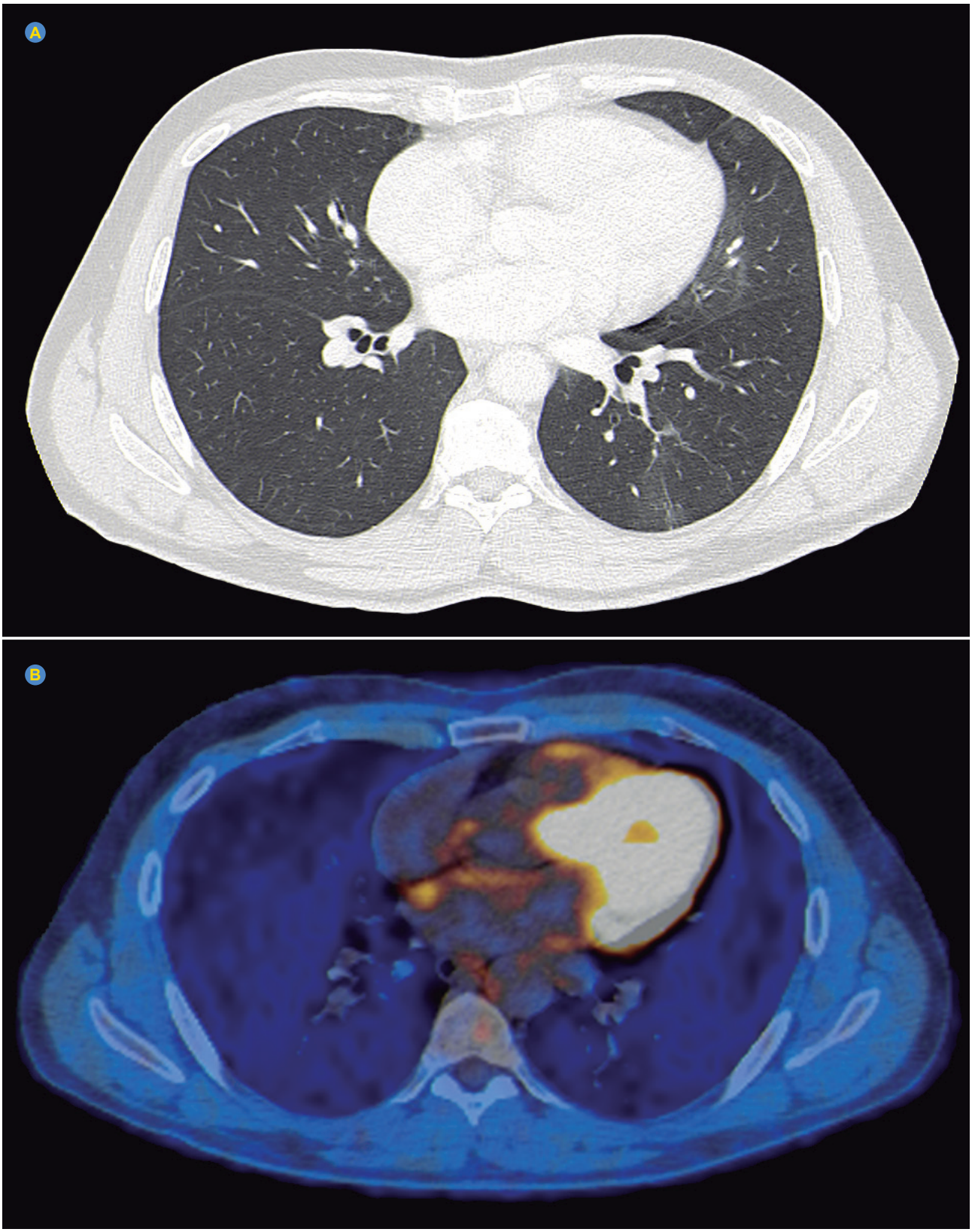

Figure 2 – Chest CT (A) and PET scan (B) showing complete metabolic response on the chest

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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MF has declared that no competing interests exist.

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REFERENCES

1. Registo Oncológico Nacional. Registo oncológico nacional de todos os tumores na população residente em Portugal, em 2020. Porto: Instituto Português de Oncologia do Porto Francisco Gentil; 2023.
2. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heis RS. Lung cancer. Lancet. 2021;10299:535-54.
3. Infarmed. Relatório de avaliação de financiamento público de Tagrisso (osimertinib). 2021. [cited 2021 Mar 17]. Available from: https://www.infarmed.pt/documents/15786/1424140/Relatório+de+avaliação+de+financiamento+público+de+Tagrisso+%28osimertinib%29+2021/16851 6a0-a4aa-ec85-bcf1-19100de89667.
4. Soria JC, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378:113-25.
5. Hendriks LE, Kerr KM, Mok TS, Nestle U, Passaro A, Peters S, et al on behalf of the ESMO Guidelines Committee. ESMO clinical practice guidelines for diagnosis, treatment and follow-up of patients with non-small-cell lung cancer (NSCLC) with oncogene addiction. Ann Oncol. 2021;32:233-53.
6. Takeyasu Y, Yoshida T, Masuda K, Horinouchi H, Yamamoto N, Ohe Y, et al. Distinct progression and efficacy of first-line osimertinib treatment according to mutation subtypes in metastatic NSCLC harboring EGFR mutations. JTO Clin Res Rep. 2024;5:100636.
7. Clark TA, Chung JH, Kennedy M, Hughes JD, Chennagiri N, Lieber DS, et al. Analytical validation of a hybrid capture-based next-generation sequencing clinical assay for genomic profiling of cell-free circulating tumor DNA. J Mol Diagn. 2018;20:686-702.

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Penile Skin as a Rare Location of Melanoma in the Balkan Region: A Case Report

Pele Peniana Como Localização Rara de Melanoma na Região dos Balcãs: Um Relato de Caso

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ABSTRACT

Skin melanoma is very rarely found in the genital region. Additionally, out of all penile skin malignancies, melanoma is one of the rarest, with no cases reported before in the Balkan region. A 68-year-old male presented with atypical and irregular pigmented skin lesions on his left flank and penile shaft. After dermoscopy and radiological work-up, both lesions were completely excised, with pathological examination revealing a high-grade dysplastic nevus with nodular melanoma in the penile location. Wide re-excision was performed one month later, followed by skin reconstruction with a rotation cutaneous flap. No postoperative complications, long-term recurrence signs, nor local or distant metastases were observed. As a very rare case of this kind of condition in the Balkan region and globally, this is the first case of penile skin melanoma described in Serbia, additionally emphasizing the importance of thorough systematic clinical examination and conducting organ-preserving surgery.
Keywords: Dermoscopy; Melanoma; Penile Neoplasms; Skin Neoplasms

RESUMO

É extremamente raro encontrar o melanoma da pele na região genital. Além disso, de todas as neoplasias malignas da pele peniana, o melanoma é uma das mais raras, não havendo nenhum caso semelhante descrito anteriormente na região dos Balcãs. Um homem de 68 anos recorreu ao médico por apresentar lesões cutâneas pigmentadas atípicas e irregulares no flanco esquerdo e na haste peniana. Após dermatoscopia e exames radiológicos, ambas as lesões foram completamente excisadas, tendo o exame histológico revelado um nevo displásico de alto grau com melanoma nodular na localização peniana. Foi realizada uma reexcisão ampla um mês depois, seguida de reconstrução da pele por retalho de rotação. Não foram observadas complicações pós-operatórias, sinais de recidiva a longo prazo, nem metástases locais ou à distância. Sendo um caso muito raro deste tipo de patologia na região dos Balcãs e no mundo, este é o primeiro caso de melanoma da pele peniana descrito na Sérvia, realçando ainda mais a importância do exame objetivo sistemático completo e da realização de cirurgia preservadora de órgãos.
Palavras-chave: Dermatoscopia; Melanoma; Neoplasias da Pele; Melanoma; Neoplasias do Pénis

INTRODUCTION

One of the rarest melanoma sites in males is the genitourinary tract (0.1% of all melanomas).[1] From the other point of view, among all penile malignancies, melanoma accounts for less than 1.4%,[2] and, based on its precise location, can be considered cutaneous or mucosal.[3,4] It is reported that penile melanoma is most commonly located on the glans (67%), which is followed by the foreskin (13%), urethral meatus (10%), and penile sheath (7%).[5,6]

Besides the fact that the disease is very rare, it usually has a poor prognosis resulting from the advanced stage at the time of diagnosis and the aggressiveness of the tumor.[4]

A case of penile melanoma has never been previously reported in the Serbian population. Therefore, this report aimed to present such a case of melanoma on the penile shaft and a successful organ-preserving surgical treatment in an adult patient.

CASE REPORT

A 68-year-old male smoker was referred to the dermatology department for an atypical skin lesion located on the left flank region. His personal history included hypertension, while the family history of malignancies was negative. The physical examination revealed a clinically suspicious pigmented skin lesion on the penile shaft, previously reported by the patient as having been present for the previous ten years and that it was small, with an increase in size and changes in color during the last few years. The mole was 31 x 21 mm in diameter, asymmetric in two axes, black, red, and blue-grey in color. Inguinal lymphadenopathy was not observed. Dermoscopy showed a slightly elevated lesion with irregular circular and dotted formations. Other dermoscopic criteria for melanoma were not observed. The usual blood work-up, pelvic magnetic resonance imaging, abdominal, inguinal, axillary, and cervical ultrasonography, as well as chest X-ray showed no pathological changes, other than the one located on the penile shaft skin, suggesting a consensual decision made by the medical oncologist, oncological surgeon, and radiologist to perform a complete excision of the lesion without sentinel lymph node biopsy.

The lesion was completely excised and examined,

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showing a high-grade dysplastic nevus with nodular melanoma. The histopathological features of the excised specimen were as follows: Breslow 1.41 mm, Clark 3, with a mitotic index over 2 and the presence of microsatellites, classified as pathohistological local stage T2b. The immunohistochemical analysis revealed positive staining for Melanin A+, S100 +, and HMB-45. No lympho-vascular or perineural invasions were observed.

One month after the first procedure the excision site was additionally widely excised to a 10 mm margin, followed by skin defect reconstruction with a rotation cutaneous flap (Fig. 1). During the postoperative recovery, no complications were observed. The subsequent follow-up examinations every three months showed no signs of recurrence or presence of local or remote metastases, until the time of writing.

DISCUSSION

The cutaneous penile shaft melanoma comprises 9% of all penile cases.[2] To the best of our knowledge, this report represents one of the first cases in the Balkan region[7] and the first verified and reported case of penile melanoma in Serbia.

In addition to genetic and constitutional characteristics, which are well-known etiological factors, its development is highly correlated with exposure to UV radiation, particularly intermittent sun exposure,[8] which makes the penile location less common. It usually presents as a painless, pigmented lesion that gradually grows larger and, at the advanced stages, ulcerates with the development of local inguinal lymphadenopathy.[3,4] A poor prognosis is associated with delayed diagnosis and the aggressiveness of the tumor,[3,4] with the presence of ulceration, high Breslow, mitotic and Clark indices, irregular growth pattern, presence of satellite

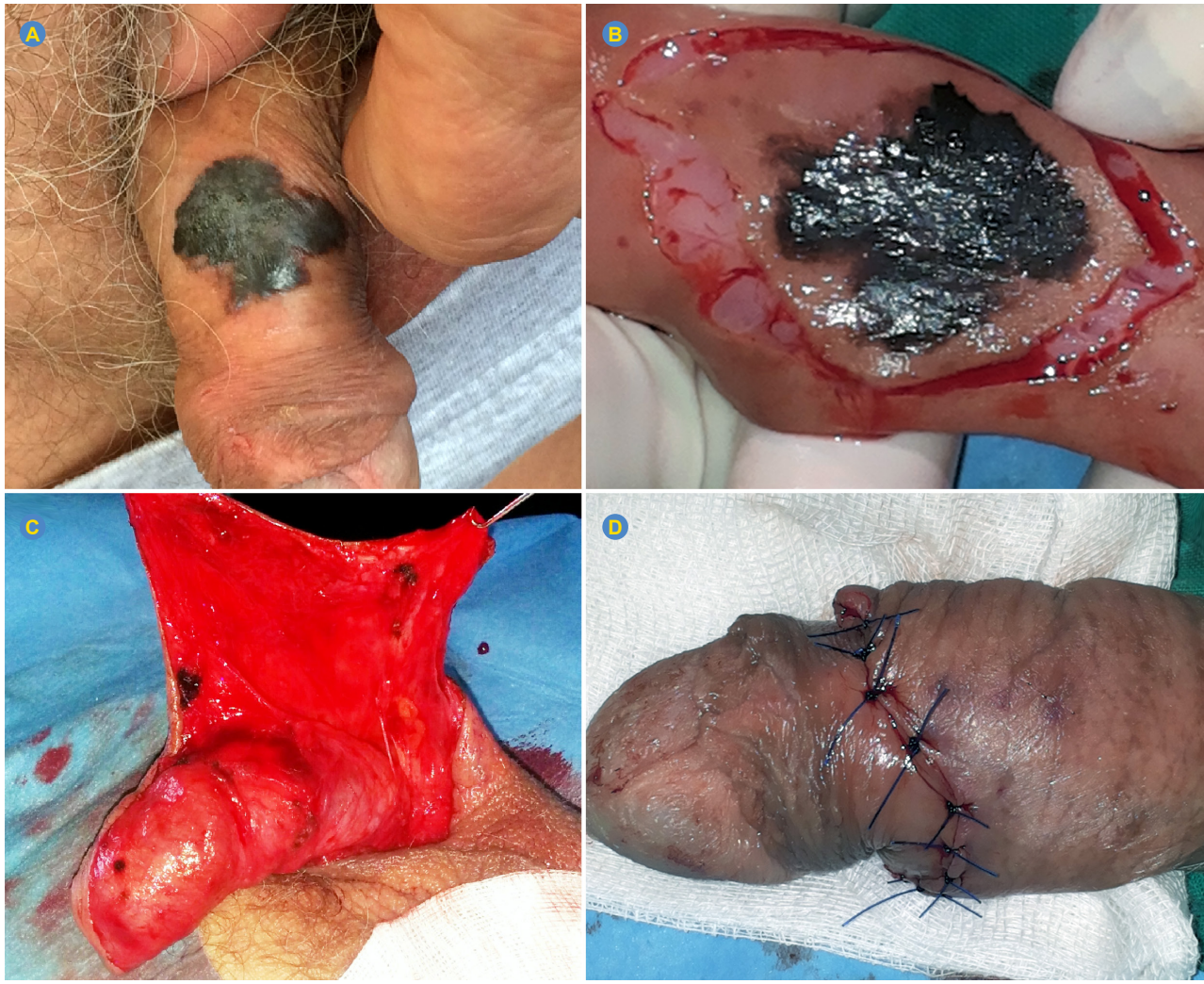

Figure 1 – Clinical presentation of the patient: (A) Initial clinical examination; (B) Initial surgical treatment; (C) Additional surgical excision (second surgical treatment); (D) Final result

nodules, lymphovascular invasion, tumor thickness greater than 3.5 mm, diameter greater than 15 mm, and regression pattern being the most important poor prognostic factors.[9]

Due to its rarity, no specific guidelines have been recommended so far for treating penile melanoma. Guidelines for treating penile malignancies in general do not differ depending on the type of cancer but depend on its invasiveness and stage. Surgical treatment of penile melanoma varies depending on the stage of the lesion.[10] Melanomas *in situ* and melanomas that have a Breslow index under 0.75 mm are widely excised. In larger lesions, partial or total penectomy remains the standard of surgical treatment. Sentinel lymph node biopsy followed by inguinal lymphadenectomy is usually recommended if there is micro-metastatic disease or inguinal lymphadenectomy,[11] neither of which was observed in our case. In the case of metastasis of the inguinal lymphatic nodes, radical lymphadenectomy does not improve the chances of survival.[10]

Early diagnosis led to positive outcomes in the presented case during the two-year follow-up period after the organ-preserving surgical treatment and no recurrent disease or palpable lymph nodes were detected.

