

# EMJ

Rare Disease Issue

Review  
of the European  
Conference on  
Rare Diseases  
2022

**Editor's Pick**

Measuring the Impact of  
the COVID-19 Pandemic  
on Diagnostic Delay in  
Rare Disease

**Interview**

Yann Le Cam

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EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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EMJ is distributed through controlled circulation to healthcare professionals in the relevant fields across Europe.

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EMJ is indexed on DOAJ, the Royal Society of Medicine, and Google Scholar®; selected articles are indexed in PubMed Central®.

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## This Publication

ISSN 2397-6764

EMJ is published **once** a year. For subscription details please visit: [www.emjreviews.com](http://www.emjreviews.com)

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*Koutsouki*

**Evgenia Koutsouki**

Editor

Welcome to our third issue of the EMJ flagship for 2023, which focuses on rare diseases. Our team attended the European Conference on Rare Diseases (ECRD) at the end of June, and we are delighted to bring you the highlights from the event. The ECRD saw patients, clinicians, policy makers, and other key stakeholders come together to enable innovation and help drive rare disease policies across Europe.

Our ECRD coverage includes an interview with Yann Le Cam, Chief Executive Officer at EURORDIS, in which he discusses the progress and ongoing challenges for patients with rare diseases. We have also chosen to cover two of the sessions from the ECRD, which discuss the impact of disease invisibility on equality for people with rare diseases and diagnostics, respectively.

As part of the issue on rare diseases, we have included a selection of articles on rare diseases. Our Editor's Pick discusses the impact of the COVID-19 pandemic on diagnostic delay in rare disease. This article examines the evidence on how the pandemic affected primary care, referrals, and diagnostic services for people with rare diseases, among other factors, and makes recommendations based on these findings.

I would like to take this opportunity to thank the organisers of ECRD for putting together such a great event, and for giving the EMJ team the opportunity to attend and cover the conference. A big thank you also goes out to our authors, reviewers and editorial board for helping us deliver this high-quality content.

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# Foreword

Dear Colleagues,

It is my pleasure to present the latest issue of *EMJ*, which is, as ever, filled with a great deal of excellent content. The newest addition to the EMJ family of flagship journals takes rare diseases as its general focus, and includes coverage of the European Conference on Rare Diseases (ECRD 2022). The ECRD congress took place entirely online this year, bringing together experts from around the world, and discussing the three “visionary goals” of the association. These aim to make life better for patients with rare diseases through promoting wellbeing, reducing inequality, and improving industry, innovation, and infrastructure.

My Editor’s Pick for this issue is a fascinating article by McKay et al., entitled ‘Measuring the Impact of the COVID-19 Pandemic on Diagnostic Delay in Rare Disease’. This devastating virus has caused innumerable delays for patients in receiving correct diagnoses within the rare disease community. As we are still navigating this pandemic, and employing different

strategies around the globe to try and live alongside COVID-19, I cannot stress enough the importance of this research.

Continuing this theme is a wealth of peer-reviewed articles which focus on rare diseases, such as isolated renal hydatid disease caused by parasitic tapeworm larvae in children; Cotard’s delusion; and diencephalic syndrome.

Our comprehensive review of ECRD 2022 includes a detailed congress review. Alongside two engaging internal features, you can find abstract review highlights, research summaries, and late-breaking research from the congress. *EMJ* 7.3 also includes an interview with Yann Le Cam, Chief Executive Officer of EURORDIS-Rare Diseases Europe.

I extend my gratitude to all of the authors, interviewees, reviewers, and Editorial Board members who have made contributions to this issue of *EMJ*, and hope that this wonderful flagship journal will prove an interesting and valuable read to colleagues all over the world.



**Markus Peck-Radosavljevic**

Professor of Medicine, Chairman of the Department of Gastroenterology and Hepatology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria





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**EMJ**

# ECRD 2022



## Review of the 11<sup>th</sup> European Conference on Rare Diseases and Orphan Products 2022

**Date:** 27<sup>th</sup> June–1<sup>st</sup> July 2022

**Citation:** EMJ. 2022;7[3]:10-12. DOI/10.33590/emj/10057417.

<https://doi.org/10.33590/emj/10057417>.

THE 11<sup>th</sup> European Conference on Rare Diseases (ECRD), partner organisation of the EURORDIS-Rare Diseases Europe, is the largest patient-led rare disease policy event. The fully virtual conference took place from 27<sup>th</sup> June to 1<sup>st</sup> July 2022 and saw over 1,000 attendees, including patient advocates, policymakers, researchers, clinicians, healthcare professionals, healthcare industry representatives, academics, payers, regulators, and member state representatives. Guests were invited to attend sessions and discussions across 5 days from over 100 speakers, panellists, and chairs.

The conference allows for collaborative dialogue, learning and conversation, the shaping of goal-driven rare disease policies, and for important and innovative discussions on a national and an international level to take place. The conference is an unrivalled opportunity to network and exchange invaluable knowledge with over 1,500 stakeholders in the rare disease community with worldwide contribution.

The ECRD scientific programme was notably inclusive and sustainably responsible, and the event days were dedicated to discussions on how to reach three visionary goals for people living with a rare disease. The three goals are aligned with the United

Nation's (UN) Sustainable Development Goals, and were inspired by the Rare 2030 project. They include ensuring healthy lives and promoting wellbeing for all people living with a rare disease at all ages; reducing inequalities for people living with a rare disease; and building resilient infrastructure, promoting inclusive and sustainable industry, and fostering innovation for people living with a rare disease.

Rare 2030 was a pivotal 2-year foresight study, supported by the European Parliament and European Commission (EC), that guided a large-scale and multistakeholder reflection on rare disease policy in Europe through 2030. The concluding recommendation of Rare 2030 was the need for a new European policy framework on rare diseases with measurable and actionable goals, given that current actions at member state level alone, or legislative changes in specific areas, are not enough. Moving forwards in a post-COVID-19 world will require the adoption of collective strategies at the European level that facilitate the implementation of policy coherence and mutually reinforcing activities across Member States.

The closing plenary session on the final day of the conference reminded participants that rare diseases must be addressed globally, across and beyond





Europe. The audience were given a clear call to action in the immediate, medium, and long-term future.

This year's ECRD provided a unique opportunity for patients, practitioners, and other stakeholders to not only reflect on recent policy recommendations, but also engage in an open and supportive dialogue with the aim of generating high-quality and concrete action plans. This represents a crucial step in tackling the unmet medical needs and complex challenges experienced by people living with a rare disease in Europe. ●

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**"The ECRD scientific programme was notably inclusive and sustainably responsible, and the event days were dedicated to discussions on how to reach three visionary goals for people living with a rare disease."**

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# Diagnostic Testing Technologies, Care, and Treatments: Best Practices and Evidence

**Authors:** Evgenia Koutsouki, Editor

**Citation:** EMJ. 2022;7[3]:13-16. DOI/10.33590/emj/10140001. <https://doi.org/10.33590/emj/10140001>.



IN THIS year's European Conference on Rare Diseases & Orphan Products (ECRD), experts, patients, and other stakeholders came together in a session to discuss the best practices for diagnosis and care for people with rare diseases. Elizabeth Vroom, World Duchesne Organization, Veenendaal, the Netherlands, opened the session by introducing the speakers of the session, which focused on evidence and good practice during the continuum of care to inspire action at the European Union (EU) national level. The speakers highlighted the main factors affecting access to diagnosis, and discussed how care pathways and innovative approaches to therapies can affect outcomes. Starting the session, Sandra Courbier, European Organisation for Rare Diseases (EURORDIS) Paris, France, presented preliminary results of the Rare Barometer survey on the journey to diagnosis for people living with a rare disease, which aims to identify personal and external factors influencing the process of obtaining a timely and accurate diagnosis from a patient perspective. The full results of the survey will be published in the near future.

## VALUE OF TREATMENT APPROACH

Vinciane Quoibach, European Brain Council (EBC), Brussels, Belgium, discussed the evidence on access to highly specialised healthcare and designing rare disease care pathways to improve outcomes for people with phenylketonuria (PKU). Quoibach started by introducing the work of the EBC, a network bringing together key players in the area, which works with societies as well as patient associations and industry partners.

Quoibach introduced the concept of the 'value of treatment' as an innovative research approach taken up by the EBC, which combines health economics with outcomes research and examines different elements such as the impact of care pathways on outcomes, the costs of optimised

care pathways compared to cure and care, and how to translate evidence into policy recommendations. Quoibach discussed the results of a survey for patients with PKU taken up in three metabolic care units in Dublin, Ireland; Santiago Compostela, Spain; and Birmingham, UK. The survey focused on the needs of both adult and paediatric patients, the treatment gaps, the role and value of the centres of expertise, and how to best connect with the European reference networks; and was also conducted among patients with ataxia and dystonia, which were presented separately.

What came out from the survey very prominently, was the lack of holistic treatment for PKU and the mental health impact that the disease had on patients. Quoibach highlighted the challenges of PKU as being the lack of consistency in newborn screening across the European

countries, as well as the limitations in certain countries to accessing sapropterin and pegvaliase, which are the current treatments for PKU.

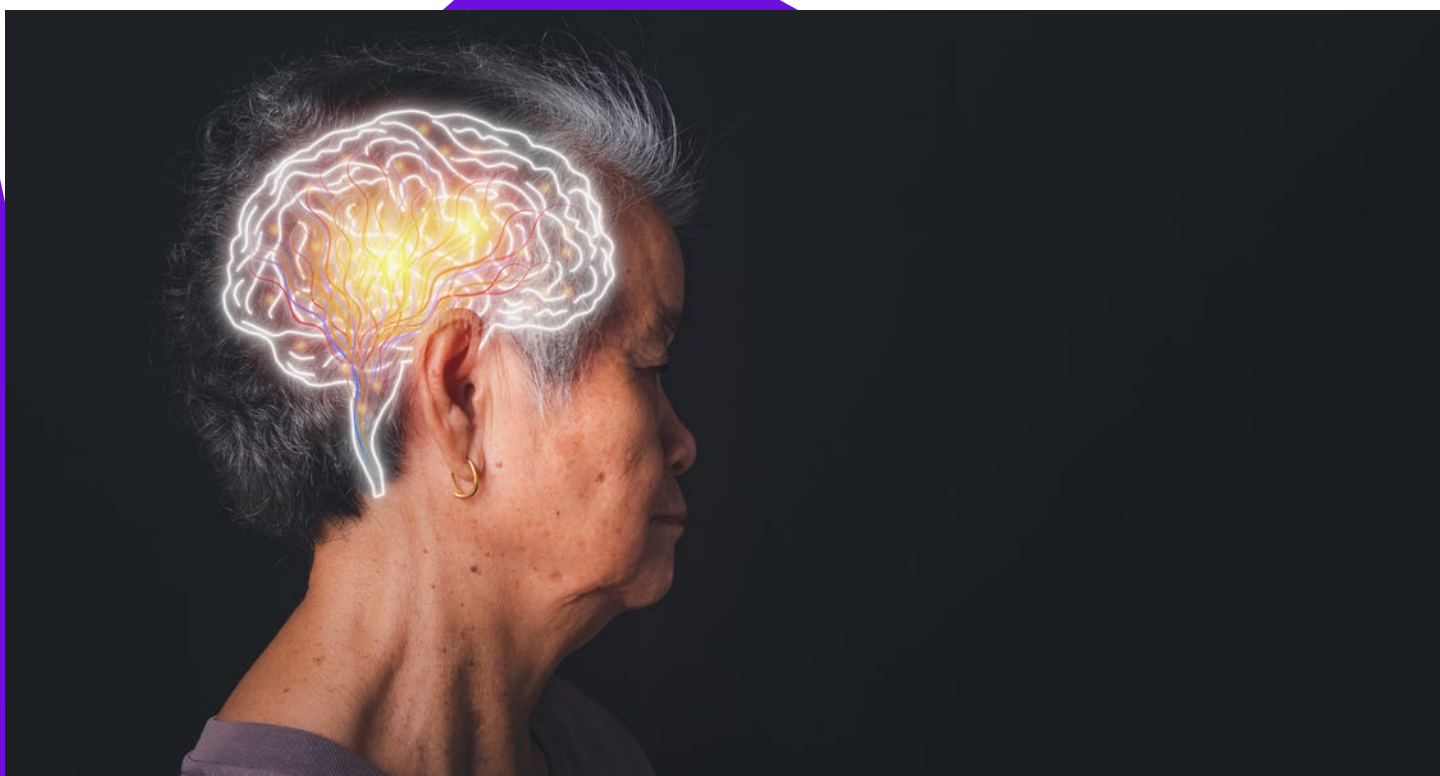
The survey highlighted common treatment gaps for ataxia, PKU, and dystonia, namely: delayed detection and diagnosis, barriers to accessing specialised care and treatment options, lack of co-ordination and continuity in care, high prices, and lack of knowledge accompanied by limited sharing of best practices and expertise. The survey was released during Brain Awareness Week in March 2022 and will be followed up by scientific publications.

### **TRANSITION PATHWAYS FROM PAEDIATRIC TO ADULT CARE IN RARE DISEASE**

Eduard Pellicer, Quality and Patient Experience Department, Sant Joan De Déu, Barcelona Hospital, Spain, discussed the A10! Transition programme from paediatric to adult care using a real-life case of a patient with recessive dystrophic

epidermolysis bullosa who started the transition to adult care at the age of 14. The programme aims to have a positive impact on professional practice and experience as well as on patients' and families' experiences, guaranteeing the continuity of care and integrating psychosocial aspects for the patients. The programme promotes the development of a collaborative network of knowledge and experience between paediatric and adult services. After 4 years of implementation of this programme, it appears that the factors that have contributed to its success are the planification, the personalised attention, and the co-ordination, all of which are based on the family and the patient's needs.

The programme adopts the approach to decision making and information access of 'nothing about me without me'. This means that patients and their families actively participate in the management of care, which is a transformative care model where the systems and professionals adapt their interventions to the patients and their families, and not the other way around.





Pellicer emphasised that certain aspects of this model still need to be worked on, namely: a compromise of policymakers and progression of health education and social care systems is needed in order to improve quality of care that people receive, but also to optimise and humanise interventions. Standardisation of care between adult and paediatric changes is also important, Pellicer explained.

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**“The survey highlighted common treatment gaps for ataxia, PKU, and dystonia, namely: delayed detection and diagnosis, barriers to accessing specialised care and treatment options, lack of co-ordination and continuity in care, high prices, and lack of knowledge accompanied by limited sharing of best practices and expertise.”**

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### **THE PATIENT AT THE FOREFRONT OF PARKINSON'S DISEASE MANAGEMENT**

Sanne Bouwman, ParkinsonNet, Nijmegen, the Netherlands, introduced the mission of ParkinsonNet programme as aiming to improve the lives and guarantee the best possible care for people impacted by Parkinson's disease (PD). Bouwman discussed the difference in care between 2004, back when there was no specific expertise, the professional was in the lead of case, and there were only isolated interventions for PD; and the current vision of ParkinsonNet, where there would be Parkinson's experts, an

integrated team approach, and where the patient would be in control. The idea is that this could potentially lead to empowered professionals and patients, as well as empowered teams.

At present in ParkinsonNet the patient is seen as the centre of care, with over 3,700 trained professionals participating from 19 different disciplines. It contains 70 regional networks over the Netherlands. The primary aim of the organisation is quality of life, achieved through quality of care and self-management of the patient. As Bouwman explained, healthcare professionals are given the opportunity of building expertise and collaboration with other experts, and the patient is seen as a partner. A high caseload for the healthcare professionals ensures that they are able to build and maintain the expertise and knowledge around PD. The co-ordination centre of ParkinsonNet helps and supports healthcare professionals by providing professional training, transparency on healthcare topics, regional support, and having a personal regional contact person in the network.

One of the most challenging aspects of what the network does is to select and certify healthcare professionals in order to help them keep up to date with the requirements that they need to meet. They also promote the care of therapists who treat people with PD. In addition, they provide patient education alongside the patient association. The centre also works with different organisations for guideline development





and technological innovations, and organises an annual congress.

As explained by Bouwman, the initiative for patient empowerment includes an online healthcare tool called 'Parkinson's Healthcare finder', where patients can find therapists nearby of different disciplines that they can reach out to. Aiming to 'transport knowledge, not patients', ParkinsonNet also created a TV show of over 85 episodes of PD topics ranging from addiction to medication featuring experts on the topic and always including a neurologist and a patient in the discussion.

Looking back, the achievements of the network include provision of better care, fewer complications, and lower costs.

Bouwman listed the ingredients for success of ParkinsonNet: a medical leader with dedication, time and patience; a local project lead; local experts who live your mission and vision; and working together with patients, healthcare professionals, and stakeholders.

## CONCLUSIONS AND CLOSING REMARKS

In her closing remarks, Vroom, thanked all the speakers for their presentation and summarised the conclusions, emphasising the importance of transition programmes to adult care and of integration and collaboration between healthcare allied therapies, professionals, and patients. ●

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**“Bouwman listed the ingredients for success of ParkinsonNet: a medical leader with dedication; time and patience; a local project lead; local experts who live your mission and vision; and working together with patients, healthcare professionals, and stakeholders.”**

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# Seeing Is Believing: Invisibility Exacerbates Inequality for Patients Living with Rare Disease

**Authors:** Darcy Richards, Editorial Assistant

**Citation:** EMJ. 2022;7[3]:17-22. DOI/10.33590/emj/10149519. <https://doi.org/10.33590/emj/10149519>



AT the 11<sup>th</sup> European Conference on Rare Diseases (ECRD), held virtually between 27<sup>th</sup> June and 1<sup>st</sup> July as an official event of the 2022 French Presidency of the Council of the European Union (EU), experts discussed how invisibility in rare disease acts as a roadblock to reducing inequalities. The session, chaired by Ana Rath, Orphanet, French National Institute for Health and Medical Research (Inserm), France, provided insight into the inequalities, inequities, and injustice that people living with rare disease (PLWRD) face, referencing the United Nations (UN) Resolution on PLWRD 2021<sup>1</sup> and the UN Sustainable Development Goals (SDG).<sup>2</sup> The panel also highlighted how we can act at the local, regional, national, and global levels to bring rare diseases into focus, affect change, and start to bridge the inequality gaps.

## **SUSTAINABLE DEVELOPMENT GOALS: THE IMPACT OF LIVING WITH RARE DISEASE**

Alongside the physical symptoms PLWRD experience, the functional, educational, financial, occupational, and social impacts have been chronically overlooked due to rare disease invisibility.

Rath discussed how lack of data on the functional and social impacts of rare diseases exacerbates the inequities and inequalities that PLWRD experience. This was addressed further by Flaminia Macchia, Rare Diseases International (RDI), who discussed how rare disease impacts all aspects of a person's life. To start, Macchia highlighted the UN Resolution on PLWRD 2021,<sup>1</sup> which focuses on "Recognising the need to promote and protect the human rights of all persons, including the estimated 300 million PLWRD worldwide," and stated that this resolution interlinks several of the UN SDGs.<sup>2</sup>

Elaborating further, Macchia explained how the entire family of PLWRD can experience poverty as a result of reduced occupational opportunities for PLWRD and their caregivers, impacting SDG 1 (no poverty).<sup>2</sup> This links to SDG 5<sup>2</sup> on gender equality, where Macchia reported that testimonies demonstrate that females are disproportionately discriminated against as either the patient or the primary caregiver, frequently having to reduce or stop paid work to support their family member. In terms of SDG 3<sup>2</sup> (good health and wellbeing), unnamed rare diseases often have no available treatment and there is little knowledge around them, which leads to poorer health outcomes as well as social isolation and exclusion. Quality education (SDG 4)<sup>2</sup> is affected as PLWRD often experience difficulties integrating into mainstream education systems due to the lack of knowledge and support, leading to inequalities from an early age. Macchia also reported the impact of rare disease on SDG 8<sup>2</sup> (decent work and economic growth) as PLWRD experience






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**"Lack of data on the functional and social impacts of rare diseases exacerbates the inequities and inequalities PLWRD experience."**

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challenges with finding, keeping, and returning to work. All these factors reveal how rare disease affects all aspects of life and is a barrier to achieving SDG 10, reducing inequalities.<sup>2</sup>

Inmaculada Placencia Porrero, Directorate General for Employment, Social Affairs and Inclusion, European Commission (EC), spotlighted the statistics on the inequalities experienced by persons with disabilities, including PLWRD. Linking to SDGs 8,3,4, and 1,<sup>2</sup> respectively, the EC identified that 50% of people with disabilities have concerns about employment, report unmet health

needs at a rate four-times higher than people without disabilities, are more likely to leave education earlier and have lower educational attainments, and experience a 28% risk of poverty compared to 18% for people without disabilities. Furthermore, 52% of people with disabilities felt discriminated against.

Elvira Martinez, Advocacy and International Relations, Spanish Federation of Rare Diseases (FEDER), discussed the conclusions from the second ENSERio study<sup>3</sup> evaluating the health and social needs of PLWRD in Spain. They found that families living with rare disease often waited >4 years for diagnosis, with one-fifth waiting for more than a decade to obtain a diagnosis. Of concern, the study showed that just 34% of PLWRD have access to treatment and 40% were not satisfied with the healthcare they receive. Furthermore, financial cover for essential products was not provided for 50% of PLWRD, resulting in financial burden to these families.



## WHAT FACTORS PERPETUATE INVISIBILITY?

Because rare diseases are rare by definition, there is a paucity of knowledge surrounding these conditions, which has led to a lack of policy and ultimately an unjust system for PLWRD. A lack of knowledge leads to difficulty in obtaining a diagnosis, acquiring access to appropriate healthcare and social services, political commitment to addressing the inequalities, and incentivising research. Without knowledge and research data, policy makers are unaware of the needs of PLWRD feeding into a self-perpetuating invisibility cycle. Anne-Sophie Lapointe, Rare Diseases Project at The French Ministry of Health and Solidarity, pointedly commented: “We need action to improve the knowledge of rare disease.”

Macchia commented: “From a global perspective, it is very clear that invisibility is indeed the first barrier towards reducing inequalities for persons living with the rare disease

and their families. The invisibility of the rare disease community is everywhere, in most, if not all healthcare and social systems,” and continued that it is “always very easy to ignore the needs of a population that is invisible. No visibility means no understanding of the specific needs to target the support and restore equality.”

Androulla Eleftheriou, Thalassaemia International Federation (TIF), a non-government, non-profit, patient organisation, spoke on TIFs vision, work, and progress in unveiling the unmet needs of persons living with thalassaemia. However, Eleftheriou also discussed how there is a lack of funding and research evaluating the epidemiology of rare disease and the needs of those with rare disease diagnoses. Therefore, ongoing research into identification of the needs and inequalities experienced by PLWRD in order to develop enforceable policies to affect change and improve quality of life and outcomes is required.

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**"From a global perspective, it is very clear that invisibility is indeed the first barrier towards reducing inequalities for persons living with the rare disease and their families."**

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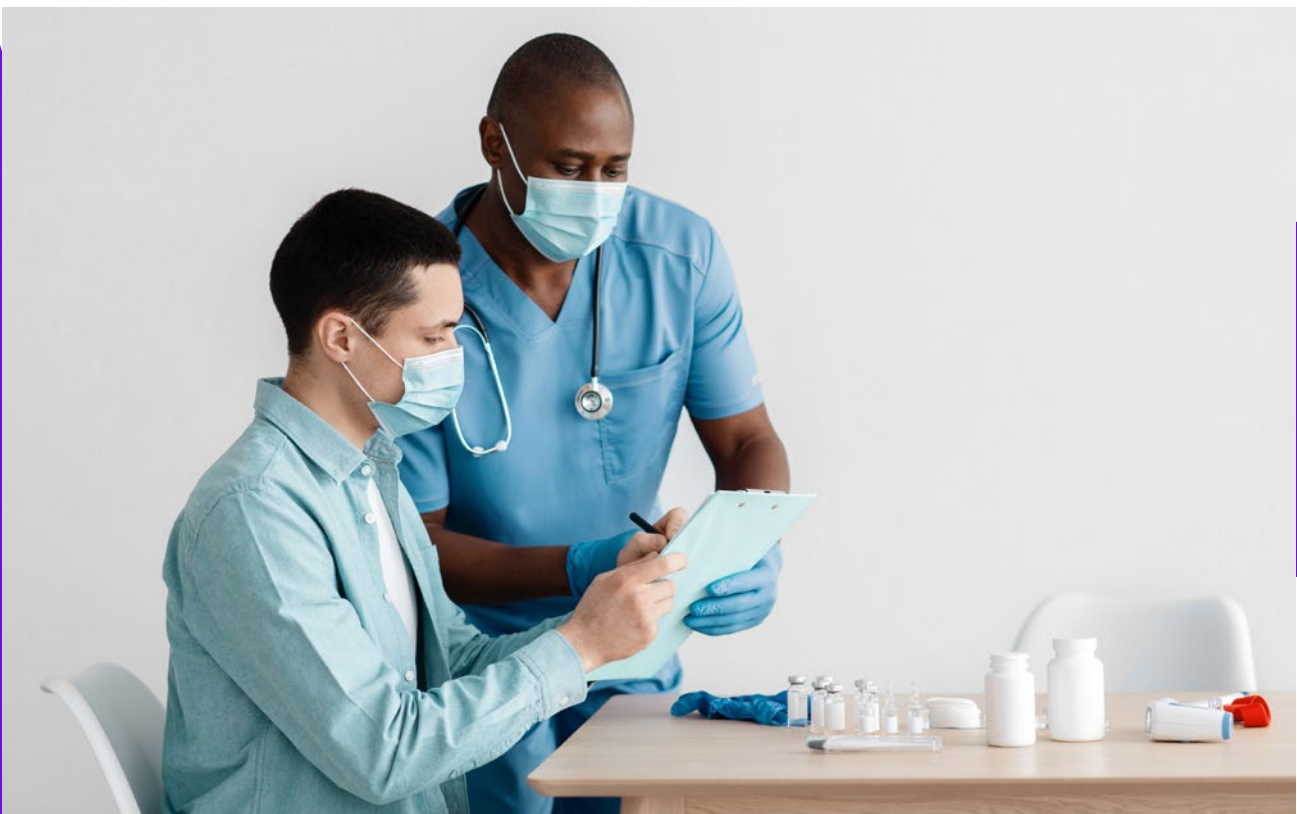
Furthermore, many of the studies that encompass rare diseases tend to group them together into a generic umbrella term, rather than indexing them as individual diseases. This was stressed by Juanita Haagsma, Department of Public Health, Erasmus University Medical Centre (Erasmus MC), Rotterdam, the Netherlands, who explained how global burden of disease studies combine data on multiple variables including the functional impact of disease, to generate a burden of disease unit, known as disability-adjusted life years (DALY). DALYs enable comparison

between diseases with different characteristics. Whilst this work is pivotal in providing the information required for agenda and priority setting, the main limitation is that rare diseases are often grouped together, rather than indexed individually and thus missing true insight into the functional impact of each individual disease.

### **TACKLING THE PROBLEM: HOW CAN WE UNMASK THE MASKED?**

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The UN pertinently sought to address the inequalities and inequities PLWRD face daily, with the UN Resolution PLWRD 2021<sup>1</sup> and SDG 10,<sup>2</sup> which focus on reducing discrimination and working towards achieving the SDGs. One of the key factors that will play a role in achieving this is to make the hidden visible, which will require efforts at local, national, and global levels. The UN Resolution and SDGs provide addressable action points for member states and a start point to begin bridging the inequality gaps.





Globally reliable geographic data are scarce, and Rath stated that “we don’t have data because we cannot identify where patients are,” further compounding the invisibility of rare diseases and resulting inequalities. Eleftheriou highlighted the need for epidemiological research and commented that whilst there have been highly important and valuable molecular studies into thalassaemia, “cornerstone research areas” such as epidemiology and screening are lacking.

Patient organisations will be key in tackling invisibility across all levels. Eleftheriou discussed the mission of TIF, which is the “promotion of disease-specific national programmes that should be co-ordinated and funded by healthcare systems.” TIF has identified that, within Europe and across the globe, PLWRD experience significant inequalities in the extent and quality of services available, which is most stark in lower income countries. In fact, even within Europe, less than 20% of patients are receiving the appropriate care for thalassaemia.

At the local level, Lapointe suggested that “training by patient organisation and patients” can help to raise awareness and increase visibility, and discussed how at national and international levels. European Reference Networks (ERN) “should become an extension of national healthcare systems” for the provision of shared knowledge and resources to improve care across Europe and that international information sharing should include medical and non-medical specialities to address all aspects of disease burden. This point was further highlighted by a direct quote from Rath: “Listen to patients; they are experts.”

The importance of robust, well-designed epidemiological research in promoting rare disease awareness and reducing inequalities was highlighted by Eleftheriou, who stated that “there is a great need to improve national registries and upgrade epidemiological work, as well as a great need to actually design new epidemiological work.”



Rath introduced the Orphanet disability project, its aim to measure the impact of rare disease on daily life, and explained that information collated from the project could be used by health and social care systems to anticipate challenges and develop strategies and solutions to improve quality of life for PLWRD. Following on from this, Martinez presented the second ENSERio study,<sup>3</sup> which was conducted by FEDER to implement policy and improve outcomes for PLWRD. The data they obtained provided crucial insight into the unmet needs of PLWRD in Spain. Martinez explained that data from these studies can raise awareness and be used as an advocacy lever to encourage decision makers to implement local policy change and that robust data collected at the local level can drive changes at the national level.

The successes of previous research could be utilised, up scaled, and applied at the global level to raise awareness, collaboratively collect data, and affect change by informing policy and developing assessment/needs frameworks.

## KEY RECOMMENDATIONS

The key recommendations that came from this discussion included collaborative work between organisations and federations to reinforce the work being performed at regional, national, and global levels, training by patient organisations and patients themselves as rare disease experts, incentivising research, and development of strong policies and assessment frameworks with adequate funding. ●

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# Advances in the Management of Acute and Recurrent Urinary Tract Infections Caused by Resistant Pathogens – What's Next?

This GSK Industry Symposium took place at the European Association of Urology (EAU) Conference on 1<sup>st</sup> July 2022, Amsterdam, the Netherlands



<b>Speakers:</b>	Debra Fromer, <sup>1</sup> Vik Khullar, <sup>2,3</sup> Florian Wagenlehner <sup>4</sup>
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<b>Disclosure:</b>	Fromer is a legal consultant for Johnson & Johnson, and a speaker and advisor for GSK. Khullar is a consultant and researcher for AbbVie, and consultant and speaker for GSK. Wagenlehner has worked as a consultant for Achaogen, Astellas, Eumedica, Janssen, Klosterfrau, Leo-Pharma, Merlion, Shionogi, Quiagen, Sysmex, and VenatoRX. As a consultant and speaker for Bionorica, GSK, MSD, Rosen Pharma, and OM/Vifor-Pharma. As a speaker for AstraZeneca and Pfizer, and as a researcher for Helperby, Phagomed and Saxonia R&D. The speakers have no conflicts of interest relating to this presentation.
<b>Acknowledgements:</b>	This symposium review article was proposed by EMJ and was written by Caroline E. Cross, Reading, UK. All speakers were given the opportunity to review the article.
<b>Support:</b>	The symposium and publication of this article was funded by GSK.
<b>Disclaimer:</b>	The opinions expressed in this article belong solely to the named speakers and do not necessarily reflect those of GSK. GSK was provided with the opportunity to review this publication prior to submission to EMJ, for the sole purpose of ensuring its data is accurately stated herein. Not all medicines and/or indications presented in this webinar may be approved for use in all countries. This medical education activity is intended for healthcare professionals only.
<b>Citation:</b>	EMJ. 2022;7[3]:23-29. DOI/10.33590/emj/10081330. <a href="https://doi.org/10.33590/emj/10081330">https://doi.org/10.33590/emj/10081330</a>



## Meeting Summary

Uncomplicated urinary tract infections (uUTI) are one of the most common infections in the community, affecting >150 million people each year worldwide, and being responsible for large amounts of antibiotic prescribing.<sup>1,2</sup> Up to 80% of females will experience at least one uUTI in their lifetime, and 45% will have recurrent uUTI.<sup>3</sup> The debilitating symptoms that accompany urinary tract infections (UTI), including



pain and urinary urgency, coupled with the unpredictability of recurrence, negatively impact quality of life (QoL).<sup>1,3</sup>

The GSK Industry Symposium took place on 1<sup>st</sup> July 2022 as part of the European Association of Urology (EAU) Conference in Amsterdam, the Netherlands, and focused on the challenges surrounding the diagnosis and management of uUTIs and recurrent UTIs in the context of increasing antimicrobial resistance.

During the presentations, speakers Debra Fromer, Vik Khullar, and Florian Wagenlehner, all specialists in urology, outlined the challenges facing clinicians and patients in treating UTIs effectively whilst maintaining good antibiotic stewardship. The wide-ranging discussions included questions around differential diagnosis, personalised approaches to treatment, and the challenges of treating recurrent UTIs.

The panel also discussed the need for new strategies to manage such infections, and highlighted alternatives to antibiotics that are under development and could help to slow the rise in antimicrobial resistance. The symposium finished on a positive note with discussions around new and emerging therapies, such as immune stimulation, vaccination, and fulguration, that could help many females to break the debilitating cycle of recurrent UTIs.

## INTRODUCTION

At least 60% of females worldwide will experience at least one UTI in their lifetime.<sup>4</sup> An array of pathogenic bacteria, both gram-negative and gram-positive, can cause the infections, although in uUTIs, *Escherichia coli* (*E. coli*) is the predominant pathogen.<sup>5</sup>

Symptoms are debilitating, and include urinary urgency, dysuria, and frequency. More than 25% of females who experience a UTI will go on to have further infections, often within 3 months, increasing anxiety levels with feelings of helplessness and dread, and reducing QoL.<sup>6,7</sup>

Oral antibiotics are the mainstay of treatment, and medications to treat UTIs currently account for 15% of all antibiotic prescriptions in the USA and Europe.<sup>2</sup> Increasingly, patients are experiencing UTIs that are resistant to first line antibiotics,<sup>8</sup> contributing to the global threat of antimicrobial resistance. Clinical guidelines for the treatment of UTIs recommend that first line antibiotics be chosen based on local antimicrobial resistance patterns.<sup>9</sup>

During this symposium, the speakers highlighted the complexities of both uncomplicated and recurrent UTIs that mean a more personalised approach to treatment could be beneficial. They also discussed the increasing prevalence

of antibiotic resistant uropathogens, and what clinicians should consider when prescribing antimicrobial medications. Discussions also covered recent clinical studies that demonstrate the value of a more clinically informed approach to treatments, and show the potential of novel treatment approaches with antibiotics and other alternatives.

This article captures the main questions discussed during the symposium and draws attention to novel therapeutic strategies that can help clinicians apply appropriate antibiotic prescribing when treating patients with uncomplicated and recurrent UTIs.

## How is the Differential Diagnosis of Urinary Tract Infection Done in Female Patients Presenting at Clinic, and What Is the Impact of These Infections on the Patient?

Most young females (>90%) who present at clinic with urinary urgency and pain whilst passing urine (dysuria) will have a UTI,<sup>10</sup> explained Fromer, who sees hundreds of females with uncomplicated and recurrent UTIs in her clinics. She commonly sees females in their mid-thirties with previous history of culture-proven uUTIs who present with dysuria, frequency, urgency,

and suprapubic pain. "However, it's also possible that patients presenting with UTI symptoms could instead have overactive bladder or bladder pain syndrome."<sup>11</sup>

Wagenlehner concurred, saying: "Diagnosis is not always straightforward. For a long time the gold standard has been lab culture of the urinary bacteria. However, in more than a third of cases, we do not get a positive culture, sometimes because the culture test is not sufficiently sensitive, and in others, the bacteria is not culturable in the lab." It has also become increasingly clear that bacteria can be present in the healthy bladder.<sup>5</sup>

The panel members agreed that the impact of UTIs on females can be pervasive. Some females have as many as six recurrent infections in a year, and the impact on individuals are significant. As Fromer outlined: "The infections are sudden, unforeseeable and distressing, taking a toll on mental health and sense of wellbeing."<sup>12</sup> Fromer drew attention to a study of 575 patients with recurrent UTIs, in which 61.9% of patients with a UTI suffered some degree of depression, and almost three quarters of females experienced anxiety. A reduction in UTIs correlated with improvements in QoL.<sup>12</sup>

Khullar added that other impacts of recurrent UTIs on patients' lives include sleep disruption, persistent fatigue, negative impacts on intimate relationships, and the financial consequences of taking time off work.<sup>13</sup>

Referring to one of his own studies, Wagenlehner said: "Using a self-administered anonymous web-based survey across five countries, we demonstrated that recurrent UTIs had a significant impact on QoL and are associated with mental stress for a high proportion of women."<sup>14</sup> Other studies also report negative QoL impacts associated with treatment failure, often caused by antimicrobial resistant strains.<sup>15,16</sup>

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**Antibiotic Resistance in Common Bacteria Has Reached Alarming Levels in Many Parts of the World Indicating that Many of the Available Treatment Options for Common Infections in Some Settings are Becoming Ineffective.<sup>8</sup> How**

## does this Impact the Management of Patients with Urinary Tract Infections?

Uropathogens such as *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) feature prominently in the World Health Organization (WHO)'s 2014 report on emerging resistant pathogens.<sup>8</sup> As Fromer explained: "There is now a high frequency of resistance to third generation cephalosporins commonly used to treat UTIs. This can lead to a reliance on carbapenems to treat severe infections, which really should be used only as a last resort."

The speakers emphasised the need for clinicians to consider antimicrobial resistance when treating patients for UTIs. "Often, when taking a patient's recent history we find that the patient has had multiple courses of antibiotics, for example for dental work. It is important to understand the resistance patterns for the individual at the time of symptom onset and prior to treatment,"<sup>17</sup> Fromer said.

Fromer reinforced the point by describing data from a retrospective study of 908 female patients with UTIs from an outpatient clinic in the USA, which identified *E. coli* as the most common organism causing UTIs (complicated UTI [cUTI] and uncomplicated UTI [uUTI]). More than a third of patients had experienced three or more UTIs in the previous year (2015–2016), and rates of resistance to three or more oral antibiotics were as high as 30%.<sup>18</sup> Antibiotic resistant infections were more prevalent in females with recurrent UTIs, and who were older.<sup>19</sup>

The speakers outlined how clinicians can support good antimicrobial stewardship and reduce inappropriate use of antibiotics. Strategies include not treating asymptomatic bacteriuria,<sup>17</sup> avoiding use of broad-spectrum fluoroquinolones,<sup>9</sup> using the shortest possible effective course of antibiotics,<sup>17</sup> and raising awareness among patients of the dangers of 'self-starting' antibiotics, and not adhering to recommended dosage.<sup>11,17,20</sup>

Wagenlehner also emphasised the complexities of diagnosing UTIs and the need for clinicians to rule out other underlying causes where possible, and to consider alternative strategies before prescribing antibiotics. Non-antibiotic interventions include behavioural changes, antiadhesive treatments, local antiseptics, topical

oestrogens, and immunomodulation.<sup>21</sup> “We use symptom questionnaires that are also used in other conditions and can provide quantitative information to help clinicians to rule out complicated UTI and assess risk factors such as treatment failure and risk of recurrence.”

### What can be Done in Clinical Practice to Assess the Risk of Antimicrobial Resistance In Patients with Urinary Tract Infection?

Wagenlehner believes we need a more personalised approach to the treatment of UTI patients, to identify patients who are more likely to have resistant pathogens. His team studied antibiotic sensitivity in 386 females with uUTIs and found that two-thirds (n=259) had infections that were susceptible to all antibiotics, but almost one-third (n=112) had infections that were resistant to one or two antibiotics, and 15 patients had infections that were resistant to multiple antibiotics.<sup>22</sup> The patients with multiple drug resistant infections were generally older, and with history of recurrent infections.

Physical examination and history taking are important in supporting UTI diagnosis. “If resistance is suspected and the patient can tolerate the symptoms until a positive culture is returned, that is preferable. But for many the symptoms are unbearable, even with increased fluids and pain medication, and sometimes there is concern over more serious infection. In these cases, empiric antibiotics are necessary,” stated Fromer. “At this point we must rely on knowledge of local uropathogen resistance patterns and any history of antibiotic allergy or intolerance when deciding which antibiotic to prescribe.<sup>9,17</sup> It is also important to consider the patient’s prior antibiotic use and previous culture results to clarify any history of antimicrobial resistance,”<sup>17,23</sup> she reiterated. Avoiding use of broad-spectrum antibiotics and fluoroquinolones, and keeping the duration of therapy to a minimum also help to reduce the chances of further resistance developing.<sup>9,17</sup>

Khullar reiterated the importance of checking for local uropathogen resistance patterns as they can vary considerably between regions and countries, with fluoroquinolone

resistance common in southern Europe,<sup>24</sup> and penicillin resistance common in the UK.<sup>25</sup> The speakers unanimously referred the audience to international clinical practice guidelines for the treatment of acute uncomplicated cystitis in the context of local resistance patterns.<sup>9</sup>

### What are the Potential Roles of the Urinary Microbiota in Homeostasis of the Urinary Tract, and How does that Influence the Host Bacterial and Inflammatory Interactions in Patients with Urinary Tract Infections?

The human microbiome consists of trillions of bacteria, viruses, and fungi that are found in the human body, and outnumber human cells by 10:1.<sup>26</sup> The intimate and complex relationships that exist between the microbiome and human cells are vital for homeostasis.<sup>26</sup> The symbiotic ecosystem which results, influences both health and disease. For example, as Khullar explained, in the bladder, ‘beneficial bacteria’ such as some *Lactobacilli* sp, can attack pathogenic organisms, communicate with the bladder, control neurological function, and destroy chemicals in the urine.<sup>26</sup>

Patients who experience recurrent UTIs often have repeated courses of antibiotics which can change the balance of microbiota in the gut and bladder. Older, post-menopausal females with low oestrogen levels had lower levels of beneficial *Lactobacilli* in their urinary tract compared to younger females.<sup>27</sup> When the DNA of bacteria in urine was analysed in both females with urgency urinary incontinence (UUI) and those without, females with UUI had more *Gardnerella* and *Enterobacteriaceae*, and fewer *Lactobacilli*.<sup>5</sup> The differences were confirmed when bacteria were cultured from bladder biopsies.<sup>5</sup> Khullar also highlighted a study that suggests *Lactobacillus crispatus*, one of the beneficial *Lactobacilli*, when given as a probiotic intravaginally, may help to reduce recurrent UTIs (rUTI).<sup>28</sup>

Khullar also drew attention to experimental models of bladder infection that demonstrate that *E. coli* can invade superficial bladder epithelium, mature into biofilms, and create pod-like bulges on the bladder surface.<sup>29</sup> These



'pods' allow bacteria to evade the host's immune system defences, and can be a source of rUTI. In translational work, a study of urine sediments, prepared from females with acute episodes of rUTI caused by uropathogenic *E. coli*, found evidence of intracellular bacterial colonies in almost a fifth of cases.<sup>30</sup>

"Some people get an infection and it is cleared by the immune system, or they may have asymptomatic infection. Others have frequent painful infections and have an abnormal response to infection causing inflammation with bacteria entering the bladder wall," Khullar explained. When epithelial cells collected from the bladder lining of females without active UTI were lysed, bacteria were found inside cells. Further analysis from both cultures of the samples showed *Staphylococcus* and *Enterococci* in both groups, with more *E. coli*, *Proteus sp*, and *Micrococcus sp* in the bladder walls,<sup>31</sup> reinforcing the likelihood that bacteria in the bladder wall that are not killed by antibiotics are a source of recurrent UTIs.

With increasing evidence that microbial biofilms play a role in causing recurrent UTIs, cystoscopic electrofulguration as an experimental treatment has been used as a way to clear resistant bacteria from the bladder lining by cauterising inflammatory lesions. Fromer described a study of 95 females who received the treatment. Five-year follow up showed an 88% cure rate.<sup>32</sup>

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### What are the Risk Factors Associated with Uncomplicated Urinary Tract Infection Recurrence?

The risk of recurrent uUTIs is higher for females over 55 years old.<sup>33</sup> These females have diminishing levels of oestrogen as they enter the menopause. Other risk factors include diabetes, particularly more advanced Type 2 diabetes when the patient is receiving insulin,<sup>34</sup> vaginal atrophy, urinary incontinence, vaginal wall prolapse, and increased post-void residual volume.<sup>35</sup>

Khullar shared his clinical experience and practice, reiterating that in older, post-menopausal patients, it is important to

attempt urine culture while the patient has symptoms, while taking account of patient's history and previous antibiotic use. Additional assessments, such as urinary flow rate and post-void residual volume, will help the clinician to assess risk of recurrence. Also, if haematuria is present, cystoscopy should be carried out, and if needed, a CT urogram to examine the upper urinary tract. Additional factors that increase the risk of UTI recurrence include constipation rather than diarrhoea, and recent antibiotic use.<sup>36</sup>

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### What is the Current Guidance in the Management of Recurrent Urinary Tract Infections in Female Patients?

Based on clinical experience and practice, Khullar recommends antimicrobial prophylaxis for up to 6 months for patients with recurrent UTIs. "We tend to use nitrofurantoin or fosfomycin in line with EAU guidelines,"<sup>26</sup> he outlined. Also, postcoital prophylaxis can be used, or the antiseptic methenamine hippurate, 1 g twice daily for 6 months, which has been shown to reduce recurrent infections.<sup>37</sup> Fromer emphasised that there are currently no evidence-based guidelines for the use of antibiotic prophylaxis for recurrent UTIs, and that it should be seen as a last resort option.

There is also evidence that non-antimicrobial prophylactics are effective. For example, an oestrogen-releasing vaginal ring,<sup>38</sup> intravaginal probiotics (*L. rhamnosus*, *L. reuteri*),<sup>39</sup> or immunoactive prophylaxis.<sup>40,41</sup> *L. crispatus* given intravaginally as a probiotic, shows promise at reducing recurrent UTIs.<sup>28</sup> Topical oestrogens can help to decrease vaginal pH, while increasing glycogen production and *Lactobacillus* concentrations<sup>42</sup> and antibacterial peptide secretions.<sup>43</sup>

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### What are the Emerging Targets and Therapies In Urinary Tract Infections?

For the millions of females worldwide who live with the uncertainty of when their next debilitating UTI will strike, there is some hope. "Vaccine therapy is showing promise, although

as yet, the mechanism of action is not clearly understood,” enthused Wagenlehner. Recent data is strong, said Fromer, who presented data from a trial of a sublingual vaccine of whole-cell inactivated bacteria (*E. coli*, *K. pneumoniae*, *E. faecalis*, and *P. vulgaris*).<sup>41</sup> The study showed vaccination reduced the recurrence of UTIs at 9-months post-vaccination. Also encouraging, was that the time to first UTI post-vaccine was 275 days in the vaccine group, versus 48 days in the placebo group. Females also reported improved QoL.<sup>41</sup> Fromer added: “Interestingly, all women had similar microbiota in their bladder, despite the reduction in UTIs, and the study authors suggest that the vaccine boosts local innate immune mechanisms that might be deficient in women who experience recurrent UTIs.” Wagenlehner supported this viewpoint, suggesting that the host response to the bacteria might be more important in causing disease, rather than the bacteria themselves. “Sublingual vaccines help to boost the innate immune system and this might help to prevent severe disease,” he surmised.

The panel also discussed the potential of bacteriophages to target and kill specific bacterial species, such as specific *E. coli* isolates and *Klebsiella*.<sup>44</sup> Wagenlehner explained that these are already available in Georgia as a ‘cocktail’ of bacteriophages, but are not sufficiently tested clinically. He suggested that there is still a lot of preclinical and clinical work to be done until bacteriophages might in future provide an alternative to antibiotics. Novel  $\beta$ -lactam and  $\beta$ -lactamase inhibitors are also currently being tested in clinical phases as oral treatments for patients with UTIs.<sup>45</sup>

The panel also discussed novel antibiotics that are in the pipeline, such as Gepotidacin, which is currently in Phase III clinical development.<sup>46,47</sup> New oral carbapenems, Tebipenem<sup>48</sup> and sulopenem,<sup>49</sup> are also under development for complicated UTIs and uUTIs, respectively. The speakers emphasised that these new antibiotics could be very helpful to patients who have uropathogens that are resistant to orally administered antibiotics. However, it will be important to ensure they are only used under appropriate antibiotic prescribing stewardship.

