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EMJ

Climate Change Health Emergency: The Role of Healthcare Professionals

Infographic

The Impact of Heat Stress on Kidney Disease

Interviews

Grant Blashki and Karly Hampshire

Contents

"The impact that climate change can have on human health is becoming increasingly obvious, from effects on respiratory health and kidney health, to an impact on the incidence of vector-borne diseases."

+ ARTICLES

Editorial Board

VIEW IN FULL ←

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EMJ Welcome letter

Dear Readers,

I am delighted to welcome you to our June issue of EMJ. EMJ aims to be an advocate for the United Nations (UN) sustainable development goals, which include championing climate action, and we are proud to bring you this issue with a mini-focus on climate change and healthcare.

The impact that climate change can have on human health is becoming increasingly obvious, from effects on respiratory health and kidney health, to an impact on the incidence of vector-borne diseases. Meanwhile, healthcare practices and policies can form part of the solution, as enabling greener and more sustainable healthcare practices and increasing awareness among patients can play a pivotal role in climate action.

In this issue we share content discussing the impact of climate change on human health and how healthcare provision and healthcare professionals themselves can make a difference to climate action. Our Editor's Pick focuses on how air pollution exposure might be a risk factor for people with chronic obstructive pulmonary disease. The journal also features an infographic discussing how heat-related stress can affect kidney health, alongside interviews and articles outlining how healthcare practitioners may play their part in climate action through their practice.

Our journal would not be complete without a plethora of articles across a number of topics, ranging from inflammatory bowel disease to imaging features of cysts of the pancreas, to name a few.

We hope that this issue can contribute towards taking action against climate change by adding to the knowledge around the topic. The EMJ team and myself hope that you enjoy this issue, and would like to thank our authors, reviewers, and journal Editorial Board for their immense contribution in bringing this issue together.

Koutsouki

Evgenia Koutsouki, PhD.

Editor

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Foreword

Dear Colleagues,

In this issue of *EMJ* I am happy to present you with a mini-focus on climate change and health, a very timely topic examined in our informative infographic on climate change and kidney health, as well interviews with climate change experts. In addition, you will find summaries from presentations of the Green Radiology Department at the European Congress of Radiology (ECR), and health emergencies of climate change from the Royal Society of Medicine (RSM).

Along these lines, the article on air pollution exposure as a relevant risk factor for chronic obstructive pulmonary disease is very much on the spot: while many efforts in this field rightly have focused on harm reduction by reducing active and passive smoking, particular attention is paid to the fact that there are very few gender-specific published data, which will require attention in future analyses. A very interesting narrative review featured in this issue addresses the shortage of conclusive data on the use of sodium-glucose co-transporter 2 inhibitors for the use in patients with heart failure with preserved ejection fraction. Even though the meta-analytic approach is suggestive of a benefit for sodium-glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction, the cut-offs for ejection fraction on the high and low end need to be better defined in the future. This issue is complemented with a story on the potential cutaneous side effects of severe acute respiratory syndrome coronavirus 2 messenger RNA vaccines, exemplified in a few cases of herpes zoster reactivation post-vaccination, and with a case of diabetic ketoacidosis precipitated by COVID-19.

Another understudied population are older patients with inflammatory bowel disease, either with a late diagnosis, or with long-standing disease. A contribution in this issue addresses the different perceptions on frailty, structured frailty assessment, and goals of therapy between physicians and patients in this particular age group, and calls for a more structured and evidence-based medicine-based approach.

I am confident that we were able to find a good mix of highly relevant and interesting topics in this issue on climate change and health, which we hope you will enjoy reading.

Markus Peck-Radosavlijevic

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

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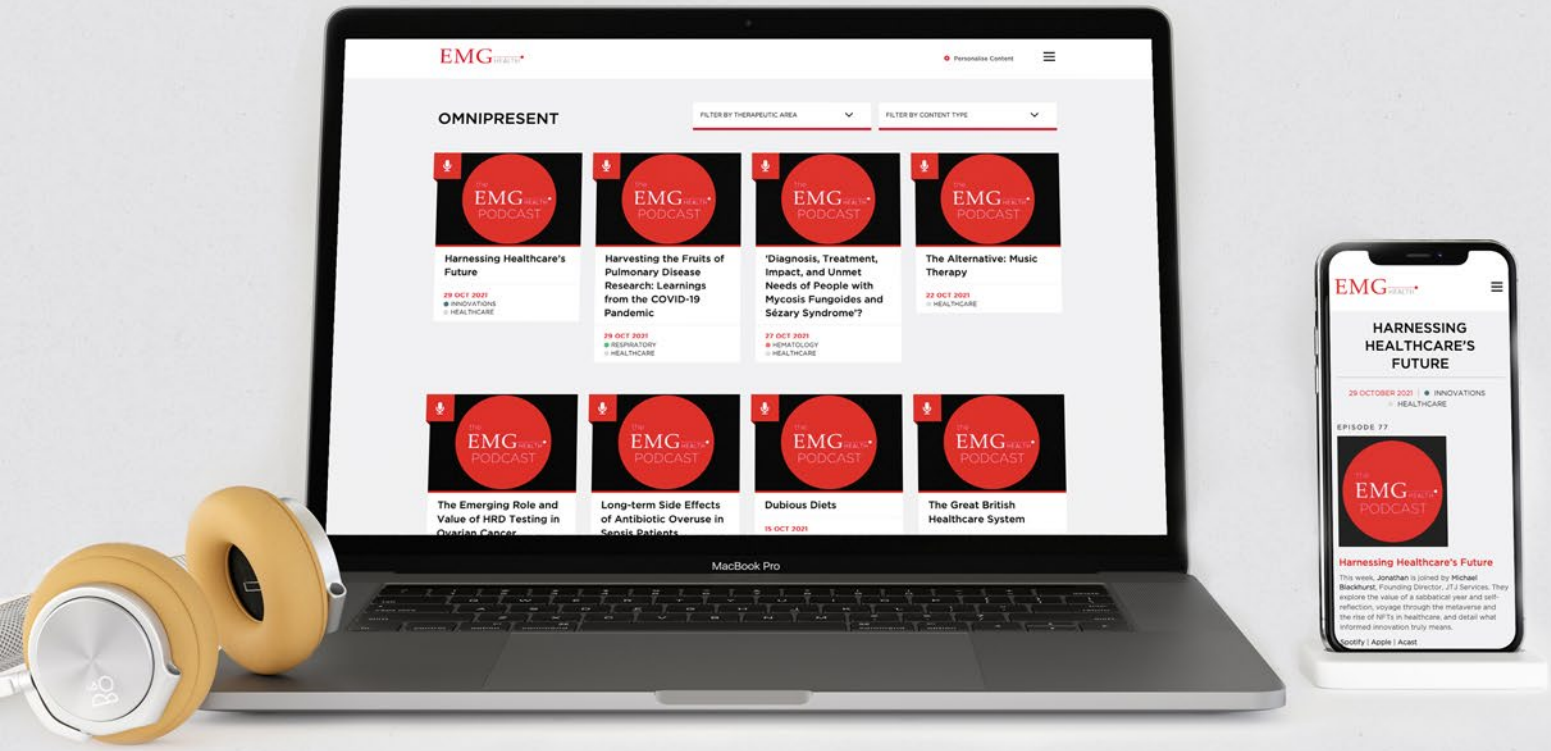

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Climate Change Health Emergency: The Role of Healthcare Professionals

Katherine Colvin
Editorial Manager

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THE IMPACT of climate change is clear, urgent, and formidable, with the effects of climate change on health an immediate threat to patients and populations both now and in the future. The Royal Society of Medicine (RSM) shared a series of 10 expert-led presentations on the 'Health Emergency of Climate Change' in 2021, with the closing presentation focusing on the role of healthcare professionals in addressing the health impacts of climate change. Linda Luxon, RSM Council Trustee, hosted a discussion between Cheryl Holder, President of the Florida State Medical Association and Co-chair of the Florida Clinicians for Climate Action, USA; David Pencheon, Founding Director of the National Health Service (NHS) Sustainable Development Unit, UK; and Rita Issa, Clinical Research Fellow in Climate Change, Migration and Health at University College London, UK, and Co-founder of Doctors for Extinction Rebellion. Their discussion highlighted the scope of the issue facing healthcare professionals, identifying strategies that can allow clinicians to be advocates for the health of their patients as well as have an impact on wider policy and systems-level changes to address this health emergency.

ROLE FOR ADVOCACY

"Whether its pollution, whether its excess heat, or whether it's where vectors fly and carry disease, we know that the impacts on health of climate change are happening now." This statement from Jeremy Farrar, Director of the Wellcome Trust, London, UK, opened the discussion between the clinicians. Each of the speakers shared their thoughts on why doctors and healthcare professionals should take up the mantle of advocacy as part of their healthcare practice.

Pencheon spoke of the value of normalising climate change advocacy as part of the role for doctors by "framing climate change as a health issue. It is our duty of care." He suggested that clinicians and healthcare professionals use the 'small talk' of their consultation to address topics of climate change, as this is a less provocative or lecturing way to introduce these elements to clinical practice. He gave examples of mentioning what is in your lunchbox or explaining why you are perspiring following cycling to work: "Give licence to introduce the topic as a normal topic of conversation about how we live our lives today."

Holder drew parallels to her prior professional experience with the early pandemic days of HIV and AIDS in the 1980s, "recognising the role that we played as clinicians to be activists, advocates, educators." She spoke of the need to address social and environmental determinants

of health as both part of healthcare but also as a mechanism for addressing climate change: "Centring health is centring life because health is a lot more than the physical loss, but is where you live, where you work, where you play, and if we address those factors, especially for poorer people, we will get an immediate response and achieve that reduction in less than ten years."

Pencheon highlighted the value of every healthcare professional taking the opportunity to discuss the impact of climate change on health, due to the respect that patients have for the insights of their clinicians and the scope of practice: "Health professionals are dangerously influential: people actually believe what we say;" and "In the NHS, we interact with one million people every 36 hours: that is a huge opportunity."

Issa cautioned that discussions around climate change and health should look beyond interactions with individual patients, to the institution or clinic level, community level, and wider healthcare systems. She highlighted how prescription choices, review of foods offered in hospital canteens, and consideration of transport options to clinics and hospitals centres the focus on institution-led change rather than placing the onus solely on individual patients.

HEALTH SYSTEMS SOLUTIONS

The discussion looked beyond individual patient interactions and community- or institution-level advocacy to consider the impact that healthcare professionals can have on entire healthcare systems and wider policy.

Issa particularly championed the view that doctors as professionals and as a profession could have a greater advocacy role and greater involvement in the climate change movement at a political and systems level. Currently, she believes, many advocacy actions taken by doctors are focused on their local health services and practices, and the actions of their colleges and societies; however, she believes that the medical profession should become more involved in political advocacy in the climate change movement. Sharing her thoughts when first marching in Extinction Rebellion protests: "I was marching because I care about the health of my patients, and I recognise that climate change is one of the greater health threats that we have

"Whether its pollution, whether its excess heat, or whether it's where vectors fly and carry disease, we know that the impacts on health of climate change are happening now."

globally. To me, not to act on the climate crisis went against my duties as a doctor, where I'm bound by good clinical practice to hold human life with the utmost respect and to practice from a scientific evidence base."

"recognising the role that we played as clinicians to be activists, advocates, educators."

Holder drew attention to the population groups affected by environmental change, pollution, and heat stress, and how policy-based and inter-industry attention is needed to improve the health of populations affected by asthma, allergies, and cancers that have resulted from climate change: "these were populations that were reacting to the pollution, to what we were doing to our climate. And instead of us responding by valuing the population, we kept putting it 'not in my backyard', kept putting it somewhere else. So, the deeper issue in our society comes back again to equity and looking at the policies that drove a population to be impacted." She highlighted that a systems-level impact is necessary for health justice as well as effectiveness of response.

QUESTIONS FOR THE EXPERTS

"What's Holding Doctors and Medical Professionals Back from Promoting a Diet of Plant-Based Foods?"

Holder explained that diet is often a cultural and economic issue, not just a health and environmental issue. "I don't believe in pushing change by lecturing; you motivate folks by empowering them and having them buy into the system." In her own interactions with patients, she emphasises the health impacts of dietary change, particularly on cholesterol, blood pressure, and weight, as this allows for the conversation around reducing red meat in their diets to be framed as both a health solution and a climate solution.

Pencheon highlighted that the scale and scope of health systems internationally means that there are innovations already in practice that we can learn from. He pointed to the example of hospitals in Malaysia that are meat-free: "One of the best ways to introduce large-scale change in a complex system like a health service is to find someone who's doing it already and just 'big it up'."

Issa highlighted her work at the Bromley-by-Bow practice, London, UK, a clinic known to be the 'birthplace of social prescribing', where the clinic includes a community vegetable garden that general practitioners can refer patients, with the chance to learn from the gardeners about growing healthy, seasonal food and to take healthy cooking classes. She spoke about how allowing patients to "put their hands in the soil" empowered them with knowledge and healthier choices, as well as proving beneficial for mental health and community-building.

"How Can Doctors Influence Beyond Medicine to Make a Difference?"

The three speakers agreed that healthcare professionals should have more of a voice in policy: social policy, industrial policy, and political policy, as all these elements contribute to the social and environmental determinants of health.

"One of the best ways to introduce large-scale change in a complex system like a health service is to find someone who's doing it already"

Issa is confident that healthcare professionals are capable and valuable in health advocacy, as they are trained to take complex scientific information and present it to their patients in a way that is going to be understandable and that encourages change. Pencheon underlined the importance of engaging with people both emotionally and rationally; he highlighted clinicians' skills at tailoring their consultation style to suit individual patient's needs and understanding, but feels that this nuanced tailoring of engagement is not translated to how clinicians interact with politicians, policy makers, and the public. He advocated this tailored approach for communication as a valuable tool for engaging

"If doctors are understanding that we are working for health and health improvement, it becomes less political"

with policy makers and politicians. Holder drew parallels with the success of health practitioners in addressing the early days of the HIV and AIDS pandemic, using this as an example of doctors championing policy progress: "If doctors are understanding that we are working for health and health improvement, it becomes less political."

"What Can Quickly Emphasise the Urgency of this Situation?"

Issa proposed that better collaboration and communication among small groups, community groups, clinics, and health services trusts that have local programmes and policies in place would leverage this local passion for systems-level change in the wider health service.

Holder highlighted that immediate change in the USA health system needs to be cost-saving, so she recommended a sustainability employee in every hospital, with some immediate focus on things like reviewing single-use plastics and thermostat settings for speedy impact. Demonstrating an impact from these interventions would then serve to justify faster action towards larger changes.

Finally, Pencheon recommended combining social and environmental governance with financial governance (in all big institutions, not only health systems and health institutions) to better allow institutions to live up to their responsibilities, particularly to Do No Harm. ■

The Green Radiology Department

Theo Wolf
Senior Editorial Assistant

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GLOBALLY, hospital-based care has a substantial ecological footprint. In the USA, the health sector generates approximately 10% of the nation's greenhouse gas emissions. Radiology departments are known to be major energy consumers, particularly through the use of CT scanners, MRI systems, reading workstations, and interventional suites. At this year's European Congress of Radiology (ECR) 2022 Overture, 2nd–6th March, a panel of experts explored ways to make the discipline more environmentally sustainable.

THE 'GREEN FINGERPRINT' PROJECT

Joachim Hohmann, Professor of Radiology, University Hospital Basel, Switzerland, began by providing an overview of his 'Green Fingerprint' project, which measured the power consumption of 32 radiological reporting stations over a period of approximately 194 days. Hohmann and collaborators then considered a hypothetical scenario to reduce energy waste.

In total, three main patters of power consumption were identified: mainly off, mainly on, and always off. The study demonstrated that the different distributions were due to the standby modes, usually the S1 (power on suspend) Advanced Configuration and Power Interface state. In this state, processor caches are flushed and the central processing unit stops executing instructions; however, power to the central processing unit and random-access memory is maintained. Hohmann revealed that "these states were configured to be activated after 4 hours of inactivity." However, "even in the default standby mode, a reporting station consumed around half of the power of the on-mode," said Hohmann. Based on this, an initial scenario to save energy was devised. "Half of the time, the reporting stations are idle. They are waiting for standby," commented Hohmann. This was found to result in a wait-time consumption of 18,000 kWh. "If we changed our standby modus to a modus in which the reporting stations just wait for 1 hour to shut down [...] we can save about 24 kWh just in our department," remarked Hohmann. This equated to a total reduction of 45% of the initial energy consumption.

In his closing remarks, Hohmann discussed the real-word implications of the project. The overall consumption of the reporting stations was 53,170 kWh. Therefore, "we could achieve an energy saving of about 24,000 kWh per year," emphasised Hohmann. He continued: "If we extrapolate this number from our relatively small country, we came up to about 1,500,000 kWh per year, which we can save with this very easy scenario."

ENVIRONMENTAL SUSTAINABILITY AND THE RADIOLOGY DEPARTMENT OF THE FUTURE

"Green radiology, is this a dream or a necessity? Of course, it's a necessity. We're working towards net-zero healthcare, which is really tough," stressed Andrea Rockall, Clinical Chair of Radiology, Imperial College London, UK.

"In the USA, the health sector generates approximately 10% of the nation's greenhouse gas emissions."

Rockall highlighted a study from Switzerland th at investigated the energy consumption of three CT scanners, four MRI scanners, and their associated cooling systems in a university hospital radiology department. Energy consumption of CT and MRI scanners accounted for 4% of the total yearly hospital energy consumption. Dedicated cooling systems alone comprised 44% of the total energy needed for the operation of the imaging systems. For CT, 66% of energy consumption took place during the idle state. For MRI, 33% of the energy consumption was during the system-off state. According to Rockall, "this is an area where we potentially have an opportunity to make savings without impacting on the care we give our patients."

