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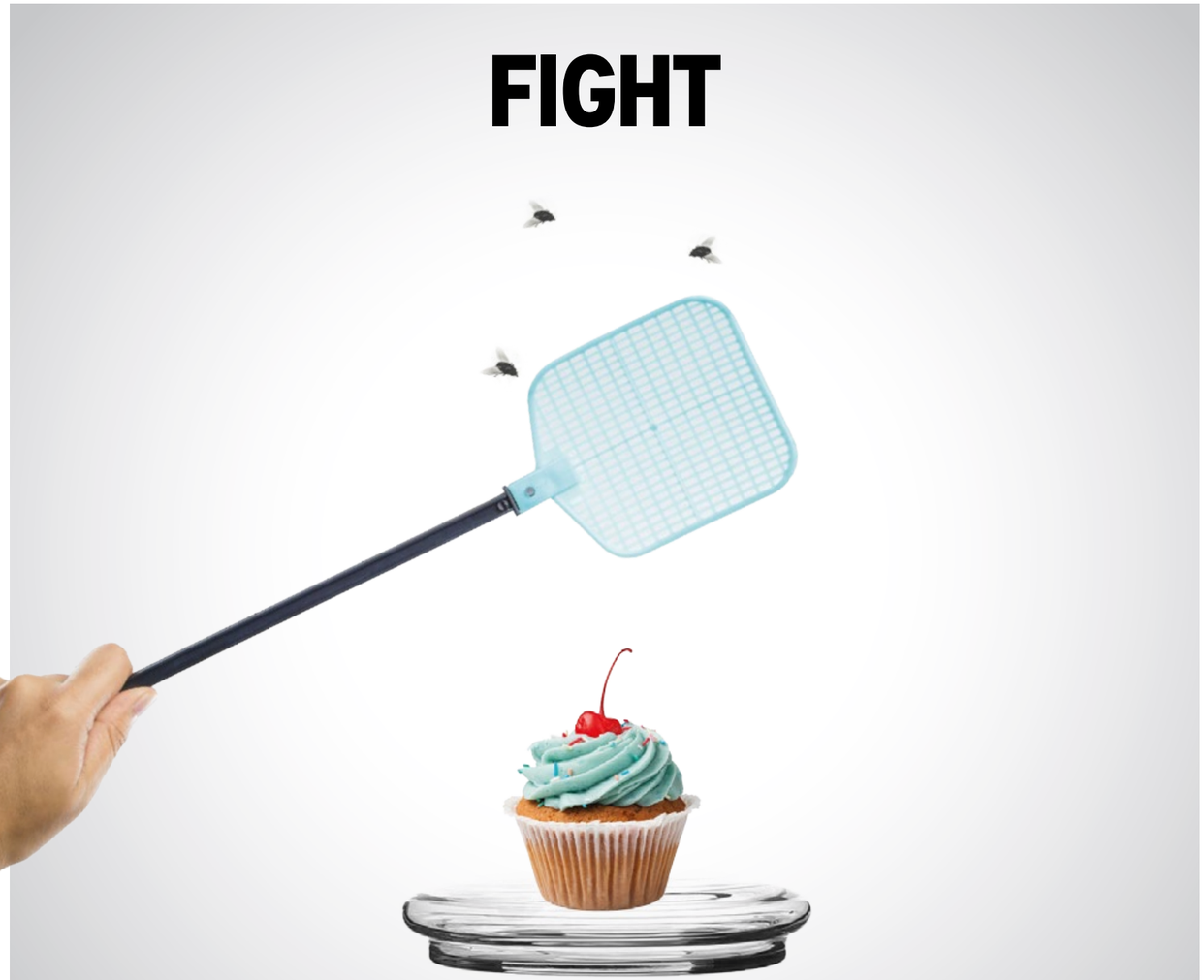
# EMJ

Editor's Pick

## Relating Ventilatory Support and Drug Treatment Strategies to the Fundamental Pathophysiology in COVID-19 Illness

Prevalence of Scoliosis in Hypermobile Ehlers-Danlos Syndrome

Pretransplant Determinants of Outcome in Patients with Myeloma Undergoing Autologous Transplantation in Lower Resource Settings





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Reporting of Suspected Adverse Reactions
Adverse reactions should be reported according to local guidelines.



January 2021
MAT-40487

**References:**
**1.** Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28. **2.** Kyntheum® (brodalumab) EU Summary of Product Characteristics. July 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kyntheum. Last Accessed: January 2021. **3.** Brembilla NC et al. *Front Immunol* 2018;9:1682. **4.** Pappu R et al. *Immunology* 2011;134:8–16. **5.** Baker KF and Isaacs JD. *Ann Rheum Dis* 2018;77:175–87.

PASI 100 at 12 weeks with Kyntheum®: 44% in AMAGINE-2 (n=612) and 37% in AMAGINE-3 (n=624) using NRI for missing data.[1]
IL, interleukin; NRI, non responder imputation; PASI, Psoriasis Area and Severity Index.

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LEO

# Contents

*"I would like to thank all the contributors and expert authors for their valued collaboration and input, and extend my appreciation to the entire Editorial Board for their dedication and hard work during these difficult times."*

Spencer Gore, CEO

# Editorial Board



VIEW IN FULL ←

## Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

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 6.2

# Welcome

Dear Readers,

It is my great pleasure to introduce the newest issue of our multidisciplinary flagship journal, *EMJ*, which brings together the latest advancements across the medical field that matter most. These pages contain a promising selection of peer-reviewed studies and review articles covering therapeutic areas such as cardiology, dermatology, respiratory medicine, and rheumatology.

As coronavirus disease (COVID-19) continues to spread around the world, we are publishing a topical article by Lewis et al., which relates ventilatory support and drug treatment strategies to the fundamental pathophysiology in COVID-19 illness. The authors explain why understanding the mechanisms and timings of alveolar damage can allow for tailored interventions. As well as being highly relevant, this comprehensive review is also the Editor's Pick for our latest issue of *EMJ*.

For the haematologists amongst you, we have the review by Nair on the pretransplant variables that impact the outcome of autologous stem cell transplantation in patients with multiple myeloma. Although the presence of high-risk cytogenetics is considered the main adverse factor predicting shorter survival, there are numerous other potential determinants associated with post-transplant outcomes that are explored in this fascinating paper. Nair also delineates the growing interest in minimal residual disease measurements as a potent prognostic marker in myeloma.

In addition, a timely piece by Russell et al. explores the rationale behind the use of oxy-hydrogen gas as a novel and sustainable treatment for COVID-19. The authors outline how a combination of hydrogen and oxygen can affect cellular processes at the molecular level, focussing on the evolutionary requirement for these gases. This is coupled to an investigation of emerging preclinical and clinical data concerning the safety and efficacy of this approach in treating inflammatory-related disorders. This review has both theoretical and practical significance, which will appeal to both pulmonologists and a wider healthcare audience alike.

Finally, I would like to thank all the contributors and expert authors for their valued collaboration and input, and extend my appreciation to the entire Editorial Board for their dedication and hard work during these difficult times. I hope you, the reader, enjoy the important research inside this flagship issue of *EMJ*.

Spencer Gore

Chief Executive Officer, EMG-Health

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# Foreword

Dear Colleagues,

It is my pleasure to present the latest issue of the flagship journal, *EMJ*. The overarching theme is coronavirus disease (COVID-19) infections, focussing on pathophysiologic mechanisms in order to facilitate a targeted management approach. A variety of articles on COVID-19, as well as other disease areas, are presented.

The Editor's Pick for this issue is a review paper titled: "Relating Ventilatory Support and Drug Treatment Strategies to the Fundamental Pathophysiology in COVID-19 Illness" by Lewis et al. COVID-19, which induces multi-organ disease and lung pathology, is a major cause of intensive therapy unit admissions. Pathophysiologic and radiologic features of alveolar inflammation, subsequent secondary or concurrent endothelial infection and dysfunction, and coagulopathy are reviewed. Understanding the basic disease mechanisms and timings of alveolar damage can inform the nature of ventilatory support required and the timing of targeted pharmacotherapies.

Russell et al. review the use of oxy-hydrogen gas, a gaseous mixture of molecular hydrogen and oxygen, as a treatment in COVID-19 lung inflammation. Reactive oxygen species promote inflammation, especially in hypoxic environments. Oxy-hydrogen gas reduces oxidative stress, attenuates inflammation, and is cytoprotective. It may also have therapeutic effects in the management of other lung inflammatory conditions, such as asthma and chronic obstructive pulmonary disease.

COVID-19 infection is associated with a high frequency of thromboembolic phenomena. A systematic review and meta-analysis of thromboembolic complications is presented by Pergola et al. Furthermore, Galván-Casas et al. present a fascinating case report, in which the most striking COVID-19 manifestation was dermatological.

Other disease areas covered include pretransplant determinants of outcomes following autologous stem cell transplantation in multiple myeloma; rifampicin-induced thrombocytopenia; prevalence of scoliosis in hypermobile Ehlers-Danlos syndrome; novel therapies for acute myeloid leukaemia; musculoskeletal brucellosis in the United Arab Emirates; and an audit review on emergency oxygen prescribing.

In conclusion, the boundaries of disease pathophysiology continue to expand. I thank all the authors and peer reviewers for committing time to this issue, despite the pressures of COVID-19.

**Prof Ian C Chikanza**

Consultant in Adult and Paediatric Rheumatology, Department of Rheumatology, Barts Arthritis Centre, Barts and the Royal London Hospital, London, UK; Professor of Medicine, Catholic University, and Professor in Rheumatology and Immunology, University of Zimbabwe, Harare, Zimbabwe

# Pioneering Best Practices in Atopic Dermatitis: Results from the Quality of Care Initiative

This virtual symposium took place on the 29th October 2020, as part of the 29th European Academy of Dermatology and Venereology (EADV) Virtual Congress


**Chairperson:** Emma Guttman[1]

**Speakers:** Emma Guttman,[1] Mette Søndergaard Deleuran,[2] Eric Simpson[3]

1. Mount Sinai School of Medicine, New York City, New York, USA
2. Aarhus University, Aarhus, Denmark
3. Oregon Health & Science University, Portland, Oregon, USA



**Disclosure:** Prof Guttman has received consultancy fees from AbbVie, Aditum Bio, Almirall, Amgen, Arena Pharmaceuticals, Asana, AstraZeneca, Bluefin, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Cara Therapeutics, Celgene, DBV Technologies, Dermira, EMD Serono (Merck & Co), Eli Lilly and Company, Evidera, Galderma, Ichnos Sciences, Janssen, Kyowa Kirin, LEO Pharma, LARRK Bio, Medscape, Novartis, Pfizer, Principia Biopharma, RAPT, Realm, Regeneron, SATO Pharmaceutical, Seanergy Dermatology, Seelos Therapeutics, Serpin Pharma, Siolta, Sonoma Biosciences, Vanda Pharmaceuticals, Ventyx Biosciences, Vimalan Biosciences, and Sanofi-Aventis; and has been a member of the scientific advisory board for Sanofi-Aventis. Prof Deleuran has received grants and personal fees, including research support, consulting/advisory board agreements, and/or honoraria for lectures, from AbbVie, Almirall, Eli Lilly and Company, LEO Pharma, Meda Pharma, Pfizer, Pierre Fabre, Regeneron, and Sanofi Genzyme. Prof Simpson has received grants and/or personal fees from AbbVie, Dermira, Eli Lilly and Company, Forte Bio Rx, Incyte, Kyowa Kirin, LEO Pharma, Menlo Therapeutics, Merck, Novartis, Ortho Dermatologics, Pfizer, Regeneron, and Sanofi Genzyme.

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## Meeting Summary


Pioneering global best practices in atopic dermatitis (AD) and implementing them in the clinic are important steps towards optimising patient care. This satellite symposium, held as part of the 2020 European Academy of Dermatology and Venereology (EADV) Virtual Congress, featured a panel of leading dermatology experts who discussed key findings from the recently published Atopic Dermatitis Quality of Care Initiative.

## Purpose and Mission of the Atopic Dermatitis Quality of Care Initiative

### Professor Emma Guttman

For many years, AD has been deprioritised in favour of services deemed more medically urgent. New systemic therapies that are able to effectively treat both the disease and its comorbidities have also become available. More recently, patient advocates have taken important steps to increase awareness of AD. However, to reap the full benefits from these changes, Prof Guttman explained that AD care itself must also evolve.

Against this backdrop, the Global Atopic Dermatitis Quality of Care Initiative was conceived.[1] Its vision is to demonstrate the imperative for, and to improve the quality of, AD care worldwide. The mission of the initiative is to catalogue, analyse, and report the challenges to and best practices for quality AD care from renowned healthcare centres around the world. These key findings will then be disseminated to educate other healthcare providers on the priorities and best practices needed to improve and maintain quality care in AD.

The Global Atopic Dermatitis Quality of Care Initiative was overseen by an international steering group consisting of four leading AD experts with responsibility for guiding the initiative, providing practical clinical input, and evaluating the ensuing information. The study was conducted by KPMG, who carried out the collection, study, analysis, and interpretation of the data, as well as the preparation of the final report, which was commissioned and funded by Sanofi Genzyme and Regeneron.

The methodology of the initiative involved a five-step process.[1] Firstly, a stringent literature review was carried out to understand current challenges and good practices in AD care. This was augmented by in-person site visits to leading international centres using structured interviews to document key data with the aim of learning good practice directly from medical leaders in the field. A total of 32 centres from 17 countries around the world were visited, including sites in the USA, Europe, South America, and Asia. The next step was the documentation of good practice interventions for AD care using specially created centre-specific reports and good practice case studies. These findings were then reviewed by the steering committee to ensure challenges and good practices were accurately captured and articulated. The final stage in the process was preparation of the finalised, comprehensive report, which is available online.

## Global Challenges of Atopic Dermatitis and the Opportunities They Present to Improve Quality Care

### Professor Mette Deleuran

Prof Deleuran discussed the four main challenges to quality of care that currently exist across the patient pathway in AD.

The first challenge is misconceptions regarding the causes and triggers of AD; people with AD can experience stigmatisation and isolation because of misconceptions that AD is contagious and are frequently affected by social and sexual issues. AD is also underappreciated by patients and often dismissed as simply a childhood disease. Even for healthcare professionals (HCP), AD can be difficult to explain and prone to misconceptions, not least because physicians themselves may have received limited training on the disease despite its prevalence. These issues are illustrated by findings from the Global Atopic Dermatitis Quality of Care Initiative, in which the vast majority of centres (91%) acknowledged that patient knowledge of, and education on, AD is lacking. Over one-half of centres (56%) also reported a need for dedicated programmes to further enhance HCP education.[1] Collectively, these medical and societal misconceptions around AD can often combine to exert a negative impact on a patient's quality of life (QoL).

The second key obstacle to quality of care in AD is delayed referral and access to AD specialists. Across healthcare systems, primary care referral is typically required to secure access to an AD specialist; however, the referral process itself is often inefficient and swamped by overwhelming demand. Prof Deleuran explained that in many

parts of the world it can be very difficult, or even impossible, to obtain an appointment with an AD specialist. Consequently, primary care physicians (PCP) remain the HCP most likely to encounter patients with AD, and misdiagnosis is commonplace. Several different diseases can mimic AD presentation, and individual patients often display widely disparate clinical manifestations. Accurately determining AD severity can prove particularly challenging for PCP. Together, these gaps in PCP education and healthcare system capabilities may hinder the ability of patients to receive timely referral and access to AD specialists.

The third critical issue is poor patient access to AD treatments coupled with suboptimal adherence. AD is associated with a significant treatment burden and patients often grow tired of regular and rigorous application of topicals that can be greasy, malodorous, and damaging to clothing. Fear of treatment side effects, in particular corticophobia, is another issue that can drive poor adherence and underdosing. Evidence indicates that corticophobia, which relates to worries and negative beliefs concerning topical corticosteroids, is present among both parents of children with AD and the HCP involved in caring for them.[2] In some healthcare settings, AD treatment may also carry a direct financial burden for patients. For HCP, time constraints are a perpetual problem resulting in limited capacity for patient education, particularly on dosage expectations. Prof Deleuran conceded that the biggest challenge in a busy practice can often be finding time to talk to patients and parents and answer all of their questions. In this respect, nurses can prove a vital resource for improving channels of communication with patients. Within healthcare systems, there may be limited, variable, or indeed any coverage of or reimbursement for AD therapies, with limited treatment options for paediatric patients. Collectively, these shortcomings across healthcare systems lead to limited treatment options and access for patients with AD.

The fourth and final challenge to quality of care in AD is managing disease complexity and comorbidities to reduce the burden on patients. Prof Deleuran explained that there has been an increasing realisation in recent years that AD is a multisystem disease driven by type 2 inflammation and is associated with multiple comorbidities. It is important for HCP to recognise and respond to such potential comorbidities, including asthma and allergic rhinoconjunctivitis, as well as mental health disorders, such as anxiety, depression, and suicidal ideation. For patients with AD, comorbidities can have an impact on multiple components of their QoL. The lifelong requirement for medical management also exerts a heavy toll on patients. Within healthcare systems, managing complexity of AD and its comorbidities may be confounded by limited availability or access to relevant specialists within the setting of a multidisciplinary team (MDT). The overall result is that HCP, patients, and healthcare systems alike are all adversely impacted by the intricate nature of AD health management.

## Good Practice Implementation Priorities that Optimise Quality of Care in Atopic Dermatitis

### Professor Eric Simpson

The Atopic Dermatitis Quality of Care Initiative identified key challenges in achieving quality of care in AD that resonated with HCP globally. Prof Simpson reviewed five data-driven, good practice interventions devised to address these challenges and highlighted the important benefits they may yield. Interventions were organised into easy, difficult, and advanced steps that practising physicians can take to improve overall clinical care for their patients with AD.

Intervention 1 related to the clinical assessment and diagnosis of AD; easy steps that physicians could take to improve this aspect of care include taking a more nuanced clinical history, performing a thorough clinical assessment and evaluation of treatment response (what has worked, what has not, and why), and taking into consideration the psychological impact of AD. Prof Simpson stressed the importance of clinical assessment that encompasses the whole patient, focussing on accurately evaluating AD severity and understanding key disease drivers. More difficult next steps could include additional diagnostic assessments, such as patch testing for challenging cases or biopsy to rule out cutaneous T-cell lymphoma; shorter disease assessment tools; and consideration of the holistic impact

of AD. Advanced interventions may involve diagnostic criteria assessments, comprehensive disease assessment tools, and a focus on the long-term impact of AD.

Prof Simpson highlighted patient-reported outcomes as particularly useful assessment tools for clinicians and noted that validated 'AD control' instruments are now available online that can help to objectively determine if a patient's disease is well controlled. The potential benefits of improved clinical assessment and diagnosis for patients with AD include more timely and accurate diagnosis, quicker access to care, faster symptom relief, and improved QoL. In turn, HCP and healthcare systems stand to benefit from a reduced burden of misdiagnosis and costs, alongside an optimised disease management approach. Prof Simpson concluded that, above all, it is vital to ensure patients with AD receive a timely and accurate evaluation, diagnosis, and assessment of their disease using established instruments which will, in turn, accelerate access to care and prevent disease progression.

Intervention 2 aimed to wield the advantages afforded by a co-ordinated and structured MDT. Easy steps to enhance MDT collaboration include identifying appropriate specialists, pinpointing those providers who would make good AD team members, and assessing relevant comorbidities in clinical consultations. More difficult MDT implementation strategies could involve participating in meetings and training with external specialists, and collaborating in cross-speciality research. Multidisciplinary clinics, cross-speciality units, specialist patient teleconsultations, and cross-speciality patient group events represent examples of advanced MDT collaboration. Prof Simpson highlighted a number of examples of best practice in the area of MDT at all levels of intervention from participating centres in the study. These included increased involvement of nurse practitioners (Utrecht, the Netherlands), paediatric- and adult psychologist-led consultation and support groups (Sao Paulo, Brazil), and input from pharmacists to boost adherence to topical steroids (Barcelona, Spain). Patients managed in an MDT setting gain better access to diagnostic tests and advice from experts in their field, expedited treatment initiation, and a reduced travel burden. In turn, HCP and healthcare systems benefit from streamlined referrals and more efficient patient management, improved communications, a reduced burden on resources, less duplication, increased effectiveness, and lower costs. Prof Simpson concluded that MDT involvement is vital for complex patients. This would include a structured and co-ordinated approach that provides holistic patient care and co-ordination between treating HCP and specialists, who serve to streamline and improve patient health management.

Medicine is increasingly focussed on assessing delivered quality of care, noted Prof Simpson, and good-practice Intervention 3 reflects this by monitoring and evaluating care quality. Easy steps towards achieving this include defining care goals, processes, and outcomes; analysis of patient outcomes; and implementation of patient surveys and satisfaction questionnaires. More difficult and advanced approaches could include cross-centre evaluation and HCP assessment, ongoing patient databases, patient dashboards, and external audit of services. Implementing measures to monitor and evaluate care quality gives patients the opportunity to provide direct input that can improve their quality of care, thereby instilling greater confidence in the care provided. HCP benefit from improved patient outcomes, increased patient satisfaction, and better care efficiency, as well as the ability to deliver consistent standards of care. Overall, monitoring and evaluation within centres and amongst wider networks allow for continuous improvement, explained Prof Simpson. Consistent standards of care raise awareness of improvement areas yielding better patient outcomes, patient satisfaction, and care efficiency.

Intervention 4 centres on the important area of patient education and communication, with the aim of improving patient and caregiver understanding of AD and its effective management. Consultant-led patient education, patient intervention plans, referral to patient support groups, and question and answer opportunities are all simple patient education strategies that can be easily applied in daily clinical practice. More difficult and advanced approaches could include intensive educational initiatives, in-house patient support groups and technologies (e.g., bespoke digital apps), patient games and role play, expert patients, and satellite clinics. The benefits of better patient and caregiver education and communication

are obvious, said Prof Simpson, because when patients understand something, adherence is greater and, in turn, outcomes are improved. HCP and healthcare systems therefore benefit from a reduced demand on time, services, and resources. Therefore, overall, better patient involvement in case decisions decreases the burden on patients, HCP, and healthcare systems alike, Prof Simpson concluded.

The final change identified by the Atopic Dermatitis Quality of Care Initiative focusses on the importance of collaboration and exchange with patient groups. The simplest and easiest approach, which can be adopted anywhere, is for all AD treatment centres to routinely direct patients to patient advocacy groups, and vice versa. Prof Simpson emphasised that working collaboratively and exchanging information with patient groups educates and empowers patients and caregivers to actively participate in their AD. Patient access to the resources of patient groups also improves self-management, which in turn decreases clinical and healthcare system burden.

A detailed summary of these key high-priority good practice interventions is contained in the Quality of Care Initiative report.[1]

## Launching the Global Atopic Dermatitis Quality of Care Initiative

### Professor Emma Guttman

Prof Guttman discussed the launch of the Global Atopic Dermatitis Quality of Care Initiative, explaining that the final report from the initiative capturing best practice quality of care from all 32 involved treatment centres is now launched and available online.[1]

This interactive website contains all key results from the report, logically presented and fully searchable. Prof Guttman described the report as having very useful applications for everyday clinical practice, in particular for improving clinical care for patients with AD and stepping up treatment where required to maximise QoL and reduce the burden on both patients and wider society. The report also provides the opportunity to compare and contrast clinical practice in AD from around the world, noted Prof Guttman, allowing clinicians to understand regional differences and embrace examples of good practices wherever they occur.

## Discussion

During discussions, all experts agreed that a shift in the landscape of care for AD is urgently needed and that the Global Atopic Dermatitis Quality of Care Initiative will have an important role in delivering this. The availability of the report as a free reference tool accessible by all will also help to raise wider awareness of AD, which panel members highlighted as a key priority. Prof Simpson pointed out that the amalgamated experiences from 32 centres across 17 different countries show that similar clinical challenges in AD are being faced around the world and that the five key strategies outlined in the report can be used successfully to overcome these.

The panel agreed that AD care is entering an exciting era with the availability of improved treatment options but that more needs to be done to optimise outcomes from this expanding therapeutic armoury. Prof Guttman explained that a common misconception amongst patients, fuelled by short-duration clinical trials, is that AD is not a chronic disease and that symptoms will resolve, and treatment can be stopped within a set timeframe (6–12 weeks). Another challenge is that patients with very severe AD can tolerate a high disease burden, so even a slight improvement in symptoms may be seen as treatment success. There is a need to educate patients on these critical issues, said Prof Guttman, to ensure that adherence is maintained over the long term and treatment outcomes improve. On the subject of patient education, experts agreed that this is particularly important at the outset of the patient journey, when it is vital to outline good practices and treatment expectations. Prof Deleuran suggested that it was worth investing more time in education upfront and adopting a holistic approach involving nurses, dietitians, and other members of the MDT to improve overall outcomes for patients. Enhanced collaboration with patient groups and patient organisations was also highlighted as a key focus area by the panel, who emphasised the importance of ensuring teenage and adult patients are not overlooked. “As dermatologists, it is essential

that we partner with patient organisations," stressed Prof Guttman, "because, ultimately, to bring new drugs to patients we need to listen to the patients' voices and understand the direction they want to go in."

Considering comorbidities of AD, in particular the mental health impact, Prof Guttman explained that patients with depression can experience improvements in their depressive symptoms when they receive effective systemic AD therapies, especially if they present with severe AD that affects multiple aspects of their life. Therefore, it is important to understand that some of the comorbidities of AD are induced by the severity of the disease and once the condition is well controlled, these can be minimised or even resolved. Prof Simpson agreed that use of more aggressive therapy can often mitigate the impact of comorbidities on patients, in particular the mental health effects that can be directly attributed to the severity of skin disease.

All panel members acknowledged that primary care doctors currently have the biggest role in treating AD in the USA and Europe because of a lack of dermatologists. A key priority for specialists is therefore to educate general practitioners so that they can better help patients with AD in the primary care system. Disease severity assessment, rather than diagnosis per se, represents one of the biggest challenges currently faced in AD management. It needs to be emphasised that, irrespective of time constraints, assessing the full body surface area is key, said Prof Guttman. This is the single most important factor that indicates the need to step-up treatment from topicals. Prof Simpson concurred, explaining that by making better therapeutic decisions for patients, QoL will be significantly improved and ultimately lead to a cost burden reduction for the healthcare system if patients are well controlled.

Drawing the symposium to an end, panel members issued a call to colleagues around the world to access and read the Global Atopic Dermatitis Quality of Care Initiative report. Even those who are considered experts in AD can learn something from this initiative, concluded Prof Guttman, who stated that there is always scope to evolve and improve our practices to help all AD patients globally benefit from the best care possible.

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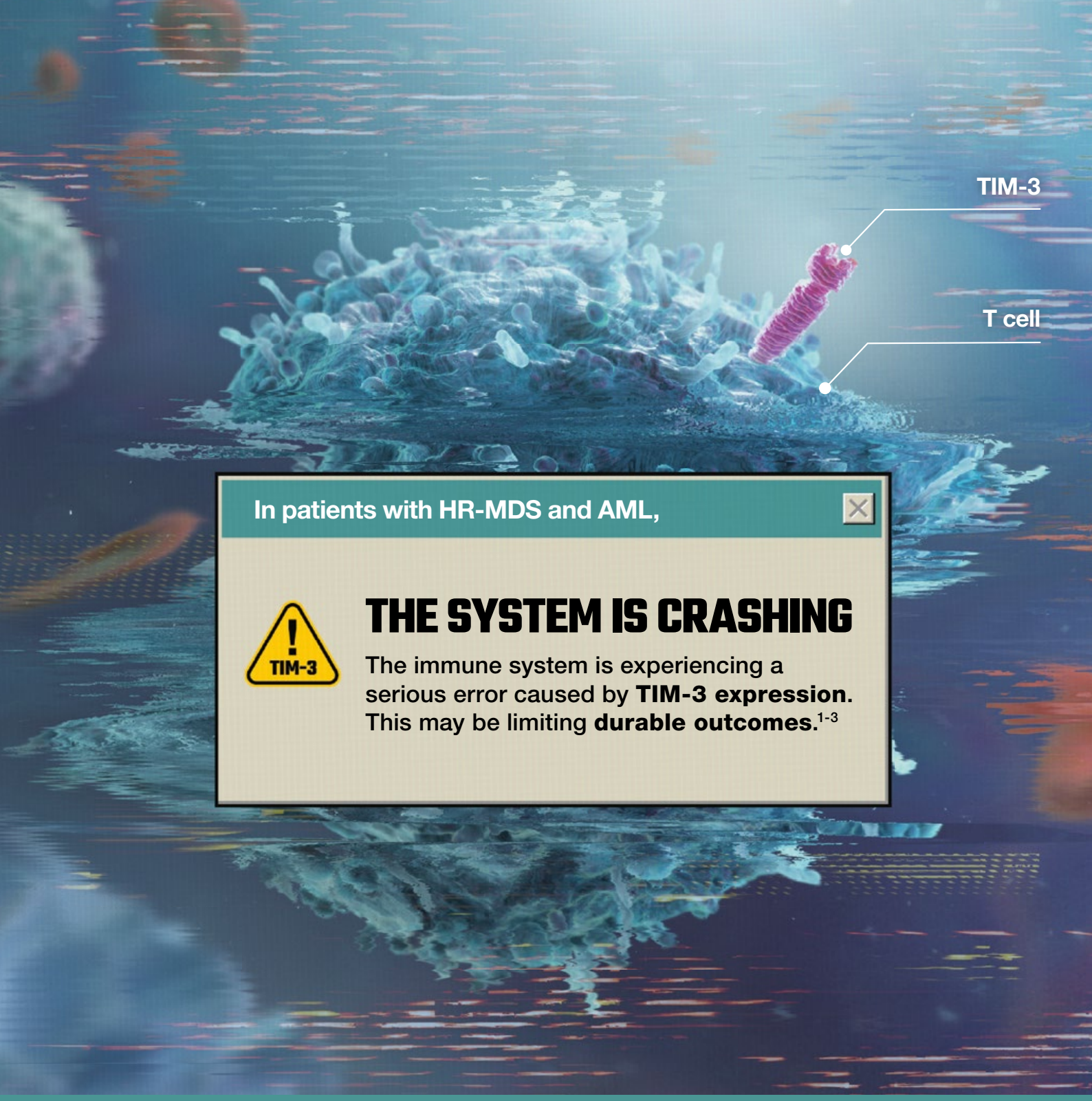


AN UNDERSTANDING OF IMMUNO-THERAPEUTIC APPROACHES FOR MYELOID DISEASES (SUCH AS IMMUNO-MYELOID THERAPY) IS EMERGING.

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AML, acute myeloid leukemia; HR-MDS, higher-risk myelodysplastic syndrome; TIM-3, T cell immunoglobulin and mucin domain-3.

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# Late-Breaking Abstracts: Health Status Benefits of Mavacamten in Obstructive Hypertrophic Cardiomyopathy and the Modifying Effect of Ejection Fraction on the Therapeutic Benefit of Omecamtiv Mecarbil in Heart Failure

These poster presentations took place between 15th and 17th May 2021, as part of the American College of Cardiology (ACC) Virtual Conference


**Presenters:** John Spertus,[1] John Teerlink[2]

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## Meeting Summary

Two late-breaking abstracts at the American College of Cardiology's (ACC) virtual meeting ACC.21 delved further into the data of two pivotal trials, demonstrating the additional benefits of new cardiac treatments for obstructive hypertrophic cardiomyopathy (HCM), heart failure (HF), and heart failure with preserved ejection fraction (HFpEF).

John Spertus, consultant cardiologist and director of cardiovascular education and outcomes research at Saint Luke's Hospital, Kansas City, Missouri, USA, presented an analysis of health status data collected during the EXPLORER-HCM randomised clinical trial of mavacamten in obstructive HCM.

Consultant cardiologist and director of heart failure and clinical echocardiography at San Francisco Veterans Affairs Medical Center, San Francisco, California, USA, John Teerlink, spoke about a secondary analysis of data from the GALACTIC-HF trial. His team evaluated the modifying effect of baseline ejection fraction (EF) on the treatment effect of omecamtiv mecarbil.

# Results from the EXPLORER-HCM Randomised Clinical Trial: Health Status Benefits of Mavacamten in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy

John Spertus

In the EXPLORER-HCM trial, mavacamten, a novel direct myosin inhibitor, met its primary endpoints of improving peak oxygen consumption ($pVO_2$), and New York Heart Association (NYHA) classification in obstructive HCM.[1] The trial's secondary endpoints assessed changes in post-exercise left ventricular outflow tract (LVOT) gradient, $pVO_2$, NYHA class, Kansas City Cardiomyopathy Questionnaire (KCCQ), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB).

Spertus presented the results of a secondary analysis of the results, which sought to better understand the treatment's impact on health status.

Explaining the background, he said that HCM was a primary myocardial disorder of unexplained left ventricular hypertrophy, often caused by pathogenic variants in sarcomeric genes. Current treatment guidelines focus on improving symptoms and function with β-blockers, verapamil, and disopyramide; more invasive options are reserved for those with refractory symptoms. Mavacamten works by targeting the underlying pathophysiology of HCM and reducing the number of excessive myosin–actin cross-bridges in the sarcomere.

During the EXPLORER-HCM trial,[1] 251 patients were randomised to either escalating doses of mavacamten (2.5, 5.0, 10.0, or 15.0 mg per day), or to placebo for 30 weeks. They were reassessed 8 weeks after end of treatment (Week 38 end-of-study). Ninety-two per cent of the patients were on HCM monotherapy with β-blockers or calcium channel blockers. Just four people in the treatment group and 16 in the placebo group were not on any background treatment. To provide a more complete understanding of the benefit from the patients' perspective, Spertus went on, quality of life was assessed prior to randomisation, at the 30-week end-of-treatment point and again at Week 38 end-of-study.

Researchers used the 23-item, disease-specific KCCQ, which explicitly asks patients about their symptoms, physical function, social function, and quality of life. KCCQ overall summary scores (KCCQ-OS) range from zero to 100, with higher scores indicating fewer symptoms, better function, and higher quality of life.

As patients with HCM may not necessarily consider themselves to have HF, Spertus said they took part in cognitive debriefing interviews, during which the study team confirmed the relevance and understandability of KCCQ.

Changes from baseline KCCQ-OS were plotted, using the means and standard errors, over each assessment. The primary analysis focussed on the differences between the treatment and placebo groups at 30 weeks. A responder analysis was also performed to inform the observed mean differences.

Thresholds for responder analysis were defined as:

- ≤-5 points: worsened
- -5 to <5 points: unchanged
- 5 to <10 points: small improvement
- 10 to <20 points: moderate to large improvement
- ≥20 points: large to very large improvement.

## Results

"The baseline demographics show great comparability between the treatment and placebo groups, with mean KCCQ-OS scores of 66-plus suggesting a moderately significantly impacted population of patients," said Spertus.

The primary results demonstrated a "very early separation" between the mavacamten-treated patients and the placebo-treated patients. This was observed as soon as 6 weeks and maintained at 30 weeks. At the end of 30 weeks, there was a 9.1-point greater change in KCCQ-OS among mavacamten-treated patients than placebo-treated patients (Figure 1).

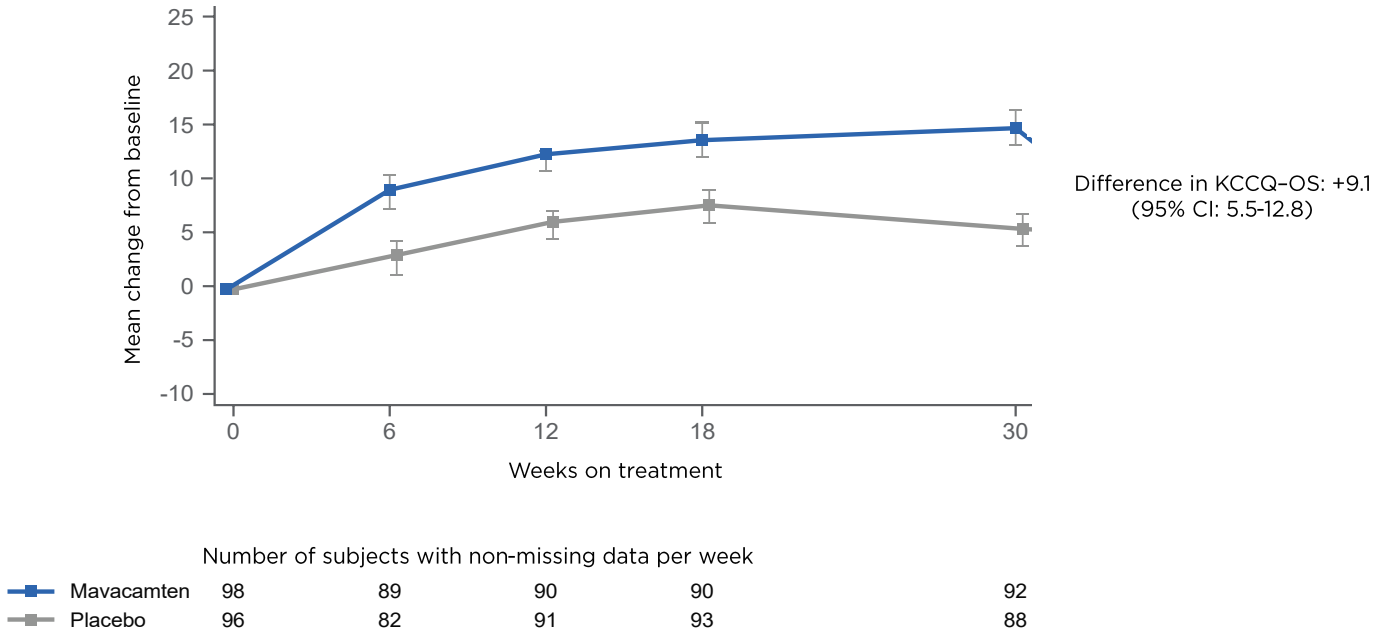


**Figure 1: Mean change in KCCQ-OS.**

CI: confidence interval; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary Score.