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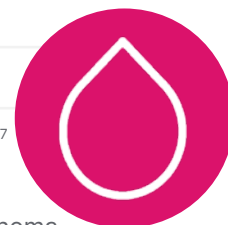
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July 2022



# Management of Thrombosis in High-Risk Patients: Focus on Cancer-Associated Thrombosis

This symposium took place on 11<sup>th</sup> July 2022, as part of the International Society on Thrombosis and Haemostasis (ISTH) Congress in London, UK

<b>Chairpeople:</b>	Ajay Kakkar, <sup>1</sup> Gary Raskob <sup>2</sup>
<b>Speakers:</b>	Mari Thomas, <sup>3</sup> Paula Bolton-Maggs, <sup>4,5</sup> Giancarlo Agnelli <sup>6,7</sup> <ol style="list-style-type: none"> <li>1. Thrombosis Research Institute, London, UK</li> <li>2. University of Oklahoma Health Sciences Center, Oklahoma City, USA</li> <li>3. University College London, UK</li> <li>4. University of Manchester, UK</li> <li>5. UK Haemovigilance Scheme, Manchester, UK</li> <li>6. University of Perugia, Italy</li> <li>7. Istituti Clinici Scientifici (ICS) Maugeri, Pavia-Milan, Italy</li> </ol>
<b>Disclosure:</b>	Kakkar reports research support and personal fees from Bayer, Sanofi, and Anthos Therapeutics. Raskob reports personal fees from Anthos Therapeutics, Alnylam, AMAG Pharma, Bayer, BMS, Daiichi Sankyo, Janssen, Pfizer, Portola, and XaTek. Thomas has attended advisory boards for Ablynx, Sanofi and Bayer; reports speaker fees for Bayer, Sanofi, and Anthos Therapeutics; and consultancy for Bayer and Anthos Therapeutics. Bolton-Maggs reports personal fees from Anthos Therapeutics, Roche, and the British Society for Haematology. Agnelli reports speaker fees for Bristol-Myers Squibb and Pfizer; and has been a member of study steering committees for Anthos Therapeutics (ASTER and MAGNOLIA), Daiichi Sankyo (Cope), and Sanofi (Omero).
<b>Acknowledgements:</b>	Medical writing assistance was provided by Steph Carter, Lyrical Medical Writing Services, Manchester, UK.
<b>Support:</b>	This symposium was intended as scientific exchange of medical information for healthcare professionals only. The publication of this article was funded by Anthos Therapeutics. The views and opinions expressed are those of the authors and not necessarily of Anthos Therapeutics. Factor XI inhibitors are investigational and are not approved for sale in any country.
<b>Citation:</b>	EMJ. 2022;7[3]:30-39. DOI/10.33590/emj/10175843. <a href="https://doi.org/10.33590/emj/10175843">https://doi.org/10.33590/emj/10175843</a> .



## Meeting Summary

This symposium took place during the International Society on Thrombosis and Haemostasis (ISTH) Congress, 2022. Ajay Kakkar, Thrombosis Research Institute, London, UK, opened the symposium by highlighting the extent to which patients with cancer are affected by thrombotic disease. Subsequently, Mari Thomas, University College London, UK, described the current treatment options for patients with cancer-associated thrombosis (CAT). Thomas highlighted the current unmet needs faced by these patients, with the risk of bleeding continuing

to be the main issue affecting anticoagulation treatment. Paula Bolton-Maggs, University of Manchester, UK, and UK Haemovigilance Scheme, Manchester, UK, gave an overview of Factor XI (FXI) inhibition and outlined why this factor is a potential attractive anticoagulation drug target. Multiple therapies targeting FXI are currently in development, with seven clinical trials published to date.<sup>1-7</sup> Although there are some similarities between these agents, there are also many differences in terms of their administration route and frequency, the timing of onset of action, and methods of metabolism and excretion. Giancarlo Agnelli, University of Perugia, Italy, and Istituti Clinici Scientifici (ICS) Maugeri, Pavia-Milan, Italy, then described the importance of conducting clinical trials that are designed to address the unmet needs of patients with CAT. In particular, he highlighted the ongoing Phase III ASTER and MAGNOLIA studies that are aiming to demonstrate that the FXI inhibitor abelacimab is superior to standard of care treatments in terms of bleeding rates for patients with CAT, including those with gastrointestinal (GI) or genitourinary (GU) tumours. Concluding remarks were given by Gary Raskob, University of Oklahoma Health Sciences Center, Oklahoma City, USA, who re-emphasised the unmet needs in the treatment of CAT, and the promise that FXI inhibitors hold for the future.

## Opening Remarks

### Ajay Kakkar

Kakkar opened the symposium by highlighting the burden of thrombotic disease in patients with cancer with a discussion of data from the Global Anticoagulant Registry in the FIELD - Venous Thromboembolism (GARFIELD-VTE) registry.<sup>8</sup> Patients with active cancer and a confirmed diagnosis of venous thromboembolism (VTE) had a two-fold increased risk of recurrent VTE, a five-fold increased risk of a major bleed, a four-fold increased risk of a stroke or a transient ischaemic attack, and a 15-fold increased risk of all-cause mortality, compared with patients with a VTE but without cancer.<sup>8</sup> An analysis of treatment patterns in the same study demonstrated the adoption of direct oral anticoagulants (DOAC), both in the short-term and long-term in patients with a VTE (Figure 1). However, it also revealed that over time, a large number of patients discontinued anticoagulation, with this often occurring quite early in the natural history of their thrombosis; for example, in the GARFIELD-VTE registry almost one-third of patients (30.4%) discontinued anticoagulation within 9 months of their original VTE.<sup>8</sup> Undertreatment with anticoagulants has also been reported in the European PREFER in VTE Registry, where low use was reported in higher-risk patients.<sup>9</sup> There are likely to be many reasons underlining this undertreatment; however, fear and risk of bleeding continue to

be a major deterrent to optimal anticoagulation, even in the era of DOACs.

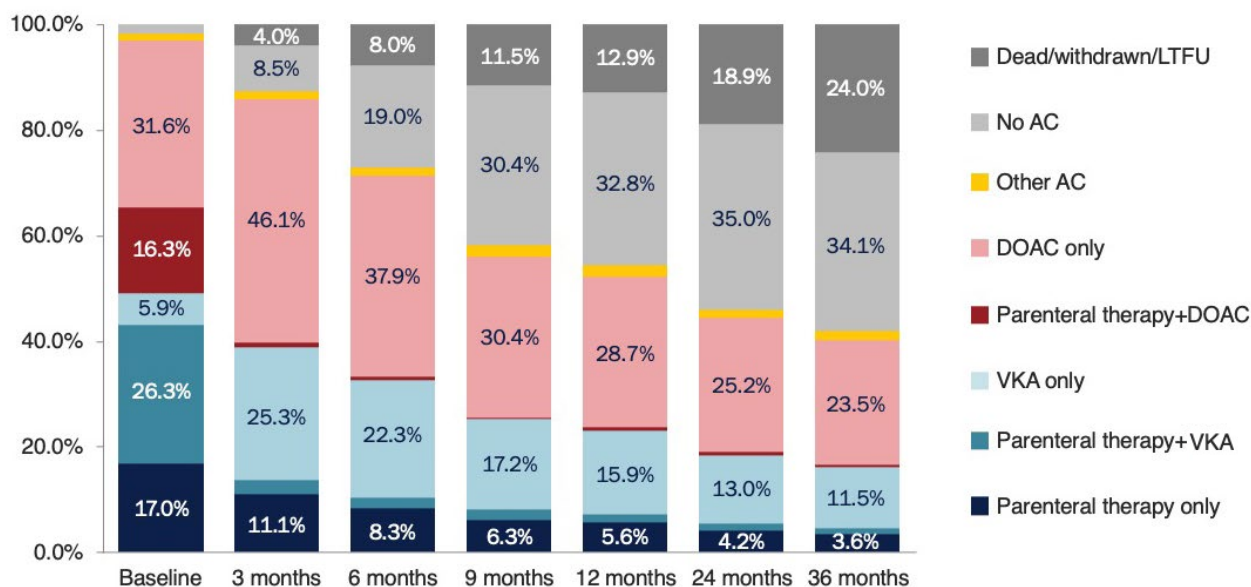
Kakkar concluded the introduction by highlighting the challenges faced in the management of high-risk patient populations, both in terms of addressing the pathophysiology underlying the thrombosis risk and implementing interventions that lead to favourable clinical outcomes. Ensuring that patients with cancer who already have a high burden of treatment can adhere to anticoagulation therapies over time is also vitally important.

## Cancer-Associated Thrombosis: Burden of Disease and Current Treatment Options

### Mari Thomas

Thomas began her presentation by describing the dramatic increase in the incidence of VTE in patients with cancer during the past 20 years.<sup>10</sup> As patients with cancer are living longer, the incidence of CAT has increased markedly,<sup>10</sup> where the main driver of this increase is the improvements in cancer treatments. However, the increased thrombotic risk associated with some of these anticancer therapies also needs to be taken into account. Thomas also emphasised the considerable burden associated with CAT, as illustrated by a study reported in

**Figure 1: Patterns of anticoagulation prescription over time in patients with a venous thromboembolism enrolled in the GARFIELD-VTE registry.<sup>8</sup>**



AC: anticoagulant; DOAC: direct oral anticoagulant; LTFU: long-term follow-up; VKA: vitamin K antagonist.

2007 by Khorana et al.,<sup>11</sup> which reported that thromboembolism was the second leading cause of death in patients with cancer who were receiving outpatient chemotherapy.<sup>11</sup> Although CAT is less common in early-stage cancer since these patients have a better prognosis, they may have more to gain from anticoagulant treatment.<sup>12</sup> However, anticoagulation in patients with cancer can be more challenging than in patients without cancer, as highlighted in a study by Prandoni et al.,<sup>13</sup> which evaluated outcomes for patients with a clinically suspected deep vein thrombosis (DVT) who received initial treatment with unfractionated heparin or low molecular weight heparin (LMWH) followed by a vitamin K antagonist (VKA) for at least 3 months.<sup>13</sup> In this study, the 12-month cumulative incidence of a recurrent VTE was 20.7% in patients with concomitant cancer, compared with only 6.8% in patients without cancer.<sup>13</sup> The 12-month cumulative incidence of major bleeding was also considerably higher in patients with versus without cancer (12.4% versus 4.9%).<sup>13</sup> The outcomes for patients with CAT have improved; the introduction of DOACs has reduced the risk of recurrent VTE for patients with CAT,<sup>14</sup> but

the high risk of bleeding remains a key unmet need, particularly for patients with GI or GU cancers.<sup>15,16</sup> For example, a meta-analysis of four clinical trials showed that patients with CAT had a 38% reduced risk of recurrent VTE if they were treated with a Factor Xa (FXa) inhibitor compared with LMWH.<sup>14</sup> However, in this same analysis, a trend for an increased risk of major bleeding was observed with the FXa inhibitors, although this did not reach statistical significance.<sup>14</sup> In the Hokusai VTE Cancer and SELECT-D studies, this increase in major bleeding was driven predominantly by patients with GI cancers.<sup>15,16</sup> In the CARAVAGGIO trial, the risks of major bleeding were similar between the LMWH and apixaban groups, although Thomas noted that there were fewer patients with upper GI cancers enrolled in this study, compared with the Hokusai VTE Cancer and SELECT-D studies.<sup>17</sup> Based on the available evidence, international clinical guidelines now recommend the use of DOACs in patients with CAT, with most stating that DOACs and LMWH are preferred over VKAs.<sup>18-22</sup> However, there remains a degree of uncertainty in the guidelines for patients at a high risk of bleeding, such as those with GI or GU cancers. For these



patients, guidelines currently recommend using DOACs cautiously,<sup>18,20,22</sup> or using LMWH in preference.<sup>21</sup>

Thomas also highlighted several unmet needs for patients with CAT who are receiving anticoagulation therapy, including the increased risk of bleeding compared with patients without cancer, and the challenges associated with prescribing for patients with brain metastases, renal impairment, low platelets, or poor GI absorption due to nausea and vomiting. Physicians should also consider the impact of other cancer treatments when prescribing anticoagulants for CAT, including drug interactions with anticancer therapies, and the potential for disruption to treatment for surgery. Thomas emphasised that there remains a considerable degree of uncertainty in the field of CAT, as current therapies have limitations, and there are still patients who cannot be managed effectively with currently available treatments. Also, higher-risk patients are often excluded from CAT studies, which means that the results from randomised controlled clinical trials may not always be generalisable to all patients with CAT. With patients with cancer living longer, persistence with anticoagulants is particularly key, and patients with active cancer should be considered for long-term anticoagulation therapy after a venous thromboembolic event. However, adherence to anticoagulants is known to be poor in patients with CAT, and this challenge was recently highlighted in a real-world claims-based study presented at the American Society of Clinical Oncology (ASCO) conference in 2022.<sup>23</sup> In this study, the median treatment time was only 3.2 months for DOACs and warfarin, and 1.8 months for LMWH.<sup>23</sup> Therefore, patients with CAT received anticoagulants for a markedly short duration compared with that recommended in international guidance. Thomas concluded the presentation with a summary of the significant progress that has been made in the field in recent years. However, she highlighted that this progress mainly relates to efficacy, and the principal issue that still remains is the increased bleeding rates in this population. To address this issue, therapies that target FXI are of increasing interest.

## New Antithrombotic Approaches: The Promise of Targeting Factor XI

Paula Bolton-Maggs

Currently available anticoagulants function by either blocking thrombin or FXa (DOACs and heparin), or depleting vitamin K levels and preventing the activation of clotting factors (VKAs). These agents reduce the risk of thrombosis, but with a concomitant increase in bleeding risks, particularly for high-risk patients. For example, in elderly patients with atrial fibrillation, annual rates of major bleeding on DOACs can be as high as 12%.<sup>24</sup> As an alternative, novel agents are being developed that target the contact activation system, including therapies that target Factor XII and FXI. These agents are currently being investigated in animal and human studies, with preliminary data showing that reducing FXI activity can reduce the thrombotic risk without increasing the risk of bleeding.<sup>25,26</sup>

Factor XI is an appealing target for antithrombotic drugs for several reasons. Firstly, congenital FXI deficiency results in only a mild bleeding disorder, and is only associated with bleeding after surgery in areas of high fibrinolytic activity, such as the mouth and GU system.<sup>27</sup> Secondly, deficiency of FXI is not associated with spontaneous bleeding.<sup>27</sup> Thirdly, there is a minimal relationship between FXI coagulant levels and bleeding risk, but there is an association between high FXI levels and thrombosis.<sup>25,27,28</sup> Finally, there is a surprisingly high prevalence of congenital FXI deficiency in the general population across continents, suggesting that there may even be a possible survival advantage to having lower levels of FXI.<sup>29</sup>

These observations can potentially be explained by emerging data that indicate FXI is an attractive target for new anticoagulants, as it may be critical in thrombosis development but only plays a minor role in the physiological process of haemostasis.<sup>30</sup> In haemostasis, FXI acts at the interface between the process of tissue factor-initiated thrombin generation and the contact activation pathway (the kinin-kallikrein system).<sup>31,32</sup> In this model, FXI(a) has only a supporting role in haemostasis and does not make a significant contribution if a strong tissue factor signal is present.<sup>32</sup> Conversely,

there is a growing body of evidence supporting an important role of FXI in thrombosis. To begin with, FXI deficiency has been shown to protect against thrombotic stroke,<sup>33</sup> DVT,<sup>34,35</sup> and cardiovascular events (composite of myocardial infarction [MI], stroke, and transient ischaemic attacks).<sup>35</sup> In addition, in large case-control studies, high levels of FXI were associated with an increased risk of VTE<sup>36,37</sup> and MI.<sup>38</sup> Finally, treatment of patients deficient in FXI with FXI concentrates has resulted in thrombotic events.<sup>39</sup> A role for FXI inhibition in anticoagulation is also supported by animal studies. For example, Factor XII and FXI knockout mice are protected from arterial and venous thrombosis without evidence of bleeding.<sup>40,41</sup> Studies with antisense oligonucleotides that reduce the hepatic synthesis of FXI in rodents and monkeys have also demonstrated the prevention of thrombosis without excessive bleeding.<sup>42</sup>

Bolton-Maggs also discussed the factors that may contribute to the variable bleeding risk observed in individuals with FXI deficiency, including low normal levels of other coagulation factors. Importantly, the capacity for thrombin generation is not related to the activated partial thromboplastin time-based FXI level. To illustrate this, Bolton-Maggs described a patient with congenital FXI deficiency and a history of thrombotic events, including MI and spontaneous DVT. Despite low FXI activity, thrombin generation was similar to a control patient at all tissue factor concentrations, indicating that the concentration of tissue factor rather than the activity of FXI affected thrombin generation (Gillian Pike, personal communication). Bolton-Maggs also explained that thrombin generation tests under specific conditions with low tissue factor concentration could identify patients with FXI deficiency and a history of bleeding from patients with a similar deficiency but no bleeding tendency. In 2015, Pike et al.<sup>43</sup> published a study that showed that a thrombin generation assay performed in platelet-rich plasma with the inhibition of the contact activation pathway could identify patients deficient in FXI with a known bleeding tendency.<sup>43</sup>

Several agents are currently under clinical development that target FXI, including antibodies, small molecules, natural inhibitors, antisense oligonucleotides, and aptamers. Although there are some similarities between

these agents, there are also many differences, which may affect their efficacy, safety, and level of patient adherence, which all must be considered, if approved, in the real-world clinical setting (Table 1).<sup>25</sup> Results from clinical trials will be required to determine which will be the most appropriate agent to meet a particular clinical need.

Agents currently in clinical development include abelacimab, a fully human monoclonal antibody that binds to FXI and locks it in the zymogen (inactive precursor) conformation.<sup>3</sup> In studies in healthy volunteers, abelacimab treatment was safe and well tolerated, and resulted in robust and sustained prolongation of activated partial thromboplastin time and FXI suppression.<sup>44,45</sup> Abelacimab was subsequently studied in a randomised Phase II trial in patients receiving a total knee arthroplasty.<sup>3</sup> Patients receiving a total knee arthroplasty are typically the model of choice for proof-of-concept studies of new anticoagulants due to the high bleeding risk associated with this procedure, and the short duration of anticoagulation. In this study, a single intravenous infusion of abelacimab at doses of 75 mg or 150 mg was effective for the prevention of VTE, and showed superiority over daily LMWH (enoxaparin [Figure 2A]).<sup>3</sup> A low risk of bleeding was observed in all treatment arms in this study (Figure 2B).<sup>3</sup> The evidence supporting abelacimab has also been expanded by four pre-clinical *in vitro* studies presented at ISTH 2022. These studies demonstrated that pharmacodynamic interactions between abelacimab and two commonly used antiplatelet agents, aspirin and ticagrelor, are unlikely;<sup>46</sup> that abelacimab had no impact on platelet aggregation *in vitro*;<sup>47</sup> that recombinant Factor VIIa can potentially be used to manage bleeding in patients treated with abelacimab;<sup>48</sup> and that abelacimab may be a useful anticoagulant for patients receiving haemodialysis.<sup>49</sup>

Asundexian is a small molecule oral agent that targets FXI and is currently in clinical development. In a randomised, double-blind, Phase II study (PACIFIC-AF) in patients with atrial fibrillation, asundexian at doses of 20 mg or 50 mg resulted in reduced bleeding when compared with the DOAC apixaban (Figure 2C).<sup>7</sup> Although the results from this study were promising, there were several limitations which must be taken into consideration, including

Table 1: Properties of anticoagulant therapies targeting Factor XI.

	Antibodies <sup>44-47</sup>	Small molecules	Natural inhibitors	ASOs	Aptamers
Mechanism	Bind target protein	Bind target protein	Bind target protein	Block biosynthesis	Bind target protein
Administration route	IV or SC	IV or oral	IV	SC	IV or SC
Administration frequency	Monthly	Daily	Daily	Weekly to monthly	Daily
Onset of action	Rapid	Rapid	Rapid	Slow	Rapid
Offset of action	Slow	Rapid	Rapid	Slow	Rapid
Renal excretion	No	Yes	Uncertain	No	No
CYP metabolism	No	Yes	No	No	No
Potential for drug–drug interactions	No	Yes	Unknown	No	No

*Adapted from Fredenburgh and Weitz<sup>25</sup>*

ASO: antisense oligonucleotide; CYP: cytochrome P450; IV: intravenous; SC: subcutaneous.

the fact that the trial was not powered to test differences in thrombosis rates between groups. In addition, the number of bleeding events was half of the anticipated number, and no major bleeding events occurred. As a result, the magnitude of the effect of asundexian compared with apixaban could not be accurately determined.<sup>50</sup> There are several FXI inhibitors in clinical development, and results obtained so far suggest no increased risk of bleeding.<sup>3,7</sup>

Although clinical data for these investigational FXI inhibitors are promising, Bolton-Maggs cautioned that real-world experience might be different, as patients are very carefully selected for clinical trials. In particular, other factors may influence the capacity for thrombin generation, which may relate to bleeding risk. Furthermore, reversal of FXI inhibition may be required for patients requiring emergency invasive procedures. Although it should be noted that both tranexamic acid and low-dose recombinant FVIIa have been shown to be effective for

patients with congenital FXI deficiency with inhibitory antibodies, and therefore a similar strategy may be of value for patients receiving therapeutic FXI inhibitors who are bleeding or undergoing invasive procedures.<sup>51</sup> Bolton-Maggs concluded her presentation by emphasising that there is a need for further studies in atrial fibrillation and CAT to provide more information on the efficacy and bleeding risks associated with FXI inhibition in these clinical settings.

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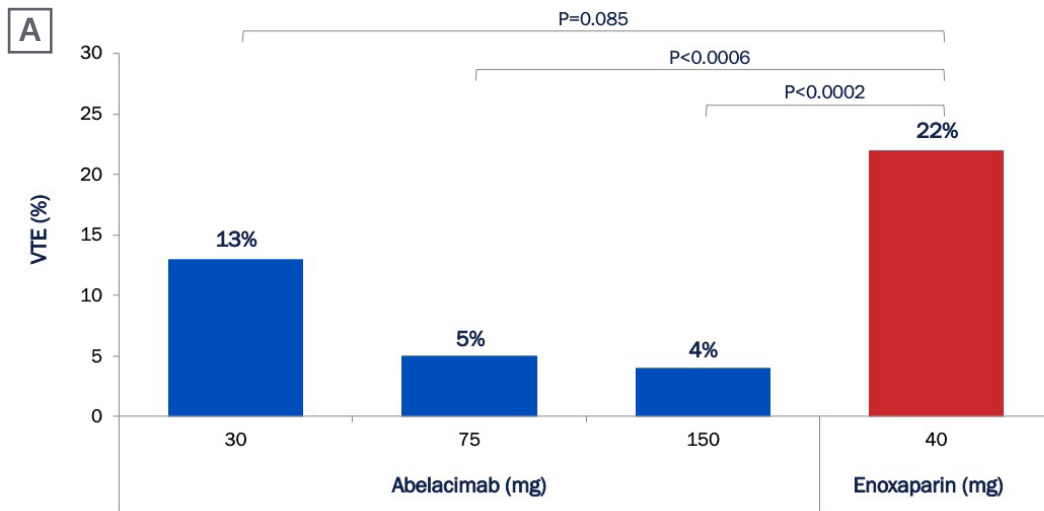
## Designing Trials for the Treatment of Cancer-Associated Thrombosis

Giancarlo Agnelli

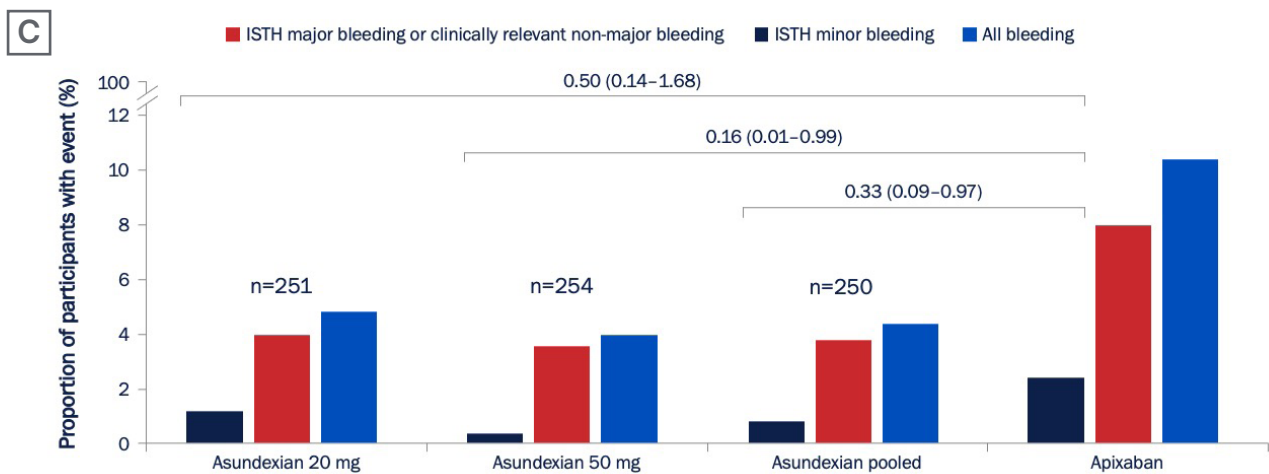
Agnelli began his presentation by acknowledging that DOACs are an effective alternative to LMWH in a large spectrum of patients with VTE and cancer, with the advantage of improved practicality compared with daily administered



Figure 2: Rates of (A) venous thromboembolism and (B) bleeding in patients receiving abelacimab or enoxaparin after total knee arthroplasty in the ANT-005 TKA Phase II trial,<sup>3</sup> and (C) rates of bleeding in patients with atrial fibrillation receiving asundexian or apixaban in the PACIFIC-AF Phase II trial.<sup>7</sup>



	Abelacimab, 30 mg (N=102)	Abelacimab, 75 mg (N=104)	Abelacimab, 150 mg (N=99)	Enoxaparin, 40 mg (N=104)
Major or clinically relevant nonmajor bleeding to day 30 – no. (%)	2 (2)	2 (2)	0	0
Major bleeding – no. (%)	0	1 (1)*	0	0
Clinically relevant non-major bleeding – no. (%)	2 (2)	2 (2)	0	0
Receipt of blood transfusion up to day 30 – no. (%)	6 (6)	8 (8)	9 (9)	7 (7)



ISTH: International Society on Thrombosis and Haemostasis; no.: number; VTE: venous thromboembolism.

parenteral therapies. However, unmet clinical needs remain, including reducing the risk of bleeding complications, particularly in those patients with a tumour that originated in the GI tract. Therefore, patient characteristics, including bleeding risk, cancer origin, and comorbidities must be carefully considered when prescribing DOACs.

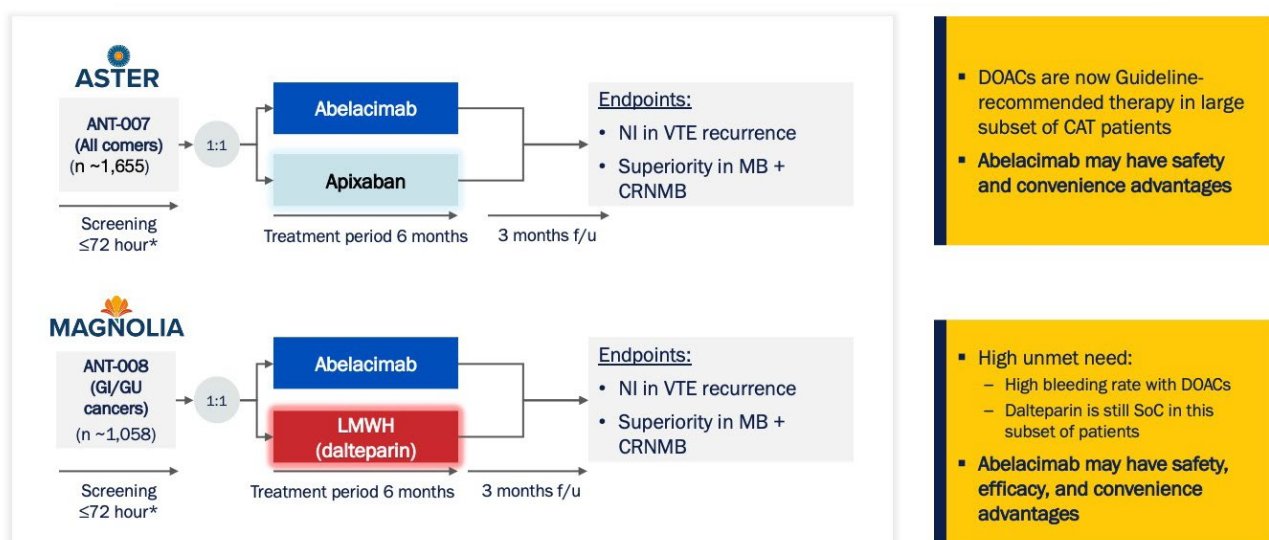
To address this unmet need, clinical trials should be designed to determine whether it is possible to reduce rates of clinically-relevant bleeding while maintaining the efficacy that has been observed with DOACs. Selecting an appropriate population for a clinical trial of anticoagulants for CAT is critical, as rates of VTE recurrence and bleeding can vary between different cancer sites. In a sub-analysis of the CARAVAGGIO study, the highest rates of VTE recurrence occurred in patients with gynaecological cancer (10.9%) and GI cancer (8.8%).<sup>52</sup> The prevalence of major bleeding was greatest in patients with GI or GU cancer (7.2% and 4.8%, respectively).<sup>52</sup>

Agnelli highlighted the two ongoing Phase III trials from the abelacimab Phase III CAT programme (Figure 3). These two complementary

studies are aiming to enrol approximately 2,700 patients across 220 sites in more than 20 countries. This is the largest program of any anticoagulant performed in CAT to date.

The ASTER and MAGNOLIA Phase III trials are international, multicentre, randomised, open-label, blinded endpoint evaluations that have been designed to address a key unmet need for patients with CAT, the risk of clinically-relevant bleeding.<sup>53,54</sup> ASTER is designed to compare abelacimab to apixaban in patients with CAT for whom DOAC treatment is recommended.<sup>53</sup> In contrast, MAGNOLIA is designed to compare abelacimab to LMWH (dalteparin) in patients with a GI or GU cancer-associated VTE, for whom DOAC treatment is not recommended due to the increased risk of bleeding.<sup>54</sup> In both studies, the primary endpoint is the non-inferiority of abelacimab at preventing VTE recurrence, and the secondary endpoint is to show superiority of abelacimab versus apixaban (ASTER) or dalteparin (MAGNOLIA) in the rates of major bleeding and clinically-relevant non-major bleeding.<sup>53,54</sup> The comparator arm for both trials represents the current standard of care in their respective patient populations.

Figure 3: Abelacimab Phase III cancer-associated thrombosis programme.<sup>53,54</sup>



\*SoC treatment during screening.

CAT: cancer-associated thrombosis; CRNMB: clinically relevant non-major bleeding; DOAC: direct oral anti-coagulant; f/u: follow-up; GI: gastrointestinal; GU: genitourinary; MB: major bleeding; NI: non-inferior; SoC: standard-of-care; VTE: venous thromboembolism.

## Closing Remarks

### Gary Raskob

Raskob concluded the symposium by emphasising the large unmet need to reduce the risk of major and clinically-relevant bleeding in patients with CAT, particularly for those with GI or GU cancer. Many of these patients remain inadequately anticoagulated due to the fear of bleeding, and clearly safer and more tolerable antithrombotic strategies are required to reduce the burden of VTE in this population. As an alternative to agents targeting FXa, thrombin, or vitamin K, FXI has recently emerged as an attractive therapeutic target for anticoagulants. Patients with congenital FXI deficiency have been studied for decades, and all the evidence collected to date suggests that these patients are at no higher risk of intracranial or GI haemorrhage than the general population.<sup>50</sup> This

is reassuring and suggests that FXI inhibitors might be associated with fewer and less life-threatening bleeding episodes. Phase II studies completed to date with FXI inhibitors have yielded promising results, and have shown that FXI inhibition is efficacious at preventing VTE without increasing the bleeding risk.<sup>3,7</sup> However, further studies are now needed to confirm these preliminary results. For patients with CAT, the ongoing Phase III ASTER and MAGNOLIA studies are designed to address current unmet needs in this population, including reducing bleeding risk and increasing adherence to therapy. The potential results that may be generated from the ASTER and MAGNOLIA studies has been recently recognised by a regulatory agency, where the U.S. Food and Drug Administration (FDA) has granted fast-track designation to abelacimab as a treatment for CAT, reflecting the large unmet need in this population.<sup>55</sup>

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# Interview



## Yann Le Cam

Chief Executive Officer, EURORDIS-Rare Diseases Europe

**Citation:** EMJ. 2022;7[3]:40-44. DOI/10.33590/emj/10118971.  
<https://doi.org/10.33590/emj/10118971>.

### **Q1** How did you enjoy the 11<sup>th</sup> European Conference on Rare Diseases (ECRD) and what were your highlights from this event?

The conference happens every 2 years and the purpose is to formulate strategies at a national, international, and European level. The conference also provides an opportunity to look at legislative and non-legislative policies and learn about the latest research. The scope is broad, covering the entire spectrum of rare diseases.

Essentially, ECRD is a policy conference. We want to promote certain areas of policy with the help of the Programme Committee, speakers, and stakeholders. The virtual format worked well. We had a great studio in Paris, France, for the plenary sessions and most of the presentations that took place online were live. In addition, professionals and patients had the opportunity to record testimonials in advance of the conference. Being online definitely allowed for seamless attendance.

### **Q2** What were the recommendations from the Rare2030 Foresight Study?

Firstly, let me state the issue. There are approximately 6,000 different rare diseases, which are currently estimated to affect 20 million people throughout

the 27 European Union (EU) Member States and 30 million individuals in the World Health Organization (WHO) European Region. Seventy percent of these rare diseases appear in childhood. Furthermore, 94–95% have no specific treatments approved. That does not necessarily mean that patients are not taking treatment because there is the option to use off-label medications in some instances. Clearly, the unmet needs are still extremely high and not yet satisfied. In terms of diagnostics, the average time to diagnosis is still 5 years across Europe and across all rare diseases. Obviously, it has improved in the last 10–20 years for some rare diseases; however, the average remains 5 years, which is not acceptable.

It was for the above-mentioned reasons that the Rare2030 Foresight Study was conducted. We have 20–30 years of action to reflect on in Europe, the USA, and internationally. Based on this knowledge base, can we identify big trends in terms of science, healthcare, product development, and social services over the next 10–20 years? Answering this question was the purpose of Rare2030. Next, a multistakeholder platform developed four scenarios based on the results of the analysis. At the 2020 conference, the community then voted on one of the scenarios. Based on that scenario, the

multistakeholder platform synthesised eight recommendations. The main recommendation is that we need a new policy framework in Europe for the next 10–15 years. We also need to put an end to policy silos.

The study concluded by emphasising that we need a strategy for rare diseases, which is based on our current level of knowledge, maturity, and opportunities in science. We also need to set goals. This represents a substantial transformation because the focus is no longer on creating centres of expertise, establishing registries, or product production. Ten years from now, we are hoping to achieve diagnosis within 6 months instead of 5 years; we should have 1,000 new products, of which 30–40% are curative for rare diseases; we should reduce premature mortality in children aged less than 5 years by one-third; and, finally, we should reduce the socioeconomic burden faced by families by one-third. We believe that these goals can be reached with the appropriate strategy. So, this was the main outcome of Rare2030. The seven other recommendations detail how these goals can be achieved.

### **Q3** How important was the ECRD conference in delivering the messages of Rare2030?

Thanks to our speakers, it was very important. The conference was an official event of the French Presidency of the Council of the EU. It took place after the high-level conference on rare diseases we held on 28<sup>th</sup> February in Paris at the Ministry of Health, which involved EU Member States. This time, it was a community and stakeholder event but with the label of the French EU Presidency. The ongoing Czech Presidency will organise an expert conference on 25<sup>th</sup>–26<sup>th</sup> October in Prague, Czechia, in order to continue moving the needle towards a new European action on rare diseases.

The conference helped to deliver the message of commitment from Member States such as France, Czechia, and Sweden. The Belgian and Spanish health ministers were also in attendance. These countries were calling for greater collaboration in different areas of healthcare and the implementation of actions to increase access to medicines and diagnostics.

The second strong message was from the European Parliament. Several members of the European Parliament participated in the ECRD conference, and they referred to their previous plenary session organised on 24<sup>th</sup> November 2021 in Strasbourg, France. This plenary session was dedicated to rare diseases and involved 19 members of the European Parliament from different parties, countries, and committees. They were united in their call for a new European action plan on rare diseases. During the ECRD conference, they argued that action had to be taken in 2022–2023. The European Court of Auditors also had a representative. Two years ago, they published a report on cross-border healthcare and concluded that there was a need to revise the policy on rare diseases in order to take into account new developments. The European Commission (EC) agreed to this and, therefore, it should be delivered. The above messages were also echoed by industry representatives as well as clinicians and researchers. Clearly, the community knows what they want and there is no lack of concrete solutions.

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**"We wish Europe to be a leader in the development of innovative therapies, not just a follower of the USA"**

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**Q4** Was there an active decision by the Programme Committee to include topics such as health data ecosystem, General Data Protection Regulation, sustainability, infrastructure? How are these decisions made?

The Programme Committee wanted to concentrate on the question of data because it is important in diagnostics, healthcare management, and the development of and access to medicines. Regarding diagnosis, in the context of the European Health Data Space, it is agreed as one of the standards that in a patient's electronic record, the rare disease will be mentioned. Not only are there International Classification of Diseases (ICD) codes but there are also ORPHA codes (codes of the rare diseases). In the future, this will enable a better and more harmonised collection of quality data. Clearly, this is very important in the context of research. Data is also important at the time of diagnosis. There is a common standard for recording the genotype and phenotype and this means we know the exact profile of an individual. Again, this is crucial for future research. We are able to quickly identify the number of patients with a particular geno-clinical profile and then conduct research, especially clinical trials.

Healthcare digitalisation was also discussed at the conference. As a result of the COVID-19 pandemic, there have been rapid developments in the fields of teleconsultation and telemedicine, which are welcomed by patients and their families as well as healthcare professionals themselves. At this year's ECRD, there was discussion around the governance aspect and execution of these technologies within EU Member States.

**Q5** At the conference, you spoke in the session 'Can Europe be attractive and sustainable at the same time?' What did this session focus on and how was this addressed with regard to therapies for rare diseases?

We wish Europe to be a leader in the development of innovative therapies, not just a follower of the USA. On the one hand, we are seeing more possibilities to create startup companies in Europe and more access to funding. However, when we look at the products approved in Europe, they are mostly derived from USA-based companies. This is why we are calling for a policy that makes Europe more attractive. The regulatory environment is essential to achieving this. This includes incentives in the upcoming revisions of regulations on orphan drugs and paediatrics; the overall regulatory framework, such as conditional marketing approval and co-ordination between the European Medicines Agency (EMA) and Health Technology Assessment (HTA); and measures to accelerate and de-risk therapeutic development within Europe.

Non-legislative policies are also important. For instance, we need European networks not just for care but also for rare diseases and clinical research. Care networks should be focused on natural history study, registries, research on clinical endpoints, and patient-reported outcomes, which are key elements to perform a clinical trial. Such networks exist in the USA and we hope to align the two networks and share the same standards. This will allow us to conduct trials across the continent quickly.

Although we might have more products approved, this alone is not sufficient. They need to be accessible and sustainable for society and payers. This will require competent authorities within EU Member States to collaborate at the European level and negotiate the price. This is particularly true for the most expensive medicines, such as biologics or cell and gene therapies, which are used for rare diseases.

**Q6** In her winning speech, the recipient for the 2022 Young Patient Advocate Award, Danielle Drachmann said: "I am an expert by necessity, not an expert by choice." What is your take on this?

I think this is an excellent definition of patient advocacy. It is not something you have chosen. Instead, you are trying to transform your personal story into a collective action, which generates public interest and ultimately creates benefit. Importantly, it is not just to help yourself or the current generation. It extends to the next generation and across all rare diseases. The actions of patient advocates will likely have long-term and far-reaching impact. This is particularly true in the context of clinical trials. Specifically, the motivation for a patient advocate to participate is only 30% for themselves and 70% to help others. Personally, I find this extraordinary. So, your expertise is based on experience but also knowledge. You have to learn and therefore we offer plenty of training opportunities.

**Q7** Do you think there are enough patient advocates on boards and in committees for rare diseases? What efforts could be made by organisations to involve patient advocates in scientific advice and protocol assistance?

The short answer is "Yes" for today's needs but "No" for tomorrow's needs. As you mentioned, what we have tried to do over the years is not only promote policies based on the needs and perspectives of the people but also to promote solutions. The other very important part of our strategy is to be part of the execution. That means being part of the management boards, scientific committees, and assessments. For that reason, at the EMA there are patient representatives on the different scientific committees, including orphan drugs, paediatrics, pharmacovigilance, and in many other subgroups. More and more, we have been able to involve patient representatives in scientific advice and protocol assistance at the EMA, which is great.



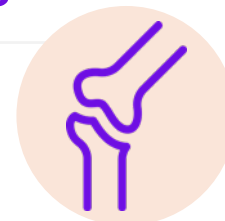
However, we are not always able to have the participation of patient representatives. Although we can typically identify a patient representative for a particular disease, you also need to find someone who can speak on the disease beyond their own case. This requires several years of experience at the collective level and at the national, European, or international level. It also means that they will need to speak English. All these meetings are in English, which is a big barrier. Ideally, you also need to have them trained in the basics of protocol assistance and scientific advice as well as the essential steps of a clinical trial. In order to have an impact, patient representatives need to bring something specific to the discussion. To do that, we have developed the EURORDIS Open Academy training courses, which is on clinical trials, drug development, and European clinical affairs. We have also developed workshops on HTA as well as pricing and reimbursement. We have schools focusing on various diagnostic aspects, research, and healthcare organisation at the European level. We have also contributed to initiatives such as Patient Engagement

Through Education (EUPATI). However, we need to scale up. We need more patient representatives not only for the EMA but also for HTA, especially now that patients will be involved in the early scientific advice of HTA and the joint clinical assessment. We also need patient representatives to work with industry along the value chain of the medicine. This could encompass the different steps of development, ranging from early research to access. Importantly, the same patients cannot be involved with both industry and the public regulators or HTA. Therefore, we require double the capacity.

Also, you do not want just one patient representative speaking about a specific disease. In each procedure, you want to have at least two from two different countries. You also need to have representatives across a large number of diseases. This is because of the unmet needs and also the rapidly growing pipeline of projects under development. For each of these therapeutic areas, we should have several patient representatives ready to engage with the developers of medicinal products and also with the authorities. So, we need to expand the training of patients advocates. I am confident that we can achieve this because there is a new generation across Europe, who usually speak more English than previous generations. There is also more openness to working online. We need resources to do this but it remains one of our objectives. ●



# Tackling Unmet Medical Need: How Slow-Release Intra-articular Corticosteroids Could Play a Role in Improving Quality of Life and Reducing Risk in Osteoarthritis



<b>Interviewees:</b>	Philip Conaghan, <sup>1</sup> Lee S. Simon <sup>2</sup>
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<b>Disclosure:</b>	Conaghan reports consultancies or speaker fees from AbbVie, BMS, Eli Lilly, Galapagos, GSK, Merck, Novartis, Stryker, and UCB. Simon is a consultant for Eupraxia and Xalud including injectable therapies; has consulting fees from Affinergy, Astrazeneca, Abraxis, Alpha Rx, NuvoResearch, Roche, Pfizer, Novartis, PLx Pharma, Hisamatsu, Dr Reddys, Avanir, Cerimon, Leerink Swann, Alimera, Nomura, Luxor, Paraixel, Bayer, Rigel, JP Morgan, Regeneron, XTL, Inmedix, Eupraxia, Fidelity, Extera, Wyeth, Asahi, Samumed, Metabolex, Shire, Anthera, Antares, Vical, Daiichi Sankyo, Flexion, AcelRx, Inotek, Gilead, Sandoz, Knopp, Abbott, Omeros, Jazz, Takeda, Teva, Zydus, Proprius, Alder, Cephalon, Purdue, EMDSerono, Altea, Talagen, Tigenix, Agenus, Forest, Genzyme, CaloSyn, pSivida, Horizon, Pozen, Eicos Sciences, Analgesic Solutions, Kowa, Array, JRX Biopharm, Imprimis, Dara, Genco, Neos, Durect, Sanofi, Lilly, Idera, Medac, Remedy, and Kiniksa.
<b>Acknowledgements:</b>	Medical writing assistance was provided by Amanda Barrell, Brighton, UK.
<b>Support:</b>	The publication of this article was supported by Eupraxia.
<b>Disclaimer:</b>	The opinions expressed in this article belong solely to the named interviewees.
<b>Citation:</b>	EMJ. 2022;7[3]:45-51. DOI/10.33590/emj/10023791. <a href="https://doi.org/10.33590/emj/10023791">https://doi.org/10.33590/emj/10023791</a> .



## Interview Summary

Osteoarthritis (OA) is the fastest growing cause of disability worldwide, but, with few proven therapeutic options, it is an underserved condition. With increasingly ageing populations contributing to a rising global prevalence, this unmet need only threatens to worsen in the coming years. To date, researchers have tried and failed in their bids to develop new ways to treat the pain and loss of function that significantly impacts health-related quality of life (HrQoL) and leaves people vulnerable to accumulating disability and at risk of cardiovascular disease (CVD), comorbidities, and mortality. Now, a novel way to deliver one of the only proven interventions for pain and inflammation, corticosteroid injections, is on the horizon for knee OA. Slow-release formulations could possibly prolong the clinical benefit of a single injection from 6 weeks to 6 months, providing a new option to improve HrQoL for people with OA, and maybe even breaking the cycle of inflammation that likely contributes to progression.

In this key opinion leader article, Philip Conaghan and Lee Simon discuss OA's significant Quality of life (QoL) and long-term health impact. They also outline the current, inadequate treatment landscape, and explain how slow-release corticosteroids could potentially help tackle a huge unmet medical need.

## THE LONG SHADOW OF OSTEOARTHRITIS

OA is a chronic disease of the joints that causes pain, inflammation, and loss of function. The progressive condition, characterised by multiple tissue pathologies involving cartilage, bone, and synovium, can lead to disability that may necessitate joint replacement. Affected joints vary, but the most common site is the knee, followed by the hand and the hip.<sup>1</sup> While younger people may experience trauma-initiated OA, it is primarily an age-related condition attributable to slow accumulation of structural damage over time.<sup>1</sup> In line with ageing populations worldwide, its prevalence among older people is on the increase. Data from the 2019 Global Burden of Disease (GBD) study show a 113.25% increase in cases, from 247.51 million to 527.81 million, between 1990 and 2019. The same period also saw a 114.5% increase in years lived with disability caused by OA.<sup>1</sup>

OA is the fastest growing cause of disability worldwide,<sup>2</sup> and the impact can be significant, said Conaghan. "Not everyone has severe symptoms, but roughly one-third will have severe symptoms with impact on QoL," Conaghan told EMJ. "People have pain and stiffness in their joints, and sometimes this pain and stiffness are inseparable considerations for patients. They then lose muscle strength because they are not using the affected limb properly, which affects mobility." One of the significant impacts of knee arthritis, in particular, they went on, was the loss of function and the associated loss of independence. Even simple things, like getting out of the bath, standing up from sitting, using stairs, or getting out of a car, become tough, adding to a loss of independence, Conaghan explained. "I see people at 45 who have had to give up their physically demanding job and thought they had another 20 years to pay off their mortgage. It is a big deal," they went on.