Reducing energy waste in CT and MRI will require direct action from industry, such as the development of sleep, standby, and power save modes. Going forward, "we need heat-waste recovery from cooling systems, and we need refurbishment of old scanners to upgrade rather than endlessly new builds," stressed Rockall. At the governmental level, a European Union (EU) directive could mandate energy savings in healthcare. Finally, Rockall considered specific strategies that could be adopted by radiology departments to decrease energy consumption: "Efficient workflow will ensure that we scan our patients but without a lot of idle time." It is also recommended that departments of the future monitor energy consumption, optimise the layout of scanners to share cooling systems, and implement energy dashboards.

In addition to larger-scale changes, "we can all look at small areas where we can make daily changes," noted Rockall. "We've already heard about this fantastic Green Fingerprint project [...] changing the wait period of the standby period to 1 hour from 4 hours. Overall, there was a 45% reduction in the original consumption. And we can do this now, we just have to think about it." Automatic shutdown of picture archiving and communication systems, projects, and monitors; care with water usage, air conditioning, and heating; and the use of biodegradable equipment are further steps that require little effort to implement, but may have a positive cumulative impact on the environment. It is also necessary to consider the whole life cycle of the diagnostic process, and Rockall, therefore, suggested three questions that radiologists could ask themselves: "Is the test necessary," "are we doing the correct test for the first time," and "do we need contrast in every test?" Similar to COVID-19 vaccine passports, the concept of radiology passports was introduced as a potential method for avoiding repeat procedures.

Rockall concluded by sharing her vision for the radiology department of 2030. Crucially, environmental impact will be monitored and actions taken to reduce consumption.

CONCLUSION

These presentations have highlighted promising opportunities to reduce the ecological footprint of radiology departments without compromising patient care. Importantly, there are a number of minor but significant changes that can be implemented in order to make radiology services more environmentally friendly. This was illustrated by session co-chair Adrian Brady, Mercy University Hospital, Cork, Ireland, who encouraged the audience to "think a little bit about your energy expenditure, and your use of resources. Some of the practical things we've heard about are things you can apply in your life at work and outside of work." Clearly, achieving sustainability in radiology is not a big mountain to climb. As more countries commit to low-carbon health systems, approaches to green the radiology department will become increasingly important going forward. ■

THE IMPACT OF HEAT STRESS ON KIDNEY DISEASE

Heat stress
Water shortage
Over-exertion

Low-grade rhabdomyolysis

Hyperosmolarity

Hyperthermia

Extracellular volume depletion

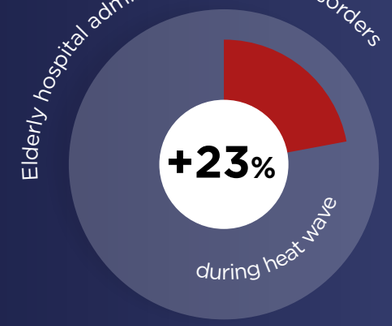
Vasopressin effects on the kidney tubule
Fructose metabolism in proximal tubule with oxidant and chemokine release
Uricosuria and urate crystal formation in urine
Hypokalaemia-mediated ischaemic injury to the kidney
Renal ischaemia

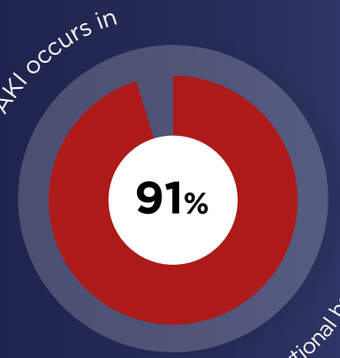
Repeated acute kidney injury
Chronic interstitial fibrosis

Brazil 2000–2015:

>7%

of all hospital admissions for kidney disease attributed to hotter temperatures



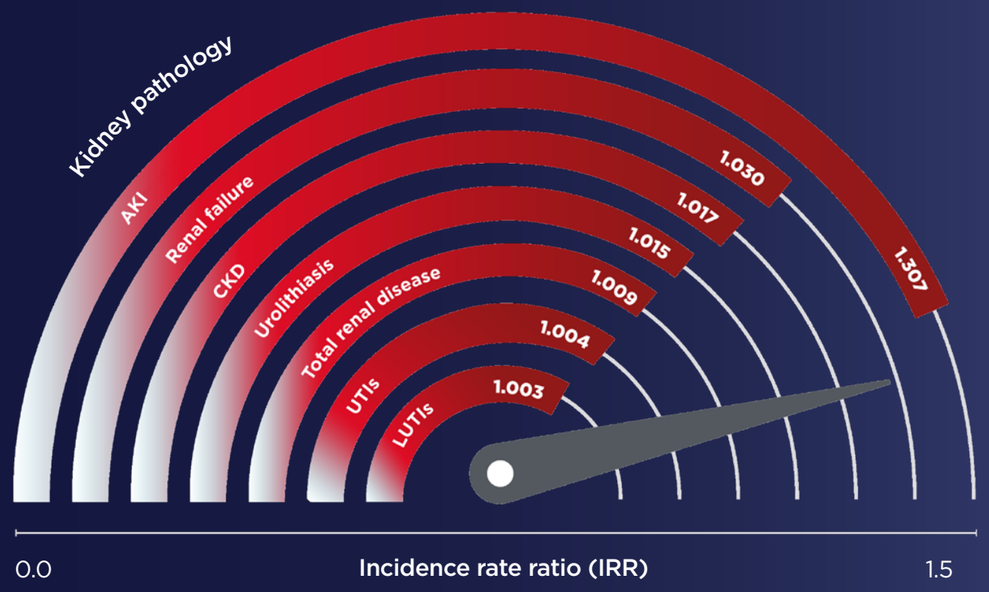


By **2050**:

1.6–2.3 million

climate-related cases of kidney stones

1 °C increase in daily minimum temperature was associated with an increase in daily emergency department admissions



AKI: acute kidney injury; **CKD:** chronic kidney disease; **LUTI:** lower urinary tract infection; **UTI:** urinary tract infection.

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Beyond Aesthetics: Hyaluronic Acid Fillers as a Therapeutic Treatment

This symposium took place on 31st March 2022, as part of the Aesthetic and Anti-ageing Medicine World Congress (AMWC) held in Monaco

Chairpeople: Patrick Trevidic[1]

Speakers: Paula Rosso,[2] Sabrina Shah-Desai[3]

1. Expert 2 Expert, Paris, France
2. Centro Médico Estético Lajo Plaza, Madrid, Spain
3. Perfect Eyes Ltd., London, UK

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Meeting Summary

Soft tissue fillers treatments historically aimed at correcting signs of ageing such as wrinkles and loss of volume or contour in the face and neck. The ever-expanding range of formulations available on the market have progressively broadened the scope of indications which can be efficiently treated through these minimally invasive modalities,[1] including therapeutic applications with targeted volume restoration in specific patient categories, going beyond the scope of anti-ageing and beautification.[2,3]

Coincidentally, recent research from across disciplines is converging to reveal a far more anatomically organised and functionally dynamic role of facial tissues than initially thought.[4,5] These continuous improvements in the understanding of facial anatomy have fostered innovation in the formulation of new hyaluronic acid (HA) gels, aiming to propose products designed to support and fill specific tissue layers, while accompanying and adapting to facial movement through adapted rheological properties.[6-7] Therefore, HA fillers have met new clinical needs through customised formulations tailored to specific injection depths, anatomical areas, and facial movement.[6,9-13]

In this context, clinicians have proposed new injection techniques with dedicated products to support natural facial dynamism.[14,15]

HA gels have thus gained popularity and evolved from their 'wrinkle filling' role to become viable alternatives to surgery in therapeutic indications such as facial lipoatrophy, scarring, post-traumatic reconstruction, and facial asymmetry, as well as congenital or acquired facial deformities.[2,16,17] Treating these conditions can significantly improve a patient's quality of life, social interactions, and psychological wellbeing.

During the symposium 'Beyond Aesthetics', held at the 2022 AMWC in Monaco and moderated by Patrick Trevidic, Expert 2 Expert, Paris, France, Teoxane's anatomy, techniques, products (ATP) approach was shown to be a valuable strategy to treat facial asymmetry and remodelling facial

volumes after a significant weight loss. Live demonstrations were respectively performed by Paula Rosso, Centro Médico Estético Lajo Plaza, Madrid, Spain, and Sabrina Shah-Desai, Perfect Eyes Ltd., London, UK.

Part 1: How an ATP Approach Can Help to Treat Difficult Cases

Paula Rosso

Any filler injection requires a bespoke treatment approach and a thorough anatomy knowledge to minimise procedural risks and achieve natural-looking results.[18,19] The ATP approach implies an injection tailored to each patient, considering their medical and personal history, as well as anatomical specificities related to their age, gender, or ethnicity.[20,21] Treating difficult cases, meaning here uncommon facial volume loss or asymmetry, requires a perfect understanding of the facial tissue layers' arrangement and dynamism. It also requires a proper patient assessment to perform an optimal volume restoration, without adversely affecting facial expressions. In specific anatomical regions (e.g., the midface), adopting a systematic and adapted multilayering treatment approach may be advantageous, and limit overall injection volumes for the same outcome.[21]

Rosso introduced this session, highlighting that soft tissue fillers injections in aesthetic medicine should not be exclusively devoted to beautification. They may also represent a real option for patients suffering from congenital or acquired conditions, helping them gain self-confidence, and improving their quality of life.

As an example of a difficult case, Rosso reported her own patient case presenting with Moebius syndrome, a rare congenital and non-progressive disease affecting cranial nerves, resulting in facial palsy or bilateral facial paralysis (facial diplegia) and difficulties in eye abduction.[22] Facial palsy creates hypertrophic muscle activity on the non-paralysed side of the face, as opposed to atrophic static muscles on the contralateral side. Therefore, the treatment was specific to each side of the face to compensate differences in volume due to unequal muscle activity and thus homogenise facial expressions.

Figure 1A shows the before and after photographs of her patient's treatment with targeted TEOSYAL® (Teoxane, Geneva, Switzerland) fillers' injections (as detailed in Figure 1B). The most visible change is in the perioral area, with the elevation of the corner of the mouth. In this category of patients, the treatment not only brings a physical change but induces an emotional change impacting social interactions and overall wellbeing.

Although this is a rare syndrome, similar facial asymmetry can affect other patient types. Indeed, multiple causal agents may lead to the development of facial asymmetries, including pathological, traumatic, functional, or developmental factors. Overall, the aetiologies of facial asymmetry can be grouped into hereditary factors of prenatal origin and acquired factors of postnatal origin.[23]

Part 2: Live Demonstration - How to Treat an Asymmetrical Face with Hyaluronic Acid Fillers?

Paula Rosso and Patrick Trevidic

Rosso continued her introduction on asymmetry with the live injection of a 46-year-old female patient presenting a moderate facial asymmetry of congenital origin. As with facial palsy, one side of the face was more hypertonic than the other, while the hypotonic side presented with less wrinkles.

An iterative approach was adopted, adapting the treatment plan depending on the outcomes of each injection step on the overall asymmetry. As recommended for any 'full face' treatment, injections were started in the midface to anticipate any impact on other areas of the face.[24] In patients who are asymmetrical, two treatment sessions may be required to achieve optimal results: a first one to tackle the asymmetry, followed by a 'beautification' session.

B

Left hemiface (paralysed side)	Right hemiface (non-paralysed side)
Upper cheek: 1.2 mL HA_{UD} Cannula: 25 G/50 mm	Temple: 0.6 mL HA_{UD} Needle
Cheek (pre-auricular area): 0.6 mL RHA_4 Cannula: 25 G/50 mm	Pyriform fossa: 0.6 mL RHA_4 Cannula: 25 G/50 mm
Oral commissures: 0.6 mL RHA_4 Cannula: 25 G/50 mm	

Chin : 0.6 mL

HA_{UD}

Needle: 27 G/13 mm

Figure 1: The treatment of a female patient presenting with facial asymmetry.

A) Before and after photographs of a female patient with a Moebius syndrome-associated facial asymmetry, who was treated with TEOSYAL fillers. **B)** Treatment summary.

HA_{UD}: TEOSYAL PureSense Ultra Deep; RHA_4: TEOSYAL RHA 4.

Midface

A 25 G/50 mm cannula was used for injecting the deep fat pads of the midface from a single lateral entry point on the zygoma, pinching the skin to ensure deep positioning of the cannula. Injecting the right side only, a highly cohesive and strong projecting filler (TEOSYAL PureSense Ultra Deep [HA_{UD}; Teoxane]) was deposited in these static fat compartments.[25] The product was delivered very slowly in small boluses, in the medial and lateral sub-orbicularis oculi fat (mSOOF, lSOOF), and in the deep medial cheek fat (DMCF), injecting 0.6 mL overall on this side to reduce the bilateral asymmetry.

Upper face

Moving to the left side of the face, a 'gunshot' technique was performed with a 27 G/13 mm needle in the temple, aiming to put a stiff product very deep to push up the temples and lift up the eyebrow. The technique aimed to touch the bone with the needle and slide it, bevel down, to avoid the deep temporal artery and veins running within the muscle.[26] A 0.6 mL volume of HA_{UD} was thus deposited supraperiosteally.

Perioral Area and Lower Face

Pyriform fossa

Progressing to the lower part of the left side, a deep injection of HA_{UD} was performed in the pyriform fossa (i.e., the soft triangle found lateral to the ala of the nose). A bolus (0.4 mL) was deposited in the pyriform fossa with a 25 G/50 mm cannula technique introduced through an entry point on the nasolabial line, advanced first in a superficial plane until the alar fossa before pushing it more deeply to touch the periosteum.

Given that the facial artery (FA) is superficial in that area, the filler should be placed deeply, which is also possible with a needle introduced directly close to the ala of the nose with a perpendicular angle to the skin, until touching the bone with the tip to ensure proper placement.[27]

Nasolabial folds

The nasolabial folds (NLF) were an important treatment zone in this patient, who showed hyperactivity of the muscles on her left side, exaggeratedly lifting the left upper lip, and emphasising the asymmetry of her facial expressions. Therefore, this treatment step aimed to push down the lifted tissues trough a dedicated left NLF and lower face treatment.

Another volumising but more dynamic filler (TEOSYAL RHA 4 [RHA_4; Teoxane]) was selected to slightly fill the patient's marked expression lines. Despite its high strength score, RHA_4 retains a good stretch capacity (i.e., a propensity to deform under facial movement).[10] This duality allows it to be placed superficially and moulded after injection to prevent any bump formation.

RHA_4 was injected in the left NLF (0.6 mL), introducing a 25 G/50 mm cannula in the immediate subdermis to avoid the FA running very superficially in this area. The entry point was located at the bottom of the nasolabial line to perform a fanning technique, depositing linear threads of product along the fold.[28]

Perioral area

Afterwards, RHA_4 was injected superficially in the marionette lines and oral commissures with a 25 G/50 mm cannula inserted through an entry point in the paramedian chin. A volume of 0.6 mL was injected on each side using a fanning technique, also treating the labiomental line to soften it.

Key vascular dangers of this region were summarised by Trevidic. The inferior labial artery runs underneath the depressor anguli oris and the ascending mental artery lying within the submuscular plane, approximately 6 mm lateral from the midline of the chin, thus advocating the use of cannulas in the superficial plane.[29-31]

Lips

Moving to the lips, Rosso reminded the audience of the more painful nature of injections performed in this sensitive area. She then emphasised the importance to look at the teeth to establish a treatment plan, as any asymmetry in the teeth means a different support on each side of the mouth.[32] The lip treatment step aimed at correcting an asymmetry in the upper lip, which was slightly more elevated on the left side. The injection was performed with a HA filler (TEOSYAL RHA Kiss [Teoxane]) combining high cohesivity and malleability, manufactured with a low HA modification degree, specifically indicated to enhance the contour of the lips.

Entering from the vermilion border and staying very superficial, a volume of 0.5 mL was deposited in micro aliquots, using a 30 G/12 mm needle to correct the asymmetry of the upper lip.

In this area, the main vascular danger is the superior labial artery, which supplies the most lateral third of the half upper lip subcutaneously, then crosses the muscular plane and runs under the mucosa in the in the most medial two-thirds.[33,34]

Jawline

The finishing touch of this full-face treatment focused on redefining the contours of the patient's lower face. Both sides of the face were injected, as this final step was an additional treatment of rejuvenation and beautification, rather than mere correction of remaining asymmetry.

In this area, lateral to the mandibular ligament lies the static part of the lower face (i.e., the posterior jawline and the gonial angle), where the masseter directly adheres to the bone without intermediate fat.[5]

In the lower face, particular attention should be paid to the FA and marginal mandibular branch of the facial nerve. The FA runs deep, just anterior to the masseter where it is easily palpable; hence, it can be avoided by staying in the subcutaneous layer, gently lifting the skin away from the mandible while injecting.[35,36] There are two fixed points in the jawline respectively represented by the mandibular ligament in front of the jowl and the pre-masseteric ligament behind the jowl. The contraction of the depressor labii inferioris, depressor anguli oris, and platysma muscles in relation to those fixed points contribute to the disruption of a straight mandibular line during ageing, as they pull the soft tissue downwards, causing a depression zone creating the jowl.[12] Therefore, injections should be constrained anterior and posterior to the jowl, whilst the jowl itself must never be filled to avoid worsening this effect.

In this patient, a multilayering technique was used to redefine the mandibular angle and the posterior jawline, recreating a straighter line. First, HA_{UD} was injected deep along the posterior jawline, entering from the jowl with a 25 G/50 mm cannula. This product recreates a structure by acting like an implant. As a second step, Rosso performed a second entry point at the mandibular angle and moved in a more superficial plane to deposit RHA_4 on top of HA_{UD} injections, preferring a dynamic and easily mouldable product to prevent the formation of bumps or irregularities at the skin surface. To tackle the patient's lower face asymmetry, Rosso injected 0.6 mL and 0.8 mL of filler in her right mandibular angle and posterior jawline, respectively, versus 1.2 mL and 0.6 mL on the left side.

Treatment Overview

The main goal of the full-face treatment was to symmetrise bilateral facial volumes. The overall harmony of the face was improved with minimal product quantities, in part due to the multilayering techniques employed in appropriate areas. Before and after 3D photographs taken with a dedicated equipment (using LifeViz® Mini [Quantificare, San Francisco, California, USA]), which can be seen in Figure 2.