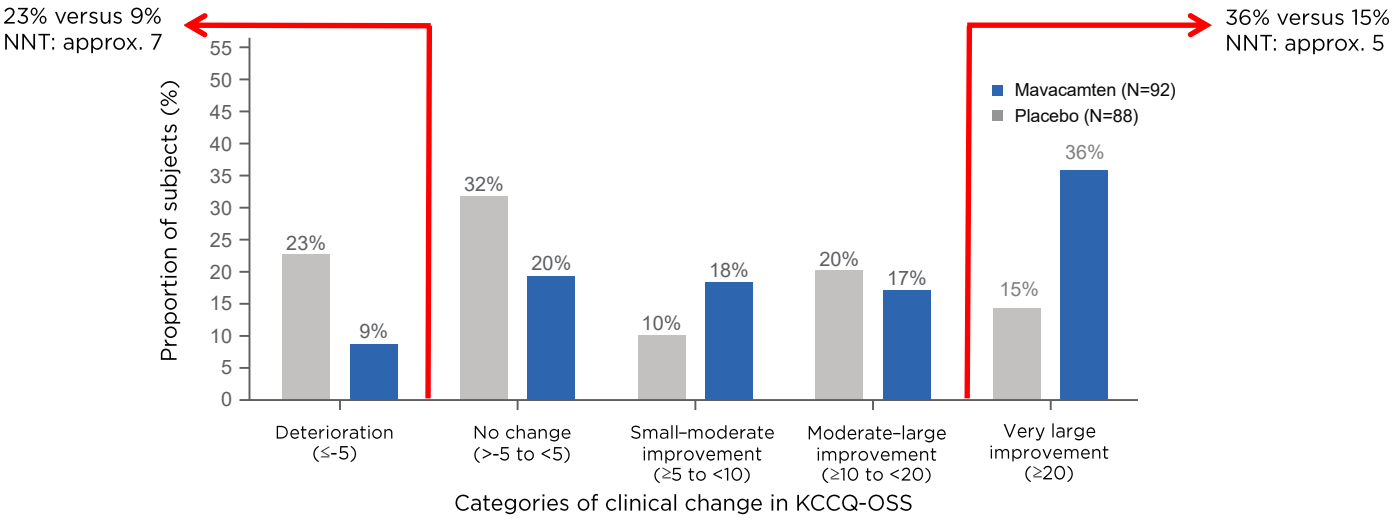


**Figure 2: Percentage of participants who changed by clinically important amounts at 30 weeks.**

Approx.: approximately; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; NNT: number needed to treat.

"That was highly statistically and clinically significant," said Spertus. The team also looked at what happened after the drug was stopped at Week 30. "What we found was when patients came off of treatment, this benefit immediately dissipated. The health status of the mavacamten-treated patients returned to baseline and was no different than the placebo-treated patients," said Spertus.

The responder analysis looked at the proportion of patients who got much better and those who got worse. Spertus said: "There was a much larger proportion of placebo patients who got worse over 30 weeks, 23% versus 9% as compared with mavacamten. Most impressively, when you look at the patients who derived a very large improvement from treatment, 36% of the mavacamten-treated patients got substantially

better, compared to only 15% of the placebo patients. That 21% absolute difference results in a number-needed-to-treat of only about a five, which is a very large benefit in the health status of patients treated with mavacamten." (Figure 2).

Highlighting the limitations of the study, Spertus said this was a short-term trial, so much research is needed before clinicians can be sure of the long-term impact of mavacamten treatment on health status. In addition, there were some missing data; however, the team conducted extensive analyses, and found no observable biases.

## Conclusions

Summing up, Spertus said mavacamten was associated with substantial health status improvements in patients with symptomatic obstructive HCM, and that clinicians would only need to treat five people to achieve one improvement of >20 points as measured by KCCQ-OS. "These benefits were observed early after initiating treatment, and they regressed when treatment was stopped."

# Secondary Analysis from GALACTIC-HF: Impact of Ejection Fraction on the Therapeutic Effect of Omecamtiv Mecarbil in Patients with Heart Failure and Reduced Ejection Fraction

John Teerlink

The Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial achieved its primary endpoint of reducing the risk of cardiovascular death in patients with HF and reduced EF or HF with preserved ejection fraction (HFpEF).[2]

"But given its mechanism of increasing cardiac function, and based on prespecified subgroup analyses, we assessed the modifying effect of the baseline EF on the beneficial treatment effect of omecamtiv mecarbil," said Teerlink.

## GALACTIC-HF

GALACTIC-HF enrolled patients with symptomatic chronic HF with EF of ≤35%. A total of 8,256 patients were randomised to either omecamtiv mecarbil or placebo, in addition to their usual HF therapy.[2] Teerlink described it as "one of the broadest ranges of patients enrolled in a HFpEF trial to date."

"It was a positive trial, significantly reducing the primary composite endpoint of time to first HF event or cardiovascular death by 8%," said Teerlink. "For the first time, these results confirm the hypothesis that selectively increasing cardiac function with something such as omecamtiv mecarbil could actually improve clinical outcomes in patients with HFpEF."

"Within the data, those with more severe HF appeared to have a greater benefit," he went on.

## Secondary Analysis

Teerlink and his team carried out a secondary analysis to investigate the modifying effect of EF on the beneficial treatment effect of omecamtiv mecarbil. While all GALACTIC-HF patients had an EF of ≤35% at baseline, >70% had an EF of ≤30%. Those in the highest quartile (Q4) had an EF of ≥33%.

Patients in the lowest quartile (Q1) had an EF of ≤22%. As well as a lower prevalence of multiple cardiovascular conditions, more nonischaemic cardiomyopathy, and lower BMI, these patients also had greater use of angiotensin receptor neprilysin inhibitors (ARNi), digoxin, ivabradine, and device therapy.

"The primary composite endpoint was the time to first HF event or cardiovascular death," he explained. "Despite excellent baseline HF therapies, 20–50% of the patients in the placebo group had an endpoint event within one year, with the rate markedly increasing with decreasing EF [...] Those in the omecamtiv mecarbil group also had an increasing event rate with decreasing EF, ranging from approximately 22% to 32%."

In the omecamtiv mecarbil group, there was a progressive beneficial reduction in the absolute event rate with decreasing EF. Treatment also decreased the relative risk of

the primary endpoint and had a greater relative treatment effect in patients with lower EF.

With respect to other variables and events of interest, Teerlink said there was no significant difference in systolic blood pressure, serum potassium, or creatinine between the two groups. In addition, serious adverse events and adjudicated arrhythmic and ischaemic event rates were also similar.

## Conclusions

In conclusion, Teerlink said that the drug appeared safe, and that fewer than 12 patients would need to be treated to prevent one HF event or cardiovascular death. "Thus, omecamtiv mecarbil represents a novel therapy that holds the promise of improving clinical outcomes in patients with severely reduced EF; the very patients who were the most challenging for us to treat," he said.


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# Relating Ventilatory Support and Drug Treatment Strategies to the Fundamental Pathophysiology in COVID-19 Illness

EDITOR'S PICK

The Editor's Pick for this issue is the excellent review by Lewis et al., which discusses the current pathophysiologic and radiologic findings related to the different coronavirus disease (COVID-19) stages, as well as mechanisms behind alveolar epithelial damage caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). An improved understanding of the nature of this damage is paramount for better informing targeted pharmacotherapies and ventilatory support.

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## Abstract

This article relates the current pathophysiologic and radiologic findings to the fundamental idea of acute lung epithelial infection, alveolar inflammation causing leak into the interstitial space, and subsequent secondary or concurrent endothelial infection and dysfunction. Understanding the mechanisms and timings of alveolar damage can better inform the types of ventilatory support required and timing of targeted pharmacotherapies.

## INTRODUCTION

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2);[1] as of September 2020, there were >33 million cases and almost 1 million deaths worldwide.[2] An unknown number of people are asymptomatic carriers of SARS-CoV-2 but symptoms in the early phase of viral replication include fatigue, anosmia, fever, sore throat, and cough. Around 85–95% of people make an uncomplicated recovery within 10 days; however, some individuals develop worsening cough, dyspnoea, and persistent (higher) fever, some of

whom require hospital admission with hypoxia and interstitial pneumonia.[3] This more severe illness is from viral infection within the lung tissue and the associated immune dysfunction, with loss of regulation of the inflammatory cascade leading to further lung damage, worsening hypoxia, and other organ dysfunction.

## FUNDAMENTAL PATHOPHYSIOLOGY

Two possible inflammation mechanisms (not mutually exclusive) can result in fluid accumulation in the lung alveoli: 1) direct viral and immune-mediated damage to the epithelium, affecting alveolar movement and reducing pulmonary fluid clearance; 2) a secondary or parallel injury to the endothelium or its basement membrane that results in capillaritis with further leak of fluid from the plasma into the interstitial space and thereon into the air spaces.

## IMPACT OF EPITHELIAL DAMAGE

SARS-CoV-2 targets and damages pulmonary epithelium,[4] particularly ciliated airway epithelial cells and Type 2 pneumocytes through the abundant angiotensin-converting enzyme 2 receptors in the lung. The virus relies on cell membrane serine protease TMPRSS2 cleaving and subsequently activating S-proteins and furine protease activity.[5] Hydrostatic and osmotic forces determine fluid movement from the vascular space to the interstitium through the extracellular matrix and the endothelial glycocalyx layer. Once the normally tight alveolar epithelial barrier is breached, alveolar oedema ensues. The epithelium also performs an important function in reabsorption of fluid through the asymmetric distribution of sodium channels and pumps throughout the alveoli and small airways. Sodium from the alveolar fluid passively enters the apical part of epithelial cells via the sodium channel and is pumped out of the cell via a sodium–potassium pump on the basal membrane. This shift of sodium causes an osmotic gradient leading to movement of water out of the alveoli, avoiding or resolving oedema in the alveolar air space (Figure 1).[6] Inflammatory damage that increases permeability of the epithelial barrier or a reduction in the number of epithelial cells, channels, and/or pumps would therefore impair an important clearance mechanism that helps avoid or resolve pulmonary oedema. Hypoxia itself is extremely proinflammatory and can further exacerbate tissue damage through cytokine release in a self-perpetuating and rapidly escalating autoimmune cycle of harm. Hypoxia further attenuates the basal pumps' highly energy-dependent sodium-potassium pump clearance mechanism.

## POTENTIAL VENTILATION OR VENTILATOR DAMAGE TO THE PULMONARY ENDOTHELIUM OR EPITHELIUM

Normal breathing at tidal volume can further stretch damaged and friable epithelium or endothelium and increase the permeability further. Excessive movements of damaged alveolar units through mechanical stress or sheer stress exacerbate extravasation of fluid, worsening hypoxia. In this regard, the authors propose that ventilatory support strategies should allow enough alveolar capillary oxygenation with a minimal degree of alveolar movement. Reducing physical movement of a leaky epithelium would reduce leak, attenuate further hypoxia, and buy more time for the body to clear the virus or for the antivirals to take effect, and for timely, targeted immunosuppression to reduce bystander cellular damage.

## EVIDENCE FROM PULMONARY IMAGING

CT chest scans report ground-glass opacities, often together with areas of consolidation and lung interlobular septal thickening, predominantly in subpleural and middle/lower lung fields.[7-10] Plain chest radiographs show multiple patchy shadows,[7,8,11] and ultrasounds report B-lines ranging "across a continuum from mild alveolar interstitial pattern, severe bilateral infiltration pattern to lung consolidation".[12]

Serial CT scans show early subpleural bilateral patchy focal infiltrates, which coalesce into large confluent patchy areas, becoming geographically connected in a 'crazy-paving' pattern and ultimately progressing to diffuse lung consolidation.[13,14] These sequential images represent progressive areas of alveolar epithelial damage, consistent with a spreading infection and local associated immune reaction.

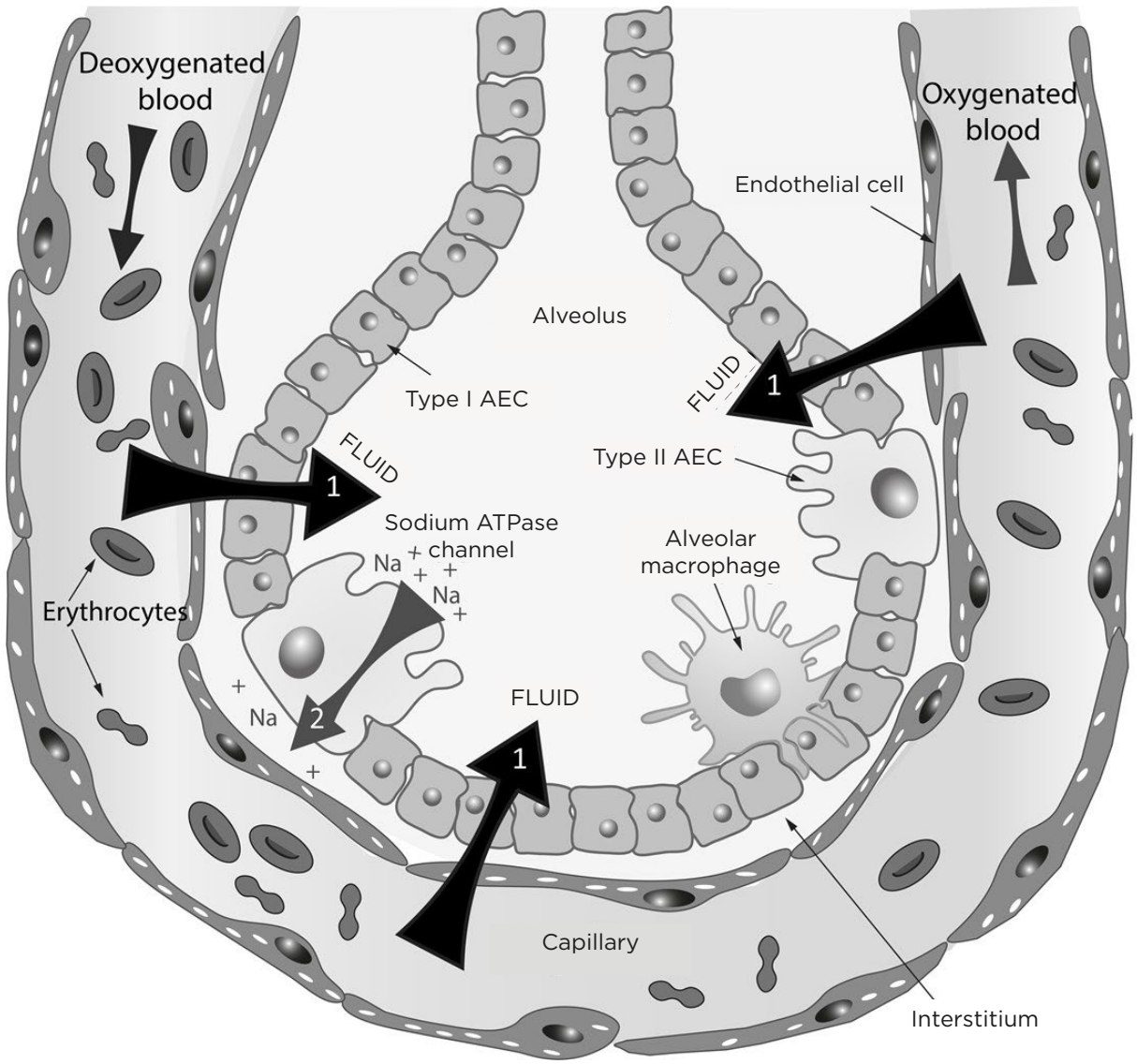


**Figure 1: Fluid movements across the alveolar–capillary barrier (black and grey arrows).**

AEC: alveolar epithelial cells; Na: sodium.

This patchy distribution supports an aerogenous route of pulmonary infection.[15] CT scans usually correlate with clinical severity,[7] but unlike traditional models of acute respiratory distress syndrome (ARDS) there can be severe radiological changes in relatively well and even asymptomatic people. Conversely, some symptomatic patients may present with a normal CT, especially in the early phase.[16]

Imaging in acute COVID-19 is entirely consistent with patchy progressive infection and distal alveolar inflammatory leak.[12] Pleural effusions are rare in COVID-19 because the leak into the third space is not due to hydrostatic back-pressure, but due to small multifocal areas of patchy alveolar epithelial and endothelial damage.[7,9]

## EVIDENCE FROM GROSS LUNG PATHOLOGY

Gross thoracic changes include uneven mottled red to blue-red colour, increased lung weight, oedema, severe congestion, pleuritis, consolidation thrombi, and often secondary bacterial infection.[17,18]

## EVIDENCE FROM LUNG HISTOPATHOLOGY

Antemortem histopathological changes were seen coincidentally in samples of lung tissue taken for other reasons. Findings included alveolar

oedema, fibrinous exudate, inspissated protein, haemorrhage, mononuclear inflammation, and multinucleated giant cell formation.[18,19] Two patients developed severe COVID-19, and one of these patients died.[20]

Postmortem histopathological changes included desquamation of the alveolar epithelium, reactive Type 2 pneumocyte hyperplasia, intra-alveolar exudates with organising fibrin, hyaline membrane formation, haemorrhage, excess lymphocytes, neutrophils, alveolar megakaryocytes, thrombosis of small and midsized pulmonary arteries, and some interstitial fibrosis.[14,21-23] From the autopsies of 21 individuals who died as a result of COVID-19, the primary cause of death was reported as respiratory failure, with exudative diffuse alveolar damage, and with severe capillary congestion and microthrombi in alveolar capillaries. Pulmonary embolism (n=4), alveolar haemorrhage (n=3), vasculitis (n=1), and superimposed bronchopneumonia (n=10) were also reported.[18]

The inflammation is predominantly lymphocytic with large atypical pneumocytes,[11] probably caused by viral cytopathic changes.[11,18,24] Macrophages and monocytes are increased in alveolar spaces, and virus particles or antigens are detected in the epithelial cells, Type 1 and 2 pneumocytes, and macrophages by electron microscopy, immunohistochemistry, and *in situ* hybridisation.[21]

The primary damage occurs mainly to the alveolar epithelial cells. Initially, some research proposed that the lack of direct damage to endothelial cells may partly explain why other organs (heart: 7–9%; kidney: 3–15%) are less affected than the lungs.[25-28] However, COVID-19 clearly incorporates other organ dysfunction and much more so than in other coronaviruses (severe acute respiratory syndrome and Middle East respiratory syndrome) and influenza.[29]

Endothelial cell viral infection, inflammatory cell infiltration, apoptosis of endothelial and mononuclear cells with widespread thrombosis,[30] microangiopathy, marked increase in fibrinous microthrombi, and both intussusceptive and conventional sprouting angiogenesis[31] have been reported. In one systematic pulmonary dissection study, all patients exhibited thrombosis of small or midsized pulmonary arteries.[22] Here, the authors postulate that direct infection of endothelial cells does occur and their close proximity to the epithelium in the lung is why the lung is affected most by local vascular dysregulation,[22,30,32] leading to further hypoxia without loss of lung compliance in the early phase.

## EVIDENCE FROM PATHOPHYSIOLOGY

### Intubated Patients

Standard ARDS Berlin criteria require an onset within 7 days of a clinical insult or respiratory symptoms;[33] however, in COVID-19, respiratory failure occurs typically 10–15 days after onset of symptoms.[25-28] Early cohorts had worse outcomes with over-inflation[34,35] and higher levels of barotrauma compared to ventilated patients with standard ARDS.[35] Current COVID-19 ventilator guidelines consistently recommend lower pressures, probably to reduce alveolar stretch.[36,37]

Unlike most people with ARDS, many patients with COVID-19 receiving ventilation (especially early on) have compliant lungs despite profound oxygenation failure.[38,39] Some studies have defined separate phenotypes in COVID-19 pneumonitis according to lung compliance,[40] but whether these are truly distinct or sequential stages of the same disease is in debate. Relatively high compliance is associated with high shunt fractions (50%), rarely seen in other forms of ARDS.[40] Again, this supports the idea that disrupted vasoregulation is an important contributor to poor oxygenation, at least in the early stages of COVID-19 lung injury. A major problem is the failure of the normal hypoxia-induced pulmonary vasoconstriction,[41] which depends on good endothelial function, leading to hyperperfusion of 'gasless tissue'. CT scans report areas of dilated vessels in parts of the lung that are unlikely to be well ventilated.[10,41] The improvement of oxygenation with positive end-expiratory pressure and prone positioning may be due to haemodynamic adjustment through local fluid shifts and better alveolar recruitment.[39]

The origin of the 'preserved' compliance is unknown; while it is probably beneficial for ventilation, it may have other detrimental effects. The lung possesses a highly efficient

mechanism to minimise interstitial fluid volume. The pulmonary capillary basement membrane normally has low permeability to water due to the macromolecular organisation of heparan sulfate proteoglycans. Furthermore, any increase in extravascular fluid is rapidly cleared because of the high elastance (poor compliance) of the extracellular matrix consisting of a second group of matrix chondroitin sulfate proteoglycans. Hypoxia causes fragmentation of both sets of proteoglycans, resulting in decreased elastance (increased compliance) and leading to more alveolar movement and potential oedema.[42] Applying high levels of positive end-expiratory pressure may accentuate underlying alveolar and microvascular injury and contribute to a worse outcome.[43]

The authors suggest that the respiratory distress seen in COVID-19 starts with a primary epithelial failure, followed by a secondary or concurrent endothelial vascular dysfunction. Therefore, ventilation should be guided by daily changes in radiology and estimates of capillary wedge pressure and lung water. Cardiac dysfunction from viral-induced myocarditis and/or hypoxaemia, worsening any pre-existing cardiac conditions, may also complicate vascular filling. Various fluid balance strategies have been tried in typical ARDS, based on estimated pulmonary capillary wedge pressure and extravascular lung water, but the unusual pulmonary haemodynamics seen in COVID-19 are a further complicating factor in the cardiac–pulmonary-specific interactions in intubated patients.

The wide variations in mortality of intubated patients with COVID-19[26,38,39] could be due to fixed ventilatory strategies and basing pressure or target volumes on traditional ARDS models. The authors argue that the traditional (Berlin) definitions of ARDS do not align with COVID-19 respiratory failure in terms of diagnosis or, more importantly, ventilator management of lower pressures and daily changes according to variable haemodynamics and hypoxaemia. Extracorporeal membrane oxygenation (ECMO) is increasingly used for adult patients with potentially reversible respiratory failure refractory to conventional management. ECMO beds have been increased worldwide in response to the pandemic and some countries have issued guidelines to assist in identifying eligible patients and management.[44] However, most clinicians in the ECMO service agree that the current evidence base does not allow strict criteria to determine optimal benefit and therefore encourage early referral. In reality, the experience (of the authors) has been that decisions are often made according to ECMO availability.

## Awake Patients

Hypoxic patients with COVID-19 are commonly seen taking rapid and shallow breaths.[45] Increased pulmonary interstitial pressure or volume activates pulmonary afferent C-fibre receptors, which are known to initiate a reflex that includes rapid shallow breathing and dyspnoea.[46] These receptors are stimulated by increases in pulmonary interstitial pressure or volume (as occurs in pulmonary oedema). The combination of hypoxia, hypocapnia, tachypnoea and pulmonary oedema as seen in altitude sickness,[47] traumatic 'blast lung',[48] and chemical lung injury[49] are explained by the increased minute ventilation in response to the hypoxia; there is a disproportionate elimination of $CO_2$ because its exchange is not impaired by pulmonary oedema as much as oxygen.

Awake patients with COVID-19 tolerate extreme hypoxia surprisingly well. Many patients converse freely despite peripheral oxygen saturations of 80–92% but have respiratory rates of 30–38 breaths per minute, suggesting that rapid, shallow breathing is a natural response. Deeper inspiration causes dyspnoea and often back or chest pain in individuals with radiological COVID-19 pneumonitis (personal observation from Lewis KE).

However, if patients experience worsening hypoxia and start taking strong, spontaneous inspiratory efforts, this can physically stretch an already damaged alveolar epithelium and increase tissue stresses (akin to patient self-inflicted lung injury).[50] Coexistent endothelial dysfunction with ventilation/perfusion mismatch leads to rapidly worsening hypoxaemia, more inflammation, more leak, and more hypoxia.

However, one notable difference is that dyspnoea is much less pronounced in COVID-19. Fifteen percent of patients with mild-case COVID-19 had shortness of breath, and only 38% of severe cases in China[27] and 17% of hospitalised

cases in New York, USA, with tachypnoea[51] complained of breathlessness. Whether this is of any significance in terms of respiratory control mechanisms remains to be seen.

Patients experiencing mild COVID-19 pneumonitis often have rapid, shallow breathing at rest, with normal arterial oxygen saturation. Frequently in these patients, mild exercise precipitates peripheral oxygen desaturation, consistent with an initial small reduction in pulmonary capillary gas transfer, which is sufficient to activate the pulmonary afferent C-fibre receptors and alter the breathing pattern.[46] In normal lungs at rest, however, because the blood becomes fully saturated with oxygen by the time it has travelled approximately one-third the length of the pulmonary capillary, there is sufficient reserve to allow nearly complete saturation when the patient is at rest.[52] However, with mild exercise the increased cardiac output reduces pulmonary blood transit time, so that pulmonary gas transfer now becomes diffusion-limited with consequent arterial desaturation. During recovery and rehabilitation, patients still profoundly desaturate, suggesting that it takes some time for the pulmonary capillary diffusion barriers to completely resolve.

## SUPPORTING EVIDENCE FROM CONTINUOUS POSITIVE AIRWAY PRESSURE

Despite early experience with invasive ventilation, many healthcare professionals are moving towards noninvasive ventilation strategies for hypoxic COVID-19.[53] Mild-to-moderate oxygenation failure in COVID-19 responds to high-flow nasal oxygen (HFNO) systems or continuous positive airway pressure (CPAP).[3] These treatments allow the patient to eat, drink, communicate, and self-position. By reducing the work of breathing and inspiratory effort, it can reduce mechanical sheer stress, ventilation-induced lung injury, tracheostomy, ventilation-associated pneumonia, and difficulty in weaning. CPAP may delay or avoid the need for mechanical ventilation in patients with COVID-19.[27,53-55] When intensive treatment unit resources are scarce, inappropriate use of invasive ventilation may stop access to life-saving treatment to those that need it. CPAP is part of the UK recommendations for the management of COVID-19.[41,56] It is effective in the treatment of chemical lung injury with pulmonary oedema, reduced gas transfer, and high shunt fraction.[57]

These pathophysiological mechanisms explain how a ventilatory support strategy using CPAP and HFNO maintains both a physical pressure gradient and a partial-pressure gradient to allow continuous oxygen diffusion down the airways and across gently splinted-open alveoli that do not need to move much. This also allows rapid, small breaths to minimise movement of damaged epithelial and endothelial interfaces and supports fatigued muscles. Combining CPAP with HFNO allows maximum diffusion at the alveolar–capillary interface with minimum alveolar movement (Figure 2).

## ADDITIONAL IMPORTANT TREATMENTS

Adequate fluid replacement is important as patients are prone to dehydration through increased insensible losses (fever, tachypnoea, occasionally diarrhoea) and reduced oral intake (nausea, CPAP masks).

Prone positioning can help oxygenation in some patients (while awake, on CPAP and ventilators). Presumably, prone positioning helps recruit more or different alveoli and therefore aligns with the hypothesis of localised inflammation and alveolar leak, rather than alveolar oedema from heart failure or increased hydrostatic pressure, which often worsen when lying supine or prone.

Management of coexistent medical conditions, especially diabetes, cardiac dysfunction, pulmonary emboli, and superadded bacterial or fungal lung infections, is also crucial. Worsening symptoms (including new confusion), worsening hypoxia, higher ventilatory pressure support, new raised temperature, rising inflammatory markers (neutrophils and C-reactive protein), raised procalcitonin, and especially focal consolidation and fluid or cavities on chest X-rays or CT scans, should alert clinicians to coincidental/secondary infections. Bacterial and fungal infections are reported in at least 10–30% of postmortem lung specimens of people who died of COVID-19.[18,21-23]

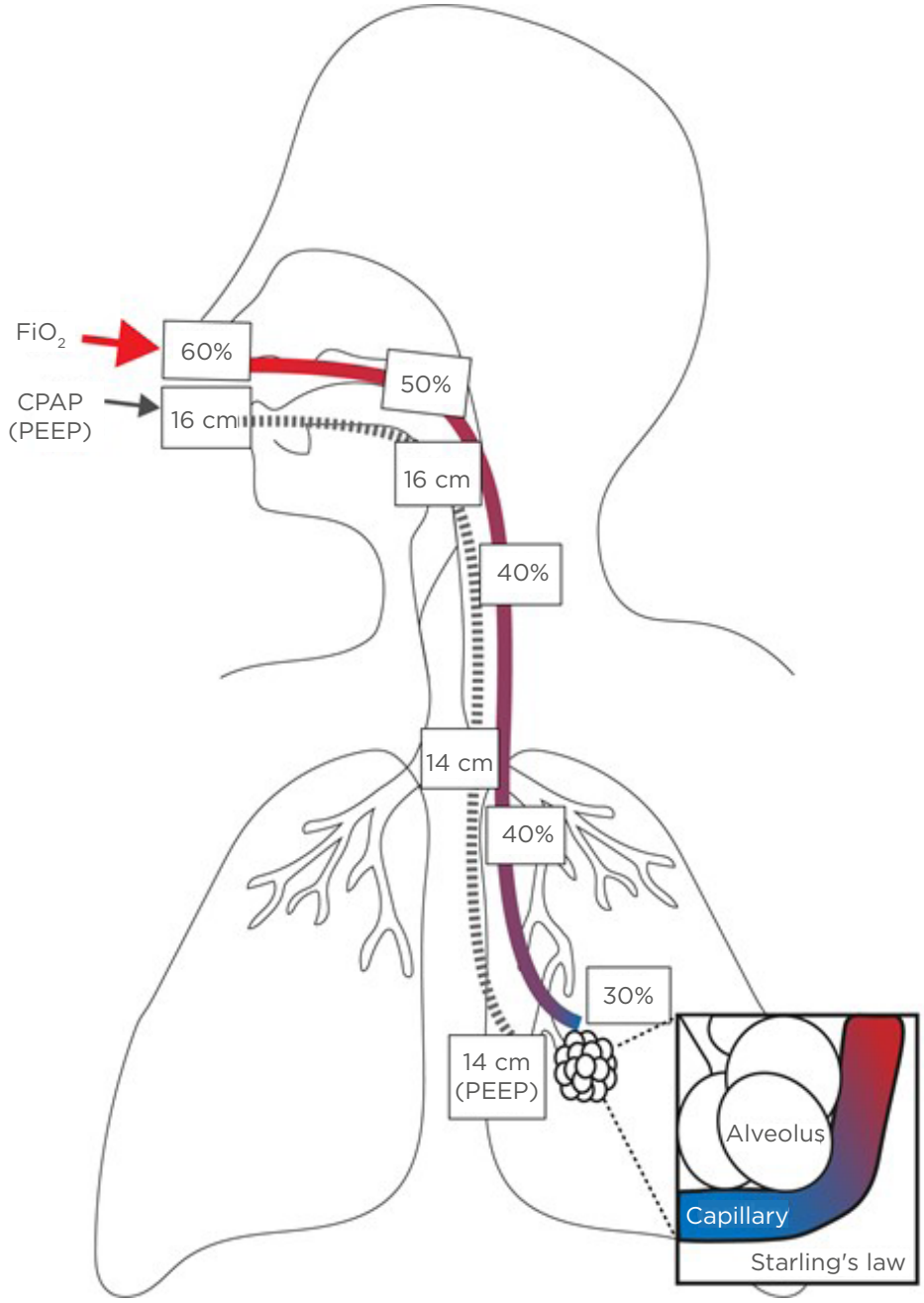


**Figure 2: Combined benefits of airway pressure and oxygen.**

CPAP: continuous positive airway pressure; $FiO_2$: fraction of inspired oxygen; PEEP: positive end-expiratory pressure.

## SUPPORTING EVIDENCE FROM DRUG TREATMENTS

A detailed review of all current pharmacological treatments is beyond the scope of this article. However, the predominant success so far of immunosuppressant and immunomodulatory drugs fits with the idea of reducing primary inflammatory epithelial/endothelial damage. The UK multicentre RECOVERY trial showed dexamethasone reduced deaths in ventilated patients (rate ratio: 0.65; 95% confidence interval [CI]: 0.48–0.88; p=0.0003) and deaths in patients receiving oxygen (rate ratio: 0.80; 95% CI: 0.67–0.96; p=0.0021). There was no benefit among those patients not requiring respiratory support (rate ratio: 1.22; 95% CI: 0.86–1.75; p=0.14)[58] presumably because there was no bystander immune-related damage at this point.

A meta-analysis showed that systemic steroids improve mortality in critically ill patients with COVID-19, likely due to cytokine storms and because steroids reduce bystander immune-related alveolar damage.[59]

Pathogenic T cells and inflammatory monocytes incite cytokine storms with large amounts of IL-6; therefore, monoclonal antibodies that target the IL-6 pathways may potentially curb these inflammatory storms. Tocilizumab, a monoclonal antibody against IL-6, appears to reduce mortality by approximately 24% and duration of organ support by around 1 week,

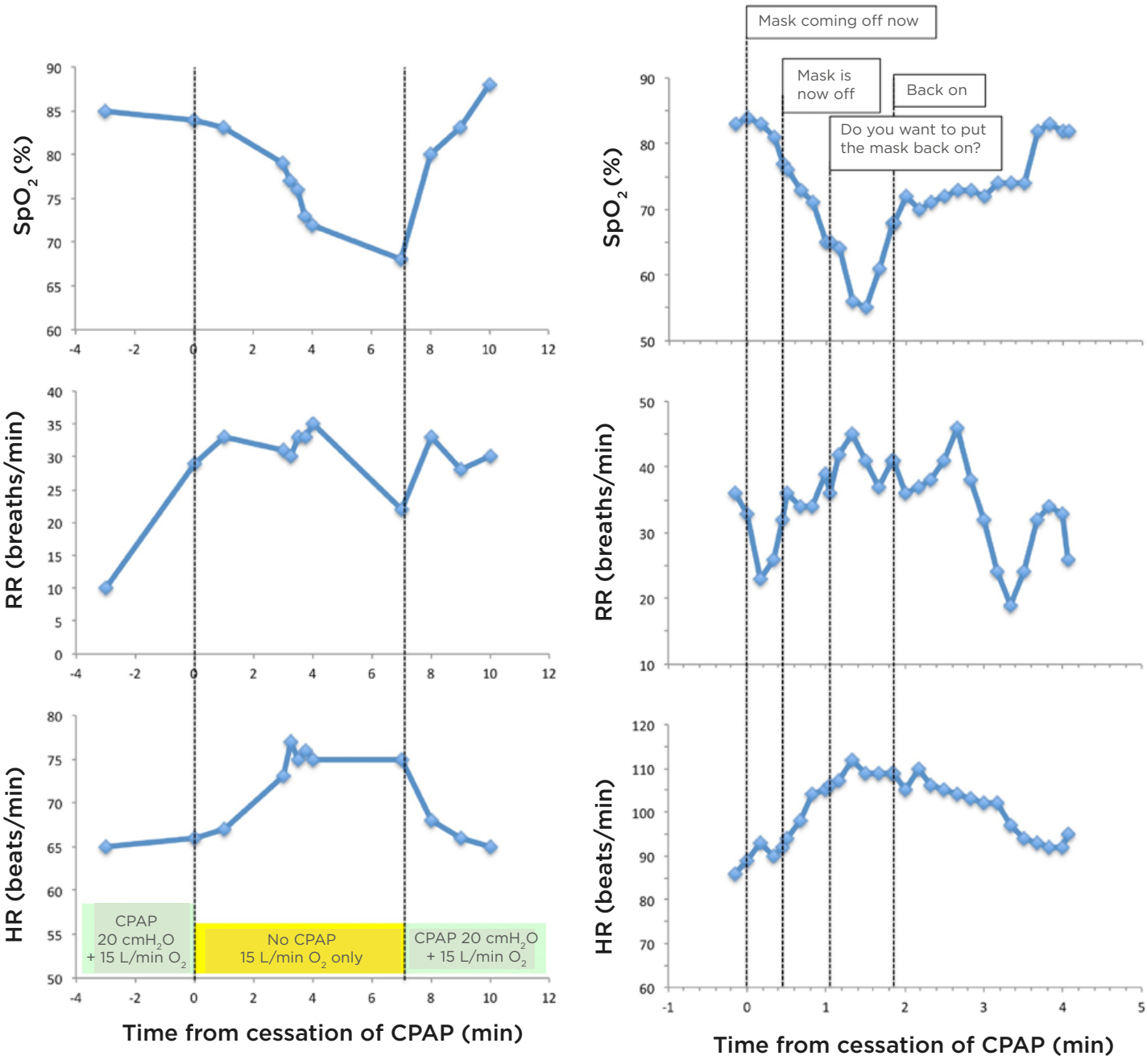


**Figure 3: Changes in arterial oxygen saturation (skeletal muscle oxygen saturation, pulse oximetry), RR, and HR, on replacement of CPAP with high-flow oxygen during clinical care (to allow eating and drinking), and subsequent reintroduction of CPAP.**

Comments on traces for Patient 3 were taken from audio recording coincident with cardiorespiratory monitoring.
CPAP: continuous positive airway pressure; HR: heart rate; RR: respiratory rate; $SpO_2$: arterial oxygen saturation.

in patients in intensive care units who need ventilatory support and have already received steroids (number needed to treat: 12).[60] Tocilizumab may not prove to be so effective in patients less critically ill and who only require oxygen.[61]

Other inflammatory and immunomodulatory drugs blocking endothelial activation and injury[62] or boosting pulmonary epithelial cell clearance of alveolar oedema (Figure 1) may also be useful.[63] Other therapies such as the antiviral drugs remdesivir, lopinavir, hydroxychloroquine, and interferon have not been shown to reduce mortality or initiation of ventilation.[64] Convalescent plasma and hyperimmune immunoglobulins are still being tested.