This loss of mobility can impact every other element of health, explained Simon. "As you are increasingly in pain and disabled, you move around less. This lack of activity, combined with pain raising the blood pressure, leads to an increased risk for CVD," Simon said. A whitepaper submitted to the U.S. Food and Drug Administration (FDA) by March et al.<sup>3</sup> in 2016 said people living with OA had a pooled prevalence for overall CVD pathology of 38.4% and were almost three times as likely to have heart failure or ischaemic heart disease than those who did not have the condition. It also said that OA significantly limited a person's ability to self-manage other conditions, such as diabetes and hypertension, and that this, combined with reduced levels of physical activity, was associated with increased all-cause mortality.<sup>3</sup>

The direct and indirect healthcare system costs associated with OA are also significant.<sup>2,3</sup> In 2003 in the USA, total costs attributable to arthritis and other rheumatic conditions were around 128 billion USD, or 1.2% of the country's gross domestic product for that year. Direct costs from medical expenditure were 80.8 billion USD, while indirect costs from lost earnings were 47 billion USD.<sup>3</sup> In the UK, OA is the leading cause of work absence, costing the economy more than 18 billion GBP yearly. Along with other musculoskeletal diseases, it accounts for almost one-tenth of the total annual National Health Service (NHS) budget and 12% of primary care consultations.<sup>2</sup> "This is a massive burden on the healthcare system," said Conaghan.

## ARID TREATMENT LANDSCAPE

Despite the considerable impact of OA on individuals, society, and healthcare systems, it remains a significant area of unmet medical need with an inadequate treatment landscape. Conaghan explained that QoL loss derived from the pain and loss of function leads to loss of physical fitness, poor sleep, low mood, and fatigue. "These are important to people, they

are a big part of life," they said. Treatment for these important symptoms, however, is lacking, said Simon: "We have nothing to modify what is considered a progressive, destructive disease."

There is weak evidence, for example, to support the efficacy of paracetamol or heat or ice packs in OA.<sup>4</sup> On oral non-steroidal anti-inflammatory drugs (NSAID), which have been available as an OA treatment option since the 1960s and are recommended in the Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis,<sup>4</sup> Simon said: "These drugs are appealing because they decrease pain and inflammation, but they also carry risk." The drugs have been associated with an increased risk of heart attacks and stroke, and can result in mucosal injury in the upper, mid-, and lower gastrointestinal tract, which can bring about ulcers, perforation, and bleeding.<sup>5</sup> "Probably two-thirds of people cannot tolerate or should not be on anti-inflammatory drugs," said Conaghan. "Many people experience burning and dyspepsia after they take the drugs, and if you've got uncontrolled blood pressure, cardiac disease, or kidney problems, you should not be on an anti-inflammatory." This is particularly relevant considering the high number of comorbidities among patients with OA.<sup>6</sup> While gastrointestinal risks are lower with selective cyclooxygenase-2 inhibitor NSAIDs, they are "not absent,"<sup>5</sup> said Simon, adding that while topical NSAIDs are effective and are likely to carry fewer risks, there is currently no evidence regarding their long-term, chronic use. Conaghan also highlighted the practical difficulties associated with using such products. "They probably help, but they may need multiple daily applications, which is not easy for knees if you have trousers or stockings on," he said.

So-called 'weak opioids,' such as codeine, are often recommended, despite the low evidence base and high-risk profile. "They constipate you. If you are old, they can make you have falls, and their efficacy is unclear,"<sup>7</sup> said Conaghan, adding that if they have a benefit, it was likely only to be short-term. Simon agreed, saying that many patients on opioids become dysphoric and experience falls.<sup>7</sup> "If they fall and fracture their hip, one in three will die in the first year," Simon said.<sup>8</sup>

Both doctors said there was limited evidence to support hyaluronic acid injections, or viscosupplementation, which aims to reduce pain and increase function by lubricating the joint. A systematic review and meta-analysis published in the British Medical Journal (BMJ) looked at data from >21,163 randomised participants in 169 trials.<sup>9</sup> The authors found 'strong conclusive evidence' indicating that the approach 'leads to a small reduction in knee osteoarthritis pain compared with placebo,' yet the difference was 'less than the minimal clinically important between-group difference.' Similar results were observed for function, where sub-analysis found a 'small, non-clinically relevant improvement.'<sup>9</sup>

While instant release intra-articular corticosteroid injections can ease OA symptoms, they are far from an ideal treatment option. "They work, and there is evidence that they work, but only in the short term,"<sup>10</sup> said Conaghan. Conaghan also pointed to a 2015 Cochrane review that found the clinically important benefits of corticosteroid injections after 1–6 weeks were unclear.<sup>10</sup>

In terms of toxicity, every joint injection also comes with infection risk, albeit small.<sup>11</sup> In addition, there is an argument that long-term corticosteroid injection use can have a detrimental effect on cartilage integrity.<sup>12</sup> However, Conaghan said just one trial, by McAlindon et al.,<sup>12</sup> had investigated this question with adequate cartilage measurement and there were limitations in the design. "It used eight injections in a two-year period, which in my experience is more than most patients would get," they said, adding that the injections were administered independently of pain. "It did show about 50  $\mu$ m loss of cartilage over two years.<sup>12</sup> It was a small loss: is that clinically meaningful? I have no idea, but I suspect not." Whether corticosteroid use accelerates cartilage destruction is still an open question, said Simon, highlighting a recent head-to-head study that compared intra-articular corticosteroids to hyaluronic acid and found no difference in disease progression.<sup>13</sup> Conaghan and Simon agreed the main concern with corticosteroid injections was the short-term benefits, as repeat injections are burdensome for patients and healthcare systems. "We know how to make people feel better when they have an episode of significant pain, swelling, and inflammation," said Simon. "The problem is how successful is

this therapy? For 2–3 weeks after an injection, you feel better, and most people will stay better for months." However, that is not the case for everyone, meaning more options are still needed.

When all other forms of treatment fail, joint replacement may be the only option. An estimated 33.1% of people with knee OA underwent total knee arthroplasty (TKA) in the USA between 2005 and 2010.<sup>14</sup> In the UK, around 90% of >120,000 knee replacements conducted each year are due to OA.<sup>15</sup> Simon described the surgical intervention's results as a 'miracle,' but added that it was far from perfect. "Does it have risks? Yes. Is everyone a candidate? No," Simon said. Considerations include the patient's age, cardiovascular status, and ability to adhere to post-operative advice. Conaghan said TKA was very effective for people with moderate to severe symptoms, but "it is not straightforward" and "a lot of people do not want a joint replacement. The earlier you have your joint replacement, the more likely you will need revision surgery," Conaghan said. Around 6% of those who undergo TKA will need revision within 5 years. It is a more technically challenging operation that takes longer than original TKA and is associated with a higher risk of complications, including infection.<sup>16</sup> In addition, joint replacement operations are carried out by highly skilled orthopaedic surgeons. As OA prevalence continues to rise, healthcare systems will likely not have the volume of specialist staff needed to meet the corresponding increase in TKA demand, said Conaghan.

They went on to say that preventive, non-pharmacological interventions, including weight loss in patients who were overweight and quadriceps strengthening exercises, are extremely important. However, there is often a lack of support for lifestyle-based approaches in primary care and the community, said Conaghan. What's more, they are most effective when used early in the disease course, and increasing pain, loss of function, and decreased mobility can hinder patients' efforts to remain active and maintain a healthy weight in the long term.

## CHALLENGING PROBLEM

Researchers have attempted to address this unmet medical need for some time, but a lack of knowledge regarding the underlying disease

mechanisms has hampered efforts. Simon described OA progression as a heterogenous, intermittent process, adding: "Although everyone talks of this as being a cartilage disease, the origination is very unclear. In the 1970s, it was believed alterations in the subchondral bone meant the cartilage began to bear more transitional forces, leading to degeneration within the cartilage. However, this has never been resolved, and the aetiology is probably multifactorial and different in different people."

"Whatever the aetiology, relieving pain and maintaining function are among the treatment goals most important to patients," said Conaghan. "All patient surveys show that these are the things they care about, probably because these are the symptoms their loss of QoL is derived from." Any new treatment needs to address these endpoints, but the link between structure and symptoms is far from clearcut.

Simon explained: "There are many experimental therapies trying to alter the natural history of the disease, and some people use the term disease-modifying osteoarthritis drugs. But the question is, what does that mean?" A trial of sprifermin, a recombinant human fibroblast growth factor intra-articular injection, published in 2019, demonstrated small regrowth of cartilage.<sup>17</sup> "But there was no alteration of symptoms, so we do not know what that means, or the clinical relevance." Bisphosphonates, which have slowed progression in animal models of OA, are another candidate with disease-modifying potential. However, a 2-year study of 2,483 patients failed to deliver symptom relief despite recording a reduction in C-terminal crosslinking telopeptide of Type II collagen, a marker of cartilage degeneration in progressive OA.<sup>18</sup> "Some people got better, but it was not going to treat them all. The same thing happened with metalloproteinase inhibitors," said Simon. "Some people have tried TNF inhibitors, others have tried IL-1 inhibitors directly into the joint, none of which have worked."

The challenges to developing new drug products for this patient group are multiple, Simon explained. "It does appear that we might be able to do something for progressive patients, but we do not know how to select them upfront," said Simon, adding that while work to identify biomarkers is underway, it is still in development.



"We are challenged by trial design in the development of drugs and by the heterogeneous nature and progression of the patients," they said.

## **A NEW BREED OF STEROIDS?**

While research into treatments from biologics to cell therapies continues, an ever-growing number of patients remain in pain and accumulating disability. Finding new ways to use existing, proven medications could be the answer to tackling this unmet need.

"When you look at the evolution of steroids, they are a miracle drug," said Simon. "Edward Calvin Kendall, Tadeus Reichstein, and Philip Showalter Hench, who invented synthetic steroids, won the Nobel Prize in Physiology or Medicine 1950 for curing rheumatoid arthritis."<sup>19</sup> Simon went on: "These potent anti-inflammatory drugs work, but they have potential side effects over the long term and only offer short-term benefits."

A new breed of long-acting corticosteroids, however, could tip the risk–benefit profile. Zilretta® (Flexion Therapeutics Inc., Massachusetts, USA), a novel, microsphere-based, extended-release triamcinolone acetonide formulation, has been shown to provide symptom relief for up to 12 weeks.<sup>20</sup> However, it is only available in the USA.

EP-104IAR (Eupraxia Pharmaceuticals Inc., Victoria, British Columbia, Canada), a sustained-release fluticasone propionate, is a promising candidate.<sup>21</sup> Currently in development, it utilises Eupraxia's proprietary Particle Release Technology to enable a low early burst of drug release, followed by steady drug release over time (Figure 1). A Phase I, randomised, double-blind placebo-controlled trial of 32 patients found EP-104IAR well tolerated. While the study was not powered to assess efficacy, the authors analysed patient-reported outcome measures to evaluate pain and symptom relief. They found the product provided an immediate improvement in OA symptoms, and these effects persisted for 8–12 weeks.<sup>21</sup> If the results can be reproduced in larger trials, Conaghan and Simon said, the product could benefit patients, including those requiring repeat injections.

"There are clearly patients who will need recurrent injections to alleviate their pain and improve their function," said Simon. "You want to control their pain and make them more mobile, both of which will improve their blood pressure and decrease cardiovascular risk." The current debate, Simon said, was how often to administer these injections, with many experts advocating for either more or less frequently than thrice yearly. "All of that has never been resolved, and there are no prospective trials that look at it," they said. A corticosteroid injection with a 6-month effect, however, would render the question irrelevant. "I think this might be a very important therapeutic to add to our armamentarium," added Simon.

Conaghan highlighted that this new approach focused on obtaining prolonged benefits from a known, effective therapy. "To be able to leave the drug inside the joint for a longer period addresses two issues. First, if we could give people 6 months of pain relief with a single injection, it could have a lot more effect on their QoL. It would give them the time, function, and ability to work on important things like muscle strengthening." The second potential benefit is less body exposure to the steroid, Conaghan exclaimed. "What you inject into the joint will get absorbed into the bloodstream. The amount is small, but if you are having repeated injections, it could add up over time." Slow-release products could have less effect on serum glucose than immediate-release corticosteroid injections, they suggested, benefitting the metabolism of patients with OA in general, and those with comorbid diabetes in particular.<sup>22</sup>

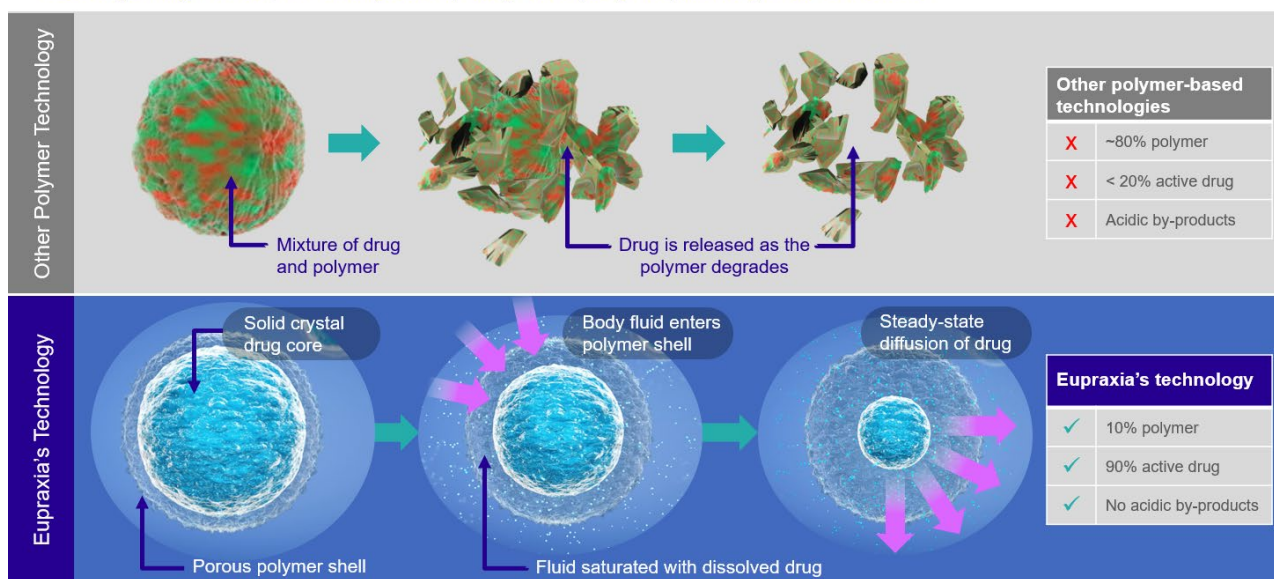
A longer-acting therapeutic effect, Simon went on, could also potentially help break the cycle of inflammation contributing to progression. "This may be very important because the inflammation may cycle from low grade to high grade, but if you break the cycle, it may be quiescent," Simon said. "If you alter this cycle, you might change the degeneration of cartilage: it may not regrow cartilage, but it may not worsen." If this is the case, they went on, it could "change the debate", but trials are still ongoing.

## **CONCLUSION**

OA is a debilitating, disabling condition that negatively impacts QoL, increases

Figure 1: How Eupraxia's particle release technology works.

Steady drug levels, low early burst, very little polymer, locally well tolerated



mortality, and places enormous pressure on healthcare systems. Despite OA's significance and increasing prevalence, the treatment landscape is currently inadequate. There is limited support and resources for non-pharmacological interventions, such as weight loss and muscle strengthening, and the only proven pharmacological treatments, NSAIDs and corticosteroid injections, are far from ideal. In addition, work on disease-modifying osteoarthritis drugs, to date at least, has primarily proved fruitless, leaving a significant area of unmet medical need.

Novel, longer-acting steroids, which may be able to extend the current therapeutic benefit from just weeks to up to 6 months, could be the solution. "If it lasts longer, QoL will be improved, and people will be more mobile. Mobility should give them more control of their blood pressure and more control of their weight, and decreasing weight is associated with decreasing pain in the knees," said Simon. "Social functioning will be improved, and, for those who need to get recurrent injections, they would not have to keep coming back in to see their doctor and get another needle into their joint."

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# Novel Biomarkers and Drug Targets in Non-Small Cell Lung Cancer



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<b>Disclosure:</b>	Dy has received honoraria/consulting fees from AstraZeneca, Eli Lilly, Amgen, and Mirati Therapeutics. Dy did not receive financial compensation for this piece of work.
<b>Acknowledgements:</b>	This article was authored by Eleanor Roberts, Beeline Science Communications Ltd, London, UK.
<b>Support:</b>	The publication of this article is fully funded by Sanofi.
<b>Disclaimer:</b>	The opinions expressed in this article belong solely to the named interviewee.
<b>Citation:</b>	EMJ. 2022;7[3]:52-59. DOI/10.33590/emj/10113934. <a href="https://doi.org/10.33590/emj/10113934">https://doi.org/10.33590/emj/10113934</a> .



## Interview Summary

Despite therapeutic advances, the prognosis of non-small cell lung cancers (NSCLC) is still very poor, especially when first diagnosed at later stages involving metastases. NSCLC classification can be aided by identifying genetic, molecular, and histological subtypes that are important biomarkers in treatment selection. The majority of targeted therapies are now first-line treatment options for eligible patients with advanced stages of NSCLC. Here they have been shown to improve overall survival (OS) and progression free survival (PFS). Such treatments include those aimed at driver mutations in NSCLC, such as the genes for *EGFR* and *ALK*, and immune checkpoint inhibitors such as those targeting programmed death protein 1 or its ligand (programmed death ligand 1 [PD-L1]). In antibody-drug conjugates (ADC), cytotoxic payloads are conjugated to monoclonal antibodies (mAb) that deliver the drug to tumour cells expressing the corresponding target antigen. While there are still no ADCs specifically approved for NSCLC by the U.S. Food and Drugs Administration (FDA), several agents have shown promise and are being investigated as therapy in NSCLC. Emerging biomarkers as targets for ADCs with potential relevance in the treatment of NSCLC include products of the genes *CEACAM5*, *TROP2*, *HER2*, and *c-MET*. Herein, this interview provides an overview of biomarkers and targeted therapies, with a discussion with Grace Dy, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA, on their potential clinical utility.

## INTRODUCTION

Surgical resection is a major treatment approach in early-stage NSCLC, along with chemoradiation for locally advanced disease.<sup>1</sup> For patients with locally advanced or metastatic NSCLC, selection

of therapy for NSCLC depends on several factors, including disease stage, pattern of local and/or metastatic spread, patient performance status, and comorbidities, along with biomarkers such as histological, mutation profile, and protein expression markers.



To better understand how these biomarkers and drugs could be utilised in clinical practice, EMJ discussed the success of current biomarker-based therapies, unmet needs for patients with NSCLC, the use of novel biomarkers in NSCLC, and the potential role of these biomarkers as drug targets, which are being investigated in a number of clinical trials.

## THE SUCCESS OF CURRENT STANDARD OF BIOMARKER-BASED CARE FOR PATIENTS WITH NON-SMALL CELL LUNG CANCERS

Progress is being made in management of late stage NSCLC due to development of targeted therapies against various biomarkers due to better knowledge of tumour biology.<sup>2</sup> Driver mutations in NSCLC include those involving different genes such as *EGFR*, *ALK*, *KRAS*, etc.<sup>2</sup> For patients with newly diagnosed stage IV, relapsed/recurrent advanced NSCLC, and those without actionable oncogenic biomarkers, choice of therapy may include the use of immune checkpoint inhibitors (as monotherapy or in combination with chemotherapy) especially where there are no driver mutations.<sup>1</sup> Such immune checkpoint inhibitors include pembrolizumab, nivolumab, cemiplimab, and atezolizumab, which target programmed death protein 1 or its ligand, PD-L1;<sup>1,3-5</sup> and ipilimumab, which targets cytotoxic T-lymphocyte-associated protein 4, with use dependent on expression levels.

In the advanced setting, biomarker testing is routinely used at diagnosis to select options for first and subsequent lines of treatment.<sup>1</sup> For example, in the UK, National Institute of Health and Care Excellence (NICE) guidelines recommend the use of biomarker testing to detect *EGFR* tyrosine kinase mutations in all patients with previously untreated, locally advanced or metastatic NSCLC.<sup>6</sup> Dy stated that “testing is only carried out when there’s an impact on clinical practice. For example, testing for *EGFR* mutation status in NSCLC was only applicable in the advanced setting before December 2020 in the USA because that’s the only setting where therapy was shown to be effective. However, we now test for *EGFR* mutation status in earlier stages of disease as well as in the adjuvant setting in patients who

meet criteria for adjuvant therapy with the tyrosine kinase inhibitor (TKI) osimertinib.”

In patients with later stages of NSCLC, therapy with inhibitors against these targets can improve median PFS and/or OS.<sup>1</sup> For instance, in people with *EGFR*-mutated tumours and previously untreated locally advanced or metastatic NSCLC, treatment with osimertinib demonstrated a very high overall response rate of 80%, and a median PFS of 18.9 months in the FLAURA study, along with superior OS compared with patients who receive a first generation *EGFR* TKI.<sup>7,8</sup> In patients with treatment-naïve advanced *ALK*-positive NSCLC, the ALEX trial of alectinib showed an overall response rate of more than 80.0%, a median PFS of 34.8 months, and superior 5-year OS compared with crizotinib.<sup>9</sup> For patients with *KRAS p.G12C*-mutated advanced NSCLC previously treated with standard therapies, sotorasib has shown a response rate of around 37.0%, with a median PFS of 6.8 months, and 2-year OS of 32.5% in a pooled analysis.<sup>10</sup>

With results such as these, Dy discussed how biomarker-based treatments that were initially evaluated as second-line therapies have subsequently been approved for first-line therapy.<sup>1</sup> A potential exception to this generalisation, she discussed, are situations where the tumour remains sensitive to immunotherapy despite harbouring actionable mutations such as in NSCLC with a *KRAS p.G12C* mutation. “For those patients,” Dy suggested, “we would still be very comfortable starting with immunotherapy-based treatment because many patients with *KRAS* mutations can derive prolonged duration of benefit from immunotherapy if there are no additional biomarker alterations to suggest inferior outcomes with immunotherapy such as co-mutation with serine/threonine kinase 11.”<sup>11,12</sup>

To illustrate, pembrolizumab has been investigated in a series of studies as mono- or combination therapy for patients with metastatic NSCLC. The KEYNOTE 024 trial showed a median OS of 30.0 months with pembrolizumab alone compared with 14.2 months with chemotherapy alone in patients with *EGFR/ALK* wildtype NSCLC harbouring a PD-L1 tumour proportion score of  $\geq 50\%$ .<sup>4</sup> Where participants were included with any PD-

L1 tumour proportion score of >1%, OS was 17.7 months in the pembrolizumab group compared with 13.0 months in the chemotherapy group.<sup>13</sup> When pembrolizumab was combined with pemetrexed-platinum in non-squamous NSCLC without *EGFR/ALK* alterations, a median OS of 22.0 months versus 10.7 months with chemotherapy alone was shown,<sup>3</sup> with a median OS of 17.1 months with pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus 11.6 months for placebo plus chemotherapy.<sup>14</sup> Similar superior OS signals were seen with ipilimumab plus nivolumab-based regimens compared with chemotherapy alone.<sup>15</sup> Such results demonstrate why immune checkpoint inhibitor-based regimens are now first-line therapy for later disease stages of NSCLC.<sup>1</sup>

Brain metastases are common in NSCLC, occurring in up to 40% of patients.<sup>16</sup> Dy reported that treatment choice may be influenced by the presence of such metastases, as some therapies have better central nervous system penetrance than others.<sup>17</sup> “Many, if not all, of these agents with better brain activity have been adopted as preferred treatment in the first-line setting,” explained Dy. The classic example is osimertinib, which has better central nervous system penetrance compared with early generation TKIs and is now the preferred first-line treatment in the USA.<sup>18</sup>

## NEW BIOMARKERS AND DRUG TARGETS IN NON-SMALL CELL LUNG CANCERS MANAGEMENT

According to Dy, “there remains a need for both new drug targets as well as platforms in testing for drug targets.” Four emerging biomarkers in NSCLC are *CEACAM5*, *TROP2*, *HER2*, and *c-MET*. Mutation or amplification of these genes, or overexpression of the corresponding proteins, can influence NSCLC prognosis and treatment outcomes.<sup>19-22</sup>

Carcinoembryonic antigen cell adhesion molecule 5 (*CEACAM5*) is a protein involved in cell adhesion, migration, and anoikis inhibition. This latter property may facilitate tumourigenesis and metastasis and its expression in a variety of cancers has led to it being investigated as a biomarker and therapeutic target in NSCLC.<sup>19</sup> Tumour-

associated calcium signal transducer 2 is involved in calcium transduction as well as tumour growth, invasion, and neovascularisation. Overexpression is associated with a poor clinical course in people with lung adenocarcinoma.<sup>20</sup> Mutation, amplification, and over-expression of the transmembrane glycoprotein receptor gene *HER2* is well documented in NSCLC and associated with poorer prognosis and resistance to *EGFR*-focused TKIs in some patients with NSCLC.<sup>21</sup> C-mesenchymal epithelial transition factor, a tyrosine kinase receptor, is involved in cancer cell survival, proliferation, migration, invasion, and angiogenesis and is also associated with *EGFR* and *ALK* TKI resistance.<sup>22</sup>

In the case of *CEACAM5*, while not all NSCLC-associated tumours express this marker to a high degree (as assessed, for instance, by rating immunohistochemical stain intensity and proportion of positive stained cells), such expression was found in approximately 24% of specimens in one study.<sup>23</sup>

*CEACAM5* expression on circulating tumour cells can also be monitored in the circulation.<sup>24</sup> However, explained Dy, “a caveat here is that *CEACAM5* is non-specific. Inflammatory conditions, diarrhoea, or smoking can cause it to go up. Nonetheless, it is helpful overall in monitoring trends over time especially in lung cancer patients who are non-smokers, who have elevated *CEACAM5* levels prior to therapy.” *HER2* mutations are much rarer,<sup>21</sup> and for *c-MET* “it is more complicated,” reported Dy, “as exon 14 mutation, amplification, or protein overexpression may be potentially used as biomarkers depending on the therapeutic platform utilised.”<sup>22</sup>

However, while these biomarkers are known, Dy explained how, in the clinic, “we don’t routinely test these currently because they’re not necessarily actionable in terms of standard of care therapies. With that being said, for example, when we do find acquired resistance to TKIs such as those mediated by *c-MET* overexpression, we can now triage patients into *MET*-based trials.”

## THE POTENTIAL ROLE OF EMERGING BIOMARKERS AS DRUG TARGETS IN THE TREATMENT OF PATIENTS WITH NON-SMALL CELL LUNG CANCERS

There is a role for these emerging biomarkers as drug targets, according to Dy. More recently the use of ADCs associated with CEACAM5, TROP2, HER2, and c-MET expression have been investigated for NSCLC. These consist typically of a mAb, such as tusamitamab, sacituzumab, trastuzumab, or telisotuzumab, targeting the tumour-expressed antigen, conjugated to a cytotoxic drug (termed a 'payload' or 'warhead'), such as ravtansine, deruxtecan, or vedotin. Attaching the payload to the mAb in the ADC is made possible through 'linker' molecules. The goal of ADCs is to maximise tumour cell kill, while minimising systemic toxicity to healthy cells.<sup>25</sup> Examples of these are shown in Table 1.

Notably, Dy explained that "many of the ADCs in development have toxicities that are better tolerated."<sup>25,26</sup> However, she added the caveat that, "of course, the toxicity profile will vary among ADCs, not just because of the target but

also because of the differences in payloads that may have unique side effects that oncologists may not be familiar with initially.<sup>25,26</sup> But over time, we become more vigilant in monitoring a patient's symptoms, for example with ocular toxicities associated with maytansinoid DM4."

Dy also explained how there are many ADC trials exploring combinations with immunotherapy in the first-line setting. "We don't anticipate ADCs to replace immunotherapies," she said, "but we are looking at how we complement existing treatments. For instance, do we combine ADC with immunotherapy or targeted therapy first-line? I do foresee that ADCs would have some role, but it takes a while to develop these drugs. We must first prove the therapy's value before we can routinely implement them as a standard of care. Testing for the relevant biomarkers would certainly be absorbed into practice once we show benefit of these newer therapies." Other questions she posed that need investigating included: "How do we modify the chemotherapy regimen that is combined with immunotherapy now and do we drop one of the agents to minimise myelosuppression, depending on the payload?"

**Table 1: Examples of antibody-drug conjugates.**<sup>25-30</sup>

Target	Antibody	Cytotoxic payload	Linker	Payload target
CEACAM5	Tusamitamab	Ravtansine (DM4)	SPDB	Mi
TROP2	Sacituzumab	Govitecan (SN38)	Acid-labile ester	Tli
	Datopotamab	Deruxtecan (DXd)	Cleavable tetra-peptide based molecule	Tli
HER2	Trastuzumab	Emtansine (DM1)	MCC thioether	Mi
	Trastuzumab	Duocarmazine	DHA	Tli
	Trastuzumab	Deruxtecan (DXd)	Non-cleavable maleimidocaproyl	Tli
c-MET	Telisotuzumab	Vedotin (MMAE)	Valine-citrulline	Mi

CEACAM5: carcinoembryonic antigen cell adhesion molecule 5; c-MET: c-mesenchymal epithelial transition factor; DHA: duocarmycin-hydroxybenzamide-azaindol; MCC: maleimidomethyl cyclohexane-1-carboxylate; Mi: microtubule inhibitor; MMAE: monomethyl auristatin E; SPDB: succinimidyl 4-(2-pyridyldithio) butyrate; Tli: topoisomerase I inhibitor; TROP2: tumour-associated calcium signal transducer 2.

One issue associated with ADC therapy, highlighted Dy, “is the efficacy of the payload itself and the linker technology that may enable bystander killing effect.” She also highlighted how the level of molecular biomarker expression may not always correspond to how well a drug works. For instance, Dy discussed how, in her experience, the ADC trastuzumab-deruxtecan can work even in patients with *HER2* mutated NSCLC despite low *HER2* expression, as has been shown in people with advanced breast cancer with low *HER2* expression.<sup>31</sup> Additional prospective studies are needed to validate and confirm these observations. However, Dy stressed that, “we’re still very enthused because we have all these new ADCs coming into the clinic showing promise in clinical trials. The next phase though is how do we incorporate testing in the setting of limited tissue and biological variations such as intra-tumour heterogeneity.”

## CLINICAL UNMET NEEDS FOR PATIENTS WITH NON-SMALL CELL LUNG CANCERS

“The biggest challenge in NSCLC,” discussed Dy, “is the stage at diagnosis as usually patients are diagnosed with an advanced or a metastatic stage not amenable to surgery.” This, she highlighted, necessitates lung cancer screening programmes, as these have demonstrated benefits in terms of early diagnosis and lung cancer-specific survival and mortality outcomes.<sup>32</sup>

Other challenges involve therapy options at different stages, and the success of such lines of treatment, and how best to treat specific metastases. Dy reported that, “while we’re able to optimise first-line therapies for specific patient populations where targeted therapy or immunotherapy can be superior to chemotherapy, the vast majority of patients, even those eligible for these therapies, will inevitably experience disease progression.” This is potentially due to resistance to targeted therapy or immunotherapy, discussed Dy, who commented that for almost all patients “we have to define what the mechanism of acquired resistance is because sometimes there is a subsequent therapy to address that resistance. Inevitably though,” she continued, “at some point, the evolutionary biology of cancer resistance

outpaces our ability to understand things and develop therapies rapidly in real-time in response to these resistance mechanisms.”

Another unmet need Dy discussed was identifying better biomarkers for immunotherapy and the need to improve on immunotherapy treatment outcomes in ‘cold tumours’ (where effector immune cell activity is suppressed) or ‘immune deserts’ (where immune cells are not in the vicinity of the tumour). There is also the problem, she highlighted, that large proportions of patients have tumours that either do not have a targeted therapy option available or are unlikely to respond well to immunotherapy.

While in Dy’s centre they look for biomarker protein overexpression using immunohistochemistry, she explained how challenges arise in the early phases of drug development due to not having standardised methods for, for example, choosing a positive/negative cut-off, defining overexpression, or having specific reagents such as the antibody for protein detection with immunohistochemistry. This, she explained, makes it difficult to rapidly implement certain biomarkers into routine practice.

A further limitation, Dy discussed, is that “tissue biopsies from patients with lung cancer are limited in amount, and it might not be easy to re-biopsy to get more tissue in many situations.” She stressed how “having multiple targeted therapies available will not be useful unless we are able to test for actionable mutations properly and expediently.” With newer biomarkers, Dy explained how they are currently mostly used for academic research. “We have all these newer pathology techniques that are being developed that might actually be tissue-sparing but at this point, deciding when to do testing is still potentially problematic because even the current standard of adequate mutation profiling is still not met for many patients.”

More widely, Dy discussed the problem of general resource variance when it comes to being able to detect, analyse, and treat NSCLC. This is not only between low- versus high-income countries, but even within the same country, for example, metropolitan versus rural areas. Cost was also an issue raised in that while there may be a number of biomarkers



that could be used to analyse NSCLC, in many countries only a limited number of biomarkers are currently covered by healthcare and insurance providers. She emphasised that even though current guidelines endorse biomarker testing for newly diagnosed patients, due to deficits in local resources, many with advanced NSCLC “may not get beyond *EGFR* and *ALK* testing despite the fact that we now have multiple effective targeted therapies.”<sup>33</sup>

## ONGOING CLINICAL TRIALS OF EMERGING BIOMARKERS

There are several ongoing Phase II and III trials of therapies associated with emerging biomarkers. For instance, in the case of *CEACAM5*, the CARMEN studies are investigating the use of tusamitamab ravtansine, including in a global Phase III trial where it is being compared with docetaxel (CARMEN-LC03; NCT04154956),<sup>34</sup> and a Phase II single arm trial combining tusamitamab ravtansine with ramucirumab to examine efficacy and toxicity (CARMEN-LC04; NCT05245071).<sup>35</sup> Also underway are CARMEN-LC05 (NCT04524689), evaluating tusamitamab ravtansine either with pembrolizumab or pembrolizumab and platinum-based chemotherapy with or without pemetrexed,<sup>36</sup> and CARMEN-LC06 (NCT05245071), evaluating tusamitamab ravtansine in participants with negative or moderate *CEACAM5* expression and high circulating carcinoembryonic antigens.<sup>35</sup>

For *TROP2* mutations, there are several ADCs in development, including several TROPION trials investigating datopotamab-deruxtecan,<sup>37-43</sup> and the EVOKE trials investigating sacituzumab govitecan-hziy (NCT05089734 and NCT05186974).<sup>44,45</sup> For *HER2* mutations, there

are the DESTINY trials investigating trastuzumab deruxtecan (NCT05048797).<sup>46</sup> Other *HER2* selective agents under investigation include tucatinib (NCT04579380),<sup>47</sup> or those that can dually targeted *EGFR* and *HER2*, such as BDTX189 (NCT04209465)<sup>48</sup> or BAY2927088 (NCT05099172).<sup>49</sup>

With *c-MET* mutations, Dy discussed how, aside from ADCs, other antibody-based approaches include selective agents being tested in combination with, for instance, those targeting *EGFR* mutations. Amivantamab, an *EGFR/c-MET* bispecific antibody, is approved for treatment in patients with an *EGFR* exon 20 insertion mutation in the second-line setting.<sup>50</sup> It is also being tested in combination with chemotherapy upfront for this patient population in the PAPILLON trial (NCT04538664).<sup>51</sup> Amivantamab is additionally being tested in combination with lazertinib as a first-line option (NCT04965090)<sup>52</sup> or in combination with chemotherapy after osimertinib failure (NCT04487080)<sup>53</sup> in patients with classic *EGFR* mutation in the MARIPOSA trial.

## CONCLUSION

Despite therapeutic advances, the prognosis of NSCLC is still very poor.<sup>54</sup> Identification of genetically and molecularly defined NSCLC subtypes has led to development of biomarkers for such and the use of targeted therapies. Many more are also in the clinical trial phase. While use of such biomarkers and therapies has led to gains in NSCLC in terms of PFS and OS, current limitations include access to the means to analyse tumours, to the tissue needed to carry out a number of analyses, and to the therapies themselves.

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# Findings and Implications of the REVEAL-CKD Study Investigating the Global Prevalence of Undiagnosed Stage G3 Chronic Kidney Disease

## Interviewees:

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## Disclosure:

Tangri has received grants and personal fees from AstraZeneca; personal fees from Otsuka, Janssen and Boehringer Ingelheim/Eli Lilly; grants, personal fees, and other from Tricida, Klinrisk, and ClinPredict; and other from PulseData outside the submitted work. De Nicola has served as a scientific consultant and/or lecturer for Astellas, AstraZeneca, Bayer, and Novo Nordisk.

## Acknowledgements:

Writing assistance was provided by Stevan Rakovic, Witney, UK.

## Support:

The publication of this article was funded by a medical educational grant from AstraZeneca to support the knowledge and practice of healthcare professionals involved in the management of patients with chronic kidney disease. AstraZeneca had no role in the drafting, review or approval of the article content.

## Disclaimer:

The opinions expressed in this article belong solely to the named interviewees.

## Citation:

EMJ. 2022;7[3]:60-65. DOI/10.33590/emj/10063690. <https://doi.org/10.33590/emj/10063690>.



## Interview Summary

Chronic kidney disease (CKD) is a progressive condition that can lead to kidney failure and the requirement for renal dialysis or transplantation. Early-stage CKD is often missed because the disorder is initially asymptomatic; hence, many patients with CKD already have symptomatic advanced disease (Stages G4–G5) at the time of diagnosis. This is an important issue because the drugs available for the treatment of CKD are most effective when given during the early stages of the disease (Stages G1–G3). EMJ conducted interviews in July 2022 with two key opinion leaders, Navdeep Tangri from the University of Manitoba, Winnipeg, Canada, and Luca De Nicola from the University of Campania Luigi Vanvitell, Naples, Italy, both of whom have a wealth of experience in the management of patients with CKD. The experts provided important insights into the ongoing REVEAL-CKD study, which was designed to explore the global prevalence of undiagnosed Stage G3 CKD. This article describes the main findings of the REVEAL-CKD study published to date and their implications. Possible approaches to improving the diagnosis of CKD are also discussed.



## INTRODUCTION

CKD is a progressive disorder associated with considerable morbidity and mortality. The global prevalence of CKD was 9.1% in 2017,<sup>1</sup> and the prevalence of the disease is predicted to increase during the next few years.<sup>2</sup> The severity of CKD is staged according to the glomerular filtration rate (GFR), which reflects renal function, and albuminuria, which reflects kidney damage. GFR is usually estimated using equations that consider serum creatinine level, age, sex, and/or race.<sup>3</sup> There are five estimated GFR (eGFR)-based stages of CKD and three albuminuria-based stages. Stage G1A1 (eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup> and no albuminuria) represents mild disease, and Stage G5 (eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>) denotes a patient who is approaching kidney failure.<sup>3</sup> Patients with end-stage kidney disease (ESKD) require renal replacement therapy or kidney transplantation; however, the 5-year survival and quality of life of most patients undergoing renal replacement therapy for ESKD is poor.<sup>4</sup> It is now recognised that CKD progression can be delayed if lifestyle modifications and pharmacological therapy are implemented early in the course of the disease.<sup>3,5</sup> However, CKD is asymptomatic during the initial stages and so is frequently diagnosed at an advanced stage, once symptoms have appeared.<sup>6</sup> REVEAL-CKD is a multinational, observational, longitudinal study designed to evaluate the prevalence of undiagnosed Stage G3 CKD in general populations across several countries, and to identify factors associated with undiagnosed Stage G3 CKD.<sup>7</sup> In this article, two nephrology experts, Tangri and De Nicola, discussed the importance of the REVEAL-CKD study and the implications of the results that have been published to date. Both key opinion leaders highlighted the consistently high rate of undiagnosed Stage G3 CKD in all countries included in the study, and emphasised the need to improve the early detection of CKD so that treatments can be initiated to delay disease progression and prevent the need for dialysis.

## WHY THE EARLY DETECTION OF CHRONIC KIDNEY DISEASE IS IMPORTANT

De Nicola explained that the management options for CKD have expanded during the past 30 years, and that the availability of new treatments developed recently has increased the importance of diagnosing CKD at an early stage. He noted that 30 years ago, nephrologists were focused on kidney dialysis as the main treatment method because medical therapies were considered ineffective even for moderate degrees of CKD (defined by serum creatinine levels in the range of 1.5–2.0 mg/dL). De Nicola stated: “Dialysis was the greatest innovation in nephrology at that time.” However, De Nicola went on to say that although renal replacement therapy remains a life-saving treatment, it is now recognised that advances in dialysis have plateaued and, at present, it remains a therapy with limited effects on the long-term survival and quality of life of patients. In fact, he highlighted that the mortality rate for patients on dialysis has not changed in the last 15–20 years. According to De Nicola, the major focus of CKD treatment has now shifted from substitution of renal function (for example, with haemodialysis or peritoneal dialysis) to preservation of renal function through the use of multifactorial (conservative) therapy that aims to prevent not only ESKD but also cardiovascular events, which are major complications of CKD. He stressed that the “mission of every nephrologist should be to avoid dialysis” in their patients. De Nicola mentioned antiproteinuric intervention as the key component of multifactorial therapy to improve long-term kidney survival, and emphasised that these treatments show the greatest potential to slow the progression of CKD to ESKD when initiated at an early stage.

Tangri noted that CKD is asymptomatic during the initial stages and that symptoms only occur once more than 70% of kidney function has been lost, at which point the window to intervene is closed or closing rapidly. Tangri explained that diagnosis of CKD at Stages G1–G3, and ideally at Stages G1–G2, with albuminuria as the diagnostic test, allows the implementation of therapies that have the potential to avoid the need for dialysis. Tangri noted that diagnosing and treating CKD at Stage G4 of the disease can only delay the time to kidney replacement therapy, and is too late to prevent a lifetime of dialysis.

## MEDICAL THERAPIES THAT ARE AVAILABLE FOR CHRONIC KIDNEY DISEASE

Tangri considered a renin-angiotensin-aldosterone system inhibitor (angiotensin converting enzyme inhibitor or angiotensin receptor blocker) and a sodium-glucose co-transporter-2 inhibitor as foundational therapy for CKD, and noted that most patients with CKD benefit from these drugs. He also indicated that patients with diabetes and Stage G1–G3 CKD may additionally benefit from finerenone, a non-steroidal mineralocorticoid receptor antagonist. The same pharmacological agents were described by De Nicola, who also mentioned that anti-endothelin drugs were being investigated as potential new therapeutic options for CKD. Tangri emphasised the importance of controlling blood pressure and blood glucose levels in patients with CKD.

According to Tangri, CKD progression and cardiovascular disease are the two main contributors to healthcare costs in patients with CKD. Since the drugs available for the treatment of CKD both slow disease progression and reduce the incidence of cardiovascular events, Tangri argued that timely diagnosis and intervention would not only directly benefit the health of the patient, but also reduce treatment costs for health systems and payers.

## GUIDELINES FOR THE SCREENING AND DIAGNOSIS OF CHRONIC KIDNEY DISEASE

De Nicola stated that, in his view, the most comprehensive position paper considering these aspects is the consensus established at the recent Kidney Disease: Improving Global Outcomes (KDIGO) conference on 'Early Identification and Intervention in CKD', the findings of which were published in 2021.<sup>5</sup> Tangri also referred to the KDIGO recommendations<sup>3,5</sup> and mentioned the National Institute for Health and Care Excellence (NICE) guideline available in the UK.<sup>8</sup>

## WHY ARE DIAGNOSES MISSED IN PATIENTS WITH STAGE G3 CHRONIC KIDNEY DISEASE?

According to both experts, the major reason for missed diagnoses is that early-stage CKD is asymptomatic, or manifests only with subtle symptoms. De Nicola also suggested that a lack of awareness of CKD among primary care physicians, and consequently among their patients, contributes to a diagnosis not being made. In the opinion of Tangri, CKD has been viewed for many years as a complication of diabetes and hypertension rather than as a standalone entity, because management strategies were focused on the 'underlying' diseases. He continued that although the relevant guidelines are understood by the nephrology community, these have not been well disseminated among primary care physicians, who have the challenge of being aware of and implementing many different guidelines for various medical conditions.

## THE REVEAL-CKD STUDY

REVEAL-CKD is a real-world, multinational, observational study designed to evaluate the prevalence of, and factors associated with, undiagnosed Stage G3 CKD in general populations from several countries.<sup>7</sup> Tangri is the principal investigator of the REVEAL-CKD study, and contributed to the design of its protocol. De Nicola is on the steering committee of the REVEAL-CKD study, and became involved in the project because his main field of research is the conservative therapy of CKD.

Tangri explained that the primary purpose of REVEAL-CKD was to "shine a spotlight" on how often CKD is undiagnosed by looking at the gap between claim-based diagnoses, when CKD is coded in the medical records, and laboratory-based 'gold standard' diagnoses based on eGFR. De Nicola elaborated that REVEAL-CKD was designed to estimate the prevalence of undiagnosed Stage G3 CKD by identifying patients with at least two eGFR levels, recorded at an interval of at least 3 months, that are indicative of Stage G3 CKD ( $\geq 30$  mL/min/1.73 m<sup>2</sup> and  $< 60$  mL/min/1.73 m<sup>2</sup>), and then verifying whether these patients did receive a diagnosis of CKD according to a standard International

Classification of Diseases 9/10 diagnosis code for CKD in the medical records. Tangri added that the study would also explore whether coding the disease in medical records affected disease management, including the prescribing of disease-modifying treatments and the attainment of blood pressure control and glycaemic control targets. Both experts emphasised that REVEAL-CKD is the largest multinational study to address the important issue of CKD underdiagnosis. Tangri highlighted the global context as a unique advantage of REVEAL-CKD, with the same statistical protocol and analysis used consistently in different settings to identify global health problems that are not limited to a single country.

### Findings of the REVEAL-CKD Study Published to Date

Results from the REVEAL-CKD study for patients in France, Germany, Italy, Japan, and the USA have been presented at several major scientific meetings and published in the form of abstracts.<sup>9-13</sup> De Nicola explained that the main finding in Italy, obtained using databases from 900 Italian general practitioners that included over 1.2 million patients, was that 77% of patients with proven Stage G3 CKD were undiagnosed by their general practitioners. The published data indicate that the rate of undiagnosed Stage G3 CKD reported for Italy was broadly consistent with that observed in France (94%), Germany (74%–84%), Japan (87%), and the USA (62%).<sup>9-13</sup>

Both experts highlighted the finding that the rate of undiagnosed Stage G3 CKD was higher in older patients, females, and those with Stage G3a CKD (GFR  $\geq 45$  mL/min/1.73 m<sup>2</sup> and  $< 60$  mL/min/1.73 m<sup>2</sup>) versus those with Stage G3b CKD (GFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> and  $< 45$  mL/min/1.73 m<sup>2</sup>). Tangri speculated that the higher rate of undiagnosed CKD in older adults might reflect a “fatalistic view” of CKD as a consequence of ageing, rather than as a disease in its own right. He also suggested that the higher rate of undiagnosed CKD in females may be related to how GFR is estimated, with some physicians focusing on the serum creatinine value, which is lower in females than males because of less muscle mass, rather than on a slightly lowered eGFR, which accounts for body size. Given the above, Tangri noted that older females with Stage G3 CKD may be particularly disadvantaged

in regard to timely diagnosis, and thus might be less likely to receive optimal treatment.