Part 3: How to Restructure a Face After a Significant Weight Loss?

Sabrina Shah-Desai

Shah-Desai started the second live injection with a reminder on the important role of aesthetic doctors in restoring their patients' quality of life; aesthetic medicine not being just about vanity.

She then introduced her 36-year-old female patient, a smoker with a recent history of significant weight loss (8–10 kg) due to work-

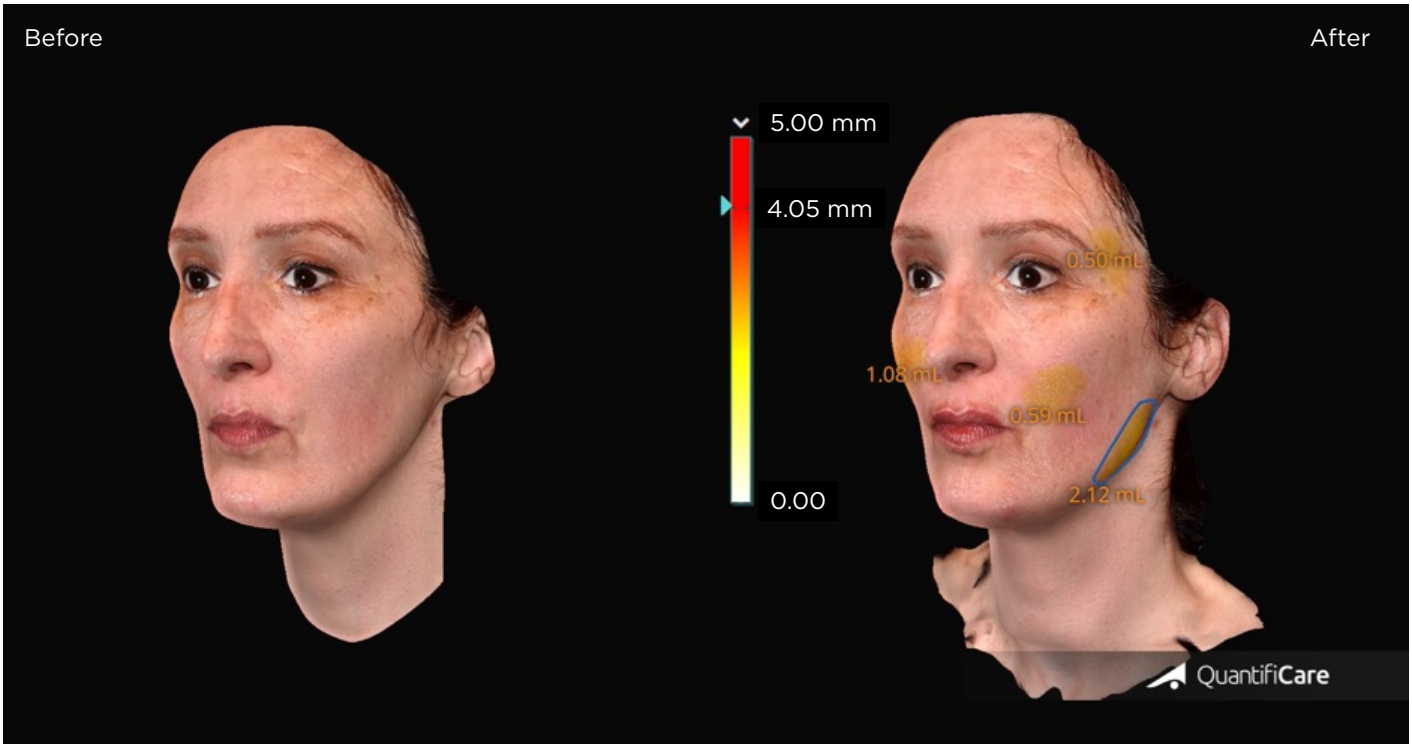

Figure 2: Before and after photographs of Rosso's patient, who was injected live to showcase the treatment of an asymmetrical face.

The measuring principle is based on a structured light projection. Pre-/post-treatment volumetric changes are presented on the right photograph.

Photographs were taken with the 3D camera LifeViz® Mini and its software, LifeViz® App (Quantificare, San Francisco, California, USA).

related anxiety. Her weight loss induced a rapid resorption of her facial superficial fat, which had accelerated the emergence of early signs of ageing, accentuating the bags under her eyes, and giving the impression of a collapsed and sunken face. Consistently, a recent study by Valente DS et al.[37] brought forward evidence that a sudden change in body weight causes a change in age perception, potentially making patients appear older than their actual age.

Other patient types may present similar characteristics due to varying conditions resulting in drastic weight loss, such as females who are post-menopausal, patients who have received chemotherapy or bariatric surgery, and patients with HIV presenting facial lipoatrophy (FLA) due to highly active antiretroviral therapy. Interestingly, while volume deflation in the deep fat pads appears to be the primary mechanism that causes 'pseudoptosis' of the overlying tissues, weight loss, and HIV-associated FLA manifestations also induce substantial atrophy of the superficial fat (Figure 3).[38,39]

Whenever possible, particular attention must be paid to the cause of the weight loss (e.g., diet, medication, disease) and whether the patient is at risk of regaining this weight (or intends to regain it), as this could impact the treatment plan. Assessing the patient in a frontal view showed the need for midface projection and temple augmentation as these areas presented significant (and slightly asymmetrical) hollowness. The patient also showed prominent eyebags, eligible for infraorbital treatment with fillers, albeit too severe to be fully camouflaged non-surgically. Finally, Shah-Desai asked the patient to smile to visualise her face in a dynamic expression, which showed how her muscles pulled differently on each hemiface, accentuating the asymmetry. The main goal of the treatment was to rebalance the volumes of the patient's hemifaces, as her right side looked hollower while her right cheekbone had more projection.

Midface

Shah-Desai relied on the patient's anatomical landmarks to locate her deep fat compartments, drawing a first vertical line down from the lateral orbital rim and a second one following the tear trough (TT) to the mid-cheek groove. The DMCF is found at the confluence of these marks, with the mSOOF and the lSOOF above it, respectively medial and lateral to the vertical line of the face running from the lateral canthus.

HA_{UD} was very slowly injected in the deep static fat pads using a 25 G/38 mm cannula inserted from an entry point in the lSOOF, pulling the tissues up to ensure deep cannula placement. Small boluses of 0.2–0.3 mL were placed supraperiosteally in the DMCF and 0.1 mL in the mSOOF (total volume on the left: 0.4 mL; total volume on the right: 0.5 mL), followed by post-injection moulding. Asking the patient to sit up allowed Shah-Desai to assess the need for additional volume, which was addressed by subcutaneous injections of RHA_4, a dynamic filler suitable for accompanying facial movement in the mobile superficial compartments of the midface. Entering from the same entry point, RHA_4 was thus injected using a fanning technique (left: 0.6 mL; right: 0.8 mL), while being cautious to not worsen the patient's temporal hollow.

Upper Face and Periorbital Area

Temple

Injection in the temple started by marking the temporal crest, which can be felt by rolling the thumb in a medial-to-lateral direction over the forehead, until a dip is felt, then marking the lateral orbital rim boundary and the upper border of the zygoma to delineate the visible temple. The audience was reminded of the main vascular dangers, with first the frontal branch of the superficial temporal artery, which can be palpated lateral to the orbital rim.[40] As for the deep temporal artery, its anterior branch may be found within the temporalis muscle, when positioning the probe 1 cm superolaterally to the distal end of the eyebrow.[41] Finally, a danger zone can also be marked approximately 1–2 cm above the zygomatic arch, where the middle temporal vessels lie.

In this patient, Shah-Desai delivered several retrograde linear threads of filler (TEOSYAL RHA 2 [Teoxane]), 0.5 mL on each side in the deep layer of the inter-fascial plane, using a 25 G/50 mm cannula. The product was then massaged to obtain the desired outcome (i.e., a fuller, but not completely convex temple) to not give the patient a wider look.

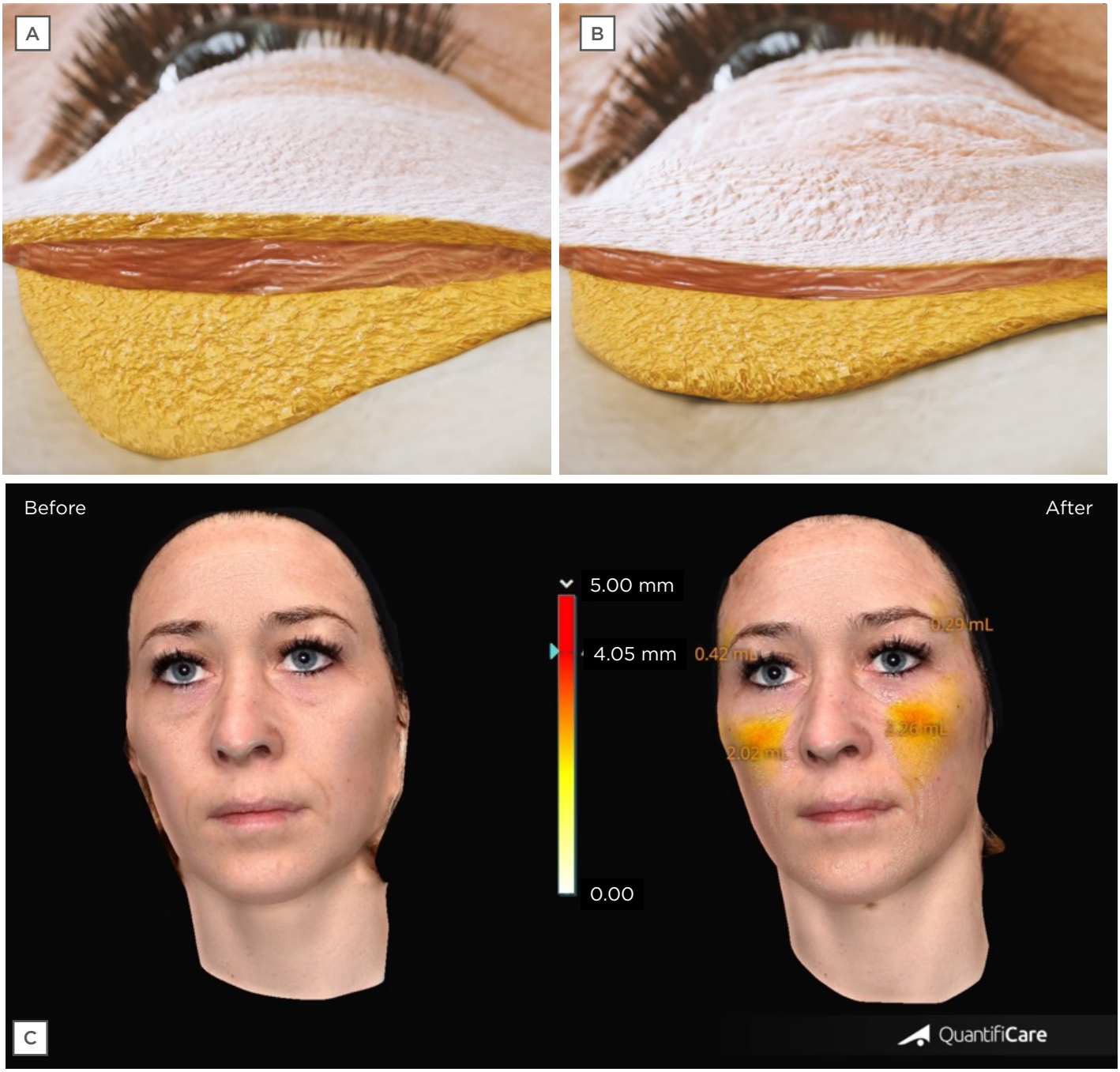

Figure 3: Midface soft tissues after weight loss.

Schematic section of the midface soft tissues **A)** before and **B)** after weight loss, illustrating the atrophy of fat layers. **C)** Before and after photographs of Shah-Desai's patient, who was injected live to showcase the treatment of facial volume changes after a significant weight loss. Pre-/post-treatment volumetric changes are presented on the right photograph.

Photographs were taken with 3D camera LifeViz® Mini and its software, LifeViz® App (Quantificare, San Francisco, California, USA).

Infraorbital hollows

The patient presented visible infraorbital hollows, with marked TT and palpebromalar groove that were accentuated by the bulging appearance of the infraorbital fat. Patients with very large and pronounced eyebags are generally poor candidates for filler injection. The 'push' test can be used to evaluate the potential benefits of the procedure. Furthermore, if the aetiology

of eyebags is explained by the presence of fluid accumulation rather than prolapse of the orbital fat, treatment with HA fillers may be either disregarded or performed with smaller amounts administered over several treatment sessions to minimise the risk of further impeding the lymphatic drainage.[42-45]

In this case, it was essential to educate the patient and inform her on the limitations of HA filler injections, as she might have benefit more from a surgical treatment on the long-term. Accessing the area with a 25 G/38 mm cannula, which was introduced laterally, tiny aliquots of TEOSYAL PureSense Redensity 2 (Teoxane) were injected supraperiosteally in her TT and palpebromalar groove (0.5 mL each side) to soften her infraorbital groove with this specifically designed filler.[46] Placing the finger of the non-dominant hand above the injected area helped prevent the filler from entering the infraorbital septum. In the TT part of the infraorbital hollows, a little subcision helped detach the cutaneous adhesion of the TT ligament, facilitating cannula gliding along the bone.

Nasolabial Folds

The procedure ended with the treatment of the patient's NLF. The main danger in this area is the FA, which lies under the zygomatic major muscle and/or just above it in the subcutaneous plane, then becomes very superficial in the upper third of the fold.[47-51] As the goal was to inject 0.2 mL of RHA_4 into the patient's left and right pyriform fossa to soften her folds, a cannula entry point was performed at the bottom of the NLF, to advance a 25 G/38 mm cannula superficially before going deep in the upper third to position the filler bolus.

Treatment Overview

Before and after photographs of Shah Desai's patient can be seen in Figure 3C, with visible changes in surface/volume ratios, as well as an overall appearance improvement, the patient's face looking less gaunt and less sunken.

Conclusion

Over the past decades, facial aesthetic surgery has lost ground to less invasive procedures that, in the right hands, may provide similar benefits through less traumatic, relatively painless, and less daunting treatments with minimal social downtime.

Capitalising on their well-established efficacy and safety profile, HA fillers have evolved with dedicated formulations adapted to the specific anatomy and mobility of each treatment area. As a result, a good knowledge of facial anatomy combined with cautious choices of techniques and products achieves natural-looking results with HA fillers which have become a viable alternative to surgery, for both reconstructive and therapeutic indications. In such indications, adopting an ATP approach ensures patient-centred care with safe injection techniques. The 'A' for 'anatomy' and 'assessment' should be the foremost consideration in regard to the patient's personal and medical history, in addition to general anatomical principles. Most importantly, the psychosocial impact of the treated conditions in this category of patients is often critical, and treatment goals are essential to improve quality of life. A successful treatment may contribute to a more regular life with further social interactions and improved self-confidence, thereby taking part in a global physical and mental healing process.

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The Role of Harm Reduction in Smoking Cessation Strategies

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Interview Summary

Smoking kills more than 7 million people every year and is associated with approximately one in four deaths from cardiovascular diseases (CVD). Cigarette smoke affects platelet function, fibrinolysis, endothelial function, oxidative processes, inflammation, lipid oxidation, and vasomotor function, contributing to the development of atherosclerosis and superimposed thrombotic phenomena. According to the European Society of Cardiology (ESC), smoking cessation is the most cost-effective CVD prevention intervention, and all smokers should be encouraged and supported to quit. However, many people fail to stop, even after a cardiac event. For those who are unwilling or unable to stop due to nicotine addiction and psychological elements, there is going evidence that harm reduction strategies can help. Varies studies have shown that switching to smoke-free products such as heat-not-burn (HNB) systems, which exposes people to fewer carcinogens and toxicants than cigarette smoke.

In this article, Nebojsa Tasic, Cardiovascular Research Center, Dedinje Cardiovascular Institute, Belgrade, Serbia, and Emil Toldy-Schedel, General Director, St. Francis Hospital, Budapest, Hungary, discuss the role of harm reduction strategies in smoking cessation, and which patients may benefit from switching to smoke-free products. They also outline the current data, identify gaps in the evidence base, and set out a vision for a world where neither smoking cessation nor tobacco harm reduction strategies are necessary.

LEADING WORLDWIDE KILLER

Worldwide, tobacco use causes more than 7 million deaths every year, a death toll that could increase to 8 million by the end of the decade if global trends continue unabated.[1] It is the single biggest risk factor for lung cancer, causing 70% of cases,[2] and is a leading cause of CVD morbidity and mortality.[3]

Tasic said: "We are living in a world of war and pandemic but, for the last 100 years, smoking has proven to be one of the most dangerous risk factors. It contributes to CVDs and to many different types of cancer, including lung, oesophageal, throat, and tongue cancers. This is really important: CVDs are killing around 50% of the adult population in Europe,[4] and cancers account for around one in six deaths

worldwide.[5] Taken together, smoking is one of the leading killers."

It also has a significant impact on quality of life. "This habit puts a lot of limits on people. They are restricted to certain areas to smoke, making them feel like an animal in a cage. The only place they can smoke freely is at home, but when they do that, they endanger their loved ones," he said, explaining that passive smoking just as dangerous as active smoking.

SMOKING, CARDIOVASCULAR DISEASE, AND CESSATION

Cigarette smoke affects platelet function, fibrinolysis, endothelial function, oxidative processes, inflammation, lipid oxidation, and vasomotor function, contributing to the development of atherosclerosis and superimposed thrombotic phenomena. While many of these pathways are reversable, atherosclerotic plaque formation is not.[6] This makes smoking a significant CVD risk factor. It causes half of all avoidable deaths in smokers, 50% of which can be attributed to atherosclerotic cardiovascular disease.[6] It is also one of the world's leading risk factors for disability adjusted life-years, second only to high systolic blood pressure.[7]

Talking about the overall impact of smoking on CVDs, Tasic said: "When people have these conditions, they cannot contribute to society as they did before, which is terrible for them. Around half of people with stroke, myocardial infarction, or severe peripheral arterial disease cannot work anymore. The problems are even greater when we combine smoking with diseases like diabetes, which can lead to accelerated atherosclerosis, premature myocardial infarction, and strokes." Furthermore, he went on, younger smokers who have diabetes are much more prone to myocardial infarction in the earlier stages of life, which can leave them having to cope with a comorbidity at a relatively young age.