## CLINICAL CASES

The following clinical cases illustrate the pathophysiology and response to CPAP treatments.

A 59-year-old male was brought to hospital by ambulance. He was mildly overweight and had controlled hypertension. On arrival, his peripheral capillary oxygen saturation ($SpO_2$) was 67%, despite receiving oxygen 15 L/min via a nonrebreather mask. Arterial blood gases confirmed severe Type 1 respiratory failure (partial pressure of arterial oxygen: 5.3 kPa; partial pressure of $CO_2$: 4.3 kPa). His quick sepsis-related organ failure score was 1 (blood pressure: 130/60 mmHg; respiratory rate: 38 breaths/min; Glasgow coma score: 15) but despite hypoxia he was able to speak on the phone. $SpO_2$ improved to 80% and respiratory rate reduced to 24 breaths per minute with nasal CPAP (12 $cmH_2O$ pressure) with entrained oxygen at 15 L/min. Improvement in temperature and oxygenation occurred 5 hours after receiving 500 mg of intravenous methylprednisolone. CT confirmed bilateral extensive ground-glass shadowing and confluent infiltrates. A swab was positive for viral RNA of SARS-CoV-2. He was not intubated but continued CPAP with HFNO for 15 days with gradual weaning of both. He received six further doses of high-dose steroids (pre-RECOVERY results) and was discharged after 21 days.

Figure 3 displays transcripts from real-time videos of ward monitors from Patient 2 (53- year-old male, nonsmoker) and Patient 3 (58-year-old male, nonsmoker). Neither had any known lung or heart disease. Both patients were receiving 15 L/min of oxygen entrained through their CPAP machine (Trilogy Evo, Philips, Amsterdam, the Netherlands) set at 12–15 $cmH_2O$ pressure.

The graphs demonstrate abrupt falls in oxygen saturations and rises in pulse and respiratory rate, because the CPAP mask was removed to allow the patients to drink and take short breaks. Both were immediately switched to oxygen nasal cannulas at 15–20 L/min. Neither felt unduly breathless on removing their masks; however, Patient 3 reported feeling tired. Their $SpO_2$ and pulse improved within 20 seconds of reapplying the positive pressure, suggesting that combining CPAP with HFNO is beneficial in people where oxygen alone is not sufficiently effective.

## CONCLUSION

By relating underlying changes in epithelia, subsequent endothelial infection and dysfunction, and the pathophysiology of alveolar leak, the different disease stages and why certain combinations of treatments are most effective can begin to be understood. More importantly, the rapid increase in knowledge, based initially on observational physiology and now interventions, supports the concept of sequential epithelial and endothelial failure and explains differences in individuals over time and the variable response to treatments. Most importantly, understanding why and how pathophysiology changes so quickly allows for tailored interventions. Appropriate selection of early CPAP and timely immunosuppression should further improve outcomes. Certainly, one (treatment) size does not fit all, and one size will not fit one person over time.

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# Understanding the Impact of Non-Dystrophic Myotonia on Patients and Caregivers: Results from a Burden of Disease Healthcare Survey

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## Abstract

Non-dystrophic myotonias (NDM) manifest as delayed muscle relaxation leading to muscle stiffness. This may diminish or worsen with repeated contractions, depending on NDM subtype. These are divided into those affecting the chloride channel CLC-1, due to *CLCN1* gene mutations, and those affecting the sodium channel NaV1.4, due to *SCN4A* gene mutations. Depending on NDM subtype,

additional symptoms and clinical signs of NDM can include transient weakness, myalgia, cramps, fatigue, dysphagia, dysphonia, and muscle hypertrophy. Two surveys, carried out independently but collectively named IMPACT (Impact of non-dystrophic Myotonia on PAtients and Caregivers' qualiTy of life), were conducted to help elucidate how symptoms affect adults with NDM and those who care for adults or children with this condition. The patient survey not only confirmed NDM symptoms experienced by participants, but also highlighted how such symptoms affect a person's quality of life, mental health, and abilities including problems with work, study, childcare, and socialising. Additionally, details of the diagnostic pathway, treatment, and healthcare professionals involved in NDM were revealed. The caregiver survey found that almost one-third of those who cared for someone with NDM did so for at least 10 hours per week. It also highlighted how a carer's physical and mental health could be impacted by caregiving, potentially due to the finding that half of respondents felt that they had little or no support. Presented here are highlights of the IMPACT survey along with insights from five NDM clinical experts: Jordi Diaz-Manera, Channa Hewamadduma, Giovanni Meola, Federica Montagnese, and Sabrina Sacconi.

## INTRODUCTION

Non-dystrophic myotonias (NDM) manifest as delayed muscle relaxation (myotonia) leading to muscle stiffness that may diminish or worsen with repeated contractions, depending on NDM subtype.[1] Symptoms and clinical signs, also dependent on subtype, can include transient weakness, myalgia, cramps, fatigue, dysphagia, dysphonia, and muscle hypertrophy.[2,3]

NDM arise due to skeletal voltage-gated muscle channel defects caused by mutations in *CLCN1* or *SCN4A* genes.[3] *CLCN1* codes the chloride channel CLC-1, so related conditions are classified as 'chloride channelopathies'; *CLCN1* mutations lead to Thomsen myotonia congenita (TMC;[4] in an autosomal dominant pattern of inheritance) or to Becker myotonia congenita (BMC;[5] in an autosomal recessive pattern of inheritance). *SCN4A* mutations, also inherited in an autosomal dominant manner, code the NaV1.4 channel, with related conditions classified as 'sodium channelopathies'; these NDM include paramyotonia congenita (PMC),[6] sodium channel myotonia, and hyperkalaemic periodic paralysis.[3]

Considering that NDM is a rare condition, with point prevalence estimates ranging from 0.75 to 1.70 per 100,000 people,[7,8] it is unlikely that many healthcare professionals (HCPs) will diagnose a patient with NDM throughout their clinical career.

## IMPACT SURVEY

While descriptions of NDM symptoms and signs can be found easily,[3] the impact of NDM on daily life is not clearly established. A thorough analysis of this could lead to better understanding of NDM, clearer ideas about treatment, and design of scales to better monitor symptoms and treatment response.

With this in mind, between August and October 2020, market research in the form of an online survey among adults (≥18 years) with NDM and another among carers of people with NDM, collectively named IMPACT (Impact of non-dystrophic Myotonia on PAtients and Caregivers' qualiTy of life), was conducted by admedicum®, Cologne, Germany, partnering with Lupin Neurosciences, Zug, Switzerland. The surveys were reviewed by patient experts prior to finalisation and were available in English, Dutch, French, Italian, Spanish, and German. Methods and preliminary results were presented at the 16th International Congress on Neuromuscular Diseases, 2021.[9]

The surveys questioned respondents on diagnosis, prior and current symptoms, abilities affected, impact on quality of life (QoL), treatment, and support. Both surveys were anonymous and confidential, with declaration of NDM/carer status completed by the respondent only. No data were collected that would permit participant identification. Respondents were recruited via patient organisations, HCPs, and social media promoted through Google advertisments.

The patient survey was completed by 181 people from 27, mostly European, countries. The highest numbers of respondents were from the USA (n=39), Germany (n=35), the UK (n=32), the Netherlands (n=15), and Spain (n=10). Respondents were predominantly female (62%) and between 31 and 65 years of age (71%), with 24% aged 18–30 years.

The caregiver survey included self-identified, non-professional caregivers of both minors (29%) and adults (71%). A total of 59 caregivers from 12 countries responded, with most from the UK (n=18), Germany (n=14), USA (n=7), Spain (n=4), Italy (n=4), and Sweden (n=4). Most respondents were female (75%), the patient's parent (42%) or partner (39%), and aged between 18 and 45 years (65%) or 46 and 65 years (32%).

At a roundtable meeting, five clinical experts, Jordi Diaz-Manera, Channa Hewamadduma, Giovanni Meola, Federica Montagnese, and Sabrina Sacconi, discussed NDM symptoms, diagnosis, treatment, and outcomes from the IMPACT surveys. Their views on the IMPACT survey results and their clinical expertise is presented here.

## DIAGNOSIS

NDM diagnosis starts with ascertaining age of onset, family history, symptoms, and exacerbating factors, such as exercise, cold, menstruation, hunger, dietary potassium, psychological stress, and alcohol.[2,3] Key initial diagnostic steps are neurological examinations and 'bedside' tests of motor function, including observations of stiffness level when initiating movement and muscle relaxation after a contraction.[3]

As a consultation is only a 'spot check' of symptoms because of their unpredictability, Meola recommended patients fill out a symptom diary to help reveal exacerbating factors. This could be a paper diary or an interactive voice response system to record daily symptom severity and frequency.[10]

### Follow-Up Tests

Electromyography can reveal electrical myotonia as distinct Fournier patterns of self-sustained bursts of discharge after a short exercise test (sometimes with cooling).[11] While this can guide towards NDM categorisation, there are crossovers between the genetically distinct NDM subtypes.[11,12]

Genetic testing can help confirm NDM subtype[3] and with rapid sequencing the panel reported how wait-time for such confirmation should be only a few weeks. However, in the IMPACT survey, 19.3% of respondents had not had their diagnosis confirmed genetically.

### Diagnostic Delays

The IMPACT patient survey revealed that 65% of respondents experienced symptoms for more than 10 years prior to diagnosis; for others this was 5–10 (15%) or 2–5 (12%) years. According to Hewamadduma, one reason for diagnostic delay is that younger patients may be told that symptoms are just a normal part of growing up so "they put up with [them] until maybe [...] at a sports event when the pistol goes, they can't start running."

According to Hewamadduma, once a patient presents to their general practitioner (GP), there may be a delay as "the GP may not have encountered a patient with myotonia before." Diaz-Manera agreed, saying that "sometimes [symptoms are] tightness, for others it's weakness or many other complaints that are not specific, so...for GPs it's difficult to think about congenital myotonia as an option."

Further delay may occur if a patient is not sent for appropriate specialist care. For example, instead of being referred to a neuromuscular specialist, patients might see a rheumatologist, orthopaedist, or general neurologist. While the latter may seem suitable, Diaz-Manera highlighted how even general neurologists are sometimes not familiar with NDM. This is compounded, according to Montagnese, by NDM-specific examinations not being part of a common neurological training or education. Encouragingly, Sacconi reported that in her centre, educating general neurologists to include NDM-focused electromyography has led to increased referrals of patients with NDM to neuromuscular specialists.

## SYMPTOMS

Of the 181 IMPACT respondents, 28.2% had TMC, 25.4% had BMC, 17.1% had PMC, 4.4% had 'potassium-aggravating myotonia', and 2.2% had 'periodic paralysis'. The remainder reported undefined 'myotonia congenita' (11.0%), a general/other NDM diagnosis (5.0%), or were awaiting classification (6.6%).

NDM subtypes can be somewhat distinguished by age of onset and symptoms. Chloride channelopathies usually start at approximately 10 years of age.[3,13,14] Although some BMC and TMC symptoms are similar, such as myotonia decreasing after a 'warm-up' period, others, such as muscle pain and hypertrophy, transient weakness, and upper limb involvement, are more likely in BMC, while lower limbs are predominantly affected in TMC.

Sodium channelopathies tend to start at approximately 5 years of age with symptoms including facial stiffness (often involving eyelid myotonia), pain, and episodic weakness, all exacerbated in cold weather.[3] In PMC especially, myotonia may increase after repetitive contractions, while for some with sodium channel myotonia, potassium consumption can aggravate the symptoms.[3]

Although some symptoms may differ by diagnosis, nearly all IMPACT respondents reported experiencing many of the core symptoms, such as limb muscle stiffness and mobility problems, on a daily or continuous basis and experiencing other symptoms, such as muscle pain and headache, at least sometimes (Table 1). Other symptoms reported at least sometimes were gastrointestinal issues (69%), being unable to open their eyes after sneezing/blinking (64%), a risk of dropping drinks (62%), and their throat closing up when consuming cold drinks or food (45%).

**Table 1: Symptoms experienced, quality of life factors, and emotional, social, and psychological issues listed by respondents when asked "Within the last 6 months, how often have you experienced the following symptoms?" (N=181).**

| | Frequency (% of respondents reporting) | |
|---|---|---|
| | At least sometimes* | Often/continuously† |
| **Symptoms experienced** | | |
| Muscle stiffness/delayed muscle relaxation in legs | 99% | 81% |
| Muscle stiffness/delayed muscle relaxation in arms | 97% | 73% |
| Overall mobility problems | 93% | 68% |
| Muscle stiffness/delayed muscle relaxation in face | 93% | 45% |
| Persistent tiredness | 91% | 47% |
| Muscle pain, aching limbs, headache, or back pain | 90% | 43% |
| Problems taking off clothes | 84% | 39% |
| Problems speaking | 83% | 20% |
| Physical/muscle weakness following exercise | 82% | 27% |
| Difficulty swallowing/chewing | 80% | 16% |
| Inability to release grip when shaking hands | 78% | 33% |
| Poor sleep quality | 75% | 33% |
| Frequent falls related to stiffness | 74% | 10% |
| **Abilities affecting quality of life** | | |
| Exercising/playing sport | 86% | 30% |
| Working/studying | 73% | 24% |
| Socialising/communicating with others | 65% | 18% |
| Leaving the house/carrying out basic tasks | 54% | 17% |

**Table 1 continued.**

| | Frequency (% of respondents reporting) | |
|---|---|---|
| | At least sometimes* | Often/continuously† |
| Carrying out simple daily tasks independently in the home | 52% | 16% |
| Driving a car | 49% | 12% |
| Using public transport | 48% | 14% |
| Caring for a child | 38% | 11% |
| **Emotional, social, and psychological issues** | | |
| Lack of confidence in my abilities | 82% | 35% |
| Constant worry due to unpredictability | 80% | 40% |
| Worried about progression of the disease | 80% | 22% |
| Embarrassed due to inabilities caused by symptoms | 79% | 32% |
| Sad/depressed | 78% | 20% |
| Social anxiety | 78% | 32% |
| Nervous when moving in public | 77% | 27% |
| Felt stressed from constantly comparing my inabilities to others | 68% | 22% |
| Felt panicked/anxious | 60% | 17% |
| Lost interest in many things they used to enjoy | 65% | 22% |

*Sometimes: a few times per year or month; regularly: weekly; often: usually daily; continuously: several times per day.
†Often: usually daily; continuously: several times per day.

Participants could also provide free-text comments about how symptoms affected them:

- "Crossing the street is a big problem."
- "Eating bananas, even a small piece, makes my body stiff."
- "Inability to concentrate, especially in the mornings after I have exercised the day before."
- "Constant feeling of exhaustion. More than normal pain and longer restitution time needed after exercising."

## QUALITY OF LIFE

NDM symptoms can greatly impact a person's QoL; while 48% of IMPACT patient respondents rated their QoL as high (at least 7 on a scale from 0 to 10 [worst to best possible condition]), 27% rated it as low (0 to 4). Many also reported constant worry due to symptom unpredictability and about NDM progression (Table 1).

IMPACT results revealed that areas of life affected included exercising/playing sport, working/studying, and socialising/communicating with others (Table 1), as well as attending classes (36%) or finding a partner (19%). Understanding and addressing factors beyond physical symptoms could help improve the QoL for a person with NDM.[15] According to Hewamadduma, the symptoms that most interfere with QoL depend on a person's specific circumstances. For example, one patient, a cricket player, had few problems practising in the summer but struggled in the winter cold. For another, their problem was being unable to walk their child to school and for a third, throat spasms when eating anything cold were problematic. Montagnese also pointed out how pain is another fundamental complaint impairing QoL.

NDM effects also include major life events. Over half (52%) of 122 participants said that NDM had restricted their abilities, indicating that it had also negatively impacted their education or career at least once. Over a quarter felt unable to apply for

their preferred education/job (26%) and some had to terminate/lose a job (19%) or were not able to carry out their trained profession (17%).

Patients also expressed how NDM affected them psychologically (Table 1); for example, many felt sad or depressed, lacked confidence in their abilities, experienced social anxiety, or were embarrassed due to their limiting symptoms. Some revealed that having NDM made them feel isolated (57%), feel alone and helpless (49%), and cry a lot (49%). Over a third (39%) reported that they had been bullied due to NDM.

Respondents provided free-text comments regarding how NDM symptoms affected them psychologically/socially:

- "Fear of open spaces…severe anxiety, depression."
- "Discrimination when I go to the gym because I can't do everything…and can't tolerate bright lights and music."
- "Explaining to people who did not realise your limitations can be embarrassing."
- "Pain and fatigue have the most effect on mental state. Not having energy enough to do things others do…always having to make concessions."

To help with this aspect of NDM, Hewamadduma discussed how well-structured mental health support is essential and Meola emphasised the importance of encouraging patient networking groups, especially as there is no formal patient association for NDM.

## TREATMENT

The survey results found that only 23% of respondents were 'satisfied' or 'very satisfied' with current symptom management, with 33% 'moderately satisfied' and 34% 'not satisfied.' While 29% of respondents reported they were not receiving or had never received NDM-specific treatment, 59% were currently taking/had taken a medication for NDM, 33% received physiotherapy, and 16% received psychological support.

There is currently no disease-modifying treatment for NDM; however, the Class IB antiarrhythmic mexiletine has European Medicines Agency (EMA) approval as an orphan drug to treat myotonia symptoms in adults with NDM. Mexiletine reduces or abolishes muscle hyperexcitability for both chloride and sodium ion channelopathies by inducing a slower sodium influx, thus enhancing fast inactivation and faster repolarisation of sodium channels.[3] Randomised, placebo-controlled and n-of-1 clinical trials have shown mexiletine's effectiveness for reducing muscle stiffness, weakness, and pain and in improving QoL in NDM.[10,16] Treatment requires cardiac monitoring prior to or during mexiletine as it may exacerbate pre-existing arrhythmia.[17] Other off-label treatments include lamotrigine (the only other drug with a placebo-controlled trial in NDM[18]), carbamazepine, flecainide, acetazolamide, and ranolazine.[3]

Of the 89 IMPACT respondents currently taking a medication, mexiletine was the most commonly prescribed (n=45), followed by lamotrigine (n=10), flecainide (n=9), carbamazepine (n=9), acetazolamide (n=8), quinidine sulphate (n=7), calcium antagonists (n=6), phenytoin (n=2), baclofen (n=1), magnesium (n=1), or propafenone (n=1).

Figure 1 shows how often the most-experienced NDM symptoms occurred: the higher the number, the more often a symptom was experienced (1=never; 5=continuously). These were also reported as the symptoms patients most wanted improved by treatment. Also shown in Figure 1 is how much these symptoms were generally improved by drug treatment for those respondents receiving treatment: the higher the number, the more significant a symptom was improved (1=did not improve at all; 5=significant improvement).

Free-text responses regarding drug treatment included positive and negative comments. Comments were separated from other responses and aggregated so cannot be tied to a particular medication:

- "Through medication my QoL has increased. I can participate in more things or preserve longer."
- "In terms of my ability to communicate via eye contact, facial impressions, and gestures, my QoL has improved significantly."
- "It has definitely improved self-belief/self-confidence that I can walk across a parking lot without getting stiff halfway across."

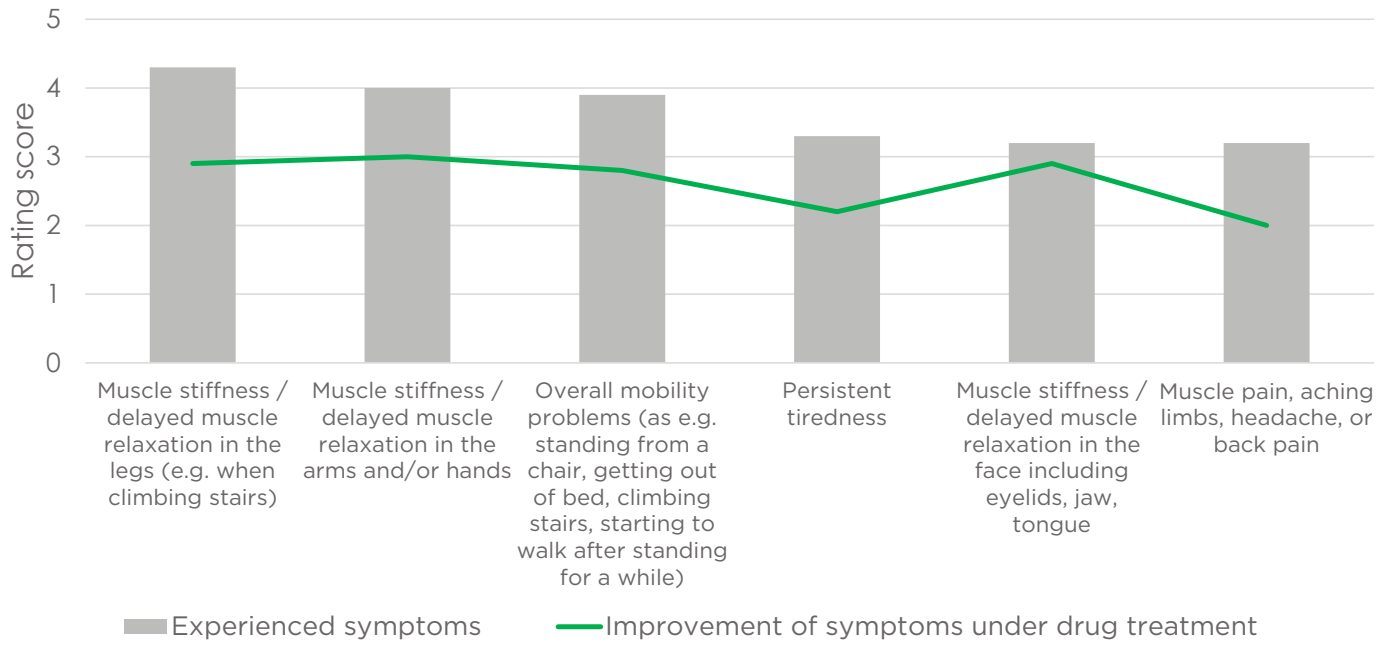


**Figure 1: Correlation between frequency of experienced symptoms and improvement of symptoms under drug treatment for the top six symptoms experienced.**

Mean for experienced symptoms: the higher the number, the more often a symptom was experienced (1=never; 5=continuously). Mean for improvement of symptoms: the higher the number, the more significantly a symptom was improved (1=did not improve at all; 5=significant improvement).

- "Overall speaking, minimal improvement of symptoms."
- "The symptoms of myotonia were hardly attenuated and other symptoms appeared that made my life quite complicated."

Patients with NDM also wanted treatment to address QoL factors and reported how their ability to carry out tasks, including leaving the house, driving, exercising, working/studying, socialising, and using public transport, was improved with drug treatment. Of note, however, the average improvement of QoL symptoms, which was also on the 1–5 scale above, was between 2–3, indicating an unmet need for more comprehensive treatment in NDM to enhance their QoL.

## Targeting Treatment to Symptoms Experienced

The panel agreed that NDM treatment must consider individual needs and have a holistic understanding of each patient's behaviours, habits, and comorbidities. According to Sacconi, it is essential that the HCP and patient set treatment goals together, with Montagnese highlighting that it is vital to discuss that while the drugs are effective for some symptoms, they do not cure NDM.

Although some symptoms can be alleviated with drug treatment, Hewamadduma emphasised how in his experience, pain and tiredness are the hardest to manage: "[Patients] need a lot of counselling and goal-setting conversations, particularly those who have increased tiredness; we teach them about pacing, so [the treatment is] not only the drug itself." "Pain is something that we are not paying enough attention to," confirmed Diaz-Manera. That most patients are seeking pain relief was, he suggested, reflected in the practitioners that patients with NDM reported visiting, including an acupuncturist, kinesiologist, osteopath, and herbalist.

## Addressing Those Not Receiving Drug Therapy

While drug treatment may help, 74 of the 181 NDM respondents reported they had not taken any NDM-directed medication. For some, this

was simply because they did not want to take any medication (27%) or felt their symptoms were managed well enough without (16%). Indeed, according to Montagnese: "if we think the patient is not hugely affected in everyday life, if they are concerned about the drug and we ourselves are not sure they need a medication, it's right not to prescribe anything."

However, a major reason these respondents gave for not trying a drug treatment was fear of side effects (49%). "Of course, any drug has some side effects," discussed Meola, "but we need to make the right titration and spend time to educate the patient." A diary could be useful here, according to Sacconi, "to understand the best doses for therapy, [so as] not to have an adverse event."

Also reported was that some did not receive treatment because their doctor did not prescribe any (28%), or they (8%) or their doctor (9%) were not aware of NDM treatment. Indeed, the big problem, confirmed Meola, is that some neurologists do not know enough about NDM myotonia treatments to feel confident prescribing them.

Patients also, according to Sacconi, enquire about an NDM-specific diet. While no targeted approach currently exists, Meola stressed the important role of the dietitian in his practice for helping some patients to understand how myotonia could be influenced by potassium.

## CAREGIVER SURVEY

While surveys of people who care for someone with other muscle-related disorders, such as muscular dystrophy, highlight how caregivers can experience considerable burden,[19] to date, no such survey has been carried out regarding NDM caregivers. This was addressed by the caregivers' component of the IMPACT survey.

The diagnosis of the caregiver's charge was predominantly myotonia congenita (BMC: 37%; TMC: 12%; non-defined: 20%), followed by PMC (8%), potassium-aggravating myotonia (5%), or periodic paralysis (2%). Many reported being a caregiver for >20 years (12%), 10–20 years (37%), or 5–10 years (31%). Almost half (45%) spent ≥5 hours per week caring, with 29% spending ≥10 hours per week. Looking at how NDM subtype may affect care, most who cared for someone with BMC reported spending <6 hours per week caregiving (19 of 22 caregivers), while four of seven caring for someone with TMC and four of five with PMC spent ≥10 hours per week providing care.

Though many caregiving respondents reported a high QoL (76% rated 7 or higher on a 0–10 point, worst to best scale), some thought that their mental health (42%) and their physical health (25%) had worsened due to caregiving, with burden linked to time spent on care. Many reported that they were 'happy' to care for the person with NDM and 'felt fulfilment' from their caregiving tasks 'frequently' (69% and 36%, respectively) or 'often' (19% and 22%, respectively); however, others reported that they were 'not at all' (2% and 10%) or 'only sometimes' (3% and 19%) happy to be a caregiver or felt fulfilment from their tasks, respectively.

Additionally, many caregivers reported that they were worried about NDM progression, were concerned about the future, and were worried about their own health at least sometimes (88%, 86%, and 61%, respectively) or permanently (19%, 14%, and 0%, respectively). Carers also, at least sometimes, reported being overwhelmed by caring (61%), having inadequate sleep (54%), feeling isolated (41%), or feeling nervous (59%).

Free-text comments from caregivers were also provided:

- "I have a complete sense of helplessness as I don't know how to ease their pain or discomfort, and a sadness that they have lost out in many ways by not being able to participate in sports, drama, and physical activities."
- "All the therapies, the appointments, it takes a massive toll on the whole family not just the carer or the person affected, siblings suffer too."
- "Child has times where she is severely affected…so needs a lot of time and help with massage, getting dressed, moving up and down stairs."

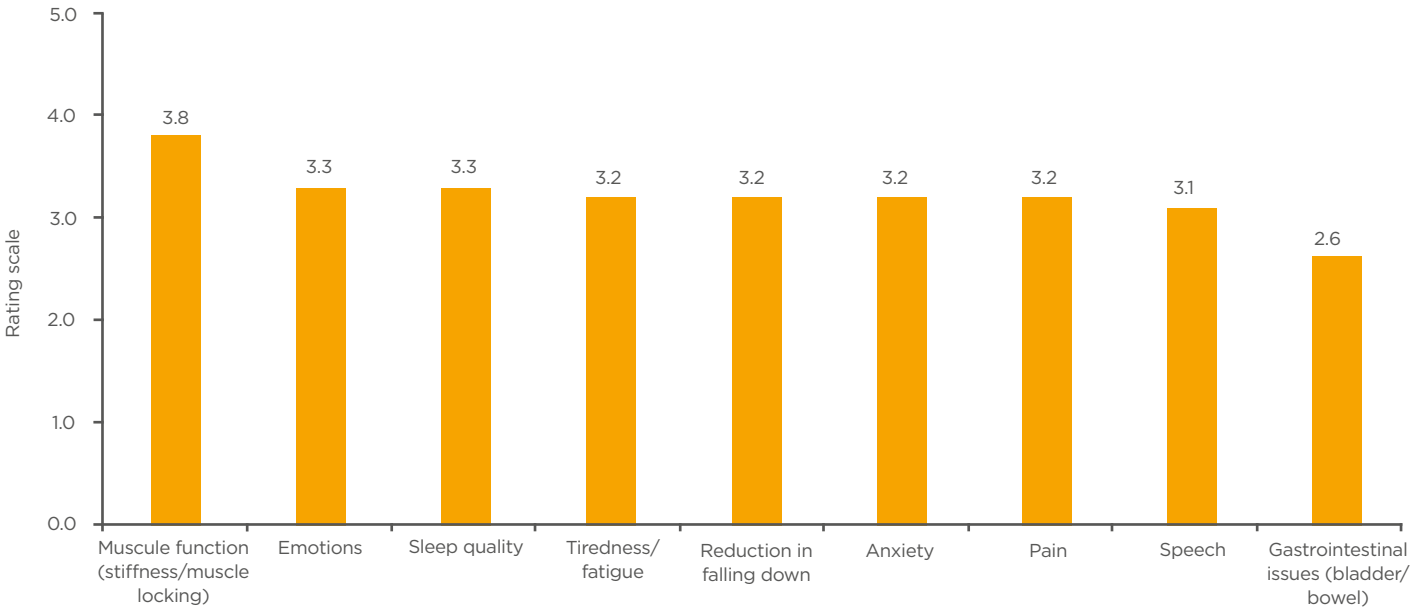


**Figure 2: Results from caregiver respondents when asked: "Please rate how an improvement of symptoms of the person you care for helps (or would help) to reduce the need for your care?" (multiple choices possible).**

Rating scale: 1=not helpful at all; 5=significant improvement of quality of life.

Support is something that carers need as well as patients. While 51% 'regularly', 'often', or 'permanently' 'felt strongly supported by others', 27% said this was only 'sometimes' and 22% said 'not at all'. Discussing one case, Hewamadduma recounted how the mother of a child with NDM needed help because of the psychological impact of her caregiver burden. "This was not a couple of hours, this was days of psychological input as she was suicidal at one point."

A further free-text comment was provided:

- "A big challenge/worry is very limited support from medical professionals who have little to no experience with NDM. As I don't know if/ how it will progress, it's worrying that they won't be able to provide me with treatment options and advice I could trust."

Caregiver burden was also reflected in the effect on carer's abilities. For example, approximately half reported that caregiving duties affected their ability to work, exercise, or pursue a hobby, meaning they had to, at least sometimes, change plans or combine caregiving with their own activities. A few reported that caregiving negatively impacted their education/career choices (six parents, one partner), that they had to reduce their working hours (five parents, one partner), or were no longer able to work (four parents, one partner).

Similar to those with NDM, caregivers reported that improvement of NDM symptoms of the person they cared for would, at least moderately, help reduce their caregiving burden (Figure 2).

## CONCLUSION

The IMPACT surveys for the first-time shed light on the extent of NDM burden for people living with the disease and those caring for them. Currently, there are no formal guidelines or consensus recommendations for NDM; the IMPACT survey results could help HCPs understand unmet needs in terms of diagnosis, treatment, and support for people with NDM and their caregivers.

The results suggest that wider access to genetic testing and earlier referral to specialised neuromuscular centres is needed, which can lead to more targeted therapy according to aetiology. There are needs to develop a globally standardised NDM symptom diary; to work with patients and HCPs to create easily accessible, reliable information about NDM

and treatment options; and to develop NDM patient-to-patient exchanges so that they can find support and educate each other.

Opening the survey to more people with NDM and their caregivers could add to the current findings but more data are also needed, including international co-operation and multicentric natural history studies.

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# Oxy-hydrogen Gas: The Rationale Behind Its Use as a Novel and Sustainable Treatment for COVID-19 and Other Respiratory Diseases

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## Abstract

Oxy-hydrogen gas (HHO) is a gaseous mixture of molecular hydrogen and molecular oxygen that is generated by the electrolysis of water and delivered in a 2:1 ratio (66% and 33%, respectively) through the use of noninvasive inhalation devices such as nasal cannulas or nebulisers. Although there is a paucity of scientific evidence supporting this new and emerging therapy, initial investigations indicate that HHO proffers cytoprotective qualities, typically by reducing oxidative stress and attenuating the inflammatory response. These aspects are particularly favourable when considering respiratory medicine because underlying inflammation is known to drive the pathological progress of numerous respiratory conditions, including asthma, chronic obstructive pulmonary disorder, and, pertinently, coronavirus disease (COVID-19). Direct delivery to the lung parenchyma is also likely to increase the effectiveness of this emerging medical therapy.

This narrative review aims to delineate how this particular combination of gases can affect cellular processes at the molecular level by focussing on the evolutionary requirement for both oxygen and hydrogen. Furthermore, the authors assess the current available data for the safety and efficacy of HHO in a clinical setting.

## INTRODUCTION

During both acute and chronic respiratory conditions, including severe coronavirus disease (COVID-19) infection, the primary physiological response is to synthesise distress proteins, which include cytokines, chemokines, and growth factors. This phenomenon is known as the cytokine storm, an event which can exacerbate the inflammatory response and rapidly increase the host's temperature in an attempt to eradicate pathogens.[1] Such proinflammatory mediators increase the production of reactive oxygen species (ROS) both within the mitochondrial electron transport chain (ETC) and within recruited immune cells, such as neutrophils and macrophages,[2] by the activation of enzymes such as NADPH oxidases.

Mitochondrial dysfunction often occurs when cellular demand for the high-energy phosphate molecule ATP increases during times of cellular stress.[3] This situation can lead to congestion in the flow of electrons within the ETC, resulting in excessive leakage of electrons. Rogue electrons are free to combine with molecular oxygen at will, forming free radicals including the superoxide anion, which dismutates to hydrogen peroxide. The reaction within the immune response cells, however, is entirely different. The mitochondrial content within these cells is considerably lower than in somatic cells, and therefore is not a significant source of ROS. Instead, granulocytes utilise NADPH oxidase enzymes to produce a highly oxidative respiratory burst containing a myriad of ROS,[4] which can include superoxide anions, hydrogen peroxide, hydroxyl radicals (in the presence of iron [Fe] ions), and hypochlorous acid, the latter through the action of myeloperoxidase. Mounting evidence suggests this is important when considering respiratory medicine because elevated levels of granulocytic cells are often observed in the bronchoalveolar lavage fluid of patients with astringent pulmonary diseases.[5,6]

ROS delivered by such granulocytes can be extremely damaging to biomolecules, including proteins, carbohydrates, lipids, and nucleotides, with intense and acute elevation of ROS consistent with acute and chronic inflammatory conditions.[7] Within the delicate parenchymal tissue, such assault often induces degeneration of epithelial cells, producing hyalin fluid. This process is known to contribute significantly to cellular hyperplasia and reduce the capacity for oxygen exchange. Raised ROS levels can also directly modify DNA nucleotides, affecting genetic transcription, and form adducts upon essential epigenetic and metabolic enzymes.[8-10] Such post-translational oxidative modifications to either nucleotides or proteinaceous enzymes often lead to aberrant enzymatic activity, causing fluctuation of essential energy-producing processes and affecting mitochondrial function, as well as influencing genetic transcription events.

HHO is an emerging medical gas, generated from the electrolysis of water. HHO inhalation is a noninvasive therapy done via a nasal cannula or mask, allowing the gas mixture to directly enter the respiratory system. In addition to oxygen delivery, HHO also provides molecular hydrogen ($H_2$) promptly to the lung parenchyma, the target tissue for respiratory infections. Research into $H_2$ therapy is rapidly gathering momentum and studies have identified $H_2$ as having antioxidant scavenging properties,[11,12] neutralising the deleterious hydroxyl radical and peroxynitrite ion. Presumably, other modes of action of $H_2$ are also important as the reaction kinetics between $H_2$ and these respective biomolecules remain in question.[13]

Despite research into the efficacy of HHO therapy still being in its infancy, HHO inhalation has been recommended by the Chinese government as a treatment of nosocomial COVID-19 symptomology.[14]

## AIMS

As the global COVID-19 pandemic threatens both individual health and healthcare systems globally, and, as yet, there is little effective treatment for this novel disease, this review aims to explain the HHO generation process and the molecular benefits of combining oxygen and hydrogen inhalation therapy for COVID-19 and other inflammatory respiratory conditions. The authors have collated data from empirical and evolutionary studies and in-human clinical trials and offer an explanation as to how the molecular mechanisms behind HHO therapy may be beneficial for respiratory health.