Both experts pointed out that the rate of undiagnosed Stage G3 CKD was almost as high in patients with known risk factors for CKD, such as diabetes, heart failure, or hypertension, as in patients without any of these risk factors. De Nicola explained that this finding was unexpected because it is well known among clinicians that patients with these comorbidities are at an increased risk of developing renal dysfunction, and hence need to be tested for CKD. Both experts agreed that this finding may be related to the perception among many physicians that CKD is a consequence or complication of a comorbidity rather than a disease in its own right, and both experts concurred that this mindset must be changed to improve the diagnosis of early-stage CKD. Another possibility raised by Tangri was that a physician may not feel the need to code for CKD in a patient being treated for hypertension with a renin-angiotensin-aldosterone system inhibitor because the patient is already receiving an appropriate therapy for CKD. However, Tangri added that failing to code for CKD in the medical record may mean that the patient is less likely to receive one of the newer agents available for CKD, or any treatment developed in the future.

Tangri also commented on why patients who were undiagnosed for CKD at the index date were unlikely to receive a later diagnosis. He suggested that the low rate of subsequent diagnosis may reflect the “reluctance” of some physicians to diagnose CKD, perhaps because they view CKD as a complication of other diseases. Tangri speculated that the minority of patients who did receive a subsequent diagnosis of CKD may have had declining eGFR values rather than relatively stable levels during the follow-up period, which prompted the physician to code for CKD.

Tangri confirmed that the REVEAL-CKD study is ongoing. He explained that the next phase of REVEAL-CKD is crucial because it will evaluate whether recording a diagnosis of CKD makes it more likely that the appropriate targeted treatment is given. Tangri also stated that the study will investigate the link between undiagnosed CKD and outcomes, although this analysis will be more exploratory because

outcomes are related to factors other than treatment, such as patient-related, social, and economic factors. It is expected that the findings will be published in waves, with an initial publication in the next few months, followed by a series of additional papers.

### Implications of the REVEAL-CKD Study Findings and Calls to Action

Both experts proposed actions that healthcare professionals and others should consider taking, based on the findings of the REVEAL-CKD study published to date. De Nicola emphasised that non-nephrologists, especially primary care physicians but also specialists such as cardiologists and diabetologists, need to receive straightforward and easy-to-follow guidance on CKD diagnosis and management. This guidance should focus on three critical points: who to screen (those with risk factors for CKD such as diabetes, hypertension, heart failure, obesity, and older age); how to screen (serum creatinine measurement and urinalysis for proteinuria); and when to refer a patient to a nephrologist (Stage G3b or worse CKD [ $<45$  mL/min/1.73 m<sup>2</sup>], or albuminuria at any stage). Tangri agreed that all patients with diabetes or hypertension should be screened for albuminuria as an indicator of CKD. He also highlighted other groups that might benefit from screening, including anyone with a family history of kidney failure (i.e., renal dialysis or transplantation) and people in high-risk geographical locations or ethnic communities (e.g., the First Nations community in Canada, South Asian communities in the UK, and agricultural communities in the developing world).

In the opinion of De Nicola, better communication is needed to make healthcare professionals, patients, and the public more aware of the therapies available for CKD so that there is a shift in the perception of CKD from an 'untreatable' to a 'treatable' disease. De Nicola argued that the focus of patient organisations should encompass not only the interests of patients needing dialysis or kidney transplantation, but also those of the larger population of patients with non-dialysis-dependent CKD, since this will promote the implementation of preventive strategies that slow the progression of CKD to ESKD. De Nicola suggested that the involvement of patient organisations and the public would help to influence decision-makers at health institutions,

and thereby alter healthcare policies to improve the early detection of CKD. He added that input from patients will require publicity in the media, including radio, television, and social media networks, to promote CKD awareness.

Similarly, Tangri's call to action was to improve the recognition of CKD among primary care physicians as a standalone disease with its own specific therapies, as this would lead to a change in mindset in how the disease is viewed. He stated that achieving this goal will need a multiple-prompt approach, including journal articles, presentations, and social media messaging, because healthcare professionals vary in their resource and knowledge-sourcing preferences. Tangri also advocated distilling guidelines down to actionable messages and recommendations aimed at primary care providers, since he considered CKD to be a 'primary care disease'. In addition, Tangri mentioned that disease-specific foundations and charities can play a significant role in distributing evidence-based information to the public.

Tangri argued that improving workflow automation would be of help to busy primary care physicians who deal with the diagnosis and management of a wide range of health conditions, each with their own guidelines. He proposed that the diagnosis of CKD should be automatically entered in the electronic health record if the gold standard diagnostic criterion is met (i.e., two abnormal GFR measurements more than 90 days apart), with the physician retaining the autonomy to remove the diagnosis if it was subsequently concluded that CKD was not the underlying cause. Tangri also suggested the introduction of a prompt in the medical record for eligible patients who had not received a screening test for CKD, since this might help primary care physicians to implement evidence-based recommendations. He emphasised that automation and workflow assistance represent an unmet opportunity to improve CKD screening in patients who meet the appropriate criteria, but he also highlighted the challenge of electronic health record providers implementing necessary changes to such systems.

### FUTURE PROSPECTS AND CONCLUSIONS



De Nicola concluded that efforts are needed to change the mindset of clinicians, and especially primary care physicians, so that they perceive CKD as a standalone, treatable disease. He stressed that patient organisations could play a role in driving changes in healthcare policy to improve the diagnosis of CKD, because the “value and efficacy of negotiations and communication definitely improve when the ‘voices’ of patients are involved.”

Tangri concluded that primary care physicians need to be made aware of the importance of

diagnosing CKD, stating: “Diagnosis matters because you are more likely to treat better.” He proposed that the dissemination of straightforward recommendations for CKD diagnosis and treatment, and the automation of workflow, may improve the diagnosis of early-stage CKD, and hence patient outcomes in the future.

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# Measuring the Impact of the COVID-19 Pandemic on Diagnostic Delay in Rare Disease

## Editor's Pick

This review article comments on the delay in patients receiving a correct diagnosis, termed 'the diagnostic odyssey'. Sharing data obtained from the Action for Rare Disease Empowerment (ARDEnt) coalition, the authors highlight the detrimental impact of the COVID-19 pandemic on the rare disease diagnostic journey. From this data, three key recommendations were proposed to temper the impact of the pandemic. Whilst a rare disease, is rare in and of itself, collectively, rare diseases are not uncommon, making this a meaningful choice as our Editor's Pick.



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### Disclosure:

Menzies has received personal consultancy fees from Mendelian Limited, a rare disease digital health company, outside the submitted work. Evans is an employee of Mendelian Limited. Evans has received honoraria from Takeda, Orphazyme, and Intrabio.

### Acknowledgements:

The three founding organisations of ARDEnt: Medics4RareDiseases, Cambridge Rare Disease Network, and Rare Revolution Magazine, are grateful to all the organisations and individuals who joined us in our quest to protect patients with rare diseases, and the services and organisations they depend on. Thank you to the other participants involved in Theme 1 of ARDEnt: Helena Baker, Mary Bythell, Ceridwen Hughes, Kerry Lee-son-Beevers, Nick Meade, Lauren Roberts, and Gisela Wilcox. Thank you to the patient community for their contributions to the work of ARDEnt.

### Received:

13.10.21

### Accepted:

26.04.22

### Keywords:

COVID-19, diagnosis, diagnostic delay, genetics, health informatics, pandemic, rare disease, telemedicine.

### Citation:

EMJ. 2022; DOI/10.33590/emj/21-00181.  
<https://doi.org/10.33590/emj/21-00181>.

## Abstract

Rare diseases are individually rare but collectively common, with a combined prevalence of 3.5–5.9%. A common feature of many diseases is a substantial delay in patients receiving a correct diagnosis; this protracted path to diagnosis is termed ‘the diagnostic odyssey’. During the COVID-19 pandemic, significant concerns have emerged from both clinicians and patients regarding a disproportionate effect of the pandemic on diagnosis and management of rare disease. Such concerns prompted a study to explore this question further, the results of which are presented here.

A cross-sector multi-stakeholder coalition was formed, Action for Rare Disease Empowerment (ARDEnt), with representation from patients with rare diseases and carers, patient advocacy groups, clinicians, academics, data scientists, and industry. A mixed methods approach was used to collect and collate information about the impact of the pandemic on diagnostic delay in rare disease. Currently, there is a lack of systematic recording and reporting of rare disease diagnosis in the UK, which created challenges in directly measuring diagnosis rates. Therefore, the group was dependent on a mix of data sources to reflect healthcare provided during 2020 compared with previous years. The findings were synthesised to describe the impact of the pandemic along the path to diagnosis, from the moment of first concern and engagement with health services, to the availability of definitive testing.

In conclusion, evidence suggests the pandemic has exacerbated the problem of diagnostic delay for rare diseases, affecting all points on the path to diagnosis. The authors recommend three actions to help address this: optimising remote clinical consultations; enhancing the use of health informatics in rare diseases; and proactively identifying patients with undiagnosed rare diseases missed due to the pandemic. This study also highlights the need for better reporting of rare disease diagnoses, a core metric to measure the impact of health system changes that may be put into place to address the priorities of The UK Rare Diseases Framework, also published this year.

## Key Points

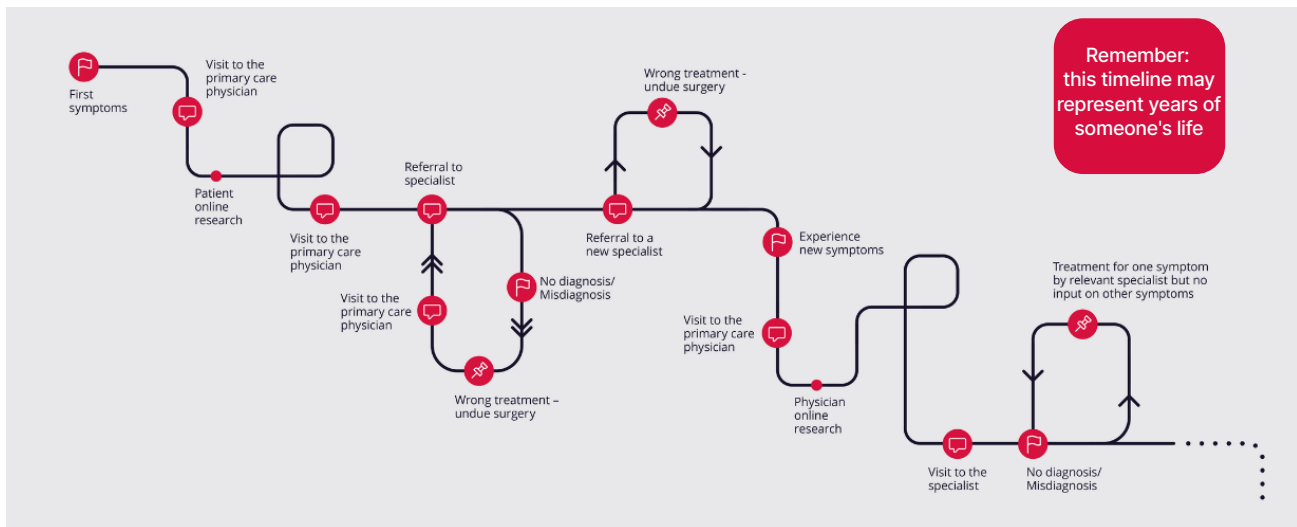
1. Evidence suggests the COVID-19 pandemic disproportionately exacerbated diagnostic delay for rare diseases, affecting all points on the path to diagnosis.
2. To capture the impact and opportunities for the rare disease community, a cross-sector multi-stakeholder coalition, Action for Rare Disease Empowerment (ARDEnt), was formed.
3. The group made three key recommendations for mitigating the effect of the pandemic on the ‘diagnostic odyssey’ in rare disease: optimising remote clinical consultations; enhancing the use of health informatics in rare diseases; and proactively identifying patients with undiagnosed rare diseases missed due to the pandemic.

## INTRODUCTION

Rare diseases, defined as affecting fewer than 1 in 2,000 individuals,<sup>1</sup> are individually rare but collectively common, with an estimated combined prevalence of 3.5%–5.9%.<sup>2</sup> Frequently, patients with rare diseases spend years, or even decades,

on a path to diagnosis, hence the described ‘diagnostic odyssey’.<sup>3,4</sup> Along this path, patients undergo multiple referrals, investigations, often misdiagnoses, and the frustrations of unanswered questions and unaddressed deterioration in their condition. Many patients with rare diseases never receive an accurate diagnosis<sup>5,6</sup> (Figure 1).

Figure 1: The early stages of the diagnostic odyssey.



The COVID-19 global pandemic has led to significant morbidity and mortality, and a substantial impact on all aspects of life including the provision of health and social care.<sup>7</sup> The full extent of the impact continues to emerge. In England there was a substantial drop in primary care consultation rates that only recovered in May 2021, 2 years post the start of the pandemic. This drop was also reflected in the number of secondary care referrals, with numbers in January 2021 still below the 4 year average. The number of diagnoses for a range of chronic conditions also fell significantly. The impact of the pandemic was not experienced evenly across all patient groups. For example, it was widely recognised early in the pandemic that direct morbidity and mortality was greatest in the elderly population; however, indirect health impacts, although harder to capture, were almost certainly more widely spread, with young patients, especially those under 11 years, experiencing the largest fall in consultation rates, and largest drop in number of GP appointments.<sup>8</sup>

It was recognised early in the global pandemic that the rare disease community may be disproportionately affected. Many rare conditions make those affected more vulnerable to the complications of COVID-19, so shielding and socially isolating oneself was recommended for many. This led to further psychosocial impact on patients and their families due to a profound and prolonged reduction in contact with others

and wider society.<sup>9</sup> Patients with rare diseases are often young, and are often frequent users of health and social care services; with the pandemic causing disruption of these services, patients with rare diseases were therefore disproportionately affected.<sup>10</sup> With reduced access to health services and the halting of some diagnostic services, there was concern that the diagnostic odyssey would be further protracted. In addition, with both pre-clinical and clinical research halted or limited, the opportunity for advances in disease understanding and treatments were curtailed.

To capture the impact and learnings from the COVID-19 pandemic, as well as the potential opportunities that may arise for the rare disease community, a cross-sector multi-stakeholder coalition was formed, Action for Rare Disease Empowerment (ARDEnt). ARDEnt is made up of over 30 individuals and groups, including patients, advocates, healthcare practitioners, industry representatives, scientists, data specialists, and clinical trial organisers. The principal aim of this group was to obtain and collate information in order to inform the Action Plans outlined in the UK Rare Diseases Framework,<sup>1</sup> published in January 2021, and to suggest best practice for UK patients with rare diseases post-pandemic. This was successfully published via the ARDEnt report entitled: 'Making the unseen seen: Rare disease and the lessons learned from the COVID-19 pandemic.'<sup>11</sup>



## METHOD

The ARDEnt group was founded by three patient advocacy group leaders in the rare disease field, who put out an open invitation in April 2020 to rare disease stakeholders to join a meeting regarding the impact of the pandemic on the rare disease community. Additional members were recruited to ensure complete cross-sector representation of stakeholders, and to address specific gaps in knowledge by both snowballing and purposive recruitment. Following initial discussion by the ARDEnt group, three priority themes were identified, under which evidence would be collated based on expert opinion. These themes were agreed to be of critical priority, and were subsequently included in the UK Rare Diseases Framework as three of the four priorities described by The Department of Health and Social Care.

Theme 1: Diagnostic Delay

Theme 2: Health and Social Care Coordination

Theme 3: Research and Drug Development including Access to Treatment

A mixed methods approach was used to synthesise both quantitative and qualitative data.

Information was collected by the following methods: review of published literature, review of grey literature (including government, patient advocacy, and public health documents), and interviews with key stakeholders (e.g., patients, clinicians, nurse specialists, and representatives of patient advocacy groups).

A literature search was performed in Pubmed and Google Scholar, using the keywords "COVID-19" and synonyms, combining this with the term "Rare disease" and synonyms. Due to the paucity of relevant literature in the initial searches, this search was repeated on further occasions. Additional literature was identified by manually reviewing the references of identified literature. Due to the emerging nature of the pandemic, much of the literature identified was not published in academic journals. The grey literature was identified on the government webpage and patient advocacy group searches, with additional insights and inputs advised by members of the multi-stakeholder ARDEnt team.

The interviews were semi-structured, using a standard questionnaire with open questions. Interviews were transcribed, and quotes were used in the subsequent report. A systematic literature review was not performed, due to a general lack of peer-reviewed literature on the effect of the pandemic on rare disease, and relevant information appearing in a range of sources.

Although the focus of this review was the UK, the information search was not restricted to the UK.

Discussion within the ARDEnt Theme 1 group identified the following sub-themes, under which information would be captured:

- Pre-engagement with healthcare
- Primary care
- Referral to secondary care
- Secondary and tertiary care
- Diagnostics

These sub-themes reflect the steps in a diagnostic path for a rare disease. Additionally, a specific cohort of patients was identified and examined separately: children aged 0–5 years.<sup>12</sup> This cohort was highlighted, following discussion with multiple stakeholders, because 70% of rare diseases present in childhood and rare diseases that present at this age frequently have a time-critical diagnosis, with even modest delay significantly affecting outcome.<sup>2</sup>

Both quantitative and qualitative data was captured, and the elements synthesised to draw conclusions and recommendations for reducing diagnostic delay in rare disease. A similar approach was used by Theme 2 and Theme 3 of ARDEnt. The group published their findings on all three themes and their recommendations in an online report called: 'Making The Unseen Seen: Rare disease and the lessons learned from the COVID-19 pandemic', which has been presented to The Department of Health and Social Care.

## RESULTS

### Absolute Diagnosis Rate

Because of the challenges in collecting absolute numbers of people diagnosed with a rare disease in a given time period, four rare liver disorders were examined as a proxy. These conditions were chosen as the diagnosis is made as an inpatient and associated with a liver biopsy, enabling robust identification in Hospital Episode Statistic (HES) data. The average number of diagnoses per month in January–September 2020 showed a reduction of 36% in comparison to the same months in 2019 (Bythell, personal communication), suggesting the pandemic caused an exacerbation of delay.

A specialist nurse recorded new presentations of one rare metabolic condition to specialist services dropping from an average of 13 per year in 2017–2019 to only seven in 2020 (Bell, personal communication), four of whom were diagnosed in January or February.

Patient groups have also noted the decline in the number of newly diagnosed families requesting information and registering for services. One group supporting patients and families affected by rare genetic conditions reported a 33% decline in 2020 compared to 2019. SWAN UK reported a 52% reduction in online registrations in 2020 compared to 2019 (Roberts, personal communication).

International experience has shown similar reductions in rare disease diagnosis. For example, in the Italian region of Campania, rare disease certificates (a record of new diagnoses) reduced from 1,272 in the first 4 months of 2019 to 774 in the same period of 2020.<sup>13</sup>

### Pre-Engagement with Healthcare

'Stay at home. Protect the NHS. Save lives'<sup>14</sup> messaging by the UK Government from March 2020, resulted in four people in 10 feeling too concerned about burdening the NHS to seek help from their GP in April 2020.<sup>15</sup> People were confused about what services were still available, and concerned about the danger of going to hospitals. Emergency department attendances reduced by approximately 25% across the UK.<sup>16–28</sup> In a survey conducted in April 2020, one-

third of paediatricians working in emergency departments or paediatric assessment units witnessed delayed presentations.<sup>29</sup>

### Primary Care

Diagnosis of a rare condition often depends on multiple consultations and a holistic view of the patient, a challenge even before the pandemic. During the pandemic, the number of primary care appointments fell from 6,026,140 in the first week of March 2020, to 4,225,502 in the last week.<sup>30</sup> Even in December 2020, although numbers had recovered somewhat, primary care appointments were still 11% below January's numbers (calculated from data<sup>30</sup>). Of these, the number of face-to-face consultations declined from 80% before the pandemic to 60%, replaced by telephone and video consultations.<sup>31</sup>

### Referrals to Secondary Care

Referrals to specialist services fell during the pandemic.<sup>32–34</sup> Clinical Genetics service referrals in some areas fell by >50% during April–June 2020 in comparison to the same months in 2019 (Menzies, personal correspondence).

### Secondary and Tertiary Care

Outpatient appointments, inpatient, and diagnostic services changed significantly, especially during the lockdowns driven by peaks in COVID-19 cases. Services such as Clinical Genetics have looked to assess both the challenges and potential benefits of the increase in telemedicine, including both telephone and video consultations. The Clinical Genetics Society Telemedicine Survey 2020 captured 2,204 responses from clinical genetics doctors, genetic counsellors, and specialist nurses across 13 centres in the UK (Menzies, personal communication). The majority of appointments were being carried out by telephone call, with video being the next most frequent form of consultation. The survey highlighted some of the challenges in maintaining services during the pandemic: adapting the remote service for specific user needs; inability to examine the patient; and difficulty explaining complicated genetic concepts remotely. Advantages of using telemedicine were also identified: patients being in their own environment enabled them to relax, have family members with them, and easier

access to personal records. Patients did not need to travel, and this provided a safe solution for those who were self-isolating or shielding (Menzies, personal communication).

## Diagnostic Services

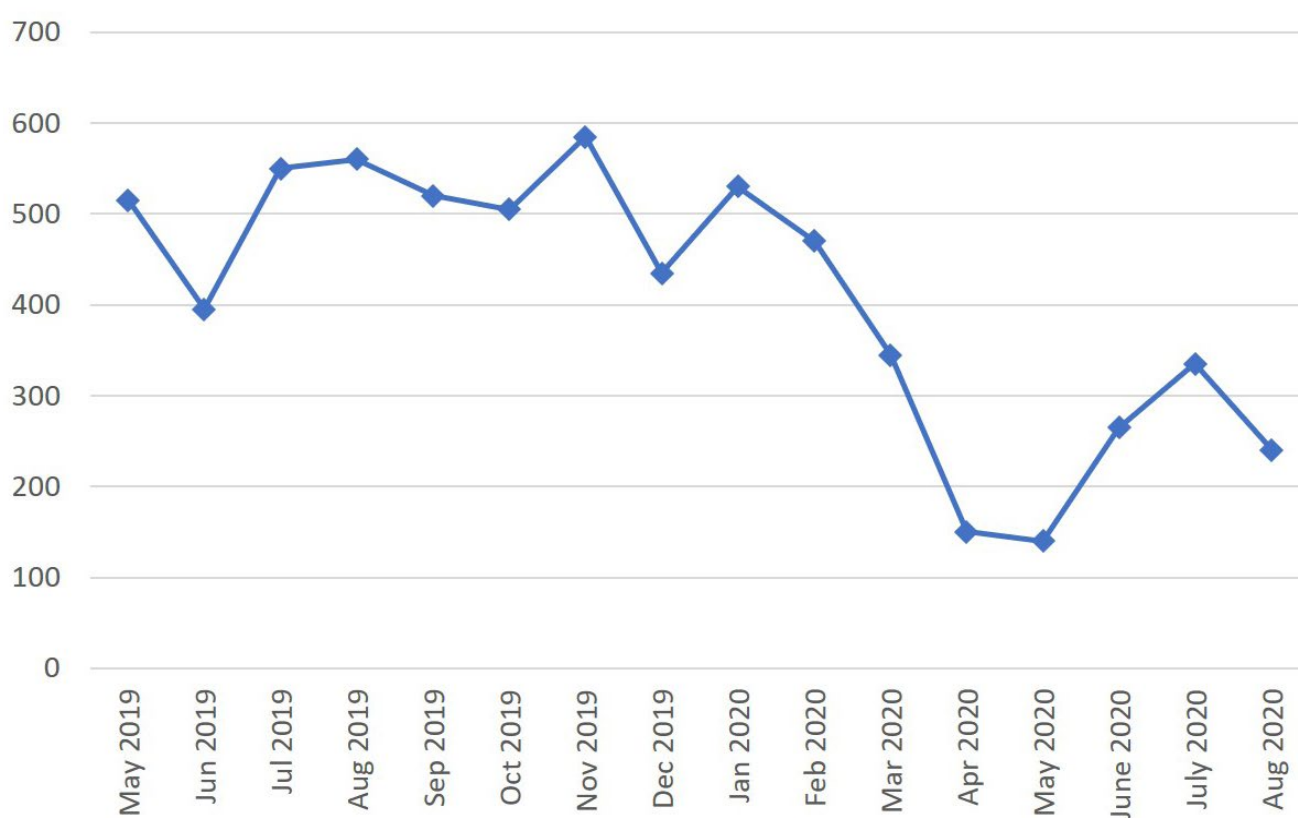
There was a significant reduction in activity in the 15 most frequently requested investigations in England, from a mean of 1,967,376.25 per month in 2019 to 1,521,507.17 per month in 2020.<sup>35</sup> This was reflected in three of the investigations most commonly used in rare disease diagnostics, those being Echocardiography, Radiology with contrast (including MRI, CT, and non-obstetric ultrasound), and Gastroscopy, according to HES data.<sup>36</sup> When comparing the average for April–December 2019 to April–December 2020, there was a 40% reduction of gastroscopies, 30% reduction in echocardiography, and 24% reduction in radiological investigations with contrast.<sup>35</sup>

Genomic testing, key for most rare diseases, was rationalised with guidance on testing prioritisation issued by NHS England in March 2020.<sup>37</sup> Genetic laboratories were instructed to reduce testing to urgent services only, in part to release capacity to support COVID-19 testing. Requests for microarrays, often the first line genetic test for many patients suspected of having an undiagnosed rare disease, substantially reduced (Figure 2).

## Children Aged 0–5 Years

70% of rare conditions present in childhood, and 30% of people with a rare condition die before their fifth birthday.<sup>1,2</sup> Infant Physical Examinations (one element of the 'Newborn and Infant Physical Examination' [NIPE]) were delayed 2 weeks, and performed at single consultations with first immunisations,<sup>38</sup> reassuringly without impact on NICE key performance indicators. Data for how 1- and 2-year checks have been impacted during

Figure 2: Number of microarray requests over a 16 month period from 2019 to 2020.



Data from an NHS genetics laboratory serving a UK urban population of 5 million people. Reproduced with permission from Menzies, personal communication, 2020.

this time period remains unpublished 2 years later. The 'Babies in Lockdown' report presented an online survey of 5,474 expectant mothers, parents of infants and toddlers, of whom fewer than one in 10 had seen a health visitor face-to-face in the 103 days of the first lockdown.<sup>39</sup> The 'Working for Babies Report' identifies "threats to physical health as a result of lockdown, reduced health services and parental reluctance to access them" as a key hidden harm of lockdown on young children.<sup>39</sup>

Restrictions in social interactions have seriously reduced the number of people young children encounter, including their wider family, social network, and healthcare professionals. This has left parents to oversee their children's developmental progress without external support. A nurse specialist highlighted the case of an infant who received a diagnosis of a rare metabolic condition during the first national lockdown because their condition was identified by their grandmother. They recognised the enlarged abdomen when changing their nappy as similar to that of their late child who had died 30 years previously. With this knowledge, they demanded that they were seen in A&E urgently, which led to their diagnosis. Had this child not lived with their grandparent, the diagnosis may not have been made.

## DISCUSSION

This is the first attempt that the authors are aware of to capture the impact of the pandemic on the path to diagnosis for patients with rare diseases. The breadth of information captured in this report is a reflection of the ARDEnt group, a broad coalition of stakeholders with a broad range of experience and expertise, adding to the value and applicability of the findings and conclusions. The group acknowledges limitations in its methods of sampling including a lack of representation of some voices (e.g., those of young people and ethnic minorities). This reflects a far-reaching need for better diversity and inclusion within rare disease advocacy, necessitating the creation of groups, campaigns, and reports that highlight this particular issue.<sup>40-43</sup>

Based on the findings, the group makes three recommendations for mitigating the impact of the COVID-19 pandemic on diagnostic delay in rare disease: optimising remote clinical consultations; enhancing the use of health informatics in rare

diseases; and proactively identifying patients with undiagnosed rare diseases missed due to the pandemic. These recommendations have been put to The UK Rare Disease Implementation Board for consideration when drawing up the action plans for the UK framework.

The fundamental question, "has the pandemic impacted rare disease diagnosis rates?", was difficult to clearly answer. The authors used a narrow and defined subset of rare liver disease diagnoses as examples, as these diseases were chosen to ensure confidence in the accuracy of the numbers. The authors' inability to provide data for a greater number of diseases with the same degree of confidence, an acknowledged limitation of this study, reflects how rare diseases are coded in UK hospital data sets. This limitation in coding had an additional impact on the rare disease community early in the pandemic, when shielding guidance was decided by diagnostic coding in these records. The lack of specificity of rare disease coding led to inappropriate advice given to many patients with rare diseases. This blindspot, the inability to accurately assess the impact on diagnosis, is applicable beyond this specific question of the pandemic, and has relevance when assessing any external impact or intervention on rare disease diagnosis. How will the actions taken to address the first priority of the UK Rare Disease Framework: helping patients get a faster diagnosis, be measured for their impact? Consequently, one of the authors' three recommendations is to enhance health informatic use in rare diseases. Specifically, they recommend increased resourcing of the National Disease Registration Service (NDRS) to enhance their rare disease scope, and ensuring the standardisation of rare disease clinical coding terms.

Despite this limitation, the authors have collected a range of personal experiences and data that demonstrates a drop in rare disease diagnosis, from initial engagement with health services, referral for investigation or specialist assessment, and registering with patient advocacy groups for support. For example, there was a significant reduction in the number of diagnostic tests such as echocardiograms, radiological investigation, and gastroscopies performed, as well as genetic testing with microarrays. Microarrays are a powerful indicator of the impact on rare disease diagnosis; they are largely requested by secondary care specialists who are not geneticists, and requested



as part of the diagnostic workup of patients with developmental delay/intellectual disability, autism spectrum disorder, and multiple congenital anomalies, i.e., patient cohorts that are enriched with undiagnosed rare diseases.

The change in consultation method in primary care, from a largely face-to-face model to a substantially greater use of video or telephone consulting, is also occurring in secondary care, and is perhaps the most significant change in the day-to-day practice of medicine of the pandemic. As of April 2021, primary care still had 41% of all consultations held via video or telephone consulting, an increase of 27% when compared to April 2019.<sup>44</sup> Although a welcome adaptation for many patients, and one broadly encouraged to continue, the widespread adoption is balanced by some associated risks. Ensuring that remote consulting is used appropriately is the second recommendation, the optimisation of remote clinical consulting. This includes greater clarification of which type of consultations are appropriate to be performed remotely and which are not, building on the evidence base for what, when, and with whom remote or face-to-face consultation is optimal, with specific attention paid to the risk of exacerbating health inequality. Optimal use of remote consulting also requires that the systems themselves can sustain this way of working. This requires suitable investment in IT platforms, protected times for clinicians, and training to ensure excellent standards of care, and that remote diagnostics are available, with laboratory testing set up to enable remotely-collected samples to be analysed sometime after their collection. Also, there needs to be better interlinking of local and national services, so that information held in electronic health records can be shared and available to those that need it. With suitable investment, game-changing opportunities such as a multidisciplinary team approach for the diagnostic workup of those undiagnosed, but suspected of having a rare disease, could be implemented with members of the multidisciplinary team and the patient remote to one another. This would enable national collaboration and the opportunity to bring the expert to the patient earlier in their diagnostic workup.

The pandemic has led to an increased number of undiagnosed patients with rare diseases. The size of this population is less clear, emphasising the

need for suitable investment in the collection of data through organisations such as NDRS, so that the longer term effects of the COVID-19 pandemic on diagnostic delay and resulting outcomes are understood, and systems put in place to mitigate them in future public health emergencies.

It needs to be acknowledged that people living with an undiagnosed rare disease will have been missed. This report highlights that even before engagement with health services, reduced social interaction reduced the number of opportunities for problems to be identified and flagged by extended family members or social circle. The authors' third recommendation is proactively identifying undiagnosed patients with rare diseases missed due to the pandemic. They suggest a face-to-face developmental assessment for every child aged 0-5 years, who has not been seen face-to-face by services since March 2020. They are asking for a plan on how the inevitable backlog of investigations will be addressed, and evidence to confirm that referral and diagnostic requests are returning to a pre-pandemic level. In order to catch up diagnoses, the authors recommend putting pathways in place to enable much earlier guidance for testing than prior to the pandemic, with the aid of remote consulting where appropriate.

## CONCLUSIONS

The COVID-19 pandemic exacerbated the problem of diagnostic delay in rare diseases, and it is likely that the true extent of this delay will not be fully understood for a number of years. The authors identify specific issues and gaps in how the impact of the pandemic on rare disease diagnosis could be assessed, gaps which would be equally applicable to another external event, or an intervention put in place to improve diagnosis. They also highlight some opportunities that have arisen, such as remote consulting, that could improve rare disease diagnosis going forwards. Many of the challenges outlined in the ARDEnt report simply represent exacerbated existing problems. A positive side effect of the pandemic is improved collaboration and cross-sector engagement around how to solve these issues. The three recommendations proposed would help mitigate the lasting impact of the COVID-19 pandemic, and ensure that the lessons learnt will improve rare disease diagnosis.

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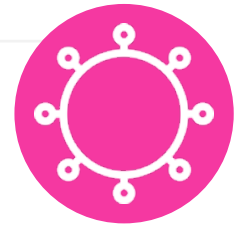
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# Tackling Extended Hospital Stays in Patients with Acute Bacterial Skin and Skin Structure Infections

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## Disclosure:

All authors have received an honorarium from ADVANZ PHARMA for their involvement in the writing of this article. Barlow has, in the last 2 years, received an honorarium from Pfizer Vaccines UK for serving on an advisory board. Wilke has shares in the Medical School Hamburg and Pfizer; is managing partner of Inspiring-health GmbH, which received a research grant from Correvio GmbH (now ADVANZ PHARMA) to conduct health-economic analyses on dalbavancin; and has received honoraria for lectures and research grants unrelated to this research from Abbott, Accelerate, bioMérieux, Orion Pharma, Pfizer, and Shionogi. Béraud received honoraria from Correvio (now ADVANZ PHARMA), GILEAD Sciences, and MSD in the last 2 years.

## Acknowledgements:

Writing assistance was provided by Eleanor Roberts, Beeline Science Communications Ltd, London, UK.

## Support:

The publication of this article was fully funded by ADVANZ PHARMA.

## Disclaimer:

The opinions expressed in this article belong solely to the named interviewees.

## Citation:

EMJ. 2022;7[3]:76-85. DOI/10.33590/emj/10095006. <https://doi.org/10.33590/emj/10095006>.

## Summary

Hospitalisation rates for acute bacterial skin and skin structure infection (ABSSSI) are rising and represent a large pharmaco-economic burden as treatment may involve an extended number of days of antibiotic therapy. This article first aims to provide a review of treatment challenges associated with ABSSSIs in both hospital and outpatient settings, and shows that while more traditionally treatment has been conducted in a hospital setting, for a number of patients, a variety of considerations, including pharmaco-economics, infection control, and patient preference, has led to the development of recommendations to assess the eligibility of patients for early discharge from hospital to complete their antibiotic regimen in the outpatient setting. However, such patients require monitoring for drug adherence to oral regimens or complications associated with daily intravenous administration, such as injection site reactions and infection. This review also focuses on one of a number of new antibiotics for ABSSSI, dalbavancin, as the long-acting glycopeptide with the



most clinical experience to date. This antibiotic has been shown to be as effective as a daily/twice daily regimen with similar safety profiles. Health economic analysis of dalbavancin is also presented. It has shown that in some, though not all, clinical settings a reduction in the overall treatment cost is evident as, despite a higher medication cost, the lower hospitalisation time can lead to greater cost savings. In conclusion, while the burden of ABSSSI is rising, new treatment options provide additional therapeutic choice, although pharmacoeconomic considerations might limit use in some cases.

## INTRODUCTION

ABSSSIs include cellulitis/erysipelas, wound infections, and major cutaneous abscesses. They are defined by lesion size ( $\geq 75$  cm<sup>2</sup>), and are demarcated by area of redness, oedema, or induration.<sup>1</sup> An ABSSSI is considered 'complicated' when surgery is required in addition to antibiotic treatment and/or the infection reaches deeper subcutaneous tissue.<sup>2</sup> Around a third of ABSSSI are caused by methicillin sensitive (MSSA) or methicillin resistant *Staphylococcus aureus* (MRSA). Another major cause is *Streptococcus* species, with fewer ABSSSI being due to *Klebsiella* and *Enterococcus* species, *Pseudomonas aeruginosa*, and *Escherichia coli*.<sup>3,4</sup>

Risk factors and comorbidities associated with ABSSSIs include prior episodes; older age; diabetes; intravenous (IV) drug use; cardiovascular disease; chronic wound or ulcer presence; peripheral vascular disease; chronic renal failure; malnutrition; smoking; skin conditions; obesity; and cirrhosis.<sup>3,5</sup> The most common risk factors for a complicated ABSSSI are antibiotic use within 30 days and hospitalisation within 6 months.<sup>2</sup> Patients with comorbidities and complicated ABSSSI experience higher rates of reinfection or recurrence (9.6% versus 5.2% without comorbidities); longer hospital stays (mean: 19.9 days versus 13.3 days); a longer time to clinical stability (10.4 days versus 7.1 days); and a higher mortality rate (4.0% versus 1.1%).<sup>6</sup>

This article presents an overview of ABSSSI treatment and the challenges associated with such in a hospital or community setting; provides a checklist to help determine eligibility for early discharge of a patient hospitalised with an ABSSSI; and discusses efficacy, tolerability, and pharmacoeconomic data for one of the new antibiotics for an ABSSSI, dalbavancin, as the

long-acting glycopeptide with the most clinical experience to date.

## TREATMENT FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

ABSSSI treatment is directed by clinical manifestation, infectious agent(s), and purulence. Important aspects of clinical care include stabilisation of physiology if sepsis exists; surgical drainage; mechanical or chemical debridement; and antibiotic therapy.<sup>3,7,8</sup> Table 1 shows examples of antibiotic options for an ABSSSI. For mild infections, oral formulations are recommended, with IV delivery reserved for moderate–severe infections.<sup>10</sup> To mitigate recrudescence, treatment is usually recommended for 7–10 days or longer if symptoms/signs do not adequately resolve.<sup>3</sup>

Antibiotic treatment recommendations differ by indication and country-specific guidelines.<sup>7</sup> According to Michael Wilke, Inspiring-health GmbH, Waldmeisterstrasse, Munich, Germany, and Medical School Hamburg, Am Kaiser Kai, Germany, and colleagues, choice of therapy for a bacterial disease is a case of "choosing the right antibiotic at the earliest possible moment to maximise the chances of curing the infection [...] and minimising risk of developing resistance."<sup>11</sup>

## KEY CHALLENGES ASSOCIATED WITH TREATING A PERSON WITH AN ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION AS AN INPATIENT

Hospitalisation for and rates of ABSSSIs are rising.<sup>12</sup> Cellulitis was found to have an incidence rate of 24.6/1,000 persons/years in a UK-based study.<sup>13</sup> As such, ABSSSIs represent a large

Table 1: Examples of antibiotics prescribed for an acute bacterial skin and skin structure infection.<sup>3,7,8,9</sup>

	Mild	Moderate	Severe	MRSA
Cefazolin IV		✓	✓	
Ceftaroline IV			✓	✓
Ceftriaxone IV		✓	✓	
Clindamycin IV/PO		✓	✓	✓*
Dalbavancin IV			✓	✓
Daptomycin IV			✓	✓
Delafloxacin IV/PO		✓	✓	✓
Doxycycline PO	✓	✓		✓
Flucloxacillin IV/PO	✓ <sup>†</sup>	✓	✓	
Linezolid IV/PO			✓	✓
Minocycline PO	✓	✓		✓
Omadacycline IV/PO		✓	✓	✓
Oritavancin IV			✓	✓
Oxacillin IV		✓	✓	
Penicillin IV/PO‡	✓	✓		
Piperacillin–tazobactam IV			✓	
Tedizolid IV/PO			✓	✓
Teicoplanin IV			✓	✓
Telavancin IV			✓	✓
Tigecycline IV			✓	✓
Trimethoprim–sulfamethoxazole PO	✓	✓		✓ <sup>§</sup>
Vancomycin IV			✓	✓

\*Not always susceptible, especially healthcare-associated strains.

†PO

‡*Staphylococci* are often resistant.

§Not always susceptible.

IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; PO: by mouth.

pharmaco-economic burden.<sup>14</sup> For example, a study of non-severe ABSSSI examining data from Spain, Italy, and Austria estimated a total annual expenditure of 13.5 million EUR, 9.9 million EUR, and 3.4 million EUR, respectively.<sup>15</sup>

Issues associated with ABSSSI treatment include hospitalisation and length of stay (LOS). A prospective study of 94 patients presenting to the emergency department found that for

85.1% the primary reason for admission was IV antibiotic need, a major driving factor for LOS.<sup>16</sup> While patients may also be admitted to monitor comorbidities, an observational study involving 520 hospitals and 600,000 patients found that 60% of those admitted with an ABSSSI had no significant systemic symptoms or comorbid conditions.<sup>17</sup>

MRSA-related ABSSSI present an increased cost burden when hospital stay is extended,<sup>18</sup> with the need for patient isolation and enhanced healthcare professional protection measures.<sup>19</sup> An analysis of German healthcare data found that average LOS for patients with MRSA was 25.8 days (mean cost: 16,024 EUR/stay), compared with 14.6 days for patients without MRSA (mean cost: 8,198 EUR/stay). As costs per day were similar (621 USD versus 561 USD, respectively), the cost difference was predominantly attributed to LOS.<sup>19</sup> This may be problematic financially as in many countries, treatment for a named condition is compensated by insurance companies to a set amount based on average cost per patient. This means with an LOS longer than the mean, the hospital/healthcare authority will be responsible for additional costs.<sup>11</sup>

For the patient, long LOS presents medical, social, and psychological difficulties, such as the chance of picking up another infection,<sup>20</sup> or an infection/complication associated with MRSA and vancomycin-resistant enterococci.<sup>21,22</sup>

Longer hospitalisations are also associated with feelings of isolation, depression, worry about an inability to maintain family responsibilities, and financial problems due to inability to work.<sup>20,23</sup> Medically, extended LOS are associated with pressure sores, deep vein thrombosis, and deconditioning, especially in elderly patients who may also experience increased confusion, loss of function, and immobility.<sup>20</sup>

## TREATING ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS IN THE OUTPATIENT SETTING

An economic model developed to compare in-versus outpatient treatment of Gram-positive ABSSSI when using a daily IV antibiotic found that total ABSSSI treatment costs were lowest when patients were treated in the outpatient setting.<sup>24</sup> This has led to identification of appropriate patients with ABSSSI eligible for early discharge when home treatment is viable.<sup>25</sup> A checklist designed by Wilke and colleagues can be used at the bedside to assess if a person with an ABSSSI could potentially be discharged to home care (**Box 1**). These criteria also take into account clinical experience of the authors and a meta-analysis which showed that, following

assessment of clinical and infection stability, over one-third of hospitalised patients with MRSA could be eligible for early discharge.<sup>26</sup>

In some countries, outpatient treatment is formalised as outpatient parenteral antimicrobial therapy (OPAT), which may include a patient self-administering an antibiotic at home or with the help of a carer/healthcare professional, and/or them coming into an outpatient clinic as needed.<sup>27</sup> Good practice recommendations for OPAT delivery have been published in the UK.<sup>28</sup>

Outpatient treatment of an ABSSSI can be via oral or IV antibiotic therapy. However, challenges with home-based treatments include that while oral antibiotics are convenient and as effective as IV preparations when taken correctly,<sup>7</sup> non-adherence may occur. A study of linezolid use following hospital discharge found that 24.1% of 1,046 patients did not pick up their prescribed medication from their pharmacy, indicating non-adherence.<sup>29</sup> Similarly, a study with people with uncomplicated ABSSSI (n=87) found that while 96% reported full adherence on questionnaires, electronic bottle cap opening data recorded full adherence in only 57%. After 30 days of treatment, 46% had a poor clinical response, associated with lower adherence.<sup>30</sup> An alternative to this, with better rates of adherence, is the use of long-acting antibiotics, discussed below.<sup>3</sup>

One advantage of inpatient treatment is that tests for clinical assessment or therapeutic drug monitoring can be conducted more rapidly. In OPAT, testing is less frequent, and results may take longer to be reported. Other potential problems associated with OPAT are that the patient might need to be responsible for peripherally inserted intravenous device care, and for attending appointments.<sup>27,31</sup>

Antibiotic treatment-associated complications, such as nephrotoxicity, venous access issues, drug-related adverse events (AE), and skin rash, need to be closely monitored in the outpatient setting.<sup>32</sup> One study examining home infusion therapy found AE rate to be 7.7/1,000 OPAT days for vancomycin (n=1,105) and 3.2/1,000 OPAT days for daptomycin (n=83). The rate of antimicrobial interventions was 27.1/1,000 and 5.6/1,000 OPAT days, respectively, with hospital readmissions of 18% for vancomycin and 21% for daptomycin.<sup>33</sup>

**Box 1: Checklist to determine eligibility for early discharge to outpatient antibiotic therapy.<sup>26</sup>**

Infection parameters improving (e.g., C-reactive protein and white blood cell count decreasing or stable)  
 Infection stable/declining (e.g., a core temperature of <38 °C)  
 Clinical parameters stable (e.g., a systolic blood pressure  $\geq$ 100 mmHg)  
 No recent prior or planned surgery  
 Wound dressings that can be changed in the home/day clinic setting  
 Able to take oral medication (where indicated)  
 Able to adhere to medication regimen  
 Well-controlled comorbidities  
 Suitable social circumstances and ability to travel for daily therapy, if needed

Analysis of National Health Service (NHS) England hospital episode statistics showed that over 20% of people who had been discharged following hospitalisation for cellulitis were readmitted, with over half in the first month. This was estimated to cost 29 million GBP per year.<sup>34</sup> Readmission for cellulitis may occur for a variety of reasons, including undertreatment with antibiotics<sup>35</sup> and misdiagnosis.<sup>36</sup>

### **DALBAVANCIN USE IN ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS: EFFICACY AND SAFETY**

Newer drugs approved for ABSSSI include the long-acting antibiotics dalbavancin and oritavancin. Their prolonged half-lives mean that a single infusion can deliver antibiotic efficacy over several days.<sup>3</sup> As the long-acting glycopeptide with the most clinical experience to date, the focus here will be on dalbavancin, an intravenously delivered semisynthetic lipoglycopeptide antibiotic with proven potency against MSSA, MRSA, and other ABSSSI-related staphylococci, enterococci, and streptococci.<sup>37,38</sup> Resistance to dalbavancin is rare.<sup>39</sup> Dalbavancin was approved by the European Medicines Agency (EMA) in 2015 for the treatment of ABSSSI in adults.<sup>37,40</sup> Similar lipoglycopeptide antibiotics include teicoplanin and vancomycin,<sup>41</sup> although dalbavancin has faster bactericidal activity and a longer half-life than these.<sup>41</sup>

Due to its long terminal half-life of around 15 days,<sup>40-42</sup> dalbavancin is administered either as a single 1500 mg infusion or a 1000 mg infusion on Day 1, followed by a 500 mg infusion on Day 8.<sup>37</sup>

Clinical success rates and AEs are non-inferior between dosing regimens.<sup>43</sup> Another benefit is that IV administration does not require placement of a peripherally inserted intravenous device,<sup>41</sup> as may be needed for daily IV administration, thereby decreasing the risk of complications of such.<sup>32</sup> The long half-life of dalbavancin may mitigate the risk of recurrence of ABSSSI in some patient groups, in keeping with results of a trial of short course (six versus 12 days) therapy in severe cellulitis.<sup>35</sup>

Double-blind, non-inferiority trials found clinical response times and percentage of participants with an early clinical response were similar (around 80%) for IV dalbavancin (525/659) and vancomycin±linezolid (521/653) administered IV every 12 hours for  $\geq$ 3 days, with the option to switch to twice-daily oral linezolid for 10–14 days. Over 90% in each group achieved an early clinical response, and around 97% of patients with MSSA or MRSA achieved a clinical response by the end of treatment.<sup>44</sup>

Occurrence of any AE (32.8% versus 37.9%, respectively), diarrhoea (0.8% versus 2.5%), and pruritis (0.6% versus 2.3%) was significantly lower with dalbavancin, with therapy discontinuation due to an AE being approximately 2% for both groups. In these trials, the most frequent AE with dalbavancin was nausea (2.5% compared with 2.9% in the vancomycin-linezolid group). A serious AE was reported in 2.6% of the dalbavancin group and 4.0% of the vancomycin-linezolid group ( $p=0.16$ ). While it may be considered that the extended half-life of dalbavancin could lead to longer time with an AE, these trials showed mean AE duration was similar between groups



(8.7 days),<sup>44</sup> in keeping with the authors' clinical experience.