Penile melanoma has a poor prognosis due to late diagnosis and the presence of negative prognostic factors. Median survival time is 1.7 years for disease with inguinal lymphadenopathy or remote metastasis at the time of diagnosis. For localized disease without a palpable inguinal lymphatic node at first examination, median survival time is 2.8 years from the moment of diagnosis.[4] Therefore, early detection is crucial for improving survival rates, but the hidden location often delays diagnosis. Also, diagnosing this condition in its early stages may be impacted by the patient's willingness to attend an appointment (as a result of possible benign initial aspects of the disease and social/cultural aspects) and physicians' awareness of genital diseases, both of which may lead to delay in diagnosis and compromising outcomes.[12,13] Therefore, efforts should be made in order to remove any hurdles from both the patients' and physicians' side in order to ensure detection of such a malignancy in its early stages.

CONCLUSION

The unusual location makes penile melanoma a clinical challenge. However, despite the rarity of the location, it is important to conduct a thorough systematic clinical examination to prevent misleading diagnosis. Proper diagnosis in early stages and evidence-based choice of treatment are extremely important for successful management. Since surgical excision remains the standard of care, it is important to conduct organ-preserving surgery for penile melanoma whenever possible in order to prevent a decrease in these patients' quality of life.

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AUTHOR CONTRIBUTIONS

JG, AL, MLB, JB, MN: Conception and design of the work, data acquisition, analysis and interpretation, drafting and critical review of the manuscript.

SN: Data acquisition, analysis and interpretation, drafting and critical review of the manuscript.

All authors approved the final version to be published.

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DATA CONFIDENTIALITY

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

PATIENT CONSENT

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COMPETING INTERESTS

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REFERENCES

1. Brady KL, Mercurio MG, Brown MD. Malignant tumors of the penis. Dermatol Surg. 2013;39:527-47.
2. Leitão LF, Orellana FM, Simões JP, Lellis RF, Maia M, Fernandes RC, et al. Penile melanoma. Braz J Oncol. 2021;17:e-20200040.
3. Sánchez-Ortiz R, Huang SF, Tamboli P, Prieto VG, Hester G, Pettawayet CA. Melanoma of the penis, scrotum, and male urethra: a 40-year single institution experience. J Urol. 2005;173:1958-65.
4. Jabiles AG, Del Mar EY, Perez GA, Vera FQ, Montoya LM, Dezaet CM.

Penile melanoma: a 20-Year analysis of six patients at the National Cancer Institute of Peru, Lima. Ecancermedicalscience. 2017;11:731.
5. Bechara GR, Schwindt AB, Ornellas AA, da Silva DE, Lott FM, de Camposet FS. Penile primary melanoma: analysis of 6 patients treated at Brazilian National Cancer Institute in the last eight years. Int Braz J Urol. 2013;39:823-31.
6. Kouyaté M, D'horpock AF, Aman NA, Traore ZC, Coulibaly ZI, Koui BS, et al. Melanoma of the penis: a case diagnosed at the anatomic pathology laboratory of the treichville teaching hospital. Hum Pathol: Case Reports. 2018;11:32-3.
7. Tchernev G, Temelkova I. Preputial melanoma. Wien Med Wochenschr. 2021;171:41-2.
8. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353:2135-47.
9. van Geel AN, den Bakker MA, Kirkels W, Horenblas S, Kroon BB, de Wilt JH, et al. Prognosis of primary mucosal penile melanoma: a series of 19 Dutch patients and 47 patients from the literature. Urology. 2007;70:143-7.
10. Andrei R, Cioplea M, Mageriu V, Chuaibi A, Cauni V, Zurac S, et al. Primary penile melanoma. Rom J Intern Med. 2014;52:121-5.
11. Muneer A, Bandini M, Compérat E, De Meerleer G, Fizazi K, Gietema J, et al. Penile cancer: ESMO-EURACAN clinical practice guideline for diagnosis, treatment and follow-up. ESMO Open. 2024;9:103481.
12. Skeppner E, Andersson SO, Johansson JE, Windahl T. Initial symptoms and delay in patients with penile carcinoma. Scand J Urol Nephrol. 2012;46:319-25.
13. Teichman JM, Mannas M, Elston DM. Noninfectious penile lesions. Am Fam Physician. 2018;97:102-10.

ACTA MÉDICA PORTUGUESA
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Bone Infarction of the Jaw with Regional Hematoma Collections: A Rare Complication in Sickle Cell Disease

Enfarte Ósseo da Mandíbula com Coleções Hemáticas Regionais: Uma Complicação Rara da Drepanocitose

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Keywords: Anemia, Sickle Cell/complications; Bone Diseases; Infarction; Mandible
Palavras-chave: Anemia Falciforme/complicações; Doenças Ósseas; Enfarte; Mandíbula

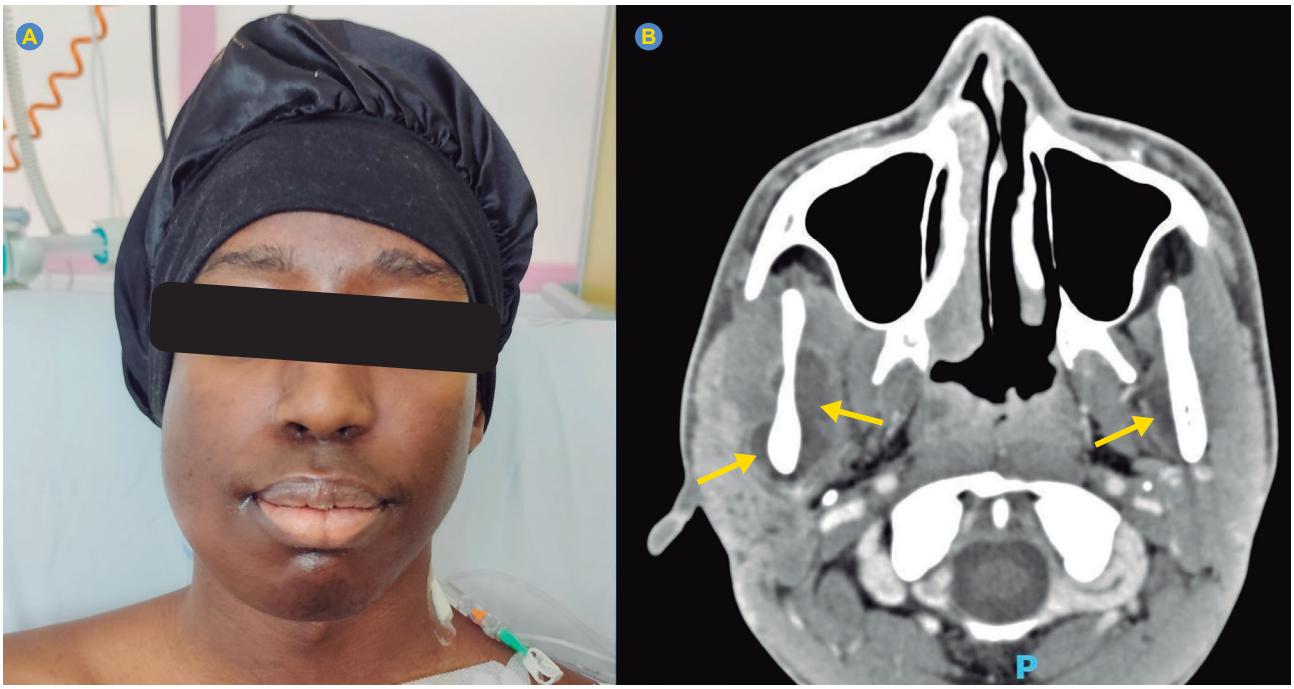

Figure 1 – Right mandibular edema in a young patient with sickle cell disease (A). Computed tomography of the face: subperiosteal collections in the ramus and body of the right mandible and in the left mandibular ramus with peripheral enhancement after contrast administration (arrows); edema and soft tissue densification in the right portion of the lower face with thickening of the right masseter muscle; no destruction or erosion of the mandible (B).

A 19-year-old male patient with sickle cell disease was hospitalized for left limb vaso-occlusive crisis pain management. During hospitalization, he developed fever, swelling, and pain in the lower right-hemiface (Fig. 1A), along with leukocytosis, neutrophilia, elevated C-reactive protein and a slight increase in hemolysis parameters without worsening of anemia. Despite four days of anti-inflammatory and amoxicillin/clavulanic acid treatment, there was no improvement. A facial computed tomography scan revealed bilateral mandibular bone infarcts with perimandibular hematoma collections (Fig. 1B). These were surgically drained (with subperiosteal dissection of the mandibular ramus), with symptom relief. The microbiological examination was negative.

Bone infarction in sickle cell disease results from microvascular occlusion, with mandibular involvement being rare due to limited medullary space.[1] Blood extravasation from necrotic vessels can cause adjacent hematoma collections.[2,3]

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This rare complication of an increasingly prevalent disease in Portugal[4] may mimic dental abscesses, vaso-occlusive crisis, or mandibular osteomyelitis, highlighting the need for greater awareness.

AUTHOR CONTRIBUTIONS

LCBR, SG: Study design, writing of the manuscript.
CE: Critical review of the manuscript.
All authors approved the final version to be published.

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PATIENT CONSENT

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COMPETING INTERESTS

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FUNDING SOURCES

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REFERENCES

1. Saito N, Nadgir RN, Flower E, Sakai O. Clinical and radiological manifestations of sickle cell disease in the head and neck. RadioGraphics. 2010;30:1021-34.
2. Alsuhaibani AH, Marzouk, MA. Recurrent infarction of sphenoid bone with subperiosteal collection in a child with sickle cell disease. Ophthalmic Plast Reconstruct Surg. 2011;27:e136-8.
3. Watanabe M, Saito N, Nadgir RN, Liao JH, Flower EN, Steinberg MH, et al. Craniofacial bone infarcts in sickle cell disease: clinical and radiological manifestations. J Comput Assist Tomogr. 2013;37:91-7.
4. Rodrigues D, Marcão A, Lopes L, Vilarinho L. Rastreio neonatal da drepanocitose em Portugal: resultados do estudo-piloto em 100.000 RN. Bol Epidemiol Observ.2024:26-31.

ACTA MÉDICA PORTUGUESA
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Recomendações sobre Contraceção em Mulheres com Cancro Ginecológico: Do Diagnóstico ao Pós-Tratamento

Recommendations for Contraception in Women with Gynecologic Cancer: From Diagnosis to Post-Treatment

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RESUMO

A incidência de cancro ginecológico em mulheres durante a idade fértil está a aumentar, suscitando uma preocupação crescente com a preservação da fertilidade. Nesse contexto, torna-se essencial oferecer aconselhamento contracetivo adequado a estas doentes. Na escolha do método contracetivo, é fundamental considerar o tipo histológico do tumor e a sua expressão de recetores hormonais, bem como o momento em que o aconselhamento está a ser prestado no cuidado da doente oncológica, seja na fase de diagnóstico, de tratamento ou após o tratamento oncológico. A Sociedade Portuguesa da Contraceção e a Secção de Ginecologia Oncológica da Sociedade Portuguesa de Ginecologia apresentam recomendações sobre contraceção nas mulheres com diagnóstico de cancro ginecológico submetidas a tratamentos preservadores da fertilidade, desde o diagnóstico até ao término da idade fértil.
Palavras-chave: Contraceção; Contracetivos Orais; Dispositivos Intrauterinos; Neoplasia Genital Feminina

ABSTRACT

The incidence of gynecologic cancer in women of reproductive age is increasing, as is the trend towards fertility-sparing treatments, highlighting the importance of safe and effective contraceptive counseling. Selecting a contraceptive method requires careful consideration of the tumor's histological subtype, its hormonal expression, and the timing of counseling within the cancer care continuum (diagnosis, treatment, and post-treatment phases). The Portuguese Society of Contraception and the Section of Gynecologic Oncology of the Portuguese Gynecological Society present recommendations about contraception in women with gynecologic cancer who have undergone fertility-sparing treatments, from diagnosis to the end of the reproductive age.
Keywords: Contraception; Contraceptives, Oral; Genital Neoplasms, Female; Intrauterine Devices

INTRODUÇÃO

A incidência de cancro ginecológico em mulheres durante a idade fértil está a aumentar, assim como a tendência para terapêuticas que preservam a fertilidade, que são possíveis nos estádios iniciais e tipos histológicos de baixo grau da maioria dos cancros ginecológicos (Tabela 1).[1-7]

Não obstante, apesar de a preservação da fertilidade ser uma questão premente nos cancros ginecológicos diagnosticados em mulheres jovens, o desejo de completar o seu plano reprodutivo não exclui a importância de um aconselhamento contracetivo eficaz. Pretende-se que estas mulheres tenham uma conceção programada, de forma a reduzir as gravidezes indesejadas, as complicações obstétricas e os desfechos adversos relacionados com a sua patologia oncológica.