## DISCUSSION

### Generation, Delivery, and Safety Profile of Oxy-hydrogen

HHO is a stoichiometric mixture of $H_2$ (66%) and $O_2$ (33%) obtained through the electrolysis of water ($H_2O$). As pure water has a low electrical conductivity and requires an excess of energy to degrade the hydrogen bonds that hold the molecule together, it is therefore necessary to add a water-soluble electrocatalyst (e.g., $K^+$, $Mg^{2+}$, or $Na^+$) to reduce the activation threshold.[15] HHO gas can be easily generated by adding electrolyte compounds, such as sodium or potassium hydroxides, to distilled water and applying a low-voltage (9–13 V) direct current.[16] The $O_2$ and $H_2$ would collect in the gas phase as the water would become rapidly saturated and gases such

as $H_2$ have a relatively low solubility, as discussed by Hancock et al.[17]

In its simplest form, an electrolyser cell contains two electrodes, the positive cathode and a negative anode, separated by an ion exchange membrane. Passing an electrical current through the water decomposes $H_2O$ into $H^+$ and $OH^-$ ions. These electrophilically charged molecules are then attracted to the opposingly charged electrode where they liberate as gases. The chemical activity at the anode is $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$ whilst the activity at the cathode equates to $4H^+ + 4e^- \rightarrow 2H_2$. This method ensures separation utilising the $2H_2O \rightarrow 2H_2 + O_2$ reaction without returning it to the aqueous state.

As interest grows in this particular field of research, the industry surrounding the development of HHO products is also expanding. An HHO generator's standard specification incorporates an electrolysis unit, a filter, and an electronic control unit. The control unit can adjust the voltage directed to the positive and negative plates. Once formed, HHO can enter the respiratory system directly by inhalation through either a nasal cannula or an inhalation mask at a peak rate of 2–3 L/min. Gas inhalation through nasal cannulas is a safe and noninvasive delivery method widely used globally for pure oxygen inhalation within healthcare settings.

Although being comprised of the highly flammable gases hydrogen and oxygen, known to reduce the combustion threshold for most substances, the safety profile of HHO in a clinical setting can be regarded as favourable. This is partly because of the high autoignition threshold of HHO (570 °C),[18] the contained generation within a sealed system, and because HHO typically gets used as generated. Although the likelihood of explosion when using an HHO-generation device is negligible, consideration over the combustion potential in the presence of a naked flame is warranted; consequently, activities that involve use of a flame, including smoking, during treatment pose a significant risk of igniting HHO and causing potential harm.

## The Requirement for Oxygen

Rapid oxygenation of the Earth's atmosphere, known as the Great Oxygen Event, took place approximately 2 billion years ago during the early Paleoproterozoic era.[19] It is assumed that this event was triggered by photosynthesising cyanobacteria that produced oxygen as a waste product.[20] As the rapid rise in atmospheric $O_2$ presented a new challenge for cellular energetics, single-celled life forms were forced to adapt, including giving rise to multicellular life.

On a cellular level, $O_2$ is integral to the process of energy generation during aerobic respiration. The cardinal role here is for oxygen to act as a terminal electron acceptor during aerobic respiration.[21] Aerobic respiration is the biochemical process of ATP synthesis that occurs in the mitochondria. ATP synthesis is crucial to all cellular processes as it is a high-energy molecule responsible for donating energetic phosphate moieties during cellular metabolic pathways.

With eight electrons and eight protons in each molecule, $O_2$ is an electrophilically neutral diradical compound with two unpaired electrons in its outer shell. This neutrality allows the $O_2$ molecule to easily diffuse through cellular membranes and into the mitochondria where it is required to accept electrons donated by complex IV (cytochrome oxidase) in the ETC. If oxygen is not present to fulfil this role, aerobic respiration, responsible for producing a theoretical 38 ATP per glucose molecule, discontinues and the less efficient anaerobic respiratory pathway is initiated, generating a mere two ATP per glucose molecule.[22] Prolonged anaerobic activity is unsustainable in higher life forms as the energy produced is insufficient to sustain essential cellular functions. Granulocytic leukocyte cells, such as neutrophils, rely much more on glycolytic production of ATP because of a lack of mitochondrial presence in these specific cells,[23,24] a factor that allows these cells to continue functioning even during hypoxaemia where oxygen supply is notably reduced.

As described above, oxygen is fundamental to the survival of higher organisms and the average adult (63 kg) consumes approximately 200 mL of $O_2$ every minute at standard temperature and pressure,[25] equating to 400 L per day. Once $O_2$ is inhaled into the lungs from the atmosphere, it is exchanged for $CO_2$ as $O_2$ has a higher binding affinity with iron-containing haemoglobin in red blood cells. Healthy saturation of haemoglobin, a measurement of the percentage of haemoglobin molecules that carry $O_2$, is between 94% and 98%.[26] Saturation

levels below this threshold typically lead to hypoxaemia, which if unrectified can lead to hypoxia: a condition where tissues do not receive adequate amounts of $O_2$. This situation can progress to acute respiratory distress syndrome, multiple organ failure, and potentially death if left untreated.

Estimated oxygen usage in ambulances in the UK is reported to be in excess of 2 million times each year, equating to 34% of attended call-outs.[26,27] In these cases, $O_2$ therapy is not typically used to alleviate the symptoms of respiratory distress; instead, it is often used to prevent hypoxaemia in emergency conditions, including cardiac arrest and trauma. Oxygen is given to approximately one in five patients in nosocomial care.[27] In this setting, $O_2$ inhalation is prescribed for a vast array of life-threatening conditions, including those that cause a rapid onset of depressed breathing, such as anaphylaxis, COVID-19, opioid overdose, and pneumonia, as well as for persistent hypoxaemic complaints. By providing $O_2$ therapy, clinicians are able to increase oxygen tension in the alveoli during such events, thereby decreasing the respiratory system's workload by fulfilling the cellular demand for $O_2$.[28] Although widely used in emergency medicine, it is important to note that oxygen is also prescribed for the alleviation of chronic respiratory complaints such as asthma, chronic obstructive pulmonary disorder (COPD), cystic fibrosis, and paediatric respiratory disease.

## The Requirement for Molecular Hydrogen

As the most basic element within the universe, it may come as no surprise that molecular hydrogen has played a pivotal role in the evolutionary process. One intriguing theory, highlighted by Andersson and Kurland,[29] implies that the bacterial endosymbiont's original function was to provide the host cell with $H_2$.

The hydrogen hypothesis advocates for an archaeon host cell with a facultative anaerobic means of respiration, making use of $CO_2$ as a metabolic substrate and producing $H_2$ as a by-product, instead of being a committed aerobe with an immediate demand for ATP as suggested in the traditional endosymbiotic theory.[29] Indeed, the last universal common ancestor has been described as having all enzymes associated with both mitochondria responsible for ATP production in aerobic organisms, and hydrogenosomes that facilitate metabolic processes in anaerobic organisms. Their later divergence can be explained by environmental pressures that ultimately led to natural selection events.

Although this debate has yet to be rectified, it has raised some thought-provoking questions worthy of further exploration. When considering the hydrogen hypothesis, of particular appeal is the homologous protein expression profile noted within both mitochondria and hydrogenosomes.[30] Despite both organelles differing in their biochemical activities, they each have the capacity to encode for proteins of both complex I and II of the ETC. However, it is only the mitochondrial genome that can encode for elements of complexes III–IV and, importantly, ATP synthase. If, as suggested by Lewis et al.[31] and others,[32,33] hydrogenosomes and mitochondria are delineated from the same original symbiont, it is likely that mitochondria once had the ability to produce $H_2$.

Yet another link to the evolutionary requirement for $H_2$ in eukaryotes are the hydrogenase enzymes found in many species of photosynthesising organisms, including algae and higher plants. To exemplify, the single-celled green alga *Chlamydomonas reinhardtii* contains two Fe- hydrogenases (HYDA1 and HYDA2) that can receive electrons from ferredoxin during photosynthesis,[34] reducing proton accumulation with the reaction $2H^+ + 2e^- \rightarrow H_2$. Furthermore, homologous hydrogenase enzymes are also found in higher plants, including crops such as the legume Medicago truncatula[35] and *Oryza sativa* subsp. *japonica* (rice).[36] The frequency and diversity with which hydrogen-producing mechanisms have occurred along the phylogenic tree suggest an inherent biological requirement for $H_2$ across all domains of life.

In addition to the activity of hydrogen-producing enzymes and organelles in eukaryotic species, many anaerobic bacteria metabolise $H_2$. Typically, bacterial generation of hydrogen is linked with transition metal-containing (e.g., nickle/iron [NiFe] or iron/iron [FeFe]) hydrogenase enzymes that catalyse the reversible oxidation of hydrogen with the reaction $2H^+ + 2e^- \rightarrow 2H_2$.[37] Interestingly, hydrogen-producing bacteria are known to form symbiotic relationships with both plants and

animal species, which may also fulfil the cellular requirement for $H_2$ in multicellular organisms, including humans. Here, $H_2$ is largely obtained from the symbiotic relationship between $H_2$-producing intestinal microflora (e.g., *Escherichia coli* or *Clostridium butyricum*) and the host.[38]

Aside from the largely theoretical requirement for $H_2$ in the early development of life, contemporary research is beginning to reveal that molecular hydrogen can act as a natural antioxidant in at least two possible ways: 1) through the selective scavenging of nonsignalling ROS/reactive nitrogen species, such as the hydroxyl radical and peroxynitrite, thus potentially reducing oxidative damage to cellular membranes and the inactivation of metabolic enzymes through oxidative post-translational modifications.[39] It should be made clear that the reaction kinetics here are unfavourable[13] and more research is needed before these claims can be verified and universally accepted; and, 2) via increased activity of nuclear factor erythroid 2–related factor 2 (Nrf2), a transcription factor responsible for upregulating the activity of the antioxidant response element, a cis-acting enhancer sequence located within the promotor region of more than 200 genes known to transcribe and translate antioxidant enzymes (e.g., catalase and superoxide dismutase) and cytoprotective proteins and peptides (e.g., glutathione-S-transferase and cytochrome P450 isoenzymes).[40]

In addition to the antioxidant effect $H_2$ clearly provides, there is also a wealth of laboratory evidence that describes $H_2$ as having both immunomodulatory and antiapoptotic effects in various plant and animal species. This may be largely attributed to increased activity of Nrf2.[41] To illustrate, increased Nrf2 activity has been demonstrated to causally undermine expression profiles of NF-κB,[42] a transcription factor associated with innate immunity and one responsible for promoting genetic transcription of numerous proinflammatory molecules.[43] As well as downregulating the proinflammatory response at the genetic level, Nrf2 is known to respond to and upregulate expression of haem oxygenase, an enzyme that has a canonical function in reducing and preventing vascular inflammation.[44] Also of interest, particularly when considering the broader immune response, is the influence of NF-κB on adaptive immune cells. Here, NF-κB can provoke and stimulate inflammatory T-cell differentiation.[45,46] Therefore, enhancing or even prolonging the activity of Nrf2 within the nucleus is likely to have a significant effect on the inflammatory profile during disease.

## The Benefits of Oxy-hydrogen in Respiratory Medicine

Although, as previously stated, research into the benefits of HHO as a medical gas is at an early stage, the recent pandemic concerning the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has highlighted the need for emergency respiratory care that is effective in reducing parenchymal inflammation. This need becomes of particular relevance as inflammatory exudate is known to contribute to the impairment of the alveoli's oxygen-exchange capacity, further exacerbating hypoxaemic conditions during severe infection. In a recent study involving murine models of asthma conducted by Zhang et al.,[47] 1 hour of HHO inhalation per day was demonstrated to decrease airway resistance and reduce epithelial cell hyperplasia. Furthermore, significant reductions in the expression of proinflammatory mediators were identified, including chemokines (e.g., CXCL15), cytokines (e.g., TNF-α), and multiple interleukins (e.g., IL-4 and IL-6).[47] These findings may prove to be particularly relevant as tocilizumab, an IL-6 intervention therapy, is currently being used to treat COVID-19 as well as autoimmune and other severe inflammatory conditions.[48] However, the benefits of this treatment may be outweighed by the possible side effects, which include an increased occurrence of upper respiratory tract infections, hypertension, and gastrointestinal perforation.[49]

Despite the growing popularity of HHO as a potential medical therapeutic, there is, as yet, sparse evidence on the clinical safety of using HHO generators; however, initial in-human trials into the effects of HHO in patients with tracheal stenosis reported no adverse effects of treatment (n=35).[50] Additionally, trials into the effects of HHO supplementation during severe COVID-19 infection are ongoing in the Hubei province of the People's Republic of China,[51] with Chinese health officials recommending HHO therapy in the national treatment protocol for coronavirus-associated pneumonia.[14]

Additionally, during a 3-month, in-human trial assessing the safety and efficacy of HHO inhalation therapy, a curative effect was noticed from the second week until the end of the trial in patients (n=70) with severe COPD.[52] These findings are further supported by results from a 10-day, multi-centre, randomised, double-blind study that reported easement of COPD symptoms on observing days 1–7 (n=54).[53] Similar findings have also been reported in studies of chronic inflammatory respiratory diseases, including asthma, cystic fibrosis,[54] and COVID-19.[55] Here, increased oxygenation and the cellular protective effects of molecular hydrogen has been shown to recover poor blood saturation levels of $O_2$ and reduce the inflammatory response, thus preventing and rectifying hypoxaemia and reducing the likelihood of Type 1 respiratory failure.[57]

## Future Perspectives

Research into the biochemical properties of medical gases is beginning to reveal that, alongside $O_2$, $H_2$ may also be of evolutionary significance, perhaps by acting as part of the suite of gaseous signalling molecules. However, laboratory trials utilising human-derived cell cultures and animal models will be necessary if the molecular mechanisms that influence somatic responses are to be elucidated. *In silico* models of distribution patterns, reaction kinetics, and longevity will also be required if a full understanding of signalling behaviours is to be reached. Furthermore, as much of the clinical data available have yet to be substantiated, data obtained from patient trials will need to be hastened if HHO therapy is to be widely used as a treatment in general medicine.

## CONCLUSION

HHO treatments become of particular relevance when considering the increasing occurrence of highly contagious and novel viruses; therefore, there is an urgent need for sustainable and effective treatment protocols that can alleviate the most severe symptoms of such respiratory tract infections without the need for critical care.

Emerging clinical and preclinical[54,55] data suggest that HHO inhalation is both safe and efficacious in treating inflammatory-related pulmonary disorders. Interestingly, despite objective research into the efficacy of HHO therapy being relatively new, initial findings suggest inhalation of these gases in stoichiometric proportions can provide symptomatic relief from chronic and acute respiratory conditions, with asthma, COPD, and cystic fibrosis being examples. Therefore, it is conceivable that combining oxygen, a substance known to alleviate respiratory distress by increasing alveolar oxygen tension and improving $O_2$ saturation of haemoglobin, with hydrogen, an element that displays anti-inflammatory and antioxidant qualities, in analeptic doses reduces the significant burden on lung parenchyma during disease. In order to confirm the data generated by preliminary investigations into HHO inhalation, further clinical, preclinical, and laboratory analysis is necessary.


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# Prevalence of Scoliosis in Hypermobile Ehlers-Danlos Syndrome

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## Abstract

**Objective:** The main purpose of this study was to evaluate the prevalence, form, and severity of scoliosis in a population of adults meeting the 2017 criteria for hypermobile Ehlers-Danlos syndrome (hEDS). The second objective was to compare the prevalence of scoliosis versus other criteria at initial hEDS diagnosis.

**Methods:** A retrospective study looking at the frequency and severity of scoliosis in adults (N=28) meeting the 2017 diagnostic criteria for hEDS through analysis of a full spine EOS® X-ray (EOS imaging, Paris, France) performed at the initial diagnosis. Severity was defined by the Cobb angle.

**Results:** At the initial diagnosis, the mean age was 30.1 years (standard deviation [SD]: ±10.18 years). Twenty-nine percent (n=8/28) of patients fulfilling hEDS criteria presented with scoliosis. Thirty-two percent (n=9/28) of patients had scoliotic inflection and 39% (n=11/28) had no scoliosis. Scoliosis was mild-to-moderate with a mean Cobb angle of 13.6° (SD: ±3.5°). None of the patients had severe scoliosis requiring surgery. Compared to the 2017 diagnostic criteria, it is noteworthy that scoliosis prevalence in this present study population ranks at the level of the most frequent ones.

**Conclusion:** This study provides interesting information regarding frequency of scoliosis and scoliotic inflection in a group of patients with hEDS. Although the patients did not present with severe forms of scoliosis at initial diagnosis, the results highlight the importance of systematically looking for scoliosis in adult and young patients, in order to follow progression and ensure appropriate management.

## INTRODUCTION

Joint hypermobility is often asymptomatic.[1] It can sometimes progress to joint instability, causing sprains, dislocations, or pain suggestive of Ehlers-Danlos syndrome (EDS). Joint hypermobility can also be associated with other pathologies, such as neuromuscular diseases, Marfanoid syndromes, or skeletal dysplasia.[1] The diagnostic process for symptomatic joint hypermobility must be rigorous and structured to guide the diagnosis.

EDS are a heterogeneous group of inherited connective tissue disorders caused by different mutations in genes involved in the structure or biosynthesis of collagens and extracellular matrix proteins.[2] The collagens involved are Types I, III, V, and XII.[2] Some EDS are the result of abnormalities in the synthesis of glycosaminoglycans.[3] There are currently 14 types of EDS.[2,4] The phenotypic hallmarks include joint hypermobility, skin hyperextensibility, and tissue fragility. The prognosis and management of each type of EDS are different, requiring precise clinical diagnosis and genetic confirmation. EDS are rare diseases, with an estimated global frequency of one in 5,000.[5] Inheritance is most often autosomal dominant but with variable expression in the same family.[3] Hypermobile EDS (hEDS) is the most common type.[6] It mainly affects women.[7] Its diagnosis remains clinical, in the absence of clearly identified molecular bases. An interview on personal and family clinical history, followed by a rigorous clinical examination using a checklist of diagnosis criteria, confirms the diagnosis.[2] It is cautious and useful, especially with young patients and adolescents, to reassess the patient several times before confirming the diagnosis of hEDS.

Scoliosis is a structural deformity of the spine in the three dimensions of space. The diagnosis is confirmed when the Cobb angle is 10° or higher and axial rotation is recognised on the X-ray. It should not be confused with a scoliosis attitude, which originates outside the spine (such as in length inequality of the lower limbs or pelvic rotation) and is totally reducible when patients lie down. It normally does not progress to scoliosis.[8]

Twenty percent of scoliosis are not idiopathic and may be linked to an underlying disease with hypermobility; as a consequence, it was one of the clinical criteria discussed but not included during the establishment of the new 2017 criteria for hEDS.[9]

Limited data exist in the literature regarding the prevalence and severity of scoliosis in EDS and, in particular, in hEDS.[10-12] The main objective of this study was to assess the prevalence, form, and severity of scoliosis in hEDS through a retrospective study in a homogeneous population of adults fulfilling the 2017 criteria for hEDS. The second objective was to compare the prevalence of scoliosis relative to the prevalence of other clinical features at diagnosis.

## METHODS

### Patient Selection

This was a retrospective study based on the analysis of medical records of patients who visited the reference centre of rare diseases between 2017 and 2020. Twenty-eight patients were selected. Eligibility criteria included patients aged ≥18 years, fulfilling the 2017 criteria for hEDS, and who had a full spine X-ray at the time of diagnosis.[2,13] Pregnant patients and those without full spine X-ray available were not included in the study.

### Diagnostic Procedures for hEDS and Evaluation of Generalised Joint Hypermobility

Each patient had been clinically examined by an expert physician from the reference centre of rare diseases to confirm hEDS diagnosis. The 2017 diagnostic criteria were evaluated to confirm the diagnosis, following the checklist provided by the international EDS consortium.[13]

During the examination, patients underwent a generalised joint hypermobility measure using the Beighton score.[1,14,15] Each hypermobile joint scores one point, making it possible to define a total score out of 9. The positivity threshold must be adapted according to age.[16] Authors consider generalised joint hypermobility with a score of 5 out of 9 for men and women <50 years old, and 4 out of 9 in adults over >50 years old; in prepubertal children and adolescents, the threshold is 6 out of 9 (Box 1A). The interobserver reproducibility is rather good (kappa: 0.80).[17] Because joint laxity decreases with age in the

general population and in hypermobile patients, the Hakim and Grahame simplified questionnaire (five-part questionnaire) was also used to evaluate history of hypermobility.[1] Positive response to two or more questions between five items brings an additional point to the measured Beighton score (Box 1B). The Beighton score and the Hakim and Grahame simplified questionnaire are two criteria of the 2017 criteria for hEDS.

An objective of clinical examination was also to eliminate other connective tissue disorders (e.g., other types of EDS, Marfan syndrome, and Loeys-Dietz syndrome). Moreover, according to 2017 recommendations, all the patients underwent a cardiac ultrasound to evaluate both the mitral valve and aortic root.[2]

## Detection of Scoliosis Using Full Spine X-ray

During the measure of the Beighton score, the authors evaluated the ability for patients to put their hands flat on the floor with knees extended; this evaluation would unmask the presence of thoracic or lumbar scoliosis. After checking for pregnancy, patients with hEDS benefited from a complete spine radiographic examination using the EOS® method (EOS imaging, Paris, France). The EOS methodology uses a radiation dose 10-times lower than conventional radiology techniques, 1,000-times lower than that of a scanner, and optimises the follow-up and management of patients with osteoarticular pathologies of the spine and lower limbs (e.g., scoliosis and static disorders). The reconstructions in two- or three-dimensions, with lateral, frontal, and horizontal views, allow a very precise analysis of the deformities of the spine, from the head to the pelvis. This system is also of interest in terms of therapeutic monitoring.

**Box 1: Beighton score and five-part questionnaire for generalised joint hypermobility.**

A

| | |
|---|---|
| Dorsiflexion of the 5th metacarpophalangeal joint to >90° | 1 point for right, 1 point for left |
| Opposition of the thumb to the volar aspect of the forearm | 1 point for right, 1 point for left |
| Hyperextension of the elbows to >10° | 1 point for right, 1 point for left |
| Hyperextension of the knees to >10° | 1 point for right, 1 point for left |
| Ability to place hands flat on the floor with knees fully extended | 1 point |
| Total score | /9 |

B

| | | |
|---|---|---|
| Can you now or could you ever touch your hands flat on the floor without bending your knees? | Yes | No |
| Can you now or could you ever bend your thumb to touch your forearm? | Yes | No |
| As a child, did you amuse your friends by contort-ing your body into strange shapes or could you do the splits? | Yes | No |
| As a child or teenager, did your shoulder or knee-cap dislocate on more than one occasion? | Yes | No |
| Do you consider yourself 'double jointed'? | Yes | No |

**A)** Beighton score for generalised joint hypermobility measure. A positive Beighton score is ≥5/9 for adults; ≥4/9 for adults over the age of 50 years; and ≥6/9 points for children and adolescents. **B)** Five-part questionnaire for generalised joint hypermobility. A positive response to two or more questions brings one additional point to the Beighton score.

The EOS report included the measurement of sub-pelvic parameters (pelvic incidence, sacral slope, and pelvic version), the existence of disorders of the frontal or sagittal balance of the spine, the existence of a scoliotic inflection, scoliosis, its type (thoracic, thoracolumbar, or lumbar), and the Cobb angle measured for each curvature. Other spinal abnormalities such as spondylolisthesis, history of Scheuermann's disease, and vertebral abnormalities could also be detected. A classification of morphotypes defined by Roussouly in 2005 allows different types of sagittal profiles to be identified.[18] Of interest in this classification (which has only been validated in adults) is its ability to understand degenerative disorders of the spine. Morphotypes with low pelvic incidence (Type 1 and 2) will be more prone to degenerative pathologies of the disc and pain, while morphotypes with high pelvic incidence (Type 3 and 4) will be more at-risk of degenerative slips such as spondylolisthesis.

## Statistical Analysis

The characteristics of the population (e.g., sociodemographic) were described using means ± standard deviation (SD) for continuous variables, and frequency for qualitative variables.

## Ethical Considerations

Retrospective registry-based studies do not require ethics committee approval under French law. Patient data were extracted from the patient electronic record from the reference centre of rare diseases. Patient data were then collected in a database approved by the National Commission for Data Protection and Liberties (CNIL).

# RESULTS

## Patient Characteristics

Twenty-eight patients (27 female and one male) with a diagnosis of hEDS were selected and underwent a complete spine X-ray using EOS method and analysis (Table 1). The mean age at diagnosis was 30.10 (SD: ±10.18 years; range 19.00–50.00 years). The mean BMI was 25.19 (SD: ±4.88). Seventy-one percent (n=20/28) were employed at the time of diagnosis. Twenty-one percent (n=6/28) had at least one orthopedic surgery at the time of diagnosis and 7% (n=2/28) had three or more surgeries.

## Prevalence of the 2017 Criteria for hEDS in the Patient Population

This study evaluated retrospectively the prevalence of the 2017 diagnostic criteria, which made it possible to confirm the diagnosis of hEDS. Prevalence of these 2017 criteria in the patient population are detailed in Table 2. Generalised joint hypermobility was found in 100.0% of patients. The mean Beighton score was 6/9 (SD: ±2). Sixty-four percent of patients were able to place their hands completely flat on the floor with their knees extended; 7.1% had done so in the past. Other clinical signs were found: bilateral piezogenic papules of the heels (53.6% of patients); moderate skin hyperextensibility (46.4%); unusually soft and velvety skin (42.9%); large unexplained striae (39.3%); arachnodactyly (25.0%); and a bilateral thumb sign (Steinberg's sign) and bilateral wrist sign (Walker's sign) in 17.9% and 7.1% of patients, respectively. Furthermore, 39.3% of patients presented with swan-neck deformities of the fingers, 17.9% presented with dental crowding and/or a high or narrow palate, and 14.3% presented with atrophic scars in at least two places. One patient (3.5%) presented with aortic root dilation and two patients (7.1%) presented with mitral valve prolapse on their ultrasound. One patient (3.5%) had an arm-span-to-height ratio ≥1.05 and one patient (3.5%) presented with recurrent and multiple abdominal hernias. No patients had pelvic, rectal, or uterine prolapse in their history (Table 2). Family history was found in 50.0% of patients.

## Prevalence and Types of Scoliosis in the Patient Population

In this patient population, scoliosis was found in almost 29% (n=8/28). None of these patients had undergone spine surgery (Table 1). Among the 29% of patients with scoliosis, 12.5% (n=1/8) had a right thoracic form, 12.5% (n=1/8) had a left thoracic form, 50.0% (n=4/8) had a thoracolumbar form, and 25.0% (n=2/8) had a unique lumbar form. A mild form of scoliosis with Cobb angle ≤19° was found in 87.5% of patients (n=7/8), 12.5% (n=1/8) had a moderate form (Cobb angle <29°), and none had a severe form (Cobb angle >30°). The mean Cobb angle was 13.6° (SD: ±3.5°).

**Table 1: Patient characteristics, demographic and spinal features, and EOS parameters.**

| Age, sex | BMI | BS | Ability to put hands flat on the floor | PI | SS | PT | Roussouly type | Type of scoliosis | Cobb angle |
|---|---|---|---|---|---|---|---|---|---|
| Patients with scoliosis | | | | | | | | | |
| 28, F | 24.46 | 6 | No | 48 | 32 | 16 | 1 or 2 | Left lumbar L1–L4 | 12° |
| 25, F | 23.19 | 5 | Yes | 45 | 38 | 4 | 3 | Left thoracic T1–T6 | 10° |
| 49, F | 31.63 | 7 | Yes | 75 | 42 | 33 | 3 | Right lumbar | 10° |
| 25, F | 22.20 | 7 | Yes | 53 | 45 | 8 | 3 | Right thoracic | 13° |
| 21, F | 21.20 | 6 | No | NA | NA | NA | NA | Left thoracolumbar | 15° |
| 36, F | 32.47 | 6 | Yes | 89 | 37 | 52 | 3 | Thoracolumbar | 13° |
| 20, F | 19.71 | 5 | Yes | 49 | NA | NA | NA | Thoracic and lumbar | 15–16 and 22° |
| 26, F | 17.80 | 4 | Yes | 32 | 35 | 4 | 3 | Thoracolumbar | 14° |
| Patients with scoliotic inflection | | | | | | | | | |
| 27, F | 22.99 | 5 | Yes | 40 | 33 | 6 | 1 or 2 | Right thoracic, left lumbar | NA |
| 33, F | 31.25 | 6 | NA | 44 | 34 | 10 | 1 or 2 | Left thoracolumbar | NA |
| 27, F | 22.06 | 5.5 | Yes | 62 | 55 | 6 | 4 | Left cervicothoracic | NA |
| 19, F | 23.15 | 6.5 | Yes | 56 | 51 | 5 | 4 | Left thoracolumbar | NA |
| 26, F | 25.35 | 8 | Yes | 38 | 25 | 12 | 1 or 2 | NA | NA |
| 20, F | 35.56 | 8 | Yes | 43 | 35 | 9 | 3 | Left lumbar | NA |
| 24, F | 25.39 | 5 | Yes | 49 | 33 | 16 | 1 or 2 | Right lumbar | NA |
| 28, F | 19.23 | 7 | Yes | 76 | 53 | 23 | 4 | Left lumbar | NA |
| 47, F | 23.80 | 5.5 | Yes | 52 | 17 | 35 | 1 or 2 | NA | NA |
| Patients without spinal abnormalities | | | | | | | | | |
| 21, F | 24.51 | 8 | No | 27 | 28 | -1 | 1 or 2 | NA | NA |
| 41, F | 26.40 | 8 | Yes | 55 | 43 | 13 | 3 | NA | NA |
| 50, F | 26.26 | 4 | Yes | 51 | 41 | 11 | 3 | NA | NA |
| 26, M | 35.24 | 7 | No | 47 | 22 | 25 | 1 or 2 | NA | NA |
| 22, F | 30.49 | 5 | Yes | 63 | 61 | 2 | 4 | NA | NA |
| 48, F | 31.59 | 9 | Yes | 38 | 37 | 2 | 3 | NA | NA |
| 47, F | 26.31 | 5.5 | Yes | 62 | 37 | 26 | 4 | NA | NA |
| 25, F | 22.84 | 5 | Yes | 37 | 26 | 11 | 1 or 2 | NA | NA |
| 21, F | 19,95 | 8 | Yes | 48 | 27 | 21 | 3 | NA | NA |
| 42, F | 20,45 | 6 | Yes | 50 | 48 | 2 | 4 | NA | NA |
| 19, F | 19,88 | 6 | No | 36 | 30 | 6 | 1 or 2 | NA | NA |

BS: Beighton score; EOS: EOS® X-ray (EOS imaging, Paris, France); F: female; M: male; NA: not assessed; PI: pelvic incidence; PT: pelvic tilt; SS: sacral slope.

**Table 2: Prevalence of the 2017 diagnostic criteria for hypermobile Ehlers-Danlos syndrome and scoliosis in the patient population.**

| 2017 criteria for hypermobile Ehlers-Danlos syndrome | Frequency |
|---|---|
| Generalised joint hyperlaxity | 100.0% |
| Bilateral piezogenic papules of the heels | 54.0% |
| Positive family history | 50.0% |
| Moderate skin hyperextensibility | 46.0% |
| Unusually soft and velvety skin | 43.0% |
| Large unexplained striae | 39.0% |
| Swan-neck deformities of the fingers | 39.0% |
| Arachnodactyly | 25.0% |
| Bilateral thumb sign | 18.0% |
| Dental crowding and/or a high or narrow palate | 18.0% |
| Atrophic scars in at least two places | 14.0% |
| Mitral valve prolapse | 7.0% |
| Bilateral wrist sign | 7.0% |
| Aortic root dilation | 3.5% |
| Arm-span-to-height ratio ≥1.05 | 3.5% |
| Recurrent and multiple abdominal hernias | 3.5% |
| Pelvic, rectal, or uterine prolapse | 0.0% |
| **Frequency of spinal deformity and spine surgery** | |
| Scoliotic inflection | 32.0% |
| Scoliosis | 29.0% |
| Spine surgery | 0.0% |

In addition, 32.1% of the patients (n=9/28) presented with a simple scoliotic inflection and 39.3% (n=11/28) had neither scoliosis nor a scoliotic inflection (Table 1).

## DISCUSSION

In this study, the authors evaluated the frequency and severity of scoliosis in patients with hEDS. Limited data regarding scoliosis in hEDS are currently available in the literature. Results showed that 29% of the patients with hEDS presented with scoliosis at the initial diagnosis. Scoliosis was not retained among the diagnostic criteria for hEDS in the 2017 classification. This choice could be challenged in light of other subjective criteria retained in this classification, the prevalence of which are identical or even lower. The question remains for the potential relationship between scoliosis, hypermobility, and hEDS, which was not the objective of this study.

### Natural History of Scoliosis and the Impact of Joint Hypermobility

None of the patients had a severe form of scoliosis; most were benign. However, regarding natural history of scoliosis, it is critical to diagnose scoliosis early in order to ensure regular follow-up and appropriate management of hypermobile patients.

Idiopathic scoliosis is frequent, with an overall prevalence of 1–3% most often cited in the literature. [19] The female-to-male ratio ranges from 1.5:1 to 3:1 and increases substantially with increasing age.[20] The prevalence of generalised joint hypermobility among children and adolescents varies significantly (7–65%), depending on measurement method, sex, age, and ethnicity.[21] Several studies suggested that generalised joint hypermobility is more common in subjects with scoliosis compared to a control population of patients of the same sex and age. A 2011 study by Czaprowski et al.,[22] which observed 70 subjects with idiopathic scoliosis (59 girls and 11 boys), found generalised joint hypermobility in >50.8% of girls (n=30/59) and 54.5% of boys (n=6/11) compared with a control group of healthy subjects (21.0% of girls and 16.0% of boys); this difference was significant.[22] A second study by Czaprowski et al.[9] in 2014 confirmed these data in 155 girls aged 9–18 years with idiopathic scoliosis compared to a control group of 201 girls without scoliosis. It was revealed that 23.2% of girls with scoliosis were hypermobile compared to 13.4% in the control group (p=0.02).[9] However, joint hypermobility did not seem to influence the prognosis of scoliosis. In this study, there was no correlation between the presence of generalised joint hypermobility and the severity of scoliosis. There was no correlation between the measured Beighton score and the Cobb angle (p=0.93).[9]

A 2018 study carried out among 822 Turkish students (413 boys and 409 girls) with an average age of 12.2 years (SD: ±1.3 years) found hypermobility in 151 subjects, i.e., 18.6% of the study population (10.2% of girls and 8.4% of boys). Scoliosis was found in 5.2% of children (n=43/822), of which 23.2% (n=10/43) were hypermobile and 76.8% (n=33/43) were not. The presence of hypermobility was not associated with the presence of scoliosis.[23]

Interestingly, a study by Haller et al.,[24] performed in 570 women with idiopathic scoliosis, looked at whether the Beighton score was predictive of scoliosis surgery. Between the different elements of the Beighton score measure, only the inability to put hands flat on the floor was predictive of the progression of scoliosis to surgery. Generalised joint hypermobility did not influence the risk of surgery, while lack of hypermobility (a Beighton score of 0/9) increased the risk of surgery in scoliosis. The authors specified that women who could not put their hands flat on the floor had a 2.1-times greater chance of having surgery compared to those who could (p=0.001).[24] This single measure was useful and easy to perform for predicting the progression of idiopathic scoliosis. The hypermobility and flexibility of the spine could be, according to the authors, factors of better response to the brace, avoiding aggravation and need for surgery.

## Scoliosis and Ehlers-Danlos Syndrome

EDS is one of the possible diagnoses to consider in the presence of unusual or secondary appearance scoliosis. Ligament laxity, postural abnormalities, and muscle weakness found in EDS could be factors favouring this scoliosis.[23] There are limited data available in the literature regarding the frequency and severity of scoliosis in the different forms of EDS.[12] In kyphoscoliotic EDS, scoliosis is secondary to severe muscle hypotonia and ligament laxity.[11] It appears early in infancy and is part of the diagnostic criteria. Molecular biology can confirm the diagnosis. In these early forms, the progression of scoliosis is severe and surgical treatment is often necessary.

In 2000, Stanitski et al.[10] published a large series of patients affected by three different forms of EDS (hypermobile, classic, or vascular) in whom scoliosis was evaluated.[10] Thirty-three percent of patients had scoliosis (30% of hEDS, 33% of vascular EDS, and 36% of classic EDS). Scoliosis therefore seems slightly more frequent in classic EDS, a feature already found in a previous publication according to the authors. No patient presented with scoliosis requiring surgery (Cobb angle >50°). The curves were mild-to-moderate in 71% of cases with hEDS. No significant correlation was found between back pain and the existence of scoliosis.[10] Analysis of EOS spine X-ray of the patients confirmed the data available in the literature. Twenty-nine percent of patients with hEDS presented with mild-to-moderate scoliosis. No patient had a severe scoliosis. Interestingly, 32% of patients presented with a scoliotic inflection, not to be confused with scoliosis. This scoliotic inflection could be linked to an external phenomenon, such as inequality in length of the lower limbs or a tilting of the pelvis.