To be a viable option, the efficacy and safety of dalbavancin needs to be proven to be similar to other antibiotic choices. A network meta-analysis (NMA), including 17 studies of which three involved dalbavancin, found similar efficacy and safety for dalbavancin compared to vancomycin, daptomycin, teicoplanin, linezolid, and tigecycline. There was also a similar incidence of AE rates (44.9%) compared with all other antibiotics (46.8%). For all-cause mortality, there was a significantly higher risk with vancomycin, linezolid, and tigecycline versus dalbavancin. For serious AEs, there was a significantly higher risk with vancomycin and daptomycin, and for AE incidence there was a significantly higher risk with linezolid only. However, these results are to be viewed with caution due to the considerable design heterogeneity of included studies.<sup>45</sup>

Another NMA found dalbavancin had similar efficacy and early clinical response to vancomycin and oritavancin for complicated Gram-positive ABSSSI including MRSA.<sup>46</sup> Oritavancin is an IV lipoglycopeptide with a half-life of 10.2 days, administered as a single infusion, used for Gram-positive bacteria including MRSA and vancomycin-resistant enterococci.<sup>47</sup> This NMA found fewer overall AEs with dalbavancin compared to standard of care (SoC) (odds ratio: 0.77; 95% confidence interval: 0.64–0.93), although the odds of serious AEs were similar, and there were similar AEs/serious AEs as otrivancin.<sup>46</sup>

Clinical trials of oritavancin have shown efficacy similar to vancomycin with nausea, headache, vomiting, cellulitis, increased alanine aminotransferase, and infusion site phlebitis being the most frequent AEs. In the oritavancin group, 3.6% discontinued due to a treatment-emergent adverse event, namely cellulitis, infection, or osteomyelitis.<sup>48</sup> Caution is advised if oritavancin is administered with drugs with a narrow therapeutic window predominantly metabolised by an affected cytochrome P450 enzyme, as concentrations increases or decreases may occur. As oritavancin binds to or prevents the action of phospholipid reagents that activate coagulation, blood concentrations of oritavancin following a 1200 mg dose may lead to falsely

elevated results in some laboratory coagulation tests.<sup>49</sup>

Following formal clinical trials, several studies have investigated dalbavancin efficacy and safety in real-life settings. In an Austrian cohort, 26 patients treated for a Gram-positive ABSSSI showed a clinical cure rate of 77%, with 23% of patients switching to a different antibiotic.<sup>50</sup> An similar clinical cure rate (75%) was found in an Italian study (n=170), where dalbavancin was found to be tolerable with AEs occurring in 5.4% of patients and one occurrence of Stevens-Johnson syndrome.<sup>51</sup>

However, in a large retrospective study in the USA (n=418) where patients received either dalbavancin or SoC with another antibiotic, overall treatment success rate was significantly higher with SoC (85% versus 74%; p=0.004). There were also lower 30-day ABSSSI-related readmissions overall (SoC: 14.83%; dalbavancin: 26.32%; p<0.01), although dalbavancin had a better odds ratio for readmission in treatment naïve patients who had not received antibiotics over the past 30 days (0.4; 95% confidence interval: 0.2–0.9).<sup>52</sup>

An Austrian retrospective, multicentre study of 101 patients (10.9% with an ABSSSI) found that reasons for dalbavancin use included its long half-life; previous antibiotic failure, allergic reaction, or AE; pathogen resistance to other antibiotics; or patient non-compliance. Investigation of 90-day outcomes found that 89% of 94 patients had no evidence of infection, with treatment failure in 5%.<sup>53</sup> An observational, retrospective study in 29 Spanish hospitals (n=69; 21.7% with an ABSSSI) found that most patients (97.1%) received prior antibiotic therapy before receiving dalbavancin. Switching to dalbavancin was most often carried out for antibiotic administration ease (73.9%); previous treatment failure (30.4%); antimicrobial resistance (18.8%); and  $\beta$ -lactam allergy (14.5%).<sup>54</sup> Finally, in a USA study, the main reasons documented for dalbavancin use over other IV antibiotics was a history of IV drug use; contraindications to other antibiotics; lack of outpatient infusion options; and history of non-adherence to outpatient IV antibiotics.<sup>55</sup> In selected patients therefore, dalbavancin appears to be a useful addition to the ABSSSI therapeutic armamentarium.

## DALBAVANCIN USE IN ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS: ADHERENCE AND CONVENIENCE

Recurrent ABSSSI are prevalent in people who inject drugs (PWID)<sup>56</sup> where medication adherence may be a concern.<sup>57</sup> As such, it is postulated that the single-dose regimen of dalbavancin may help optimise treatment adherence.<sup>37,58</sup> A retrospective observational study found that even with dalbavancin administration, only 53% of 32 patients, of whom 88% were PWID, completed the intended therapy course, with 31% lost to follow up.<sup>59</sup> However, it also found that, compared to PWID discharged into an outpatient antibiotic program prior to dalbavancin use, patients treated with dalbavancin had significantly improved outcomes including shorter hospital LOS, higher clinical cure rates, and lower readmission rates.<sup>60</sup>

Incidence<sup>61</sup> and hospitalisation rates for people with an ABSSSI are highest in those  $\geq 65$  years, and LOS is on average longer.<sup>12,14</sup> Prolonged hospitalisations for such patients has been associated with complications including immobility, deconditioning, pressure sores, deep vein thrombosis, and nosocomial infections.<sup>20</sup> As such, this is another patient population that could benefit from the use of long-acting antibiotic therapy, as it can provide a reduction in LOS in clinically stable patients over 65 years old who do not need to be in the hospital for another reason.<sup>18</sup>

A further advantage of dalbavancin is to quality of life. A post hoc analysis comparing the two dosing regimens of dalbavancin found that those treated as outpatients (n=386) compared to inpatients (n=312) were more satisfied with their therapy with regard to treatment and care received, effect of treatment, and treatment location. A significantly larger percentage ( $p < 0.001$ ) found outpatient therapy interfered less with their daily activities. However, while a similar percentage in each group were 'unconcerned' about their antibiotic treatment (43% versus 44%, respectively), 28% of outpatients versus 6% of inpatients answered the question 'How often were you concerned about receiving your antibiotic treatment?' with the choices 'most/all of the time' ( $p < 0.001$ ), suggesting the need to optimise patient

education and reassurance when treated as an outpatient.<sup>62</sup>

## DALBAVANCIN AND PHARMACOECONOMICS

Although there are many advantages of dalbavancin, drug cost may limit its use in some settings. However, as discussed previously, LOS for people hospitalised with an ABSSSI is paramount in pharmacoeconomic considerations. In the ENHANCE trial, dalbavancin use (n=43) reduced LOS by almost 2 days when compared with SoC.<sup>63</sup> Another study utilised French registry data of dalbavancin administration (n=154) for a range of infections including ABSSSI. Here, LOS was found to be almost always shorter in patients who received dalbavancin compared with SoC, by up to 13 days. Cost savings particularly occurred in patients where dalbavancin was used early in treatment.<sup>64</sup>

With this in mind, it is proposed that reductions to LOS could lead to cost savings that outweigh the price of using dalbavancin. Wilke and colleagues devised a model to determine the economic effects of a single dose of dalbavancin in hospitalised patients in Germany. In those with an ABSSSI, MRSA presence was associated with an increased LOS of 6.45 days and an excess cost of 5,145 EUR per patient. The use of dalbavancin combined with early discharge was projected to lead to average savings of 2,964 EUR.<sup>65</sup>

A number of studies have examined actual costs and LOS. A pharmacoeconomic study utilising data from Italy, Spain, and Romania (involving around 30,000 patients) estimated a LOS reduction of 2.50–4.15 days with dalbavancin compared with SoC. In the Italian cohort, while drug cost was 37.0% more with dalbavancin, it was offset by a 38.5% decrease in other treatment resources, accounting for slightly lower costs compared to SoC. However, in Romania and Spain, treatment brought a slight increase in cost with dalbavancin use, by 0.1% and 1.0% respectively, compared with SoC.<sup>66</sup> In a study examining data from Italy, Spain, and Austria, LOS/1,000 patients hospitalised with a non-severe ABSSSI was reduced by 601.8–782.6 days following dalbavancin use. This led to estimated cost savings of 370,269 EUR–1.1 million

EUR.<sup>15</sup> Analysis of data from 17 patients with ABSSSIs treated with dalbavancin in a Scottish hospital outpatient setting found that cost of 14 days' hospitalisation, not including treatment, would have been 53,000 GBP.<sup>67</sup>

A number of USA studies have all found comparable results, with one showing that LOS was 4.3 days with dalbavancin (n=44) compared with 8.0 days for a SoC comparator group (n=945; p<0.001) and 5.0 days for the national average. Mean total direct cost per person was 2,889 USD for the dalbavancin group compared with 7,863 USD for the comparator group, showing considerable cost savings.<sup>68</sup> Another study (n=37) showed mean cost reductions of 40,414 USD/patient and a total of 617 hospital days saved.<sup>55</sup> Finally, a meta-analysis using USA healthcare costings found that in comparison to inpatient costs using SoC, outpatient use of dalbavancin was equivalent or lower when hospitalisation costs (6.5–10 days of treatment) were taken into consideration.<sup>46</sup> This reduction in hospital days is significant when considering the risks associated with extended hospital stays, especially during the COVID-19 pandemic. Of note though, in another USA study, where the primary outcome was average net cost of care to the healthcare system per patient, calculated as the difference between reimbursement payments

and the total cost to provide care to the patient, dalbavancin-related healthcare costs were significantly higher than SoC (4,804 USD±2,271 USD versus 2,709 USD±5,281 USD; p<0.01).<sup>52</sup>

## CONCLUSION

ABSSSI treatment may necessitate an extended hospital stay. Taken as a whole, the studies discussed above demonstrate that judicious use of dalbavancin in selected patient groups could lead to enhanced adherence and overall cost savings when administered to patients who, according to **Box 1** criteria, are eligible for early hospital discharge to continue their outpatient antibiotic therapy. While the overall healthcare economy cost benefit of dalbavancin is likely marginal, and is largely dependent upon the local drug price, there are clearly populations of patients who would benefit from this novel form of therapy. Dalbavancin may allow a decrease in LOS or early discharge, and should be anticipated as opposed to being dedicated to compassionate use after multiple prior courses of treatment. Further research is required to clarify its clinical- and cost-effectiveness versus  $\beta$ -lactam antibiotics, which remain the mainstay of outpatient and inpatient ABSSSI therapeutics in areas with low MRSA endemicity.

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Job Code: ADV/MISC/PM/0061;  
Date of Preparation: August 2022

# Diencephalic Syndrome: A Rare Entity with Its Anaesthetic Management and Post-operative Complications of Diabetes Insipidus and Thrombocytopenia

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## Disclosure:

The authors have declared no conflicts of interest. The parents' informed consent was obtained.

## Received:

07.02.22

## Accepted:

14.06.22

## Keywords:

Case report, craniopharyngioma, diencephalic syndrome (DS), emaciated, suprasellar mass.

## Citation:

EMJ. 2022; DOI/10.33590/emj/22-00037.  
<https://doi.org/10.33590/emj/22-00037>.

## Abstract

Russell first described the diencephalic syndrome in 1951. It is a rare syndrome and usually presents in children as a cause of failure to thrive despite normal, or even increased appetite, with preservation of linear growth. The treatment options vary from endoscopic biopsy followed by chemotherapy to definitive surgical resection of the tumour. The authors here describe a case of an 8-year-old 10 kg emaciated child who presented with headache, vomiting, rage attacks, decreased weight, and diminution in vision. The child had bilateral optic atrophy; however, hormonal profiles were within normal limits. MRI of the brain gave an impression of craniopharyngioma.

Thus, the child was planned for subtotal resection of the tumour. There were various anaesthetic concerns in this case. The low weight predisposed them to hypothermia, electrolyte abnormalities, titrating the dose of drugs accordingly, positional challenges due to fixed flexion deformity of limbs, and the need for extensive post-operative care. Post-operatively, the child developed diabetes insipidus 2 hours after surgery, which was medically managed, but the repeat episode occurred again the next day. On second post-operative day, the child succumbed to dyselectrolyemia and thrombocytopenia, despite resuscitative measures. The literature available on the anaesthetic management for definitive surgical resection is scarce, especially the post-operative complications encountered in this case. Thus, this case report could help in elaborately understanding the spectrum of the disease, especially regarding this histopathological type with its associated complications and, therefore, the steps that could be taken to mitigate them.

## Key Points

1. Children with the diencephalic syndrome are prone to poor prognosis due to their severely emaciated state and associated complications; hence, vigilant screening in failure to thrive children could help early diagnosis before landing in such an emaciated state.
2. The histological subtype of craniopharyngioma further adds to the anticipated complication in forms of diabetes insipidus, which could be challenging to manage in these syndromic patients.
3. Tailoring the peri-operative anaesthetic management to the specific considerations in these cases and providing appropriate post-operative care is crucial for better surgical outcomes for such patients.

## INTRODUCTION

Diencephalic syndrome (DS), first described by Russell in 1951, is a rare cause of failure to thrive in infants and young children with preservation of linear growth.<sup>1</sup> Due to misdiagnosis of these children, these conditions are diagnosed quite late and, by then, the children already would be in a state of severe emaciation. This delay makes them candidates for poor prognosis, even when they get definitive treatment. Most of the literature available for this rare syndrome focuses on the chemotherapy aspect of the treatment. The literature on anaesthetic considerations and post-operative complications after surgical resection of these brain tumours is scarce. This mode of therapy is usually not opted for considering their anatomical location, which could make complete resection difficult. But since the tumour in the indexed case was so large, the debulking of the tumour was chosen to increase the efficacy of planned post-operative chemotherapy. The authors of this report elaborate on the anaesthetic management and post-operative complications of diabetes insipidus and thrombocytopenia in an emaciated 8-year-old male child, weighing 10 kg, with suprasellar mass posted for debulking and subtotal excision of the tumour.

## CASE REPORT

### Clinical Findings: History and Physical Examination

An 8-year-old male child, weighing 10 kg (Z score: -12.29), presented with a complaint of headache for 2 years, which was gradually progressive and mainly involved the frontal

region. There was also a history of vomiting for 6 months, drowsiness for 2 months, and increased head size and diminution of vision for the past month. The parents also gave an account of rage attacks and decreasing weight despite increased appetite, but no history of fever, seizures, or trauma.

About 1 month previously, the child became drowsier and, at that time, they were diagnosed with hydrocephalus on radiological imaging. A ventriculoperitoneal shunt was performed with the uneventful post-operative course. The patient was referred to the authors' tertiary care centre for further management. On examination, the child was conscious and co-operative with the Glasgow coma scale (GCS) of eye opening (E) 4; verbal response (V) 5; and motor response (M) 6. Their visual acuity was severely reduced, with the right eye's perception of light but the perception of light was absent in the left eye. Bilateral optic atrophy was diagnosed on fundoscopy. There was fixed flexion deformity at bilateral elbows, hips, and knees, with the power of three out of five in all the limbs. The child's low weight and fixed flexion deformity of the limbs had crucial significance as the dosage of the drugs should be modified as per the lean bodyweight of the child, and positioning of the child should be done with utmost care with proper cushioning of the pressure points.

### Diagnostic Assessment

#### Biochemical work-up

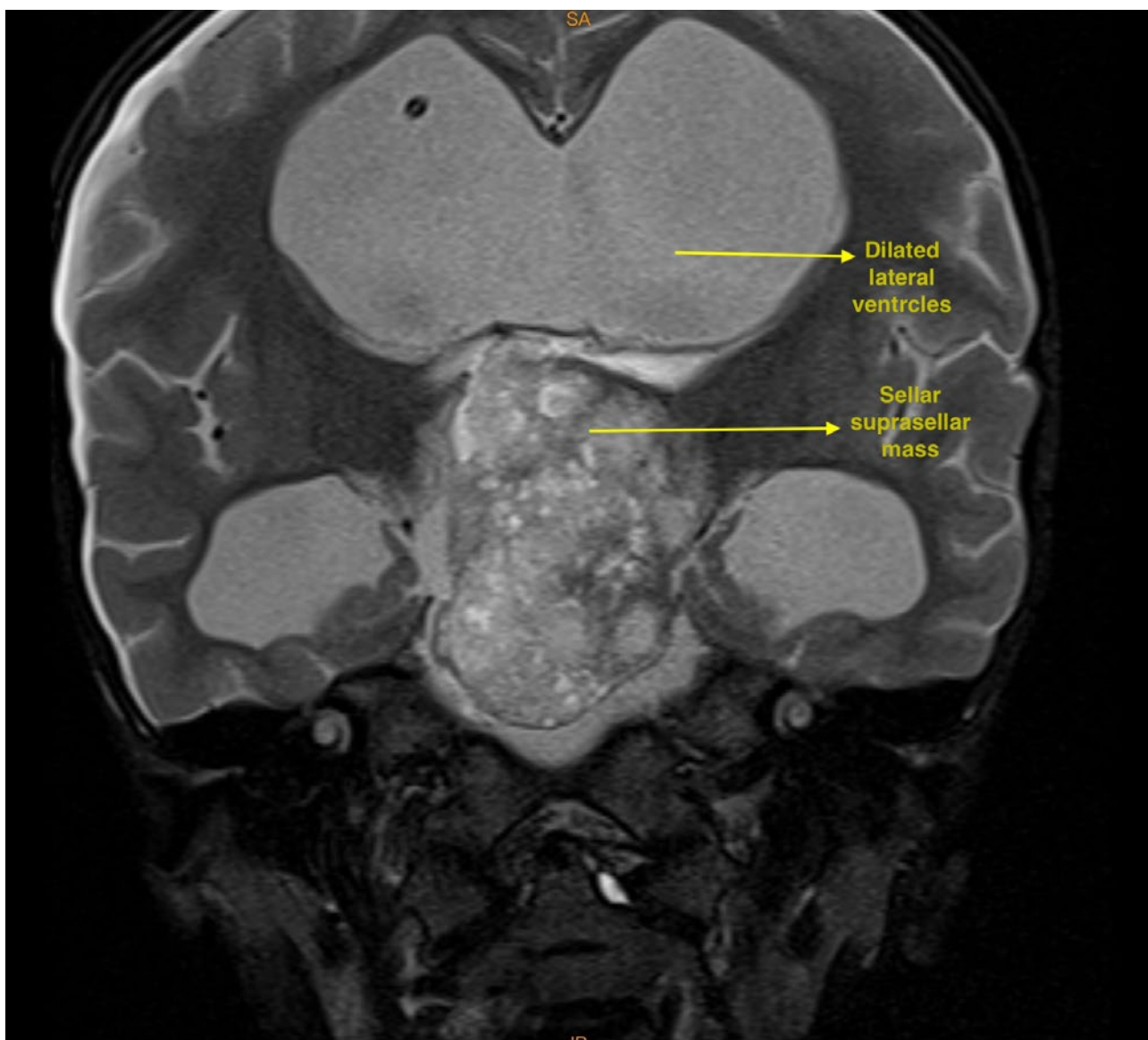
Routine investigations were all within normal limits. The initial haemoglobin was 11.5 g/dL, leading to a maximum allowable blood loss of 110

mL. The baseline platelet count was  $3.87 \times 10^3$  cells/ $\mu\text{m}$ m; growth hormone 2.45 ng/mL (normal: up to 3 ng/mL); adrenocorticotrophic hormone 13.4 pg/mL (normal: up to 46 pg/mL); and thyroid function tests (triiodothyronine: 6.5 ng/dL; thyroxine: 6.65  $\mu\text{g}$ /dL; thyroid-stimulating hormone: 1.53  $\mu\text{IU}$ /mL) and cortisol (8.4  $\mu\text{g}$ /dL) were within normal limits. The endocrinologist's opinion was taken, and they suggested that since all the hormones were within normal limits, no additional supplementation in the form of steroids and thyroxine was required.

### Radiological Evaluation

MRI of the brain suggested that a well-defined lobulated solid cystic mass, measuring  $4.5 \times 3.5 \times 5.5$  cm, involving the sellar and suprasellar regions was causing expansion of the sellar (Figures 1 and 2). Superiorly, the lesion was uplifting and compressing the optic chiasma and also abutting and displacing the A1 segment of bilateral anterior cerebral artery. Inferiorly, the lesion was compressing the pituitary gland. Laterally, the lesion abutted bilateral cavernous sinuses, with the normal bilateral internal carotid artery. Posteriorly, it was compressing the pons, midbrain,

**Figure 1:** T2 coronal MRI showing a dilated lateral ventricles and large hyperintense sellar and suprasellar mass.





and basilar artery, splaying the mid-brain and cerebral peduncles. It was also compressing the third ventricle and aqueduct of Sylvius, causing gross dilatation of bilateral lateral ventricles with an Evan's Index (EI) of 0.62 and the radiological impression of craniopharyngioma. Considering the tumour's proximity to neurovascular structures, invasive modalities such as invasive arterial blood pressure monitoring and central venous cannulation were planned.

### Therapeutic Intervention

Given the large size of the tumour, chemotherapy would not have been very effective. Hence, the patient was planned for left pterional craniotomy and debulking of the tumour under general anaesthesia, which was to be followed later by chemotherapy.

### Intraoperative Anaesthetic Management

The pre-operative assessment, including airway examination, was typical, with a Modified Mallampati score of 1. After confirming nil per oral status on the day of surgery, the patient was taken to the operating theatre. Their baseline non-invasive blood pressure was 110/75 mmHg, pulse rate 102 /min, and oxygen saturation 99% on room air. Proper positioning with cotton padding of all pressure points was completed to prevent peripheral nerve injury. The forced-air warming blanket was used to avoid hypothermia, and the operating room's temperature was maintained at 25 °C. The intraoperative temperature was monitored using a skin temperature sensor and adjusted for core temperature. Pre-medication with injection glycopyrrolate 0.05 mg was done. Intravenous induction was achieved with an injection of fentanyl 20 µg and propofol 20 mg. Muscle relaxation was achieved with an injection of vecuronium 1 mg and intubated with a cuffed endotracheal tube sized 5.0 mm without difficulty. Maintenance of anaesthesia was performed with oxygen and air (40:60), sevoflurane 1 minimum alveolar concentration, and intermittent boluses of vecuronium and fentanyl. Ventilation was done to maintain end-tidal carbon dioxide 33–5 mmHg. The right dorsalis pedis artery was cannulated for the beat-to-beat blood pressure monitoring. Right subclavian central venous access was done with a 5.5 Fr triple lumen central venous cannula. As preoperative cortisol levels were within normal limits, intraoperative steroids were not supplemented.

### Surgical Management

Intraoperatively, the surgeon observed that the pituitary gland and stalk could not be separately identified, and optic apparatus was splayed and thinned out. The tumour was infiltrating the hypothalamus and abutting the brain stem. Hence, the surgeon decided to leave the posterior attachment of the tumour on the brainstem and the remaining part of the tumour was removed; thus, haemostasis was achieved. The total duration of anaesthesia was 8 hours. Intraoperatively, blood loss of 300 mL was replaced with 150 mL packed red blood cell. Intraoperative arterial blood gas and blood sugars were within normal limits. Normothermia was maintained throughout the intraoperative period. The patient was shifted to the neurological intensive care unit for elective ventilation and delayed extubation.

### Follow-Up and Outcomes

Urine output increased (120 mL /hour for 4 hours) 2 hours post-operatively. The anticipated post-operative complication of craniopharyngioma, diabetes insipidus, was suspected and serum electrolytes were sent. Hyponatremia was detected, with postoperative sodium levels tabulated in [Table 1](#). There were no other electrolyte derangements. However, serial measurements of urine osmolality and serum osmolality would have been a better predictor for diagnosis and prognosis. Still, they could not be done as they were unavailable at the authors' institute at that time.

Free water (50 mL every 3 hours) was administered through a nasogastric tube and 0.45% of normal saline intravenously, 30 mL per hour. An injection of desmopressin 0.05 mg was administered after consultation with an endocrinologist. Over the next 4 hours, urine output started decreasing appropriately. On the first post-operative day, they were extubated as the child gained full consciousness, responded to commands, and had intact airway reflexes.

A repeat episode of increased urine output and hypernatraemia occurred after 24 hours. The injection of desmopressin 0.05 mg was repeated but, gradually, the patient's GCS started deteriorating to E3V3M4. The patient was put on mechanical support again. The specimen's histopathological biopsy confirmed the craniopharyngioma diagnosis (World Health Organization [WHO] Grade 1).

Figure 2: T1 sagittal MRI showing a large hypertense sellar and suprasellar mass.

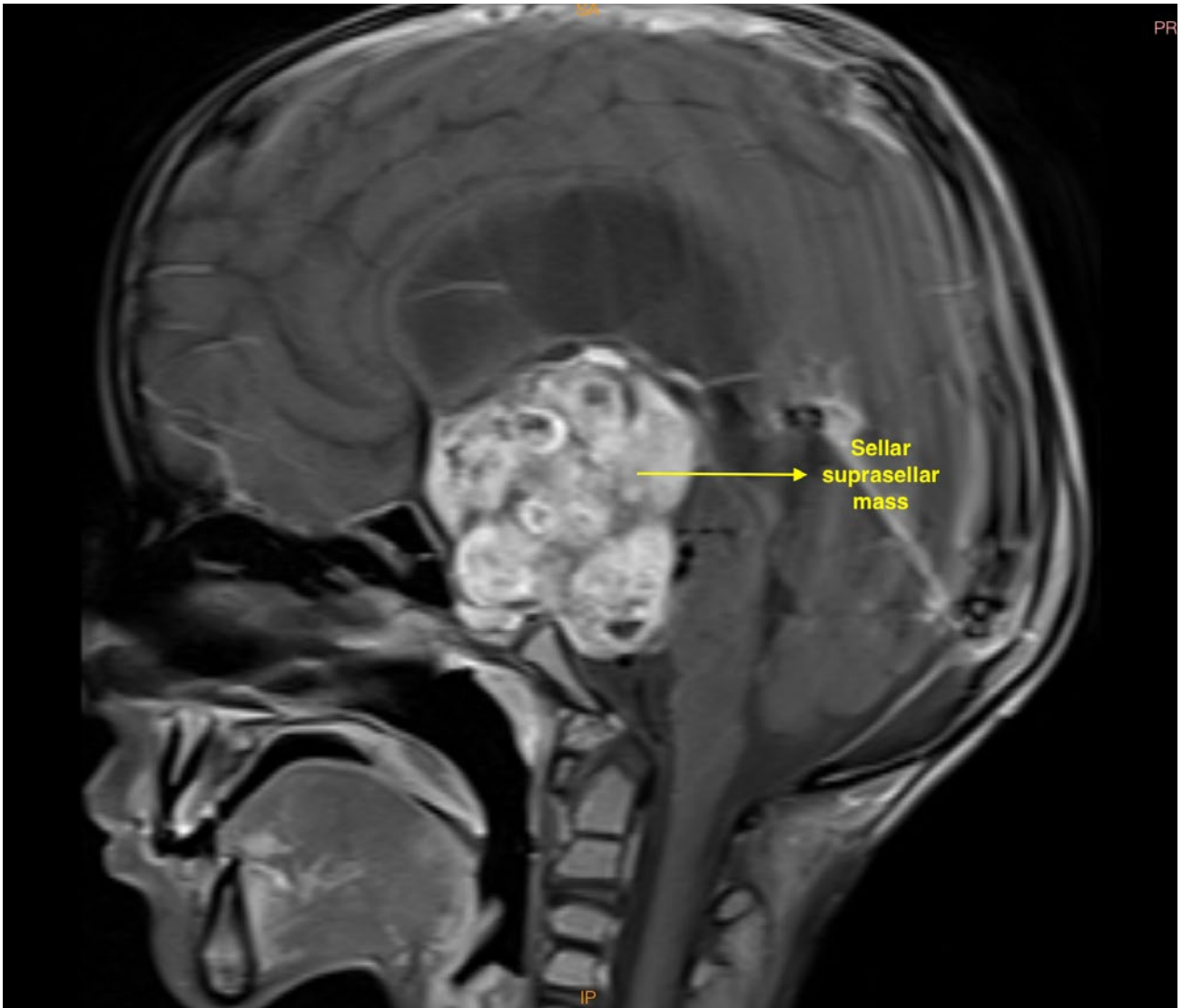


Table 1: Serial serum sodium levels.

Time	Serum sodium levels (mmol/L)
4 hours post-operative	161.4
8 hours post-operative	159.0
12 hours post-operative	148.0
24 hours post-operative	144.0

On the second post-operative day, the patient developed new-onset nystagmus, their GCS further decreased to E2V non-testable M3, and they developed haemodynamic instability with hypotension. They were started on an injection noradrenaline infusion at 0.1 µg/kg/min and titrated according to blood pressure. A complete blood count revealed an unanticipated complication of thrombocytopenia with a 1,4000 /µmm platelet count, and four random donor platelet transfusion units were done. A non-contrast CT brain scan showed no sign of haemorrhage. Unfortunately, despite all the resuscitation measures, the patient succumbed to dyselectrolyemia due to diabetes insipidus and thrombocytopenia the next day.

### Timeline of Events

In December 2019, the child started having a frontal headache, which progressed in intensity over 2 years. From June 2021, the child developed vomiting, rage attacks, and decreased weight despite increased appetite. In October 2021, their parents noticed drowsiness in the child. From November 2021, the child complained of diminution in vision. At that time, on evaluation, he was diagnosed with hydrocephalus, and a ventriculoperitoneal shunt was performed. In December 2021, child was brought to our tertiary care centre for further management. They were clinically examined, and it was found that they had a low weight for their age (Z score: -12.29), and there was bilateral optic atrophy. The patient was investigated thoroughly with blood investigations, including hormonal profiles, which were within normal limits. Radiological evaluation with MRI brain gave an impression of craniopharyngioma, and they were planned for sub-total resection of the tumour. Post-operatively, the child developed diabetes insipidus 2 hours after surgery, which was medically managed; however, a repeat episode occurred again the next day. It was further complicated by the onset of thrombocytopenia. The child succumbed to dyselectrolyemia due to diabetes insipidus and thrombocytopenia on the second post-operative day.

## DISCUSSION

An 8-year-old child with loss of weight, average linear growth, and the absence of gastrointestinal symptoms and other neurological signs had a diagnosis made favouring DS.<sup>2</sup> DS is associated with various types of tumours of the hypothalamic and optic chiasmatic region, the most common being low-grade glioma followed by astrocytoma.<sup>3</sup> However, in this case, the histopathology was craniopharyngioma (WHO Grade 1).

The usual age of presentation is 18 months in an emaciated child in the presence of average linear growth despite normal or even increased appetite. These children attain typical milestones as per age and appear to be more than happy for their state, which could be because of personality changes owing to the tumour itself. The Boston Children's Hospital, Massachusetts, USA, and the Dana-Farber Cancer Institute, Boston, Massachusetts, USA, showed the incidence of hyperkinesia (9%), nystagmus (27%), and emesis (36%).<sup>3</sup>

The pathophysiology of this rare disease is still unclear, although increased growth hormone and ghrelin, as well as decreased insulin and leptin levels, have been suggested. However, these hormonal changes were claimed to be related to the patient's nutritional status rather than causality.<sup>4,5</sup> This patient had a typical hormonal profile, although the tumour was close to the hypothalamus and pituitary gland. The possible explanation for this finding could be that the tumour had not compressed the pituitary gland enough to alter the hormonal profile.

The survival rate without treatment after the onset of symptoms is 12 months.<sup>6</sup>

The treatment can vary from chemotherapy after the endoscopic biopsy to definitive surgical excision of the lesion. The concept of the HIT-LGG-1996 study recommends early chemotherapy instead of radiotherapy in younger children with low-grade gliomas.<sup>7</sup> Conventional frontline therapy for patients with DS consists of chemotherapy, typically with agents like carboplatin and vinca alkaloids.<sup>8</sup> Kim et al.<sup>9</sup> conducted a retrospective study of 8 patients with DS in 2015. Three patients received concurrent chemoradiotherapy, two received chemotherapy, and three did not receive treatment. On follow-up evaluation, two patients

were still receiving chemotherapy, and three patients showed improvement and remained in stable remission.

Radiotherapy is not chosen, given the endocrinological and neurological consequences in paediatric patients. The most recent case reported was by Roncall et al.<sup>10</sup> in 2019, of case of DS in an 8-year-old child posted for endoscopic biopsy and ventriculoperitoneal shunt under general anaesthesia.<sup>10</sup> The child was discharged home after the uneventful post-operative course, with the initiation of chemotherapy.

The treatment protocol for DS has not been standardised to date, and no clear guidelines are available on which treatment can be based. The protocols are usually chosen based on the specific type of tumour causing DS. Chemotherapy appears to play a significant role in the management of DS in young children.<sup>11</sup>

As this was suspected as craniopharyngioma, considering the WHO guidelines for new onset craniopharyngiomas. Sub-total resection of the tumour was planned first as it was a large tumour. Hence, debulking the tumour using surgical resection would help increase the success of postoperative chemotherapy for residual tumour.

Anaesthetic considerations specific to this case were: positioning with padding of all the pressure points due to loss of subcutaneous fat and fixed flexor deformity of joints; risk of hypothermia due to loss of subcutaneous fat and postoperatively due to hypothalamic injury; drug dosing and fluid management as per the weight of the child; massive fluid shift, electrolyte imbalance, and haemodynamic instability due to diabetes insipidus; and caloric requirements of the child to be met post-operatively.

The post-operative thrombocytopenia that the authors encountered in the case study presented here could be dilutional in aetiology due to a massive fluid shift due to diabetes insipidus, as the patient was given free water via nasogastric tube as well as 0.45% normal saline intravenously. This was supported by the finding of thrombocytopenia on blood haemogram, despite normal platelet count pre-operatively. Although correction of hypernatremia was given as per the free water deficit calculation, the patient showed an exaggerated response, which manifested as

an overcorrection of their serum sodium levels (Table 1). The complication of diabetes insipidus is quite common after craniopharyngioma surgery. Still, it was more detrimental here as the child was severely emaciated, and thus had a lower percentage of total body water and could not cope with the diabetes insipidus. Therefore, a timely diagnosis and case-tailored management in such cases are essential before the stage of emaciation sets in. The post-operative neurocritical care in these patients is targeted on an illiberal fluid replacement to prevent fluid overload, management of diabetes insipidus, preventing hypothermia, meeting caloric requirements, preventing bed sores due to pressure necrosis, and guided ventilation to prevent respiratory complications.

To the best of the authors' knowledge, no case has been reported where diabetes insipidus has been observed in patients with the diencephalic syndrome. Thus, this case report can help further understand the spectrum of disease and its complications.

## LIMITATIONS

There were a few limitations in this case study. The child presented with emaciation due to delayed diagnosis, which increased the probability of complications. Also, the massive size of the suprasellar tumour also increased the chances of complications.

## Parents' Perspective

The parents did not know that their child had a brain tumour for a long time. They saw their child losing weight daily in front of their eyes, and they saw their child start to develop new symptoms as the days passed; however, they could not find the reason for it and kept wondering if there was hope of finding treatment. After coming to the authors' hospital, the patients found out that their child had a brain tumour. The delay in getting therapy could have been one of the reasons for the untimely death of their child. Had they received a timely diagnosis and management, maybe their child could have been saved. The doctors and staff did their best to manage their child, but things did not turn up in their favour and parents lost their child.



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# Marfan Syndrome and Autosomal Dominant Polycystic Kidney Disease: A Case of Rare Co-occurrence or Coincidence?



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<b>Disclosure:</b>	The author has declared no conflicts of interest. The patient gave their consent.
<b>Received:</b>	03.03.22
<b>Accepted:</b>	17.08.22
<b>Keywords:</b>	Aneurysm, cyst, Marfan.
<b>Citation:</b>	EMJ. 2022;7[3]:94-98. DOI/10.33590/emj/10008375. <a href="https://doi.org/10.33590/emj/10008375">https://doi.org/10.33590/emj/10008375</a> .

## Abstract

**Background:** Marfan syndrome (MFS) and autosomal dominant kidney disease (ADPKD) are two separate genetic disorders. The author describes the case of a young male with ADPKD who incidentally had Marfan-like features. A literature review was carried out to see if these two disorders could be linked.

**Case presentation:** A young male presented for incidentally found renal cysts. Kidney function was well preserved, but the patient had positive family history of ADPKD. During routine follow-up, a history of aortic valve disease was mentioned. This, along with the patient's tall, lean stature and long extremities raised the concern for MFS. A detailed physical examination and workup by other specialists confirmed a clinical diagnosis of MFS. They had no known family history of MFS. The patient has been followed at Associates in Kidney Care, Des Moines, Iowa, USA, for the past 2 years.

**Discussion:** There are several reports of overlap of ADPKD and connective tissue disorders with an overlap of vascular disorders. ADPKD and MFS are caused by totally different mutations. However, the literature review showed that vascular abnormalities and connective tissue diseases may be more common with ADPKD. Studies have shown that there could be a common signalling pathway for connective tissue disorders when both genes are affected simultaneously. Further research is needed to identify these pathways. More frequent screening of vascular abnormalities might be warranted in those with both phenotypes.

## Key Points

1. The co-occurrence of Marfan syndrome (MFS) and autosomal dominant polycystic kidney disease (ADPKD) is uncommon, as these disorders affect 1 in 3,000–5,000 and 1 in 500–5,000, respectively.
2. MFS and ADPKD result in systemic connective tissue symptoms, which can appear to overlap; however, more research is needed to identify genetic pathways that could cause this overlap in these disorders.
3. According to the author, patients with ADPKD and aortic vascular abnormalities should also be evaluated for the co-occurrence of other connective tissue diseases such as MFS.

## BACKGROUND

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with an incidence of 1 in 3,000–5,000.<sup>1</sup> Autosomal dominant polycystic kidney disease (ADPKD) is a disorder with an incidence of 1 in 500–5,000 that causes fluid-filled cysts, most commonly on the kidneys.<sup>2</sup> The author describes here a case of co-occurrence of the two, which has been described previously but remains an uncommon co-occurrence.

## CASE PRESENTATION

### Initial Visit

A 25-year-old male presented to the nephrology clinic for evaluation of renal cysts found incidentally on an abdominal sonogram a few months earlier. The sonogram was done for work-up of abdominal pain and it revealed a gallbladder polyp and mild pancreatitis. This was managed conservatively. The kidneys showed numerous cysts bilaterally, and the longest dimension of the kidney was 14 cm. Liver cysts were absent.

Blood pressure was at goal at 120/70 mmHg and other vitals were stable. On focused physical examination, the patient was tall at 193 cms, with a lean body frame at 136 lbs (BMI: 17) and long extremities. Urinalysis was bland, creatinine 0.7 mg/dL and haemoglobin 14.6 g/dL. The patient's father had a known diagnosis of ADPKD, and was being followed by a nephrologist. Based on family history and ultrasound criteria, the patient was diagnosed with ADPKD. They were taking bupropion for depression.

### Second Visit

Six months later, urinalysis remained bland and creatinine was 1 mg/dL. Repeat renal sonogram showed a slight increase in kidney size with largest renal dimension at 15 cm (previously 14 cm). The author discussed tolvaptan to slow glomerular filtration rate (GFR) decline and renal size with the patient, but they declined as they did not have health insurance at the time.

### Third Visit

One year later, creatinine was stable at 0.83 mg/dL. Sonogram showed stable-sized kidneys. The patient's mother accompanied them on this visit, and mentioned that they had a history of 'aortic disease' with aortic root dilatation. Details were uncertain, but reportedly a cardiologist had told the patient they no longer needed follow-up. With their body stature and aortic disease, concern for MFS was raised. They acknowledged that this was considered by prior doctors, but no formal diagnosis was ever made.

On detailed physical examination based on Ghent's criteria; the patient had positive wrist plus thumb sign (explained below); pectus excavatum; flat feet; 3 out of 5 facial features present (explained below); aortic root dilatation; arm span: 204 cm; height: 193 cm; and upper segment: 88 cm.

Upper segment to lower segment ratio was 0.84, and arm span to height ratio was 1.06, which are positive markers for MFS.

The patient also had scoliosis. Ocular exam by an ophthalmologist confirmed ectopia lentis. They had no known family history of MFS.

Description of positive physical exam findings of MFS:

1. Positive thumb sign: this sign is elicited by making a fist over the clenched thumb. The thumb extends beyond the ulnar margin of the wrist.<sup>3</sup>
2. **Figure 1:** this shows positive wrist sign. The patient was asked to grip his wrist with his opposite hand. The thumb and fifth finger overlap, hence the sign is positive.<sup>4</sup>

Positive facial features of MFS that the patient had include: micrognathia, malar hypoplasia, and downward slanting palpebral features.

A transthoracic echocardiogram showed aortic root dilation with aortic diameter  $Z > 2$ .

A literature review using Pubmed, Google Scholar, and Semantic Scholar did reveal associations with ADPKD and connective tissue disorders.

This appears to be one of the very rare cases of MFS with coincidental ADPKD.

## DISCUSSION

ADPKD has been associated with increased risk of intracranial aneurysms<sup>5</sup> and connective tissue disorders.<sup>6</sup> ADPKD is the most common monogenic form of inherited kidney disease worldwide.<sup>7</sup> It is a common cause of end-stage kidney disease. Growth of renal cyst size and kidney volume over time precedes GFR decline. Kidney volume assessment by imaging is used for prognostication purposes. There is currently no defined treatment to reverse cyst size. Strict blood pressure control was shown to reduce adverse outcomes,<sup>8</sup> and a low-sodium diet plus maintaining a dilute urine (as tolerated) is recommended. More recently, antidiuretic hormone antagonists like tolvaptan have been shown to reduce growth or renal cysts and slow the rate of GFR decline.<sup>9</sup> One study showed benefit in GFRs above 60 mL/min/m<sup>2</sup>.<sup>10</sup> This patient's most recent estimated GFR measurement was 120 mL/min/m<sup>2</sup> per CKD-EPI equation.

MFS is a predominantly autosomal dominant disorder with rare case reports described as recessive inheritance.<sup>11</sup> The clinical presentation is broad, with clinical features involving ocular, cardiovascular, musculoskeletal, and, in some cases, lung, skin, and nervous system abnormalities. Most patients with the typical Marfan phenotype harbour mutations involving the *FBN1* gene. *FBN1* mutations can also show milder phenotypes. The details of genotypes and phenotypes of MFS is beyond the scope of this review. The diagnostic criteria is based on the presence or absence of family history of MFS. Based on aortic root dilatation, ectopia lentis, and systemic score (Ghent classification), this case had MFS. Surveillance imaging is recommended every 6 months to look for aortic root enlargement, and is the plan going forward for this patient.

## Overlap Between *PKD1* and *FBN1* Mutations

A co-occurrence between cystic kidney disease and Marfan-like features was first described by Booth et al.<sup>12</sup>

ADPKD is primarily due to *PKD1* and/or *PKD2* gene mutations on chromosome 16 (resulting in polycystin-1 and polycystin-2 abnormalities, respectively) while MFS is due to *FBN1* gene mutation on chromosome 15 (which results in upregulation of TGF- $\beta$ ). Cerebral vascular aneurysms have been reported with ADPKD.<sup>5</sup> Aortic aneurysms also have been reported with ADPKD at a rate of 7.3-times greater than chance association alone.<sup>13</sup> A possible reason for higher association of aneurysms and vascular problems in ADPKD could be advanced kidney disease itself. However, there are hypotheses that connective tissue defects could contribute to the pathogenesis of ADPKD,<sup>14</sup> and that ADPKD by itself could be a disorder of connective tissue.

A study in 1993 by Samlo et al.<sup>6</sup> studied patients with ADPKD and overlap connective tissue disorders. It suggested that coexisting connective tissue and vascular issues in ADPKD could be an 'extension' of *PKD1* phenotype. One possibility discussed was that the disorders are produced by independent, but genetically linked, mutations. Hateboer et al.<sup>15</sup> carried out a study to look at the genetic linkage between these two diseases.



Figure 1: Positive wrist sign.



Their conclusion was that these diseases do not appear to be genetically associated, and co-occurrence previously has been reported as a chance event. Per the original paper, which was carried out in Europe, the prevalence of ADPKD then in Europe was 1 in 1,000, and the rate of MFS in the UK was 1 in 14,000. Therefore, per their calculation, the chance of co-occurrence is 1 in 14 million.

There are reports that *PKD1* mutations can cause a TGF- $\beta$  upregulation, which exacerbates the MFS phenotype. A study was conducted by Liu et al.<sup>16</sup> in mice, to investigate a potential genetic interaction between *PKD1* and *FBN1* mutations. Mice heterozygous for *PKD1* were matched with those heterozygous for *FBN1*. Double heterozygotes for *PKD1* and *FBN1* mutations showed severe aortic abnormalities

compared with those without dual mutations. That study went a step further and stained the aortic vascular walls. There was increased aortic staining for connective tissue growth factor in double heterozygotes. TGF- $\beta$  signalling was increased in vascular smooth muscle cells isolated from *PKD1* and *FBN1* heterozygotes.

Aortic vascular abnormalities occurring in the setting of *PKD1* mutations in isolation without other abnormalities have not been reported.<sup>17</sup> Thus, the presence of aortic vascular abnormalities in patients with ADPKD should prompt clinicians to further evaluate patients for co-occurrence of other connective tissue diseases.

Studies have shown that angiotensin 2 induced the TGF- $\beta$  pathway in ADPKD and aneurysm

formation.<sup>18,19</sup> Angiotensin receptor blockers were potent inhibitors of this pathway in *FBN1* mutant mice, which could play a significant role in their management.

## CONCLUSION

MFS and ADPKD are disorders that result in systemic connective tissue symptoms that can appear to overlap. However, there does not appear to be an actual genetic association between these two diseases.