Existem diferentes métodos contracetivos, que vão desde os métodos 'naturais' (métodos baseados na monitorização do período fértil) passando pelos métodos de barreira e pelos métodos contracetivos hormonais. Cada método funciona com base num princípio diferente, com diferentes níveis de eficácia. O Índice de Pearl, definido como o número de gravidezes não planeadas por 100 mulheres no primeiro ano de utilização do método, é uma medida usada para avaliar a eficácia de um método contracetivo.[13]

Uma revisão de Mansour *et al* demonstrou que os métodos contracetivos reversíveis de longa duração (*long-acting reversible contraceptives* — LARC), nomeadamente os implantes subcutâneos e o dispositivo intrauterino libertador de levonorgestrel (DIU-LNG) são os métodos mais eficazes, com eficácia comparável apenas à esterilização feminina, seguindo-se o dispositivo intrauterino de cobre (DIU-Cu). Os métodos hormonais de curta duração dependentes da utilizadora, nomeadamente a contraceção hormonal combinada (CHC) oral, transdérmica e vaginal, e a contraceção progestativa oral, apresentam maiores Índices de Pearl (0 - 2,5) devido a possíveis erros relacionados com a sua administração (menor adesão, má absorção, interações medicamentosas). No entanto, apresentam maior eficácia em relação ao preservativo masculino (Índice de

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Pearl 2,5 - 5,9) e aos métodos naturais (Índice de Pearl 3,8 - 20,4).[14]

Em relação ao cancro ginecológico, as recomendações específicas sobre o uso de contraceção para cada tipo de tumor, durante e após o tratamento, são limitadas. Além disso, a informação sobre os efeitos a longo prazo dos contracetivos hormonais na evolução da doença oncológica é escassa.

Estas recomendações destinam-se a profissionais de saúde, não sendo vinculativas, e têm como objetivo garantir às mulheres com cancro ginecológico um aconselhamento contracetivo seguro e eficaz, em todo o processo oncológico, desde o diagnóstico até ao pós-tratamento.

Metodologia

Estas recomendações resultam de um trabalho conjunto entre a Sociedade Portuguesa da Contraceção e a Secção de Ginecologia Oncológica da Sociedade

Tabela 1 – Incidência na idade reprodutiva, critérios e tipos de tratamentos preservadores da fertilidade, por tipo de tumor

Cancro	Incidência em mulheres portuguesas em idade reprodutiva (por 100 000 pessoas-ano)	Critérios para tratamento preservador da fertilidade	Tipo de tratamento conservador
Vulva	0,3 - 1,0 30 - 49 anos	Tumores em estádio I e casos selecionados no estádio II	Excisão local radical ± avaliação ganglionar (BGS/linfadenectomia)
Vagina	0,3 - 1,0 40 - 49 anos	Tumores em estádio I (tumor confinado à vagina, com distância ao colo que permita a excisão com margens livres)	Excisão local alargada + avaliação ganglionar (linfadenectomia ± BGS[a])
Colo do útero	0,7 - 14,6 20 - 49 anos	Carcinoma pavimentocelular e adenocarcinoma tipo usual, associados ao HPV, estádios IA1, IA2 e IB1 (≤ 2cm)	De acordo com a situação clínica: - Excisão da zona de transformação - Traquelectomia simples - Traquelectomia radical - ± avaliação ganglionar (BGS/linfadenectomia)
Endométrio	0,7 - 7,5 25 - 49 anos[b]	Adenocarcinoma endometrioide grau 1, confinado ao endométrio, p53wt, e ausência de tumores ováricos síncronos; sem contraindicação para terapêutica farmacológica	Resseção histeroscópica do tumor seguida de acetato de megestrol oral (160-320 mg/dia) ou acetato de medroxiprogesterona oral (400-600 mg/dia) e/ou DIU-LNG, 52 mg, durante pelo menos seis meses[c]
Ovário	2,6 - 7,7 20 - 49 anos 0,4 - 1,5 < 20 anos	**Tumores *borderline*:** Estádio I; em casos selecionados nos estádios II a IV **Tumores epiteliais malignos:** baixo grau/grau 1, estádios IA e IC1[d] **Tumores não epiteliais malignos:** **- de células germinativas:** Estádios IA a IC, casos selecionados de estádios II-IV **- dos cordões sexuais e do estroma:** tumores de células da granulosa estádio IA e casos selecionados nos estádios IC; tumores de Sertoli-Leydig no estádio IA e casos selecionados em estádios > I	**Tumores *borderline*:** Anexectomia ipsilateral, quistectomia uni/bilateral (se seroso bilateral), estadiamento peritoneal[e] ± apendicectomia[f] **Tumores malignos:** Anexectomia uni/bilateral e estadiamento peritoneal[e] ± linfadenectomia[g] ± apendicectomia[f] Nos tumores das células da granulosa deve ser realizada uma biópsia endometrial.

Os estádios considerados são os da Federação Internacional de Ginecologia e Obstetrícia (FIGO), atualizados para os respetivos tumores (*update* vulva 2021; *update* vagina 2021; *update* colo 2021; *update* ovário 2021);[8-11] As incidências são as do Registo Oncológico Nacional (RON), 2020;
BGS: biópsia de gânglio sentinela; HPV: vírus do papiloma humano; p53wt: subtipo molecular p53 *wild-type*; DIU-LNG: dispositivo intrauterino libertador de levonorgestrel.
[a]: Dada a raridade do cancro da vagina, a biópsia de gânglio sentinela não está validada como método isolado de avaliação ganglionar.
[b]: Incidência para o corpo do útero, segundo o RON 2020, em que o cancro do endométrio corresponde a > 90% dos casos.[12]
[c]: A dose ótima de acetato de megestrol e de acetato de medroxiprogesterona, assim como a duração ideal do tratamento, ainda não estão bem estabelecidas. Terminado o tratamento, a resposta ao mesmo é definida pela ausência de qualquer forma de hiperplasia em duas biópsias endometriais consecutivas, com um intervalo mínimo de três meses.[5]
[d]: Outros tipos histológicos, como o carcinoma seroso de alto grau estádio IA, são sujeitos a decisões individualizadas.
[e]: O estadiamento peritoneal inclui colheita de lavado peritoneal ou de líquido ascítico, omentectomia e biópsias peritoneais múltiplas.
[f]: Ponderar apendicectomia no estadiamento dos tumores mucinosos (*borderline* ou malignos).
[g]: O estadiamento ganglionar é questionável nos carcinomas serosos de baixo grau e nos tumores mucinosos expansivos e não está recomendado nos tumores malignos não epiteliais.

Portuguesa de Ginecologia e foram elaboradas com base numa revisão narrativa da literatura. Foram consultadas as bases de dados MEDLINE, Embase e Scopus, incluindo artigos publicados no período de janeiro de 2010 a dezembro de 2024. Na pesquisa foram utilizados termos relacionados com contraceção e cancro ginecológico. Foram incluídas *guidelines*, revisões sistemáticas, revisões narrativas, estudos de coorte, transversais e opiniões de peritos, publicados em inglês ou português. Estudos disponíveis apenas sob a forma de resumos, relatos de caso ou comentários editoriais foram excluídos da análise. Os estudos tinham de incluir pacientes com cancro ginecológico e a utilização de contraceção, independentemente do tipo, dose ou via de administração. Na ausência de estudos sobre contraceção hormonal para um tipo histológico específico, foram incluídos na pesquisa estudos sobre terapêutica hormonal da menopausa (THM).

A segurança da utilização do contracetivo será avaliada em três momentos distintos ao longo do processo oncológico (Fig. 1): 1) Pré-tratamento; 2) Fase ativa (durante o tratamento e nos primeiros seis meses após a remissão clínica); 3) Após a fase ativa. A classificação da segurança do método contracetivo será realizada com base nos Critérios de Elegibilidade para o Uso de Contraceção da Organização Mundial de Saúde (OMS), quando aplicável (Tabela 2).[15]

Sempre que possível, serão feitas recomendações específicas para os vários tipos histológicos de tumores. Uma vez que os tumores de células claras do ovário e os sarcomas não têm indicação para cirurgias preservadoras da fertilidade, estes casos não serão abordados nestas recomendações. Do mesmo modo, em relação ao cancro do colo do útero, apenas serão abordados os subtipos histológicos pavimentocelular e adenocarcinoma do tipo usual, associado ao vírus do papiloma humano (HPV), que são os subtipos elegíveis para terapêuticas conservadoras.

Para além dos cancros ginecológicos enunciados na Tabela 1, será também abordada a segurança da utilização dos vários métodos contracetivos na neoplasia gestacional do trofoblasto.

Práticas contracetivas das mulheres com cancro ginecológico

As sobreviventes de cancro utilizam menos contraceção, métodos pouco eficazes e recorrem mais a contraceção de emergência

Quando comparadas com a população em geral, as sobreviventes de cancro utilizam menos contraceção e, quando a usam, recorrem a métodos menos eficazes.[16-18] A falsa perceção de infertilidade e a preferência por métodos não hormonais são apontadas por alguns estudos como causas para a menor utilização de contraceção e para a escolha de métodos menos eficazes, respetivamente.[17,19] Nestas doentes observam-se maiores taxas de gravidez indesejada e de recurso a contraceção de emergência em comparação com a população em geral.[20]

Numa revisão sistemática e meta-análise conduzida por Harris *et al* sobre aconselhamento contracetivo em mulheres com diagnóstico de cancro, entre os 15 e os 49 anos, apenas 50% das mulheres receberam aconselhamento ao longo das fases de diagnóstico, tratamento e pós-tratamento. Além disso, o aconselhamento recebido foi referido como sendo limitado e de baixa qualidade.[18]

É assim fundamental um adequado aconselhamento contracetivo a estas doentes, que deve ter em conta a opção da mulher, a presença de comorbilidades, o risco tromboembólico e o risco de recidiva da sua patologia oncológica.

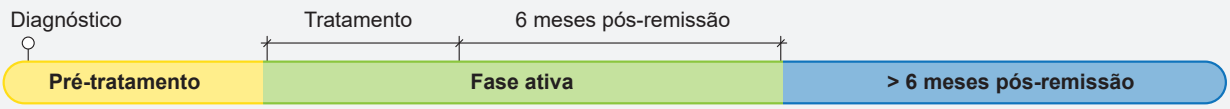

Figura 1 – Três momentos distintos do processo oncológico, onde será avaliada a segurança da utilização dos métodos contracetivos

Tabela 2 – Critérios médicos de elegibilidade para o uso de contraceção segundo a OMS

	Categoria	Decisão clínica específica	Decisão clínica global
1	Não existem restrições ao uso do método	Método a usar em todas as circunstâncias	Sim (Pode usar o método)
2	As vantagens do uso do método superam os riscos provados ou teóricos	Método geralmente a ser usado	
3	O risco provado ou teórico de uso do método supera as vantagens	O uso do método não é recomendado a menos que outro não esteja disponível ou não seja aceite	Não (Não usar o método)
4	O uso do método representa um risco inaceitável para a saúde	Método a não usar	

Contraceção de emergência

Os contracetivos de emergência atualmente disponíveis são hormonais orais (acetato de ulipristal e levonorgestrel) e o DIU-Cu.

Todas as mulheres, incluindo as doentes oncológicas, são elegíveis para o uso de contraceção de emergência hormonal oral.[20,21]

O DIU-Cu não deve ser usado como primeira linha na fase de pré-tratamento no cancro do colo do útero, do endométrio e na neoplasia gestacional do trofoblasto com suspeita ou evidência de doença intrauterina (*vide*: "Pré--tratamento").

Critérios de elegibilidade para o uso de contraceção em mulheres com cancro ginecológico

Pré-tratamento

Enquanto aguardam tratamento, praticamente todos os métodos são elegíveis (Tabela 3). O Centers for Disease Control and Prevention (CDC) e a OMS classificam o cancro do ovário, o cancro do endométrio e a neoplasia gestacional do trofoblasto como condições que aumentam o risco de eventos adversos para a saúde em caso de gravidez.[15,22] Considerando que nestes casos a prevenção da gravidez é prioritária em relação aos potenciais riscos de progressão tumoral associados ao uso de contracetivos hormonais, todos os métodos contracetivos são elegíveis no período pré-tratamento.