In adulthood, only 10% of cases of mild-to-moderate scoliosis have a risk of progression;[24] in theory, there is therefore very little risk of

progression of scoliosis in the population of patients with hEDS. Even if joint hypermobility seems to influence the development of scoliosis, it seems that its presence is reassuring regarding the possible progression of scoliosis.[24] It also seems to be the case in the hypermobile adult population of this study, where no severe scoliosis requiring surgery was found. During clinical examination, the ability to put hands flat on the floor, assessed by the Beighton score and found in 75% (n=6/8) of patients with a scoliosis, also seems to be an interesting element in the prediction of the favourable evolution of scoliosis. Further studies are needed to determine if the ability to put hands flat on the floor could be a factor explaining the good response to brace treatment in hypermobile patients with moderate or progressive scoliosis, and whether this could explain the absence of severe scoliosis in patients with hEDS.

Scoliosis was not retained among the diagnostic criteria for hEDS in the 2017 classification. This choice can be challenged in light of other subjective criteria retained in this classification, the frequency of which are identical or even lower.

## Study Limitations

This present study should be considered with certain limitations. Firstly, the study was performed using a small population size and it would therefore be necessary to assess the exact prevalence of scoliosis in a larger population of patients with hEDS. Secondly, prevalence was not compared with a group of patients presenting with only joint hypermobility. Currently, it is not possible to conclude if scoliosis could be linked to hypermobility itself or if it could be considered as an additional criterion in hEDS diagnosis. A comparative study with a control group should be considered. Moreover, it is worthy of note that hEDS is mainly seen in the female population in which scoliosis is much more frequent, meaning that some scoliosis could be linked to sex and not to disease itself.[7] Thirdly, absence of genetic confirmation in hEDS makes the diagnosis difficult since it is mainly based on clinical examination plus some echographic features.

Highlighting the prevalence of scoliosis in patients with hEDS, this study supports the importance of considering screening for scoliosis in any patients meeting the criteria for hEDS. Regular follow-ups could avoid scoliosis progression by appropriate management. It seems fundamental, given the preponderance of females in the hEDS population, to be attentive to screening for scoliosis at the first signs of puberty. Repeated use of EOS makes it possible to monitor scoliosis until patients are adults.

## CONCLUSION

This retrospective study showed that scoliotic inflections and scoliosis are frequent in patients with hEDS. Considering this observation, the authors recommend performing full spinal X-ray in all patients with hEDS at the time of initial diagnosis and regularly during follow-up.


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# Musculoskeletal Brucellosis in Adults in the United Arab Emirates: A Retrospective Study

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## Abstract

**Introduction:** Brucellosis is a zoonotic infection caused by the aerobic Gram-negative bacteria coccobacilli, and is considered a public health problem in the Mediterranean region and Arabian Peninsula. This paper studied the clinical characteristics of musculoskeletal brucellosis and the outcomes of treatment in Al Ain City, United Arab Emirates.

**Method:** A retrospective chart review study was conducted at Tawam Hospital over seven years: January 2009–January 2016. Risk factors for brucellosis, musculoskeletal (MSK) manifestations, duration of Brucella infection (acute, subacute, chronic), and treatment were studied.

**Results:** A total of 99 patients were diagnosed with brucellosis during the study period; the mean age was 44 years, the majority were males (71%), and the male to female ratio was 3:1. The most common risk factor for Brucella infection in the cohort was drinking raw milk (43.4%). Fever was the most common presenting symptoms (93%), followed by arthralgia, fatigue, and loss of appetite in 35, 21, and 14%, respectively. The clinical manifestations of brucellosis in the cohort were MSK involvement (30%), hepatitis (17%), epididymo-orchitis (2%), and endocarditis (1%). Thirty percent of patients (n=30) had MSK-specific symptoms and only one-third (n=10) had confirmatory positive radiographic findings. The majority of patients had lumbar and sacroiliac joint involvement. Most of the patients received antibiotics for a 4–8-week duration and the overall relapse rate of Brucella infection was 10%.

**Conclusion:** This study demonstrates that MSK involvement is a common manifestation in brucellosis, occurring in one-third of the cases. The index of suspicion should be high in brucellosis-endemic countries for early recognition and treatment.

## INTRODUCTION

Brucellosis is a zoonotic infection, historically known as Maltese fever, caused by aerobic Gram-negative coccobacilli, which was first identified by Sir David Bruce in 1887.[1] Worldwide, the true prevalence of brucellosis is unknown; however, it is considered a public health problem in the

Mediterranean region, Arabian Peninsula, India, Mexico, and part of the USA. Pappas et al.[2] estimated the global incidence of brucellosis to be more than half a million cases annually, and the incidence in endemic disease areas to be from <0.01–>200 cases per 100,000 of the population. In the United Arab Emirates (UAE), the total brucellosis notification rate between 2010 and 2015 was estimated to be 3.3 per 100,000 people per year in Abu Dhabi city, the capital of the UAE.[3]

Brucella is a facultative intracellular bacterium that infects animals and has various different species: *Brucella melitensis* (goats, sheep, camels), *B. abortus* (bovine, cattle, camels), *B. suis* (swine, cattle), *B. canis* (dogs), *B. ovis* (ram, sheep), and *B. neotomae* (desert rats).[1] An epidemiological study measuring the prevalence of Brucella in 6,126 livestock in Abu Dhabi reported higher prevalence in sheep and goats (8.4%) compared to camels (4.4%).[4] Risk factors of Brucella infection include drinking unpasteurised animal milk products, direct contact with infected animals, inhalation of aerosolised particles, and occupational and work-related diseases (shepherds, abattoir workers, veterinarians, dairy-industry professionals, and microbiologic laboratory workers).[1,5,6] Clinical manifestations of Brucella infection vary depending on the organ involved. Common presenting symptoms are fever (78%), chills (45%), sweats (54%), fatigue (39%), weight loss (26%), arthralgia (65%), and abdominal pain (19%) due to hepatomegaly or splenomegaly.[7] Brucella infection is classified based on the time of clinical presentation as acute brucellosis (0–2 months), subacute brucellosis (2–12 months), and chronic brucellosis (>12 months). The laboratory findings might reveal leukocytosis (9%), leukopenia (10%), anaemia (40%), thrombocytopenia (10%), elevated liver enzymes (24%), and inflammatory markers (>50%; C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]). The majority of patients (94%) will have a positive Brucella titre (tube agglutination test) and bacteraemia may be encountered in approximately 11% of cases.[5]

Musculoskeletal (MSK) involvement of brucellosis represents 10–85% of reported clinical manifestations such as peripheral arthritis, bursitis, sacroiliitis, osteomyelitis, spondylitis, and paraspinal abscess.[8,9] Spinal brucellosis is common in the elderly and predominately affects the L4–L5 spinal segment of the lumbar spine, followed by thoracic and cervical spine.[9,10] Diagnosis of osteoarticular brucellosis requires laboratory tests to confirm Brucella infection and imaging studies. MRI produces a high yield of images that detect radiological features of spinal brucellosis. There is no prior study, to the authors knowledge, describing the clinical manifestations of MSK brucellosis in the UAE; therefore, a retrospective study was conducted, with the aim of identifying the clinical characteristics of MSK brucellosis and outcomes of treatment in Al Ain, UAE.

## METHODS

A retrospective chart review study was conducted at Tawam hospital (tertiary hospital, Al Ain, UAE) over seven years (January 2009–January 2016). Ethical approval was obtained from Tawam Human Research Ethics Committee (T-HREC). Adult patients (>16 years of age) diagnosed with brucellosis during the study period were involved. The diagnosis of brucellosis was confirmed by either a positive Brucella titre of >1:160 and/or positive blood culture. Citizens were described as 'nationals' and non-citizens as 'non-nationals'.

Demographic, clinical, and laboratory data were collected and analyzed using descriptive analysis. Risk factors for Brucella infection and clinical presenting symptoms were studied. Patients were classified into subgroups according to arthritis types, either peripheral or axial. Brucella infection was classified based on the time of clinical presentation as acute brucellosis (0–2 months), subacute brucellosis (2–12 months), and chronic brucellosis (>12 months).[5] Relevant blood tests were included, and confirmatory radiographic imaging was obtained in all patients with MSK complaints (plain radiograph/X-ray, CT scan, or MRI). Treatment of MSK brucellosis and outcomes were identified.

## RESULTS

A total of 99 patients were diagnosed with brucellosis during the study period. The mean age was 44 years, the majority were males (71%), and the male to female ratio was nearly 3:1. Two-thirds of patients were nationals (63 out of 99;

63.3%). The most common factor for Brucella infection in the cohort was drinking raw milk (43 out of 99; 43.4%); the remaining are summarised in Table 1.

Fever was the most common symptom and accounted for 93% of all patients, followed by arthralgia, fatigue, and loss of appetite in 35, 21, and 14%, respectively. Brucella infection was confirmed in all patients based on elevated Brucella titres (*B. melitensis* and *B. abortus*) of >1:160. Brucella bacteraemia (positive blood culture) was identified in only 57 patients. Other laboratory investigations revealed leukocytosis (white blood cell count >11x10$^9$/L in 10 out of 99; 10.1%), anaemia (30 out of 99; 30.3%), abnormal liver enzymes (47 out of 99; 47.5%), and elevated CRP (83 out of 99; 83.8%). Systemic complications of brucellosis in the cohort were MSK involvement (30%), hepatitis (17%), epididymo-orchitis (2%), and endocarditis (1%).

Of the patients with MSK involvement (n=30), only one-third (n=10) had confirmatory positive radiographic findings. The most common joint involved was the lumbar spine, accounting for 34.5% (n=10) of the cases; followed by sacroiliac and shoulder joints, each accounting for 23.3% (n=7); and then the hip and knee joints, accounting for 13.3% (n=4).

**Table 1: Demographic of patients (n=99), risk factors for Brucella infection and the presenting symptoms.**

| | **N=99** |
|---|---|
| **Demographics** | |
| Male | 71 |
| Female | 28 |
| **Risk factors** | |
| Farm contact with animals | 18 |
| Raw milk drinking | 43 |
| Boiled milk drinking | 3 |
| Fresh cheese ingestion | 1 |
| Ingestion of raw meatballs | 1 |
| Laboratory worker | 0 |
| Unknown transmission | 33 |
| **Symptoms** | |
| Arthralgia | 35 |
| Fatigue | 21 |
| Back pain | 23 |
| Fever | 94 |
| Sweating | 15 |
| Headache | 10 |
| Weight loss | 10 |
| Loss of appetite | 15 |
| Nausea | 3 |
| Vomiting, abdominal pain | 10 |
| Scrotal pain and swelling | 3 |

The radiographic imaging using X-ray and MRI were positive in 10 patients with MSK brucellosis (9 males, 1 female). Five patients had Brucella bacteraemia and all had high Brucella titres, ranging from 1:320 to 1:10,240. The majority of patients had lumbar and sacroiliac joint involvement, with radiographic imaging findings such as disc involvement, vertebral body destruction or abscess, unilateral sacroiliitis, and osteomyelitis. Two patients had septic arthritis related to Brucella infection involving the hip and knee joints, with positive radiological findings of joint effusion. The majority of patients with MSK brucellosis who had positive radiographic changes were diagnosed during the acute phase (90%; n=9) (Table 2, Figure 1).

Details of brucellosis treatment were available in 88 out of 99 patients. All patients received combination therapy with at least two antibiotics. A third agent, mostly an aminoglycoside, was added to treatment in 27 patients (30.6%) for MSK involvement. The most common antibiotics used were doxycycline (87 out of 88; 98.8%), rifampin (76 out of 88; 86.3%), gentamicin (20 out of 88; 22.7%), trimethoprim/sulfamethoxazole (14 out of 88; 15.9%), and ciprofloxacin (5 out of 88; 5.6%). The duration of therapy varied depending on severity and organ involvement. A majority of patients received 4–6 weeks of antibiotics (64 out of 88), followed by 8 weeks of therapy in 15 patients; only two patients required prolonged antibiotic treatment of more than 8 weeks. Surgical therapy was provided for patients (n=2) with MSK brucellosis for draining vertebral abscess, septic arthritis, and discitis. The overall relapse rate of Brucella infection in the cohort (n=99) was 10%.

## DISCUSSION

The burden of Brucella infection and its multisystem involvement is under-reported in some endemic areas. In a meta-analysis of the clinical manifestations of human brucellosis, adult males were affected in 56% of studies, and MSK complaints were common presenting symptoms (65% arthralgia, 47% myalgia, and 45% back pain). The potential risk factors identified for brucellosis were consumption of unpasteurised dairy products in 64% of the studies, followed by contact with livestock in 42%, occupational exposure in 6%, and positive family history of brucellosis in 20% (ranging from 17% to 46%). Interestingly, some studies advocated for Brucella screening among families where one member had been diagnosed, due to the possibility of sharing the same risk factors.[5,7,11]

This study reports 99 cases of confirmed brucellosis; the mean age of patients was 44 years, and men were three times more affected than women. This demonstrates an increased risk to those men involved in animal husbandry. The most significant risk factor was consumption of unpasteurised milk. These findings are consistent with a study conducted in the same region, in which the disease affected mostly men with a mean age of 40 years and where the risk factors constituted of consumption of unpasteurised milk and dairy products.[3] This may explain the importance of cultural and environmental impact.

The presenting symptoms of Brucella infection are nonspecific, and many cases were identified during work-up for fever of unknown origin. Differential diagnosis often includes other infectious and non-infectious chronic inflammatory conditions. Pourbagher et al.[10] noted that fever, fatigue, loss of appetite, nausea, and diarrhoea were the main reported symptoms in the acute phase, while weight loss and palpitation were observed during the subacute phase and the osteoarticular manifestation during the chronic stage.[10] Similarly, in this study, fever was the most common presenting symptom in 93% of patients, followed by arthralgia, fatigue, and loss of appetite in 35, 21, and 14%, respectively. In contrast, osteoarticular involvements in this cohort were diagnosed during the acute phase. Physician education, a higher level of suspicion, and easy availability of serological testing and positive blood cultures may account for this finding.

In this cohort, 30 adult patients were identified with MSK-specific symptoms; one-third had confirmatory positive radiographic findings as described earlier. The reported MSK involvement in different studies varied; along with variation at the affected site, rheumatic complaints were reported in 20–85% of brucellosis cases.[12-14] In a study conducted in Turkey with 251 patients, 45.4% (n=114) of cases reported osteoarticular involvement, with the most common site being the sacroiliac joint (28.3%) followed by lumbar spine (10.4%).[10]

**Table 2: Clinical characteristics of patients with musculoskeletal brucellosis and positive radiological findings.**

| | Age | Gender | Stage | Blood culture | Brucella titre* | Complications | Radiographic changes |
|---|---|---|---|---|---|---|---|
| **Case 1** | 33 | Male | Acute | Negative | 1:640 | Right sacroiliitis | X-ray SIJ: no abnormalities<br>MRI SIJ: unilateral right sacroiliitis |
| **Case 2** | 89 | Male | Acute | Positive | 1:10,240 | Lumbar abscess collection<br>Hepatitis | X-ray lumbar spine: intervertebral space narrowing L1–L2, L3–L4, and L5–S1<br>MRI lumbar spine: collection in the lumbar spine |
| **Case 3** | 80 | Male | Acute | Negative | 1:1,280 | Lumbar discitis and osteomyelitis | X-ray lumbar spine: vertebral body destruction L4/5<br>MRI lumbar spine: L4/L5 disc and endplates signal abnormality, highly suspicious of discitis and osteomyelitis |
| **Case 4** | 35 | Male† | Acute | Negative | 1:2,560 | Left knee monoarthritis (septic) | X-ray left knee: no abnormalities<br>MRI left knee: effusion |
| **Case 5** | 20 | Male | Acute | Positive | 1:2,560 | Septic right-sided sacroiliitis | X-ray SIJ: no abnormalities<br>MRI SIJ: mild right-sided septic arthritis with small collection underneath the anterior sacroiliac ligament |
| **Case 6** | 35 | Male | Acute | Positive | 1:2,560 | Lumbar disc involvement<br>Hepatitis | X-ray lumbar spine: disc involvement<br>MRI lumbar spine: disc involvement L5/S1, nerve compression |
| **Case 7** | 28 | Female | Acute | Negative | 1:640 | Left hip monoarthritis (septic)<br>Osteomyelitis | X-ray hip: no abnormalities<br>MRI left hip: joint effusion |
| **Case 8** | 18 | Male | Acute | Positive | 1:10,240 | Septic left-sided sacroiliitis | X-ray SIJ: no abnormalities<br>MRI SIJ: left sacroiliitis |
| **Case 9** | 71 | Male | Subacute | Negative | 1:640 | Lumbar discitis<br>Hepatitis | X-ray lumbar spine: no abnormalities<br>MRI lumbar spine: disc involvement, discitis D1/L1 and L3/L4 |
| **Case 10** | 31 | Male | Acute | Positive | 1:320 | Sacroiliac sclerosis | X-ray SIJ: left SIJ sclerosis |

*both (*Brucella abortus* and *B. melitensis*).

†expatriate.

SIJ: sacroiliac joint.

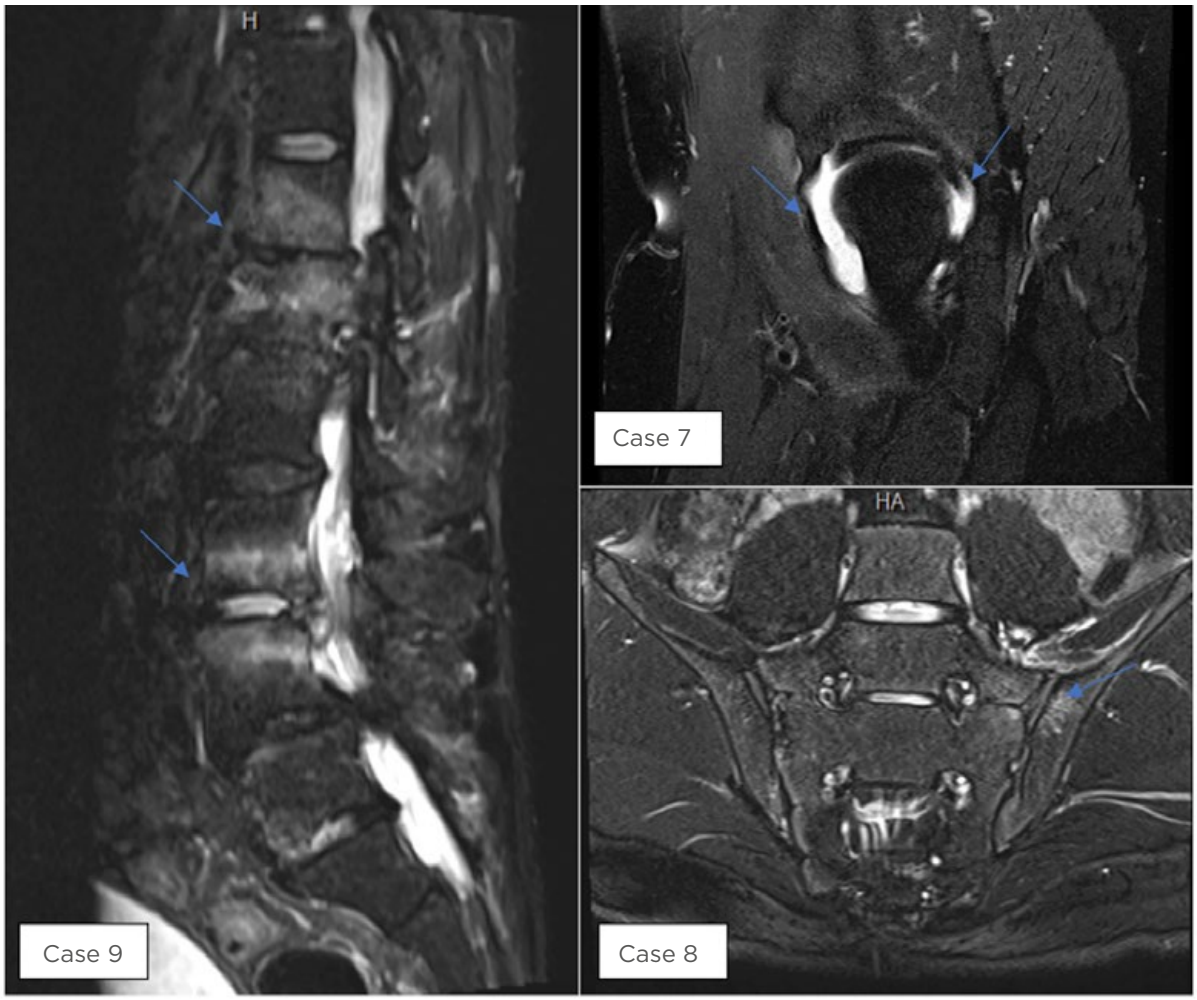


**Figure 1: Positive MRI findings in selected cases as described in Table 2.**

In another study from Saudi Arabia, with 84 cases of brucellosis, MSK complication was the most common symptom and 64% were found to have either peripheral arthritis, sacroiliitis, or spondylitis.[15] In this study, almost 80% (n=8) of patients had axial involvement affecting lumbar and sacroiliac joints with positive radiographic imaging (disc involvement, discitis, vertebral body destruction, unilateral sacroiliitis). Peripheral involvement is less common compared with axial involvement. Furthermore, Buzgan et al.[5] reported osteoarticular Brucella involvement in 260 cases out of 1,028 patients (25.3%), involving peripheral arthritis (56.5%), sacroiliitis (24.6%) (unilateral in 51 cases), spondylitis (12.3%), and paraspinal abscess (3.5%). They received various therapeutic regimens for a duration of approximately 6–12 weeks and the overall relapse rate was 4.7% (in osteoarticular involvement: 8.5%).[5]

The imaging modalities used to diagnose MSK Brucella involvement varies in published literature. For peripheral arthritis, ultrasound can detect effusion. In one study, 5.2% of patients presenting with arthralgia, diagnosed with bursitis (13 out of 251 Brucella-infected cases) using ultrasound, had negative synovial fluid culture.[10] Brucellosis with sacroiliac joint involvement can be diagnosed using a plain radiograph (late findings), radionuclide bone scintigraphy (bone scan), or MRI. It is estimated that two-thirds of cases will have unilateral sacroiliitis and only one-third will be bilateral. A bone scan showed increased uptake in the sacroiliac joints.[5, 9, 10] Radiographs in vertebral brucellosis may reveal abnormalities in vertebral endplates, associated with irregularities and narrowing intervertebral disk spaces in subacute and chronic Brucella infection. MRI is very sensitive for detecting spondylodiscitis, vertebral destruction, spinal stenosis/abscess,

and osteomyelitis. It is fundamental to rule out tuberculosis infection, which has predilection to same articular involvement (Pott's Disease) with chest radiographs, QuantiFERON tests, and acid-fast bacilli stain and culture on biopsy.[9,10]

The aim of medical therapy in cases of brucellosis is to prevent complications and relapse and to control the acute illness. Monotherapy and short duration of <4 weeks are not recommended in the treatment of brucellosis due to high risk of treatment failure and relapse. In a meta-analysis, the combination of streptomycin for 2–3 weeks plus doxycycline for 6 weeks had a lower failure rate than doxycycline plus rifampicin for 6 weeks.[16,17] Other antibiotics, such as quinolones (e.g. ciprofloxacin and ofloxacin), aminoglycosides (e.g. gentamicin), and trimethoprim/sulfamethoxazole, have been used along with other combinations and have shown variable effects.[8,18] The optimal duration of therapy for MSK brucellosis is not well established, but prolonged therapy is required for complicated cases. In the current cohort, all patients were on a combination of two antibiotics (doxycycline plus rifampicin regimen being the most common) and patients with MSK involvement required the addition of aminoglycosides (gentamicin). The majority of the patients received antibiotics for a duration of 4–8 weeks. The overall relapse rate in our cohort was 10%, of which three cases were related to noncompliance to medication, and of which one case had an earlier diagnosis of MSK brucellosis. Treatment-related complications were not reported in the study.

## CONCLUSION

This study has demonstrated that MSK manifestation in brucellosis accounts for one-third of the cases. The index of suspicion should be high in brucellosis-endemic countries. Clinical symptoms, risk factors, specific laboratory findings, and clinical images are important for early recognition and treatment.

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# Prevalence of Thromboembolic Complications in COVID-19 Infection: A Systematic Review and Meta-Analysis

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## Abstract

**Introduction:** The coronavirus disease (COVID-19) infection is proved to be involved in the onset of thromboembolism episodes. This study aims to evaluate the prevalence of thromboembolic complications in patients with COVID-19 from March until May 2020.

**Methods:** A literature review was conducted in MEDLINE (via PubMed), Scopus, Embase, Cochrane, and CINHAL without any language and date of publication restriction (Prospero registration number CRD42020186925). The inclusion criteria were as following: 1) patients with diagnosis of COVID-19; 2) occurrence of thromboembolic event, and 3) patients older than 18 years of age.

A multi-variable random effects model was computed accounting for correlations among outcomes by considering a heterogeneous compound symmetry covariance matrix.

**Results:** Observational studies included 2,442 participants from 268 to 7,999 participants per study, 1,014 (41.52%) were male and 825 (33.78%) were female. The multi-variable pooled event rate of acute myocardial infarction was rare, estimated to be 0.03 (95% confidence interval [CI]: 0.00–0.07; p=0.23); this is also true for the meta-analytical estimate of disseminated intravascular disease which was 0.04 (95% CI: 0.00–0.08; p=0.03). Conversely, other events were found to be more frequent. Indeed, the pooled proportion of pulmonary embolism was 0.14 (95% CI: 0.08–0.20; p<0.001), while the venous thromboembolic event rate is 0.15 (95% CI: 0.09-0.30; p=0.04). The pooled intrahospital mortality rate was equal to 0.12 (95% CI: 0.08–0.16; p<0.001).

**Conclusions:** Thromboembolic events, particularly venous thromboembolic event rate and pulmonary embolism, are a frequent complication in patients hospitalised with COVID-19. These findings suggest that the threshold for clinical suspicion should be low to trigger prompt diagnostic

testing and that evaluation of therapeutic treatment should be considered in patients in intensive care units with COVID-19.

## INTRODUCTION

The novel coronavirus disease (COVID-19) has posed an unprecedented threat to global healthcare systems. The case fatality rate has been estimated to be as high as 15% in some countries.[1] The reason for high mortality rates of the new coronavirus infection is still unclear.

Clinical manifestations may vary from asymptomatic patients to acute respiratory distress syndrome, shock, and multi-organ failure associated with an increased risk of death.[2] Coagulation abnormalities have been reported since the start of the pandemic. Some authors supposed that these abnormalities might be similar to those reported in the previous severe acute respiratory syndrome coronavirus (SARS-CoV-2) infections. Chong et al.[3] reported an incidence of 11.4% for pulmonary embolism (PE) and 20.5% for deep venous thrombosis (DVT) in SARS-CoV-2-infected patients.[3] The clinical course of COVID-19 infection is often accompanied by systemic inflammation, endothelial dysfunction, and coagulation activation, which may evolve into overt disseminated intravascular coagulopathy (DIC).[4] Moreover, the systemic activation of blood coagulation and pulmonary thromboinflammation with local vascular damage caused by COVID-19 may increase the risk of venous thromboembolism (VTE) and pulmonary artery thrombosis.[5]

From a pathogenetic point of view, the mechanism of hypercoagulability in patients with COVID-19 infection is quite clear;[6] however, there are still no clear data on the incidence of those episodes in patients with COVID-19 despite the numerous reports and studies related to thromboembolic episodes.

Better understanding of COVID-19-related thromboembolic risk will help to optimise diagnostic strategies and guide the design and conduction of randomised controlled trials on thromboembolic prevention.

Thus, the aim of this meta-analysis was to estimate the prevalence of thromboembolic complications in patients admitted for COVID-19 from March until May of 2020. As the disease and its treatments are rapidly evolving, this meta-analysis represents events during the first and the beginning of the second wave of COVID-19 infection.

## MATERIALS AND METHODS

### Study Design

This is a systematic review and meta-analysis. The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. The study was registered in Prospero with the number CRD42020186925. Research strategy was developed according to the Population, Intervention or exposure, Comparison, and Outcomes (PICO) study design model; these factors were patients with COVID-19, thromboembolic event, none, and incidence of thromboembolic events, respectively. The research strategy was then adapted according to the specific characteristics of each database.

### Data Sources and Search

The literature review was conducted in MEDLINE (via PubMed), Scopus, Embase, Cochrane and CINAHL without any language and date of publication restriction. The following search terms were used and adapted in each database with proper Boolean operator: COVID-19, severe acute respiratory syndrome coronavirus-2, SARS-CoV-2, thrombosis, thromboembolism, cerebrovascular accident, myocardial infarction, hypercoagulability, heart attack, coronary disease, ischaemic heart disease, coronary heart disease, vascular disease, and cardiovascular disorder. The reference list of the retrieved studies was also searched. The last update was made on the 7th of May 2020.

### Eligibility Criteria

The inclusion criteria were as follows: 1) patients with diagnosis of COVID-19; 2) occurrence of thromboembolic event (without restrictions to the damaged organ); and 3) patients older

than 18 years of age. There was no restriction in the design of the studies included. Studies evaluating the outcomes of interest postmortem were excluded.

## Study Selection

As reported in Figure 1, the study selection procedure was performed according to the PRISMA guidelines.[7] The software Covidence[8] was used in all the phases of data collection and extraction. Two blinded reviewers screened the articles in each phase. In each stage, the disagreements between the reviewers were solved by another senior expert in the field.

## Data Extraction

For each article, two reviewers extracted the following data: country, study design, author, and patient population characteristics (i.e., age, sex, comorbidities, laboratory exam results, use of invasive mechanical ventilation, use of antithrombotic medications, ward, length of stay, mortality, type of thromboembolic event occurred, and number of events).

## Outcomes

The outcome of interest was the prevalence of both arterial and venous thromboembolic events in patients with COVID-19. The authors included prospective and retrospective studies, case series and case reports in order to better understand the dimension of the problem.

## Quality Assessment

The risk of bias was evaluated by two independent reviewers. The Joanna Briggs Institute Critical Appraisal tools were used for quality assessment, according to the design of the study[9] (e.g., prospective studies, prevalence data, case report, and case series).

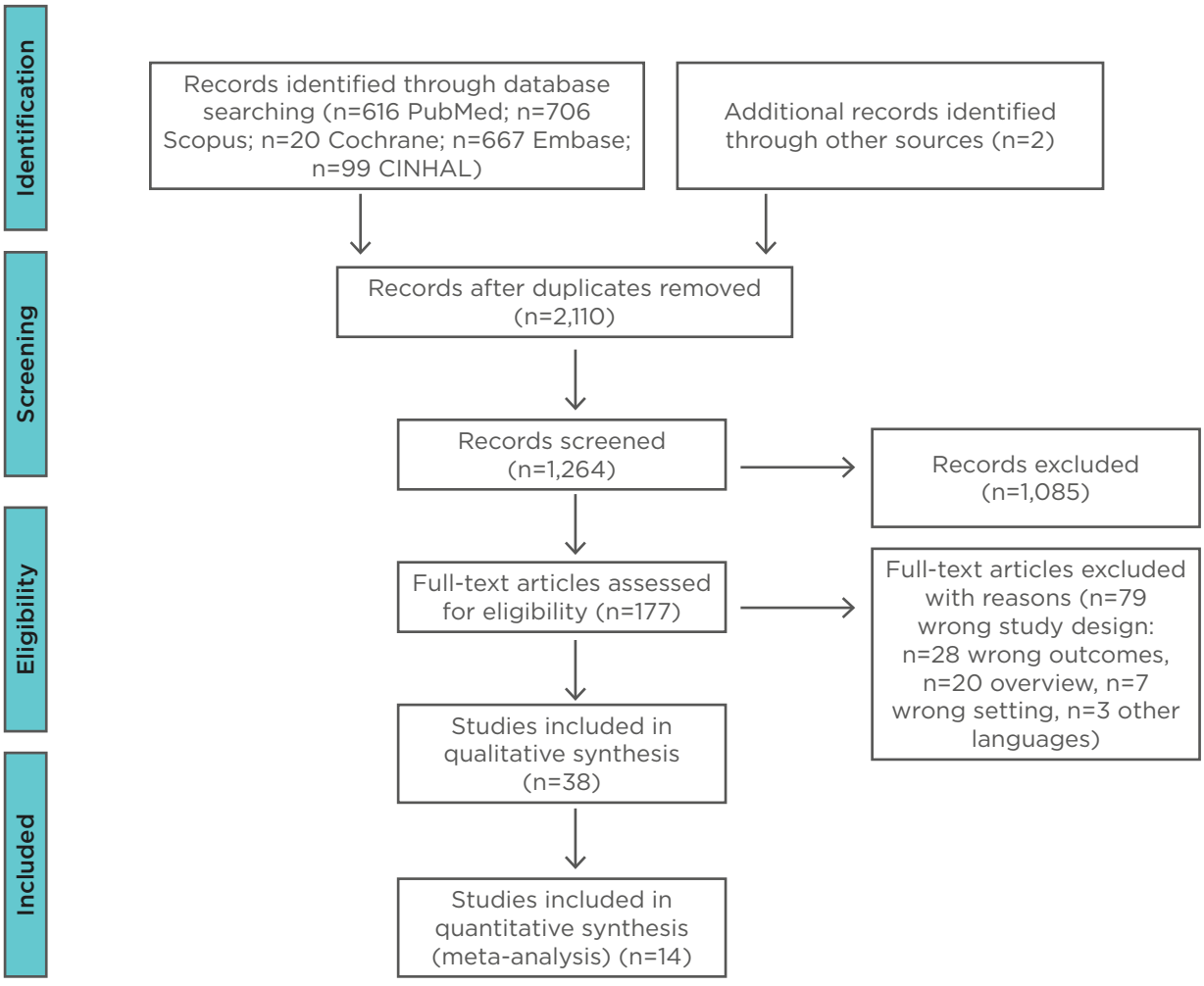


**Figure 1: PRISMA flow chart of retrieved articles.**

## Agreement

Cohen's Kappa was used to evaluate the interrater agreement among two reviewers in the full-text selection. The percentage of agreement was 56.98%. This could be explained by the large difference experience in metanalysis between the operators. A third expert reviewer reconciliated the disagreement between operators.

## Data Synthesis

A multi-variate random effects model was computed accounting for correlations among outcomes by considering a heterogeneous compound symmetry covariance matrix. The multi-variate $I^2$ heterogeneity was also calculated following the approach proposed by Jackson et al.[10] A multi-level random effect meta-regression model was used to deal with heterogeneity ($I^2$>75%), accounting also for correlation among the outcomes. Restricted cubic spline was considered for nonlinear effects. The estimates obtained with the multi-level random effect models have been adjusted by using, as moderators, the geographic areas (Europe and China), the study design (retrospective and prospective), and the median age of the study participants.

The univariate pooled random effect meta-analysis, together with the 95% confidence interval (CI), was also estimated for comparison purposes.

The incidence of discharge pooled estimate was computed using an incidence rate random effect meta-analysis calculating the events over the person time (length of hospitalisation) for each study.

Results and study level estimates were represented in a forest plot. The publication bias has been assessed via funnel plot graphical representation. Correlation matrix was computed among outcomes event rates with a 95% CI. Only endpoints reporting more than two pairwise comparisons have been computed for the correlation matrix. The analyses were conducted using R 3.6.2,[11] and rms[12] and metafor[13] packages.