Specifically, aortic vascular issues in those with ADPKD should prompt clinicians to evaluate patients for other aetiologies. More research is needed to identify the common signalling pathways in these rare disorders. Some studies described above have suggested that a more 'muted' form of *FBN1* mutations in the presence of *PKD1* mutations can increase the characteristics of MFS. Strict blood pressure control (preferably with angiotensin receptor blockade) and close surveillance for vascular abnormalities will be an integral part of

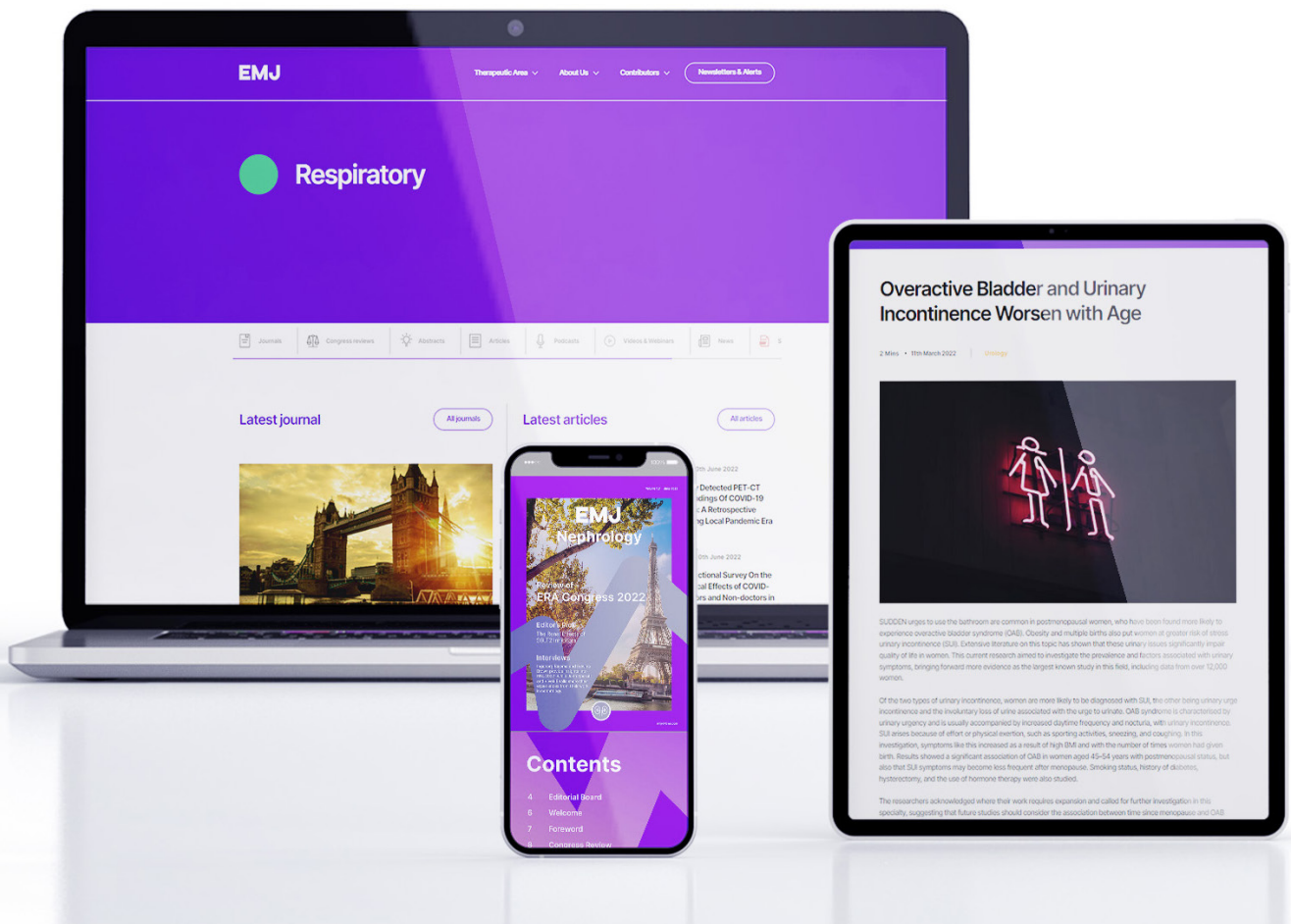
management. This is especially important as the severity of vascular abnormalities can be more pronounced when the diseases co-exist.

This patient's blood pressure was below 120/70 without medication, and they are being followed closely for surveillance of aortic disease. This report has some limitations because of the lack of specific genetic testing due to the patient's financial constraints, as they have no medical insurance. This also limited some follow-up testing. Images for aortic root dilatation were not available.

However, the author can confirm that the patient has ADPKD, based on sonological criteria and family history, and MFS confirmed by clinical testing. The teaching point for nephrologists is that ADPKD and MFS can overlap. However, based on current data, this is purely a chance event, but further research is needed to identify common genetic pathways that could cause overlap between both disorders. This review of existing literature does show that ADPKD and connective tissue disorders can present together.

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# Cotard's Delusion with Sequelae of Adult Onset Failure to Thrive: A Case Report

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## Disclosure:

The authors have declared no conflicts of interest.

## Received:

04.10.21

## Accepted:

24.05.22

## Keywords:

Antipsychotics, case report, clinical gestalt, Cotard's syndrome, electroconvulsive therapy, failure to thrive, prescription medications, medical power of attorney, systems thinking.

## Citation:

EMJ. 2022;7[3]:100-108. DOI/10.33590/emj/21-00216. <https://doi.org/10.33590/emj/21-00216>.

## Abstract

Patients can present with chief complaints and symptoms that differ from the eventual diagnoses. The differences between aetiologies versus complications must be appreciated through careful evaluation and use of clinical investigations, laboratory testing, trial of hypotheses, and clinical gestalt. Herein, this article discusses the case of a 58-year old individual who presented with impaired physical functioning, malnutrition, depression, and cognitive impairment. These four symptoms are known collectively as failure to thrive, and they often portend adverse patient outcomes. The internal medicine care team initially attributed the failure to thrive to the combination of an ongoing cervicofacial infection and a pre-existing mood disorder, but its true aetiology was more complex. In the context of various physical and psychiatric health derangements, the patient displayed clear signs of a rare disorder called Cotard's syndrome. Due to the concern of the care team and the patient's acting medical power of attorney, the eventual working diagnosis was made, and electroconvulsive therapy and aripiprazole combination therapy initiated, resulting in significant and improved outcomes. In addition to discussing the patient's course of care, this case report also addresses the caution inherent in prescribing medications, the evaluation of decision making capacity, and the utilisation of a medical power of attorney. The authors also present their thoughts on minimising inefficiencies in care delivery to better the patient's health outcomes.

## Key Points

1. Cotard's delusion (CD) follows a two-hit hypothesis, where an insult challenges the identification of an individual's body, and another fails to resolve the psychological conflict.



2. The patient in this case study had started to improve before the COVID-19 pandemic; however, social isolation and a lack of in-person physical therapy helped to worsen their mental and physical health.

3. A rare condition, most research into CD is through case studies, which the authors reviewed to summarise the efficacy of CD treatment options.

## INTRODUCTION

Cotard's delusion (CD) is a rarely described condition in which patients present with a constellation of symptoms. There are multiple types of Cotard's syndrome: psychotic depression (depressive episodes with secondary psychotic elements), Cotard's Type 1 (nihilistic delusions), and Cotard's Type 2 (a mix of anxiety, depression, and delusions).<sup>1</sup> Of these types, there also lies a progression of illness categorised by the level of severity of the psychopathological presentation. Firstly, the germination stage presents with hypochondriasis and cenesthopathy. Secondly, the blooming stage introduces nihilistic delusion and delusion of negation of one's own body or body part(s). Lastly, the chronic stage cements the mood changes and systematic delusions of the patient.<sup>2</sup> Herein, the authors describe a unique case of CD with sequelae of a syndrome known as Adult Onset Failure to Thrive.

## PATIENT INFORMATION

The patient is a 58-year-old individual with history of hypertension, hyperlipidaemia, Type 2 diabetes, recent left cerebellar cerebrovascular accident (CVA) in January 2020, with focal frontal white matter ischaemic changes and subcortical insults in the basal ganglia, and remote history of major depressive disorder with psychotic features, for which they received inpatient treatment as a teen, likely superimposed on an evolving neurocognitive disorder of vascular aetiology (Figures 1 and 2). They presented to the emergency department with a 2-day history of right-sided facial and neck swelling, concerning for acute sialadenitis versus cellulitis with associated dysphagia and subsequent poor oral intake. CT indicated extensive oedema of the superficial and deep spaces of the right neck and blood cultures grew methicillin-susceptible *Staphylococcus aureus*

bacteria, prompting a screening echocardiogram that showed normal systolic function and ejection fraction without signs of valvular vegetation. Per the recommendations of Oral and Maxillofacial Surgery; Ear, Nose and Throat; and Infectious Diseases departments, the internal medicine team pursued antibiotic treatment without surgical intervention.

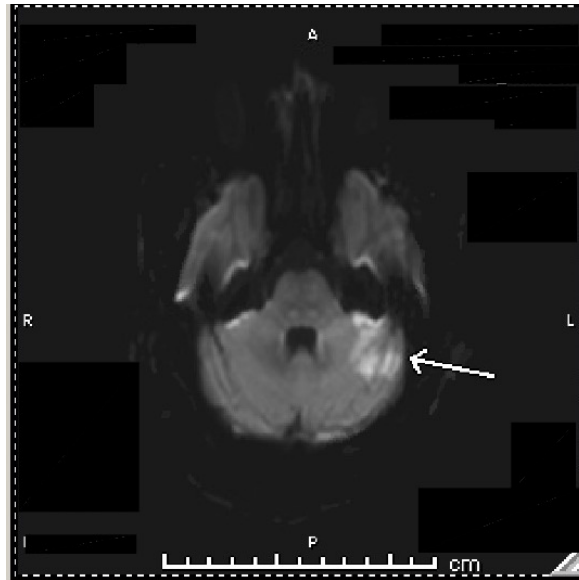
The patient transitioned to physical therapy in February after the CVA, and had been making progress in recovering baseline function when the COVID-19 pandemic hit. According to the patient's children, they were an active church member, had a great appetite, and were independent in most, if not all, activities of daily living. Unfortunately, the social isolation in combination with lack of in-person physical therapy brought on by distancing measures precipitated a decline in their mental and physical health that manifested as worsening functional status.

## CLINICAL FINDINGS

By the end of August 2020, the patient was bedridden and needed extensive assistance. They were neglectful of personal hygiene, socially withdrawn, and refused any oral intake, including medication and food. When the internal medicine service admitted the patient in November 2020, they had lost 70 lbs since January.

While the infection and associated dysphagia improved with intravenous antibiotic treatment, their nutritional status did not. They continued to refuse oral intake, and developed worsening psychomotor retardation, depression, and delusions, along with a severe pathological guilt perception. On multiple occasions, they disclosed that their illness was punishment for not adhering more stringently to their religious beliefs. When the care team enquired about their reluctance to eat, they simply stated that their

Figure 1: Axial CT images of the head from the skull base to the vertex without contrast.



Brain and bone algorithms were performed and reviewed. A prominent recent infarction involving the superior portion of the left cerebellum is associated with slightly increasing deformity of the left side of the fourth ventricle. No haemorrhage was evident. There was a potential for eventual development of hydrocephalus, although that was not present at the time. A moderate remote infarction was again seen about the anterior horn of the left lateral ventricle and basal ganglia. The brain parenchyma, ventricles, and subarachnoid spaces are otherwise unremarkable in appearance.

“insides are rotting,” and that their stomach and other various organs no longer existed, a set of beliefs known as CD. At this point in treatment, they were experiencing a significant amount of anal pain and constipation (despite having consistent bowel movements), and endorsed 10 out of 10 pain according to the Numerical Rating Scale.<sup>3</sup> They stated that a demon in the room was responsible for inflicting this abdominal pain, the presence of which invalidated their claim that they no longer had “insides” (Table 1).

## DIAGNOSTIC ASSESSMENT

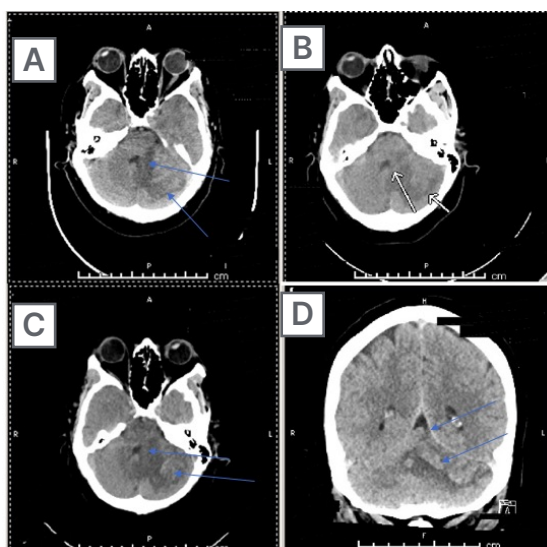
With the decline in the patient’s cognitive function over the period of around 8 months, several contributory factors were considered. These include a precipitating episode of a mood disorder, substance- or medication-induced psychosis, catatonia, dementia, metabolic disorders, infection, and CD. With the patient’s history of major depressive disorder with psychotic features, an episode of such was the most likely diagnosis. Other psychiatric problems

with similar presentations include catatonia, a treatable condition, and dementia, a long-term health condition caused by the degeneration of neuronal cell bodies, often diagnosed through clinical exploration.

The patient’s mental status, nevertheless, might have been affected by other derangements. The patient was taking lorazepam, a drug known for precipitating psychosis or delirium in patients, which with the cessation of the medication resolved. The adverse effect of medications along with infectious aetiologies, a well-known cause of altered mental status, and the main reason for the patient’s initial presentation, were considered and ruled out as part of the clinical investigation.

The ultimate diagnosis of CD was one of exclusion, taking into account the constellation of delusions that our patient demonstrated. An important consideration regarding this diagnosis was the sequelae of a syndrome known as adult onset failure to thrive, with which the patient clearly manifested in their initial presentation.

Figure 2: Axial CT images of the head from the skull base to the vertex without contrast.



Brain and bone algorithms were performed and reviewed. Hypoattenuation was again noted in the left cerebellar hemisphere, along with findings of cortical laminar necrosis and petechial type haemorrhage. Mild mass effect is again noted on the fourth ventricle, but without cephalisation. Of note are old left basal ganglia and left frontal periventricular infarctions. There was no evidence of new oedema, midline shift, new intracranial haemorrhage, or extra-axial fluid collection. An acute cortical infarction is not apparent. Demonstrated here is **(A)** subacute swelling and **(B)** subcortical damage from mass effect, all secondary to **(C)** the initial cerebellar stroke. The initial injury and the impingement on the fourth ventricle led to damage in the patient's brain in the subcortical space and the basal ganglia **(D)**.

More common in the geriatric population, especially those with chronic or existing comorbidities, failure to thrive is characterised by cognitive impairment, malnutrition, decline in physical function, and depression.<sup>4</sup> While the deterioration in physical and nutritional health could be mistaken for symptoms of a melancholic depression with delusions or even hallucinations, the patient's nihilistic delusions, along with the accompanying religious persecutory undertones seen in many other CD cases, make this aetiology more likely.<sup>5</sup>

## THERAPEUTIC INTERVENTION

The initial approach to CD requires meticulous assessment of the patient's psychiatric and medical features. The treatment of underlying medical or neuropsychiatric disorders should take precedent. In particular, for severe cases presenting with feeding refusal, as in this case presentation, enteral nutrition should be considered until by-mouth fluid and food intake is

resumed. The patient had a Dobhoff tube (DHT) placed. Nutritional deficiencies can precipitate or exacerbate delusions and psychosis, thereby reiterating the importance of its treatment. After addressing the more life-threatening conditions, efforts should shift towards treatment of CD if symptoms have yet to resolve.

The patient was initially restarted on home medications that included olanzapine 10 mg each bedtime and sertraline 50 mg/day, albeit with little to no improvement. The patient reported continued severe depression and CDs, and they had poor oral intake even with motivational interventions. Eventually, alprazolam 0.25 mg was administered prior to meals to reduce the anticipatory anxiety from the dysphagia. Due to its significant sedative effects and precipitation of psychosis, however, they were weaned off the medication and started on electroconvulsive therapy (ECT) and aripiprazole combination therapy.

Table 1: Patient timeline.

1980s	As a teenager, the patient received inpatient treatment for major depressive disorder with psychotic features.
January 2020	Patient presented to Level 1 trauma facility with left cerebellar CVA.
February 2020	The patient transitioned to physical therapy in February after the CVA and had been making progress in recovering baseline function.
March 2020	Beginning of the COVID-19 pandemic. According to the patient's children, they were an active church member, had a great appetite, and were independent in most if not all activities of daily living.
March–August 2020	Unfortunately, the social isolation in combination with lack of in-person physical therapy brought on by distancing measures precipitated a decline in their mental and physical health that manifested as worsening functional status.
August 2020	Patient was bedridden and needed extensive assistance.
November 2020	Patient had lost 70 lbs since admittance in January. Then they presented with a 2-day history of right-sided facial and neck swelling concerning acute sialadenitis versus cellulitis with associated dysphagia and subsequent poor oral intake.

CVA: cerebrovascular accident.

After the medical power of attorney consented to ECT treatment, their sessions occurred every Monday, Wednesday, and Friday. As ECT targets depressive symptoms, improvements in oral intake and effort were anticipated. ECT was further ideal for this patient as it is indicated with depression with psychotic features, prior treatment resistance, and poor food and fluid intake, all of which were seen in this patient. Aripiprazole was initiated prior to their first ECT appointment and was uptitrated to 10 mg/day, with which they were discharged to continue outpatient as an adjunct to the ECT. Research comparing aripiprazole to other antipsychotics suggests its poorer efficacy relative to olanzapine, but its metabolic effects and sedation are more tolerable.<sup>6</sup> The patient, specifically, has a history of hyperlipidaemia that precludes the use of olanzapine.

## OUTCOME

The patient showed a favourable response to ECT within a couple weeks after its initiation, and tolerated the treatments well. Their oral intake markedly improved and ultimately their DHT was removed. The patient's speech rate and fluency also improved, and their social interactions started to include humour in greater frequency. They reported mild headaches and short-term memory loss after a few ECT sessions, but the symptoms self-resolved. Ultimately, the combination of aripiprazole and ECT was most effective in reducing the severity of the CD and treating the patient's depression. The patient's rapid and significant response to ECT treatment is consistent with prior research.

One of the central issues encountered by the care team involved the patient's anxiety surrounding swallowing food. This anxiety had to be assuaged through the use of a benzodiazepine, which is a medication with the potential to worsen acute or chronic psychosis.



This side effect occurred in the case of the patient in discussion. The third leading cause of patient morbidity and mortality is iatrogenic; therefore, ensuring that new or worsening symptoms are not caused by the treatment strategy is key to ensuring patient safety and quality of life.<sup>7</sup> Through carefully examining the side effect profiles of different medications and weighing the need for its use, the physician cares first for the patient and works to fulfill the oath to 'do no harm'.

The second key clinical pearl involves patient capacity and autonomy. Patient autonomy is held to the highest regard in healthcare; however, its adherence can conflict with the physician's duty to protect their patients when they demonstrate self-neglect or self-injurious thoughts or behaviours. Decision-making capacity is especially limited in those with CD due to its characteristic nihilistic and fatalistic delusions. The delusions hampered the treatment and recovery of the patient, prompting an assessment and subsequent decision that their child step in as medical power of attorney. However, a critical point to note is that decision-making capacity is a time-based assessment that can improve or change over the course of treatment. The Decision-Making Capacity Assessment (DMCA) is the gold-standard of patient-centred care, and can be reassessed at any point in care by the physician. This rule allows for a precise and accurate representation of patient decision-making capacity on a temporal scale, which ensures that patient autonomy is respected.

The third and final key principle is systems thinking and solutions to ensure that the patient receives the best care possible. While the patient made a full recovery, the journey towards restoring their baseline health was anything but promising. Their ECT treatments were a demonstration in systemic failures and its cost to timely care. The team responsible for transporting them to the treatment facility at Seton Main Hospital, Austin, Texas, USA, was often late, although they could not control traffic, challenging patients, poor directions, or miscommunication, etc. When tardiness was not the issue, however, paperwork was. The transportation team somehow misplaced the signed consent form that accompanied their paper chart during the first trip, so the initiation of treatment was

postponed until the primary care team repeated the necessary steps to get informed consent. ECT is so limited in availability that rescheduling can be very challenging. The care team tried to co-ordinate for an inpatient transfer to Seton Main Hospital to circumvent the transportation mishaps, but there were no available beds. Without any other foreseeable or permanent solutions, the care team worked with the case manager to implement workarounds. The team started to arrange for transportation to pick them up 2 hours prior to their appointments to account for the late starts, and made sure the paper charts had the consent form attached before handing it off. The team then had the patient's child meet them at Seton Main Hospital to ensure that the documentation was still on their person.

The patient had to defer a couple other ECT sessions due to a missed order about stopping their DHT feedings. Per ECT protocol, patients are supposed to be nil by mouth 24 hours prior to treatment. This information was communicated both verbally to the night nurse and electronically in their medical chart as an order, but the DHT was sometimes on continuously up until the patient's transport to Seton Main Hospital. It was not until they arrived at the facility that the mishap came to light. The care team found that taping a note written in large letters about when to discontinue the patient's DHT to be most effective. Other similar strategies can and should be implemented to ensure that systems work in the benefit of the patient.

## **PATHOPHYSIOLOGY**

Pathophysiological explanations of Cotard's syndrome remain under investigation in the medical community, but several ties to specific psychopathological and neurobiological disease states offer clarity.<sup>8</sup> The presentation of Cotard's syndrome is most apparent in the psychiatric interview rather than traditional imaging, as the most profound and common clinical signs are depression and nihilistic delusion.<sup>9</sup> In this case study, the CVA event superimposed on the patient's history of depression and subsequent isolation were likely inciting factors.<sup>10,11</sup> Subcortical and basal ganglia damage, as seen in the imaging herein (Figure 2), has previously been documented as probable aetiologies of Cotard's-like delusions.<sup>12</sup>

Vascular damage to the insular cortex could also offer an organic explanation to Cotard's syndrome. CD is believed to follow a two-hit hypothesis, where one insult can challenge the internal identification of one's own body, and the second fails to resolve the psychological conflict when presented with evidence of the contrary. The insula allows control of introspective homeostasis, emotion, and other properties of mood. Damage here, the first hit, could lead to loss of external or internal interpretation of one's own body, leading to the hallmark sign of nihilistic delusion, or failure to recognise one's body.<sup>13</sup> Additionally, damage to any of the connections of the limbic system to cortical recognition areas could lead to loss of recognition of one's body parts, leading to the cognitive progression of nihilistic delusion.<sup>12</sup> Ischaemic insults to frontal lobe parenchyma has led to a variety of misidentification delusions, of which pertains to CD. The current understanding is that deep vascular frontal lesions could obliterate connections from the frontal lobe with basal ganglia structures, leaving the patient unable to executively resolve the conflict of misidentification, thereby establishing the second hit. These vascular challenges are consistent with the patient presentation. This two-hit hypothesis for misidentification delusions can thus be applied to the various themes of the delusions experienced by patients, including religiously-reinforced delusions, delusions of negation, and nihilism.

## DISCUSSION

Given its rarity, most research on CD are case studies. Although further research is necessary to improve the strength of the evidence behind treatment modalities, the aim of the following is to review available case studies and summarise the efficacy of pharmacological, ECT, and other treatment options used in CD.

Medications trialed in previous literature include antipsychotics, anticonvulsants, antidepressants (selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors), and benzodiazepines. Clinical symptoms generally guide the class of medication used in treatment. When affective symptoms predominate, typically antidepressant monotherapy is first line. However, when psychotic symptoms predominate, antipsychotic monotherapy is preferred. It is important to remember to also rule out other

causes of a patient's symptoms prior to treating the patient solely on an assumption that their affective and/or symptoms are purely secondary to mental illness.

Monotherapy with antipsychotics has proven to be effective in a number of CD cases. Monotherapy with olanzapine at a dose of 5 mg/day has been successful in case reports involving younger patients who developed CD subsequent to chronic psychoactive substance use and a traumatic brain injury.<sup>14</sup> Quetiapine at doses of 50 mg/day was shown to be efficacious in treating CD symptoms in a patient with Parkinson's disease (PD) as well as in another patient presenting with CD in the context of multiple organ dysfunction syndrome secondary to a traumatic bone injury.<sup>15</sup> Studies have shown a statistically significant increased risk of mortality with the use of atypical antipsychotic medications in PD, but quetiapine has the weakest association.<sup>16</sup> Although serious consideration must be taken when prescribing antipsychotics for patients with PD and CD, quetiapine has some advantages.

Another antipsychotic used in treatment of CD is risperidone, and its use as a monotherapy was sufficient to treat several patients diagnosed with CD.<sup>17</sup> Optimised risperidone doses ranged from 0.5 to 6.0 mg/day. Risperidone has been used in combination with other pharmacological agents as well, including valproic acid and lithium. The data suggests positive responses to treatment. A female diagnosed with postpartum depression showed signs of improvement after 2 weeks of combination therapy with 750 mg sodium valproate and 4 mg risperidone.<sup>18</sup> In a male patient experiencing both Capgras delusion and CD, treatment with 6 mg/day risperidone and 900 mg/day lithium carbonate demonstrated some efficacy.<sup>19</sup>

Antidepressants are also effective in treating CD. Venlafaxine and duloxetine reported good responses in controlling CD when combined with various antipsychotics. In a patient diagnosed with major depression, a 4-week course of venlafaxine 150 mg/day and quetiapine 400 mg/day showed improvements in their CD.<sup>20</sup> Duloxetine used in combination with amisulpride at doses of 60 mg/day and 400 mg/day, respectively, in an elderly individual experiencing complicated grief also demonstrated efficacy. Their delusions and depressive symptoms subsided, and they were discharged after 2

months of hospitalisation.<sup>21</sup> Risperidone 6 mg/day combined with imipramine 150 mg/day was used in the case of a patient in their 30s with severe depression. They became asymptomatic a few months after discharge from inpatient treatment.<sup>22</sup> Benzodiazepines have reported positive outcomes when used as an adjunct.<sup>23</sup> In a case of a patient with CD and catatonia, lorazepam 1 mg three times daily was prescribed, along with olanzapine 15 mg/day and mirtazapine 30 mg/day.<sup>24</sup>

Evidence suggests that patients with Cotard's are more responsive to ECT than to pharmacological treatment.<sup>25</sup> ECT has shown efficacy when pharmacological treatment was unsuccessful in several patients, and is both well-tolerated and efficient in its treatment of CD.<sup>26</sup> When successful, ECT demonstrated immediate results with long term symptomatic improvement. ECT can be used as first line treatment, but its availability may be limited. ECT has also been used in combination with atypical antipsychotics, including risperidone, amisulpride, and olanzapine. There were some specifically satisfactory responses to olanzapine and ECT co-administration;<sup>24</sup> however, details of dosing for olanzapine were not reported. The concomitant use of ECT and typical antipsychotics were documented with the use of perphenazine, flupentixol, trifluoperazine, thioridazine, and haloperidol.<sup>27</sup> In one case, ketamine was used along with ECT.<sup>28</sup> ECT and nomifensine were paired successfully to treat CD in a medically handicapped patient.<sup>23</sup> The use of ECT with tricyclic antidepressants was reported in severe cases of CD that presented with self-injurious behaviour, guilt and ruin delusions, and marked weight loss. In a patient who was pregnant, the combination of ECT with chlorpromazine and dothiepin led to sustained recovery.<sup>27</sup>

In a complex patient presenting with CD in the context of limbic encephalitis, olanzapine, escitalopram, and lorazepam elicited no response, so ECT was later utilised. The patient reported symptomatic relief.<sup>29</sup> Patients who developed CD in the setting of frontotemporal dementias were treated successfully with ECT after pharmacological therapy was ineffective.<sup>30</sup> Discontinuation of identified neurologically offending agents have had positive results in some cases. After haemodialysis was performed on two patients presenting with CD

secondary to valacyclovir administration, there was complete remission of neuropsychiatric adverse effects. There were two other cases wherein the patients' psychiatric sequelae was resolved after withdrawal of valacyclovir. Throughout the patient's evaluation, self-injury and self-starvation should be assessed, as well as exploring the benefit of cognitive behavioural therapy and behavioural rehabilitation. Transcranial magnetic stimulation was assessed in a patient who underwent cognitive behavioural therapy had some suggested efficacy.<sup>27</sup>

## CONCLUSION

As there may have been many reasons to explain the patient's mental status, only by working through a differential diagnosis by process of elimination did it become clear that the patient had CD. Between the altered mental status, refusal of oral intake, and intense abdominal pain, the providers were confident in their diagnosis. The care team was able to successfully treat the patient with a DHT, and a combination of ECT and aripiprazole. Throughout this case study, the importance of iatrogenic causes of disease, systemic failures leading to issues with patient care, and care in the balance between what the patient wants and what is best for the person were demonstrated. These clinical pearls are vital in the building of clinical decision making, and are key when evaluating how best to care for patients.

## PATIENT PERSPECTIVE

While undergoing treatment, the patient still had residual delusions, as well as newfound difficulty with memory and word fluency, known side effects of ECT therapy. The team could not accurately assess patient perspective until the complete remission of symptoms, mainly because their reasoning and decision-making capacity remained impaired. Unfortunately, the patient was discharged home to their family's care and finished the course of ECT as an outpatient. Hospital policy at the time of the pandemic strongly recommended that patients deemed stable be discharged to conserve resources for more emergent cases, and to limit their overall risk of getting a nosocomial infection. The attempts to contact the patient after their discharge were not successful.

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# Primary Renal Hydatid in Children

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## Disclosure:

The authors have declared no conflict of interest. Written informed consent was obtained from the patient and their mother for the anonymised information and the accompanying images published in this article.

## Received:

26.01.22

## Accepted:

21.03.22

## Keywords:

Case report, *Echinococcus granulosus*, hydatid, hydatidosis, puncture-aspiration-injection-reaspiration (PAIR), pericystectomy, renal cyst.

## Citation:

EMJ. 2022; DOI/10.33590/emj/22-00032. <https://doi.org/10.33590/emj/22-00032>.

## Abstract

Isolated renal hydatid disease, caused by the larvae of the parasitic tapeworm *Echinococcus granulosus* is a rare phenomenon and accounts for only 2% of all reported cases. The authors report a case of a 12-year-old female who presented with right flank pain. Initial abdominal ultrasound revealed a complex cystic mass in the upper pole of the right kidney. A contrasted CT scan better defined it as a well-circumscribed cyst with multiple thin septations. Laboratory investigations showed eosinophilia and a positive IgG *Echinococcus* serology. Considering these radiological and laboratory findings, a tentative diagnosis of primary renal hydatid was made. With perioperative antihelminthic therapy, the authors used a combination of an open puncture-aspiration-injection-reaspiration technique pericystectomy to manage the isolated renal hydatid. Renal hydatid can easily be misinterpreted pre-operatively for more sinister renal cystic pathology, including cystic renal cell carcinoma. An accurate pre-operative diagnosis requires a high index of suspicion, especially in endemic regions. Surgical therapy, with perioperative antihelminthic therapy, offers the best chance of cure.

## Key Points

1. *Echinococcus granulosus* is a parasitic tapeworm that primarily affects individuals who live in sheep- and cattle-raising communities through ingestion of infected matter.
2. Renal hydatid disease largely affects the liver (75% of cases) and the lungs (15% of cases).
3. Renal hydatid disease can be difficult to diagnose as patients often remain asymptomatic until the cyst enlarges and symptoms begin to present.

## INTRODUCTION

Human hydatid disease is caused by the larvae of the parasitic tapeworm *Echinococcus granulosus*. It is endemic to many sheep- and cattle-raising parts of the world, including the Mediterranean, Africa, South America, the Middle East, Australia, and New Zealand.<sup>1</sup> Isolated renal hydatid disease is a rare phenomenon and accounts for only 2% of reported cases.<sup>2</sup> The liver and lungs are by far the most common organs affected as these acts as the first two anatomical 'filters' of *Echinococcus* larvae as they enter the portal circulation. The authors report a case of a 12-year-old female with an isolated renal hydatid and review the relevant literature.

## CASE PRESENTATION

A 12-year-old female presented to the authors' department with a two-month history of progressively worsening right-sided flank pain. They reported no dysuria, haematuria, or other urinary symptoms and were otherwise healthy with no previous medical or surgical history of relevance. Notably, the patient lived in an

informal settlement in a rural, impoverished area of the province. On clinical examination, their vitals were unremarkable. They only exhibited slight right flank tenderness on palpation, but no apparent masses could be felt. Initial abdominal ultrasound revealed a large complex cystic mass of 5.4×7.0×5.4 cm located in the upper pole of the right kidney (Figure 1). A subsequent abdominopelvic contrasted CT scan confirmed the ultrasound findings and better defined it as a well-circumscribed cyst with multiple thin septations (Figure 2). The cyst did not appear to have any calcifications. The left kidney appeared normal in size and function, and the rest of the abdomen, pelvis, and chest appeared unremarkable. Laboratory investigations showed eosinophilia as well as a positive IgG *Echinococcus* serology with a weak positive titre of 26. Her renal function and electrolytes were normal, and urine microscopy and culture showed no parasites or small daughter cysts.

In light of the positive *Echinococcus* serology, together with the suggestive CT scan findings, a diagnosis of primary renal hydatid cyst was made. She was initiated on anthelmintic therapy with three cycles of albendazole, with a window of 14 days. Thereafter, the authors performed

**Figure 1: Transabdominal ultrasound findings showing a large complex cystic mass with multiple thin septations in the upper pole of the right kidney.**

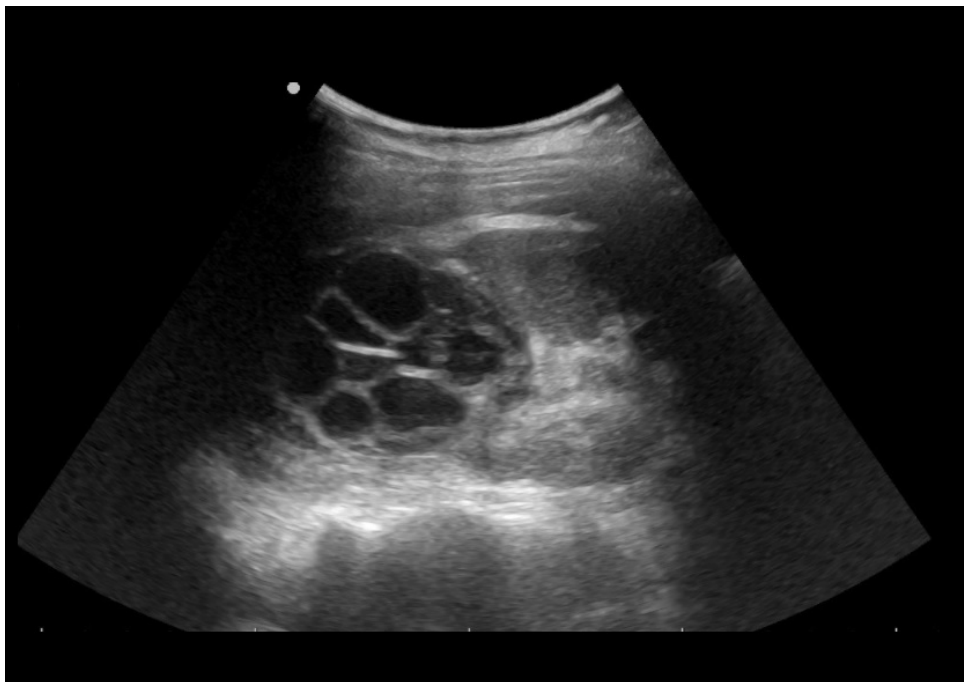


Figure 2: A) Pre-operative contrasted CT abdomen findings showing a well-circumscribed cystic lesion of the right kidney with multiple thin septations. B) Post-operative contrasted CT abdomen demonstrating re-expansion of the right kidney after pericystectomy with minimal scarring of the upper pole.



Figure 3: Photograph showing aspirated fluid and multiple collapsed daughter cysts isolated from the cystic lesion.



a right open pericystectomy of the primary renal hydatid through a small extraperitoneal right flank incision. The authors used 20% sodium chloride as an intra-operative scolicalidal agent and followed the puncture, aspirate, inject scolicalidal agent, re-aspirate (puncture-aspiration-injection-reaspiration [PAIR]) principles before opening the cyst to remove all daughter cysts and entire endocyst (germinal) layer (Figure 3), while packing off surrounding tissues with abdominal swabs soaked in the authors' chosen scolicalidal agent.

The cyst cavity was drained overnight with a nephrostomy tube. The drain was noted to have a persistently high output post-operatively. A retrograde ureteropyelography showed a small communication between the cyst cavity and an individual upper pole calyx. A double-J ureteral stent was inserted and drainage from the cyst cavity ceased, the drain was subsequently removed, and the patient was discharged. The double-J stent was removed without complications two weeks after discharge. The patient completed another cycle of oral albendazole post-operatively.

A follow-up CT scan 6 months after surgery (Figure 2) demonstrated re-expansion of the right kidney that was previously compressed by the cyst, with minimal scarring of the upper pole and a normal renal function. The patient will continue follow-up at the authors' facility to detect for any recurrence.

## DISCUSSION

Urogenital hydatid disease is a rare manifestation of hydatidosis, comprising only 2–3% of all cases.<sup>3</sup> The kidney is the most common involved urogenital organ but its isolated involvement is an extremely rare clinical entity.<sup>4</sup> The parasitic tapeworm *E. granulosus*, inhabits the small intestines of infected canines, the primary host. Infected parasite eggs are excreted in the stool in large numbers and the intermediate hosts (i.e., sheep, cattle, and goats) then ingest these infected eggs. Humans are infected through direct contact with an infected definitive host or by ingesting contaminated soil, food, and water. The eggs hatch and produce larvae in the small intestine of the host that goes on to penetrate the jejunum and gain access to the venous and

lymphatic system of the host, with subsequent spread to distant organs and manifestation as hydatid cysts.<sup>1</sup>

The liver and the lungs account for most of all cases, 75% and 15%, respectively. Genitourinary involvement, especially isolated renal hydatid disease, is very rare.<sup>5</sup> Patients may be asymptomatic for many years before becoming symptomatic due to the progressive enlargement of the cyst.<sup>6,7</sup> Symptoms include flank mass, haematuria, vague lumbar or flank pain, and dysuria. Less commonly, renal hydatid disease is complicated by cyst rupture into the collecting system, resulting in hydatiduria,<sup>8</sup> which is pathognomonic of renal hydatidosis. Hydatiduria, which is the presence of daughter cysts and larvae (hydatid sand) in urine, is only present in 5–18% of cases and should not be relied upon for a diagnosis to be made.<sup>9</sup> Diagnosis is notoriously difficult, unless clinicians keep a high index of suspicion, especially in endemic areas. A combination of clinical history, imaging studies, serological, and urine investigations yields a reliable pre-treatment diagnosis in only 50% of cases, and a presumptive diagnosis in 71%.<sup>10</sup> Moderate eosinophilia is a non-specific finding on blood work but is only present in 20–50% of cases.<sup>2</sup> Blood serum with the use of indirect haemagglutination, counter immunoelectrophoresis, ELISA, and gold labelled antibody may be used in the diagnosis of human echinococcosis.<sup>11</sup> The sensitivity of these tests varies according to the site where the infection is found and the viability of the cyst. In extrahepatic disease, the sensitivity of these tests reduces to about 25–56%, limiting the use of serology to aid in the diagnosis.<sup>12</sup>

The authors' patient had a weak positive titre of 26 on *Echinococcus* indirect haemagglutination serology testing. Renal hydatidosis often has characteristic appearances on imaging modalities. On a plain abdominal radiograph, a ring-shaped calcification can be seen. On ultrasonography, the appearance of a renal hydatid cyst may vary considerably from unilocular cysts that resemble a simple renal cyst to hypoechoic multicystic, or multiloculated cysts with daughter cyst and hyperechoic hydatid sand. As the patient changes position, a 'falling snowflake pattern' created by the multiple echogenic foci and produced by the hydatid sand can be seen under real-time imaging. In addition,



detachment of the endocyst from the pericyst gives an appearance of 'floating membranes' and multivesicular mother cyst with daughter cysts separated by radiating septae representing cyst walls and hydatid sand or matrix may give rise to a 'wheel-spoke' pattern.<sup>7,13,14</sup> CT is more accurate and sensitive and shows unilocular (Type I), or multilocular cysts (Type II) with mixed internal attenuation and daughter cysts with lower attenuation than that of the maternal matrix, and a completely calcified cyst (Type III).<sup>15-17</sup> MRI can delineate the cyst more accurately but offers no advantage over CT, and it is also expensive, therefore it is not routinely used for diagnosis.<sup>15</sup>

Management options include medical treatment, percutaneous intervention, and surgical treatments. According to the World Health Organization (WHO) guidelines, monotherapy with albendazole is the recommended antihelmintic drug of choice for visceral disease.<sup>14,18</sup> Albendazole before surgery, sterilises the cyst by killing the scolices and renders the cyst inactive, reduces cyst wall tension, and reduces the risk of intra-operative cyst rupture.<sup>19,20</sup> In addition, post-operative antihelmintic therapy also prevents recurrence. Albendazole (10–15 mg/kg/day) is administered for 1–4 weeks before surgery, and continued for 1–3 months after the procedure is recommended.<sup>14,21</sup> This protocol was followed in the authors' patient.

The PAIR technique has been described as a safe and effective treatment modality for a renal hydatid.<sup>22</sup>

Surgical treatment offers the best chance of cure, and nephron-sparing options such as a cystectomy, pericystectomy, and partial nephrectomy should be performed where possible. A simple nephrectomy is indicated for non-functional kidneys. Whatever modality is selected, measures must be taken to prevent intra-operative rupture of cysts and intra-peritoneal spillage, which will result in post-operative recurrence.<sup>23</sup> Post-operative antihelmintic therapy, as mentioned above, is also crucial to prevent a recurrence.<sup>14,21</sup> The authors' used a combination of an open PAIR technique with a pericystectomy in view to achieve the best possible result.

## CONCLUSION

Renal hydatid disease is an uncommon disease and can be misinterpreted pre-operatively for more sinister renal cystic pathology including cystic renal cell carcinoma. An accurate pre-operative diagnosis requires a high index of suspicion especially in endemic regions. Surgical therapy, with perioperative antihelmintic therapy, offers the best chance of cure and involves completely excising the entire endocyst (germinal layer) with daughter cysts without spillage of the viable cyst contents. It is pertinent that patients are followed up at regular intervals to detect early recurrence of disease, especially if there has been any intra-operative spillage of the hydatid cyst or if the pericystectomy was incomplete.

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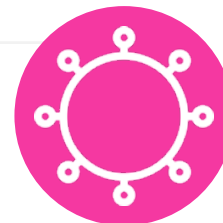
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# Overlapping Clinical Manifestations of Multisystem Inflammatory Syndrome in Children with Other Endemic Diseases of Pakistan: A Case Report

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**Disclosure:** The authors have declared no conflicts of interest.

**Acknowledgements:** Informed written consent was taken from the patient to publish this case.

**Received:** 27.10.21

**Accepted:** 14.07.22

**Keywords:** Case report, COVID-19, dengue, paediatric, typhoid.

**Citation:** EMJ. 2022. DOI/10.33590/emj/10073472. <https://doi.org/10.33590/emj/10073472>

## Abstract

Multisystem inflammatory syndrome (MIS-C) is a challenging disease associated with COVID-19. Clinical manifestation of MIS-C may mimic many endemic illnesses of tropical and subtropical countries, making early diagnosis more difficult. The authors present the case of an 8-year-old who presented with non-specific febrile illness which was managed as extensively drug-resistant typhoid with meropenem. The patient developed abdominal pain and hypotension during the hospital stay. Surgical causes were ruled out and managed with fluid protocol of dengue shock syndrome on the basis of falling platelets and fluid leak on ultrasound. But refractory condition and new-onset cardiac dysfunction prompted alternate diagnosis. Diagnostic criteria of MIS-C were fulfilled and the patient was managed with a single dose of intravenous Ig, pulse therapy of methylprednisolone, and temporary pacemaker placement. MIS-C should be kept in the differentials of diseases with multisystem involvement in the wake of the COVID-19 pandemic, as its clinical spectrum closely mimics other endemic illnesses of tropical and subtropical regions.

## Key Points

1. In the wake of the COVID-19 pandemic, multisystem inflammatory syndrome in children should be kept in the differentials of all tropical fevers by paediatricians.

2. Meticulous clinical examination and relevant laboratory investigations will not only aid in early diagnosis, but also help in prompt management.

3. Multisystem inflammatory syndrome is a challenging medical condition, but appropriate management can cause positive impact on its outcome.

## INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 has become increasingly recognised worldwide. Early identification is crucial owing to its severe multiorgan involvement and lethal outcomes. It has been reported 2–4 weeks post-COVID-19, and attributed to immune response to severe acute respiratory syndrome coronavirus 2.<sup>1</sup> Clinical presentations of this disease can cause variable organ involvement as the pandemic emerges. It may overlap with many endemic illnesses in tropical regions, and it can be difficult to differentiate COVID-19 with dengue due to similar laboratory parameters.<sup>2</sup> Thus, the impact of both dengue and COVID-19 can lead to devastating consequences in tropical and subtropical areas worldwide.<sup>3</sup> The authors report the case of an 8-year-old patient who had an unusual course of disease, managed from enteric fever turned dengue shock syndrome, and eventually fulfilled the criteria of MIS-C. To the best of the authors' knowledge, there are no cases reported from Pakistan regarding MIS-C mimicking other endemic illnesses of tropical countries.

## CASE PRESENTATION

### Patient Information and Clinical Findings

A thriving 8-year-old male presented in the outpatient department of the Khan Research Laboratories (KRL) Hospital, Islamabad, Pakistan, with the complaint of fever for 4 days. The patient was already taking oral antibiotics prescribed by a general practitioner, but had not improved. He was brought into hospital with a high-grade fever. He did not have a cough, abdominal pain, vomiting, headache, or skin rash. Past history was also insignificant. Examination was unremarkable except some dehydration.

### Diagnostic Assessment

Laboratory workup was sent, as shown in [Table 1](#), and the patient was managed with intravenous ceftriaxone; however, his fever progressively increased to 103 °F. Keeping in mind the multidrug-resistant enteric fever endemic in Pakistan, the patient was switched to meropenem on Day 2 of admission, awaiting blood culture report.

On Day 4 of admission, the patient developed abdominal pain which continued to worsen. He had tachypnea (respiratory rate 44 /min), tachycardia (110 /min), oxygen saturation of 96% in air, and blood pressure of 95/56 mmHg which was below the 50<sup>th</sup> centile for the patient's age, gender, and height. The patient had abdominal tenderness more in the epigastric region with no visceromegaly. Chest and neurological examination was unremarkable. Blood tests were repeated ([Table 1](#)); erect X-ray and ultrasound abdomen was also done to rule out enteric perforation. Erect X-ray negated abdominal perforation. Ultrasound abdomen showed evidence of dengue leak syndrome in the form of mild left side pleural effusion, gall bladder thickness of 4 mm, and mild free fluid in the pelvis. The blood complete picture showed thrombocytopenia, with falling trend of haematocrit (from 37.0% to 29.6%), which also supported dengue. Clinical scenario of tachycardia, cold peripheries, and pulse pressure of 20 mmHg, along with signs of plasma leak, prompted immediate management of dengue shock syndrome. The patient required two crystalloid and one colloid bolus along with red cell concentrates to improve urine output.

After 18 hours of fluid management, the patient again became hypotensive with narrow pulse pressure and increased work of breathing. The patient was reassessed for complications of severe dengue, and relevant blood work was sent ([Table 1](#), Day 5). The ECG showed



Table 1: Significant laboratory results during stay in hospital.