Porém, existem exceções, como o cancro do colo do útero, o cancro do endométrio e a neoplasia gestacional do trofoblasto com suspeita ou evidência de doença intrauterina. Nestes casos, os dispositivos intrauterinos, DIU-LNG e DIU-Cu, se já estiverem a ser utilizados, podem ser continuados, mas não devem ser iniciados como método de primeira linha devido ao maior risco de infeção, hemorragia e perfuração uterina aquando da inserção.[15,22]

Dada a raridade dos cancros da vagina e vulva nesta faixa etária, não existem recomendações específicas para a contraceção nestas doentes. No entanto, o tipo histológico mais frequente (carcinoma pavimentocelular) não é considerado hormono-dependente, não existindo contraindicação à utilização de contraceção hormonal nestes casos.[23]

Fase ativa: durante o tratamento e até seis meses após a remissão clínica

O CDC não recomenda a utilização de contraceção hormonal combinada (CHC) nem de progestativo injetável durante o tratamento e até seis meses após a remissão clínica – fase ativa (com exceção do cancro de pele não melanoma), devido ao elevado risco tromboembólico associado (Tabela 4).[22]

Após a fase ativa

O CDC e a OMS não definem critérios de elegibilidade para sobreviventes de cancro ginecológico (mais de seis

Tabela 3 – Critérios de elegibilidade para o uso de contraceção em mulheres com diagnóstico de cancro ginecológico, enquanto aguardam tratamento

	CHC (O,T, V)	PO	Progestativo injetável	Implante	DIU-LNG		DIU-Cu		Barreira		
					I	C	I	C	P	E	D[a]
Colo do Útero	2	1	2	2	4	2	4	2	1	2	1
Endométrio	1	1	1	1	4	2	4	2	1	1	1
Ovário	1	1	1	1	1		1		1	1	1
NTG sem doença intrauterina	1	1	1	1	2	1	2	1	1	1	1
NTG com doença intrauterina	1	1	1	1	4	2	4	2	1	1	1

CHC: Contraceção hormonal combinada (O = oral, T = transdérmico, V = anel vaginal); PO: progestativo oral; DIU-LNG: dispositivo intrauterino libertador de levonorgestrel; DIU-Cu: dispositivo intrauterino de cobre; I: iniciação do método; C: continuação do método; P: preservativo; E: espermicida; D: diafragma; NTG: neoplasia gestacional do trofoblasto.
[a]: Não existem diafragmas comercializados em Portugal, no entanto estes podem ser adquiridos *online*.

Tabela 4 – Critérios de elegibilidade para o uso de contraceção em mulheres com diagnóstico de cancro ginecológico, durante a fase ativa da doença

	CHC (O, T, V)	PO	Progestativo injetável	Implante	DIU-LNG		DIU-Cu		Barreira		
					I	C	I	C	P	E	D
Cancro ginecológico ativo	4	2[a]	3	2[a]	2[a]		2		1	1	1
NTG sem doença intrauterina	1	1	1	1	2	1	2	1	1	1	1
NTG com doença intrauterina	1	1	1	1	4	2	4	2	1	1	1

CHC: Contraceção hormonal combinada (O = oral, T = transdérmico, V = anel vaginal); PO: progestativo oral; DIU-LNG: dispositivo intrauterino libertador de levonorgestrel; DIU-Cu: dispositivo intrauterino de cobre; P: preservativo; E: espermicida; D: diafragma; NTG: neoplasia gestacional do trofoblasto.
[a]: A exceção à utilização de contraceção progestativa (oral, implante, e DIU-LNG) aplica-se aos tumores do ovário: seroso de baixo grau, endometrioide de baixo grau e seroso *borderline* de alto risco (com implantes peritoneais invasivos, padrão micropapilar ou microinvasão estromal), em que esta está contraindicada (*vide* secção: "Após a fase ativa").

meses após a remissão clínica), uma vez que consideram que, no geral, o tratamento padrão destas patologias deixa a mulher estéril.[15,22]

No entanto, com base na literatura disponível, depois da fase ativa, podemos considerar dois grupos de métodos contracetivos:

1. **Métodos não hormonais:** Os métodos de barreira e naturais não estão contraindicados, no entanto o seu uso está associado a um alto índice de Pearl.[14] O DIU-Cu pode ser uma opção para estas mulheres, especialmente no contexto de contraindicação ou recusa de métodos hormonais.[23,24]

2. **Métodos hormonais:** A escolha do método deverá ter em conta o tipo histológico e a expressão de recetores hormonais (Tabela 5). O termo "contraceção hormonal (CH)" doravante incluirá a contraceção estroprogestativa e a progestativa, exceto quando especificado.

2.1. Carcinoma da vulva e vagina

Os tumores da vulva e vagina são mais frequentemente diagnosticados em mulheres na pós-menopausa.[25] No entanto, os tumores da vulva associados ao HPV estão a aumentar nas mulheres jovens.[26] A maioria dos tumores da vulva e vagina são carcinomas pavimentocelulares e não são hormonodependentes, pelo que serão elegíveis para CH. Não se podem fazer recomendações sobre CH para os adenocarcinomas vulvar e vaginal uma vez que não existem estudos sobre a sua evolução com THM ou

Tabela 5 – Contraceção hormonal em sobreviventes de cancro ginecológico

Tumor	Recomendação
Vulva e vagina	
- Carcinoma pavimentocelular	Pode ser usada
- Adenocarcinoma	Não existem recomendações
- Melanoma	Pode ser usada nos estádios iniciais
- Outros mais raros (ex.: sarcoma vulvar)	Não existem recomendações
Colo do útero	
- Carcinoma pavimentocelular - Adenocarcinoma do tipo usual	Pode ser usada
Endométrio	Contraceção progestativa pode ser usada; CHC não recomendada
Ovário	
Tumores Epiteliais	
Carcinoma seroso de baixo grau	Não recomendada
Carcinoma endometrioide de baixo grau	Não recomendada
Carcinoma mucinoso	Pode ser usada
Tumores *borderline*	Pode ser usada Não recomendada em tumores serosos *borderline* de alto risco (implantes peritoneais invasivos, padrão micropapilar ou microinvasão estromal)
Tumores Não-Epiteliais	
Tumores de células germinativas	
- Digerminoma	
- Teratoma Imaturo	
- Tumor do saco vitelino	Pode ser usada
- Carcinoma embrionário	
- Coriocarcinoma	
Tumores dos cordões sexuais e do estroma	
- Tumor de células da granulosa	CHC não recomendada; contraceção progestativa pode ser usada
- Tumor Sertoli-Leydig	Não existem recomendações
Neoplasia Gestacional do Trofoblasto	Pode ser usada

CHC: Contraceção Hormonal Combinada

CH. Os melanomas são sensíveis aos estímulos hormonais mas os estudos sobre o efeito estrogénico nos melanomas são controversos.[27] Nestes tumores, em estádios precoces, a THM com estrogénio parece ser segura, abrindo uma janela de oportunidade para a utilização de CH neste contexto.[26]

2.2. Carcinoma do colo do útero

A classificação de tumores da OMS 2020 divide os carcinomas do colo do útero naqueles associados ao HPV e HPV independentes.[28] O carcinoma pavimentocelular associado ao HPV é o tipo histológico mais comum e não é hormonodependente, pelo que é elegível para CH.[23]

Em relação ao adenocarcinoma tipo usual associado ao HPV, não exitem recomendações específicas em relação à CH. Embora os recetores de estrogénio sejam frequentemente expressos neste tipo histológico (em até 39%), a sua presença não influencia a sobrevivência global ou livre de doença.[29] A escassa literatura existente não demonstrou diferenças significativas na taxa de recidiva ou de sobrevivência em mulheres com adenocarcinoma cervical, submetidas a THM.[30,31] Deste modo, extrapolando as recomendações sobre THM, poderemos inferir que a CH poderá também ser oferecida a estas doentes.[30,31]

Após conização ou traquelectomia (técnica cirúrgica de preservação da fertilidade no cancro do colo do útero que consiste na remoção do colo, podendo, nas formas mais radicais, incluir excisão da porção proximal da vagina e dos paramétrios), tanto o DIU-Cu quanto o DIU-LNG são opções válidas, estando descritas a sua utilidade, sobretudo do DIU-LNG, na prevenção e tratamento da estenose cervical associada a estes procedimentos cirúrgicos.[32-34]

2.3. Carcinoma do endométrio

Nas doentes com carcinoma do endométrio candidatas a terapêuticas preservadoras da fertilidade, o tratamento recomendado inclui a utilização de progestativos orais em alta dose e/ou o DIU-LNG, que têm um efeito duplo: terapêutico e contracetivo.[23]

É desejável que a gravidez ocorra o mais precocemente possível após evidência de resposta completa, incluindo logo no mês seguinte.[25]

Uma vez que o risco de recidiva após tratamento conservador é de aproximadamente 35%, ocorrendo em média 15 meses após a suspensão da terapêutica, é importante uma vigilância apertada, com exame clínico e biópsias endometriais a cada três a seis meses até à gravidez.[5,25] O tratamento definitivo, com histerectomia, é encorajado após conclusão do projeto reprodutivo, uma vez que estão descritas recidivas a longo prazo.[5] Para as mulheres que recusem terapêutica definitiva ou que pretendam planear uma segunda gravidez, está recomendada a utilização do DIU-LNG, 52 mg.[35]

2.4. Tumores do ovário

De acordo com a classificação da OMS 2020, os tumores primários do ovário subdividem-se em três categorias principais: tumores epiteliais, tumores de células germinativas e tumores dos cordões sexuais e do estroma.[28] Os tumores malignos do ovário são na sua maioria de origem epitelial (85% - 90%), enquanto que os tumores malignos de células germinativas e dos cordões sexuais e do estroma perfazem menos de 10% de todos os cancros do ovário.[7] Apesar de serem mais raros, os tumores não epiteliais são os mais comuns em mulheres jovens.[7]

Devido à sua alta heterogeneidade, com diferente expressão de recetores hormonais, cada tipo histológico apresenta recomendações específicas no que se refere à CH.

2.4.1. Epiteliais

O carcinoma seroso de alto grau perfaz 70% de todos os carcinomas do ovário.[25] Não é considerado um tumor hormonodependente, pelo que é elegível para contraceção hormonal.[36]

O carcinoma seroso de baixo grau e o carcinoma endometrioide de baixo grau são potencialmente hormonodependentes, expressando recetores hormonais[25,37] pelo que a CH não está recomendada nestes tumores.[36]

Em relação aos tumores serosos *borderline*, existe um *continuum* de progressão tumoral para cancro do ovário, nomeadamente para carcinoma seroso de baixo grau.[25] Sendo este último hormonodependente, não está recomendada a CH após tratamento preservador da fertilidade de tumor seroso *borderline* que apresente fatores de risco histológicos, nomeadamente implantes peritoneais invasivos, padrão micropapilar ou

microinvasão estromal, associados a maior risco de carcinoma seroso de baixo grau. Porém, na ausência destes fatores, a CH pode ser recomendada.[36]

O carcinoma mucinoso é considerado não hormonodependente, pelo que é elegível para CH.[36] Do mesmo modo, nos tumores mucinosos *borderline* a CH pode ser prescrita.[36]

2.4.2. Não epiteliais

Os tumores de células germinativas não são hormonodependentes, não existindo evidência de que a CH aumente o risco de recidiva, pelo que esta pode ser recomendada.[7,36]

Em relação aos tumores dos cordões sexuais e do estroma, o subtipo histológico mais frequente é o tumor de células da granulosa, seguido do tumor de Sertoli-Leydig. Os tumores de células da granulosa são considerados tumores hormonodependentes e têm na hormonoterapia uma possível arma terapêutica (agonistas da GnRH, tamoxifeno, progestativos e inibidores da aromatase).[7] Assim, apesar de não existirem estudos sobre contraceção nas sobreviventes destes tumores é razoável evitar a CHC, sobretudo pela componente estrogénica, à semelhança do descrito para a THM.[7,36] Já a contraceção progestativa pode ser uma opção, atendendo ao seu potencial benefício nestas doentes.[36]

Em relação aos tumores de Sertoli-Leydig, acredita-se que estes sejam hormonodependentes, estando descritas respostas terapêuticas a agonistas da GnRH.[7,33] Sendo assim, nestes tumores a THM está contraindicada.[7] No entanto, não existem recomendações sobre CH para estes casos.

2.5. Neoplasia gestacional do trofoblasto

A doença gestacional do trofoblasto (DGT) refere-se a um grupo heterogéneo de tumores benignos, potencialmente malignos e malignos que se originam a partir da proliferação anormal de células do trofoblasto. As formas malignas da DGT são coletivamente designadas como neoplasia gestacional do trofoblasto (NGT) e incluem a mola invasiva, o coriocarcinoma, o tumor trofoblástico do sítio placentário e o tumor trofoblástico epitelióide.[25,38]

De um modo geral, o tratamento de primeira linha da NGT é a quimioterapia. A monitorização da resposta ao tratamento faz-se com medições seriadas dos níveis de gonadotrofina coriónica humana (hCG). Deste modo, é fundamental uma contraceção eficaz para diferenciar se um aumento nos níveis de hCG se deve a uma nova gravidez ou à resistência à quimioterapia. Aproximadamente 75% das recidivas ocorrem no primeiro ano, pelo que a vigilância inclui medições de hCG mensais durante um ano após o tratamento. Por este motivo, a gravidez no primeiro ano deve ser evitada.[25,38]

Embora inicialmente se pensasse que a CH atrasava a normalização da hCG, pelo risco teórico de estimulação hormonal do tumor, vários estudos vieram refutar esta ideia, sendo a CH eficaz e segura nestas mulheres.[39,40]

O CDC e a OMS são consensuais a referir que a contraceção hormonal combinada e contraceção progestativa oral, injetável e subcutânea são seguras, mesmo durante a quimioterapia.[15,22] No entanto, as mesmas divergem quanto à contraceção intrauterina. A OMS contraindica o seu uso em qualquer fase da DGT (mesmo com níveis em decrescendo ou indetectáveis de hCG) e na doença maligna, enquanto as orientações mais recentes da CDC permitem-na, mesmo se se verificarem níveis de hCG persistentemente elevados ou doença maligna, desde que não haja suspeita ou evidência de doença intrauterina.[15,12]

A National Comprehensive Cancer Network recomenda as pílulas contracetivas orais em vez de dispositivos intrauterinos porque suprimem os níveis endógenos da hormona luteinizante (LH) e da hormona folículo-estimulante (FSH), que podem interferir na medição de hCG em níveis baixos.[38]

CONCLUSÃO

As mulheres jovens sobreviventes de cancro ginecológico submetidas a tratamentos conservadores merecem um aconselhamento contracetivo seguro e eficaz, respeitando o direito à saúde sexual e reprodutiva. A recusa de métodos hormonais pelo receio de recidiva deve ser desmistificada e contraposta com o risco de uma gravidez não planeada, associada a riscos obstétricos e possível interferência com os tratamentos oncológicos.