# RESULTS

The search identified 2,110 studies. After title, abstract, and full-text screening, 38 studies were included in this review. Eighteen out of 26 studies were case reports and eight were case series. The remaining studies included in the meta-analysis were observational, eight were retrospective and six were prospective (Figure 1). The studies included in the metanalysis are shown in Table 1.[14-51]

## Descriptive Characteristics of the Studies Included in Quantitative Analysis

Observational studies included 2,442 participants ranging from 26 –799[18,16] participants per study, of these 1,014 (41.52%) were male and 825 (33.78%) were female. They were mainly located in China[16,22,27,52] and in France,[17-19,21,23,25] the mean age reported was 49–70 years. Comorbidities were reported in 12 studies, 740 (30.30%) patients had at least one comorbidity (Table 1). Most patients included in the retrieved studies were admitted to the intensive care unit, except for those in the studies by Arachchillage et al.[14] and Grillet et al.[17] Antithrombotic therapy was routinely used in seven studies. They all used low-molecular weight heparin but with different dosage depending on the therapeutic or prophylactic usage. Only one study, by Llitjos et al., compared the prophylactic versus the therapeutic usage of anticoagulant[18] in patients in ICU. The thromboembolic events and the number of events for each study are reported in Table 1. The considered events were grouped in the following categories: pulmonary embolism, venous thromboembolism, acute myocardial injury, arterial thromboembolism, and disseminated intravascular disease. PE was the most frequently reported event.[17,20,21,23-26]

## Descriptive Characteristics of the Studies Included in Qualitative Analysis

Case report and case series studies are reported in Table 1. These retrieved studies reported the data of 56 participants overall (40 males [71.42%] with a median age of 60.53 years). These studies were mainly located in Italy[28-30,35,38,47] and the USA.[39,43,48-50,53]

**Table 1: Descriptive characteristics of retrieved studies.**

| Author (year) | Country | Age (mean)* | N | Comorbidities | D-dimer (ng/mL) | Fibrinogen (g/L) | IMV (N) | Sex | Antithrombotic | Ward | Type event (N) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Retrospective cohort studies** | | | | | | | | | | | |
| Arachchillage DRJ et al.[14] (2020) | China | 54.1 | 183 | 75 | 66,000.00 | 4.55 | NA | 98 M, 85 F | NA | ICU | DIS (16)<br>D (21) |
| Cattaneo M et al.[15] (2020) | Italy | 70.0 | 64 | NA | 458.00 | 4.76 | 11 | 35 M, 29 F | NA | ICU | LOS (9)†<br>VT (0) |
| Chen T et al.[16] (2020) | China | 62.0 | 799 | 133 | 1,100.00 | NA | 119 | 171 M, 103 F | NA | ICU | D (113)<br>DIS (21)<br>DI (161)<br>LOS (5)† |
| Grillet F et al. [17] (2020) | France | 66.0 | 100 | 92 | NA | NA | 34 | 30 M, 70 F | NA | NA | PE (23) |
| Llitjos JF et al.[18] (2020) | France | 68.0 | 26 | NA | 1,750.00 | 699.00 | 26 | 6 M, 20 F | LWMH | ICU | PE (6)<br>D (3)<br>VT (18) |
| Lodigiani C et al.[19] (2020) | Italy | 66.0 | 388 | 183 | 5,633.07 | NA | NA | 124 M, 264 F | LWMH | ICU/ward | D (92)<br>PE (10)<br>DIS (8)<br>LOS (10)†<br>AMI (4)<br>VT (4)<br>CS (9) |
| Middeldorp S et al.[20] (2020) | Netherlands | 61.0 | 173 | 18 | 1,100.00 | NA | NA | 130 M, 68 F | LWMH | ICU/ward | D (38)<br>VT (39)<br>T (2)<br>PE (13) |
| Poissy J et al.[21] (2020) | France | 57.0 | 107 | NA | NA | NA | 67 | 13 M, 44 F | LWMH | ICU | PE (57)<br>D (15) |
| **Prospective cohort studies** | | | | | | | | | | | |
| Cui S et al.[22] (2020) | China | 59.9 | 81 | 33 | NA | NA | NA | 37 M, 44 F | NA | ICU | |
| Helms J et al.[23] (2020) | France | 68.0* | 77 | 77 | 2,270.00 | 699.00 | NA | 63 M, 14 F | LWMH | ICU | PE (9)<br>DI (36)<br>AMI (0)<br>VT (0)<br>D (10) |

**Table 1 continued.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Klok FA et al.[24] (2020) | Nether-lands | 64.0 | 184 | 75 | NA | NA | 45 | 139 M, 45 F | LWMH | ICU | PE (25) DI (22) AMI (0) VT (3) D (23) AT (3) |
| Leonard-Lorant I et al.[25] (2020) | France | 64.0 | 106 | NA | NA | 7.00 | NA | 70 M, 36 F | LWMH | ICU | PE (32) LOS (24)† |
| Tavazzi G et al.[26] (2020) | Italy | 68.0 | 54 | NA | NA | 657.00 | 54 | 44 M, 10 F | LWMH | ICU | PE (2) D (1) AMI (1) VT (8) |
| Wei JF et al.[27] (2020) | China | 49.0 | 101 | 54 | NA | NA | 11 | 54 M, 47 F | NA | ICU | D (3) LOS (5)† AMI (16) |
| **Case reports** | | | | | | | | | | | |
| Audo A et al.[28] (2020) | Italy | 59.0 | 1 | 0 | NA | NA | 1 | M | NA | ICU | PE |
| Cellina M et al.[29] (2020) | Italy | 60.0 | 1 | 1 | 5,411.00 | NA | NA | M | NA | NA | PE |
| Danzi GB et al.[30] (2020) | Italy | 75.0 | 1 | 0 | 21,000.00 | NA | NA | F | NA | NA | PE |
| de Barry O et al.[31] (2020) | France | 79.0 | 1 | 0 | NA | NA | NA | F | NA | NA | VT |
| Dominguez-Erquicia P et al.[32] (2020) | Spain | 64.0 | 1 | 0 | 749.00 | NA | NA | M | NA | NA | AI |
| Fabre O et al.[33] (2020) | France | 45.0 | 1 | 1 | NA | NA | 1 | F | NA | ICU | PE |
| Foch E et al.[34] (2020) | France | 50.0 | 1 | 0 | 3,020.00 | NA | NA | M | NA | NA | PE |
| Giacomelli E et al.[35] (2020) | Italy | 67.0 | 1 | 1 | 10,482.20 | 432.00 | NA | M | LMWH | NA | AT |
| Harsch IA et al.[36] (2020) | Germa-ny | 66.0 | 1 | NA | 14,903.00 | NA | NA | F | NA | NA | PE |
| LeBerre A et al.[37] (2020) | France | 71.0 | 1 | NA | 17,280.00 | NA | NA | M | LMWH | NA | AT, PE |
| Martinelli I et al.[38] (2020) | Italy | 17.0 | 1 | NA | 16,400.00 | 602.00 | NA | F | LMWH | Mater-nity hub | PE |
| Moshayedi P et al.[39] (2020) | USA | 80.0 | 1 | 1 | NA | NA | NA | M | NA | NA | IS, MI |
| Rotzinger DC et al.[40] (2020) | Switzer-land | 75.0 | 1 | 0 | NA | NA | NA | M | LMWH | NA | PE |

**Table 1 continued.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sulemane S et al.[41] (2021) | UK | 60.0 | 1 | 1 | 32,228.00 | NA | 1 | M | NA | ICU | PE |
| Ueki Y et al. [42] (2020) | Switzer-land | 82.0 | 1 | NA | 10,000.00 | NA | NA | M | NA | NA | PE, MI |
| Ullah W et al.[43] (2020) | USA | 59.0 | 1 | 1 | 1,280.00 | NA | NA | F | LMWH | NA | PE |
| Xie Y et al. [44] (2020) | China | 57.0 | 2 | NA | NA | NA | NA | 2 M | NA | NA | PE |
| Zhou B et al.[45] (2020) | China | 69.0 | 1 | 1 | 8,000.00 | NA | NA | M | NA | NA | AT, VT |
| **Case series** | | | | | | | | | | | |
| Beyrouti R et al.[46] (2020) | UK | 69.8 | 6 | 5 | 25,261.00 | NA | NA | 5 M, 1 F | NA | NA | IS |
| Bozzani A et al.[47] (2020) | Italy | 67.0 | 3 | 3 | 115,727.00 | NA | NA | 3 M | NA | NA | VT |
| Griffin DO et al.[48] (2020) | USA | 60.0 | 3 | NA | NA | NA | NA | 2 M, 1F | LMWH | NA | AT |
| Griffin DO et al.[49] (2020) | USA | 61.0* | 3 | 3 | 12,597.00 | NA | NA | 3 M | NA | NA | PE |
| Oxley TJ et al.[50] (2020) | USA | 60.0 | 5 | NA | NA | NA | NA | 4M, 1 F | NA | NA | IS |
| Vulliamy P et al.[51] (2020) | UK | 67.0 | 2 | NA | NA | NA | NA | 2 M | NA | NA | AT |

*Median age

†LOS was reported as number of days

AMI: acute myocardial injury; AT: arterial thromboembolism; CS: cerebrovascular stroke; D: deceased; DI: discharge; DIS: disseminated intravascular disease; F: female; ICU; intensive care unit; IMV: intermittent mandatory ventilation; IS: ischaemic stroke; LOS: length of stay; LWMH: low-molecular weight heparin; M: male; MI: myocardial infarction; N: number of patients; NA: not applicable; PE: pulmonary embolism; T: thrombophlebitis; VT: venous thromboembolism.

The reported thromboembolic events were PE, venous thromboembolism, arterial thromboembolism, ischaemic stroke, myocardial infarction, and arterial thromboembolism. The most frequent thromboembolic event was PE, which was reported in 15 studies. Comorbidities were evaluated in 27 participants (48.21%). Ischaemic stroke was reported only in the studies of Oxley et al.[50] and Moshayedi et al.[39] The first study, included five patients admitted with severe large-vessel stroke according to National Institutes of Health Stroke Scale (NIHSS).[50] In the second study[39] the ischaemic stroke happened after coronary angioplasty and stent deployment, as the patient was admitted for an ST-elevation myocardial infarction. Myocardial injury alone was reported only in two patients,[39,42] both in their eighties.

## Risk of Bias of the Included Studies

Confounding factors were unclear in observational studies as showed in risk of bias assessment.[17,20,23,25] Questions related to confounding factors were not applicable to some observational studies.[18,21,22,26-27,54] Adverse events questions did not apply to case reports.

## Meta-Analysis Results

Fourteen studies were considered in the meta-analysis. The correlation among event rates is

estimable only for mortality and thromboembolic endpoints, reporting more than two pairwise event rates across studies. The correlation matrix among outcomes event rates is higher across PE and VTE outcomes, but it is not significant for all the pairwise comparisons. Some events were rare in the considered study populations; for example, the multi-variable pooled event rate of acute myocardial injuries was estimated to be 0.03 (95% CI: 0.00–0.07; p=0.23), while the meta-analytical estimate of disseminated intravascular disease is 0.04 (95% CI: 0.00–0.08; p=0.03) (Figure 2). Conversely, other events were found to be more frequent, the pooled proportion of pulmonary embolism was 0.14 (95% CI: 0.08–0.20; p<0.001), while the venous thromboembolism rate is 0.15 (95% CI: 0.09–0.30; p=0.04) (Figure 2). The pooled in-hospital mortality rate was equal to 0.12 (95% CI=0.08–0.16; p<0.001). The multi-variable funnel plot does not reveal publication bias across reported evidence, only the study by Llitjos et al.[18] was outside the triangle.

The multi-variable and univariate pooled estimates were similar especially for reported outcomes in more than six studies.

The $I^2$ heterogeneity levels, for all the reported outcomes (AMI, PE, VTE, disseminated intravascular disease, mortality), reveals a substantial heterogeneity with values exceeding the 60%. A significant modifying effect of the country (-0.081; 95% CI: -0.133, -0.029; p=0.0024) and study design (0.061; 95% CI: 0.007, 0.114; p=0.0274) has been evidenced. Moreover, mean age (0.009; 95% CI: -0.012, -0.005; p=<0.001) explains a considerable amount of heterogeneity by bringing $I^2$ values below the 75% threshold as indicated in the literature.[55]

## DISCUSSION

This meta-analysis showed that thromboembolism, particularly PE and VTE are frequent in patients hospitalised for COVID-19 with a pooled hospital mortality rate of 0.12. Coagulopathy is a common complication in patients with severe forms of COVID-19. In a recent study of 191 patients with COVID-19, 50% of in-hospital deaths were in individuals who had coagulopathy, compared to 7% of survivors. Of note, D-dimer levels >1,000 µg/L were associated with death,[56] while IL-6 levels may correlate with disease severity, and a procoagulant profile.

In a recent study on 183 patients, International Society on Thrombosis and Haemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC) were met in 71% of patients who died.[4] Some studies have reported that the incidence of DIC episodes were lower, ranging from 2% to 9% in patients admitted to ICU. Arachchillage et al.[14] reported a higher incidence, probably because their patients had a great percentage of comorbidities 75 (41%) and higher levels of D-dimer (66,000 ng/mL).

SARS-CoV-2 may activate the coagulation system by using different pathogenetic mechanisms such as endothelial dysfunction, systemic inflammation, and a procoagulatory state; this may lead to pulmonary arterial thrombosis.[58-60]

Moreover, the clinical presentation of PE may overlap with that of COVID-19 pneumonia and may hinder the recognition of PE symptoms in patients who are already complaining of dyspnoea. Grillet et al.[17] and Leonard-Lorant et al.[25] reported higher proportions of PE compared to other studies, likely because they only included patients who underwent CT angiogram. Poissy et al. compared the prevalence of PE in patients admitted in ICU in the same period of 2019 and 2020. Among patients in ICU with COVID-19 they reported 22 (20.6%) PE cases, which correspond to an absolute increase of 14.4% (95% CI; 6.1–22.8%) against control group of ICU patients admitted from February 27th to March 31st 2019.[21]

The authors suggest that actual estimates are more likely an underestimation of the real thrombosis prevalence in COVID-19. This has been confirmed by a recent autopsy study[54] where deep VTE was found in 58% of the cohort, and 30% of the patients had a PE as the direct cause of death. A recent metanalysis on 3,487 patients shown an incidence of VTE of 26% (95% prediction interval: 6, 66%) with an incidence of PE with or without DVT in 2% of patients (95% prediction interval: 2, 46%).[5]

Even in the studies where antithrombotic therapy (low-molecular weight heparin at prophylactic or therapeutic dosage) was routinely administered, the risk of thromboembolic complications seemed to remain considerable.

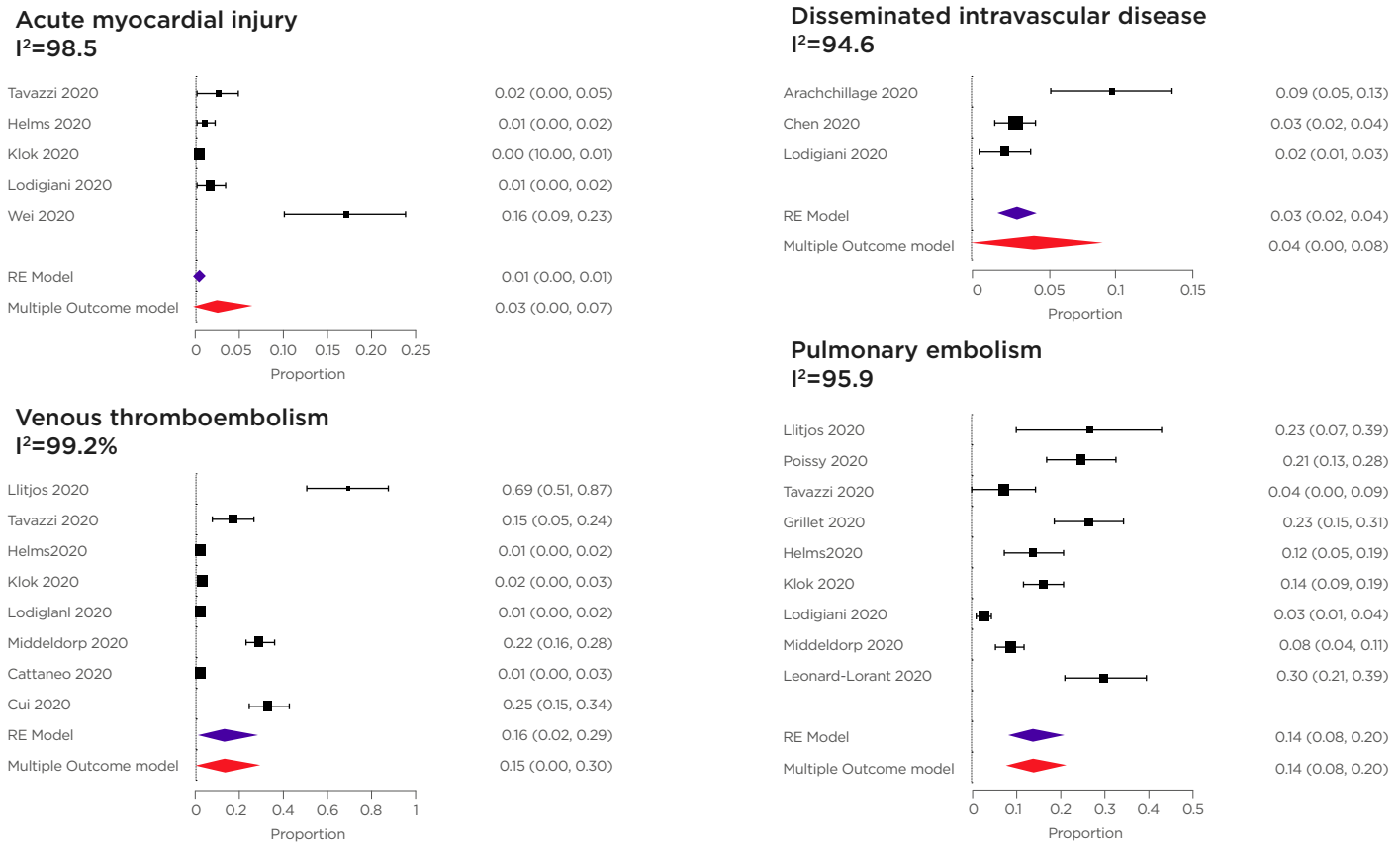


**Figure 2: Forest plots of acute myocardial injury disseminated intravascular disease, venous thromboembolism, and pulmonary embolism.** The random effect multi-variate pooled estimate has been reported together with the separate random effect meta-analysis pooled estimate with the 95% confidence interval.

This study confirms that in patients in ICU, the risk of thromboembolism is particularly high; therefore, use of therapeutic dose of anti-thrombotic drugs may be preferable. Despite this, the vast majority of the selected studies involved patients admitted to ICU, the incidence of VTE in patients with COVID-19 appeared to be higher than previously reported in critically ill patients with sepsis or septic shock.[61] Llitjos et al.,[18] in particular, reported a high prevalence of VTE (69%), which could be attributable to their performing of complex duplex ultrasound on admission as a standard of care in their ICU. In the studies with higher prevalence of VTE, except for Cui S et al.[22] and Middeldorp S et al.,[20] part of the cohort was sustained by invasive mechanical ventilation.[18,26]

Regarding myocardial events, the prevalence of myocardial lesions was found to be higher only in the study by Wei et al.[27] In fact, they reported an incidence of 33%, which is far above the 0.01% reported by Lodigiani et al.[19] and Tavazzi et al.[26] This is may be related to the use of troponin levels as the only diagnostic criteria for myocardial injury (14 pg/mL),[27] and this may overestimate the rate of true AMI due to embolic events, as differential diagnosis of elevated troponin levels includes nonspecific myocardial injury, impaired renal function, pericarditis, myocarditis, and shock, among others.

## Limitations

This is a prevalence metanalysis: the study aim was to analyse prevalence of thromboembolism in patients affected by COVID-19. Predictors of thromboembolism events were not evaluated due to the lack of information about the characteristics of patients in the retrieved articles. For the same reason, the role of thromboembolism in affecting mortality risk was not assessed.

Although the authors chose to exclude case series and case reports from the meta-analysis, the results may have some limitations. The authors are not able to stratify the analysis according to pharmacological profile or characteristics of the patients due to the lack of information on

anticoagulant therapy and characteristics of the patients. Further studies are needed to evaluate the impact of different antithrombotic treatments on thromboembolic events in this population. The design of the studies also reduced the quality of the results, as only one study had a form of group control.

## CONCLUSIONS

This meta-analysis showed a high prevalence of thromboembolic events in patients with COVID-19, in particular of VTE and PE. These findings may be of great clinical relevance, strongly suggesting to query PE in patients with COVID-19 when haemodynamic deterioration occurs, despite use of prophylactic antithrombotic treatments. These findings encourage the use of therapeutic dose of antithrombotic drugs in patients with COVID-19 in ICU. Further prospective studies are urgently needed to value the effect of prophylactic anticoagulant in such patients.

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# New Therapeutic Approaches for Acute Myeloid Leukaemia

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## Abstract

Acute myeloid leukaemia (AML) is a genetically heterogeneous haematopoietic neoplasm characterised by the accumulation of transformed immature blood progenitors in bone marrow. Since 1973, the backbone treatment has relied on the combination of cytarabine and an anthracycline, followed by allogeneic haematopoietic transplant if eligible. Therefore, the treatment decisions have largely revolved around chemotherapy drug intensity. Despite advances in our understanding of the underlying biology over the past decades, AML remains a therapeutic challenge as the overall survival is poor and treatment options are limited for relapsed/refractory AML or for unfit patients. After four decades without substantial changes, eight new noncytostatic drugs have been granted approval: vyxeos, enasidenib, gilteritinib, glasdegib, gemtuzumab ozogamicin, ivosidenib, midostaurin, and venetoclax. Despite promising preliminary results, some indications are based on early efficacy data, obtained in single-arm nonrandomised trials, highlighting the necessity for further validation in extended clinical trials. Interestingly, several druggable targets have been identified recently, associated with specific target-directed drugs. Based on the preclinical data available, great impact on clinical outcomes for patients with AML is expected, potentially increasing the therapeutic landscape for this disease.

## ACUTE MYELOID LEUKAEMIA

Acute myeloid leukaemia (AML) is a life-threatening, multifactorial haematological neoplasm characterised by the accumulation of transformed immature myeloid progenitors in bone marrow and peripheral haematopoietic organs. Multiple somatically acquired driver mutations, coexisting competing clones, and disease evolution over time account for the high heterogeneity observed in patients with AML, which results in a wide inter- and intrapatient variety of cellular phenotypes and clinical outcome.[1] Since the 1970s, the standard AML therapy consists of the '7+3' regimen, a combination of cytarabine and anthracycline.[2] This induction therapy aims to fully eliminate the leukaemic burden from the bloodstream and bone marrow. Once completed, an intensive

chemotherapy cytarabine-based consolidation therapy, together with a haematopoietic cell transplantation if eligible, is followed to eliminate any potential, not necessarily detectable, leukaemic cells that may remain after induction.[3] AML is mainly a disease of the elderly, with a median age at diagnosis of 68 years,[4] which limits the treatment options due to comorbidities. The majority of patients will be considered unfit for intensive chemotherapy and will receive as treatment options low-dose cytarabine or hypomethylating agents (HMA), which generally fail to induce durable responses.[5] Consequently, new treatment options are urgently needed for AML patients, especially for those unfit.

After decades without significant changes in treatment options, the pharmacologic landscape has unprecedentedly reshaped in the last 3 years with eight new drugs approved by regulatory agencies: vyxeos (CPX-351), enasidenib (AG221), gilteritinib (ASP2215), glasdegib (PF-04449913), gemtuzumab ozogamicin (GO), ivosidenib (AG120), midostaurin (PKC412), and venetoclax (ABT-199). However, only four drug approvals, CPX-351, ASP2215, GO, and PKC412, were based on randomised data with limitations in follow-up data availability. Optimisation of the schedule and treatment regimens, determination of safety, and potential synergistic effect with chemotherapy are still under evaluation. Nevertheless, several druggable targets have been described recently, associated with promising preclinical data that will likely have a great impact in clinical outcomes for patients with AML in the future. This review provides an overview of the novel AML treatment landscape and the most promising drugs under preclinical development that are expected to remarkably influence management of patients with AML.

## *FMS-RELATED TYROSINE KINASE 3*

*FMS-related tyrosine kinase 3 (FLT3)* is one of the most frequent mutations in AML, representing approximately 30% of mutations in patients with AML,[6] and are considered drivers in the majority of the cases. *FLT3* mutations can be found either as internal tandem duplications in the juxtamembrane domain (*FLT3*-ITD; 20%) or point mutations in the tyrosine-kinase domain (*FLT3*-TKD; 10%). *FLT3* plays a key role in controlling survival, differentiation, and proliferation of haematopoietic cells, and both *FLT3*-ITD and *FLT3*-TK constitutively activate its kinase activity. While *FLT3*-ITD has prognostic value,[7] *FLT3*-TK is weakly associated with clinical outcome.[8]

First-generation *FLT3* inhibitors, such as PKC412, are promiscuous, inhibiting several tyrosine kinases, with a transient pharmacological effect, especially when used in monotherapy in relapsed AML. This lack of specificity and high affinity may contribute to adverse effects from inhibition of multiple other kinases.[9] Although it initially demonstrated only modest single-agent activity, improved response rate and survival were achieved with PKC412 in combination with chemotherapy (complete response [CR]: 59% versus 54% in the placebo group),[10] which supported its approval by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2017. PKC412 is indicated for *FLT3* mutation-positive AML in combination with standard induction and consolidation chemotherapy. Second-generation *FLT3* inhibitors, including ASP2215,[11] crenolanib,[12] and AC220 (quizartinib),[13] display higher potency and specificity for *FLT3*, with a more restricted tyrosine-kinase recognition profile. ASP2215, a dual *FLT3/AXL* inhibitor, has been shown to be effective in a single-agent regimen in relapsed/refractory AML with *FLT3* mutation (CR: 14% versus 11% in the salvage chemotherapy control group), inducing manageable side effects,[14] leading to its recent approval by the FDA in 2018 and EMA in 2019 as a monotherapy in *FLT3* mutation-positive relapsed/refractory AML. However, extensive randomised clinical trials are needed for these drugs to properly define the AML patient population suitable for each *FLT3* inhibitor approved, as approvals for PKC412 and ASP2215 were controversial due to the marginal improvement reported.[15] Based on their broad inhibition targets besides *FLT3*, these inhibitors may also improve the prognosis in AML without *FLT3* mutations.

According to the mode of binding, *FLT3* inhibitors can be further divided into Type I and II. Type I *FLT3* inhibitors target the ATP binding site of the active conformation and

are effective against *FLT3*-ITD and *FLT3*-TKD mutations. However, Type II inhibitors recognise a pocket adjacent to the ATP binding site that is accessible in the inactive conformation: only preventing the activity of ITD mutations but sparing TKD mutations. Both PKC412 and ASP2215 are Type I inhibitors, whereas AC220 belongs to the Type II group.[16] In concordance, both PKC412 and ASP2215 promoted a consistent improvement in overall survival in all *FLT3* mutation subtypes.[10,17] The Type II inhibitor AC220 does not have significant activity against *FLT3*-TKD mutations,[18] which is an established mechanism of resistance in AC220-treated patients.[19]

Despite significant progress in the development of better *FLT3* inhibitors, emergence of resistances constitutes a major challenge.[20] Resistance mechanisms include acquisition of secondary-driven mutations[21] and modulation of alternative signalling pathways.[22] Several next-generation *FLT3* inhibitors are being pre- and clinically evaluated.

## ISOCITRATE DEHYDROGENASE

The isocitrate dehydrogenases (IDH) are key enzymes implicated in metabolism, located in cytoplasm (IDH1) and mitochondria (IDH2). Mutations in *IDH1* and *IDH2* genes are found in 10% of patients with AML.[23] IDH-based targeted therapies include small molecules aiming to restore normal IDH function and block the production or downstream effects of intermediate metabolites. IDH1-specific AG120 and IDH2-specific AG221 are potent *in vivo* mutant IDH inhibitors with high treatment responses in clinical trials (AG120 CR: 29%; AG221 CR: 19%), although no control arm was included.[24,25] AG221 was approved by the FDA in 2017 for IDH2 mutation-positive relapsed/refractory AML. Similarly, the FDA also approved AG120 for IDH1-mutant relapsed/refractory AML (2018) and newly diagnosed (age ≥75 years) IDH1-mutant AML noneligible for intensive induction chemotherapy (2019). However, neither has been approved by the EMA. Mutant-IDH inhibition prompts differentiation of leukaemic cells and the emergence of functional neutrophils, suggesting that efficiency is based on differentiation induction.[24,25] A constitutive activation of the RAS/MAPK pathway was associated with low responders in AG221-treated patients and warrants further investigation and analysis of rational combinations in order to overcome this resistance.[26] However, the use of IDH inhibitors may lead to the IDH differentiation syndrome, which results in the release of inflammatory cytokines, constituting a serious safety concern.[27] Improvement in the pharmacokinetic (avoiding rapid metabolism and clearance) and pharmacodynamic (increasing the specificity for mutant IDH, reducing undesirable effects, and increasing the therapeutic window) profiles are necessary to optimise the therapeutic potential for AML; new small molecules are under preclinical and clinical evaluation.

## B-CELL LYMPHOMA 2

The B-cell lymphoma 2 (Bcl-2) family members tightly regulate programmed cell death and are divided in three different subfamilies based on their functionality: antiapoptotic multidomain proteins (i.e., Bcl-2), proapoptotic multidomain proteins (i.e., Bax), and proapoptotic BH3-only proteins (i.e., BID). Bcl-2 is overexpressed in AML cells and its expression is associated with chemoresistance.[28,29] Despite promising results in preclinical models,[30] the efficacy in monotherapy of the first clinical-grade Bcl-2-specific inhibitor, ABT-199, is limited.[31] Previously, obatoclax, a BH3 mimetic and pan-Bcl-2 inhibitor, also showed minimal activity as a single agent in patients with AML, in contrast to its potent antileukaemic effect in preclinical settings.[32] However, ABT-199 acts synergically with HMA to induce mitochondria-mediated apoptosis in AML cells (venetoclax–azacytidine CR: 37%; venetoclax–decitabine CR: 54%; no control arm was present in these studies), probably due to the HMA-mediated downregulation of Mcl-1, in which overexpression confers resistance to ABT-199.[33,34] Alternatively, the durable remission observed in combination treatment (12.5 months, no control arm was present in the study) might be due to metabolic perturbations in the most primitive leukaemic cells.[35] ABT-199 was granted approval (FDA 2018) for elderly (≥75 years) unfit patients with AML in combination with HMA, although a confirmatory Phase III clinical trial, performed as a randomised, placebo-controlled study,

will be required to definitively measure its clinical benefit. Nevertheless, resistance to ABT-199 appears in 30% of patients with AML and neither the mechanism responsible nor a biomarker have been identified.[33]

## HEDGEHOG

The hedgehog (Hh) signalling pathway plays a key role in the development and homeostasis of many organs and tissues, and its aberrant activation is associated with tumourigenesis.[36] The importance of Hh in AML is controversial as no direct evidence of an aberrant regulation of Hh in AML cells has been consistently found.[37–39] However, the development of PF-04449913, a clinical-grade smoothened (the receptor responsible for the signalling transduction) inhibitor, demonstrated that inhibition of the Hh signalling pathway severely impaired the most primitive leukaemic cell functionality and restored chemosensitivity.[40] However, the antileukaemic effect was at least partially mediated by nonhaematopoietic stroma cells, as previously demonstrated.[37] While the clinical efficacy was evident in combination with low-dose cytarabine (CR: 17% versus 2% in the control arm), the overall response rate remained modest (overall survival: 8.8 months versus 4.9 months in the control arm), suggesting that optimisation in treatment regimens are still needed.[41] Nevertheless, PF-04449913 was approved by the FDA in 2018 for untreated elderly (≥75 years) unfit patients with AML in combination with HMA.

## OLD CONCEPTS, NEW DRUGS, AND INDICATIONS

The backbone of the first-line induction therapy is composed of the combination of cytarabine and an anthracycline (either daunorubicin or idarubicin).[2] Based on the synergism associated with the coadministration of cytarabine and daunorubicin in a specific molar ratio (from 1:1 to 10:1),[42] the liposomal formulation CPX-351 containing a fixed, synergy-proven 5:1 ratio of cytarabine and daunorubicin was developed. This encapsulation of the conventional chemotherapeutics prolongs the half-life and increases the bioavailability, as compared to the free drugs, enhancing the antileukaemic effect and inducing similar side effects.[42,43] Surprisingly, CPX-351 improved response rates in unfit and relapsed high-risk AML compared to free drugs (CR: 37% versus 26% in the control arm), without significant clinical benefit in favourable- and intermediate-risk groups.[44–46] CPX-351 constitutes mainly an improved version of the conventional combination of free cytarabine plus daunorubicin; as such, a quantitative benefit is expected rather than a qualitative one. CPX-351 has recently been approved for newly diagnosed, therapy-related AML and AML with myelodysplasia-related changes, by both the FDA (2017) and EMA (2018).

GO (mylotarg™▼, Pfizer, New York, New York, USA) is a humanised anti-CD33 monoclonal antibody conjugated to the cytotoxic agent calicheamicin. CD33 is a panmyeloid marker expressed in most AML cells and healthy myeloid progenitors and mature cells. In 2000, GO received approval for CD33-positive AML in first remission not eligible for induction therapy.[47] The confirmatory study failed to demonstrate clinical benefit for GO and demonstrated a higher rate of severe adverse effects.[48] In 2010, GO was withdrawn voluntarily from the market. However, several clinical trials have recently shown a clinical benefit in newly diagnosed patients with CD33-positive AML (CR: 73% versus 72% in the control arm), although no evidence of benefit for adverse- and intermediate-risk patients has been described.[49] GO is currently approved for newly diagnosed CD33-positive AML (FDA 2017, EMA 2018) and CD33-positive relapsed/refractory AML (FDA 2017).

## IMMUNOTHERAPY-BASED TREATMENTS IN ACUTE MYELOID LEUKAEMIA

In the last decade, major efforts have been made to develop the adoptive transfer of immune cells (T or NK cells) expressing a genetically engineered chimeric antigen receptor (CAR) in AML, following the success of this approach in CD19+ B-cell acute lymphoblastic leukaemia (B-ALL).[50] Despite numerous preclinical studies targeting different antigens (i.e., CD123, CD33, FLT3, CLL-1, and LeY), relatively few CAR-based approaches have been investigated in clinical trials in AML, showing a delay in the disease

progression without achieving remission.[51] Although the first clinical-grade CAR T in AML was generated against LeY,[52] CD33 and CD123 are currently more attractive targets, especially CD123 because of its high expression on the most primitive AML cell fraction[53] and its association with poor clinical outcome.[54] Both antigens are almost ubiquitous in AML cells, and in several normal haematopoietic cell subpopulations.[55,56] To date, the fundamental biological barrier limiting the application of CAR T cell therapy to AML is the absence of truly AML-specific surface antigens.[56–58] The prolonged myeloablation resulting from CAR T cells targeting healthy myeloid and AML cells is ultimately fatal, similar to other 'on-target off-tumour' toxicities. Additionally, the AML microenvironment is highly immunosuppressive, impacting the efficacy of immune-related therapies. The potent myeloablation induced by AML CAR T cells could serve as a novel conditioning regimen prior to allogeneic transplantation.[59]

Several immune inhibitory ligands and their receptors have been extensively studied in cancer as potential modulators of key immune checkpoints. Despite the success in solid tumours, blocking monoclonal antibodies against PD-1 (nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) have provided limited results in AML.[60,61] Combination of immune checkpoint inhibitors with HMA could represent an interesting strategy in AML.[62] Other immune-related approaches based on antibody–drug conjugates, blocking antibodies, and dual-affinity retargeting (DART) proteins are under evaluation in early-phase trials.

## NEUROTRANSMITTER RECEPTORS

Classic neurotransmitter receptors have attracted increasing attention from investigators in oncology in recent years. Both dopamine and serotonin receptors are highly expressed in AML and serve as prognostic biomarkers and therapeutic targets as their pharmacological inhibition impairs AML viability in relevant preclinical models.[63,64] Furthermore, the initial results in clinical trials indicated that a promiscuous dopamine D2 receptor antagonist reduced the leukaemia burden, although several off-target side effects discourage its use.[65] Interestingly, inhibition of both neurotransmitter receptors induced terminal differentiation of AML cells, greatly affecting the most primitive leukaemic cell population. As the block in differentiation is a common feature of all AML subtypes and differentiated cells are more sensitive to chemotherapy and lose any self-renewal capacity, differentiation-based therapies are very attractive approaches. Based on the promising preclinical data,[63,64] the differential expression of both receptors enable the existence of a feasible therapeutic window to maximise the pharmacological antileukaemic effects without major side effects, supporting the further preclinical and clinical development of specific dopamine and serotonin receptor antagonists for AML.

## ORGANELLE-DIRECTED APPROACHES

Similar to solid tumour cells, AML cells present several alterations in cell organelles. At a mitochondrial level, a distinct glucose metabolism signature,[66] an increased reactive oxygen species content,[67] greater copy numbers of mitochondrial DNA,[68] and electron transportation chain dysregulation[69] are common features in AML cells to accommodate all the neoplastic requirements. Drugging mitochondrial oxidative phosphorylation (OXPHOS) using different direct and indirect approaches demonstrated promising preclinical specific antileukaemic results,[70–73] especially considering that chemotherapy-resistant AML cells are highly dependent on high oxidative phosphorylation status.[74]

Similarly, the augmented metabolic demands associated with the transformation events result in the upregulation of the lysosomal function in leukaemic cells, inducing an increase in lysosomal biogenesis and mass together with the activation of cathepsins[75] and changes in the sphingolipid metabolism.[76] As a consequence of these lysosomal changes, AML cells present fragile lysosomes because of destabilisation of the lysosomal limiting membrane and lower pH. Currently, there is a growing interest in a group of structurally diverse small molecules classified as cationic amphiphilic drugs (CAD), defined by a hydrophobic ring moiety and an amine group.[77] Due to their physicochemical properties, CAD passively diffuse through

biological membranes and a process known as ion trapping enables their accumulation in lysosomes, eventually inducing a lysosome-dependent programmed cell death.[75,78,79] Preclinical data suggest that CAD are highly specific and widely safe; however, their pharmacological profiles are suboptimal and drug delivery improvement might be required for clinical development of this drug family.

## EPIGENETIC MODULATORS

Despite its high heterogeneity, a low mutation burden is found in AML.[80] However, global alterations in DNA methylation patterns are complex, further supporting the notion that epigenetic heterogeneity better explains leukaemia identity compared with the genetic background.[81–83] Thus, the AML epigenome has emerged as a new and exciting target for drug discovery.

The histone demethylase LSD-1 plays key roles during oncogenesis, becoming an emerging target for haematological and solid tumours. Several LSD-1 inhibitors are under clinical assessment for AML, such as ORY-1001[84] and GSK-2879552.[85] Despite the promising data generated in mouse models, these LSD-1 targeted agents induced unsubstantial overall response rates in patients with relapsed/refractory AML.[86] As the preclinical data suggested the possibility of synergistic effects of LSD-1 with already approved HMA,[84] clinical trials to evaluate the combination therapy are ongoing; therefore, the future clinical development of LSD-1 inhibitors for AML therapy is uncertain.

## FUTURE PERSPECTIVE

While advances in supportive care and prognostic risk stratification have optimised the performance of standard chemotherapy, overall long-term survival remains poor. Moreover, for four decades the treatment paradigm has been based on a simple binary distinction: intensive chemotherapy (potentially curative) and low-intensity regimens (palliative). Since 2017, several new drugs have been approved, incorporating the notion of personalised treatments for AML. However, caution should be highlighted until more extensive, carefully designed clinical trial studies are terminated and analysed. Considering the preliminary data already available, novel targeted therapies based on new mechanisms of action are likely to be more successful than current treatments, as effective antileukaemic activity with reduced toxicity is expected. In any case, validation in clinical trials should be conducted.