Overall, the average life expectancy of a life-long smoker is 10 years shorter than that of a non-smoker. However, that risk can be halved if the person stops smoking before the age of 50, and almost normalised if they quit before 30.[7] As such, the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice state that stopping smoking is potentially the most effective of all preventive CVD measures. They say cessation leads to substantial reductions in myocardial infarctions and death at all ages, and recommend healthcare professionals encourage all smokers to quit.[7]

SUPPORTING CESSATION

"Smoking cessation is the absolute target for us because we know it benefits all the organs, but especially the lungs and the cardiovascular system. After just a few months it will have a huge impact on the person's health," said Tasic, explaining that smoking cessation should start with the implementation of the ESC 'Five As' rule:[6]

- Ask: systematically enquire about smoking status at every opportunity.
- Advise: unequivocally urge all smokers to quit.
- Assess: determine the person's degree of addiction and readiness to quit.
- Assist: agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and any pharmacological support.
- Arrange: schedule a follow-up appointment to discuss progress and offer any additional support that might be necessary.

Persistence and building trust are crucial parts of this process, Tasic went on: "I believe the most important factor is having a strong connection between doctor and patient. When I keep explaining the advantages and disadvantages of stopping, the quality-of-life impact, and the increased longevity, on the first visit, the second visit, and the third visit. Slowly but surely, they come round to the fact that they have to quit and that it is the only way to make their lives better."

Of course, this approach does not always work, and many people continue to smoke even after experiencing a cardiac event. Toldy-Schedel said that in his native Hungary, more than 56% do not stop after a stroke, 70% do not stop after a peripheral heart disease diagnosis, and about 40% do not stop after a heart attack. [8] "We are talking about a huge population," he said.

Across Europe, more than two-thirds of smokers say they are keen to give up, yet fewer than one

in 20% are successful.[6] Asked why so many failed in their attempts, Toldy-Schedel explained that nicotine was extremely addictive. Tasic agreed: "Quitting smoking is one of the most difficult things someone can do. Throughout my career, I have met a lot of alcoholics and many of these people have said it was harder to stop smoking than it was to stop drinking."

Both experts said there was also a psychosocial element that made the habit hard to kick. "Smoking is part of their regular activities, part of their daily routine," said Tasic, adding that the silent nature of CVDs also played a role. "Low health education is a big problem. When people feel healthy, with no symptoms or clinical signs, they feel good and so do not even consider stopping."

Broadly speaking, they said, their patients fell into one of three groups: those who want to give up and are able to; those who want to give up but fail; and those who have no intention of giving up. Each of these groups requires a different approach.

For group one, pharmacological interventions such as nicotine receptor partial agonists or nicotine patches, alongside counselling and support, is recommended.[7] However, those who fall into group two may relapse several times and eventually "give up giving up."

"There is one group who would like to stop smoking, and who we should give as many chances as we can with psychological and pharmacological support. But there is a much bigger proportion who maybe want to change but cannot because they are dependent on nicotine. We have to give them alternatives," said Toldy-Schedel, describing it as an ethical issue.

HARM REDUCTION

Nicotine addiction may be the reason many people are unwilling or unable to quit, but, as Tasic and Toldy-Schedel explained, it is not the reason smoking is so dangerous. Cigarette smoke contains thousands of chemicals, including at least 70 carcinogens. Under combustion, tobacco releases toxicants that cross the alveolar barrier and enter the bloodstream, where they elicit systemic oxidative stress and inflammatory responses.[9] "It is not the nicotine that kills people," said Toldy-Schedel.

While both experts said that smoking cessation was preferable, they agreed that there was a role for harm reduction strategies. This well-established concept in areas such as substance and alcohol misuse has been shown as far back as 2008 to be capable of reducing morbidity and mortality where abstinence is not feasible.[10] If applied to smoking, it can mean encouraging those who are unwilling or unable to stop to switch to smoke-free products such as electric cigarettes (e-cigarettes) or HNB systems.

HNB systems, for example, heat rather than burn the tobacco. This creates an aerosol that contains nicotine and tobacco flavour but with significantly fewer harmful and potentially harmful chemicals (HPHC) and cardiovascular toxicants than cigarette smoke.

A number of *in vitro*, *in vivo*, and clinical studies have suggested that this approach has the potential to reduce risk, when compared to smoking cigarettes.[11-14] Participants in a 6-month clinical study who predominantly used Philip Morris International's (PMI; New York City, New York, USA) HNB product (≥70% NHB), for example, experienced substantially reduced exposure to a broad range of HPHCs, while still having the same nicotine exposure as those who continued smoking cigarettes. The researchers also found that smokers who switched to HNB for the study duration showed improvements in clinical risk endpoints associated with CVDs, such as lipid metabolism, endothelial function, oxidative stress, and platelet function.[14]

With a growing evidence base, last year's ESC smoking cessation guidelines covered the use of smoke-free products for those who are unable to quit. The authors pointed to evidence suggesting that e-cigarettes are probably less harmful than tobacco and more effective than nicotine replacement therapy in smoking cessation. They also noted that HNB are lower in toxicants than regular cigarettes, though warned that the systems do still contain tobacco.[7]

In the USA, the U.S. Food and Drug Administration (FDA) has authorised the marketing of PMI's HNB product, IQOS, as a modified risk tobacco product. The body pointed to evidence showing that switching completely from combusted

cigarettes to the IQOS significantly reduced exposure to 15 specific HPHCs. In addition, it cited a toxicological assessment that found that, when compared with cigarette smoke, the product's aerosol contained considerably lower levels of potential carcinogens and chemicals that are toxic to the respiratory or reproductive systems. However, it is important to note that the modified risk tobacco product authorisation does not mean that the regulator has deemed the system safe or 'FDA-approved'.[15]

SECOND LINE INTERVENTION

In his practice, Tasic said he recommended HNB products as a pathway to cessation. He has witnessed success with this approach, he said, explaining that while some of his patients simply swapped from cigarettes to HNB, a larger proportion went on to quit completely, usually within 1–3 months. "I think it is very important to have this transition period," he said, adding that the evidence base does suggest that there are some advantages to switching from cigarettes to HNB. "It is important from a psychological point of view; they feel as though they have achieved something and that they are doing something for their health."

It is about giving everyone the opportunity to give up, said Toldy-Schedel. "If someone cannot stop smoking even though they have tried several times, or they cannot give up because of their nicotine addiction, we are advising (smoke-free) equipment as a secondary option. We know that the things that cause cancer and create well-known problems with the cardiovascular system are not as present in heated tobacco as they are in a cigarette. We have that data."

CLIMBING THE HIERARCHY OF EVIDENCE

Smoke-free products such as e-cigarettes and HNB systems are a relatively new development, and there are still significant gaps in the evidence base. Toldy-Schedel said that while there were multiple studies showing what HNB products do not contain, he would like to see more data on what they do contain. He also warned of the potential pitfalls of recommending e-cigarettes as part of harm reduction strategies. "In Hungary, you can buy all kinds of nicotine fluid, from China or wherever. It means you can use e-cigarettes without knowing what you are smoking. We would like to close the door on that because we would like to control what people are using so we are in a better position to help them," he said.

Tasic said there were huge amounts of evidence to show that HNB systems and e-cigarettes were less toxic than conventional cigarettes. "What we need now are sone double-blind, prospective studies. It is really important that we start to measure the advantages. If we want to recommend something to our patients, we really need a strong scientific base." As part of this drive to continue to build the evidence base, Tasic and his colleagues are currently in the planning stages of a study of the impact of HNB products on CVD outcomes. "At the end of the day, this is about reducing cardiovascular risk to decrease the number of adverse cardiovascular outcomes. If we manage to decrease the risk in patients with high or very high risk, then we will have achieved something very good. Otherwise, it is all just cosmetic," he said.

A better understanding of the thresholds between group one smokers, who can quit with support, and group two, who would benefit from harm reduction strategies, would also be useful in daily practice, said Toldy-Schedel. "If someone can stop smoking, we have to give them a chance to change their habits because cessation is always going to be better than the alternatives," he explained. He is part of a multi-disciplinary team, which includes psychologists and psychiatrists, that is building and validating a questionnaire that they hope will eventually help them to stratify people between the pathways.

FUTURE DIRECTION

As more evidence on the benefits of harm reduction strategies in tobacco use accumulates, Tasic hopes it will help drive uptake of the approach in primary care. "The general practitioners are the doctors who should advocate for the harm reduction concept because they are the first touch point for the patient. They are important because the patients already believe in them. We need to educate not just the patients but the primary healthcare physicians," he said. The approach could help people reduce

their CVD risks before they suffer a cardiac event, and meet secondary care physicians like himself and Toldy-Schedel. "They are the gatekeepers. Let's put this concept of harm reduction at the beginning of the tunnel, not at the end of the tunnel when it is already getting dark," he said.

Both doctors said they looked forward to a future where neither smoking cessation programmes nor harm reduction strategies were needed. The world is changing rapidly, said Tasic. "Only 50 years ago, people would smoke everywhere. In the old movies you see people smoking on aeroplanes and even in hospitals, but when you see it now, it looks so strange. Maybe in 50 years from now, cigarette smoking will seem that strange to our grandchildren and great-grandchildren," he said.

Toldy-Schedel echoed his colleague's sentiments. "Twenty years ago, everyone smoked at the dinner table, and now that's a shameful thing to do. Habits are changeable," he said.

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Academy™: An Online Diabetes Educational Programme for Healthcare Professionals

Interviewees: Pratik Choudhary[1,2]

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2. Diabetes Technology Network-UK (DTN-UK), UK

Disclosure: Choudhary has received personal fees from Glooko, Abbott, Dexcom, Medtronic, Insulet, Novo Nordisk, Sanofi, and Lilly.

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Interview Summary

The last decade has seen a rapid expansion in the use of technology by people living with Type 1 diabetes. But how should the information generated by this technology be interpreted and used to inform patient management? This is where Academy™ comes in, providing free certified education on best practice for using the plethora of options in diabetes technology.

In this interview with EMJ, Pratik Choudhary, Professor of Diabetes, Leicester Diabetes Centre, University of Leicester, UK, and Chair of the Diabetes Technology Network-UK (DTN-UK), outlined the genesis and development of the Academy online platform, what it currently offers, and what is in the pipeline for this unique resource.

MANAGING THE MYRIAD OF DIFFERENT DIABETES TECHNOLOGIES

For people with diabetes and their healthcare providers, managing the myriad of technologies like glucose monitors and insulin pumps, as well as the data volume that accompanies these technologies, is a well-established challenge. And while tech-based services like web-based programmes, telehealth, mobile apps, and remote monitoring are improving users' accessibility and connectivity, the adoption of these innovations has been slow.[1]

"As diabetes technology becomes increasingly widespread in routine clinical practice, we need to train all levels of our diabetes and wider health workforce in what these technologies are and how to use the large amounts of data they generate," said Choudhary. "Use of these technologies has transformed how we deliver care, especially during these challenging times. Academy provides clinicians with an easy way to understand and use technology together with their patients."

There is good reason to use diabetes technologies, as international research has linked them with better outcomes. A nationwide UK audit found that flash glucose monitoring was associated with improved glycaemic control and hypoglycaemia awareness, as well as reduced hospital admissions.[2] A Swedish study demonstrated improved glycaemic control in patients using connected pens,[3] while a meta-analysis indicated that closed loop insulin delivery increased blood glucose control and

reduced the number of hypoglycaemic events compared with sensor augmented pump delivery.[4] The German HypoDE study found that real-time continuous glucose monitoring reduced hypoglycaemic events in patients with Type 1 diabetes treated with multiple daily insulin injections and with impaired hypoglycaemia awareness or severe hypoglycaemia.[5]

As part of the National Health Service (NHS) improvement programme, the Getting It Right First Time (GIRFT) review of diabetes recommended that "staff should be trained to support patients using [diabetes] technologies and given the time that they need to complete this training, which should form part of their annual appraisal process."[6] This requirement kick-started the process for establishing Academy. During the year-long project, expert clinicians in DTN-UK produced the content, Glooko (Mountain View, California, USA) provided the platform and project management, and production was completed by DigiBete (DigiBete Global, Leeds, UK), which remains actively involved in Academy. Funding for the project came from industry partners including Abbott, AgaMatrix, Dexcom, Insulet, Medtronic, Lilly, mylife Diabetescare, Novo Nordisk, and Roche.

WHO IS ACADEMY™ FOR?

Academy is aimed at all healthcare professionals who support people using diabetes technology. While most people using complex technology such as insulin pumps and closed loop systems are generally followed up in secondary care by specialists, healthcare professionals in other specialties and those in primary care, such as general practitioners and practice nurses, will increasingly come across devices like continuous glucose monitors and connected pens. "Some 7–8% of the population has Type 1 diabetes, so healthcare professionals in all settings will come across these patients and will need some familiarity with the devices they use," noted Choudhary.

DIABETES TECHNOLOGY TRAINING: FROM FINGER PRICKS TO CONNECTED PENS

The Academy platform was developed in step with announcements on diabetes management from NHS England and in line with new National Institute for Health and Care Excellence (NICE) guidance for Type 1 diabetes. There are eight courses in total, each with a number of modules that focus on a particular type of technology. All of the information is provided in videos, which include a summary at the end, followed by self-assessment tests.

Flash glucose monitoring was the catalyst for the growing use of diabetes technology in the UK, and is the subject of the first course. "Seven in 10 people with Type 1 diabetes don't finger prick anymore," said Choudhary. "They just swipe their arm with a device and get the data. Supporting clinicians in supporting their patients with the widespread use of flash glucose monitoring across the country was the big push when we set out with this educational project." New guidelines by the NICE have recommended wider access to include continuous glucose monitoring for adults and children with Type 1 diabetes.

Following NHS England's announcement of funding for pregnant females with Type 1 diabetes to use real-time continuous glucose monitoring, a dedicated course was created for continuous glucose monitoring in pregnancy. A third course focuses on these devices in all patients with Type 1 diabetes. Access to insulin pumps varies widely across the UK, and a fourth course was designed to train clinicians to support patients using these devices. Closed-loop systems link insulin pumps and continuous glucose monitoring devices so that the correct amount of insulin is delivered based on real-time glucose readings. NHS England has funded a pilot on these systems, also called 'artificial pancreas', which prompted course number five.

The COVID-19 pandemic led to a rise in virtual consultations, so this became the topic for the sixth course. Course seven was finger prick readings for self-monitoring, which may be of particular interest to primary care practitioners. The most recent course is focused on the connected pens that are set to reach the market

within the next year. These devices can record the exact time and dose of insulin delivered and share these data with online databases. The dedicated course for this technology is coming soon.

"All of the content is device-agnostic," noted Choudhary. "As an example, we provide generic advice on how to set up an insulin pump, what therapeutic changes should be made when certain patterns are observed in the data, and what to tell the patient. The educational videos were reviewed by people with Type 1 diabetes to ensure that all important points are covered and that the language is patient-friendly. Similar content is on DTN-UK's website for patients so that healthcare professionals and people living with diabetes can speak the same language when discussing technologies."

In total, there are over 27 hours of videos, which health professionals can view in any order, at their own pace. Choudhary explained: "We wanted to stay away from a mandated, prescriptive course that you have to complete from start to finish. Individuals can choose which courses they want to do based on the needs of their job role."

Assessment and Accreditation

In response to the GIRFT recommendation that staff delivering a Type 1 diabetes service need to be able to demonstrate their understanding of diabetes technologies, the platform provides Continuing Professional Development (CPD) accredited by the Association of British Clinical Diabetologists (ABCD). Each course finishes with an assessment, and a CPD-approved certificate is awarded for successful completion. "Healthcare professionals can put the certificates into their appraisal portfolio to demonstrate that they've done the training required to deliver diabetes technology care," said Choudhary. "Importantly, the evaluation tests both knowledge and application in clinical scenarios."

Choudhary pointed out that accreditation is for health professionals at all levels of exposure to these devices. "Experienced clinicians may prefer to do the assessments only, rather than watching the educational videos," he said.

HOW TO ACCESS THE ACADEMY™ PLATFORM

Industry sponsorship means that the platform is free for all healthcare professionals, while DTN-UK maintains editorial control over the content. Healthcare professionals working in primary and secondary care can access Academy via Glooko, which is currently used by approximately 90% of secondary care clinics in the UK to access patients' glucose data.[7] Glooko® replaces diasend®, so clinics may need to migrate their Academy account to the new system. Health professionals can also access the platform via the ABCD website.[8] Clinicians who do not have an account with Glooko® for viewing device data can still access the Academy platform for free on request.

UPTAKE IS SPREADING ACROSS THE UK

It has been a busy year for Academy, with over 1,000 doctors and nurses across more than 300 clinics now taking the courses, and close to 1,200 courses currently in progress. On top of that, more than 750 CPD certificates have been attained by healthcare providers in the UK.

"The feedback has been that people have found the training really valuable," said Choudhary. "Even clinicians who have been using technologies for a while have said they learned something new. We are planning some research to examine how the courses have changed clinicians' confidence and usage of diabetes technologies. We want to know if they now feel more comfortable recommending a device and supporting patients to use it."

WHAT IS NEXT FOR ACADEMY™?

In addition to the recently added course on connected pens, a launch of the platform in Ireland is imminent. Other priorities this year are to increase coverage across the UK and respond to any feedback.