No entanto, a evidência sobre o uso de CH em doentes com cancro ginecológico é limitada. As principais recomendações sobre contraceção, do CDC e da OMS, não definem critérios de elegibilidade para sobreviventes de cancro ginecológico (mais de seis meses após a remissão clínica), uma vez que consideram que, no geral, o tratamento padrão destas patologias deixa a mulher estéril.[15,22]

Embora existam cada vez mais publicações relacionadas com o uso de THM em sobreviventes de cancro ginecológico, o mesmo não se verifica em relação à contraceção. A maioria dos estudos disponíveis centra-se nos efeitos da CH (deletério ou protetor) sobre a incidência de cancro ginecológico, em vez de abordar especificamente a segurança do seu uso em doentes já diagnosticadas. Além disso, grande parte da evidência disponível sobre a elegibilidade para o uso de CH baseia-se nos riscos teóricos relacionados com o *status* hormonal do tumor e nos efeitos da CH na incidência de determinados tipos de tumores.

Atendendo à crescente incidência de cancro ginecológico na idade reprodutiva, aliada ao adiamento cada vez mais frequente de completar o projeto reprodutivo, torna-se fundamental a necessidade de mais estudos sobre os efeitos a longo prazo da CH nestas doentes, nomeadamente em desfechos como sobrevivência global, sobrevivência livre de doença e risco de recidiva.

Considerando a evidência disponível de momento, podemos inferir as seguintes conclusões:

1. Nestas mulheres, não há contraindicação à utilização de contraceção de emergência, sendo preferíveis as formulações hormonais orais;
2. O DIU-Cu e o DIU-LNG podem ser mantidos nos cancros do colo do útero, endométrio e neoplasia gestacional do trofoblasto com suspeita ou evidência de doença intrauterina, se já estiverem em utilização. No entanto, a sua inserção está contraindicada enquanto as doentes aguardam tratamento;
3. Apesar dos métodos de barreira e naturais não estarem contraindicados, o seu uso está associado a um alto índice de Pearl;
4. Relativamente à contraceção hormonal, de um modo geral, esta não está recomendada nos tumores do ovário serosos *borderline* de 'alto risco' (os que apresentam padrão micropapilar, microinvasão ou implantes peritoneais), carcinoma seroso de baixo grau e carcinoma endometrioide de baixo grau. Nos tumores de células da granulosa a utilização de contraceção com estrogénios está contraindicada;
5. No carcinoma do endométrio, a utilização do DIU-LNG, 52 mg como método contracetivo está recomendada quando a mulher pretende planear uma segunda gravidez ou recusa a terapêutica definitiva com histerectomia;
6. Nos restantes tumores, após verificar as contraindicações absolutas/relativas (comorbilidades e outros fatores de risco), e tendo em conta a opção da mulher, poderá fazer-se uma prescrição de CH, após aconselhamento da doente, devidamente esclarecida.
7. Na doença gestacional do trofoblasto todos os métodos contracetivos são elegíveis. A única exceção aplica-se aos dispositivos intrauterinos, que não devem ser utilizados em caso de suspeita ou evidência de doença intrauterina.

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LC, MT: Desenho e elaboração do artigo, análise e interpretação dos dados, redação e revisão crítica do manuscrito, aprovação da versão final.

MP, AP, FP: Desenho e elaboração do artigo, revisão do manuscrito, aprovação da versão final.

CONFLITOS DE INTERESSE

LC recebeu honorários de consultoria, pagamentos ou honorários para palestras, apresentações, gabinetes de oradores, redação de manuscritos ou eventos educativos da AstraZeneca; recebeu apoio da Procare Health para participar no *European Congress on Gynaecological Oncology 2024*; é tesoureira da Secção de Ginecologia Oncológica da Sociedade Portuguesa de Ginecologia.

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REFERÊNCIAS

1. Registo Oncológico Nacional. Registo oncológico nacional de todos os tumores na população residente em Portugal, em 2020. Porto: Instituto Português de Oncologia do Porto Francisco Gentil; 2023.
2. Oonk MH, Planchamp F, Baldwin P, Mahner S, Mirza MR, Fischerová D, et al. European society of gynaecological oncology guidelines for the management of patients with vulvar cancer - update 2023. Int J Gynecol Cancer. 2023;33:1023-43.
3. Nout RA, Calaminus G, Planchamp F, Chargari C, Lax S, Martelli H, et al. ESTRO/ESGO/SIOPe guidelines for the management of patients with vaginal cancer. Int J Gynecol Cancer. 2023;33:1185-202.
4. Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, et al. ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer - update 2023. Virchows Arch. 2023;482:935-66.
5. Rodolakis A, Scambia G, Planchamp F, Acien M, Di Spiezio Sardo A, Farrugia M, et al. ESGO/ESHRE/ESGE guidelines for the fertility-sparing treatment of patients with endometrial carcinoma. Hum Reprod Open. 2023;2023:hoac057.
6. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019;30:672-705.
7. Ray-Coquard I, Morice P, Lorusso D, Prat J, Oaknin A, Pautier P, et al. Non-epithelial ovarian cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:Siv1-iv18.
8. Olawaiye AB, Cuello MA, Rogers LJ. Cancer of the vulva: 2021 update. Int J Gynaecol Obstet. 2021;155:S7-18.
9. Adams TS, Rogers LJ, Cuello MA. Cancer of the vagina: 2021 update. Int J Gynaecol Obstet. 2021;155:S19-27.
10. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021;155:S28-44.
11. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. Int J Gynaecol Obstet. 2021;155:S61-85.
12. Sociedade Portuguesa de Ginecologia, Secção de Ginecologia Oncológica. Cancro ginecológico. Consensos nacionais 2020 [consultado 2024 dez 06]. Disponível em: https://spginecologia.pt/wp-content/uploads/2020/01/Brochuradig_ConsensosNacionais_23_310123-002.cleaned.pdf.
13. Genazzani AR, Fidecicchi T, Arduini D, Giannini A, Simoncini T. Hormonal and natural contraceptives: a review on efficacy and risks of different methods for an informed choice. Gynecol Endocrinol. 2023;39:2247093.
14. Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. Eur J Contracept Reprod Health Care. 2010;15:S19-31.
15. World Health Organization. Medical eligibility criteria for contraceptive use. Geneva: WHO; 2015.
16. Dominick SA, McLean MR, Whitcomb BW, Gorman JR, Mersereau JE, Bouknight JM, et al. Contraceptive Practices among female cancer survivors of reproductive age. Obstet Gynecol. 2015;126:498-507.
17. Hadnott TN, Stark SS, Medica A, Dietz AC, Martinez ME, Whitcomb BW, et al. Perceived infertility and contraceptive use in the female, reproductive-age cancer survivor. Fertil Steril. 2019;111:763-71.
18. Harris ML, Feyissa TR, Bowden NA, Gemzell-Danielsson K, Loxton D. Contraceptive use and contraceptive counselling interventions for women of reproductive age with cancer: a systematic review and meta-analysis. BMC Med. 2022;20:489.
19. Massarotti C, Lo Monaco L, Scaruffi P, Sozzi F, Remorgida V, Cagnacci A, et al. Contraception in cancer survivors: insights from oncofertility follow-up visits. Gynecol Endocrinol. 2021;37:166-70.
20. Medica AC, Stark SS, Hadnott TN, Dietz AC, Romero SAD, Natarajan L, et al. Use of emergency contraception among female young adult cancer survivors. Fertil Steril. 2018;109:1114-20.e1.
21. Sociedade Portuguesa da Contraceção. Consenso sobre contraceção 2020 [consultado 2024 dez 10]. Disponível em: https://spginecologia.pt/wp-content/uploads/2021/07/spg-consenso-sobre-contracepcao-2020.pdf.
22. Nguyen AT, Curtis KM, Tepper NK, Kortsmit K, Brittain AW, Snyder EM, et al. U.S. medical eligibility criteria for contraceptive use, 2024. MMWR Recomm Rep. 2024;73:1-126.
23. Gompel A, Ramirez I, Bitzer J. Contraception in cancer survivors - an expert review part I. Breast and gynaecological cancers. Eur J Contracept Reprod Health Care. 2019;24:167-74.
24. Zapata LB, Whiteman MK, Marchbanks PA, Curtis KM. Intrauterine device use among women with ovarian cancer: a systematic review. Contraception. 2010;82:38-40.
25. Ayhan A, Fagotti A, Gultekin M, Pakiz M, Querleu D, Reed N, Taskıran C, editors.Textbook of gynaecological oncology. Platinum edition. Ankara: Güneş Publishing; 2023.
26. Donohoe F, O'Meara Y, Roberts A, Comerford L, Kelly CM, Walshe JM, et al. Using menopausal hormone therapy after a cancer diagnosis in Ireland. Ir J Med Sci. 2023;192:45-55.
27. Dika E, Patrizi A, Lambertini M, Manuelpillai N, Fiorentino M, Altimari A, et al. Estrogen receptors and melanoma: a review. Cells. 2019;8:1463.
28. World Health Organization. WHO classification of tumours editorial board. Female genital tumors: WHO Classification of Tumours, 5th Edition, Volume 4. Lyon: International Agency for Research on Cancer; 2020.
29. Bodner K, Laubichler P, Kimberger O, Czerwenka K, Zeillinger R, Bodner-Adler B. Oestrogen and progesterone receptor expression in patients with adenocarcinoma of the uterine cervix and correlation with various clinicopathological parameters. Anticancer Res. 2010;30:1341-5.
30. Richardson A, Watson L, Persic M, Phillips A. Safety of hormone replacement therapy in women with a history of cervical adenocarcinoma. Post Reprod Health. 2021;27:167-73.
31. Lee SH, Cho YJ, Cho KJ, Ko MH, Jung SY, Chon SJ, et al. Effect of tibolone on the survival of early stage cervical adenocarcinoma patients. Obstet Gynecol Sci. 2018;61:584-9.
32. Motegi E, Hasegawa K, Kawai S, Kiuchi K, Kosaka N, Mochizuki Y, et al. Levonorgestrel-releasing intrauterine system placement for severe uterine cervical stenosis after conization: two case reports. J Med Case Rep. 2016;10:56.
33. Li X, Li J, Wu X. Incidence, risk factors and treatment of cervical stenosis after radical trachelectomy: a systematic review. Eur J Cancer. 2015;51:1751-9.
34. Nasu K, Narahara H. Management of severe cervical stenosis after conization by detention of nylon threads tied up to intrauterine contraceptive device. Arch Gynecol Obstet. 2010;281:887-9.
35. Novikova OV, Nosov VB, Panov VA, Novikova EG, Krasnopolskaya KV, Andreeva YY, et al. Live births and maintenance with levonorgestrel IUD improve disease-free survival after fertility-sparing treatment of atypical hyperplasia and early endometrial cancer. Gynecol Oncol. 2021;161:152-9.
36. Rousset-Jablonski C, Selle F, Adda-Herzog E, Planchamp F, Selleret L, Pomel C, et al. Fertility preservation, contraception and menopause hormone therapy in women treated for rare ovarian tumours: guidelines from the French national network dedicated to rare gynaecological cancers. Eur J Cancer. 2019;116:35-44.
37. Escobar J, Klimowicz AC, Dean M, Chu P, Nation JG, Nelson GS, et al. Quantification of ER/PR expression in ovarian low-grade serous carcinoma. Gynecol Oncol. 2013;128:371-6.
38. National Comprehensive Cancer Network. NCCN guidelines version 2.2024. Gestational trophoblastic neoplasia 2024 [consultado 2024 dez 10]. Disponível em: https://www.nccn.org/professionals/physician_gls/pdf/gtn.pdf.
39. Hagey JM, Drury KE, Kaplan S, Davidson BA, Morse JE. Contraceptive use following gestational trophoblastic disease: a systematic review. Contraception. 2024;137:110488.
40. Costa HL, Doyle P. Influence of oral contraceptives in the development of post-molar trophoblastic neoplasia--a systematic review. Gynecol Oncol. 2006;100:579-85.

A Propósito de um Caso de Síndrome Hipereosinofílica Idiopática Tratada com Mepolizumab

A Case of Idiopathic Hypereosinophilic Syndrome Treated with Mepolizumab

Palavras-chave: Anticorpos Monoclonais Humanizados; Síndrome Hipereosinofílica/tratamento farmacológico
Keywords: Antibodies, Monoclonal, Humanized; Hypereosinophilic Syndrome/drug therapy

Caro Editor,

A síndrome hipereosinofílica idiopática (SHEi) é uma doença rara caracterizada por eosinofilia mantida (≥ 1500 células/μL) no sangue periférico associada a lesão orgânica, sem uma causa identificável após exclusão de fatores secundários como atopia, neoplasias hematológicas ou sólidas, infeções e doenças autoimunes.[1,2] A eosinofilia classifica-se como ligeira (500 - 1500 células/μL), moderada (1500 - 5000 células/μL) ou grave (> 5000 células/μL) e pode causar disfunção multiorgânica devido à libertação de mediadores tóxicos pelos eosinófilos.[3]

Os autores descrevem o caso de uma doente de 72 anos com eosinofilia grave (5240 células/μL) e manifestações cutâneas persistentes, nomeadamente prurido crónico incapacitante. Foram excluídas causas secundárias de hipereosinofilia, nomeadamente neoplasias, doença autoimune e infeções, tendo sido estabelecido o diagnóstico de síndrome hipereosinofílica idiopática. A doente apresentou boa resposta clínica ao tratamento inicial com corticosteroides, contudo, pelos efeitos adversos associados (nomeadamente aumento ponderal, dislipidemia, hipertensão arterial e fratura patológica osteoporótica), foi iniciada terapêutica com azatioprina como alternativa poupadora de corticoides. No entanto, também se verificaram efeitos adversos significativos (alopecia, mal-estar geral, alterações do equilíbrio e da visão), que condicionaram a manutenção do tratamento. A introdução de mepolizumab – um anticorpo monoclonal dirigido contra a interleucina-5 (IL-5), citocina central na maturação, ativação e sobrevivência dos eosinófilos[4] – resultou numa redução significativa da contagem de eosinófilos e permitiu a diminuição progressiva e posterior suspensão dos corticosteroides, sem efeitos adversos adicionais.