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# Improvements and Shortcomings in Emergency Oxygen Prescribing: A Quality Improvement Initiative at an Acute Tertiary Care Hospital

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## Abstract

Oxygen is one of the most commonly used yet poorly prescribed drugs. The 2015 British Thoracic Society (BTS) emergency oxygen audit highlighted the national shortcomings in oxygen prescribing and administration. A 2017 local audit at the Royal Sussex County Hospital, Brighton, UK, continued to demonstrate poor compliance with the BTS Oxygen Prescribing Guidelines in all areas audited. This study carried out yearly reaudits in November 2018 and 2019 to objectively measure the impact of implementing trust-wide and local interventions (July 2018 and August 2019).

Intervention 1 included introduction of the National Early Warning Score (NEWS2) scale and redesigning drug charts with tick-boxes for target oxygen saturations. Intervention 2 included mandatory junior doctor teaching on safe oxygen prescribing, 'oxygen safety' posters on audited wards, and reminders at handover for staff to measure and document oxygen saturations.

Following Intervention 1, all patients with valid oxygen prescriptions had a specified target saturations range. Intervention 2 ensured all patients had actual saturations within their prescribed target range, and 99% had oxygen saturations documented with sufficient frequency for their NEWS2 score. These were huge improvements from previous audits, during which a significant proportion of patients were at risk of hypercapnia, and those over- or underoxygenated were left unrecognised for hours. Despite improvements, 14% of patients continued to use oxygen without valid prescriptions in 2019, and drug charts were inconsistently signed for during drug rounds.

Although the implemented changes enabled drastic improvements for patient safety and quality in oxygen use, future work should ensure oxygen is always treated as a drug with suitable prescription and documentation.

## BACKGROUND

There have been seven national audits looking at the prescription of oxygen, the largest of which was the 2015 British Thoracic Society (BTS) Audit, which showed shortcomings in oxygen prescribing practices. This subsequently led to the publication of the Emergency Oxygen

Prescribing Guidelines and set the National Improvement Objectives.

A 2017 audit at an acute tertiary care hospital continued to highlight a failure to meet the expected standards. A reaudit was carried out to determine whether the implementation of trust-wide changes in July 2018, namely the introduction of a National Early Warning Score 2 (NEWS2) and newly designed drug charts, had impacted these behaviours. This study carried out yearly reaudits in November 2018 and 2019 to objectively measure the impact of implementing trust-wide and local interventions (in July 2018 and August 2019). The 2018 and 2019 audits aimed to compare current oxygen prescribing and delivery practices at the hospital to standards set by the 2015 BTS National Improvement Objectives, and evaluate changes made since the 2017 audit. Adult inpatients on four wards were audited on a single occasion using a standardised questionnaire validated by the BTS.

## INTRODUCTION

Oxygen is one of the most commonly used yet poorly prescribed drugs. There is a risk that patients may be given too little or too much oxygen, thereby increasing their mortality risk. Following the 2015 BTS National Emergency Oxygen Prescribing Audit and publication of the Emergency Oxygen Prescribing Guidelines, which showed national shortcomings,[1,2] a 2017 audit at an acute tertiary care hospital continued to highlight a failure to meet the expected standards for oxygen prescribing and administration.

## AIMS

To compare prescribing and oxygen delivery practices at an acute tertiary care hospital to standards set by the 2015 BTS National Improvement Objectives in yearly audits, and to evaluate improvements in oxygen prescribing from the changes that were implemented following a 2017 local oxygen prescribing audit. Improvements included introduction of the NEWS2 scale, new drug charts with a tick-box for target saturations ranges, educational initiatives for doctors, posters, and face-to-face reminders on oxygen prescribing guidelines for nursing staff.

## OBJECTIVES

### Primary Objectives

Based on the 2015 BTS National Improvement Objectives,[1] the authors aimed to achieve 95% of patients using oxygen to have a valid prescription with target saturation range; 100% of nursing and medical staff to be trained in the safe use of oxygen to local trust/health board oxygen policy; and 90% of patients using oxygen to have oxygen signed for at the most recent drug round.

### Secondary Objectives

Secondary objectives were to determine the percentage of patients receiving oxygen on four inpatient wards; the percentage of patients receiving oxygen with a valid drug chart prescription; the percentage of patients receiving oxygen with a valid drug chart oxygen prescription who have a target saturation range specified; the percentage of patients for whom oxygen saturations were documented with sufficient frequency according to their NEWS2; the percentage of patients receiving oxygen with a specified target saturation range, who had oxygen saturations actually measured within this range; and the percentage of patients who had oxygen signed for at each drug round.

## METHODS

The audit was applied to adult inpatients on four wards at an acute tertiary care hospital. The wards included the acute medical unit, two respiratory wards, and the coronary care unit. Data were collected by two doctors on a single occasion on all wards in November 2017, November 2018, and November 2019, using two standardised data collection sheets validated by the BTS.[1,2] The inclusion criteria for this audit was adult inpatients aged 18–75 years admitted to one of the four wards as described above.

There were two parts to the data that were collected. In Part 1 (Figure 1), data were collected from individual patients on each ward.

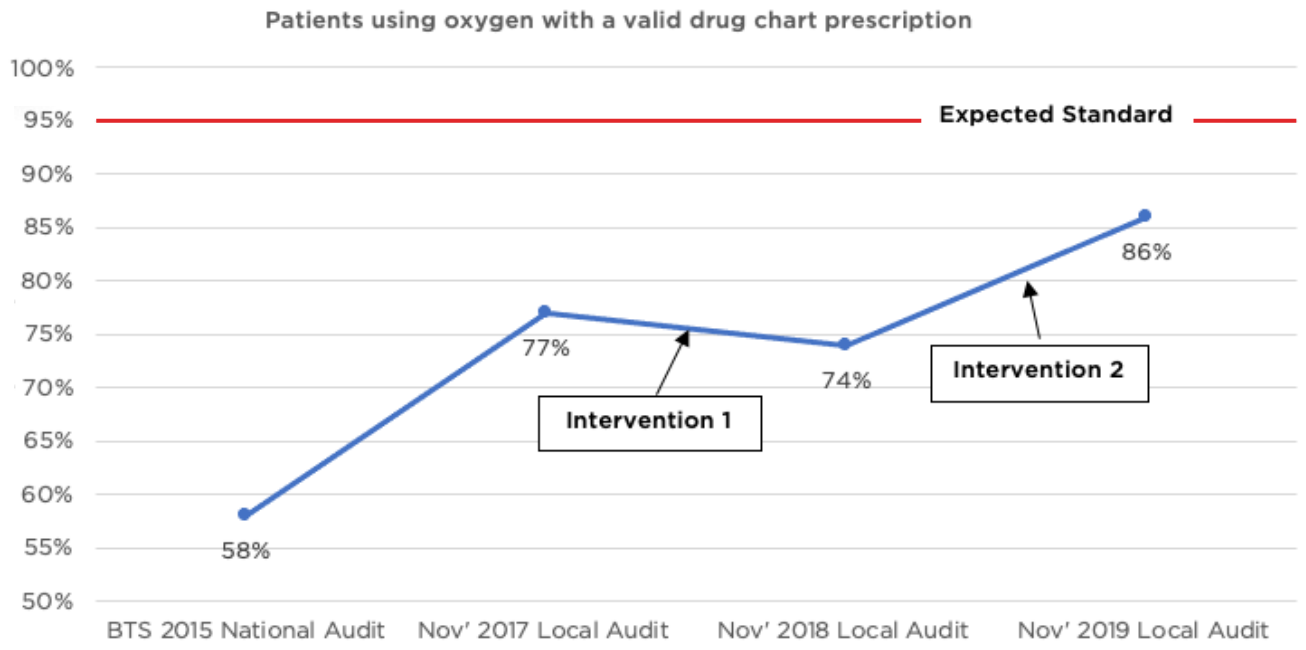


**Figure 1: Percentage of patients using oxygen with a valid drug chart prescription.**

This included patient identifier and ward details; oxygen status (whether oxygen was in use); whether a valid oxygen prescription was present; the number of drug rounds that took place in the past 24 hours; the number of times the drug chart was signed for oxygen in the previous 24 hours; the number of times oxygen should have been documented on the NEWS2 chart (based on the patient's score and observation level); the number of times oxygen saturations were actually recorded on the observation chart; and whether the oxygen saturation level of the patient was within their specified target range, and if not how far off.

In Part 2 (Figure 2), data collected from each ward were summarised. This included information on type of ward; date of audit; number of patients on each ward during the audit; number of patients using oxygen with drug chart prescriptions and specified target ranges; the total number of drug rounds in the past 24 hours and signatures on the drug chart for oxygen in the past 24 hours; the total number of observation rounds that should have taken place in the past 24 hours and how many oxygen saturations were actually monitored and recorded on the observation charts; the total number of patients with oxygen saturation levels within their specified target range, and if outside the range how great the deviation from the specified range; and the total number of patients with no oxygen prescription or target range.

Data from the above questionnaires were then collated, summarised, and analysed.

## CHANGES IMPLEMENTED

Trust-wide changes were implemented in July 2018. In Intervention 1, changes included the introduction of NEWS2 where patients with lower target saturations had a dedicated section of the observation chart, which required verification from a registrar or above, and redesigning of the drug chart to include a tick-box specifying target oxygen saturations within the dedicated oxygen prescription section.

Changes were also implemented in August–October 2019. In Intervention 2, changes included mandatory teaching for all junior doctors on safe oxygen prescribing and guidelines; posters containing 'Oxygen is a Drug' and Oxygen Prescribing Guidelines were put up around the audited wards; and reminders were given at handover meetings for nursing staff to measure, document, and administer oxygen appropriately.

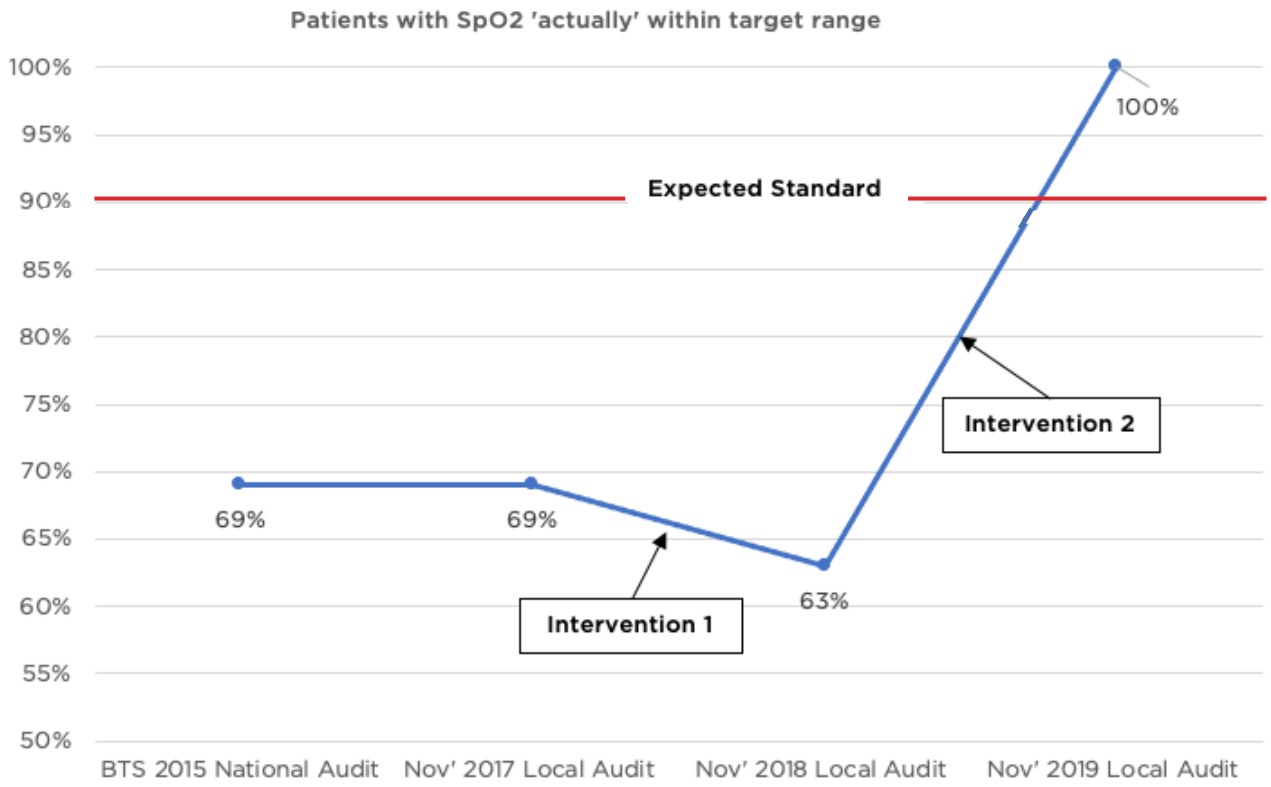


**Figure 2: Percentage of patients with oxygen saturations actually within their specified target saturations range.**

## RESULTS

Adult inpatients on four wards (acute medical unit, respiratory ward 1 and respiratory ward 2, and the coronary care unit) between the ages of 18 and 75 years were audited each year. There were 51 patients included in the 2017 audit, 61 patients in the 2018 audit, and 74 patients in the 2019 audit. Among these patients, 33% were using oxygen in 2017, 23% in 2018, and 19% in 2019.

Results (Table 1) showed that 86% of patients in the 2019 audit were using oxygen with a valid prescription, relative to 74% in 2018 and 77% in 2017 (Figure 1). One hundred percent of patients with a valid drug chart prescription had a target saturations range specified in the 2018 and 2019 audits, compared with 77% in 2017, which demonstrates a sustainable change and meets the expected standard set by the BTS. Furthermore, 99% of patients in 2019 had oxygen saturations documented with sufficient frequency for their NEWS2, which represents a 58% improvement from the 2018 audit (this outcome was not measured in the 2017 audit). There was a 37% increase (63% to 100%) in patients having actual oxygen saturations within their specified target saturation range in the 2019 reaudit, compared with the 2018 audit. This exceeded the National Improvement Objectives set by the BTS in 2015 (Figure 2). Finally, it appeared that fewer drug charts were being signed for by nursing staff to confirm administration of oxygen in the 2019 audit, relative to 2017 and 2018.

The study's reaudit in November 2018, following the changes implemented in July 2018 (Intervention 1), found that 26% of patients were still using oxygen without a valid prescription, 37% had saturations outside their target range, and only 12% of drug charts had oxygen signed. However, the new drug charts had ensured that all patients with valid oxygen prescriptions now had target saturations specified, representing a significant improvement from 2017. Whether oxygen saturations were being documented with sufficient frequency as per a patient's NEWS2 was additionally measured.

**Table 1: Comparison of yearly audited parameters with the 2015 British Thoracic Society (BTS) audit results.**

| Number of patients (%) | 2015 BTS audit | 2017 local audit | 2018 local audit | 2019 local audit |
|---|---|---|---|---|
| Patients using oxygen with a valid drug chart prescription | 58 | 77 | 74 | 86 |
| Patients using oxygen with a target saturations range specified | 58 | 77 | 100 | 100 |
| Patients with oxygen saturations documented with sufficient frequency for their NEWS2 Score | N/A | N/A | 41 | 99 |
| Patients with oxygen saturations within their target saturations range | 69 | 69 | 63 | 100 |
| Drug charts with a valid oxygen prescription with oxygen signed for at each drug round | 29 | 23 | 12 | 8 |

BTS: British Thoracic Society; N/A: not applicable; NEWS2: National Early Warning Score 2.

Based on these findings, it was recognised that not all healthcare professionals were treating oxygen as a drug, which requires appropriate prescription, monitoring, and documentation. Further changes were required to alter individual approaches to oxygen. Therefore, changes were implemented as per Intervention 2 above. The 2018 audit and its results were used to educate newly registered junior doctors of the BTS oxygen prescribing guidelines,[1,2] and the potential dangers if not adhered to, as well as provide face-to-face and poster-based reminders to all healthcare professionals. Although there were improvements in most areas audited, the proportion of valid oxygen prescriptions completed by doctors still did not meet the 95% expected standards, and drug charts were not being appropriately signed for oxygen at each drug round.

## DISCUSSION

Due to the nature of the drug and its frequent use, unfortunately, oxygen prescribing has proven to be a downfall throughout the cycles for various reasons. Poor compliance with the oxygen prescribing guidelines was found in 2017 in all areas audited. The reaudit in 2018 explored the implementation of trust-wide changes and the impact on oxygen prescribing. In the 2019 audit, 86% of patients were using oxygen with a valid prescription, compared to 74% in 2018 and 77% in 2017. Although there were improvements, the overall picture was disappointing. For an intervention to be effective past its short-term capacity, great focus should be on ongoing input from the staff on the wards in question.[3]

The significance of the implemented changes that were put into place following the 2018 audit enabled drastic improvements. There was a huge increase in the proportion of patients with a valid prescription for oxygen, target saturations range specified, and actual saturations within the specified range. These factors have a direct impact on patient safety and quality of care for those using oxygen in an acute setting. By improving these main areas, patient risk of hypercapnia and hypoxia have been lowered directly.[4-6]

Similar quality improvement initiatives, such as those carried out at a district general hospital in Somerset, UK, to improve compliance with oxygen prescribing guidelines, found that specifically targeting interventions to increase awareness of appropriate oxygen prescribing to the main groups of professionals who use oxygen (nursing staff and junior doctors) can have a significant impact.[7] Another project[3] highlighted that teaching sessions for junior and senior doctors and other allied healthcare prescribers can significantly improve the documentation and appropriate prescribing of oxygen. These projects further corroborate the research findings because they both implemented a similar strategy to drive improvement. However, another project[9] found that poster reminders and multidisciplinary team education only had a

limited impact on improving oxygen prescribing. It was the use of targeted oxygen stickers above oxygen taps that ultimately enhanced oxygen prescribing practices.

There continues to be challenges around oxygen prescribing and the related consistency with signing of drug charts.[4-6,9-11] From this study, and previous research in this area, it is has been made apparent that using focussed and targeted interventions is more likely to be able to alter attitudes around documentation and sustain this change.[4,5,12-15] By continuously reinforcing the concept of oxygen being a drug and educating staff, the changes made can not only be sustained but also used trust-wide to positively impact patient outcome. Further targeted interventions, such as oxygen target saturation stickers or wristbands, may lead to even better compliance with the oxygen prescribing guidance and ultimately improve patient safety.

## CONCLUSION

Although multiple changes were implemented over several cycles, the greatest impact was found to be from implementing staff education and awareness.[3,7] A combination of lack of awareness, not treating oxygen as a drug, and not optimally utilising the drug chart, was exposing patients to harm. Through the amalgamation of organisational changes, and smaller local changes at each hospital, there can be an overall positive impact on patient safety, which can subsequently reduce mortality and morbidity. Simple measures such as staff education, verbal and written reminders, combined with the introduction of systemic changes such as the introduction of new drug charts, and NEWS2 scales have the greatest effect on individual behaviours. Although these trust-wide changes made it easier for oxygen saturation ranges to be documented, it is through local initiatives that each team member can reflect on alterations they could make to their practice on a personal level.

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# Prominent Cutaneous Manifestation of COVID-19: A Case Report

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## Abstract

Extrapulmonary signs of coronavirus disease are becoming an important tool for patient diagnosis; this is particularly true for skin manifestations as they are visible to both the patient and physician. In this case report, the authors describe a case in which cutaneous manifestations were the most noticeable and prominent symptom in a patient with coronavirus disease.

## INTRODUCTION

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen and the subsequent coronavirus disease (COVID-19) mainly affect the lung.[1] Respiratory symptoms are key for diagnosis, however, increasing knowledge has led to the understanding that COVID-19 induces multiorgan pathology. The first descriptions of clinical symptoms reported that 0.2% of patients admitted to hospitals in China presented with a skin rash.[1] Following this, in Italy 20.4% of 88 admitted patients treated by dermatologists presented with symptoms of the skin.[2]

In April 2020, the first comprehensive classification of skin manifestations in patients within the full spectrum of COVID-19 severity, from intensive care, hospital wards, and home care, as well as those without symptoms, was published.[3] The study analysed 375 patients with PCR-confirmed diagnosis or with suspected diagnosis, meeting the European Centre for Disease Prevention and Control (ECDC) clinical criteria. Although following certain patterns, skin manifestations showed extreme variability. Five skin patterns were defined: pseudo-chilblain, vesicular, urticarial, maculopapular, and livedo/necrosis. Each pattern usually associated with a different age category, evolutionary moment of the process, and systemic severity.[3] The majority of these manifestations were non-specific and their cause–effect relationship with the virus is not fully established. The limited access to confirmatory tests and concurrence of different drugs to treat the disease make it difficult to reach any conclusions. The authors present the case of a patient in whom the most striking COVID-19 manifestation was dermatological.

## CASE REPORT

A 47-year-old female, with no relevant pathological or family medical history, presented with a dry cough, diarrhoea, and chills. Three days later, she developed a headache, myalgia, and a fever (39 °C). On Day 7, she observed anosmia and improvement of the previous symptoms. On Day 16, coinciding with worsening of headache, myalgia, chills, fever, and anosmia, she presented with a skin rash, ageusia, and nausea without vomiting. The skin eruption consisted of itchy and painful lesions, first on the abdomen and later affecting the back and limbs, including the dorsum of the hands. On examination, multiple non-scaling erythematous papules and plaques were noted.

The patient was attended to in the emergency unit. Her vital signs were a temperature of 36.4 °C, blood pressure of 130/80 mmHg, heart rate of 89 beats per minute, and oxygen saturation of 98%. Her chest X-ray was reported as normal. She was discharged home and prescribed the treatment of azithromycin 500 mg every 24 hours and dexchlorpheniramine 6 mg every 8 hours for 5 days.

In the days following, the lesions became larger and oedematous with pseudo-vesicular appearance on the dorsum of the hands (Figure 1). On Day 21, she was evaluated using teledermatology. Face-to-face consultation was recommended for examination and COVID-19 testing. On examination, her temperature was 35.5 °C, oxygen saturation was 100%, chest X-ray was normal, and nasopharyngeal PCR for SARS-CoV-2 was negative. Histopathological examination showed hyperkeratosis, parakeratosis, and acanthosis. In the dermis, a dense, sleeve-like perivascular lymphohistiocytic infiltrate with abundant eosinophils pervaded throughout the dermis. Abundant eosinophils were perivascular and interstitially located. Capillaries were conspicuously dilated and engorged with red blood cells but no fibrinoid necrosis was identified (Figure 2A). Deep eccrine glands were surrounded by moderate lymphoid and eosinophil infiltration (Figure 2A). These histopathological features have previously been observed in the skin lesions of patients with COVID-19 and have been defined as having a 'mini-chilblain' pattern (Figure 2A and 2B).[4]

The patient had follow-up home visits and was treated with paracetamol, dexchlorpheniramine, and topical mometasone once per day on the lesions. In the following days, the symptoms persisted and the lesions developed a central crusty dark area.

On Day 28, the itching began to improve, and the papules flattened and turned into hyperpigmented macules concentrically surrounded by an ecchymotic halo, sparing the skin immediately adjacent to the macules. The resolution of the lesions and the itching was gradual, totally disappearing 2 months later. Three months after the onset of symptoms, the antibody test for SARS-CoV-2 was positive. Four months later, the patient presented massive shedding. The hair loss was diffuse throughout the scalp, typical of telogen effluvium; however, they also presented round bald patches with an active border, typical of alopecia areata.

## DISCUSSION

COVID-19-associated skin manifestation reports are numerous; however, the authors believe that they are under-reported. There are several possible causes of this: the difficult recognition in patients with mild or absent general symptoms; the lack of knowledge regarding the manifestations of COVID-19; the difficulty accessing diagnostic tests; the clinical similarities among other dermatological diseases; and the self-resolving nature or short-term evolution. Due to the strain COVID-19 had on the healthcare system, skin examinations were not a priority among hospitalised or symptomatic patients, particularly in the most critical cases. Additionally, admission areas with restricted access made patient examination even more difficult, often preventing photographic record and obtainment of informed consent.

In COVID-19 pathogenesis, the host's response plays an important role. The first line of defence against SARS-CoV-2 is the innate immune system, specifically interferon-I production and natural killer (NK) cell intervention.[5] The virus dampens the initial interferon-I response to achieve uncontrolled viral replication. Subsequently, humoral and cell-mediated adaptive immunity are activated.

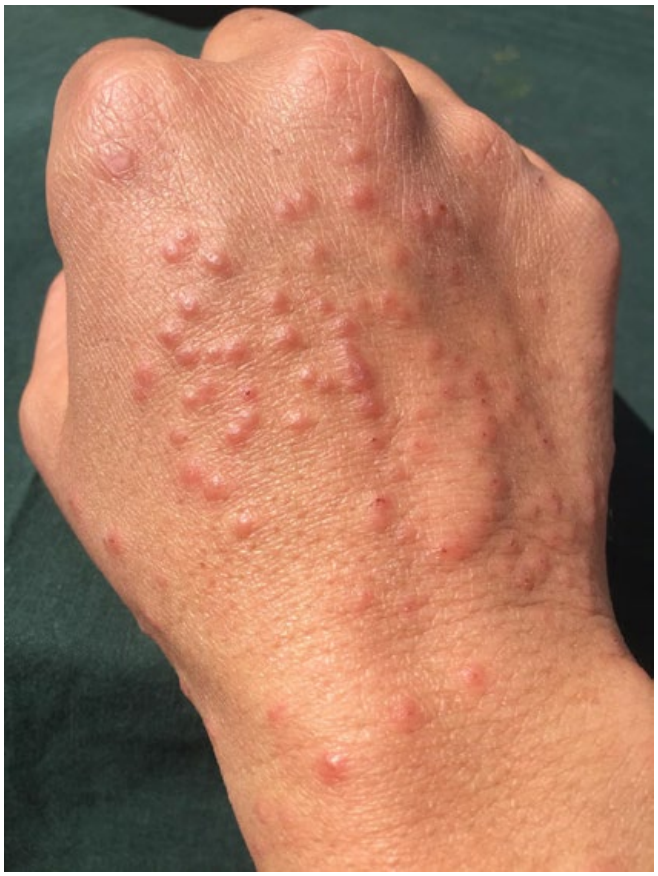

**Figure 1: Large oedematous papules on the dorsum of the hand.**

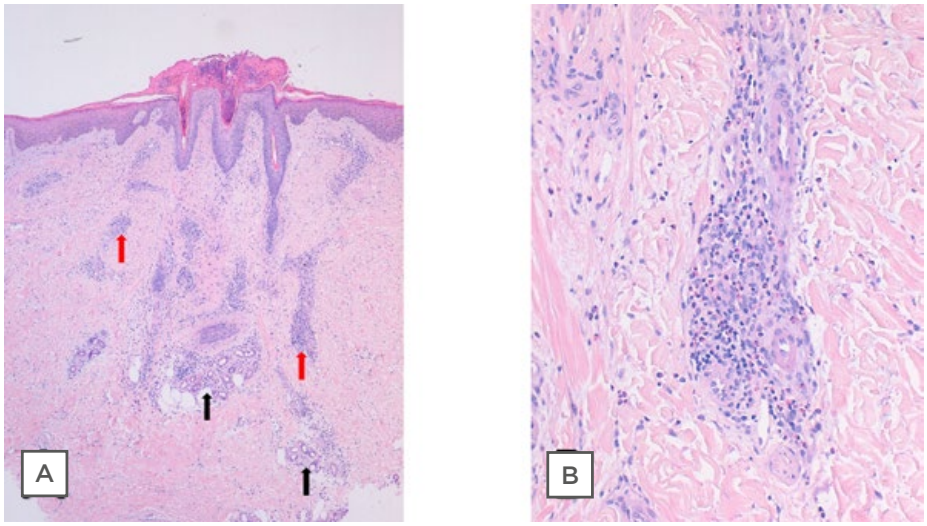


**Figure 2: Histological plates stained with haematoxylin and eosin.**

**A)** 4x: Panoramic skin biopsy showing hyperkeratosis, parakeratosis, and acanthosis. In the dermis is a dense, sleeve-like perivascular lymphohistiocytic infiltrate with abundant eosinophils. Eosinophils were abundant, perivascular, and interstitially located. Capillaries were conspicuously dilated and engorged with red blood cells, but no fibrinoid necrosis was identified (red arrows). Deep eccrine glands were surrounded by moderate lymphoid and eosinophil infiltration (black arrows). **B)** 20x: Photograph at high magnification showing lymphohistiocytic infiltrate with the presence of eosinophils.

Inflammatory cytokines and antibodies promote the recruitment of neutrophils, monocytes, and macrophages, stimulating further development of additional inflammatory cytokines. In critical cases, activation of the coagulation pathway occurs with consumption of coagulation factors,[6] leading to multiorgan thrombotic manifestations, including thrombosis of pulmonary and skin vessels.[7] In the majority of infected patients, the immune response leads to viral clearance. However, if the effector response results in an antibody-dependent enhancement (ADE), which favours the entry of the virus into macrophages, it will result in the increase of proinflammatory cytokines such as TNF and IL-6.[5] This phenomenon, known as cytokine storm, is the cause of tissue damage and multiorgan dysfunction and could also manifest on the skin.[8] Nevertheless, as well as in other organs, the different manifestations of the disease in the skin must be related to the diverse immune responses of the host.[9]

In addition to the pattern classification described prior, another interesting study proposed a classification with two groups: exanthematic and inflammatory lesions; and vasculitic and vasculopathic lesions. In the second group, the authors differentiated the purpuric vasculitic pattern, which has a low incidence, from the petechial component in some exanthematic lesions.[10] In those patterns cited, different histological and immunohistochemical findings and distinct pathophysiological hypotheses related to different host immune responses were described. A robust innate immunity response would be related to chilblain-like lesions, whereas the hypercoagulable state and cytokine storm would induce pauci-inflammatory thrombotic microangiopathy with the development of livedo or necrotic lesions.[7] Direct viral cellular damage of angiotensin-converting enzyme 2 (ACE2) receptors on basal cells would induce the vesicular pattern. Antigen–antibody complex deposits, non-specific activation of mast cells, viral endothelial damage (rich in ACE2), complement activation, and activation of the bradykinin–kallikrein system have been postulated as cause of the urticarial pattern.[11,12] In many occasions, other intercurrent causes, such as the reactivation of viral diseases or toxicoderma, cannot be ruled out.

The interest in the reported case lies in the clinical presentation of the greatly expressed skin manifestations, which is not previously described. The skin lesions were complex, long-lasting, and highly symptomatic, representing the most striking symptom of the patient's symptomatology. These lesions concurred with mild general symptoms in the second week after onset and lasted for 2 months. They produced intense itching with poor response to antihistamine treatment. They evolved from small papules without scaly component to larger, oedematous, pseudo-vesicular papules resembling erythema elevatum diutinum. Later, the papules developed a central scaling with target-like images reminiscent of erythema multiforme. In the time they were flattening into macules, they presented striking concentric ecchymotic haloes. Four weeks after the disappearance of the skin lesions, intense telogen effluvium and alopecia areata appeared: two types of hair loss with different physiopathology, which do not usually appear concomitantly. No manifestations were found in mucous membranes or nails.

Taking into account the main patterns described, a maculopapular rash can be identified. Its onset coincided with the rest of the systemic symptoms, although these had already been present for 2 weeks. The effects of the medication should not be considered since the onset of the lesions was prior to the administration of any treatment. The resolution phase, with ecchymosis surrounding the lesions, cannot be explained by scratching since it had a rounded and concentric distribution around the papules and there were no linear erosions. The relationship of this sign with endothelial damage and the tendency towards hypercoagulability in patients with COVID-19 is not supported by the histological study of the biopsy. Appearance of telogen effluvium after infectious diseases is well described and the authors unreported experience supports that it is not uncommon after COVID-19.[13] Alopecia areata is also already described.[14] Traditionally, it has been related to immune disorders and stress; the patient reported an intense emotional burden due to the pandemic, the isolation situation, and the discomfort caused by the skin rash. Interestingly, both types of alopecia have been diagnosed more frequently after the peaks of the pandemic compared to previous periods.[14,15]

Based on the literature reviewed, the authors assume that this patient's specific and dysregulated immune response led to her diverse and prolonged dermatological manifestations. Reporting cases is vital to expand information and provide a more precise approach to COVID-19 skin manifestations. The skin is an organ accessible to visual examination and can be extremely helpful in regard to this worldwide relevant disease.

Note: the patient consented to the presentation of the case and the images. This case is one of 375 cases in a published cohort study,[3] and this case report has approval from the publishing journal.

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# Pretransplant Determinants of Outcome in Patients with Myeloma Undergoing Autologous Transplantation in Lower Resource Settings

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## Abstract

The treatment landscape in multiple myeloma has significantly changed since the introduction of high-dose melphalan with autologous stem cell rescue in the 1980s. Many randomised controlled trials have clearly demonstrated the superiority of autologous stem cell transplantation in improving survival compared to conventional chemotherapy. However, outcomes in myeloma are highly variable with median survival as short as 2 years and as long as 10 years or more. The main adverse factor predicting shorter survival is presence of high-risk cytogenetics. However, there are many other potential factors that can contribute to the treatment outcomes. This review looks at the various pretransplant variables that are associated with post-transplant outcomes in myeloma.

## INTRODUCTION

Multiple myeloma is a malignant neoplasm arising from clonal proliferation of plasma cells in the bone marrow.[1] Active myeloma is defined by the presence of CRAB criteria (hypercalcaemia, renal dysfunction, anaemia, and bone lesions) and/or by the presence of biomarkers (plasma cells: ≥60%; involved-to-uninvolved serum free light chain ratio: ≥100; >1 focal lesion on MRI).[2] Despite so many advances in the field of myeloma and the availability of many newer potent agents, myeloma remains incurable. However, these newer agents have undoubtedly helped improve survival in myeloma to the extent that it can now be considered a chronic condition in some patients.[3,4]

The treatment landscape in myeloma has significantly changed ever since the introduction of high-dose melphalan with autologous stem cell rescue in the 1980s. The first randomised controlled trial (RCT) by the Intergroupe Francophone du Myélome (IFM) in 1996 clearly showed the superiority of high-dose melphalan followed by autologous stem cell transplantation (ASCT) over conventional chemotherapy.[5] Since then, high-dose melphalan with stem cell transplantation has been the backbone of myeloma treatment. However, outcomes in myeloma are highly variable with median survival as short as 2 years and as long as 10 years or more.[6] The main risk factor associated with shorter survival is presence of high-risk cytogenetics.[6] However, there are many other potential factors that can

contribute to the treatment outcomes. Hence, this review explores the various pretransplant variables that are associated with post-transplant outcomes.

## BENEFIT OF AUTOLOGOUS STEM CELL TRANSPLANTATION

The results from the first two landmark clinical trials, IFM 90 trial and UK Medical Research Council (MRC) trial, have proven the superior role of ASCT in improving progression-free survival (PFS) and overall survival (OS) compared to conventional treatment. In the IFM 90 trial, involving 200 patients, ASCT was associated with higher complete responses (CR) (22% versus 5%), 5-year event-free survival (EFS) (28% versus 10%), and higher OS (52% versus 12%).[5] In the MRC trial, involving 401 patients, results were similar to IFM 90 with improved CR, PFS, and OS in the ASCT arm.[7] Three later RCT, however, failed to show any survival benefit of ASCT.[8-10] Differential benefits on survival from these trials have to be addressed with caution as there was variability in the patients' age groups, induction and conditioning regimens, and the response criteria. The role of ASCT in the era of modern drugs, such as proteasome inhibitors (PI) and immunomodulatory imide drugs, was studied in four RCT, and had shown benefit in favour of ASCT in improving PFS in all four and OS in two.[11-14] In the largest study, involving 1,503 patients from multiple centres under the European Myeloma Network (EMN) group, ASCT improved response rates (≥very good partial response [VGPR] 84% versus 77%, and median PFS [57 months versus 42 months]), however, there was no OS benefit.[14] A meta-analysis of the aforementioned mentioned trials using novel drugs, also concluded that there was significant improvement in PFS and a trend for benefit in terms of OS (hazard ratio for PFS: 0.55; p<0.001; hazard ratio for OS: 0.76; p=0.20).[15] The main findings from the key RCT are shown in Table 1.