Component	Admission day	Day 1	Day 4	Day 5	Day 8	Normal range
Haemoglobin		12.9	12.3	12.2	13.8	12–16 g/dL
Total leukocyte count		11.7×10 <sup>9</sup>	15.9×10 <sup>9</sup>	17.3×10 <sup>9</sup>	12.4×10 <sup>9</sup>	4–11×10 <sup>9</sup> /L
Platelets		185×10 <sup>9</sup>	149×10 <sup>9</sup>	149×10 <sup>9</sup>	367×10 <sup>9</sup>	150–400×10 <sup>9</sup> /L
Neutrophils		81	83	84	77	50–70%
Lymphocytes		10	10	10	14	25–40%
C-reactive protein		69.3	284.0	279.3	97.1	<5 mg/dL
Lactate dehydrogenase		220	253	332	N/A	120–300 U/L
Prothrombin time		11.4	12.0	11.3	N/A	9.5–11.7 sec
Alanine transaminase		N/A	15	14	12	5–25 U/L
Serum creatinine		0.6	0.7	0.6	0.3	0.5–0.9 mg/dL
Serum sodium		129	125	130	136	136–149 mol/L
Serum potassium		4.5	3.7	3.7	3.0	3.5–5.0 mmol/L
D-dimers		N/A	1,315	4,042	3,624	<500 ng/mL
Serum albumin		N/A	N/A	2.0	N/A	3.2–4.5 g/dL
Creatine phosphokinase		N/A	N/A	104	N/A	15–105 U/L
Troponin T		N/A	N/A	0.15	N/A	<0.30 ng/mL
Pro-BNP		N/A	N/A	3,865	N/A	<125 pg/mL
Blood smear for malarial parasite		Negative	N/A	N/A	N/A	N/A
Urine routine examination		Normal	N/A	Normal	N/A	N/A
Dengue NS1 antigen		Negative	Negative	N/A	N/A	N/A
Dengue serology		Negative	Negative	N/A	N/A	N/A
COVID-19 PCR		Negative	N/A	Negative	N/A	N/A
COVID-19 antibodies IgM and IgG		N/A	N/A	IgG: Positive	N/A	N/A
Blood culture		N/A	N/A	No growth	N/A	N/A

BNP: B-type natriuretic peptide; N/A: not applicable; NS1: non-structural protein 1.

low voltage QRS complexes. Echocardiography revealed global hypokinesia and left ventricular dysfunction with ejection fraction of 30%, but no coronary abnormalities (Z-score <2 for the patient's age). Norepinephrine infusion at 0.1 mcg/kg/min was started to improve blood pressure while awaiting blood results. Various causes of acute myocarditis were explored as non-structural protein 1 antigen and dengue serology came back negative. The patient's clinical presentation of hypotensive shock, cardiac dysfunction, and acute gastrointestinal

symptoms in the setting of the COVID-19 pandemic strongly indicated the possibility of MIS-C. This was supported by negative blood cultures, elevated markers of inflammation (C-reactive protein, lactate dehydrogenase, D-Dimers, neutrophilia, and hypoalbuminaemia), and evidence of severe acute respiratory syndrome coronavirus 2 in the form of positive IgG levels.

## Therapeutic Intervention

The rapidly progressive nature of MIS-C in this patient in the form of worsening respiratory distress and hypotension was managed with intravenous Ig (IVIg) at the dose of 1 g/kg. IV dexamethasone was also given to hasten improvement. Meanwhile, CT scan was advised and serial blood tests were done to see multiorgan complications (Table 1, Day 5). The CT showed moderate bilateral pleural effusion and non-segmental areas of collapse in basal segments. There was no significant improvement 12 hours post-IVIg administration, and the patient's clinical status warranted elective intubation. Dexamethasone was shifted to pulse therapy of methylprednisolone (30.0 mg/kg/dose) and anticoagulation therapy (enoxaparin 0.5 mg/kg/day subcutaneously). The patient was also reconsidered for a second dose of IVIg or immunomodulation therapy. Meanwhile, the patient's heart rate started to fluctuate between 60–80 beats per min, and serial echocardiography showed similar results. The paediatric cardiology team advised urgent placement of a temporary pacemaker due to sinus bradycardia with haemodynamic impairment. After temporary pacemaker placement and inotropic support, successful extubation was achieved after 24 hours, and repeat echocardiography showed improving ejection fraction. Treatment was revised to oral steroids and aspirin, and the patient was weaned off from pacemaker 4 days after its placement. Patient length of stay was prolonged due to post-extubation lung collapse, but this was managed with antibiotics and physiotherapy.

## Outcome

Echocardiography at the time of discharge showed a structurally and functionally normal heart. The patient was discharged on tapering dose of steroids and aspirin on Day 18 of admission. Follow-up was advised to keep an eye on their cardiac status.

## DISCUSSION

COVID-19 is a public health crisis worldwide, but as it shares a similar clinical spectrum with other viral illnesses, it has become a major threat for dengue-endemic countries in particular.<sup>4</sup> Pakistan is also facing the major disease

burden of drug-resistant typhoid cases, and the estimated attack rate of typhoid is considered to be 15.5 out of 10,000 of the population. Due to non-specific presentation of typhoid, it can easily be confused with other illnesses like malaria, dengue, and COVID-19. It has been difficult to diagnose many illnesses in resource-limited settings without performing relevant diagnostic tests and, in the wake of COVID-19 pandemic, healthcare professionals are facing difficulties in differentiating these illnesses due to common manifestations.<sup>5</sup> This case highlights the diagnostic dilemma of a paediatric patient who presented with non-specific febrile illness.

Around 129 countries are at risk of dengue infection, as the disease is endemic in more than 100 countries. Asia contains 70% of the real disease burden.<sup>2</sup> Pakistan has reported around 99,264 confirmed cases of dengue virus infection from January 2014–May 2020 from all provinces, with major outbreaks observed between July and December.<sup>6</sup> Non-specific symptoms of dengue may include fever, respiratory tract infection, and rash; however, maculopapular rash, body aches, and high-grade fever are more typical symptoms. The spectrum of illness may vary, from mild disease such as dengue fever to dengue haemorrhagic fever and dengue shock syndrome, which can lead to adverse complications.<sup>7</sup> The authors' patient was managed as dengue shock syndrome due to hypotension and ultrasonographic findings of fluid leak, delaying the final diagnosis due to high disease burden of dengue epidemic in the region. However, cardiac and gastrointestinal involvement, along with shock in the setting of fever, supported with laboratory evidence of positive COVID-19 IgG antibodies and clear blood cultures, fulfilled the case definition of MIS-C by the World Health Organization (WHO).<sup>8</sup>

A case reported from Indonesia supported the similar case presentation of MIS-C and dengue, but with positive dengue infection ultimately resulting in mortality of the patient.<sup>9</sup> However, the authors' patient survived myocardial decompensation of MIS-C, thanks to the evolving management of MIS-C. Similarly, a case has been reported from India of a 9-year-old male who was managed as MIS-C, presented initially with dengue-like illness, and was discharged with a better outcome.<sup>10</sup> Cases have also been reported about co-infection of COVID-19 with other febrile

illnesses. A study carried out in Bangladesh showed 40% of the study population had typhoid fever with COVID-19. Co-infections along with comorbidities are a great matter of concern during this pandemic.<sup>11</sup> Due to the evolving nature of COVID-19, a study conducted about the clinical characteristics of MIS-C showed that about 54% patients required treatment with IVIg,

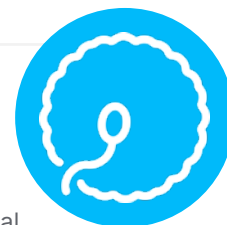
51% with steroids, 21% with remdesivir, 36% with tocilizumab, and 51% required vasopressors. Meticulous examination and critical care is required to achieve good outcomes in patients with MIS-C.<sup>12</sup> However, ongoing studies on MIS-C will help clinicians in understanding its varied clinical manifestations.

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# A Comparative Study of Local Dietary Intake Among Subjects with Hypertensive Disorders of Pregnancy Attending Antenatal Care



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<b>Disclosure:</b>	The authors have declared no conflicts of interest.
<b>Acknowledgements:</b>	The authors would like to acknowledge the staff from the Department of Obstetrics and Gynecology at the Federal Medical Centre Abeokuta (FMCA), Nigeria, for their contribution, which is highly appreciated.
<b>Received:</b>	20.02.22
<b>Accepted:</b>	27.06.22
<b>Keywords:</b>	Calcium, diet, gestational hypertension (GH), milk, pre-eclampsia (PE).
<b>Citation:</b>	EMJ. 2022; DOI/10.33590/emj/10141813. <a href="https://doi.org/10.33590/emj/10141813">https://doi.org/10.33590/emj/10141813</a> .

## Abstract

**Background:** Hypertensive disorders of pregnancy remain among the most significant causes of pregnancy-related complications. The research by the Dietary Approaches to Stop Hypertension (DASH) group revealed that non-pharmacological measures and intervention such as diet can be used to control blood pressure.

**Objective:** This study was completed to determine the frequency of consumption of local food among females who were pregnant and their relationship with pregnancy-related hypertensive disorders.

**Methods:** This was a descriptive research study of females who were pregnant with pre-eclampsia (PE) and gestational hypertension (GH) who presented at the Federal Medical Centre (FMC), Abeokuta, Nigeria. During the study period (September–October 2019) at the tertiary healthcare centre, 45 subjects who were pregnant were selected from a PE and GH group, and matched with 45 patients with normotension. Comparison of bean meal consumption (gbegiri) and bone meal (gbure-oloboro) consumption in subjects who were pregnant did not reveal statistically significant differences in those with PE and GH.

**Results:** The findings reveal a statistically significant difference in milk consumption between females who were pregnant with mild and severe PE ( $p=0.019$ ). There was



also a statistically significant difference in subjects with mild and severe GH who consumed milk ( $p=0.003$ ).

**Conclusion:** Milk consumption may be associated with a reduction in PE and GH.

## Key Points

1. One of the most significant causes of pregnancy-related complications is hypertensive disorders which include pre-eclampsia, gestational hypertension, chronic hypertension, and many more.
2. This comparative study examined the frequency of consumption of local food among females who were pregnant and their relationship with pregnancy-related hypertensive disorders.
3. Dietary approaches, including increasing milk consumption in females, may lower the risk of pre-eclampsia and gestational hypertension.

## INTRODUCTION

The American Congress of Obstetricians and Gynecologists (ACOG) Task Force on the classification of hypertension include pre-eclampsia (PE), gestational hypertension (GH), chronic hypertension, chronic hypertension with superimposed PE, and eclampsia. GH is diagnosed from 20 weeks into gestation with the absence of proteinuria, while PE presents as newly sustained hypertension with proteinuria.<sup>1</sup>

The research by the Dietary Approaches to Stop Hypertension (DASH) group revealed that non-pharmacological measures and intervention such as diet can be used to control blood pressure.<sup>2</sup>

Diets including calcium from different local foods such as dairy products, tofu, beans, and vegetables such cabbage leaves may help to regulate blood pressure (BP). The local sources of calcium within the authors' metropolis is mainly from a local delicacy, which majority of the population consume. The local diets that supply calcium are mainly from gbure-oloboro, also known as bone meal, and gbegiri, also known as bean meal. In addition to the local diets, females who are pregnant also consume milk and other dairy products.<sup>3,4</sup>

Calcium performs a role in normal metabolic function of the body, especially in the transmission of neural impulses, muscle contractions, and the release of hormones. In PE, tissues such as the arterial muscles and

neurons function via pathways that affect BP regulation. The binding of calcium ions to activator proteins such as troponin C starts steps involved in the excitation–contraction, which leads to muscle contraction.<sup>5</sup> The muscle protein calmodulin activates enzymes that break down muscle glycogen to provide energy for muscle contraction. At the end of excitation–contraction, calcium is exchanged outside the cell or into the endoplasmic reticulum until the next event cycle.

The mechanism where low serum calcium causes new-onset hypertension in pregnancy has been attributed to an increase in peripheral resistance and a rise in BP. This occurs due to the stimulation and release of the parathyroid hormone (PTH) and parathyroid hypertensive factor.<sup>5,6</sup> This leads to the production of calcitriol and subsequent activation of renin angiotensin aldosterone system. Within the arterial vascular smooth muscle cells, an increase in intracellular calcium ions via signalling pathways results in vasoconstriction, an increase in peripheral resistance, and upward trends in BP.<sup>7-9</sup>

According to the MESA cohort study,<sup>10</sup> where 3,002 males and females ( $59.0\pm 9.7$  years) without cardiovascular antecedents were followed up for 9 years, where a correlation was found between higher PTH serum concentrations and a higher risk of hypertension, even after adjusting for potential confounders (hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 1.01–1.59)<sup>10</sup>. Furthermore, a positive relationship between serum PTH and systolic BP found

that the highest quartile of serum PTH was an independent predictor of coronary heart disease in both sexes.

Lewanczuk et al.<sup>11</sup> studied the effect of parathyroid hypertensive factor by infusing plasma from rats with hypertension and humans with hypertension into the blood of rats with normotension and found an increase in the mean arterial blood pressure of the rats. They further studied the parathyroid origin of this factor by transplanting parathyroid glands of rats with hypertension into parathyroidectomised rats with normotension. A subsequent elevation in BP was shown in the rats after transplantation.

Hypertension in pregnancy is a major cause of maternal mortality and pre-term births, with an attendant consequence of increased perinatal mortality. There are no previous documented studies in this local population on the relationship of milk consumption and other local diets among females who are pregnant with PE and GH. Most studies on milk consumption in pregnancy have not included GH and were mainly done on PE.

In addressing the identified gaps in knowledge and adding to the few existing studies on the relationship of local diets and milk consumption with PE and GH, this study aimed to determine the relationship of consumption of milk and other local food products with PE and GH among females who were pregnant in the authors' local area.

## METHODS

The study was carried out at the tertiary healthcare centre, Federal Medical Centre (FMC), Abeokuta, Nigeria, which is one of the public hospitals handling referrals from lower treatment centres. FMC Abeokuta offers high-level tertiary management of obstetrical and gynaecological cases, supported by other multidisciplinary, specialist teams.

The maternity section of FMC Abeokuta used in this study includes an antenatal clinic and ward, gynaecological ward, and labour ward from the Department of Obstetrics and Gynaecology.

Abeokuta is the capital of Ogun state and is situated in the tropical region of Africa. It is situated 74 km north of Lagos along the Ogun

River. Abeokuta has a population of about 593,140 people, according to the 2006 census.<sup>12</sup>

The tertiary healthcare facility used in this study is a parastatal under the Federal Ministry of Health. It is a 300-bed specialist centre that was established in 1993 and is in the Idi-Aba area, within the Abeokuta South local government area in the outskirts of the city. It has an annual average delivery rate of 1,300 live births. Ethical approval was obtained from the hospital ethics and research unit.

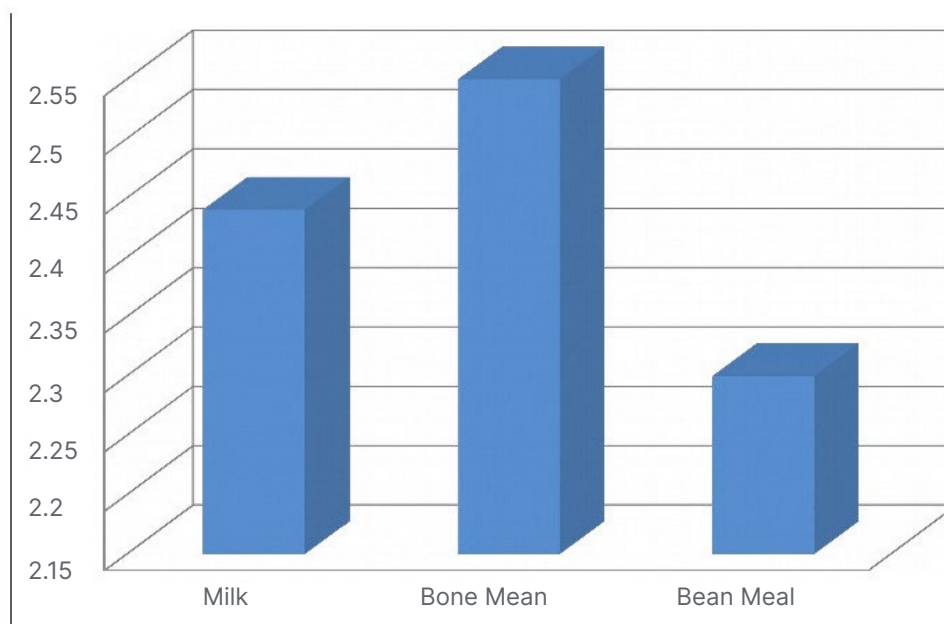
All females who were pregnant and with a pregnancy-related hypertensive disorder at the gestational age of 20 weeks and satisfied the criteria for diagnosis of pregnancy-induced hypertension were recruited into the study. Their BP was measured with accuracy, and their urine was checked for presence of proteinuria. Brachial systolic and diastolic BPs were measured using the sphygmomanometric auscultatory method, where the arm is level and the subject sitting down, relaxing at least 5 minutes prior to the measurement. Systolic BP was recorded as the appearance of the Korotkoff sounds (Phase I), while diastolic BP was recorded as the disappearance of the Korotkoff sounds (Phase V). BP was measured using a standardised aneroid sphygmomanometer, made by Accoson (Irvine, UK).

The eligible subjects were assigned into the three groups: PE, GH, and a third group of individuals with normal BP. One in three females who were pregnant with normal BP were selected until the required number of was achieved, while females with PE or GH who consented to the study were consecutively recruited until the required number was achieved. The subjects were matched for age, parity, socioeconomic status, and BMI. The sample size was determined by applying the formula for comparison of two mean:  $n=2(u+v)^2\sigma^2/(d)^2$ .

A self-explanatory questionnaire was given to the subjects by the research team to collect necessary data required for the study. The questionnaire was pre-tested in the local population prior to the actual study.

The assessment of serum calcium level was determined using the o-cresolphthalein complexone technique at 570 nm absorbance.<sup>13</sup>

Figure 1: Dietary intake and mean serum calcium level.



The normal range of serum calcium used in this study was 2.1–2.8 mmol/L. The data generated from the study was analysed with the use of IBM SPSS 23 (IBM, New York City, New York, USA).

## RESULTS

An equal number of subjects (45 in each group) with the PE, GH, and normal blood pressure participated in the study. Females who were pregnant who were at the gestational age of 20 weeks or more were selected for the study.

This study found that the mean serum calcium level in subjects who consumed milk (mean±standard deviation) was 2.44±1.27, bone meal 2.55±1.32, and bean meal 2.30±0.76. This study found no association in the mean serum calcium level between the different dietary intakes (Figure 1)

The milk consumption between females who were pregnant with mild and severe PE was statistically significant ( $p=0.019$ ). Females with mild GH were significantly more likely than those with severe GH to have consumed milk at least twice a day ( $p=0.003$ ). Comparison of bean meal consumption (gbegiri) and bone meal (gbure-oloboro) in subjects who were pregnant did not

reveal any statistically significant difference in those with PE and GH (Table 1).

## DISCUSSION

The findings from this study revealed that milk consumption was statistically significant ( $p=0.019$ ) in females who were pregnant with mild and severe PE. This is similar to the study in Norway by Nordqvist et al.,<sup>4</sup> which found that the intake of milk in the later weeks of pregnancy lowered the risk of PE. In the same study, milk intake was found to reduce the risk of pre-term delivery when instituted in the early part of pregnancy.<sup>4</sup> However, this study recruited 70,149 singleton females who were pregnant,<sup>4</sup> which is more than the number of subjects who participated in the authors' study.

In this study, it was surprising to find that this is no direct association between serum calcium level among subjects who were normotensive and subjects with PE or GH who consumed milk with local diets. The first report on the association between PE and calcium intake was in the 1980s.<sup>5</sup>

The Mayan population who live within Guatemala were found to have low incidence of PE. This reportedly followed their unique lifestyle where

**Table 1: Dietary consumption among subjects with pre-eclampsia.**

PE	No milk consumption	Once daily	Twice or more daily	p
Mild PE (n=29)	5 (17.2%)	6 (20.7%)	18 (62.1%)	0.019
Severe PE (n=16)	5 (31.3%)	8 (50.0%)	3 (18.8%)	
PE	No bone meal consumption	Once daily	Twice or more daily	p
Mild PE (n=29)	5 (17.2%)	9 (31.0%)	15 (51.7%)	0.416
Severe PE (n=16)	4 (25.0%)	7 (43.8%)	5 (31.3%)	
PE	No bean meal consumption	Once daily	Twice or more daily	p
Mild PE (n=29)	13 (44.8%)	9 (31.0%)	7 (24.1%)	0.303
Severe PE (n=16)	11 (68.8%)	3 (18.8%)	2 (12.5%)	

There were statistically significant differences between milk consumption in subjects with mild and severe PE ( $p < 0.05$ ).

There were no statistically significant differences between bone consumption in subjects with mild and severe PE.

There were no statistically significant differences between bean meal consumption in subjects with mild and severe PE.

PE: pre-eclampsia.

they soak corn in lime, which was considered to have high content of calcium and, therefore, have a high calcium intake.<sup>5</sup>

The Ethiopian population have a similar diet high in calcium and, with a high intake of calcium, were reported to have among the lowest incidence of hypertensive disorders of pregnancy.<sup>5</sup>

Several studies have opined a possible association between PE and calcium. However, the relationship between rich dietary sources of calcium and the possible link with low prevalence of PE and GH is still a subject of controversy, probably due to the inability of studies to prove a causal link and the different mechanism of reduction of PE and GH.

Findings from the authors' study could not prove any significant difference in the level of serum

calcium between participants who consumed milk and those who mainly consumed local dietary products (bean meal and bone meal). However, this study did find a statistically significant difference ( $p = 0.003$ ) in dietary milk consumption between participants who consumed milk with mild and severe GH.

Egeland et al.,<sup>14</sup> a study from Norway, found that diets that are low in calcium can lead to occurrence of new-onset PE and GH among females who were childbearing with GH in previous pregnancy. According to Egeland et al.,<sup>14</sup> adequately planned interventions that are used to increase the baseline body stores of calcium and other essential minerals can help in reducing of the burden of hypertension in pregnancy within the childbearing population.



Brantsaeta AL et al.,<sup>15</sup> in a study of occurrence of PE in primigravida, found that consumption of milk-rich food had an inverse relationship, with incidence of PE. This may have been due to milk being rich in *lactobacilli*.<sup>15</sup>

From this study, local dietary meals considered to be rich source of calcium (bone meal and bean meal) in the Western part of Nigeria revealed no statistically significant differences among participants with pregnancy-related hypertensive disorders. The mechanism associated with the reduction of incidence of pregnancy-related hypertensive disorders may be due to alteration in the inflammatory process, which may also involve microbiological flora that could occur in females who consume milk.

In a cross-sectional study of the Chinese population, Chen X et al.<sup>16</sup> found that diets consisting mainly of snacks is associated with pregnancy-related hypertensive disorders. In the Chen X et al.<sup>16</sup> study, diets that have a lot of salt increases the risk of PE and GH.

According to a study by Hillesund et al.,<sup>17</sup> a high New Nordic Diet led to reduced overall incidence of PE and pre-term births.

Among other studies, Villegas R et al.<sup>18</sup> found that

there is reduced incidence of Type 2 diabetes in those who consume a diet rich in dairy milk. Villegas R et al.<sup>18</sup> also revealed that healthy eating habits could, by health education, lead to lower risk of endocrine and cardiovascular diseases. The close occurrence of diabetes together with hypertension remains undisputed.

Guidelines by the ACOG<sup>1</sup> indicate that calcium can lower the risk of PE in populations that have a deficiency of calcium; however, the use of low-dose aspirin (60–80 mg) can reduce PE and adverse perinatal outcomes.<sup>1,19-21</sup>

## CONCLUSION

There is possibility that milk consumption may be associated with a reduction in PE. Dietary approaches, especially increasing the milk consumption in females, may lower the risk of PE and GH.

## RECOMMENDATION

Females who intend to become pregnant could benefit from advice on the need to consume milk products, which can reduce the risk and complications associated with PE and GH.

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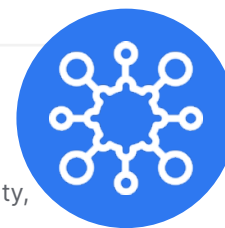
# Neratinib as a Potential Therapeutic for Mutant RAS and Osimertinib-Resistant Tumours

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## Disclosure:

Dent has received funding from Puma Biotechnology for neratinib-based studies. Booth, Poklepovic, and Hancock have declared no conflicts of interest.

## Acknowledgements:

Additional support for the present study was funded from philanthropic funding from the Massey Cancer Center and Universal Inc. Chair in Signal Transduction Research.

## Received:

09.02.22

## Accepted:

07.08.22

## Keywords:

Autophagy, Hippo, Merlin, LC3-associated phagocytosis, neratinib, RAS, RAC1, YAP.

## Citation:

EMJ. 2022;7[3]:127-133. DOI/10.33590/emj/10197202. <https://doi.org/10.33590/emj/10197202>.

## Abstract

Neratinib was developed as an irreversible catalytic inhibitor of ERBB2, which also acts to inhibit ERBB1 and ERBB4. Neratinib is U.S. Food and Drug Administration (FDA)-approved as a neo-adjuvant therapy for use in *HER2+* breast cancer. More recently, chemical biology analyses and the authors' own bench work have demonstrated that neratinib has additional targets, which open up the possibility of using the drug in cell types that either lack ERBB receptor family expression or who rely on survival signalling downstream of growth factor receptors. Neratinib rapidly disrupted mutant RAS nanoclustering, which was followed by mutant rat sarcoma virus proteins translocating via LC3-associated phagocytosis into the cytosol where they were degraded by macroautophagy. Neratinib catalytically inhibited the MAP4K mammalian STE20-like protein kinase 4 and also caused its degradation via macroautophagy. This resulted in ezrin dephosphorylation and the plasma membrane becoming flaccid. Neratinib disrupted the nanoclustering of RAC1, which was associated with dephosphorylation of PAK1 and Merlin, and with increased phosphorylation of the Merlin binding partners large tumour suppressor kinase 1/2, YAP, and TAZ. YAP and TAZ exited the nucleus. Neratinib retained its anti-tumour efficacy against NSCLC cells made resistant to either afatinib or to osimertinib. Collectively, these findings argue that the possibilities for the further development of neratinib as cancer therapeutic in malignancies that do not express or over-express members of the ERBB receptor family are potentially wide-ranging.

## Key Points

1. Neratinib was developed as an neoadjuvant irreversible inhibitor of catalytic ERBB2 for use in patients with *HER2+* breast cancer.
2. Chemical biology studies have identified additional targets for neratinib, through the disruption of mutant RAS nanoclustering and its other anti-tumour effects.
3. Although associated with gastrointestinal toxicity, alterations to the administration route of neratinib has shown a relatively benign safety profile.

## THE 'NEW' BIOLOGY OF NERATINIB

Neratinib (HKI-272) was developed as an irreversible inhibitor of ERBB2 (*HER2*) catalytic activity, which was also shown to inhibit ERBB1 (the EGF receptor) and ERBB4.<sup>1,2</sup> It gained U.S. Food and Drug Administration (FDA) approval in the USA in 2017 and by the European Union (EU) in 2018, for use in patients with *HER2+* breast cancer in combination with the 5-fluorouracil analogue capecitabine.<sup>3,4</sup> Neratinib was originally developed by Wyeth and Pfizer (New York, USA), and then licensed to Puma Biotechnology (Los Angeles, California, USA) in 2011.<sup>5</sup> All small molecule therapeutic agents have recognised on-target and off-target effects, although such was the focus of neratinib development on *HER2+* tumours that the off-target biology of the drug, *in vitro* and in patients, was not thoroughly investigated. In 2011 Davis et al.<sup>6</sup> published an extensive chemical biology screening study of over 40 kinase inhibitors, that included neratinib.<sup>6</sup> In their analyses, Davis et al.<sup>6</sup> argued that neratinib was an inhibitor of multiple MAP4K serine or threonine kinases including mammalian STE20-like protein kinase 4 (MST4). The most notable negative sequela of neratinib during its clinical development was diarrhoea and it is known that MST4 plays an essential role in the development of the gastrointestinal brush border.<sup>7</sup> These data strongly argue that MST4 is a validated *in vivo* 'off-target' for neratinib.

The authors' studies over the past 4 years examining neratinib have been performed in afatinib-resistant and osimertinib-resistant non-small cell lung cancer cells that express mutant active ERBB1 proteins, and in pancreatic, colorectal, cutaneous melanoma, and uveal melanoma cancer cells that express mutant

*KRAS*, mutant *NRAS*, and mutant Gα proteins.<sup>8-16</sup> Mutant rat sarcoma virus (Ras) proteins and mutant Gα proteins lack guanosine triphosphate (GTP)ase activity and cannot hydrolyse GTP back to guanosine diphosphate; these are hence considered 'constitutively active'. In the authors' studies, they made two unexpected discoveries. First, was that neratinib was not only an irreversible inhibitor of the ERBB receptors but that it also caused receptor internalisation and the subsequent degradation of the receptors via LC3-associated phagocytosis and macroautophagy. Other growth factor receptors which can associate with super-complexes of ERBB receptors in the plasma membrane such as c-MET and PDGFRβ, could, also in a cell-type-dependent fashion, be internalised and degraded. Second, based on the authors' receptor internalisation data, the authors hypothesised that neratinib would also cause the internalisation of plasma membrane-localised GTP binding proteins, i.e., Ras proteins and heterotrimeric Gα proteins. In both pancreatic and colon cancer cells neratinib caused endogenous mutant K-Ras proteins to localise in vesicles liminal to the plasma membrane; vesicles that co-stained for the macroautophagy protein Beclin1. Over a 6-hour time course, the expression levels of the mutant K-Ras and mutant N-Ras proteins in cutaneous melanoma, pancreatic, and colon cancer cells fell by approximately 30%. In patient-derived xenografts (PDX) uveal melanoma lines, neratinib as a single agent within 6 hours significantly reduced the protein levels of G<sub>αq</sub> and G<sub>α11</sub> by approximately 50%. In cells transiently transfected with plasmids to express green fluorescent protein (GFP) and red fluorescent protein (RFP) tagged forms of K-Ras G12V, neratinib rapidly caused the formation of GFP+ RFP+ (yellow)



vesicles that subsequently only fluoresced RFP+, and at a lower fluorescence intensity. This data is indicative that the Ras proteins were initially localised in autophagosomes and that autophagic flux had occurred with the GFP+ signal being quenched in the acidic autolysosome, and with degradation of the Ras fusion proteins.

Signalling by Ras proteins out of the plasma membrane and into the cytosol requires that not only are they in their GTP-bound state but also that they form loosely binding nanoclusters of 5–6 proteins, each with a radius of approximately 9 nm and with a half-life of less than one second.<sup>17–23</sup> Based on the concept of rapidly accelerated fibrosarcoma (RAF) protein dimerisation and cross-talk between RAF proteins, e.g., by *B-RAF* and *RAF-1* as homo- and hetero-dimers, to mediate their activation and that of the downstream extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, the concept that Ras proteins also having to form nanoclusters to foster RAF–RAF interactions for effective signalling off the plasma membrane is logical.<sup>24</sup> Using immuno-gold electron microscopy, the authors observed that the initial impact of neratinib upon Ras biology was to rapidly disrupt Ras nanoclustering in the plasma membrane that was temporally followed by Ras mislocalisation away from the plasma membrane to the intracellular site(s). Stable transfection of cells to express ERBB1 neither altered the effect of neratinib on mutant *KRAS* nanoclustering nor in the mutant *KRAS* subsequently mislocating from the plasma membrane into the cytosol. In haematopoietic cells that do not express ERBB receptors, neratinib caused Ras proteins to mislocate from the membrane to the cytosol. Clearly, for its Ras biology, receptor binding was not required.

The small GTP binding protein RAC1 also forms nanoclusters in the plasma membrane as a pre-requisite for signalling into the cell, and neratinib disrupted RAC1 nanoclustering, though unlike RAS proteins, this did not result in RAC1 mislocalisation to the cytosol. Reduced RAC1 nanoclustering was associated with the dephosphorylation of its direct interacting partner, the kinase PAK1, and of the PAK1 substrate, Merlin.<sup>25</sup> In parallel to these events, the plasma membrane of neratinib-treated cells became flaccid and the cytoskeletal target of

MST4, Ezrin, which regulates plasma membrane rigidity and its interaction with the cytoskeleton, was dephosphorylated (Figure 1).<sup>26</sup>

Neratinib acts as an irreversible inhibitor of ERBB family receptors by covalently linking to a cysteine residue in their active sites.<sup>27</sup> All Ras proteins and RAC1 only share a single conserved cysteine amino acid at position 80/81, and, at present, it is not known whether neratinib covalently attaches via this cysteine residue to Ras/RAC proteins to disrupt both their nanoclustering and their signalling off the plasma membrane and into the cell. To initially address this issue, the authors transfected cells to express *KRAS*<sup>G12V</sup>-GFP. The authors treated cells with neratinib maleate and lysed the cells 5 min, 10 min, and 30 min after drug exposure. The authors immunoprecipitated *KRAS*<sup>G12V</sup>-GFP using the GFP tag. The authors then ran the precipitate on a sodium dodecyl-sulfate polyacrylamide gel electrophoresis and blotted for *RAF-1*. Within 5 min, the amount of *RAF-1* that co-precipitated with *KRAS*<sup>G12V</sup>-GFP was significantly reduced, and the amount of *RAF-1* co-precipitating further declined after 30 min. This strongly argues that neratinib was reducing the ability of *RAF-1* to associate with *KRAS*<sup>G12V</sup> (unpublished findings). If validated by additional experimentation, this would make neratinib, at present, a unique drug, and a claimant to be 'the holy grail' drug that can directly inhibit mutant Ras proteins. Even so, neratinib can perhaps only be considered as a 'prototype' Ras inhibitory drug, and additional chemical biology work will be required to design and develop a truly potent Ras inhibitor. However, direct covalent association with Ras and RAC1 proteins may not be the only possible mechanism at play because in the authors' studies they also discovered that neratinib significantly reduced the level of phosphatidyl serine in the plasma membrane and increased the levels of cholesterol. Increased membrane cholesterol is congruent with greater membrane fluidity, as the authors had previously observed by light microscopy. And increased membrane fluidity is known to independently disrupt mutant RAS signalling. How neratinib alters phosphatidyl serine and cholesterol levels will also require additional studies.

Figure 2 is the collation of the authors' signal transduction data derived from findings in multiple tumour cell lines expressing mutant

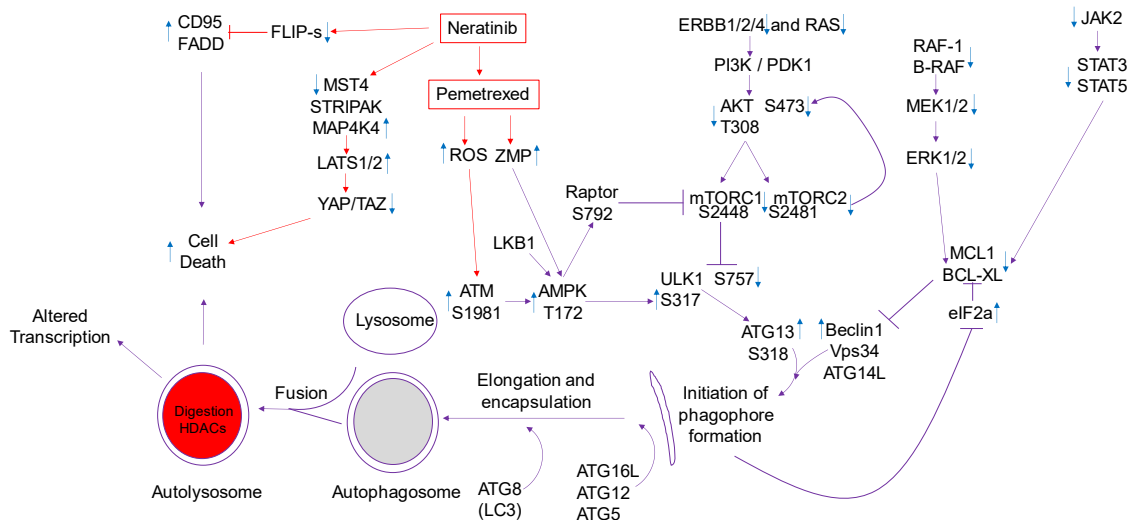
KRAS or NRAS proteins and treated with neratinib and pemetrexed. Neratinib rapidly disrupts RAS signalling concomitant with reduced phosphorylation (activity) of RAF-1 (S338), MEK1/2 (S218/S222), and ERK1/2 (T183/Y185), as well as, in the PI3K pathway, of AKT (T308 and S473), mTORC1 (S2448), mTORC2 (S2481), and p70 S6K (T389 and S424). The authors presume these broad effects are due to both reduced RAS signalling *per se* and reduced signalling by ERBB family and other receptor tyrosine kinases. Published data shows that after 8 hours of neratinib exposure, significant amounts of Ras protein have been degraded. Neratinib as a single agent causes activation of ATM (S1981) by the generation of reactive oxygen species, with

ATM-dependent phosphorylation of AMPK $\alpha$ T172. Pemetrexed as a single agent also activates ATM via DNA damage, and via its inhibition of AICART it also enhances the levels of the nucleoside ZMP, which like AMP, allosterically activates the AMPK. Thus, neratinib and pemetrexed interact to cause 'full' AMPK activation and this event co-operates with inactivation of AKT due to the loss of RTKs and Ras to cause the inactivation of mTORC1 and mTORC2. Full AMPK activation enhances ULK1 S317 phosphorylation and mTORC1 inactivation lowers ULK1 S757 phosphorylation collectively resulting in 'full' activation of ULK1. Fully activated ULK1 phosphorylates ATG13 S318, the gatekeeping

Figure 1: Amino acid sequence alignment comparing KRAS and RAC1.

<b>K-RAS4A</b>	<b>(60) QEEYSAMRDQ</b>	<b>(70) YMRTGEGFLC</b>	<b>(80) VFAINNTKSF</b>
<b>RAC1</b>	<b>(60) QEDYDRLRPL</b>	<b>(70) SYPQTDVFLI</b>	<b>(80) CFSLVSPASF</b>

Figure 2: Signaling pathways whose activities are directly and indirectly altered when non-small cell lung carcinoma cells are exposed to neratinib and the anti-metabolite pemetrexed.



AMPK: AMP-dependent protein kinase; ER: endoplasmic reticulum; ERK: extracellular regulated kinase; FADD: FAS-associated death domain protein; HDAC: histone deacetylase; LAP: LC3-associated phagocytosis; LATS: large tumour suppressor kinase; MAPK: mitogen activated protein kinase; MST4: mammalian STE20-like protein kinase 4; mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol 3 kinase; PTEN: phosphatase and tensin homologue; ROS: reactive oxygen species; STRIPAK: striatin-interacting-phosphatase and kinase; STAT: signal transducers and activators of transcription.

phosphorylation event required to trigger autophagosome formation, ultimately leading to greater autophagic flux and autophagy-dependent tumour cell killing. In parallel to these events, neratinib causes inactivation and degradation of the MAP4K MST4, which ultimately leads to enhanced phosphorylation of large tumour suppressor kinase 1/2, YAP, and TAZ with both co-transcription factors leaving the nucleus (i.e., their inactivation). Loss of YAP/TAZ function reduces the synthesis of multiple autocrine growth factors and is associated with a reduced ability of tumour cells to migrate and metastasise. Neratinib degrades the chaperone GRP78 via autophagy, which results in the activation of PKR-like endoplasmic reticulum kinase, which phosphorylates and inactivates eIF2a S51 (i.e., an 'ER stress response'). The actions of phosphorylated eIF2a result in both reduced expression of cytoprotective proteins with short half-lives such as FLIP-s, MCL1, and BCL-XL, and with increased expression of the autophagy regulatory proteins Beclin1 and ATG5, which, respectively, enhances death receptor signalling and mitochondrial dysfunction and sustains toxic autophagosome formation. All of these events act to enhance drug-induced tumour cell killing.

Neratinib, acting at the level of growth factor receptors and plasma membrane GTP binding proteins, would not be considered to have any activity in tumour cells that express intracellular oncogenes such as cutaneous melanomas expressing *B-RAF* (V600E). The treatment of tumours expressing this oncogene has been revolutionised by the development of small molecule kinase inhibitors that selectively inhibit the mutant forms of *B-RAF* such as dabrafenib, and the combination of these drugs with MEK1/2/5 inhibitors such as trametinib, which prevents compensatory survival signalling from *RAF-1* causing reactivation of the ERK1/2 pathway.<sup>28,29</sup> It has been recognised for over a decade that tumour cells expressing wild-type K-Ras and NRAS proteins can behave in a de facto manner very similar to cells expressing mutant Ras proteins due to the over-expression of paracrine factors and the constitutive activation of multiple upstream growth factor receptors.<sup>30,31</sup> As such, the authors hypothesised that neratinib, by causing growth factor receptor and Ras protein degradation, and possibly also by

causing the degradation of *RAF-1/B-RAF* all via macroautophagy, would have anti-tumour efficacy in cutaneous melanoma cells expressing mutant B-Raf proteins.

The authors initial studies compared the anti-tumour efficacy of neratinib *in vitro* alongside that of the established trametinib/dabrafenib combination in PDX models of cutaneous melanoma expressing the *B-RAF* (V600E) oncogene. The authors' first observation of note was that after 24 hours of drug exposure, low nanomolar concentrations of neratinib as a single agent, below its safe plasma C max, caused similar to greater amounts of cell death when compared with the killing effect caused by the trametinib/dabrafenib drug combination. Drug naïve MEL4 cells expressed higher levels of *B-RAF* and *RAF-1* when compared with vemurafenib-resistant MEL2 cells. Neratinib reduced *B-RAF* (V600E) and *RAF-1* expression in drug naïve MEL4 cells but not in vemurafenib-resistant MEL2 cells. The observed reduction of *B-RAF* and *RAF-1* effectively normalised protein levels between the two PDX isolates, and similar levels of killing by neratinib were observed in both the MEL2 and MEL4 cells. Although neratinib could be causing the degradation of wild-type *RAF-1* and wild-type *B-RAF* located at the plasma membrane because they are associated with Ras proteins, the authors also are cognisant that neratinib is a potent stimulator of autophagosome formation, and via macroautophagy, causes the degradation of cytosolic HSP90 and HDAC6. HSP90 is a key chaperone protein regulating the stability of both *RAF-1* and *B-RAF*. HDAC6 specifically deacetylates HSP90, enhancing its chaperoning activity. Thus, independently of plasma membrane association, neratinib can act to destabilise cytosolic *RAF-1* and *B-RAF* proteins.

Neratinib, as with ERBB receptors, not only catalytically inhibits the serine/threonine kinase MST4, but in addition, causes its autophagic degradation. MST4 is one component of striatin-interacting phosphatase and kinase (STRIPAK) complexes.<sup>32,33</sup> These complexes are plasma membrane liminal supra-molecular assemblies of proteins with components including: striatins 3 and 4, MST4, MAP4K4, ezrin, radixin, and Moesin proteins, sarcolemmal membrane-associated protein, and protein serine/threonine phosphatase 2A. The authors published studies

in other tumour cell types have demonstrated that neratinib: selectively activated *MAP4K4* but not *MAP4K1*; and inactivated MST4, caused MST4 degradation and Ezrin dephosphorylation.

Both events will rapidly alter the composition of the STRIPAK complexes, and one downstream event associated with this is the activation of large tumour suppressor kinase 1 and 2. This, in turn, results in the phosphorylation of YAP and TAZ, co-transcription factor effectors for the Hippo pathway, and causes YAP and TAZ to exit the nucleus. In cutaneous melanoma cells, the authors also found that neratinib increased the phosphorylation of YAP and TAZ at multiple sites and caused their nuclear exit.<sup>11-16</sup> YAP and TAZ are de facto oncogenes, which can substitute for *RAS* mutations and, in particular, they are known to promote the metastatic spread of tumour cells.<sup>34,35</sup> Hence, the authors' data working with neratinib has argued, not only in cutaneous melanoma cells but also in other solid and liquid tumour cell types, that regardless of drug-resistance or the lack of ERBB family receptor expression, the multi-factorial targeting of neratinib against multiple protein kinases regulating multiple signalling pathways demonstrates its broad potential utility in the treatment of cancer.

## NERATINIB AND FUTURE CHALLENGES

Based on the authors' neratinib research, there are two open Phase I clinical trials, NCT03919292<sup>36</sup> and NCT04502602.<sup>37</sup>

Up until its regulatory approvals in 2017 and 2018, neratinib had a poor reputation in the clinic during its development due to it causing Grade 3/4 diarrhoea in the majority of patients. This issue was resolved by prophylactic use prior to, and the continuing use of, loperamide-based anti-diarrhoeal drugs during therapy. The fact remains, however, that gastrointestinal toxicity is a limiting factor in the deployment of neratinib not only against *HER2+* breast cancer but also against all other tumour cell types, particularly those expressing mutant *Tas* or *G α* proteins. Based on data obtained during its development and its present use in the clinic, neratinib appears to have a relatively benign safety profile once in the plasma against the cells that form the hematocrit and line blood vessels. This suggests that the development of an intravenous neratinib formulation, which would result in a safe plasma C max values of greater than the present approximately 150 nM for oral administration could dramatically enhance the therapeutic utility of the drug against other tumour types.

In addition to being an anti-cancer drug, it also may be possible to develop neratinib as a novel therapeutic for Alzheimer's Disease (AD).<sup>38</sup> Aberrant expression and denaturation of Tau, amyloid- $\beta$ , and TDP-43 can lead to cell death and is a major component of AD pathologies. AD neurons exhibit a reduced ability to form autophagosomes and degrade proteins via autophagy. Neratinib via macroautophagy reduced chaperone levels and the expression of Tau, Tau 301L, APP, APP692, APP715, *SOD1 G93A* and TDP-43 in cancer cells, neuronal cells, and microglia. Further work will be required to determine *in vivo* whether neratinib slows down AD progression.

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# Update on New Antigens in the Pathogenesis of Membranous Nephropathy



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<b>Disclosure:</b>	The authors have declared no conflicts of interest.
<b>Received:</b>	21.04.22
<b>Accepted:</b>	07.06.22
<b>Keywords:</b>	Antigens in primary membranous nephropathy, exostosin 1 (EXT1), exostosin 2 (EXT2), neural cell adhesion molecule (NCAM), neural epidermal growth factor 1 (NELL-1), PLA2R, semaphorin (SEMA) 3B, thrombospondin-type 1 domain containing 7A (THSD7A).
<b>Citation:</b>	EMJ. 2022; DOI/10.33590/emj/22-00130. <a href="https://doi.org/10.33590/emj/22-00130">https://doi.org/10.33590/emj/22-00130</a> .

## Abstract

Previously, membranous nephropathies were divided into primary and secondary categories when the exact mechanism or pathogenetic factor were unknown. Approximately 70% accounted for primary membranous nephropathies. The remaining 30% were called secondary because they developed due to well-known diseases such as autoimmune diseases, tumours, infections, or drug assumptions. The discoveries of the M-type phospholipase A2 receptor and of thrombospondin type 1 domain containing 7A as causative antigens in a part of the so-called primary membranous nephropathies opened new knowledge on the effective causes of a large part of these diseases. The availability of novel techniques such as laser micro-dissection and tandem mass spectrometry, as well as immunochemistry with antibodies directed against novel proteins, allowed the confirmation of new antigens involved. The use of confocal microscopy and Western blot allowed detection of the new antigen on glomerular membrane, and the same antigen and relative antibodies have been detected in serum samples.

Through these techniques, four new antigens were first detected, including neural epidermal growth factor 1 and semaphorin 3B in the so-called primary membranous nephropathy, and exostosin 1 and 2 and neural cell adhesion molecule 1 in lupus membranous nephropathy.

The aim of this study is to describe the characteristics of the new antigens discovered and their association with other diseases. In addition, new antigens are on the horizon, and the story of primary membranous nephropathy is still to be completely written and understood.

## Key Points

1. Until 2002, most of the antigens that were involved in membranous nephropathy (MN) were unknown; however, other antigens have been discovered since then.
2. By using novel techniques, the authors were able to identify approximately 1,500–2,000 proteins in glomerular extracts and also four new antigens associated with MN.
3. The histological pattern for all of the primary MNs is similar, despite being characterised by different clinical and outcome findings.

## INTRODUCTION

Membranous nephropathy (MN) is an autoimmune disease in which autoantibodies directed against antigens localised on the glomerular basement membrane (GBM) activate the complement cascade and cause severe proteinuria.

The histology of the disease is similar, but the causes of MN may be quite different. Indeed, the disease may occur as primary MN without the concomitance of other associated disease (80% of cases); or secondary MN when it is associated with different diseases, such as infections, autoimmune diseases, and cancers.<sup>1,2</sup> Until 2002, the vast majority of the antigens involved in the primary MN were unknown. The aim of this review is to highlight the recent pathophysiological advances that allowed the identification of many of the antigens involved.