Este caso ilustra os desafios associados ao diagnóstico e tratamento da SHEi. A sua apresentação clínica é frequentemente multissistémica e inespecífica, o que pode atrasar o diagnóstico.[1] Os corticosteroides e imunossupressores permanecem a terapêutica de primeira linha, mas os efeitos adversos limitam a sua utilização prolongada. O recurso a terapêuticas biológicas, como o mepolizumab, oferece uma alternativa segura e eficaz, sendo atualmente aprovado pela EMA e FDA para o tratamento da SHEi.[5] A terapêutica dirigida à fisiopatologia da doença representa um avanço importante, sobretudo em doentes com contraindicação ou intolerância às opções clássicas.

Este caso salienta a importância de considerar a SHEi no diagnóstico diferencial da eosinofilia persistente com envolvimento orgânico e salienta o papel crescente das terapêuticas biológicas na sua abordagem.

CONTRIBUTO DOS AUTORES

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

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REFERÊNCIAS

1. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017; 92:1243-59.
2. Shomali W, Gotlib J. World Health Organization and International Consensus Classification of eosinophilic disorders: 2024 update on diagnosis, risk stratification, and management. Am J Hematol. 2024;99:946-68.
3. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol. 2012; 130:607-12.e9.
4. Klion AD. How I treat hypereosinophilic syndromes. Blood. 2015;126:1069-77.
5. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab for the treatment of hypereosinophilic syndrome: a multicentre, double-blind, placebo-controlled, phase 3 trial. J Allergy Clin Immunol. 2020;146:1397-405.

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Anafilaxia a Gadobutrol: Uma Complicação Rara ao Contraste de Ressonância Magnética

Anaphylaxis to Gadobutrol: A Rare Complication of Magnetic Resonance Contrast Media

Palavras-chave: Anafilaxia; Compostos Organometálicos/efeitos adversos; Hipersensibilidade a Medicamentos/diagnóstico; Meios de Contraste/efeitos adversos; Ressonância Magnética
Keywords: Anaphylaxis; Contrast Media/adverse effects; Drug Hypersensitivity/diagnosis; Magnetic Resonance Imaging; Organometallic Compounds/adverse effects

O gadobutrol (Gadovist®) é um agente de contraste de tecidos que permite uma melhor caracterização de lesões e avaliar alterações de perfusão em ressonâncias magnéticas (RM).[1]

A maioria das reações que ocorrem são de hipersensibilidade tipo I/imediatas, com uma incidência estimada entre 0,004% e 0,7%.[2]

O diagnóstico baseia-se na história clínica, testes cutâneos e provas de provocação (TP). Assim, destaca-se a importância do uso de métodos complementares *in vitro*, como o teste de ativação de basófilos (TAB).

Uma mulher de 52 anos foi encaminhada para a consulta de Imunoalergologia após reação anafilática a agente de contraste. Tinha antecedentes de enxaqueca sem história de alergias.

Foi submetida a uma RM numa unidade de saúde privada, tendo sido utilizado gadobutrol 1,0 mmol/mL). Cerca de 40 minutos após a administração, apresentou prurido cutâneo generalizado, evoluindo para dispneia, cianose periférica e síncope. Foi tratada com duas administrações de adrenalina intramuscular (0,5 mL a 1 mg/mL, com intervalo de cinco minutos) por ausência de resposta completa à primeira dose, metilprednisolona 40 mg e cetirizina 10 mg IV, com melhoria sintomática.

Foi transferida para o serviço de urgência (SU) e manteve-se em vigilância, com continuação do tratamento com corticosteroide IV e anti-histamínico em SOS. Os resultados das colheitas seriadas de triptase foram compatíveis com anafilaxia.

Na consulta de Imunoalergologia, os testes cutâneos (por picada e intradérmicos) – com agentes de contraste, utilizando diluições de 1:10 e 1:100 com leituras efetuadas aos 15 e 20 minutos (recomendações da ENDA/EAACI) – foram negativos. Foi realizado TAB com gadobutrol, que revelou aumento da expressão de CD63, confirmando a resposta mediada por IgE (Tabela 1).

Assim, foi documentada a alergia, tendo a doente recebido recomendações de evicção de gadolínio.

Tabela 1 – Resultado dos testes diagnósticos

Exame	Resultado
Teste cutâneo por picada	Negativo
Teste intradérmico	Negativo
Teste de ativação de basófilos	Positivo (CD36)

O gadolínio é tóxico quando livre, pelo que os agentes de contraste (ACBG) contêm quelantes para formar complexos estáveis. Estes podem ser lineares ou macrocíclicos, iónicos ou não-iónicos, influenciando o risco de reações. A estrutura do quelante influencia o risco de hipersensibilidade: agentes lineares tendem a ser menos estáveis e mais propensos à dissociação do gadolínio, podendo aumentar a imunogenicidade. Por outro lado, agentes macrocíclicos, como o gadobutrol, são geralmente mais estáveis e menos reativos.[3] Ainda assim, mesmo estes podem desencadear reações tipo I mediadas por IgE.

A maioria das reações adversas a ACBG são leves (náuseas, cefaleias, mialgias), mas também ocorrem síncopes vasovagais que simulam alergias.[3]

As reações de hipersensibilidade podem ser:

- Imediatas (tipo I): urticária, angioedema, broncoespasmo, anafilaxia.
- Não-imediatas (tipo IVb): exantema maculopapular, toxidermias, vasculites.[4]

O caso descrito corresponde a reação tipo I. A realização de estudo imunoalergológico, com testes cutâneos e TAB permitiu confirmar alergia a gadobutrol. O TP, sendo o *gold-standard*, está contraindicado em casos de anafilaxia prévia.[2] O TAB representa uma alternativa segura e útil nestes contextos, permitindo demonstrar ativação basofílica mediada por IgE com menor risco para o doente.[5]

Este caso realça a importância da consideração de reações alérgicas a gadolínio em contexto de ressonância magnética. Destaca-se o valor do TAB como alternativa segura na confirmação diagnóstica, especialmente quando TP está contraindicado. O encaminhamento precoce para imunoalergologia é essencial.

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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REFERÊNCIAS

1. Qu H, Li W, Wu Z, Zeng C, Yan H, Fang X, et al. Differences in hypersensitivity reactions and gadolinium deposition disease/symptoms associated with gadolinium exposure to gadolinium-based contrast agents: new insights based on global databases VigiBase, FAERS, and IQVIA-MIDAS. BMC Med. 2024;22:329.
2. Cabrera CM, Clarcast M, Palacios-Cañas A. Clinical validation of the basophil activation test in immediate hypersensitivity reactions to gadolinium-based contrast agents. Int Immunopharmacol. 2023;117:110000.
3. Weinreb JC, Rodby RA, Yee J, Wang CL, Fine D, McDonald RJ, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Kidney Med. 2021;3:142-150.
4. Jutel M, Agache I, Zemelka-Wiacek M, Akdis M, Chivato T, del Giacco S, et al. Nomenclature of allergic diseases and hypersensitivity reactions: adapted to modern needs: an EAACI position paper. Allergy. 2023;78:2851-74.
5. Gracia Bara MT, Gallardo-Higueras A, Moreno EM, Laffond E, Muñoz Bellido FJ, Martin C, et al. Hypersensitivity to gadolinium-based contrast media. Front Allergy. 2022;3:813927.

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Carta ao Editor em Resposta ao Artigo: "A Reconciliação da Medicação nos Cuidados de Saúde Primários: Práticas, Conhecimentos e Atitudes na Região de Saúde de Lisboa e Vale do Tejo"

Letter to the Editor Replying to the Article: "Medication Reconciliation in Primary Care: Practices, Knowledge and Attitudes in the Lisbon and Tagus Valley Health Region"

Palavras-chave: Cuidados Centrados no Doente; Cuidados de Saúde Primários; Erros de Medicação/prevenção e controlo; Portugal; Reconciliação Terapêutica
Keywords: Medication Errors/prevention & control; Medication Reconciliation; Patient-Centered Care; Portugal; Primary Health Care

Exm.º Editor,

A leitura do artigo intitulado "A Reconciliação Terapêutica da Medicação nos Cuidados de Saúde Primários: Práticas, Conhecimentos e Atitudes na Região de Saúde de Lisboa e Vale do Tejo"[1] permite-nos refletir sobre o panorama da reconciliação terapêutica nos Cuidados de Saúde Primários (CSP). Embora seja um processo essencial para garantir a continuidade dos cuidados e a segurança dos utentes, o estudo realizado revela que, na região de Lisboa e Vale do Tejo, apenas uma em cada quatro unidades de CSP possui um procedimento formal de reconciliação da medicação.

Este cenário reforça a urgência de uma abordagem padronizada, mas adaptada localmente, conforme recomendado pela Organização Mundial da Saúde (OMS).[2] A criação de diretrizes nacionais claras e a monitorização contínua são essenciais para garantir a uniformidade e a eficácia da reconciliação terapêutica em todas as unidades de CSP, especialmente considerando as disparidades regionais.

A baixa taxa de resposta dos médicos de família (12%) e das unidades de CSP (31%) limita a representatividade dos resultados e aponta para a necessidade de estratégias que incentivem uma maior participação. O estudo não explora as causas da baixa adesão, como a sobrecarga assistencial e a resistência à mudança entre profissionais. Compreender estas barreiras permitirá direcionar futuras iniciativas.

Segundo Salanitro AH *et al*, no estudo MARQUIS, a comunicação entre os diversos níveis de cuidados também se apresenta como uma barreira significativa. Plataformas digitais entre hospitais e CSP, com validação da medicação alertas e atualização automática do plano terapêutico, poderiam mitigar esta lacuna. Um guia de medicação prolongada em papel poderá reforçar a ligação entre consultas.[3-5]

Nos CSP, a criação de uma consulta pós-alta hospitalar que integre eficazmente a informação da nota de alta e as alterações terapêuticas, adaptando-se aos recursos de cada unidade de saúde, constituiria um pilar fundamental. É igualmente imperativo que a reconciliação terapêutica seja encarada como um processo holístico, envolvendo as diversas especialidades médicas.[5]

A maioria dos médicos de família (69,8%) considera a reconciliação terapêutica um ato médico, sustentado no raciocínio clínico e na continuidade assistencial.[1] O potencial contributo dos farmacêuticos na monitorização da medicação crónica exige uma definição clara de papéis e colaboração interprofissional para um processo seguro e centrado no doente.

Em conclusão, a padronização dos processos, a melhoria da comunicação e a formação multidisciplinar são fundamentais neste processo. Para acelerar a implementação de práticas seguras e eficazes recomenda-se a realização de estudos qualitativos, com a perspetiva dos utentes, e a integração de novos sistemas de informação.

CONTRIBUTO DOS AUTORES

Todas as autoras contribuíram igualmente para este manuscrito e aprovaram a versão final a ser publicada.

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

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REFERÊNCIAS

1. Ascenção R, Almeida M, Ribeiro C, Broeiro P, Costa J. A reconciliação da medicação nos cuidados de saúde primários: práticas, conhecimentos e atitudes na região de saúde de Lisboa e Vale do Tejo. Acta Med Port. 2025;38:5-15.
2. Mondul A, Kong M. Medication error. In: Agrawal A, Bhatt J, editors. Patient safety: a case-based innovative playbook for safer care. 2nd edition. New York: Springer; 2023. p.151-64.
3. Mueller SK, Kripalani S, Stein J, Kaboli P, Wetterneck TB, Salanitro AH, et al. A toolkit to disseminate best practices in inpatient medication reconciliation: Multi-center medication reconciliation quality improvement study (MARQUIS). Jt Comm J Qual Patient Saf. 2013;39:371-82.
4. Salanitro AH, Kripalani S, Resnic J, Mueller SK, Wetterneck TB, Haynes KT, et al. Rationale and design of the multicenter medication reconciliation quality improvement study (MARQUIS). BMC Health Serv Res. 2013;13:1.
5. de Sousa AC. View of medication reconciliation: a complex process. Gaz Med. 2022;9:240-3.

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Colonic Chagas Disease in Portugal: A Key Differential Diagnosis in Non-Endemic Areas

Doença de Chagas com Envolvimento Cólico em Portugal: Diagnóstico Diferencial Chave em Região Não Endémica

Keywords: Chagas Disease/diagnosis; Colon; Portugal
Palavras-chave: Doença de Chagas/diagnóstico; Colon; Portugal

Dear Editor,

Chagas disease has an uncertain prevalence in Europe, often being underdiagnosed. It is caused by *Trypanosoma cruzi* protozoan, affects approximately 12 million people worldwide, and can lead to cardiac, esophageal, and colonic complications during the chronic phase. In Portugal, there are 1255 cases of people infected with *T. cruzi* according to a prevalence study conducted by the World Health Organization,[1] but only eight cases have been confirmed by serological tests, corresponding to an underdiagnosis rate of 99.4%.[2] Transmission occurs through vectors of the Triatominae, blood transfusions, organ transplants, ingestion of contaminated food and congenital transmission.[3]

Although acute infection is typically asymptomatic in most individuals, approximately 5% develop a mononucleosis-like syndrome. In the chronic phase, approximately 20% of patients develop cardiac involvement and 10% gastrointestinal involvement. In the intestinal form, the parasite leads to destruction of the myenteric plexus, causing progressive intestinal stasis, which may result in fecaloma and abdominal distension.[4] The most common complications include intestinal perforation and volvulus.[5]

At our hospital, Unidade Local Saúde de Santa Maria, in Lisbon, Portugal, we received a 64-year-old Brazilian male patient who was referred due to a two-year history of constipation, unresponsive to optimal medical therapy. He reported evacuation every seven to 10 days, increasing abdominal pain over the previous two weeks, without associated nausea or vomiting. He had been living in Portugal for 23 years and was diagnosed with Chagas disease 27 years before in Brazil, where he underwent a laparoscopic Heller cardiomyotomy for megaesophagus.