A future goal is to investigate whether the uptake of technology in different UK regions correlates with the uptake of education. "One of the challenges of technology coming into the world of diabetes has been disparities in

adoption," said Choudhary. "Access to insulin pumps varies from 1–40% of patients in different trusts across the UK, while access to flash glucose monitoring ranges from 30–70% in different clinical commissioning groups. Some of that variation is due to diverse policies and funding restrictions, but we expect that some of it is healthcare professional familiarity and education on how these devices are used. One of the big ideas in this endeavour is that more widespread training could lead to more patients using devices that have been shown to improve outcomes."

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Interviews

Environmental activists Grant Blashki and Karly Hampshire spoke with EMJ about the future of healthcare, medical education, and climate change.

Featuring: Grant Blashki and Karly Hampshire

Grant Blashki

Associate Professor, Nossal Institute for Global Health, University of Melbourne, Victoria, Australia; Adjunct Associate Professor, Monash Sustainable Development Institute, Monash University, Melbourne, Victoria, Australia; Co-founder of Doctors for the Environment Australia

Q1

What led you to pursue a career in medicine and what made you decide that general practice was the specialty for you?

The beautiful thing about medicine is the combination of science and humanism. I have recently experienced some personal reminders about just how extraordinary modern, high-quality, clinical medicine is. One patient, a man in his 80s, had a stent put in within 3 hours of getting chest pain, experiencing no heart damage. Another patient, a young mother delivers a healthy baby via caesarean section following life-threatening pregnancy. Why general practice? I like that the relationship with the patient is the central part of practice; furthermore, there is no artificial boundary between demographic or clinical issues. General practice places you in a unique clinical role at the nexus of health and society. You work with families, culture, and the community, watching an entire procession of life go by.

Q2

Do you think that there are any misconceptions about your speciality of general practice?

I have taught general practice for 30 years around the world including Australia, Indonesia, and China. In doing this, I have heard the prevalent myth that general practice is suboptimal and non-specialist. This is an understanding that needs to change. General practice is the most effective way to provide primary and preventative care, continuity of care, early detection of diseases, and manage undifferentiated presentations. I would also argue that general practice provides

a lot of humanity and common sense to medicine. We see specialisation and super-specialisation, which is essential, but I think general practice maintains a real human touch. On a daily basis, general practitioners (GP) convert very complex science into understandable concepts for their patients. Finally, GPs straddle the physical and psychological aspects of care. Recent studies in Australia have demonstrated that the majority of GPs now cite psychological consultations as their most common consultation, indicating the hugely central mental health role in the community.

Q3

In previous interviews and press coverage, you have discussed the influence of mentors on your career. Can you name one individual who has impacted your career the most and in what way?

The late Professor Tony McMichael, who was a Professor of Epidemiology at the London School of Hygiene & Tropical Medicine (LSHTM), UK, and then later returned to the Australian National University (ANU), Canberra, Australia. He was a leading epidemiologist, and one of the groundbreaking researchers who really conceptualised the link between climate change and health issues. He was one of the first to really articulate that if we want to look after population health, we must first understand key environmental issues such as climate change.

Q4

Can you tell us about your new book, *Climate Health and Courage*?

Each year when preparing for my teaching units, I research the latest updates in climate science, and it can be scary. The Intergovernmental Panel on Climate Change tells us we have experienced a 1 °C rise already, and that we could be facing as much as 4 °C by the end of the century. As an Australian, living in one of the most vulnerable developed countries in the world, we have already seen extraordinary fires. We see low-lying countries in the Asian Pacific, where sea level rises will cause displacement of entire communities. A real problem, especially amongst younger people, is the hope budget. As we talk about the threat of climate change, there's a real risk of despondency and a disengagement. This book focuses on how to maintain hope.

Q5

Was there a particular event or person that initiated your interest in the impact of climate change on medicine?

I think there are a number, but probably the most influential for me would be former Vice President Al Gore. I have been fortunate enough to participate in Climate Reality training with him several times. This training brings together thousands of people from different sectors of society, like farmers, librarians, social workers, and doctors, to share and contribute what solutions or opportunities

their position offers. I think it's a strong model for empowering leaders to speak and represent their own sectors or communities.

Q6 What changes have you seen to the discussion surrounding healthcare and climate change since you published your 2007 papers, 'GPs and the environment' and 'Climate change and primary healthcare'?

I think there are less climate sceptics who are still taken seriously; that faction of scientists appears to have filtered out of the serious debate. I secondly think that it has become clear how powerful health framing of the issue is, and the degree to which this resonates with people. Within the community there has finally been a significant recognition of the health sector's carbon footprint. The move towards green hospitals, green healthcare, procurement measurements, and spending efficiencies has been significant in the past 15 years.

Q7 As an educator, where can we expect to see your focus lie in the coming years?

Something that excites me most is the education of strong leadership skills within the public health leaders of the future. These individuals need to understand the science and the mechanics of traditional public health, but also play the role of a leader, understanding the surrounding systems and governance. Many of our solutions to 'greening' our health systems lie within engineering, public transport, or manufacturing. I think our upcoming public health leaders have such exciting careers ahead of them, becoming part of the discourse with policy makers, and creating change within many different sectors of society. I think that mainstream environmental sustainability in every aspect of healthcare and clinical governance will be essential in the future.

Q8 Are there any innovations, or changing practices, in either general practice, or its relationship with climate change, that you think are particularly noteworthy?

In the future, I would consider the most important change in practice to be that doctors start to 'think beyond the consulting room', with prudent prescribing and responsible referrals becoming common practice. As we start to be more considerate of food miles, we must also consider where our medications come from. When considering waste of time and resources, physicians must consider the risk of unnecessary investigations and referrals.

Q9 Throughout your career so far as a GP, a campaigner, and an educator, what is your proudest achievement?

I'm proud of the paper I co-authored in 2008, 'Hope, despair, and transformation: climate change and the promotion of mental health and wellbeing'. It was one of the early papers that really started overlaying climate change issues with psychological and mental health issues. From there, the discourse on this subject has become more and more relevant. To me, there is nothing abstract about seeing families in Australia who have lost houses and businesses to wildfires suffering mental health impacts such as post-traumatic stress disorder. This dovetails with considerations about the hope budget and its interaction with mental health. I want to emphasise that the bad news on social media is not always accurate. There is still time and it is not the time for despondency; a 2 °C rise will certainly be much better than a 4 °C rise in global temperatures, so all our efforts are worthwhile. ■

Karly Hampshire

Medical Student, University of California, San Francisco, USA; Founder and Co-director, Planetary Health Report Card; Fellow at the University of California Center for Climate, Health and Equity, USA

Q1 What led you to want to study medicine?

Put simply, my desire to pursue a career in medicine was driven by the intimacy and power of serving people. This desire has been the result of many moments: reading heartfelt letters from patients with cancer, seeing Paul Farmer speak in high school, and witnessing childbirth. I believe medicine uniquely blends science, compassion, and care and, despite all of the flaws of the healthcare system, it's very gratifying to bear witness to some of the most transformative moments of someone's life and to help ease the suffering that can often accompany those moments.

While the climate work I engage in is rewarding in its own way, I think the pairing of more zoomed-in clinical work and more zoomed-out climate work will be critical for maintaining balance and mitigating burnout in my career. When I am feeling like the issues posed by climate change loom too enormously for me, as an individual, to make a difference, I can find solace in knowing that at least I can help the patient in front of me. And when I am exposed to all the structural issues my patients face and am feeling like efforts to address them individually are inadequate, I can take a step back and work to prevent worsening of inequities through larger scale climate action.

Q2 Was there a particular event or person that sparked your initial interest in campaigning to address climate change?

I have always been environmentally inclined. In fact, the reason I initially applied to Emory University, Atlanta, Georgia, USA, for an undergraduate degree was because they showed up on a 'most sustainable universities' list. However, my main focus in college was health and education for refugee and immigrant populations.

Through conversations with patients at the refugee and immigrant health centre that I volunteered at, I recognised climate change as an underlying force driving people from their homes, either directly through food insecurity or indirectly through the ensuing civic instability. I saw the toll it had wrought on mental and physical health, especially for the most structurally disadvantaged such as post-traumatic stress disorder, chronic conditions untreated for years, and sexual violence.

In my anthropology coursework, I explored how many of the recent displacement 'crises' had underpinnings in climate change (for example, the Syrian civil war). When I started medical school, I decided to make climate action my main focus as I saw climate change as the 'great exacerbater', threatening to worsen so many social issues, from displacement to food insecurity to homelessness to racism. I also felt like the healthcare workforce wasn't talking enough about the role that we could play in mitigating downstream suffering through climate action.

Q3 As a medical student at the beginning of your career, where can we expect to see your focus lie in the coming years?

I am passionate about applied climate and health education and I'm interested in creating collaborative resources that will catalyse scalable,

"I recognised climate change as an underlying force driving people from their homes"

efficient, high-quality rollout of climate and health education across disciplines and levels of training. For example, I'm currently working with the Global Consortium on Climate and Health Education (GCCHE) on a multi-institutional collaboration called the Climate Resources for Health Education Initiative (CRHE), which seeks to create an open-access repository of adaptable peer-reviewed, problem-based learning sets and slides for undergraduate and graduate medical education. I imagine there will be a lot of potential for further spinoffs and growth there. In addition, as I enter residency and spend much more of my time in the hospital, and have more control over my clinical practice, I envision expanding my work more into the healthcare sustainability realm, working with organisations like Health Care Without Harm (HCWH).

Q4

You have published work that focuses on the ways in which the curriculum at medical schools needs to increase its consideration of sustainability. Why do you think it is important for future doctors to be aware and conscious of climate change and sustainability?

I think there are two sides to the importance of sustainability or climate change in medical education (also called Education for Sustainable Healthcare [ESH]). Firstly, climate change and other forms of ecological destruction are the gravest threat to health in the 21st century. The World Health Organization (WHO) already attributes almost a quarter of deaths and global disease burden to environmental degradation. Future doctors need to be prepared to diagnose, treat, and counsel on the health effects of this ecological degradation. Secondly, paradoxically, the healthcare system is itself a huge contributor to ecological destruction. If the global healthcare system was a country, it would be the fifth largest carbon dioxide emitter in the world. And there are simple things that doctors can do to reduce the environmental impact of their clinical practice (i.e., using sevoflurane instead of desflurane, or prescribing dry powder inhalers instead of metered dose inhalers). But without education, they have no idea the role they can play in bringing sustainability to their workplace and being part of the solution.

Q5

How does the University of California (UC) Centre for Climate, Health and Equity, San Francisco, USA, work towards the ambitious goal of making the health and equity impacts of climate change evident, urgent, and actionable?

The newly launched UC Center for Climate, Health and Equity seeks to leverage the power of the UC coalition to drive climate action that safeguards health. Their work spans four pillars: research, education, healthcare sustainability, and policy. In the research pillar, they aim to generate research at the intersections of climate health through cross-UC research collaborations. In the education pillar, they are creating education and training programmes across the UC health science schools, as well as supporting faculty and student curricular ambassadors. In the healthcare sustainability pillar, they are working to reduce the emissions of California's healthcare sector and to increase system resilience by building patient education tools. And lastly, in the policy pillar, they are seeking to translate

academic research and implement expertise into scalable impact, partnering with community organisations. Advancing health equity is a cross-cutting focus in all pillars. For example, we recently led an educational event on the health harms of proximity to oil and gas drilling sites, a topic with timely policy and equity implications in California.

Q6

What inspired you and your Co-founders to design and initiate the Planetary Health Report Card (PHRC)?

I started medical school at UC San Francisco (UCSF) in 2018. That September, the deadly and destructive Camp Fire raged through Paradise, California, USA. Even if you weren't in California, you may have seen pictures on the news of the hazy, smoke-filled dystopian sky at that time. Contemporaneously with that awful wildfire, we were, ironically, in our pulmonary block at medical school. Yet, despite the fact that we were walking to school every day in N95 masks through an eerie dusk, breathing in some of the worst quality air in the world with many in the region, especially the most marginalised, experiencing the health consequences, there was no mention of the health effects of air pollution or wildfire smoke in our curriculum. Several classmates and I were struck by the profound lack of planetary health education. We felt that, as future health professionals, we must be prepared to address the impacts of human-caused environmental changes on our patients' health. We learned that desire for curriculum on climate change was widespread among medical students. A research study I led found that among 600 medical students at 12 geographically diverse medical schools in the USA, 84% of students believed that the health effects of climate change should be included in the core curriculum, but only 13% believed that their medical school was currently providing adequate education on the topic. To help catalyse that institutional transformation, in 2019, several other UCSF medical students and I, with the help of many wonderful mentors, founded the PHRC.

Q7

Could you explain more about what the PHRC is and why it is important to both students and practicing healthcare workers?

The PHRC is a student-led, metric-based tool for evaluating and improving planetary health

"Future doctors need to be prepared to diagnose, treat, and counsel on the health effects of this ecological degradation"

engagement in health professional schools. The PHRC spans five topic areas: curriculum; research; community outreach and advocacy; support for student-led initiatives; and sustainability. Student-led, faculty-mentored teams work collaboratively to create school-specific needs assessments based on metrics in each of these five areas and then leverage results to catalyse change.

Since its creation in 2019, the initiative has expanded rapidly to over 80 medical schools in seven nations, including the USA, UK, Ireland, Canada, Germany, Malaysia, and Japan. Its application is already bringing about transformative dialogue between students and leadership, serving as a platform to advance the curricular innovations that will fulfil the learning needs of students in a changing world. With our network of over 400 participating students across the world, we have created a robust community, facilitating dialogue among medical student climate health leaders, and hosting dynamic events such as our institutional advocacy workshop and first annual symposium. From the beginning, I dreamed of eventual expansion into other health professions and that vision is being realised with the rollout of international nursing and pharmacy pilots. Overall, for students hoping to take climate action within their spheres of influence, the PHRC helps pair the abstract complexities of tackling climate change with tangible action steps.

Q8 What was the mission you set out to achieve when you launched the Interview without Harm study, petition, and advocacy tool?

In spite of the significant health harms of climate change and climate change's role in exacerbating underlying health inequities, healthcare systems, including medical education, contribute significantly to greenhouse gas emissions. COVID-19 has lent us the opportunity to reimagine the necessity of academic travel. In particular, in-person medical school, residency, and fellowship interviews are responsible for significant carbon dioxide emissions each year, as almost 100,000 medical trainees fly across the country multiple times, spending thousands of dollars each in the process. A permanent shift to virtual interviews would mitigate the majority of these emissions and could establish a model for reducing academic travel.

In addition, given the cost savings, virtual interviews would improve equity of the application process. Applicants interviewed virtually during the past two application cycles have been satisfied with their experience and many limitations can be overcome with structural solutions. Critical decisions about the future of medical training interviews in a post-COVID-19 era will likely be made this year, making this an opportune time to advocate to permanently change these unsustainable business-as-usual practices. However, I noticed that environmental considerations were frequently left out of cost/benefit discussions; for example, a >200 page document recently released by the Coalition for Physician Accountability, which outlined recommendations for the comprehensive improvement of the undergraduate medical education–graduate medical education transition, did not mention environmental impact once. The multi-pronged campaign I developed, Interview without Harm, seeks to address that gap.

Q9 Throughout your academic career as a medical student, what has been your proudest achievement?

My most cherished accomplishment has been spearheading the PHRC and watching it grow into such a widely used and powerful tool for change. There were so many times at the beginning of its development where I felt in over my head: having to design a leadership team structure, make strategy decisions, and formulate metrics amidst all my normal medical student responsibilities. Given all the initial imposter syndrome I faced, it feels really rewarding to reflect how far the project has come. Of course, it was very much a team effort, and there is no way the initiative could have achieved these milestones without the contributions of so many. But I think, when faced with the abstract complexity and enormity of climate change, it's easy to feel futile. And I feel grateful that I found a way to push through my feelings of powerlessness and create something that is really making a tangible difference, both in ways that are easy to pin down (i.e., curriculum changes in medical education) and in ways that are more abstract (i.e., movement building). ■

Air Pollution Exposure as a Relevant Risk Factor for Chronic Obstructive Pulmonary Disease Exacerbations in Male and Female Patients

EDITOR'S PICK

This fascinating respiratory review evaluates air pollution exposure as a risk factor for patients with COPD and shares whether air pollution exposure affects patients with COPD in a sex-specific manner. The authors highlight the most recent available evidence to draw an insightful conclusion. The impact of air quality as a climate- and environment-related determinant of health is increasingly recognised, making this an important and timely choice as our Editor's Pick for this issue.

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Abstract

Chronic obstructive pulmonary disease (COPD) is a multifactorial lung inflammatory disease that affects 174 million people worldwide, with a recently reported increased incidence in female patients. Patients with COPD are especially vulnerable to the detrimental effects of environmental exposures, especially from air particulate and gaseous pollutants; exposure to air pollution severely influences COPD outcomes, resulting in acute exacerbations, hospitalisations, and death. Here, a literature review of the recent work addressing air pollution-induced acute exacerbations of COPD (AECOPD) was conducted in order to determine whether sex was considered as a biological variable in these studies, and whether air pollution exposure affected patients with COPD in a sex-specific manner. It was found that, while the majority of studies enrolled both male and female patients, only a few reported results were disaggregated by sex. Most studies had a higher enrolment of male patients, only four compared AECOPD outcomes between sexes, and only one study identified sex differences in AECOPD, with females displaying higher rates. Overall, this analysis of the literature confirmed that air pollution exposure is a trigger for AECOPD hospitalisations and revealed a significant gap in the knowledge of sex-specific effects of air pollutants on COPD outcomes, highlighting the need for more studies to consider sex as a biological variable.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a lung inflammatory disease that includes emphysema and chronic bronchitis, and is characterised by airflow blockage in the lungs.[1] A growing number of studies have recently reported sex differences in the disease pathophysiology and on its incidence. In addition, there is a substantial body of evidence from clinical and experimental studies alluding to the effects of endogenous sex factors on lung function and disease. According to mouse models, female hormones and their metabolites can trigger lung inflammatory reactions, and male hormones usually play the opposite role. Thus, the impact of air pollution as a trigger of exacerbations and the independent response of the respiratory system is an area that research efforts need to focus on.[2] However, very little information on the effects of air pollution exposure on male and female patients with COPD is available, particularly in acute exacerbations of COPD (AECOPD) and its related outcomes, as most studies conducted in this area have not taken the variable of sex into account. As differences in the sex of patients with AECOPD is under-studied, the association between exposure to gaseous and particulate pollutants and hospitalisations for COPD exacerbations was investigated in this present review, paying particular attention to the differences between males and females. The authors focused on the association of daily mean concentrations of particulate matter (PM) with an aerodynamic diameter of <10 µm (PM_{10}) and of <2.5 µm ($PM_{2.5}$), as well as other gaseous pollutants (ozone [O_3], carbon monoxide [CO], nitrogen dioxide [NO_2], sulfur dioxide [SO_2]) with hospital admissions, based on daily measurements reported in each study, while analysing the sex variable.