## FIRST ANTIGENS DISCOVERED

The first antigen discovered as cause of MN was the neutral endopeptidase (NEP). This is an infrequent cause of MN in newborns.<sup>3</sup> The disease developed because females who were pregnant had a genetic abnormality leading to NEP deficiency, caused by a mutation in the *MMF* gene that codes for NEP.<sup>4</sup> This fact causes alloimmunisation during pregnancy, and transplacental antibodies passing to the fetus, principally by the end of pregnancy.

More recently, in 2009, researchers found that many patients affected by primary MN have antibodies in the glomerular eluate against an epitope of the phospholipase A2 type M receptor (PLA2R), documenting that this protein is an

important cause of MN.<sup>5</sup> Almost simultaneously, other researchers<sup>6</sup> found a colocalisation of antibodies against anti-aldose reductase and anti-manganese superoxide dismutase (SOD2) with IgG4 and C5b-9. These data suggest that anti-aldose reductase and SOD2 are antigens responsible for MN, and that the oxidative stress may induce the SOD2 expression in the glomeruli.

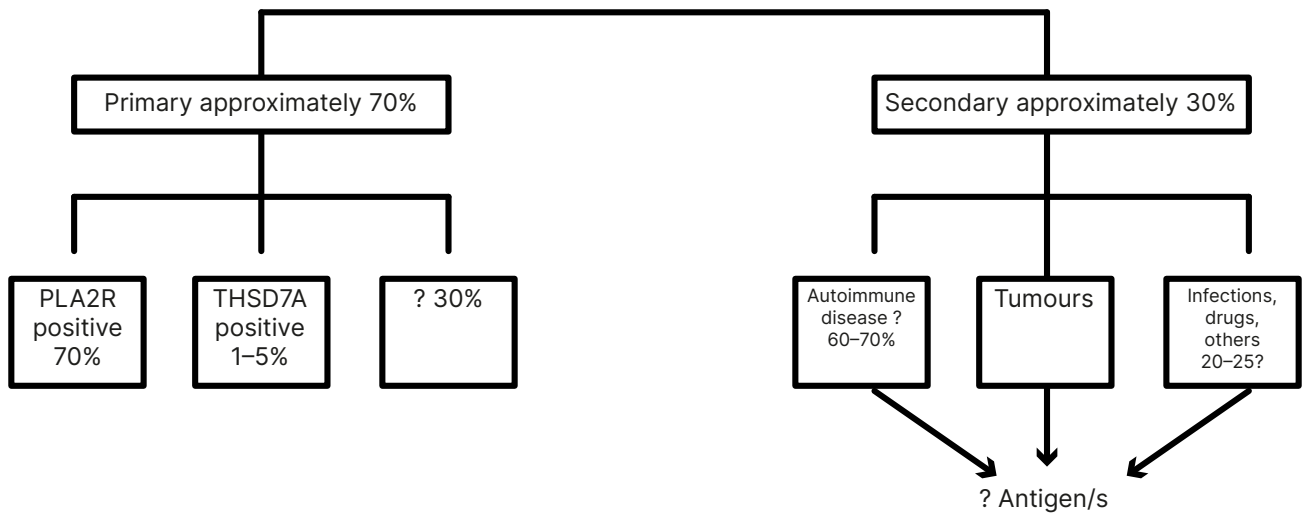
Endopeptidase neutral and PLA2R are antigens that, normally, are localised on podocytes. In adults, high levels of antibodies anti-NEP are not a sign of pathology. On the contrary, high levels of antibodies against PLA2R are sign of pathology, and help in differentiating primary MN from secondary MN.<sup>7</sup>

On 2014, Tomas et al.<sup>8</sup> found that up to 5% of patients affected by primary MN have antibodies against thrombospondin-type 1 domain containing 7A (THSD7A). THSD7A is localised on the basal portion of podocytes, and colocalises with nephrin.<sup>9</sup> Although PLA2R and THSD7A were considered to characterise primary MN, later PLA2R-related MN was documented to be also associated with hepatitis B infection<sup>10</sup> and sarcoidosis.<sup>11</sup> Additionally, THSD7A-related MN may be associated with cancer and the antigen has been found in tumour cells.<sup>12</sup> PLA2R and THSD7A were involved in 7% and 5% of primary MN (Figure 1).

## NOVEL TECHNIQUES

Thereafter, laser micro-dissection of the glomeruli, followed by tandem mass spectrometry (MS/MS) was introduced as a new technique by Sethi et al.<sup>13</sup> In this way, novel antigens examining trypsin-digested

Figure 1: Older classification of membranous nephropathies.



PLA2R: phospholipase A2 type M receptor; THSD7A: thrombospondin-type 1 domain containing 7A.

proteins could be identified. With the use of this technique, the authors could also use paraffin-embedded biopsies, allowing the identification of the antigen even in patients with immunologically inactive diseases. These novel techniques allowed the identification of approximately 1,500–2,000 proteins in glomerular extracts, and allowed a semi-quantitative measurement.

The study started from PLA2R negative biopsies. The identification of a new antigen in these trypsin digested micro-dissected glomeruli was carried out with antigen detection in subepithelial space by immunohistochemistry. MS confirmed the nature of the antigen in the biopsies. To confirm the new findings, European cohorts validated the data. Due to these techniques, four additional antigens were found between 2019 and 2020: neural cell adhesion molecule 1 (NCAM-1), exostosins 1 and 2 (EXT1/EXT2), neural epidermal growth factor 1 (NELL-1), and semaphorin 3B (SEMA 3B).<sup>13,14-16</sup> New antigens will be discovered in the future.<sup>17</sup> Figure 2 shows the molecular structures of these antigens compared with PLA2R and THSD7A. While the molecular structure will be described in chapters concerning the different antigens, Figure 2 is useful in understanding which antigens are more typical of primary MN, and their capacity to activate the complement pathways.

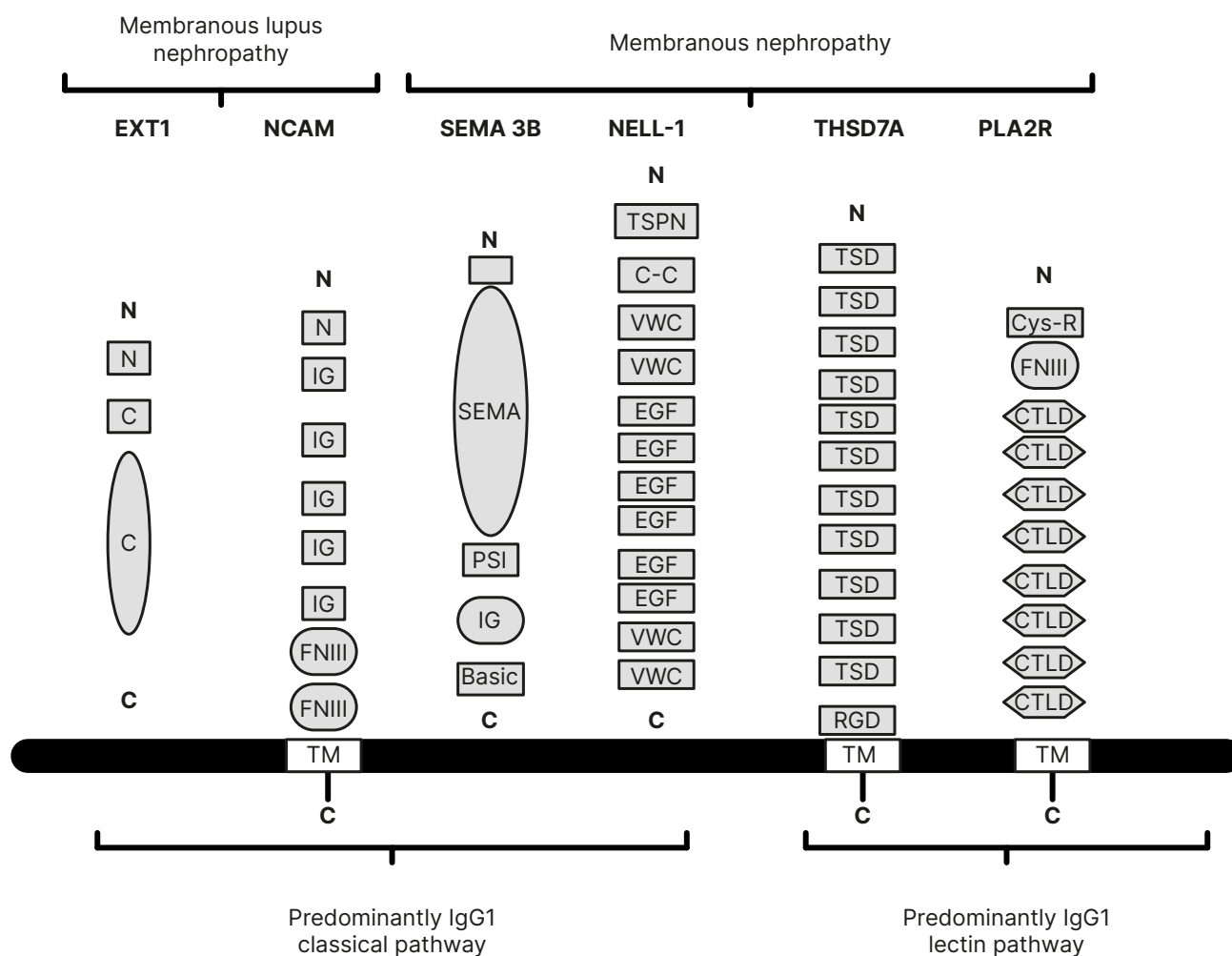
## EXOSTOSIN 1/EXOSTOSIN 2-ASSOCIATED MEMBRANOUS NEPHROPATHY

Examining with the aforementioned techniques both serum samples and glomerular eluates in patients with MN negative for PLA2R, the first antigens found were EXT1/EXT2. The GBM is principally composed of Type IV collagen, laminin, nidogen, and heparin sulfate proteoglycans. Agrin and perlecan are the main heparin sulfates in GBM. Heparin sulfates are present in the GBM, matrix, and cell surfaces.

EXTs are glycosyltransferases that provide the synthesis of the heparin sulfate, adding glycosaminoglycan residues to the core protein with the generation of complex polysaccharides.<sup>18,19</sup> EXT1/EXT2 are a heterodimeric enzyme called glycosyltransferase, which adds glycosylic residues to the protein backbone of proteoglycans.<sup>20</sup> They are transmembrane proteins situated in the endoplasmic reticulum where biosynthesis of the heparin sulphates occurs. EXT proteins have a short amino terminal cytoplasmic tail; a single transmembrane domain; a stem region; and a long, globular catalytic carboxyl-terminal domain within the Golgi lumen.<sup>21,22</sup> EXTs are secreted into the extracellular medium in a truncated form.<sup>23</sup> The heterodimer of EXT1/EXT2 shows structural



Figure 2: The molecular structures of the four new antigens compared with the old antigens.



Exostosins (EXT1) are transmembrane proteins that have a short amino-terminal cytoplasmic tail, a single transmembrane domain, and a long globular catalytic C-terminal domain. NCAM-1 contains an aminoterminnal tail, five IgG domains, two FNIII domains, and a TM domain. SEMA 3B has large SEMA domain region, a PSI domain, an Ig domain, and a short C terminal basic domain.

C: C-terminal domain; C-C: coiled-coil domain; Cys-R: cys-rich domain; CTLD: C-type Itctin-like domain; EGF: epidermal growth factor; EXT1: exostosin 1; FNIII: fibronectin Type III domains; N: short amino-terminal cytoplasmic tail; NCAM: neural cell adhesion molecule 1; NELL-1: neural epidermal growth factor 1; PLA2R: phospholipase A2 type M receptor; PSI: plexin-semaphorin-integrin; SEMA: semaphorin; SEMA 3B: semaphorin 3B; THSD7A: thrombospondin-type 1 domain containing 7A; TSD: ; TM: transmembrane domain; TSPN: thrombospondin-1-like molecule; VWC: von Willebrand factor Type C domains.

similarities and can exist as heterodimers that have increased stability and activity.<sup>24</sup> Mutations in EXT1/EXT2 cause the autosomal dominant disorder hereditary multiple exostoses.<sup>25,26</sup>

Frequently, examining serum samples by Western blot does not allow the detection of circulating anti-EXT1/EXT2 antibodies. There are

two possibilities for this: the antibodies could not be detected because they are directed to specific epitopes of the truncated protein that are absent in the recombinant EXT1/EXT2 protein; or it is possible that serum antibodies could not be detected because their titre is very low.

EXT1/EXT2-MNs are more present in females, and more than 70% of patients have abnormal laboratory values for antinuclear antibodies, anti-double stranded DNA, anti-Smith antibodies, or anti-Sjögren's syndrome-related antigen A or B.<sup>27</sup> 34% of patients have a clinical diagnosis of systemic lupus erythematosus. The antibodies present in the GBM are predominantly IgG1, and the classical pathway activates the complement.

## NEURAL CELL ADHESION MOLECULE 1

Neural cell adhesion molecule (NCAM-1) is frequently found in membranous lupus nephropathy, but may also be observed in primary MN as well. NCAM-1 is a member of the Ig superfamily of proteins of 150 kDa molecular weight. NCAM-1 was identified by Caza et al.,<sup>16</sup> adding immunoprecipitation on frozen biopsies to the techniques of Sethi et al.<sup>13</sup> NCAM-1 contains an amino-terminal tail, five immunoglobulin domains (IgG), two fibronectin Type III domains, a transmembrane domain, and an intracellular region at the C-terminal end. In adults, NCAM-1 may be found at high levels in different organs and tissue as the central nervous system, and cells within the immune system. Neuropsychiatric disorders occurred in 40% of patients who are NCAM-1 positive, probably due to NCAM-1 high expression in the central nervous system.<sup>28</sup> NCAM-1 could not be found in normal kidneys, while it was found in urinary exosomes.<sup>29</sup> In patients with lupus nephritis-related MN, NCAM-1 levels in the urine correlated with disease activity.<sup>30</sup> It is possible to find antibodies directed against NCAM-1 in the patient's sera. NCAM-1 is responsible for MN in many patients with lupus nephropathy, where it activates the complement by the classical pathway. In conclusion, NCAM-1 ranks second after EXT1/EXT2 in the list of antigens in membranous lupus nephropathy.

## NEURAL EPIDERMAL GROWTH FACTOR-LIKE 1 PROTEIN

Neural epidermal growth factor 1 (NELL-1) is a secreted, 90 kDa protein that promotes bone regeneration.<sup>31</sup> Patients with craniosynostosis have high levels of NELL-1. In pathological conditions, NELL-1 expression is higher in tubules, and from 5–25% of glomerular cells

express NELL-1 at the mRNA level.<sup>32</sup> NELL-1 is a cytoplasmic protein kinase C-binding protein. Its structure contains an amino-terminal thrombospondin-1-like molecule, coiled-coil domain, four von Willebrand-type domains, and six epidermal growth factor-like repeats.<sup>33</sup>

Sethi et al.<sup>15</sup> selected patients with PLA2R negative MN, and by laser microdissection and MS identified NELL-1. By immunohistochemistry a granular anti-NELL-1 GBM staining was documented, and by confocal microscopy there was a colocalisation of NELL-1 and IgG. By Western blot, serum antibodies to NELL-1 were detected. NELL-1 is probably localised in the podocytes, and does not derive from circulating antigens or immune complexes.<sup>34</sup>

Kudose et al.<sup>35</sup> examined more than 2,000 non-lupus MNs. 50% of them showed segmental membranous glomerulonephritis defined by subepithelial deposits involving 50% of the GBM. Among these segmental membranous glomerulonephritis, NELL-1 staining was present in 25%. According to this study, NELL-1 appears to be the first antigen in MN.

NELL-1-associated MN appears as a primary MN. However, in some cases, malignancy may be associated. According to Caza et al.,<sup>36</sup> the incidence of malignancy varies from 10% to 33%.

## PROTOCOLADHERIN 7-ASSOCIATED MEMBRANOUS NEPHROPATHY

Protocadherin-7 (PCDH7) is another recently discovered antigen related to MN. Sethi et al.<sup>37</sup> examined PCDH7 with the usual techniques, and after laser microdissection kidney biopsies, and sera of 135 patients with PLA2R negative MN. In addition, immunohistochemistry, immunofluorescence, and confocal microscopy were used to confirm the MS/MS findings. Two validation cohorts<sup>38</sup> validated all the new findings. Immunohistochemistry showed a bright granular staining along the GBM. PCDH7 and IgG were colocalised, and Western blot analysis documented autoantibodies to PCDH7.

Cadherins are a large group of transmembrane proteins that mediate cell-cell recognition and adhesion.<sup>39</sup> Their function is unknown, but is probably important in cell signalling.<sup>40</sup>

In conclusion, PCDH7 has been identified as a new antigen, and autoantibodies against PCDH7 were present in adult patients with PLA2R negative MN. PCDH7 is mostly present in older patients, complement activation is minimal, and spontaneous remission without immunosuppressive treatment is frequent. Complement activation in PCDH7-associated MN was lower when compared with other antigen associated MNs.<sup>41</sup>

After PCDH7 discovery, the new classification of MNs is reported in [Figure 3](#).

The overall incidence of primary MN that the studies reported in the beginning ranged approximately 70%, are to date about 80%. This is due to the discovery of the new antigens described. In addition to the different percentage reported in [Figure 3](#), it is interesting to examine several studies that have been made on the specificity and sensitivity of the new antigens and relative biomarkers.

In an initial study based on PLA2R, IgG4 and THSD7A,<sup>42</sup> the diagnostic performance of the three biomarkers reached 79% of sensitivity and 83% of specificity. A recent study<sup>43</sup> carefully examines all the MN-related podocyte target

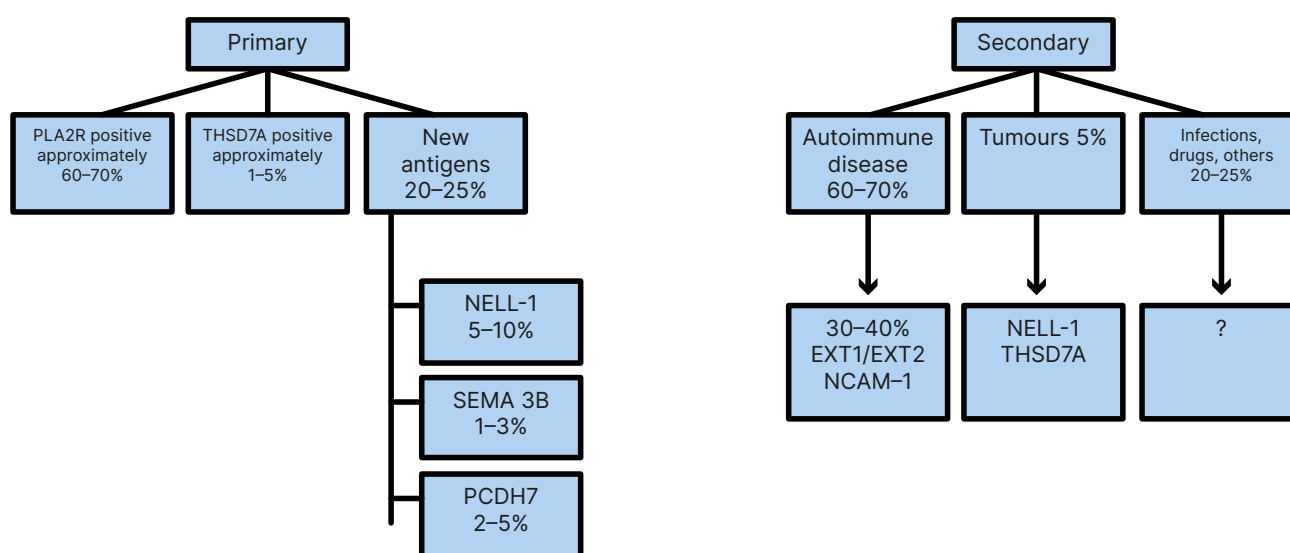
antigen and autoantibody biomarkers, but does not face the issue of their specificity and sensitivity. A different study<sup>44</sup> explores the differences in molecular mechanisms and key biomarkers between membranous nephropathy and lupus nephritis. According to this study, the best diagnostic value in differentiating patients with MN from patients with lupus nephritis is of the genes *IFI44* and *MX1*, with an area under the curve of 0.980 and 0.967, respectively, while NELL-1 has no diagnostic value.

In a very recent study by Sealfon et al.,<sup>45</sup> the authors examined in the area under the curve the accuracy in distinguishing genes of MN from those of other nephropathies. The authors found that MN classifier has the highest accuracy across different diseases in two independent cohorts.

## MORE ANTIGENS ON THE HORIZON

Other antigens will be discovered soon or in the future, as no antigen has been identified in 10–20% of primary MNs. Just recently, at last three new antigens have been discovered, as well as their mechanism of action.

**Figure 3: New and recent classification of membranous nephropathies.**



EXT1: exostosin 1; EXT2: exostosin 2; NCAM-1: neural cell adhesion molecule 1; NELL-1: neural epidermal growth factor 1; PCDH7: protocadherin-7; PLA2R: phospholipase A2 type M receptor; SEMA 3B: semaphorin 3B; THSD7A: thrombospondin-type 1 domain containing 7A.

Xu et al.<sup>46</sup> found in a male patient with MN-associated neurological disorders the presence of autoantibodies against paranodal proteins such as neurofascin 155 (NF155) and contactin-1 (CNTN1). Reviewing the literature, the authors found 22 cases of chronic inflammatory demyelinating polyneuropathy,<sup>47</sup> five of which were anti-CNTN1 antibody-associated.<sup>48-51</sup> Debiec et al.<sup>52</sup> clarified the pathophysiology of this neuro-renal syndrome.

CNTN1 and NF155 represent a structure in the paranode that improves cell adhesion and receptor stabilisation. IgG4 autoantibodies block protein-protein interactions between NF155 and CNTN1, and this facilitates the paranodal terminal loop detachment from the axon. This determines a severe nerve conduction failure that represents a severe disease, also without inflammation and complement cascade activation.

On the other hand, similar immune complexes are found formed at the basal side of the podocyte. As always, such glomerular subepithelial IgG4 deposits may be due either to an *in situ* formation of immune complexes, or to the deposition of preformed circulating immune complexes, both including the complement activation.

Caza et al.<sup>53</sup> recently found a Type III TGF- $\beta$  receptor (TGFBR3) as a new biomarker that is present in some patients with membranous lupus nephritis. After mass spectrometry and laser microdissection, confocal microscopy was used to find colocalisation of immune complexes and IgG. TGFBR3 was found principally in glomeruli and coprecipitated with IgG. TGFBR3 colocalised with IgG along the GBM in TGFBR3-associated MN. In conclusion, a diagnosis of TGFBR3-associated MN should raise the suspicion for a concomitant autoimmune disease.

The high temperature recombinant protein A1 (HTRA1) is a new target antigen recently found in primary MN by Al-Rabadi et al.<sup>54</sup> HTRA1 is a serine protease identified as a new podocyte antigen in some patients with primary MN. At immunoblotting, sera from two patients reacted either with a 51 kDa protein within glomerular extract or with recombinant human HTRA1. Anti-HTRA1 antibodies were predominantly IgG4. In the course of active disease, the patients' sera

revealed significantly higher titres of anti-HTRA1 antibody than the sera collected during the remission phase. HTRA1 was principally detected within immune deposits of HTRA1-associated MN in 14 patients identified among three different cohorts. The analysis of 118 patients who were MN-negative for any known antigen documented a prevalence of 4.2% for HTRA1.

## CONCLUSION

Since the beginning of the studies, membranous nephropathy has been distinguished into two different categories: primary or idiopathic when it is not associated with other diseases; and secondary when it is associated with diseases such as tumours, infections, or autoimmune disorders. It should be highlighted that the pathological aspects do not allow a distinction between the two forms. Primary MN is to be ascribed to an autoimmune disorder where autoantibodies are directed against antigens represented by proteins of the GBM. The first antigen discovered was NEP. The disease was discovered in newborns born to females who were pregnant who develop antibodies because of a deficiency of NEP due to mutations in the *NEP* gene. The majority of primary MN have as target antigens either PLA2R or THSD7A.

These two antigens account for the majority of primary MN, but not for all. New techniques principally introduced by Sethi et al.<sup>13</sup> allowed identifying other less frequently involved antigens. As has been described in this study these antigens are EXT1/EXT2, NELL-1, SEMA 3B, PCDH7, and NCAM-1. More recently, other antigens have been discovered as contactin associated with neurological disturbances, TGFBR3, and HTRA1. Almost certainly, other antigens responsible for primary MN will be discovered in the future. As already mentioned, the histological pattern is similar for all the primary MNs, even if each of them is characterised by different clinical and outcome findings. On this basis, in a very recent study, Sethi et al.<sup>55,56</sup> propose that any of the protein/antigen-associated MN represents a specific disease, whose histological renal aspects are similar and characterised by subepithelial immune depositions on the GBM.



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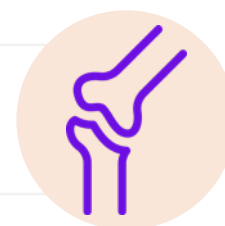
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# Vitamin D Deficiency Presenting as Proximal Myopathy: An Overlooked Diagnosis - A Case Series and Review of the Literature

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<b>Disclosure:</b>	The author has disclosed no conflicts of interest.
<b>Received:</b>	17.11.21
<b>Accepted:</b>	14.01.22
<b>Keywords:</b>	Adult coeliac disease, intact parathyroid hormone (iPTH), intramuscular vitamin D, proximal myopathy, 25 hydroxyvitamin D.
<b>Citation:</b>	EMJ. 2022; DOI/10.33590/emj/21-00248. <a href="https://doi.org/10.33590/emj/21-00248">https://doi.org/10.33590/emj/21-00248</a> .



## Abstract

The prevalence of vitamin D deficiency is ubiquitous. Severe disease can present very dramatically and can be misleading to the treating physician, resulting in mismanagement. A high index of suspicion in vulnerable patients should help circumvent this problem, including a thorough history and physical examination to lead the clinician in the right direction. Insidious onset and progressive proximal pelvic girdle myopathy, in the absence of other neurological findings, in the appropriate patient should prompt the physician to test for serum 25 hydroxyvitamin D levels.

The literature on endocrine myopathy does not highlight this condition as much as it does the thyroid, parathyroid, and adrenal aetiologies. Testing for vitamin D deficiency is simple, and treatment is available all over the world. The following article presents three patients, in different scenarios, with the condition. In all three patients, incapacitating pelvic girdle weakness resolved and quality of life improved dramatically with timely intervention. Most importantly, the correct approach prevented misdiagnosis and mismanagement.

## Key Points

1. Despite the prevalence of vitamin D deficiency, the treatment is often mismanaged due to the misleading presentation of severe disease and non-specific nature of the symptoms.
2. Sources of vitamin D include sunlight exposure and diet through the skin and gastrointestinal tract, respectively, with the older population being more at risk of vitamin D deficiency due to poor synthesis through the skin.
3. Preventing vitamin D deficiency is important to reduce morbidity, mortality, and healthcare costs; therefore, education for the general public and healthcare professionals is vital in helping to recognise vitamin D deficiency.

## INTRODUCTION

Vitamin D is essential for skeletal and skeletal muscle health. It is present in varying quantities in certain foods, but the average diet does not contain enough to meet daily needs. A good source is exposure to sunlight for sufficient time to enable the skin to synthesise the vitamin from cholesterol using the ultraviolet spectrum. In some countries, a regulated process of fortification of certain commonly consumed foods exists.

Vitamin D deficiency is found all over the world, even in sunnier, more tropical countries.<sup>1</sup> Factors contributing to this deficiency includes poor food choices, malnutrition, malabsorption, extreme obesity, religious prohibitions mandating people to cover the bodily areas, work schedules predominantly indoors, the use of P450 enzyme-inducing medications, chronic kidney disease, and lack of awareness of the condition, even among healthcare professionals.

To identify at-risk individuals, diet analysis, sun exposure time, and investigating malabsorption states are crucial. A growing number of patients developing multiple vitamin and mineral deficiencies after bariatric surgery bypasses are a recent addition.<sup>2</sup> Timely intervention can reduce morbidity and mortality to a great extent. Furthermore, prevention of this condition is most cost-effective.

Early on, clinically asymptomatic deficiency is common. As the disease progresses, bone pain, muscle aches, and muscle weakness sets in. During this phase, as a result of the non-specific nature of the symptoms, the diagnosis is often overlooked. As the condition progresses, patients may develop profound weakness in the proximal muscles of the pelvic girdle, which leads to difficulty in rising from a bed, chair, or climbing stairs. Patients may become bedridden and need multi-person assistance for their activities of daily living (ADL), compromising their quality of life. A high index of suspicion in patients presenting with pelvic girdle myopathy, in the absence of other neuromuscular findings, will lead to the correct diagnosis. This article illustrates three different case scenarios, all presenting with proximal myopathy and clinical confusion with other myopathic disorders or malignancies that can lead to disastrous consequences.

## CASE PRESENTATIONS

### Patient One

A 60-year-old female and entrepreneur of Indian descent presented with an inability to raise themselves from bed for 1 month. They had been bedridden and required the assistance of two people to perform their ADL. Their problem started 8 months earlier, with difficulty climbing stairs and became progressively worse, forcing them to shift their office to the ground level. There was no improvement after 2 months and they were finding it difficult to rise from their chair. The weakness progressed and they became bedridden. In addition, they experienced generalised pains in their muscles and bones that, at times, disturbed their sleep.

Their past medical history was significant for well-controlled hypertension, while their surgical and social history were not contributory. They had natural menopause 8 years ago and is not on hormone replacement. A review of systems was not contributory. One morning, they woke up with severe pain in their right hip and presented to an orthopaedic surgeon, fearing a fracture. The orthopaedist evaluated them and ordered X-rays, finding extreme osteopenia but no fractures. The patient had a raised serum alkaline phosphatase and low normal calcium and phosphate. A neurologist entertained a diagnosis of myopathy. The neurologist asked for an endocrinologist to see her.

The consultant noted that the patient had not received sunshine for almost a year. On examination, the consultant found the patient to be well-nourished without pallor. Their blood pressure was well controlled. Neurological examination was significant for the severe weakness of the muscles of the hip and lower back but otherwise did not reveal any abnormalities.

The endocrinologist ordered a serum of 25 hydroxyvitamin D (25[OH]D) and intact PTH (iPTH) levels. The former was less than 1.0 ng/mL and the latter was 488.0 pg/mL. A diagnosis of secondary hyperparathyroidism due to vitamin D deficiency was evident.

The patient received an intramuscular injection of vitamin D3 600,000 IU and calcium tablets



of 1,000 mg elemental calcium per day. A nutritionist counselled them on increasing their dietary calcium. The patient started noticing an improvement in their strength. Gradually, they progressed to getting up from bed on their own. In 4 weeks, they walked without support into the endocrinologist's office. Subsequently, the 25(OH)D level was 38 ng/mL and iPTH was 166 pg/mL. they continued to receive oral vitamin D 1,000 IU daily and adequate dietary calcium.

### Patient Two

A 70-year-old male, a retired postal employee, presented with an inability to stand from their chair for 4 months. They were very active during employment and after retirement 10 years previous. They had no significant past medical, surgical, or social history. One year ago, the patient's partner became bedridden. Their partner had been diagnosed with breast cancer and widespread bony metastasis. The patient spent most of their time indoors, caring for their partner. The patient paid little attention to themselves and became very depressed when their partner died 6 months before presentation.

The patient's weakness prevented their self-care. They also started getting severe bone pains and muscle aches. Fearing that they had an underlying malignancy, they approached their physician. The internist diagnosed grief but, under pressure from the patient, investigated their bone pains with a nuclear bone scan. The results were shocking: multiple symmetrical hot areas throughout the entire skeleton-rule out metastasis.

An oncologist evaluated the patient, found an enlarged prostate gland consistent with the patient's age but without nodules or induration. The serum prostate specific antigen levels were within limits and no other primary cancer was evident after extensive investigations. An endocrine consultation led to the diagnosis of vitamin D deficiency (serum levels of 25(OH) D and iPTH were 2.8 ng/mL and 366.0 ng/mL, respectively). The patient received an intramuscular injection of vitamin D 600,000 IU once as well as daily calcium supplements. They also received nutritional education for increasing calcium in their diet.

In 4 weeks, their weakness dramatically improved. They no longer found it difficult to get up from their chair. They ambulated without assistive devices and was able to perform all their ADLs. Four months later, a repeat nuclear bone scan showed that most of the hotspots had disappeared. It reassured the treating physicians that they had progressed in the right direction.

The repeat serum 25(OH) D and iPTH levels were 39 ng/mL and 144 pg/mL, respectively. They received 1,000 IU oral vitamin D daily as a maintenance dose and was encouraged to consume calcium-rich foods. After all, the patient did not have malignancy.

### Patient Three

A 36-year-old female software professional, with a history of autoimmune hypothyroidism on levothyroxine 100 mcg daily presented with multiple problems. A year previously, the patient received an out-of-turn promotion for their excellent work performance and assigned to a country where food items were fortified with all vitamins and minerals.

At that time, they noticed muscle aches, fatigue, migraine-like headaches, recurrent painful mouth ulcers, upper respiratory allergies, wheezing, and disturbed sleep. Soon, their menstrual periods started becoming irregular but there was no menorrhagia or clots. Their headaches became more frequent, and their respiratory complaints worsened. They became intolerant to dairy products, with abdominal bloating, cramps, and increased stool frequency. Unsteadiness upon standing with eyes open and closed followed. They started having increasing weakness in their hips and rising from their chair was an ordeal.

The patient's physician had treated them symptomatically for their ailments, without much relief. They met with several specialists, underwent many investigations, and received multiple diagnoses without avail. They presented to a new physician for a fresh look at their problems, who found them adequately nourished without pallor or clinically euthyroid, but significantly anxious and depressed. Neurological examination was positive for the weakness of the muscles of the hip and lower back and mild ataxia.

The new physician reviewed the patient's latest test results and found a normal serum thyroid-stimulating hormone level, an elevated red cell distribution width in their haemogram, and a high alkaline phosphatase but normal transaminases. The physician ordered iron studies and 25(OH) D.

The results were consistent with non-anaemic iron deficiency (low iron, high iron-binding capacity, and decreased ferritin but with normal haemoglobin) and secondary hyperparathyroidism due to vitamin D deficiency (25[OH]D: 8.8 ng/mL; iPTH: 266 pg/mL).

The deficiencies of iron and vitamin D, with an adequate diet with fortified foods, pointed to gastrointestinal malabsorption. This, in addition to the multiorgan symptomatology, was suggestive of adult coeliac disease. The patient tested positive for serum IgA anti-transglutaminase antibodies, with normal total IgA levels. Since the patient declined an endoscopic duodenal or jejunal mucosal biopsy, histological confirmation was not possible. However, they agreed to try a gluten-free diet. They received oral iron and vitamin D (600,000 IU orally once weekly for 8 weeks as initial treatment) and oral calcium supplements. The inability to tolerate dairy products was overcome by adding lactic acid bacillus tablets with each exchange of dairy.

In 4 weeks, the patient was able to get up from the chair without difficulty and most of their other complaints abated and they resumed their work without interruption. On follow-up, they required 4,000 IU of vitamin D daily to maintain serum 25(OH)D (34 ng/mL) and iPTH levels (41 pg/mL) in the normal range.

## DISCUSSION

### Methods of Obtaining Vitamin D

The Vitamin D is available to the body from two sources. They are the skin and the gastrointestinal tract.

#### The skin

The skin has the machinery to synthesise vitamin D from cholesterol using the ultraviolet (UV) spectrum (UV: 290–315 nm wavelength) of sunlight. The ideal time for sun exposure is

midday, when the maximum absorption of UV rays occurs. It is true not only in temperate zones but also in the tropics. The minimal erythemal dose to produce sufficient vitamin D synthesis will depend on the total area and time of skin exposed.<sup>3</sup> Excess vitamin D synthesised in the skin is metabolised to inactive compounds. Hence, toxicity never occurs by overexposure to sunlight.

**Table 1** lists impediments to vitamin D synthesis in the skin.

### The gastrointestinal tract

Some foods, like eggs and fatty fish, contain vitamin D. The liver contains large amounts. However, the average human diet does not meet the daily requirements of vitamin D. Hence, if sunlight exposure is not adequate, supplementation is necessary. It is especially true for vulnerable groups (**Table 2**). Patients who have had bariatric bypass surgery will require a much higher dose of oral supplemental vitamin D. Absorption occurs in the duodenum and upper jejunum. It is protein-mediated at low concentrations as in the diet, and by unregulated passive diffusion at higher concentrations as in pharmacologic dosing.<sup>4</sup>

### Metabolism of Vitamin D

Both sources of vitamin D are bound to the vitamin D binding protein and is transported to the liver. The next step is 25 hydroxylation in the liver. The final step is 1 hydroxylation in the proximal tubular cells of the kidney. The resultant 1,25 dihydroxy vitamin D (1,25[OH]2D) is an active hormone that binds to the vitamin D receptors (VDR) in many tissues and exerts its actions. Unfortunately, 24 hydroxylation leads to inactivation of both 25(OH)D and 1,25(OH)2D. The formation of 1,25(OH)2D is catalysed by the enzyme 1-alpha hydroxylase, enhanced by PTH. Older adults have decreased 1-alpha hydroxylase activity due to diminished renal mass. In the intestinal epithelium, 1,25(OH)2D binds to VDRs and increases calcium-binding protein synthesis, which aids calcium absorption.

### Latest Research Revealed

Adequate vitamin D maintains the (VDR) density in skeletal muscles and, thereby, the number and function of Type 2 fast-twitching

**Table 1: Impediments to vitamin D synthesis in the skin.**

Condition	Comments
Ageing	Decreased efficiency of synthetic machinery
High latitudes	Less UV radiation
Times other than midday	Suboptimal UV rays
Sunscreens	Even lowest potency products filter UV rays
Photosensitivity	Sunlight avoidance
Fear/risk of skin cancer	Sunlight avoidance
Religious prohibitions	Decreased body surface areas exposed to the sun
Cloud cover	Clouds filter UV rays
Glass windows	Glass filters UV rays; however, they do let in light and heat
Homebound or indoor workplace	Avoidance of sun exposure

UV: ultraviolet.

**Table 2: Vulnerable groups for vitamin D deficiency.**

Condition	Comments
Ageing	Decreased active vitamin D synthesis and intestinal resistance
Bedridden	Accompanying poor nutritional states
Institutionalisation	Multiple factors
Pregnancy	Increased demand
Lactation	Increased demand
Infants and growing children	Increased demand
Obesity	Increased segregation of vitamin D in adipocytes and decreased availability
CKD	Decreased active vitamin D synthesis
Therapy with p450 enzyme inducers	Increased catabolism of vitamin D
Malabsorption states	Coeliac disease; small intestinal bacterial overgrowth; short bowel due to disease or surgery; inflammatory bowel diseases; bariatric bypass procedures

CKD: chronic kidney disease.

skeletal muscle fibres. In addition, through genomic and non-genomic mechanisms, it reduces both inflammatory cytokine induced skeletal muscle damage and intramuscular adiposity by preferential differentiation of common stem cells into myoblasts instead

of adipocytes. Therefore, deficiency of vitamin D results is muscle weakness and decreased reaction speed and strength to sudden postural changes and falls are the result. Recent evidence implicates a role of vitamin D in skeletal muscle repair and regeneration.<sup>5,6</sup>

## Double Jeopardy in Older Adults

Older adults are particularly prone to the ill effects of vitamin D deficiency, due to poor synthesis in the skin, diminished 1- $\alpha$ -hydroxylase activity, and resistance to the action of 1,25(OH) $_2$ D in the intestines. A low bone mass and skeletal muscle weakness of ageing are worsened by a concomitant vitamin D deficiency. Studies of treatment in institutionalised older adults with severe vitamin D deficiency have conclusively shown a reduced incidence of falls and fractures.

## Clinical Course of Vitamin D Deficiency

Mild deficiency may be asymptomatic. The deficiency is overlooked initially due to the non-specific nature of the symptoms. As the disease progresses, patients may complain of symptoms like muscle pains, fatigue, and weakness. Bone pains occur due to osteomalacia. Later on, severe muscular weakness is a hallmark condition, with a predilection to the proximal musculature of the hip region. The reason for this is unclear. The ensuing weakness may lead to falls and fractures, or the patient may become immobile due to muscle weakness as mentioned earlier. Severe localised pain in one or more bones may be due to an incomplete fracture identified on X-rays as Looser's zones.

## The clinical course in context

See [Table 3](#) for a comparison of the clinical characteristics of the three patients.

Whenever a patient presents with proximal myopathy, it is imperative to consider many conditions in the differential diagnosis. This is dictated by the clinical presentations. The age at initial presentation did not favour hereditary myopathies. The absence of drugs such as statins, corticosteroids, and retroviral drugs excluded drug-induced myopathy. Clinical features suggesting exposure to infective agents or toxins were also absent in all three patients. Also, features of connective tissue diseases like systemic lupus erythematosus, dermatomyositis or polymyositis, and inclusion body myositis were absent in all three patients. An extensive search did not reveal a malignancy in Patient Two. Clinically there were no suggestions of hypo- and hyperthyroidism, Cushing's disease, or acromegaly to pursue these conditions by

appropriate investigations. Conditions that caused both proximal and distal myopathies, either simultaneously or sequentially, were also excluded as only the hip muscles were affected. For similar reasons, diseases affecting oculofacial and pharyngeal musculature and conditions that cause combined motor and sensory pathologies were not entertained.

All three patients did not have pre-treatment sun exposure and severe muscle weakness was a feature in all of them. This led to misdiagnosis as myopathy in the first patient who also had features of bone loss on X-rays.

## Bone pain does not warrant a bone scan

Indiscriminate use of a nuclear bone scan to investigate bone pains can lead to the erroneous diagnosis of metastatic malignancy, as noticed in Patient Two. The hotspots observed were areas of bone lysis by the elevated PTH of secondary hyperparathyroidism that disappeared after treatment, which was confirmed by a subsequent scan.

## Think adult coeliac disease

The third patient had a complex presentation, challenging even the most astute clinician. Features of a multi-system involvement, predominantly outside the gastrointestinal system, have been described in adult atypical coeliac disease. This patient had a history of autoimmune hypothyroidism, which has known associations with coeliac disease. In addition, biochemical evidence of iron deficiency in the absence of blood loss, along with vitamin D deficiency despite consuming fortified foods strengthened the probability of adult atypical coeliac disease in this patient. For a detailed description of adult coeliac disease, the reader is directed to the cited reference.<sup>7</sup> This young patient also had a secondary lactose intolerance that responded to lactic acid bacillus given orally. It supplies the deficient galactosidase enzyme to aid in lactose digestion and allows the patient to tolerate dairy products with the benefit of obtaining natural calcium.

## Bariatric surgical patients: a special group

Vitamin D deficiency is an established complication of obesity and its treatment, namely bariatric surgery. The induced malabsorption may require a high maintenance dose of vitamin D and this may not be cost-



**Table 3: Comparison of the clinical characteristics of three patients with severe vitamin D deficiency.**

Patient characteristics	Patient One	Patient Two	Patient Three
Age (years)	60	70	36
Gender	Female	Male	Female
Past sun exposure	None in 1 year	None in 1 year	None in 1 year
Food fortification	No	No	Yes
Proximal myopathy	++++	+++	++
Serum alkaline phosphatase*	747	866	353
Serum creatine kinase	Normal	Normal	Normal
Serum ALT and AST	Normal	Normal	Normal
Pre-treatment 25(OH)D (ng/mL)	1	2.8	8.8
Pre-treatment iPTH (pg/mL)†	488	366	266
Post-treatment 25(OH)D (ng/mL)	38	39	34
Post-treatment iPTH (pg/mL)†	166	144	41
Initial vitamin D treatment modality	IM injection 600,000 IU once	IM injection 600,000 IU once	Oral vitamin D sachet 600,000 IU, once weekly for 8 consecutive weeks
Maintenance requirements for vitamin D	1,000 IU orally daily	1,000 IU orally daily	4,000 IU orally daily
Initial diagnoses	Myopathy	Bony metastasis, Primary unknown	Multiple diagnoses: migraine headaches; upper respiratory allergy; bronchial asthma; aphthous ulcers; irritable bowel syndrome; anxiety; depression; fibromyalgia
Final diagnosis	Nutritional vitamin D deficiency	Nutritional vitamin D deficiency	Adult coeliac disease
Recovery of proximal myopathy with treatment	Complete	Complete	Complete

\*Normal range for serum alkaline phosphatase: 50–150 U/L.

†Normal range for iPTH: 10–65 pg/mL.

25(OH)D: 25 hydroxyvitamin D; ALT: alanine transaminase; AST: aspartate aminotransferase; IM: intramuscular; iPTH: intact parathyroid hormone.

effective during long-term therapy.<sup>8</sup> However, the Endocrine Society guidelines only mention the oral formulation.

### Parenteral vitamin D: some food for thought

Intramuscular (IM) injections of vitamin D are an alternative when very high oral doses are

required to maintain the 25(OH)D within the normal range. There are minimal or no side effects but paucity of adequate data to exclude complications such as hypercalciuria indicate that randomised controlled trials are needed to support or refute IM vitamin D for treatment. A small study from Australia reported the safety of

IM vitamin D.<sup>9</sup> The first two patients described received injections as initial treatment because high dose oral preparations were locally unavailable at that time. Subsequently, they received smaller oral maintenance doses and responded well. The third patient presented when high-dose oral formulations became available and, although suffering from malabsorption, responded well albeit needing a higher dose.

### Dosing regimen

Another issue is whether to choose a daily, weekly, or once monthly regimen for maintenance. All three regimens are effective and, the choice depends on patient characteristics (compliance issues) and provider preferences.<sup>10</sup>

### Vitamin D2 or D3? What is the difference?

Two formulations of vitamin D are available. Vitamin D2 (ergocalciferol) is from plants and Vitamin D3 (cholecalciferol) is from animal sources. Again, the choice of which compound to use will depend on patient preferences (whether they are vegan or vegetarian) or provider choices. The Endocrine Society considers them equipotential but some assays of 25(OH)D may underestimate levels when treating with vitamin D2 and may complicate management.<sup>11</sup>

### Follow-up testing

Serum 25(OH)D normalised in all three patients but iPTH normalised only in Patient Three. The normalisation of iPTH may happen later (sometimes after one or two years). The reasons behind this are not clear.

The practitioner should be cautious and not to increase the Vitamin D dose based on the iPTH level. Instead, they should use the 25(OH)D to guide replacement therapy. The Endocrine Society recommends a minimum level of 25(OH)

D of 30 ng/mL. A level between 20 and 30 is considered insufficient, while those below 20 as deficient.<sup>12</sup>

### Will the patient get vitamin D toxicity?

If guidelines are adhered to strictly, toxicity from vitamin D is rare. Caution should be the rule when treating certain patients with chronic granulomatous diseases and certain lymphomas, which produce 1-alpha-hydroxylase in their macrophages and consequently increase the production of 1,25(OH)<sub>2</sub>D in an unregulated manner.<sup>13</sup>

## CONCLUSION

Vitamin D deficiency is not a diagnosis of exclusion. A good history, physical examination, and relevant laboratory tests will lead to a timely diagnosis and appropriate therapy. Prevention saves healthcare costs and reduces morbidity and mortality. High-risk groups will need greater attention and will benefit most from intervention. Proximal muscle pelvic girdle myopathy in the correct context should prompt testing for 25(OH)D levels utilising reliable assays, which is the ideal substance in the blood that reflects body vitamin D stores. Testing for 1,25(OH)<sub>2</sub>D is not useful as its half life is short; does not reflect body stores of vitamin D; and is often normal, even in severe deficiency states. Unnecessary investigations like nuclear bone scans can be very misleading and should be discouraged. Treatment is readily available, safe, and effective, even when the disease is advanced. A full recovery is a rule, as seen in the above examples. Finally, it is vital to educate not only the general public but also healthcare professionals, both generalists and specialists, to enable them to recognise vitamin D deficiency in a timely manner and manage patients appropriately to improve healthcare outcomes.

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