Therefore, an intestinal transit test revealed adequate barium progression through the small intestine, but after four hours, the contrast remained in the distal ileum and had not reached the proximal colon. The findings of esophageal dilation with decreased propulsive wave and decreased distensibility and rigidity of the proximal stomach were compatible with the patient's surgical history.

The patient was observed by a surgeon and was electively admitted to the Colorectal Unit and a subtotal proctocolectomy with a side-to-end mechanical ileorectal anastomosis and an ileostomy diversion was performed.

The histopathological examination confirmed Chagas disease involving the colon, with evidence of plexitis and reduced number of ganglion cells in a 132 cm colectomy specimen, which included 10 cm of ileum (Fig. 1).

The diagnosis of colon involvement in Chagas disease is primarily clinical and is important to consider as a potential differential diagnosis, particularly given the increasing immigration to Portugal from Latin America. However, the lack of screening programs and limited access to diagnostic and treatment services in Europe remain significant barriers to proper disease management.

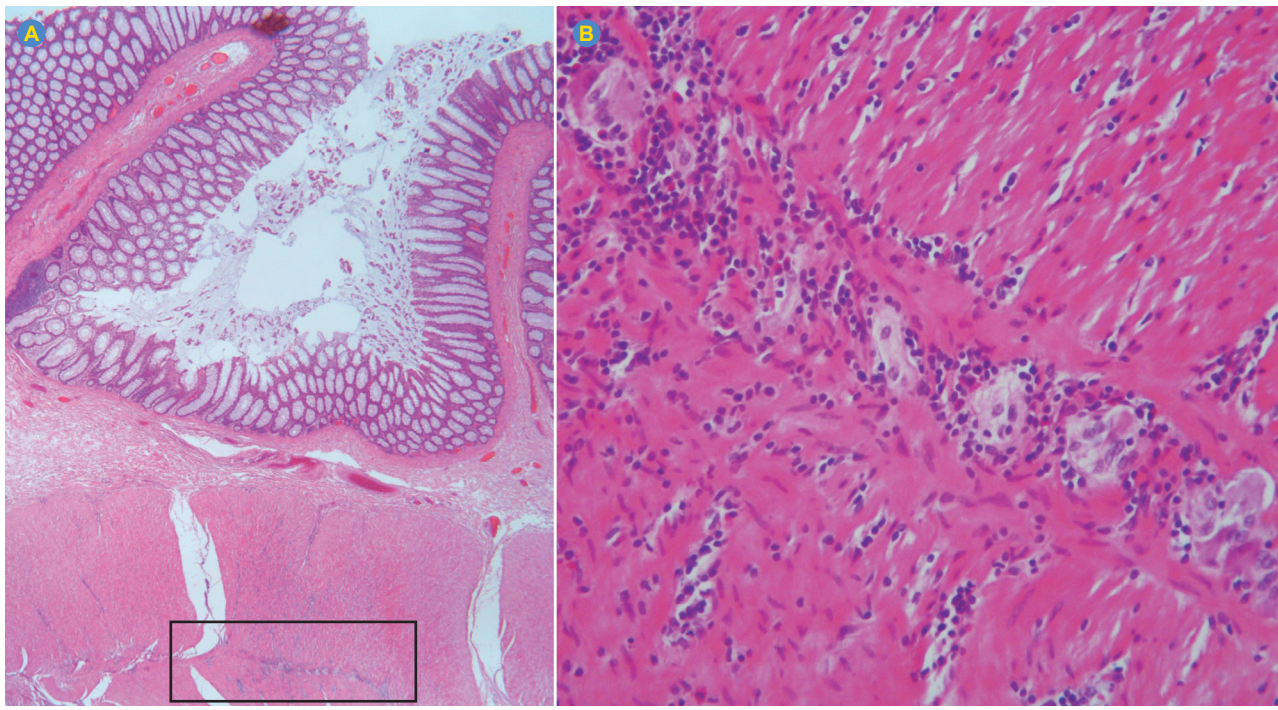

Figure 1 – Colon wall with foci of plexitis in myenteric plexus and diminished number of ganglion cells in myenteric plexus (left image, inlet, H&E 20x) (A). Chronic inflammatory infiltrate surrounding ganglion cells (H&E, 200x) (B).

AUTHOR CONTRIBUTIONS

EG: Literature review, data collection, writing of the manuscript.

EB: Study design, data acquisition, writing and critical review of the manuscript.

PR, CF: Critical review of the manuscript.

CQ: Data analysis and interpretation, critical review of the manuscript.

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PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. Basile L, Jansà JM, Carlier Y, Salamanca DD, Angheben A, Bartoloni, A et al. Chagas disease in European countries: the challenge of a surveillance system. Euro Surveill. 2011;16:19968.
2. Cortez J, Ramos E, Valente C, Seixas J, Vieira A. A expressão global da doença de chagas - oportunidades emergentes e impacto em Portugal. Acta Med Port. 2012;25:332-9.
3. Bern C. Chagas' disease. N Engl J Med. 2015;373:456-66.
4. Meneghelli UG. Chagasic enteropathy. Rev Soc Bras Med Trop. 2004;37:252-60.
5. Oliveira ÊC, Silveira ABM, Luquetti AO. Gastrointestinal chagas disease. In: Altcheh J, Freilij H, editors. Chagas disease. Cham: Springer; 2019. p. 217-32.

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Enhancing Postpartum Care in Gestational Diabetes: A Call for Preventive Action

Melhorar os Cuidados Pós-parto na Diabetes Gestacional: Um Apelo à Ação Preventiva

Keywords: Diabetes Mellitus/diagnosis; Diabetes, Gestational; Postpartum Period
Palavras-chave: Diabetes Gestacional; Diabetes Mellitus/diagnóstico; Período Pós-Parto

Dear Editor,

We read with particular interest the article entitled "Gestational Diabetes – Postpartum Screening", published in 2012 in your esteemed journal, which assessed the prevalence of women with gestational diabetes who underwent postpartum screening and explored its association with maternal characteristics. Among the results presented, we were especially struck by the fact that approximately one-quarter of the women did not undergo postpartum screening. Furthermore, among those who did, 19.3% showed abnormal results, which were significantly associated with higher maternal age and body mass index.[1]

Gestational diabetes *mellitus* (GDM) has shown a concerning upward trend over the past decade. In Portugal, the 2018 National Diabetes Observatory report estimated a prevalence of 8.8%,[2] which is twice what was reported in 2010 (4.4%). While changes in diagnostic criteria have undeniably contributed to this variation, demographic shifts in the obstetric population, particularly older maternal age and rising obesity rates, are also key contributing factors.[3]

More recent data, reported by Almeida *et al* suggest a gradual decrease in the percentage of women with abnormal results on the reclassification test (from 18.5% in the period 2003 - 2010 to 8.7% in 2017 - 2020). However, this improvement is offset by a growing percentage of women who do not undergo postpartum testing at all, rising to 37.3% in the latest period analyzed (2017 - 2020).[3]

Given these findings, what role can we, as family physicians, play to reverse this scenario?

First and foremost, we believe it is imperative to invest in preventive strategies, particularly by raising awareness of the importance of having a healthy body mass index, which may require lifestyle modifications, among women planning for pregnancy. Second, enhancing communication and coordination between primary and secondary care is essential to ensure that the reclassification test is completed. Finally, we believe it is worth considering the introduction of routine follow-up consultations for women with a history of gestational diabetes: either to monitor and manage cases with abnormal reclassification results, or, when the results are normal, to ensure these women receive annual fasting plasma glucose testing as recommended.[4]

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Carocha A, Rijo C, Amaral N, Aleixo F, Rocha T. Diabetes gestacional – rastreio pós-parto. Acta Med Port. 2012;25:165-8.
2. Sociedade Portuguesa de Diabetologia. Diabetes: factos e números – o ano de 2016, 2017 e 2018. Relatório anual do Observatório Nacional da Diabetes. 2019. [cited 2025 Apr 16]. Available from: https://www.spd.pt/images/uploads/20210304-200808/DF&N-2019_Final.pdf.
3. Almeida M, Ruas L. Registo nacional de diabetes gestacional: um caminho de 18 anos. Rev Port Diabetes. 2022;17:54-62.
4. Almeida M, Dores J, Ruas L. Consenso diabetes gestacional: atualização 2017. Rev Port Diabetes. 2017;12:24-38.

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Atrial Fibrillation Patterns on Ambulatory Electrocardiogram Monitoring and Risk of Stroke

Padrões de Fibrilhação Auricular na Monitorização Ambulatória do Eletrocardiograma e Risco de Acidente Vascular Cerebral

Keywords: Atrial Fibrillation; Electrocardiography, Ambulatory; Risk Assessment; Stroke
Palavras-chave: Acidente Vascular Cerebral; Avaliação de Risco; Eletrocardiografia Ambulatorial; Fibrilhação Auricular

Atrial fibrillation (AF) is a common rhythm disorder characterized by disorganized atrial activity and irregular ventricular contractions. On electrocardiogram (ECG), it presents as absent P waves, visible fibrillatory waves (f-waves), and irregular QRS complexes.

In ambulatory ECG monitoring, AF may either be present throughout the entire monitoring period or occur intermittently with sinus rhythm. The minimum duration required for an AF diagnosis on such devices is not clearly defined, although 30 seconds of AF-like activity is widely accepted.[1] Frederiksson *et al* defined episodes of AF-like activity with ≥ 5 consecutive supraventricular beats (SVB) with tachycardia lasting < 30 s as micro-AF.[2] Controversially, Berge *et al* proposed the lower threshold of ≥ 3 consecutive SVB.[3] However, the question arises: how should AF-like activity for < 3 consecutive SVB be classified? Is it correct to label such activity as SVB or should it be classified as distinct ultra-short episode AF? Yamada *et al* suggested calling ectopic SVB episodes < 5 s in duration short-run atrial tachyarrhythmia.[4] The diagnosis becomes challenging in patients with rapid ventricular response, where f-waves may be seen poorly. However, in patients with slow ventricular response, f-waves may be visible between or after QRS complexes, supporting a diagnosis of ultra-short AF.[5]

Based on the longest AF episode duration, the following patterns (Fig. 1) may be defined:

1. Ultra-short AF (< 3 consecutive SVB with obvious f-waves and absent P waves);
2. Micro-AF (≥ 3 consecutive SVB with AF-like activity lasting < 30 s);
3. Episodic AF (AF-like activity lasting > 30 s with at least one sinus rhythm episode);
4. Incessant AF (AF-like activity throughout the monitoring period with no sinus rhythm episode).

This classification should not be confused with paroxysmal, persistent, and permanent AF according to the 2024 European Society of Cardiology Guidelines for the management of atrial fibrillation.[1] These patterns reflect only the longest AF episode recorded on ambulatory ECG. Ultra-short, micro-, episodic, and incessant AF can occur in both paroxysmal and persistent AF. In permanent AF, only incessant AF is observed.

It is known that oral anticoagulants reduce stroke risk in AF.[1] A few studies have shown that micro-AF is associated with undiagnosed AF and an increased risk of major adverse cardiovascular events.[2,3] Even episodes of SVB lasting < 5 s are associated with increased stroke risk.[4] So, ultra-short AF should be distinguished as a distinct pattern, as it does not meet micro-AF criteria and there may be an underestimation of stroke risk if it is considered as just supraventricular beats.

AUTHOR CONTRIBUTIONS

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

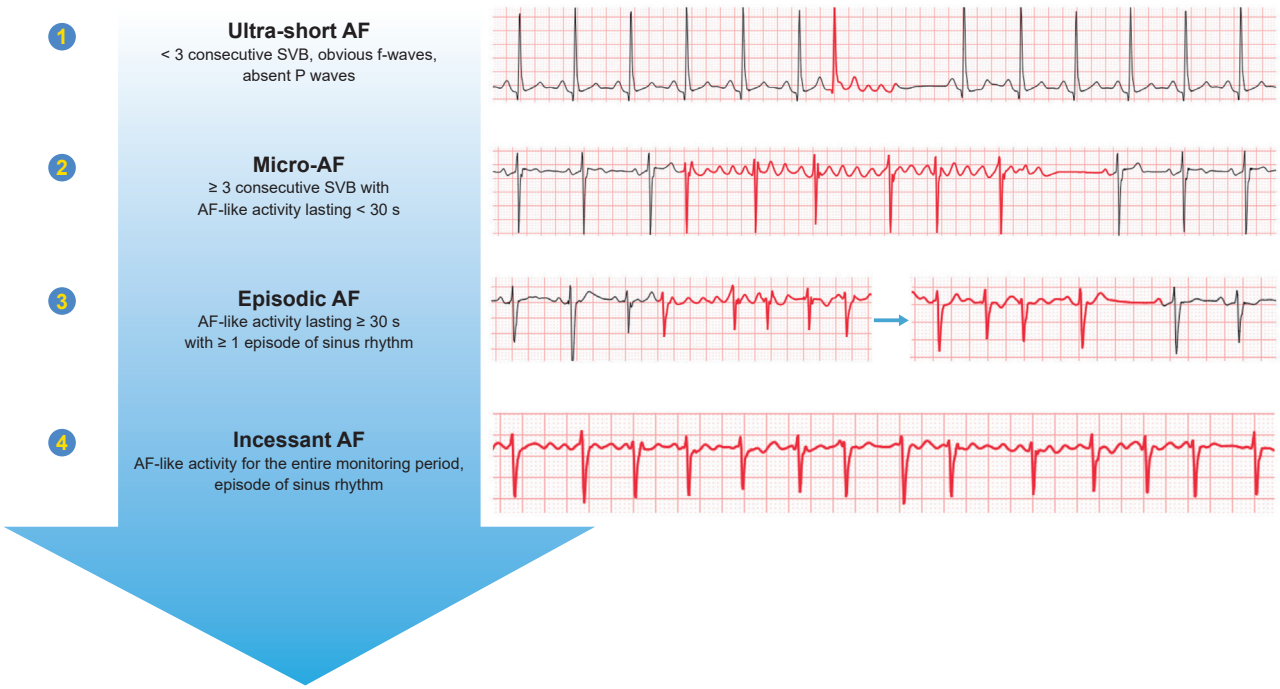

Figure 1 – Patterns of atrial fibrillation on ambulatory ECG monitoring

IV, YV: Study design, writing of the manuscript.
RD: Writing of the manuscript.
PZ: Critical review of the manuscript.
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REFERENCES

1. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Harry, et al. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024;45.3314-414.
2. Fredriksson T, Gudmundsdottir KK, Frykman V, Friberg L, Al-Khalili F, Engdahl J, et al. Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: a prospective cohort study. BMC Cardiovasc Disord. 2020;20:167.
31. Berge T, Myhre PL, Kalstad AA, Laake K, Tveit SH, Onarheim S, et al. Screen-detected atrial fibrillation and "micro-atrial fibrillation" and risk of cardiovascular events after myocardial infarction in elderly patients. Cardiology. 2022;148:72-7.
4. Yamada S, Lin CY, Chang SL, Chao TF, Lin YJ, Lo LW, et al. Risk of stroke in patients with short-run atrial tachyarrhythmia. Stroke. 2017;48:3232-8.
5. Skakun O, Symchych A, Symchych K. Ultra-short atrial fibrillation episodes: a case report. Texila Int J Publ Health. 2025;13.