COPD PATHOGENESIS

The pathogenesis of COPD includes proteinase–antiproteinase imbalance, immunological mechanisms, oxidant–antioxidant balance, systemic inflammation, apoptosis, ineffective repair, and an accelerated decline in forced expiratory volume in 1 second and forced vital capacity.[1] The diagnosis of COPD is also determined on the basis of symptoms and signs (e.g., exertional breathlessness, chronic cough, regular sputum production, frequent bronchitis, wheeze, etc.) in people >35 years of age who have a risk factor (e.g., smoking history), although these clinical findings have to be supported by spirometry, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and National Institute for Health and Care Excellence (NICE) standards.[3,4]

The development of COPD is multifactorial, and the risk factors for this disease include genetic, environmental, and sex and gender factors.[5] Among the sex (biological) factors are chromosomes, sex organs, and endogenous hormones, which differ between males and females. The gender factors, on the other hand, refer to socially constructed roles and behaviours that depend on cultural context and identity.[6,7] Female sex and gender have been independently associated with COPD development due to the differential susceptibility of the lung-damaging effects of cigarette smoking, interactions of female hormones with toxins present in tobacco products, and other factors such as exposure to household air pollution and environmental triggers.[6,8] While cigarette smoke is the most critical risk factor associated with COPD, occupational and other environmental exposures are known to cause approximately one in six cases.[9]

COPD exacerbations generally include an acute change in the frequency and severity of cough, increases in volume and changes in the character of sputum, and worsening dyspnoea beyond normal day-to-day variations, leading to an increase in medication usage.[4] Hospitalisations for COPD exacerbations are multifactorial. Common triggers include respiratory infections, poor outdoor air quality, or both. Among patients with COPD, it has been reported that 70% of cases of AECOPD are due to respiratory infections, viral or bacterial, and 30% are due to environmental pollution and other causes.[10] In addition, hospitalisation frequency varies with disease severity, the patient's age, history of antibiotic use, and the presence of one or more comorbidities.

COPD EPIDEMIOLOGY

COPD affects approximately 17.4 million people (7.3 million males versus 10.1 million females) in the

USA, and an estimated 174 million (104.3 million males versus 69.7 million females) worldwide. It is the fourth leading cause of death and the fourth leading cause of chronic disease-related morbidity and mortality, accounting for >120,000 deaths in the USA and 3.2 million deaths globally every year.[11,12] Several research studies have suggested that outdoor air pollution exposure is linked to the prevalence and incidence of COPD.

Between 1971 and 2000, the prevalence of COPD among females significantly increased from 50.8 to 58.2 per 1,000 people, while in the same time period, the prevalence in males decreased from 108.1 to 74.3 per 1,000 people.[13] More recent data have indicated that the prevalence of COPD was higher among females than males between 1998 and 2009.[9] Since the year 2000, the number of females dying from COPD has also surpassed the number of males.[14] These trends are partially explained by the higher susceptibility of females to the negative effects of smoking, which results in the earlier development of severe forms of this disease, as well as changes that have occurred over time as cultural and societal expectations for females have evolved, such as the rates of tobacco use, environmental and occupational exposures, and bias in disease diagnosis.[15,16]

AIR QUALITY AS A RISK FACTOR FOR COPD EXACERBATIONS

Air pollution exposure is estimated to contribute to approximately 7 million early deaths worldwide every year, and to >3% of disability-adjusted life years lost.[17] Air pollution has numerous harmful effects on health and contributes to the development and morbidity of cardiovascular disease, metabolic disorders, and a number of lung pathologies, including asthma and COPD.[18]

Recently, it has been found that the number of patients with COPD who do not have a history of smoking is higher than expected,[19] particularly for females.[20] Emerging data indicate that air pollution exposure alters epigenetic markers, such as DNA methylation, and that these changes influence the expression of genes that control inflammation, disease development, and exacerbation risk. Exposure to several traffic-related air pollution components, including PM, black smoke, O_3, nitrogen oxides, and polyaromatic hydrocarbons, has been associated with changes in DNA methylation in lung tissue.[21] Air pollution exposure can also stimulate pro-inflammatory immune responses, including the adaptive responses of type 2 and type 17 T-helper lymphocytes, and dysregulate anti-viral immune responses.[22] The clinical effects of acute and chronic air pollution exposure, particularly the known association between elevated levels and exacerbations of asthma and COPD, are consistent with those identified in inflammatory and immunological mechanisms activated in the lung during disease processes. For example, short-term exposure to air PM, NO_2, SO_2, and CO can trigger a neutrophil-mediated airway inflammatory response, followed by increased clinical symptoms. The deposition of PM in the respiratory tract depends predominantly on the size of the particles, with larger particles depositing in the upper and larger airways and smaller particles penetrating deep into the alveolar spaces. Ineffective clearance of PM from the airways causes particle retention in the lung tissue, resulting in chronic inflammatory responses that may be pathogenically important in both the exacerbation and progression of lung disease.[23]

Globally, exposure to household indoor air pollution in females who do not smoke also occurs via the inhalation of combustion products from biomass fuels, including wood, charcoal, animal dung, and others used for cooking.[24] Due to traditional gender roles, these exposures have significantly contributed to COPD morbidity and mortality in females.[25] It is estimated that 50% of households worldwide (approximately 3 billion people) are exposed to smoke from biomass fuel combustion. These exposures contribute to about half of the deaths from COPD, of which 75% are females, in developing countries.[24]

COPD EXACERBATION TRIGGERS

Exacerbations of COPD are episodes of worsening of symptoms that lead to substantial morbidity and mortality.[23] COPD exacerbations are associated with increased airway and systemic inflammation, and physiological changes, such as hyperinflation. These are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation. Some patients are particularly susceptible to exacerbations and show a worse health status

and faster disease progression than those who have infrequent exacerbations. The available literature indicates that COPD symptoms, but not lung function, are mainly associated with rises in air pollution levels. Of these, dyspnoea has been associated with PM_{10} with a 13% increase in odds for an interquartile range change in pollutant (95% confidence interval: 4–23%), and this association remained significant after adjustment for other pollutant exposures.[26]

The mechanisms of COPD exacerbations are complex. There is also significant heterogeneity among individuals with COPD, evident by the wide range of disease parameters, such as exacerbation, symptoms, response to treatment, rate of disease progression, and mortality, all of which refer are referred as COPD phenotypes.[27] Although we still have much to learn, phenotyping COPD individuals is crucial to make proper prognostic and therapeutic decisions and achieve meaningful outcomes. While respiratory viruses (e.g., rhinoviruses) and bacteria play a major role in the causative aetiology of COPD, in some patients, non-infective environmental factors also contribute to the disease development. Data recently published from a large observational study identified a subset of patients with a phenotype of higher susceptibility to frequent exacerbations triggered by environmental exposures.[28] Although >80% of exacerbations are managed on an outpatient basis; hospitalisation is all too common and associated with considerable health care costs and mortality. In this regard, non-invasive ventilation has greatly decreased the mortality rate for exacerbations that require ventilatory support. However, across the range of exacerbation severity, treatment failure and relapses are frequent.

Among individuals with COPD, exposure to outdoor air pollutants is associated with loss of lung function and increased respiratory symptoms, leading to exacerbations and increased mortality.[29] Some studies suggest that temperature may modify the effect of air pollution exposure, although these results are not conclusive.[30] For example, Yan et al.[31] explored the environmental effect of two different geographical locations in China on COPD exacerbations (Beijing in the summer; Sanya in the winter). It was found that the poorer air quality index and higher temperatures in Beijing were associated with a lower forced expiratory volume in 1 second, higher dyspnoea, and a relative risk of exacerbations that was twice as high as that observed in patients in Sanya.[31] The authors also reported that ambient air pollution was strongly associated with COPD exacerbations by triggering apoptosis in airway epithelial cells.[31]

Although adequate evidence for a direct relationship between ambient air pollution components and the development of COPD is lacking, higher mortality rates from respiratory and cardiovascular diseases have been reported among patients who have been exposed to air pollution for a long time.[32,33] Several reports have also pointed out the possibility that AECOPD can be caused by short-term exposures to air pollutants, as well as second-hand tobacco smoke.[6,34,35] Regarding sex differences in COPD exacerbations, the available literature indicates that outdoor air pollution affects both male and female patients, but non-smoker females are affected more frequently than males.[36]

AIR POLLUTANT ASSOCIATIONS WITH AECOPD

In the present study, the authors focused on the association of air pollution exposure and hospitalisations for COPD exacerbations with an emphasis on sex differences. Therefore, studies that included both male and female participants were selected, including those that did or did not analyse outcomes by sex. PubMed and Google Scholar were used to search for articles related to the focus of this study, especially articles that pooled results on a global scale, reported analytical pooled estimates, were written in English or had an English abstract, and studied the associations between air pollution and hospitalisation for COPD exacerbation, as well as the respiratory response to shorter-term exposure of air pollution. The literature search was limited to human epidemiological studies that described hospitalisation due to the acute exacerbation of COPD, as identified by the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes J40–J44; described a diagnosis of COPD and presentation for treatment of AECOPD, as defined by increasing shortness of breath, worsening cough, or change in sputum production at presentation; were based on research data; were from adult patients

(>18 years-old); and were published in English. Records were de-duplicated using the built-in mechanisms available from the library services at Indiana University Bloomington (Covidence software; Melbourne, Australia), with further de-duplications completed manually. Articles were then screened by their titles and abstracts for inclusion or exclusion; final selections were determined after a full reading of articles. Information on the association between daily mean concentrations of PM of PM_{10} or $PM_{2.5}$, as well as other gaseous pollutants (O_3, CO, NO_2, and SO_2), with hospital admissions was then extracted, analysing the sex variable, based on daily measurements reported in each study or other data that could be aggregated into daily mean values. The results are therefore presented as associations of 24-hour average air pollutant concentrations and daily hospital admissions for AECOPD.

The effects of air pollution exposure in 40 studies of patients with AECOPD are summarised in this review (Table 1).[37-70] Overall, it was widely reported that increases in environmental particulate and gaseous pollution concentrations were associated with an increased risk of hospitalisation for AECOPD, regardless of geographical location, with varying effects dependent on the air quality composition, pollutant concentration, and time of exposure. It was found that all but one of these studies enrolled mostly male subjects, while some enrolled males exclusively, which was surprising considering that the incidence of COPD among females has increased over the past few decades.[71] Potential factors that may contribute to this bias are the historically (although not current) higher incidence of tobacco use in males, occupational exposures, and the previously described gender bias in COPD diagnosis.[5,72]

Incremental increases in concentrations of $PM_{2.5}$ and PM_{10} were significantly associated with an increased risk of hospitalisation with AECOPD,[34,39] but also with stroke and myocardial infarction. However, the adverse influences of $PM_{2.5}$ on these diseases were generally more robust than those of PM_{10}.[62] In the Mid-Atlantic states of the USA, $PM_{2.5}$ exposure was associated with all COPD hospital admissions, with a relative risk increase of 1.83 for every 10 µg/m^3 increase in $PM_{2.5}$.[39] In Central and Eastern Europe, increases in hospital admissions were reported as being 3.3% and 2.8% greater for those exposed to PM_{10} and $PM_{2.5}$, respectively.[54]

When assessing the effects of gaseous air pollutants on AECOPD, it was found that SO_2 increases of 10 µg/m^3 were related to a 6% increase in hospital admissions for chronic bronchitis, with a 2-day lag (lag 2).[40] Comparably, an independent study found that, when modelled jointly with other pollutants, only SO_2 remained significantly associated with AECOPD (hazard ratio: 1.038), although the five pollutants assessed in this study were highly correlated (correlation coefficient: 0.89).[54] In addition, short-term exposures to SO_2 were associated with an increase in COPD exacerbation risk in a region with a relatively low air quality index (central Massachusetts, USA).[35] Regarding NO_2 and CO, both were significantly associated with AECOPD hospitalisations.[69] The magnitude of effects expanded slightly with increasing days of exposure, with a relative risk of 1.11 and 1.08 for NO_2 and CO, respectively, for a 7-day exposure average.[69] Likewise, a study in South Korea found that each 10 µg/m^3 increase in CO was associated with a 2% increase in the odds of admission for AECOPD.[47]

In multi-pollutant exposure models, significant associations between pollutant exposure and hospital admissions for COPD were found for all five air pollutants (SO_2, NO_2, O_3, PM_{10}, and $PM_{2.5}$), with higher relative risks for admission for every 10 µg/m^3 increase of SO_2, NO_2, O_3, PM_{10}, and $PM_{2.5}$, at a length of lag days that ranged from lag 0 to a cumulative lag 0–5.[35] PM_{10} and SO_2 were associated with both acute and lagged effects on emergency department visits due to COPD.[39] In addition, declines in attributable hospital admissions for AECOPD were associated with a reduction in concentrations of $PM_{2.5}$, PM_{10}, SO_2, and O_3.[58]

Finally, other environmental factors have been found to contribute to AECOPD. For example, in a study conducted in Serbia, the COPD-related emergency department admissions for all age groups were significantly associated with previous-day black smoke levels and lag 0–2 (1.60% and 2.26% increase per 10 µg/m^3, respectively).[44] Similarly, a study in Guangzhou, China, found that haze (at lag 1) and air pollution (NO_2 at lag 5; SO_2 at lag 3) combined presented more drastic effects on patients aged 19–64 years, especially for females.[52] Increases in NO_2 were associated with the highest risk of hospital admissions for total and respiratory diseases

in both single- and multi-pollutant models, and a relative risk of 1.94 in admissions in the emergency department at lag 0 for patients with COPD.[52]

INFLUENCE OF SEX AND AGE IN AIR POLLUTION EFFECTS ON AECOPD

As indicated earlier, very few studies reported the sex of the study participants or presented results that were disaggregated by sex. In this literature search, the authors found that only 7 out of 40 studies reported sex-disaggregated data, accounting for a total of 426,630 hospital admissions for COPD.[41-43,49,53,55,62] On average, there were approximately 409 admission counts per day, with males accounting for 72% (296 admissions) and females for 28% (113 admissions) of these. After adjusting for potential confounders, SO_2, NO_2, and O_3 concentrations were found to be significantly associated with increases in AECOPD hospitalisations in both sexes. Additionally, the relative risks of AECOPD hospitalisation associated with an interquartile range increase in air pollutants (10 µg/m^3 increases in PM_{10}, SO_2, and NO_2, respectively) were analysed in single models in two studies.[40,51] These studies found that the relative risks of exposure to these pollutants were lower for males than for females, except in the case of PM_{10} exposure.

The descriptive statistics on the average AECOPD daily hospitalisations and the daily levels of the six environmental risk factors from these seven studies are summarised in Table 2. Overall, all of the studies identified more male than female patients with AECOPD (42.3 males versus 16.1 females on average) in the total population analysed, although all studies also enrolled more male patients than female patients. In addition, despite reporting results of AECOPD cases by sex, three of these studies failed to report the total number of male and female patients enrolled.[43,49,53]

In studies reporting the number of male and female patients enrolled, the percentage of patients that developed AECOPD was similar for both sexes in all but one study, where the hospitalisations for female patients were twice as high as those for males (0.39% versus 0.18%, respectively).[62] Interestingly, this study reported some of the higher concentration averages for $PM_{2.5}$, PM_{10}, and SO_2 (60, 102, and 52 µg/m^3, respectively), as well as maximum values, when compared to the rest of the studies that also reported sex-disaggregated data (Table 2).

Regarding age, studies have indicated that the relative risk of AECOPD in patients aged ≤65 years is lower than that of patients aged ≥65 years. In addition, Tao et al.[42] reported that the relative risk for COPD exacerbations was higher in elderly females than males for increases in PM_{10}, NO_2, and SO_2 concentrations at lag 1–4.[42] This concurs with results from previous studies, which suggest that females and the elderly are some of the most vulnerable groups to outdoor air pollution.[73] Other population-based studies that do not address air pollution effects have also reported that females are more likely to experience moderate and severe COPD exacerbations than males, and have suggested a potential role of endogenous sex hormones on lung inflammation.[74,75] Therefore, in order to provide personalised management plans for individuals with COPD, appropriate identification and an understanding of these underlying mechanisms are necessary, especially in the context of air pollution exposure.

CONCLUSION

COPD is an inflammatory lung disease that involves chronic bronchitis and emphysema. Patients with COPD are particularly vulnerable to the detrimental effects of environmental exposures, especially from air PM and gaseous pollutants. The available evidence indicates that outdoor air pollution exposure affects lung function and triggers exacerbations in both male and female patients with COPD. However, in reviewing the available literature, it was found that most studies conducted in this area have not accounted for sex in their analyses. To the best of the authors' knowledge, this study is the first review of the literature available assessing sex differences in important outcomes of COPD pathogenesis and its relationship with air quality (i.e., hospitalisation and mortality). This has revealed a major gap in the research conducted to date around the associations of COPD with air pollution in males and females, highlighting the importance of establishing research design strategies that will identify sex- and

gender-specific factors. Therefore, future studies should consider incorporating the variables of sex and gender at the design stage and providing sex- and gender-disaggregated results in their reports and analyses.

Table 1: A review of studies that report acute exacerbations of chronic obstructive pulmonary disease as a result of air pollution exposure.