**Table 1: Key randomised controlled trials comparing autologous stem cell transplantation with conventional chemotherapy in myeloma.**

| Reference | Age | N | Regimen (ASCT versus CCT) | CR (%) | PFS (median) | OS |
|---|---|---|---|---|---|---|
| Attal et al.,[5] 1996 | <65 | 200 | VMCP/BVAP x 4–6 + (Mel 140 + Gy 8 TBI) versus VMCP/ BVAP x 18 cycles | 22 versus 5; p<0.001 | EFS at 5 years: 28 versus 10%; p=0.01 | At 5 years: 52 versus 12%; p=0.03 |
| Child et al.,[7] 2003 | <65 | 401 | AVMpC x ≥3 + Mel 200 versus ABCM x 4–12 | 44 versus 8; p<0.001 | 31 versus 19 months; p<0.001 | Median: 54 versus 42 months; p=0.04 |
| Fermand et al.,[8] 2005 | 55–65 | 190 | VAMP x 3–4 + (Mel 200 OR BU + Mel 140) versus VMCP | 36 versus 20 | EFS at 25 months versus 19; p=0.07 | Median: 47 versus 47 months; p=0.91 |
| Blade et al.,[9] 2005 | <65 | 216 | VBMCP/VBAD x 4 + (Mel 200 or Mel 140 + Gy 12 TBI) versus VBMCP/VBAD x 12 | 30 versus 11; p=0.002 | 42 months versus 33; p=NS | Median: 61 versus 66 months |

**Table 1 continued.**

| Reference | Age | N | Regimen (ASCT versus CCT) | CR (%) | PFS (median) | OS |
|---|---|---|---|---|---|---|
| Barlogie et al.,[10] 2006 | ≤70 | 516 | VAD x 4+ (Mel 140 + Gy 12 TBI) versus VAD x 4+ 1-year VBMCP ± IFN maintenance | 11 versus 11 | At 7 years: 17 versus 14%; p=0.16 | At 7 years: 38 versus 39%; p=0.78 |
| Palumbo et al.,[11] 2014 | ≤65 | 402 | RD x 4 + Mel 200 versus RD x 4 + MPR x 6, ± R maintenance | 16 versus 20 | 43 versus 22 months; p<0.001 | At 4 years: 81 versus 65%; p=0.02 |
| Gay,[12] 2015 | ≤65 | 389 | RD x 4 + Mel 200 (2) versus RD x 4 + RCD x 6, RP versus R maintenance | 33–37 versus 23–27 | 43 versus 29 months; p<0.0001 | At 4 years: 86 versus 73%; p=0.004 |
| Attal,[13] 2017 | ≤65 | 700 | RVD x 3 + Mel 200 + RVD x 2 versus RVD x 3 + RVD x 5, R maintenance | 59 versus 48; p=0.03 | 50 versus 36 months; p<0.001 | At 4 years: 81 versus 82%; p=NS |
| Cavo,[14] 2020 | 18–65 | 1,503 | VCD x 3–4 + Mel 200 x 1 or 2 ± RVD x 2 + R maintenance versus VCD x 3–4 + VMP x 4 ± RVD x 2 + R maintenance | ≥VGPR 84 versus 77; p=0.002 | 57 versus 42 months; p=0.0001 | At 5 years: 75 versus 72%; p=NS |

ABCM: adriamycin/carmustine/cyclophosphamide/melphalan; ASCT: autologous stem cell transplantation; AVMpC: adriamycin/vincristine/methylprednisolone/cyclophosphamide; BU: busulfan; CCT: conventional chemotherapy; CR: complete response; EFS: event free survival; IFN: interferon; Mel 140: melphalan 140 mg/m$^2$; Mel 200: melphalan 200 mg/m$^2$; MPR: melphalan/prednisolone/lenalidomide; NS: not significant; OS: overall survival; PFS: progression free survival; R: lenalidomide; RCD: lenalidomide/cyclophosphamide/dexamethasone; RD: lenalidomide/dexamethasone; RP: lenalidomide/prednisolone; RVD: lenalidomide/bortezomib/dexamethasone; TBI: total body irradiation; VAD: vincristine/adriamycin/dexamethasone; VAMP: vincristine/adriamycin/methylprednisolone; VBMCP: vincristine/carmustine/melphalan/cyclophosphamide/prednisolone; VBMCP/VBAD: vincristine, carmustine, melphalan, cyclophosphamide, prednisolone/vincristine, carmustine, adriamycin, dexamethasone; VCD: bortezomib/cyclophosphamide/dexamethasone; VGPR: very good partial response; VMP: bortezomib/melphalan/prednisolone; VMPC: vincristine/melphalan/cyclophosphamide/prednisolone; VMCP/BVAP: vincristine, melphalan, cyclophosphamide, prednisolone/carmustine, vincristine, adriamycin, prednisolone.

Adriamycin® (Pfizer Inc., New York City, New York, USA).

## CONVENTIONAL KARYOTYPING-BASED RISK ASSESSMENT

Conventional cytogenetics reveal abnormalities in roughly one-third of patients with myeloma.[16,17] These are mainly numerical aberrations. The low yield is caused by the low proliferative nature of plasma cells. Monosomy or deletion (q) of chromosome *13* and hypodiploidy are considered as high-risk features and are associated with inferior survival. In a report from the Mayo Clinic, 290 patients received information on conventional karyotyping: 39% had undergone ASCT and the median survival time of patients with high-risk cytogenetic abnormalities (CA) was 29 months versus 65 months in those at standard risk (p=0.006).[18] The Groupe Français de Cytogénétique Hématologique showed that among 208 patients, 75 patients had a hyperdiploidy karyotype and 63 were labelled as having hypodiploidy defined as pseudodiploid, hypodiploid, or near-tetraploid chromosomes. In a multivariate analysis, the hypodiploid group had inferior survival compared to hyperdiploid group and *del 13q* lost its prognostic value in presence of hypodiploidy.[19] Chromosome *13* abnormality retains a negative prognostic value even in patients undergoing high-dose chemotherapy and autotransplant.[20,21] However, it is to be noted that detection of *del 13q* by interphase fluorescent *in situ* hybridisation (FISH) does not have any negative impact on hyperdiploid myeloma.[22]

## FISH-BASED RISK ASSESSMENT

As a result of the poor yield by conventional karyotyping, more sensitive measures such as FISH are routinely performed for myeloma prognostication. FISH, currently considered as the standard assay, is performed on purified CD138-expressing plasma cells, or by dual-staining of cytoplasmic immunoglobulin-aided FISH.[6] The International Myeloma Working Group (IMWG) classifies myeloma as high-risk if at least one of *t(4;14)*, *t(14;16)*, *t(14;20)*, or *del 17p* is detected by FISH.[23] In addition, a gain of *1q* also confers poor risk.[24] Bortezomib-containing induction regimen combined with ASCT can overcome the poor prognostic impact of *t(4;14)* and to some extent *del 17p*. In the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) trial, in which 25% of the patients had *t(4;14)*, bortezomib/thalidomide/dexamethasone (VTD) treatment could negate the poor prognostic role of *t(4;14)* (3-year PFS of 69% in patients with *t(4;14)* versus 74% without; p=0.66), whereas the thalidomide/dexamethasone arm could not (3-year PFS of 37% in patients with *t(4;14)* versus 63% without; p=0.01).[25] Data from 354 patients with myeloma from the HOVON-65/GMMG-HD4 trial showed that bortezomib could significantly reduce the adverse impact of *del 17p*, which was present in 11% of patients. Patients were randomly assigned to cycles of vincristine/adriamycin® ([doxorubicin] Pfizer Inc., New York City, New York, USA)/dexamethasone (VAD) or bortezomib/adriamycin/dexamethasone induction followed by ASCT. In patients with *del 17p*, the bortezomib arm led to significant improvement in both PFS (median: 26 months versus 12 months) and 3-year OS (69% versus 17%).[26] Combinations of bortezomib with lenalidomide/dexamethasone[27,28] or carfilzomib with lenalidomide/dexamethasone[29] are also effective in reducing the adverse impact of *t(4;14)* and/or *del 17p* on PFS in myeloma. Major CA and their impacts are summarised in Table 2.

## THE REVISED INTERNATIONAL STAGING SYSTEM

The International Staging System (ISS) helps to stratify myeloma based on two parameters, albumin and $\beta_2$-microglobulin, and categorises patients into three groups: ISS Stage I, II, and III, with median survival of 62, 44, and 29 months, respectively.[30] The Revised-ISS (R-ISS) was formulated by combining ISS parameters with two additional parameters, namely a lactate dehydrogenase (LDH) assay and high-risk CA. It was derived from clinical and laboratory data, pooled from 11 international trials involving 4,445 newly diagnosed patients with myeloma. R-ISS stage I was defined as ISS stage I ($\beta_2$-microglobulin <3.5 mg/L and albumin >3.5 g/dL), no high-risk CA (*del 17p*, and/or *t[4;14]*, and/or *t[14;16]*), and normal LDH.

**Table 2: Important cytogenetic alterations in multiple myeloma.**

| Cytogenetic changes | Risk category | Prevalence in NDMM (%) |
|---|---|---|
| *t(4;14) (p16;q32)/IGH-MMSET/FGFR3* | Adverse | 10–15 |
| *t(14;20) (q32;q12)/IGH-MAFB* | Adverse | 1 |
| *t(14;16) (q32;q23)/IGH-MAF* | Adverse | 2–5 |
| *t(6;14) (p21;q32)/IGH-CCND3* | Standard | 2 |
| *t(11;14) (q13;q32)/IGH-CCND1* | Standard | 15–20 |
| *17p* deletion | Adverse | 10 |
| *1q21* gain | Adverse | 35–40 |
| *1p* deletion | Adverse | 30 |
| Hyperdiploidy | Good | 50 |
| *13q* deletion (by CK) | Adverse | 45–50 |

CK: conventional karyotyping; NDMM: newly diagnosed multiple myeloma.

R-ISS stage III was defined as ISS stage III ($\beta_2$-microglobulin >5.5 mg/L) and high-risk CA or high LDH. R-ISS could retain its value in delineating patients who had also undergone ASCT into the three risk groups. In total, 60% of patients had undergone ASCT and the median OS in R-ISS I, II, and III groups were 'not reached', 88 months, and 42 months, respectively.[31]

## TYPE OF INDUCTION CHEMOTHERAPY

Induction chemotherapy in transplant-eligible patients is given with the purpose of improving symptoms, performance status, regaining normal renal functions, correcting hypercalcaemia, and achieving an optimum response. Before the availability of novel agents, VAD was the main induction regimen for myeloma. Response rates were less, in the range 50–55%, and with very few patients achieving CR.[32] Toxicity related to anthracyclines, need for continuous infusion, and the risks associated with central venous catheters were the major concerns with this regimen. Later on, efforts were made to replace doxorubicin with a liposomal form, which led to similar response rates and survival, with less toxicity.[33]

After the introduction of novel agents, many studies have proven superiority to the same degree. Combination of thalidomide with dexamethasone improved response rates, both VGPR and CR, compared to VAD, before transplant.[34,35] A meta-analysis of over 6,000 transplant-eligible patients with myeloma also reported the superiority of novel agents in improving PFS compared to the VAD regimen.[36] Three-drug induction regimens are more effective than two-drug regimens in improving response rates and PFS. In two RCT and one meta-analysis, VTD improved response rates and PFS compared to thalidomide/dexamethasone.[25,36,37] In a Phase III trial comparing VTD with bortezomib/dexamethasone (VD), the former led to better response rates; however, there were no differences in PFS or OS, which could be explained by the higher numbers of patients receiving consolidation and maintenance therapy in the VD arm.[38] In the Southwest Oncology Group (SWOG) S0777 trial, combination of lenalidomide with VD (RVD) was compared against lenalidomide/dexamethasone, and the RVD arm showed improved response rates, PFS, and OS.[39] In one of the largest retrospective studies, comparing different induction regimens, RVD led to superior response rates and OS relative to bortezomib/cyclophosphamide/dexamethasone and VD.[40]

Since the introduction of next-generation PI, namely carfilzomib, which has been reported to induce very high rates of minimal/measurable

residual disease (MRD) negativity,[41] there has been a growing enthusiasm for substituting bortezomib with carfilzomib in the induction regimens. However, two recently published Phase III trials failed to demonstrate any advantage of carfilzomib over bortezomib with respect to response, PFS, or OS. In the ENDURANCE trial, 1,087 patients newly diagnosed with myeloma, without high-risk features, were randomised to nine cycles of induction with either carfilzomib/lenalidomide/dexamethasone or bortezomib/lenalidomide/dexamethasone, followed by another randomisation to lenalidomide maintenance for 2 years versus until progression or toxicity. Median PFS (35 months versus 34 months) and 3-year OS (86% versus 84%) were similar between the two groups.[42] In another Phase III trial (CLARION), in elderly patients with myeloma, similar results were obtained when patients were randomly assigned to bortezomib/melphalan/prednisolone versus carfilzomib/melphalan/prednisolone.[43] Recently, combinations of daratumumab to triple-drug induction regimens have been trialled; daratumumab was added to bortezomib/cyclophosphamide/dexamethasone, bortezomib/lenalidomide/dexamethasone, bortezomib/thalidomide/dexamethasone, and carfilzomib/lenalidomide/dexamethasone in various trials and resulted in encouraging response rates with acceptable toxicity profiles.[44]

## RESPONSE TO CHEMOTHERAPY

Many published studies have reported that stronger responses are associated with better survival in myeloma.[45] This is also applicable to responses at the end of induction therapy in patients undergoing ASCT. In a single-centre study from the UK involving 383 transplant-eligible patients with newly diagnosed multiple myeloma, achievement of partial response or CR at the end of induction therapy led to improvement in OS (median: 7.47 years in responders versus 4.89 years in nonresponders).[46] In another single-centre study involving 211 patients, CR at transplant led to better EFS (median EFS not reached in patients with CR versus 11 months in patients with less than CR).[47] At least three more studies have shown that achieving CR or PR pretransplant was associated with improvement in both EFS/PFS and OS.[48–50] These findings were further supported by a large meta-analysis of 21 ASCT studies involving nearly 5,000 patients, which showed that pretransplant maximum response (CR, near-CR, and VGPR) significantly improved both EFS/PFS and OS.[51] A reduction in post-treatment fluorodeoxyglucose avidity scores by positron emission tomography was associated with improved survival outcomes. A Deauville score value of <4 of the bone marrow and focal lesions after therapy at premaintenance phase was associated with significant improvement in PFS and OS.[52]

There is a recent growing interest in outcomes based on MRD negativity. In the MRC Myeloma IX trial, end of induction MRD negativity with multiparameter flow cytometry significantly improved PFS post-transplant, but there was no difference in OS.[53] The GEM/PETHEMA study group reported that pretransplant MRD negativity by multiparameter flow cytometry resulted in a significant improvement in PFS (5-year PFS: 80% in MRD negative group versus 25% in MRD positive group; p=0.001) and a trend toward improved OS (5-year OS: 100% versus 59%; p=0.06).[54] A PCR-based MRD assessment study, from marrow samples, demonstrated that low levels of MRD pretransplant is associated with an improvement in both EFS and OS. Median EFS (35 months versus 20 months; p=0.001) and OS (70 months versus 45 months; p=0.04) were significantly better in the low MRD group versus the high MRD group.[55] A meta-analysis of 21 studies, which measured response based on MRD criteria, reported that achieving MRD negativity could improve PFS and OS.[56]

## TIMING OF TRANSPLANT

With the availability of many highly active novel agents for myeloma treatment, the role of transplant upfront was questioned. However, in an era of both conventional and newer agents, it has been demonstrated that early transplant improves response rates and PFS. An RCT, in the era of conventional agents, compared upfront transplant (early transplant group) against conventional chemotherapy

(late transplant group). A rescue transplant was considered in the late group with progression/poor response to chemotherapy. The early group showed a better response and PFS, but with no difference to OS.[57] Later, two retrospective studies, in the era of novel agents, failed to show any benefit of early transplant with respect to either PFS or OS.[58,59] Gay et al.,[60] in a pooled analysis of two RCT (RV-MM-209 and EMN-441), reported that early ASCT was associated with significant improvement in PFS1 (median: 42 months versus 24 months; p<0.001), PFS2 (4 years: 71% versus 54%; p<0.001), and OS (4 years: 84% versus 70%; p<0.001), and that the benefit was seen across all prognostic subgroups.[60] In the only RCT using both lenalidomide and bortezomib in induction (IFM 2009), early transplant resulted in improved response rates (59% versus 48%), including MRD negativity, and better PFS (median 50 months versus 36 months), yet no difference in OS (at 4 years: 81% versus 82%).[13] Despite the lack of definite OS benefit in the majority of studies, early transplantation should still be the first choice in multiple myeloma. Moreover, given the idea that achieving the maximum possible response, even to the extent of MRD negativity, can guarantee long-term survival benefit, early transplant should be offered in all possible situations.[56] Transplant at progression, even though a reasonable choice, may be hindered because of concerns over advancing age, newly acquired comorbidities, and poorer response to salvage treatment.

In general, stem cell mobilisation is recommended after 4–6 cycles of induction chemotherapy. For mobilisation, two types of regimens are commonly used: granulocyte colony-stimulating factor alone or a combination of granulocyte colony-stimulating factor with cyclophosphamide. In case of inadequate mobilisation, plerixafor can be added. The specific mechanism of action of the latter, CXCR4 antagonism, helps to overcome the poor stem cell yield, associated with prolonged lenalidomide use in induction chemotherapy. Given the ongoing global coronavirus disease (COVID-19) pandemic, various national and international societies have recommended postponing autologous transplantation, especially in patients of standard risk.[61,62]

## CONDITIONING REGIMENS

Many different conditioning regimens have been tried in myeloma over the last 20–25 years. Based on results from two prospective RCT, melphalan 200 mg/m$^2$ (Mel 200) is now the accepted standard regimen. In the IFM 9502 trial, involving 282 patients <65 years of age, Mel 200 was compared with Mel 140 + 8 Gy total body irradiation. Mel 200 was associated with faster haematologic recovery, lower degree of mucositis, shorter duration of hospitalisation, and better OS at 45 months (66% versus 45%), even though there was no difference in EFS.[63] In an Italian multicentre study, Mel 200 was compared against Mel 100; the study concluded that Mel 200 resulted in improved PFS (median: 31 months versus 26 months; p=0.01) and a trend toward improved OS (at 5 years: 62 months versus 48 months; p=0.13).[64] Efforts to further intensify the conditioning regimen by additional chemotherapy did not show any benefit. In an RCT by the West German Myeloma Study Group, addition of idarubicin and cyclophosphamide to Mel 200 resulted in increased toxicity, high mortality, and no significant difference in response rates or survival.[65] Similarly, addition of busulfan to melphalan,[66,67] or a regimen containing thiotepa, busulfan, and cyclophosphamide (compared against Mel 200) did not result in superior outcomes.[68] Addition of bortezomib or carmustine with high-dose melphalan has been investigated in Phase II studies and show promising response rates; however, larger RCT are required for confirmation.[69,70]

## LIMITATIONS

Since this review has been written mainly from a practical point of view applicable to developing countries, where access to molecules like daratumumab is difficult and MRD measurement is not yet a routine practice, such things were not discussed in much detail. There is now strong evidence to suggest that achieving MRD negativity improves long-term survival and can be used as a surrogate endpoint for both PFS and OS in myeloma.[71,72] Similarly,

inclusion of anti-CD38 antibodies in the initial treatment regimen has improved PFS and OS in at least two RCT.[73] The author supports these changes in response assessment and treatment becoming part of routine management for patients with myeloma, including in developing countries.

## CONCLUSION

High-dose melphalan followed by ASCT is the cornerstone of treatment in medically fit patients with newly diagnosed myeloma and holds value even in the era of highly active, novel agents. There are important pretransplant variables that have a role in predicting post-transplant outcomes. CA by conventional cytogenetics (*del 13q*, hypodiploidy) or interphase FISH (*del 17p*, *t[4;14]*, *t[14;16]*, *t[14;20]*) are associated with inferior outcomes. Triple-drug induction regimens, containing a PI and immunomodulatory imide drugs, lead to the best outcomes post-transplant with respect to response rates and survival, with this particular combination negating the adverse impact of high-risk cytogenetics to a great extent. It is ideal to have the best response at the end of induction chemotherapy, which has been found to prolong survival after transplant. An early transplant rather than at the time of relapse/progression would be the ideal strategy, with Mel 200 as the standard conditioning regimen. Well-conducted clinical trials, especially RCT, should be considered for assessing the utility of MRD measurements in making treatment decisions, as MRD appears to be a powerful prognostic marker in myeloma.

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# Rifampicin-Induced Thrombocytopenia: A Case Report and Short Review of the Literature

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## Abstract

Thrombocytopenia may be associated with a variety of conditions and risks depending on its severity, ranging from mild epistaxis to life-threating bleeding. Many drugs or herbal remedies can cause thrombocytopenia by either inhibiting platelet production and/or enhancing their destruction from the peripheral blood mediated via an immunological mechanism implicating drug-dependent antibodies. The latter entity is called drug-induced immune thrombocytopenia: a life-threatening, under-recognised condition, which is often a diagnostic challenge. Rifampicin is a widely used, well-tolerated, and effective bactericidal drug. Adverse events, except for gastrointestinal effects, headache, skin rash, and pruritus, are uncommon. The authors herein report on a patient with isolated thrombocytopenia with a recent medical history of brucellosis on rifampicin and doxycycline. Thrombocytopenia was proved to be rifampicin-induced. Also presented is a short review of the literature on this rare subject, which should be of great importance to clinicians.

## INTRODUCTION

Thrombocytopenia is generally defined as a platelet count below the lower normal limit, <150x10$^9$/L, although many suggest that a cut-off value of 100x10$^9$/L is more appropriate to identify clinically significant thrombocytopenia.[1] It may be associated with a variety of conditions and risks ranging from mild epistaxis to life-threating bleeding. At the time of initial presentation, thrombocytopenia may be isolated or combined with other cytopenias. The cause of thrombocytopenia may be unclear,[2] and the clinician is usually faced with distinguishing among various possible pathologies such as sepsis, disseminated intravascular coagulation, microangiopathic processes, or autoimmune disease.[3,4] Many drugs and components, including nutritional supplements or herbal remedies,[5] can also cause thrombocytopenia by either inhibiting platelet production and/or enhancing their destruction from the peripheral blood mediated via drug-induced immune thrombocytopenia (DITP).[6]

DITP is a life-threatening, under-recognised condition, and is often a diagnostic challenge.[7] Detection of drug-dependent antibodies (DDabs) in a patient's serum or plasma with

suspected DITP is often not possible. This is untrue for heparin-induced-thrombocytopenia, for which the detection of antibodies against platelet factor 4-heparin complex can confirm the suspected diagnosis. Most patients with DITP have multiple comorbidities and other potential causes of thrombocytopenia;[7] thus, patients with DITP are often diagnosed with idiopathic immune thrombocytopenic purpura. It should be noted that heparin-induced-thrombocytopenia is a special case of drug-induced thrombocytopenia with a mechanism unrelated to other DITP.

Rifampicin is a widely used, well-tolerated, and effective bactericidal drug. It is the most commonly used drug for nontuberculous mycobacterial disease but may also be part of antituberculosis or antibrucellosis regimens, or serve as prophylaxis following exposure to *Neisseria meningitidis* or *Haemophilus influenzae*. Adverse events are uncommon, except for gastrointestinal effects, headache, skin rash, and pruritus.

Brucellosis is a zoonotic disease with a wide clinical spectrum. Haematological abnormalities have been seen in brucella-infected patients and the most encountered are anaemia and leukopenia.[8] Isolated thrombocytopenia has been reported in up to 8% of cases by Akdeniz et al.,[9] whereas immune-mediated thrombocytopenia has also been reported.[9,10] The authors of this case report describe a patient with isolated thrombocytopenia with a recent medical history of brucellosis treated with rifampicin and doxycycline. Thrombocytopenia was proved to be rifampicin-induced. They also present a short review of the literature on this rare subject.

## CASE PRESENTATION

A 38-year-old male was referred to the Department of Haematology in the hospital of the authors' place of work for thrombocytopenia. He had a medical history of brucellosis 3 months previously and he had been administered rifampicin 900 mg daily and doxycycline 100 mg twice per day. He had stopped the prescribed treatment before the completion of the recommended period of 6 weeks.

One week before his admission, he was evaluated in another hospital because of malaise, low-grade fever, and fatigue, symptoms compatible with his previous history of incompletely treated brucellosis. The patient was administered the same antibiotic medication of rifampicin and doxycycline. During his hospitalisation, he presented with ecchymoses on both upper limbs and petechial rash on the oral mucosa. His complete blood count was normal except for low platelets ($14x10^9$/L). The patient was started on corticosteroid therapy for a presumed diagnosis of immune thrombocytopenic purpura.

Upon admission, the patient's platelet count was $44x10^9$/L. Corticosteroid therapy was continued while the rest of his medication was stopped. A differential work-up for his thrombocytopenia was initiated. The peripheral blood smear confirmed isolated thrombocytopenia with no morphological abnormalities in the erythroid or myeloid lineage. Prothrombin time and activated partial thromboplastin time were within normal limits. The patient was negative for hepatitis C, HIV, Epstein–Barr virus, cytomegalovirus, and *helicobacter pylori* (breath test). Antinuclear antibodies were also negative and serum immunoglobulins were within normal range. On the same day, a bone marrow aspiration with cultures was conducted with no abnormal findings. The following day, doxycycline and rifampicin were reintroduced. A critical decrease in the number of platelets was noted from $44x10^9$/L to $7x10^9$/L. A clinical suspicion of drug-induced thrombocytopenia prompted the discontinuation of rifampicin, which resulted in a rapid increase in the number of platelets. Unfortunately, laboratory tests for DDAbs were not available in the authors' hospital.

The patient showed clinical improvements during his hospitalisation. IgM-specific antibodies for brucella and bone marrow culture were negative and IgG-specific antibodies for brucella were positive. For this reason, discontinuation of doxycycline was also decided after discharge. The patient was discharged after 5 days, having no symptoms and a platelet count of $106x10^9$/L (Figure 1). Upon follow-up 1-week postdischarge, the patient's clinical examination was unremarkable, and the platelet count was $315x10^9$/L. The patient was advised to avoid future use of rifampicin.

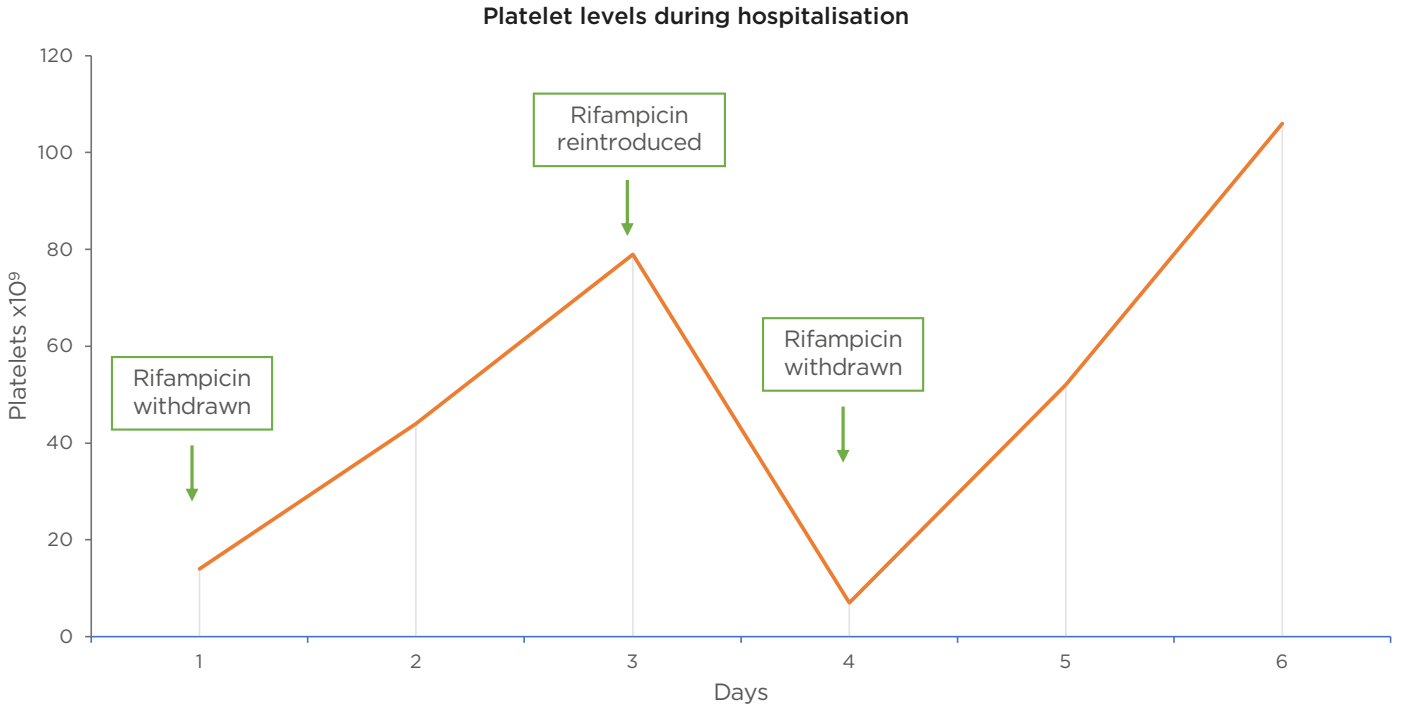


**Figure 1: Platelet levels during hospitalisation in a patient with rifampicin-induced thrombocytopenia.**

This figure illustrates the levels of platelets (PLT; x10$^9$/L) during hospitalisation. Rifampicin was stopped on Day 1 and was resumed on Day 3 (79x10$^9$/L). The next day, because of a significant decrease in the platelet count (7x10$^9$/L), rifampicin was stopped again, and the number of platelets increased rapidly thereafter. Follow-up 1 week postdischarge showed unremarkable clinical examination and platelet count of 315x10$^9$/L.

## DISCUSSION

The authors of this review present a patient with rifampicin-induced thrombocytopenia. The considered differential diagnoses in this case were vast: pseudothrombocytopenia was eliminated because there was no platelet aggregation in the peripheral blood smear; myelodysplastic syndrome or aplastic anaemia were excluded after evaluation of the peripheral blood and bone marrow. Thrombotic thrombocytopenic purpura was considered but there were no schistocytes in the peripheral blood smear, there were no symptoms of anaemia, and renal function, bilirubin, and lactate dehydrogenase were normal; disseminated intravascular coagulopathy was eliminated because the clotting screen and fibrinogen were normal. Common variable immunodeficiency was considered but Ig levels were within normal limits; infections were examined and the patient was negative for hepatitis C, HIV, Epstein–Barr virus, cytomegalovirus, and *helicobacter pylori*. Lastly, autoimmune disease was disregarded because antinuclear antibodies were also negative and the patient did not report arthralgias, sun sensitivity, skin rash, or mouth ulcers.

There are certain criteria that need to be fulfilled to prove a causal relationship between thrombocytopenia and a candidate drug, as suggested by George et al. in 1998.[11] These criteria are as follows: 1. Therapy with the candidate drug must precede thrombocytopenia, and recovery from thrombocytopenia must be complete and sustainable with the discontinuation of the drug; 2. The candidate drug must be the only one used before the onset of thrombocytopenia, or other drugs must be continued or reintroduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count; 3. Other causes should be excluded; 4. Re-exposure to the candidate drug results in recurrent thrombocytopenia.[11]

In this present case, rifampicin was a candidate drug causing thrombocytopenia

and the discontinuation of the drug led to the resolution of thrombocytopenia. Other causes of thrombocytopenia were excluded, such as normal bone marrow, negative screening for viruses, and autoimmune diseases, and reintroduction of the candidate drug caused a recurrent decrease of platelets. In addition, the proposal of thrombocytopenia caused by other drugs was excluded, because doxycycline was continued when the treatment of rifampicin was stopped and there were no other drugs administered. This patient, therefore, fulfilled all four criteria required, leading to a definitive level of evidence (Level I) that thrombocytopenia was drug-induced. The Adverse Drug Reaction Probability Scale, developed by Naranjo et al.,[12] was used with a score of 9 (Definite).

Limited epidemiologic data exist for DITP. An estimated incidence of approximately 10 cases per 1,000,000 in the population per year has been reported,[13] although this is likely to be an underestimate. DITP can be caused by two different mechanisms: suppression of platelet production (myelosuppressive drugs and drugs that affect the metabolism of folic acid) and platelet destruction. Destruction of platelets can be induced by at least three different mechanisms, which include the hapten-dependent antibodies, the platelet-reactive autoantibodies, the DDabs, or both drug-dependent and drug-specific antibodies.[14,15] Hapten-dependent antibodies bind covalently to the protein of the thrombocyte membrane and this complex induces immune-mediated cell destruction. The second mechanism encompasses antibody binding against the platelet membrane, while the third mechanism of DDabs is not well understood.[14,15] Bougie et al.[15] proposed a model in which the administration of the drug increased the affinity between DDabs and the epitope on a platelet glycoprotein.

DITP induced by DDabs is classically caused by antibodies inducing platelet destruction by the reticuloendothelial system only in the presence of the drug.[16] Quinine was the first drug recognised as being involved in this group of DITP; however 'quinine-type' antibodies typically recognise a restricted set of epitopes on glycoprotein Ib/IX[17] and glycoprotein IIb/IIIa complexes of the platelet membrane.[18] Rifampicin-induced thrombocytopenia has been linked to the presence of antiplatelet antibodies, which have higher avidity for platelet membrane in the presence of rifampicin.[19] The epitope of rifampicin-dependent antibodies is on glycoprotein IX, a subunit of the glycoprotein IX complex.[20] An experimental study showed that rifampicin-dependent antibodies also targeted glycoprotein IIb/IIIa.[21] Currently available laboratory tests can identify the causative agent in patients for whom there is suspicion and clinical evidence of DITP, including rifampicin-induced thrombocytopenia.[22,23] However, the aetiology of DITP can be established when a prompt rise in platelets occurs with the discontinuation of the drug, while its reintroduction leads to a new drop in platelet count, as noted in this patient.

Rifampicin-induced thrombocytopenia was first described by Blajchman et al.[24] in 1970. Since then, almost 40 cases have been documented in the literature and a recent review by Cooper and Ghanima[3] included rifampicin in the group of common drugs that cause immune-mediated thrombocytopenia.[3] Case reports and series of rifampicin-induced thrombocytopenia are presented in Table 1.

Rifampicin-induced thrombocytopenia usually occurs when the drug is either intermittently administered or reintroduced after a voluntary discontinuation, as is the case in this present study.[25,26] Bansal et al.[27] described a case of rifampicin-induced thrombocytopenia after re-exposure to rifampicin 10 years later. It has been suggested that drug sensitivity and induction of thrombocytopenia remains indefinitely.[57] In four cases in the literature, thrombocytopenia occurred with no previous exposure to rifampicin,[28-31] whereas in three more, reported by Lee et al.,[32] thrombocytopenia occurred following a 4-month period of rifampicin prophylaxis in a tuberculosis outbreak.[32]

Corticosteroids have been used in cases where thrombocytopenia was the result of an immune-mediated mechanism; their benefit is not proven.[58] Transfusion of platelets is indicated when a patient presents with severe thrombocytopenia or wet purpura owing to a great risk of intracranial haemorrhage.[14,33] Plasmapheresis and intravenous Ig have been used in drug-induced thrombocytopenia.[59,60] All treatment options are controversial. The most crucial step is the immediate discontinuation of the drug.

**Table 1: Cases of rifampicin-induced thrombocytopenia in literature.**

| Reference | Sample size (n) | Study design |
|---|---|---|
| Mehta et al.,[19] (1996) | 3 | Case report |
| Agrawal et al.,[22] (2012) | 1 | Case report |
| Blajchman et al.,[24] (1970) | 1 | Case report |
| Verma et al.,[25] (2010) | 1 | Case report |
| Kindelán et al.,[26] (1994) | 1 | Case report |
| Bansal et al.,[27] (2013) | 1 | Case report |
| Bashir et al.,[28] (2016) | 1 | Case report |
| Lee et al.,[29] (1989) | 2 | Case report |
| Pau et al.,[30] (1987) | 1 | Case report |
| Esposito et al.,[31] (1971) | 1 | Case report |
| Lee et al.,[32] (2012) | 87 (who received rifampicin) | Cohort study (n=3.4%) |
| Kang et al.,[33] (2010) | 1 | Case report |
| Nair et al.,[34] (2009) | 1 | Case report |
| Mauricio et al.,[35] (2019) | 1 | Case report |
| Arnold et al.,[36] (2015) | 2,500* | Observation study |
| Yakar et al.,[37] (2013) | 1 | Case report |
| Dixit et al.,[38] (2012) | 1 | Case report |
| Mori et al.,[39] (2011) | 1 | Case report |
| Davis et al.,[40] (2009) | 6† | Case report |
| Kant et al.,[41] (2008) | 1 | Case report |
| Muñoz et al.,[42] (2008) | 1 | Case report |
| Scognamiglio et al.,[43] (2008) | 2 (1 received rifampicin) | Case report |
| Garg et al.,[44] (2007) | 1 | Case report |
| Krivoy et al.,[45] (2001) | 1 | Case report |
| Pereira et al.,[46] (2000) | 1 | Case report |
| Tricerri et al.,[47] (1997) | 1 | Case report |
| Martínez et al.,[48] (1994) | 1 | Case report |
| Juang et al.,[49] (1992) | 1 | Case report |
| Bhasin et al.,[50] (1991) | 1 | Case report |
| Burnette et al.,[51] (1989) | 1 | Case report |
| Kakaiya et al.,[52] (1989) | 1 | Case report |
| Hadfield[53] (1980) | 1 | Case report |
| Poole et al.,[54] (1971) | 49‡ | Clinical trial |
| Ferguson[55] (1971) | 1 | Case report |
| Leggat[56] (1971) | 1 | Case report |

*Thrombocytopenia (121/1,000 infant days)

†Thrombocytopenia (n=1)

‡Thrombocytopenia (n=3)

The reintroduction of the drug is not indicated even if small doses are to be used;[25] however, Nair et al.[34] supported the continuation of rifampicin along with treatment for immune thrombocytopenia.

## CONCLUSION

Although thrombocytopenia is a rare side effect of rifampicin, healthcare professionals should be aware of its life-threatening risks. Thrombocytopenia can be complicated with mild bleeding events such as epistaxis or bruising but also with severe events such as gastrointestinal bleeding and acute subdural haemorrhage.[33] Notably, previous exposure to the drug is not necessary for the presentation of thrombocytopenia. Patients should be advised to avoid future use of the drug in order to prevent the potential detrimental effects of thrombocytopenia.

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