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Acute Gastroenteritis Hospitalizations in Children with and without Risk Factors: Reflections on Rotavirus Vaccination in Portugal

Internamentos por Gastroenterite Aguda em Crianças com e sem Fatores de Risco: Reflexão sobre a Vacinação contra o Rotavírus em Portugal

Keywords: Child; Gastroenteritis; Hospitalization; Risk Factors; Rotavirus Infections; Rotavirus Vaccines; Rotavirus; Vaccination
Palavras-chave: Criança; Fatores de Risco; Gastroenterite; Hospitalização; Infecções por Rotavirus; Rotavírus; Vacinação; Vacinas contra Rotavirus

Dear Editor,

We are writing in response to the article by Lucaccioni *et al*, "Burden and Trends of Severe Rotavirus Infections and All-Cause Acute Gastroenteritis Hospital Episodes in Children Under Five Years Old in Mainland Portugal," published in 2021, to offer additional insights.[1] This paper provides valuable data as the first nationwide analysis of rotavirus (RV) and gastroenteritis (AGE) hospital episodes in children under five years old in Portugal. The study is particularly relevant given the introduction of RV vaccination into the National Immunization Program in October 2021, targeting children with specific risk factors.[2]

While a vaccination strategy targeting high-risk groups is considered cost-effective in low RV prevalence settings,[3] there is a lack of literature on the impact of high-risk groups on RV burden in Portugal.

To address this, we conducted a retrospective analysis, using the same administrative database from the Central Authority for Health Systems as Lucaccioni *et al*, extending the period from 2000 to 2017. We aimed to characterize AGE hospitalizations in children under five years of age according to the presence or absence of risk factors defined by national RV vaccination guidelines. Direct costs per hospitalization were estimated using a diagnosis-related groups model, aligned with the Portuguese National Health Service reimbursement system.[4]

We identified 47 326 hospitalizations (6.6% of all hospitalizations in this age group), with at least one risk factor identified in 2.7% of cases. Children with risk factors were more frequently diagnosed with RV infection, had higher rates of complications (shock/sepsis, ventilation), and experienced a four-fold longer hospital stay, with a 22-fold higher mortality rate. Estimated mean hospitalization costs more than doubled in this group (€2912.15 *vs* €1217.99, $p < 0.001$). Total direct costs over the 18 years reached €59.7 million.

The Portuguese and European Societies of Pediatrics and Pediatric Infectious Diseases,[5,6] along with the World Health Organization,[7] advocate for universal vaccination, as specific high-risk groups for severe RV AGE cannot be clearly defined.[6] Although these patients experience disproportionately severe outcomes and incur higher healthcare costs, they comprise a minority of AGE hospitalizations. Universal vaccination could offer broader protection and reduce overall hospitalizations. However, its cost-effectiveness must be carefully weighed, particularly in countries like Portugal where severe outcomes are relatively infrequent.[3] Our findings provide data crucial for evaluating the current national strategy of vaccination, focused on high-risk groups.

AUTHOR CONTRIBUTIONS

LLA: Data collection and analysis, literature review, writing of the manuscript.

RL, IA: Critical review of the manuscript.

AF: Data collection and analysis, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

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REFERENCES

1. Lucaccioni H, Machado RS. Burden and trends of severe rotavirus infections and all cause acute gastroenteritis hospital episodes in children under five years old in mainland Portugal. Acta Med Port. 2021;34:669-76.
2. Direção-Geral da Saúde. Programa nacional de vacinação 2020: vacinação contra gastroenterite por rotavírus de crianças pertencentes a grupos de risco. 2021. [cited 2022 Jan 10]. Available from: https://www.dgs.pt/normas-orientacoes-e-informacoes/normas-e-circulares-normativas/norma-n-0072021-de-15102021-pdf.aspx.
3. Bruijning-Verhagen P, van Dongen JA, Verberk JD, Pijnacker R, van Gaalen RD, Klinkenberg D, et al. Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting. BMC Med. 2018;16:168.
4. Portugal. Portaria 839A-2009. Diário da República, I Série, n.º 147/2009 (2009/07/31). p. 4978(2)-(124).
5. Comissão de Vacinas da Sociedade de Infeciologia Pediátrica (SIP) e Sociedade Portuguesa de Pediatria (SPP). Recomendações sobre vacinas extra programa nacional de Vacinação. 2020. [2020 Sep 24].

Available from: https://www.spp.pt/UserFiles/file/Comissao_de_Vacinas/Recomendacoes%20vacina%20pneumococcica%20versao%20final.pdf.
6. Dornbusch HJ, Vesikari T, Guarino A, LoVecchio A, Hadjipanayis A, Koletzko B. Rotavirus vaccination for all children or subgroups only? Comment of the European Academy of Paediatrics (EAP) and the European Society for Paediatric Infectious Diseases (ESPID) recommendation group for rotavirus vaccination. Eur J Pediatr. 2020;179:1489-93.
7. World Health Organization. Rotavirus vaccines. Wkly Epidemiol Rec.2021;28:301-20.

Table 1 – Characteristics of hospitalized patients with acute gastroenteritis, with and without risk factors, between 2000 and 2017

	With risk factors	Without risk factors	*p*-value
Total hospitalizations for AGE, n (%)	1283 (2.7%)	46 043 (97.3%)	
Age, n (%)			< 0.001
0 - 6 months	392 (30.6%)	7864 (17.1%)	
6 - 12 months	251 (19.6%)	10 092 (21.9%)	
12 - 24 months	293 (22.8%)	12 892 (28.0%)	
24 - 36 months	149 (11.6%)	6920 (15.0%)	
36 - 48 months	115 (9.0%)	4570 (9.9%)	
48 - 60 months	83 (6.5%)	3705 (8.0%)	
Sex, n (%)			0.988
Male	712 (55.4%)	25 561 (55.4%)	
Female	571 (44.5%)	20 482 (44.5%)	
Hospital Location (NUTS2), n (%)			< 0.001
North	438 (34.1%)	18 819 (40.9%)	
Center	273 (21.3%)	10 225 (22.2%)	
Lisbon	503 (39.2%)	13 786 (29.9%)	
Alentejo	53 (4.1%)	2535 (5.5%)	
Algarve	16 (1.2%)	678 (1.5%)	
Etiology, n (%)			< 0.001
Viral	649 (50.6%)	19 548 (42.5%)	
Rotavirus	389 (30.3%)	10 486 (22.8%)	
Bacterial	113 (8.8%)	6499 (14.1%)	
Parasitic	22 (1.7%)	199 (0.4%)	
Unspecified	512 (39.9%)	20 062 (43.6%)	
Length of stay			< 0.001
Mean ± SD (days)	16.7 ± 49.5	4.1 ± 8.9	
Median [IQR] (days)	6 [3 - 13]	3 [2 - 5]	
Hospital mortality, n (%)	14 (1.1%)	24 (0.05%)	< 0.001
Complications			
Shock/sepsis	31 (2.4%)	149 (0.3%)	< 0.001
Ventilation	80 (6.2%)	145 (0.3%)	< 0.001
Estimated costs (DRG)			< 0.001
Mean ± SD (euros)	€2912.15 ± €5743.87	€1217.99 ± €1643.47	
Median [IQR] (euros)	€1552.29 [€1018.17 - 2533.32]	€964.97 [€964.97 - 1166.73]	

Data are presented as numbers and percentages (n, %) or as means with standard deviations (Mean ± SD). Median and interquartile ranges (IQR) are also reported where applicable. Statistical significance was determined using p-values, which correspond to chi-square tests comparing the overall distribution between groups across all subcategories.
AGE: acute gastroenteritis; DRG: diagnosis-related groups; IQR: interquartile range; NUTS2: nomenclature of territorial units for statistics level 2; SD: standard deviation.

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Apoio ao Artigo "A Medicina pela Paz: Imperativo Ético e Profissional"

Support to the Article "Medicine for Peace: An Ethical and Professional Imperative"

Palavras-chave: Conflitos Armados; Ética Médica; Médicos/ética; Prestação de Cuidados de Saúde; Responsabilidade Social; Saúde Global
Keywords: Armed Conflicts; Delivery of Health Care; Ethics, Medical; Global Health; Physicians/ethics; Social Responsibility

Prezado Editor,

Após a publicação *online* do artigo "Medicina pela Paz: Um Imperativo Ético e Profissional",[1] várias sociedades, associações e sindicatos médicos subscreveram a sua mensagem, que enfatiza o amplo consenso e a forte aceitação que essa posição gerou.

A comunidade médica global tem testemunhado um aumento alarmante do número de violações das leis internacionais, com ataques deliberados a civis, médicos, outros profissionais de saúde e hospitais, juntamente com a proliferação inquietante de armas, incluindo armas nucleares. Estas questões constituem, há muito, uma profunda preocupação para os médicos em Portugal e continuam a estar no cerne das nossas responsabilidades profissionais e éticas.

As sociedades científicas, associações médicas e sindicatos médicos abaixo assinados (Fig. 1), ao darem o seu apoio, procuram não só reforçar a mensagem transmitida no artigo, mas também destacar o compromisso coletivo dos médicos portugueses em defender os valores humanitários, promover a paz e defender o humanismo e a integridade da prática médica, mesmo em tempos de conflito.

Acreditamos que esta declaração conjunta irá sublinhar o amplo reconhecimento profissional das preocupações levantadas e contribuir para um maior diálogo e ação em toda a comunidade internacional.

- Associação dos Médicos Auditores e Codificadores Clínicos
- Associação dos Médicos Estomatologistas Portugueses (AMEP)
- Associação Nacional de Estudantes de Medicina (ANEM)
- Associação Nacional de Médicos de Saúde Pública (ANMSP)
- Associação Portuguesa de Avaliação do Dano Corporal
- Associação Portuguesa de Diagnóstico Pré-Natal
- Associação Portuguesa de Medicina Geral e Familiar (APMGF)

Figura 1 – Entidades que subscreveram a mensagem

- Associação Portuguesa de Urologia
- Associação Portuguesa para o Estudo Clínico da SIDA (APECS)
- Associação Portuguesa para o Estudo da Dor
- Associação Portuguesa para o Estudo do Fígado
- Faculdade de Medicina da Universidade de Coimbra
- Federação Nacional dos Médicos (FNAM)
- NOVA Medical School, Universidade NOVA Lisboa
- Sindicato Independente dos Médicos (SIM)
- Sociedade de Cuidados Intensivos Pediátricos
- Sociedade Portuguesa Da Medicina da Reprodução
- Sociedade Portuguesa de Alergologia e Imunologia Clínica (SPAIC)
- Sociedade Portuguesa de Anatomia Patológica
- Sociedade Portuguesa de Anestesiologia
- Sociedade Portuguesa de Angiologia e Cirurgia Vascular
- Sociedade Portuguesa de Aterosclerose
- Sociedade Portuguesa de Cardiologia
- Sociedade Portuguesa de Cefaleias
- Sociedade Portuguesa de Ciências da Nutrição e Alimentação
- Sociedade Portuguesa de Cirurgia
- Sociedade Portuguesa de Cirurgia Cardíaca, Torácica e Vascular
- Sociedade Portuguesa de Cirurgia Plástica, Reconstrutiva e Estética
- Sociedade Portuguesa de Cirurgia Robótica
- Sociedade Portuguesa de Dermatovenereologia
- Sociedade Portuguesa de Diabetologia
- Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo
- Sociedade Portuguesa de Gastrenterologia
- Sociedade Portuguesa de Genética Humana
- Sociedade Portuguesa de Ginecologia
- Sociedade Portuguesa de Hipertensão
- Sociedade Portuguesa de Medicina de Urgência e Emergência
- Sociedade Portuguesa de Medicina do Trabalho
- Sociedade Portuguesa de Medicina do Viajante
- Sociedade Portuguesa de Medicina Estética e Cosmética
- Sociedade Portuguesa de Medicina Física e de Reabilitação
- Sociedade Portuguesa de Medicina Interna
- Sociedade Portuguesa de Nefrologia
- Sociedade Portuguesa de Neuropediatria
- Sociedade Portuguesa de Neurorradiologia
- Sociedade Portuguesa de Oftalmologia
- Sociedade Portuguesa de Ortopedia e Traumatologia (SPOT)
- Sociedade Portuguesa de Ortopedia Pediátrica (SPOP)
- Sociedade Portuguesa de Patologia Clínica
- Sociedade Portuguesa de Pediatria
- Sociedade Portuguesa de Radiologia e Medicina Nuclear

CONFLITOS DE INTERESSE

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

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REFERÊNCIAS

1. Cortes C. A medicina pela paz: imperativo ético e profissional. Acta Med Port. 2025;38:519-20.

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