Reference	Study type	Pollutants	Period and location	Total sample (N); M:F; Age	Measured outcome	Main findings
Ko et al.,[37] (2007)	Time-series study	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, O_3	2000–2004; Hong Kong	119,225; M:F N/A; >18 years	Hospital admissions	Ambient concentrations of air pollutants increased hospital admissions for COPD, especially during the winter season (December–March), where indoor exposure to air pollution was higher.
Qiu et al.,[38] (2012)	Time-series study	$PM_{2.5}$, PM_{10}	2000–2005; Hong Kong	2,192; M:F N/A; >18 years	Hospital admissions	PM_{10} exposure was significantly associated with ED admissions for respiratory diseases, independently of other pollutants.
Kloog et al.,[39] (2014)	Case-crossover analysis	$PM_{2.5}$	2000–2006; USA	416,778; M:F 176,314:240,464; ≥65 years	Hospital admissions	$PM_{2.5}$ exposure was associated with all COPD hospital admissions with an increased RR of 1.83 for every 10 µg/m^3 increase in $PM_{2.5}$.
Leitte et al.,[40] (2009)	Time-series study	TSP, SO_2, NO_2	2001–2002; Romania	671; M:F N/A; >18 years	Hospital admissions and mortality	Chronic bronchitis was associated with PM, mainly SO_2, and dry air aggravated the adverse effect of PM.
Arbex et al.,[41] (2009)	Time-series study	PM_{10}, CO, SO_2, NO_2, O_3	2001–2003; Brazil	,769; M:F 975:794; ≥40 years	Hospital admissions	PM_{10} and SO_2 readings showed both acute and lagged effects on COPD ED visits. Increases in CO concentration showed impacts in the F and elderly groups.
Tao et al.,[42] (2014)	Time-series study	PM_{10}, SO_2, NO_2	2001–2005; China	5,301; M:F 3,663:1,638; >18 years	Hospital admissions	There were significant associations between air pollutants exposure and respiratory hospital admissions, and stronger effects were observed for the F cohort and patients aged ≥65 years.
Tian et al.,[43] (2014)	Time-series study	$PM_{2.5}$, CO, NO_2	2001–2007; Hong Kong	117,329; M:F N/A; >18 years	Hospital admissions	Ambient CO was negatively associated with the risk of hospitalisations for COPD. After adjustment for NO_2 or $PM_{2.5}$ levels, the negative associations of CO with COPD hospitalisations became stronger.
Milutinović et al.,[44] (2009)	Time-series study	BS, SO_2	2002–2003; Serbia	4,572; M:F N/A; >18 years	Hospital admissions	The ED admissions for all ages for COPD were significantly associated with previous-day levels of BS and lag 0–2. After controlling for SO_2, single lagged (lag 1 and lag 2) and mean lagged values of BS (up to lag 0–3) were significantly associated with COPD ED visits.

Table 1 continued.

Chen et al.,[45] (2004)	Time-series study	$PM_{2.5}$, PM_{10}	1995–1999; Canada	4,409; M:F N/A; ≥65 years	Hospital admissions	PM measures were significantly associated with COPD hospitalisation in areas where the level of air pollution were relatively low. The effects were not independent of other air pollutants.
To et al.,[46] (2015)	Time-series study	$PM_{2.5}$, PM_{10}, NO_2, O_3	2003–2010; Canada	21,334; M:F N/A; >18 years	Hospital admissions	The greatest increases in hospital admissions were for individuals with diabetes and COPD. Among individuals with chronic diseases, health service use increased with higher levels of exposure to air pollution, as measured by the AQHI.
Cho et al.,[47] (2014)	Case-crossover analysis	PM_{10}, CO, SO_2, NO_2, O_3	2005–2009; Korea	842; M:F N/A; >18 years	Hospital admissions	After stratification by underlying disease, PM_{10}, NO_2, and CO were positively associated with ED visits for depressive episodes in each disease strata, with the exception of COPD. SO_2, PM_{10}, NO_2, and CO significantly increased the risk of ED visits for depressive episodes, especially among individuals with pre-existing cardiovascular disease, diabetes, or asthma.
Sauerzapf et al.,[48] (2009)	Case-crossover analysis	$PM_{2.5}$, CO, NO_2, NO_X, O_3	2006–2007; UK	1,050; M:F N/A; >18 years	Hospital admissions	Among a population of a less urbanised area, this study found evidence that ambient pollutant concentrations were still associated with the risks of hospital admission for COPD.
Cai et al.,[49] (2015)	Time-series study	CO	2006–2008; China	121,463; M:F N/A; >18 years	Hospital admissions	Negative associations were found between ambient CO concentrations and daily COPD hospitalisation. An interquartile range increase of 0.6 mg/m^3 in CO concentration at lag 3 day corresponded to a −2.97% (95% CI: -4.63%– -1.31%) change in COPD hospitalisation. Short-term exposure to CO at low ambient concentration may be associated with reduced risk of COPD hospitalisation.
Yorifuji et al.,[50] (2014)	Case-crossover analysis	SPM, O_3, SO_2	2006–2010; Japan	767; M:F N/A; ≥65 years	Hospital admissions	SPM exposure 24 to <72 hrs prior to the onset, and O_3 exposure 48–<96 hrs prior to the onset were associated with increased risk of respiratory disease. Hourly changes in air pollution exposure increased the risk of respiratory disease, and SO_2 may be related with more immediate effects than other pollutants.
Schikowski et al.,[51] (2014)	Case-crossover analysis	PM, NO_X	2006–2010; Taiwan	10,242; M:F 4,348:5,894; >18 years	Hospital admissions	The only statistically significant associations were observed in the F cohort (COPD prevalence using GOLD standards: OR: 1.57; 95% CI: 1.11–2.23; and incidence: OR: 1.79; 95% CI: 1.21–2.68). None of the principal results were statistically significant.

Table 1 continued.

Zhang et al.,[52] (2014)	Time-series study	Haze, SO_2, NO_2	2008–2011; China	1,380; M:F N/A; >18 years	Hospital admissions	NO_2 was the sole pollutant with the largest risk of hospital admissions for total and respiratory diseases in both single- and multi-pollutant models and both presented more drastic effects on 19–64 year olds and in the F population. Haze pollution was associated with total and cardiovascular illnesses.
Yan et al.,[31] (2019)	Comparative study	PM, CO	2016–2018; China	139; M:F 48:91; >18 years	Hospital admissions	These findings suggested that ambient air pollution caused COPD exacerbation, and that PM exposure induced apoptosis of airway epithelial cells.
Liang et al.,[53] (2019)	Ecological analysis	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, O_3	2013–2017; China	161,613; M:F N/A; >18 years	Hospital Admissions	Increased acute air pollution episodes were significantly associated with increased hospitalisations for AECOPD, with women and patients aged >65 years showing the highest susceptibility and hospitalisation risk.
Hendryx et al.,[54] (2019)	Longitudinal study	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2	2000–2019; Australia	3,616; All F; >18 years	New COPD cases	Controlling for covariates, all five air pollutants modelled individually were significantly associated with risk of COPD. Multiple exposure sources and pollutants contributed to COPD risk, including electricity generation and mining, but extending to many industrial processes.
DeVries et al.,[35] (2016)	Case-crossover analysis	$PM_{2.5}$, SO_2, NO_2	2011–2012; USA	168; M:F 57:101; ≥65 years	Hospital admissions	Short-term exposures to SO_2 were associated with an increase in COPD exacerbation risk (OR: 2.45; 95% CI: 1.75–3.45 per 1 ppb increase) after adjustment for $PM_{2.5}$. Despite living in areas with air pollution concentrations below current USEPA NAAQS, these patients with COPD appeared to experience increased risk of COPD exacerbation following short-term exposures to increased SO_2 and NO_2 levels.
Du et al.,[55] (2021)	Time-series study	SO_2, CO, PM_{10}, $PM_{2.5}$, O_3, NO_2	2019; China	1,563; M:F 1,277:286; ≥65 years	Hospital admissions	The concentrations of six monitored pollutants and AECOPD hospitalisations showed statistically significant spatial clustering. After adjusting for potential confounders, residential SO_2, NO_2, and O_3 concentrations were significantly associated with increased AECOPD hospitalisations. Ambient air pollution was spatially correlated with AECOPD hospitalisations.
Lin et al.,[56] (2018)	Case-crossover analysis	NO_2, CO, SO_2, PM_{10}, $PM_{2.5}$, O_3	2011–2015; Taiwan	277; M:F 240:37; ≥65 years	Hospital admissions	Increased NO_2, CO, O_3, and PM_{10} concentrations and continual temperature changes (colder during cooling-down seasons or hotter during warming-up seasons) were associated with AECOPD in older patients.

Table 1 continued.

Sinharay et al.,[57] (2017)	Randomised, crossover study	BC, NO_2, PM_{10}, $PM_{2.5}$, UFP	2012–2014; UK	M:F 19:21; ≥60 years	Respiratory response to shorter-term exposure of air pollution	Participants with COPD reported more cough (OR: 1.95; 95% CI: 0.96–3.95), sputum (OR: 3.15; 95% CI: 1.39–7.13), shortness of breath (OR: 1.86; 95% CI: 0.97–3.57), and wheeze (OR: 4.00; 95% CI: 1.52–10.50) after walking down Oxford Street (high traffic pollution) compared with Hyde Park (low traffic pollution).
Wang et al.,[58] (2021)	Ecological study	$PM_{2.5}$, PM_{10}, PM_{coarse}, SO_2, NO_2, CO, O_3	2013–2017; China	483,861; M:F N/A; >18 years	Hospital admissions	Reduction in PM may result in declined attributable hospitalisations for AECOPD, while O_3 is an important risk factor following an intervention.
Chen et al.,[59] (2020)	Time-series study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3	2014–2017; China	17,655; M: F 9,234:8,421; >18 years	Hospital admissions	Air pollution increased the rate of hospitalisation for AECOPD. The risk of hospitalisation for AECOPD in the age ≥65 group was greater than for the age <65 group for all day lags. The risk of M and F hospitalisations for AECOPD after lag 3–5 was higher than that after lag 0–2, and the strongest risk of hospitalisations for both was with lag 3.
Zieliński et al.,[60] (2018)	Time-series study	$PM_{2.5}$, PM_{10}	2006–2016; Poland	12,889; M:F 7,968:4921; ≥65 years	Hospital admissions	No connection between PM_{10} concentration and COPD exacerbations were observed. The $PM_{2.5}$ influence was significant, beginning 14 days before admission (RR: 1.06) and increased up to a maximal studied period of 90 days (RR: 1.32).
Gutierrez et al.,[61] (2020)	Prospective cohort study	$PM_{2.5}$	2013–2016; USA	296; M:F 290:6; ≥65 years	Hospital admissions	Saharan dust outbreaks observed in Miami elevated the concentration of PM and increased the risk of AECOPD in patients with recurrent exacerbations.
Chen et al.,[62] (2019)	Time-series study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3	2013–2015; China	6,981; M:F 4,920:2,061; ≥65 years	Hospital admissions	The incremental increased concentrations of $PM_{2.5}$ and PM_{10} were significantly associated with increased risk of hospitalisation of AECOPD, stroke, and MI, and the adverse influences of $PM_{2.5}$ on these diseases were generally stronger than that of PM_{10} in Jinan, China.
Chen et al.,[63] (2019)	Time-series study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3	2014–2018; China	17,592; M:F 9,196:8,396; >18 years	Hospital admissions	Air pollution, relative humidity, and temperature increased the risk of admission for AECOPD. The effect of O_3 on the admission rate in the M group was higher than that in the F group. Ambient air pollution had a weak influence on the age ≤50 group.
Kwon et al.,[64] (2020)	Cohort study	PM_{10}, NO_2	2012–2017; Korea	296; M:F 238:58; ≥65 years	Respiratory response to shorter-term exposure of air pollution	Long-term exposure to PM_{10} correlated with both lung function and COPD-relevant imaging phenotypes in a Korean cohort.

Table 1 continued.

Pini et al.,[34] (2021)	Time-series study	$PM_{2.5}$, PM_{10}	2014–2016; Italy	431; M:F N/A; Age N/A	Hospital admissions	Short-term increases in exposure to PM_{10} or $PM_{2.5}$ were associated with a higher risk of ED admission and hospitalisation due to AECOPD, with a greater incidence during the winter season.
Reid et al.,[65] (2019)	Cohort study	$PM_{2.5}$, O_3	2008; USA	4,614; M:F N/A; >18 years	Hospital admissions	There were more ED visits than hospitalisations during the study period. For $PM_{2.5}$, increasing risk of asthma hospitalisations with increasing quintiles of exposure was found in the $PM_{2.5}$-only model and the mutually adjusted model. ED visits for asthma and COPD increased with increasing quintiles of $PM_{2.5}$ exposure.
de Miguel-Díez et al.,[66] (2019)	Case-crossover study	NO_2, O_3, PM_{10}, CO	2004–2013; Spain	162,338; M:F 135,598:26,740; ≥65 years	Hospital admissions and mortality	Significant associations of temperature, humidity, O_3, CO, PM_{10}, and NO_2 with hospital admissions were identified.
Stevanović et al.,[67] (2016)	Cohort study	$PM_{2.5}$	2011; Serbia	270; M:F 181:89; >18 years	Hospital admissions	The number of days with high levels of $PM_{2.5}$ per month was significantly associated with the total number of exacerbations (moderate and severe) for both asthma and COPD episodes among F and patients with obesity.
Morantes-Caballero et al.,[28] (2019)	Descriptive retrospective study	$PM_{2.5}$, PM_{10}	2016–2017; Colombia	250; M:F 103:147; ≥65 years	Hospital admissions	Patients with AECOPD had a higher median of PM 48 hrs prior to symptomatic onset, as well as greater use of antibiotics and corticosteroids.
Doneva et al.,[23] (2019)	Multi-centre, prospective, one-year observational study	SO_2, PM_{10}	2015–2016; Bulgaria	426; M:F 296:130; >18 years	Hospital admissions	Air pollution exposure led to an increased number of exacerbations and hospital stays. Patients with mild COPD had an average of 0.86 exacerbations and 2.61 days in hospital per year, while these values were 4 times higher for those with severe COPD. Outside pollution led to worsening of the disease severity and hospitalisations due to COPD exacerbations.
Peacock et al.,[26] (2011)	Cohort study	NO_2, O_3, SO_2, PM_{10}, BS	1995–1997; UK	94; All M; ≥40 years	Respiratory response to shorter-term exposure of air pollution	Outdoor air pollution was associated with adverse effects on symptoms in patients with COPD.
Medina-Ramón et al.,[68] (2006)	Case-crossover study	O_3, PM_{10}	1986–1999; USA	578,006; M:F N/A; ≥65 years	Hospital admissions	Exposure to O_3 and PM_{10} was associated with respiratory-related hospital admissions. The effect of air pollution was modified by city characteristics like meteorology, pollution sources, and socioeconomic factors.

Table 1 continued.

Yang et al.,[69] (2005)	Time-series study	NO_2, O_3, SO_2, CO	1994–1998; Canada	6,027; M:F N/A; ≥65 years	Hospital admissions	NO_2 and CO were significantly associated with hospitalisation for COPD, and the magnitude of effects increased slightly with increasing days of exposure.
Stieb et al.,[70] (2009)	Time-series study	NO_2, O_3, SO_2, CO, $PM_{2.5}$, PM_{10}	1990–2000; Canada	40,491; M:F N/A; >18 years	Hospital admissions	In this large multicentre analysis, daily average concentrations of CO and NO_2 exhibited the most consistent associations with ED visits for cardiac conditions, while O_3 exhibited the most consistent associations with visits for respiratory conditions.

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; AQHI: Air Quality Health Index; BC: black carbon; BS: black smoke; CI: confidence interval; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; ED: emergency department; F: female; GOLD: Global Initiative for Chronic Obstructive Lung Disease; hrs: hours; M: male; MI: myocardial infarction; NAAQS: National Ambient Air Quality Standards; N/A: data not available; NO_2: nitrogen dioxide; NO_X: nitrogen oxides; O_3: ozone; OR: odds ratio; PM: particulate matter; PM_{coarse}: coarse particulate matter; PM_{10}: particulate matter <10 µm in aerodynamic diameter; $PM_{2.5}$: particulate matter <2.5 µm in aerodynamic diameter; ppb: parts per billion; SO_2: sulfur dioxide; RR: relative risk; SPM: suspended particulate matter; TSP: total suspended particles; UFP: ultrafine particles; USEPA: United States Environmental Protection Agency.

Table 2: A summary of daily hospital admissions for acute exacerbations of chronic obstructive pulmonary disease in males and females, and the corresponding 24-hour average air pollutant concentrations, from studies found in a review of the literature.

	Study; location (age of participants)						
	Du et al.,[52] (2021); Jinhua, China (>65 years)	Cai et al.,[46] (2015); Shanghai, China (>18 years)	Tao et al.,[39] (2014); Lanzhou, China (>18 years)	Tian et al.,[40] (2014); Hong Kong, China (>18 years)	Chen et al.,[59] (2019); Shenyang, China (>65 years)	Liang et al.,[50] (2019); Beijing, China (>18 years)	Arbex et al.,[38] (2009); São Paulo, Brazil (>40 years)
Mean concentration of gaseous pollutants, averaged over 24 hours (Min–Max)							
CO (µg/m³)	0.7 (0.5–1.0)	1.3 (0.2–3.9)	NR	0.6 (0.1–2.1)	NR	1.2 (0.2–8.0)	2.7 (1.0–12.0)
NO_2 (µg/m³)	28.0 (10.0–48.0)	61.0 (13.0–153.0)	45.8 (4.0–26.0)	40.9 (2.5–129.2)	43.0 (13.0–125.0)	50.5 (8.0–155.0)	120.3 (30.9–390.8)
SO_2 (µg/m³)	7.2 (3.0–13.0)	53.0 (8.0–223.0)	79.1 (2.0–37.1)	NR	52.0 (3.0–333.0)	15.1 (2.0–139.0)	14.0 (2.1–42.9)
O_3 (µg/m³)	84.5 (36.0–142.0)	NR	NR	NR	58.0 (9.0–218.0)	95.8 (2.0–292.0)	95.8 (14.5–282.0)
Mean concentration of particulate pollutants, averaged over 24 hours (Min–Max)							
$PM_{2.5}$ (µg/m³)	30.9 (14.0–57.0)	NR	NR	37.6 (6.8–163.2)	60.0 (4.0–848.0)	76.7 (5.0–467.0)	NR

Table 2 continued.

PM_{10} (µg/m³)	50.1 (25.0–84.0)	92.0 (12.0–643.0)	196.6 (16.0–256.1)	NR	102.0 (8.0–912.0)	109.7 (10.0–820.0)	48.7 (9.6–169.0)
Mean number of hospital admissions of patients with AECOPD, averaged over 24 hours							
Male (% of total; Min–Max); % of enrolled (n)	106 (81.5%; 73–144); 8.3% (1,277)	72 (64.9%; 10–231); N/A	2 (69.0%; 0–13); 0.05% (3,663)	46 (80.7%; 13-91); N/A	9 (52.9%; 0–16); 0.18% (4,920)	60 (67.4%; 9–153); N/A	0.9 (52.9%; 0–6); 0.09% (975)
Female (% of total; Min–Max); % of enrolled (n)	24 (18.4%; 32–16); 8.4% (286)	39 (35.1%; 3–137); N/A	0.9 (31.0%; 0–6); 0.05% (1,638)	11 (19.3%; 0–34); N/A	8 (47.1%; 0–15); 0.39% (2,061)	29 (32.6%; 2–90); N/A	0.8 (47.1%; 0–7); 0.10% (794)
Total (Min–Max); % of enrolled (n)	130 (89–176); 8.30% (1,563)	111 (14–368); 0.09% (121,463)	2.9 (0–13); 0.06% (5,301)	57 (17–117); 0.05% (117,329)	17 (0–31); 0.39% (4,409)	89 (17–220); 0.05% (161,613)	1.7 (0–10); 0.10% (1,769)

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CO: carbon monoxide; Max: maximum; Min: minimum; n: number of participants; N/A: data not available; NO_2: nitrogen dioxide; NR: not reported; O_3: ozone; PM_{10}: particulate matter <10 µm in aerodynamic diameter; $PM_{2.5}$: particulate matter <2.5 µm in aerodynamic diameter; SO_2: sulfur dioxide.

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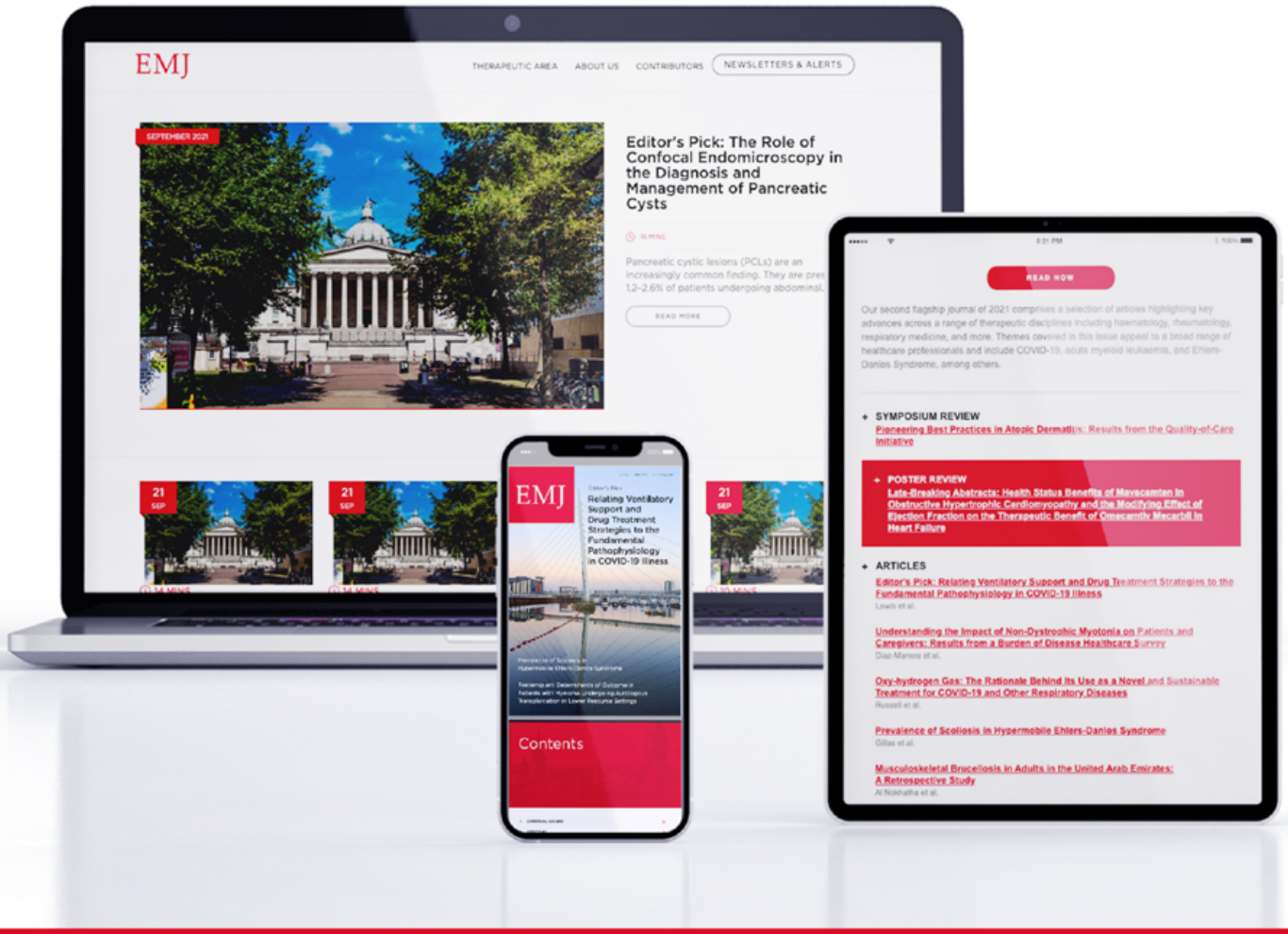

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Emetogenicity of Chemotherapy Regimens and Recommended Prophylaxis: A Review of MASCC/ESMO Guidelines

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect in patients with cancer, affecting both quality of life and treatment compliance. Despite the advances in pharmacological research of antiemetic drugs, CINV still remains one of the most feared chemotherapy side effects by patients. Currently, the numbers of patients at highest risk of CINV receiving guideline-based prophylaxis remains sub-optimal; this is due, in part, to poor adherence to evidence-based guidelines.

Adequate prevention of CINV, from the first cycle of chemotherapy, requires an understanding of the intrinsic emetogenic risk of the chosen chemotherapy regimen; an awareness of the risk of delayed CINV; and the consideration of patients' individual risk factors, as well as the dose, administration route, and schedule of each drug in the treatment regimen.

The pathophysiology of nausea and vomiting can differ, and a combination of antiemetic drugs may be required to prevent their onset. In addition, CINV that occurs in the acute phase (≤24 hours after starting chemotherapy) and the delayed phase (>25 hours after starting chemotherapy) can also require different combinations of antiemetic drugs to achieve optimal control.

Together, consideration of all these factors can allow clinicians to tailor an antiemetic prophylactic regimen for each individual patient. Optimal prevention of CINV will improve patients' quality of life and treatment adherence, which will ultimately improving outcomes.

This article reviews the impact of CINV, the emetogenic risk associated with different chemotherapy regimens in solid tumours and haematologic malignancies, and guideline-based recommendations for antiemetic prophylaxis according to emetogenic risk.

INTRODUCTION

CINV is experienced by about 70–80% of adult patients with cancer who are receiving chemotherapy, decreasing both quality of life and treatment compliance.[1-3] CINV remains one of the most feared side effects of chemotherapy, despite the availability of new and effective antiemetic medications.[4,5]

With appropriate prophylaxis, vomiting can now be prevented in most patients; however, nausea remains a significant problem.[6] In contrast to clinicians, patients typically consider the prevention of nausea to be more important than the prevention of vomiting.[7] Although nausea often leads to vomiting, these two symptoms can occur independently, with nausea occurring more frequently.[7] Indeed, it has been suggested that these symptoms may involve a different pathophysiology, and that different drugs may, therefore, be needed to control each symptom.[7]

Without prophylactic treatment (other than corticosteroids), acute post-treatment vomiting affects approximately 57% of patients receiving chemotherapy, while acute nausea affects approximately 80%.[7]

Delayed CINV, which occurs 24 hours or more after the start of chemotherapy, is more common than acute CINV.[8] It is also often less responsive to treatment.[9] Uncontrolled CINV in a previous cycle of chemotherapy is a risk factor for CINV in subsequent cycles.[10] It is also a risk factor for anticipatory CINV, a conditioned response to CINV occurring in a previous chemotherapy cycle.[1] For example, one study found that anticipatory CINV was responsible for 7% of vomiting episodes and 30% of nausea episodes in patients with cancer.[7] Effective prevention of CINV in the first cycle of chemotherapy is the best approach to reducing anticipatory CINV in subsequent cycles.

Without effective prevention of CINV, patients may experience reduced quality of life, distress, and work absence.[7] The inadequate caloric and fluid intake associated with CINV can also aggravate cancer-associated symptoms such as muscle wasting, lethargy, and weakness.[7] CINV has also been linked to reductions in cognitive function, and increased anxiety and depression.[7]

This article deals with CINV prophylaxis, with a special emphasis on understanding the estimated emetogenicity of single and combination chemotherapy regimens used in the management of both solid tumours and haematologic malignancies, and highlights current recommendations based on the current Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) guidelines for the prevention of CINV according to emetic risk.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING MANAGEMENT IN CLINICAL PRACTICE

CINV continues to be largely undermanaged in clinical practice. This is due, in part, to low adherence to guideline prescription of antiemetics.[11-14] A large multicentre observational study conducted in Europe (N=1,089) found that only 23% of patients treated with moderately or highly emetogenic chemotherapy received guideline-based antiemetic prophylaxis for both the acute and delayed nausea and vomiting.[12] Similarly, a retrospective real-world study of patients with cancer who received highly emetogenic chemotherapy (N=4,033) found that clinician adherence to guideline-based prevention was highly variable. In the study, guideline adherence rates of >90% were achieved by clinicians in just 35% of patients receiving cisplatin-based chemotherapy, and 58% of those receiving anthracycline plus cyclophosphamide. The omission of a neurokinin-1 receptor antagonist (NK_1 RA) was the principal cause of guideline nonadherence in the vast majority (>90%) of cases.[14]

These results align with a study that analysed a data set of real-world prescribing information in Europe, which included data representing 489,049 anti-cancer treatments requiring NK_1 RA-based antiemetic prophylaxis per MASCC/ESMO guidelines.[15] NK_1 RAs were prescribed in fewer than half of patients receiving cisplatin- or anthracycline plus cyclophosphamide-based chemotherapy (45% and 42%, respectively), and in as few as 19% of those receiving carboplatin-based regimens. Guideline-consistent prophylaxis with NK_1 RA plus 5-hydroxytryptamine-3 ($5\text{-}HT_3$) RA plus dexamethasone on Day 1 was prescribed only

in 18%, 24%, and 7% of these chemotherapy regimens, respectively.

It is important to note that where antiemetic guidelines are followed, a higher rate of complete protection from CINV is achieved.[12,13]

Patient adherence to antiemetic therapy is another potential cause for sub-optimal CINV prevention. For example, a quantitative survey of European oncologists found that patient non-adherence to prescribed antiemetics, due to administration mistakes or missed doses, was considered a major cause of antiemetic treatment failure, suggesting that simpler, more convenient therapies could help to improve patient compliance.[16]

It is also possible that many clinicians underestimate the emetogenicity of chemotherapy. Across three randomised clinical trials of anti-cancer treatment (N=1,090), patient-reported and clinician-reported toxicities were compared. Results showed that agreement between patients and clinicians was low for all toxicities. Nausea was under-reported by physicians in 41% of cases and vomiting in 47%.[17] Under-reporting results in the underestimation of the absolute rate of toxicity, which could lead to undermanagement of CINV.

In clinical practice, decisions regarding optimal prophylaxis should be guided by two considerations: the intrinsic emetogenicity of the chemotherapeutic agents in a treatment regimen, and whether there is a substantial risk of delayed nausea and vomiting. Additional consideration of patient-related risk factors may help healthcare providers to optimise antiemetic coverage in patients at high personal risk of CINV. This approach may make it possible to tailor the appropriate antiemetic regimen to an individual patient, who might benefit from extended or brief antiemetic coverage (Supplementary Figure 1).

EMETOGENICITY OF CHEMOTHERAPY AGENTS

Chemotherapeutic agents vary greatly with respect to their relative ability to cause emesis (i.e., their intrinsic emetogenicity).[21] They are classified into four groups: highly emetogenic chemotherapy (HEC; affecting >90% of patients), moderately emetogenic chemotherapy (MEC; 30–90% of patients), low emetogenic chemotherapy (LEC; 10–30% of patients), and minimally emetogenic chemotherapy (<10% of patients). While both HEC and MEC agents cause CINV during the acute and delayed phases and multi-target antiemetic regimens are recommended in both emetogenicity categories (Supplementary Table 1), LEC agents induce only acute CINV and a single-agent prophylaxis before chemotherapy administration is recommended (Supplementary Table 2).[21,22]

Joint guidelines published by the MASCC and ESMO have recognised carboplatin as being on the borderline between the HEC and MEC categories and have placed it in its own emetogenicity group,[22] which could be described as moderately-to-highly emetogenic (affecting approximately 90% of patients).

The overall emetogenicity of a treatment regimen is influenced not only by the individual chemotherapeutic agents used but by the dose, administration route, and schedule of these agents, as well as patient-related factors.[23]

PATIENT-RELATED RISK FACTORS

Although antiemetic guidelines are based on the intrinsic emetogenicity of individual chemotherapeutic agents, the importance of considering patient-related risk factors and prior experience with antiemetics has also been recognised.[24,25]

A recent systematic literature review identified seven key patient-related risk factors for CINV: a patient history of CINV and/or pregnancy-related nausea or vomiting; female sex, anticipation of CINV; younger age (<50 years); anxiety; and a history of no or low alcohol intake (Supplementary Table 3).[26]

For optimal CINV management, it is crucial that clinicians follow evidence-based clinical antiemetic guidelines and that they also consider key patient-related risk factors.[24] These factors can be captured during clinical assessment prior to chemotherapy, helping clinicians to predict patient's risk of developing CINV and make decisions regarding antiemetic prophylaxis.[26]

PHARMACOLOGIC THERAPIES FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING PREVENTION

Guidelines recommend that patients scheduled to receive chemotherapy containing HEC or MEC agents should receive combination prophylaxis with antiemetic drugs targeting the peripheral and central pathways to vomiting centre in the brain (Supplementary Table 4).[22,24]

The major classes of antiemetic drugs recommended for CINV prophylaxis are 5-HT_3 RAs, NK_1 RAs, corticosteroids, and olanzapine.[11,27] Current MASCC/ESMO guidelines include the following recommendations for CINV prophylaxis:

- 5-HT_3 RAs should be used in the acute phase of HEC/MEC agents and are one of the recommended options in the acute phase of LEC agents;
- Corticosteroids such as dexamethasone should be used in the acute phase of HEC/MEC regimens and the delayed phase of HEC (unless the regimen is based on the combination of an anthracycline and cyclophosphamide). They are optional in the delayed phase of MEC agents, with a known potential of delayed CINV such as oxaliplatin, anthracycline, or cyclophosphamide;
- NK_1 RAs should be used in the acute and delayed phases of HEC agents/combinations or carboplatin (which falls between the usual HEC/MEC categories in terms emetogenicity); and
- Olanzapine is optional in the acute and delayed phases of HEC regimens. Also, clinicians may opt to add olanzapine to antiemetic regimen in selected patients when nausea control may be an issue.

In general, when devising a prophylactic strategy for CINV due to combination chemotherapy, the antiemetic regimen should be tailored to the anti-cancer agent with the highest intrinsic emetogenicity. It is also important to be aware that antiemetic efficacy can be affected by the route of chemotherapy administration (Supplementary Figure 1).[23]

5-Hydroxytryptamine-3 Receptor Antagonists

The 5-HT_3 RAs block the binding of serotonin at 5-HT_3 receptors in the gastrointestinal tract.[27] This pathway is primarily associated with acute emesis induced by chemotherapeutic agents. While $5HT_3$ RAs are considered the most efficacious antiemetics for the prevention of acute CINV, their effect against delayed CINV is more modest.[6] Generally well tolerated, 5-HT_3 RAs may nevertheless be associated with constipation, headache, QTc prolongation, and slight reversible increase in liver transaminases.[6]

The efficacy of first-generation 5-HT_3 RAs (ondansetron, granisetron, dolasetron, and tropisetron) is similar; however, with a higher binding affinity for the 5-HT_3 receptor and a significantly longer half-life, the second-generation 5-HT_3 RA palonosetron is more effective in preventing delayed CINV associated with HEC/MEC regimens.[24]

Guidelines currently recommend palonosetron as the preferred 5-HT_3 RA where an NK_1 RA is not part of the antiemetic regimen.[22,24]

Corticosteroids

Single-agent corticosteroids are effective against CINV in patients receiving LEC, and they improve the effects of other antiemetics in patients receiving HEC or MEC. They are effective for the prevention of both acute and delayed CINV.[6,24]

Dexamethasone is the most investigated corticosteroid for CINV prophylaxis and it has been used in combination with other antiemetics for many years.[6,24] While other corticosteroids are also known to be effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability has established it as the guideline agent of choice in CINV.[18]

Common adverse effects of corticosteroids include weight gain, insomnia, agitation, epigastric discomfort, and hyperglycaemia.[28,29] In addition, corticosteroid-related side effects may be evident only after prolonged use of these agents during consecutive cycles of chemotherapy treatment.[30-32] Corticosteroids also have a broad immunosuppressive effect, which could potentially promote immunological tolerance to tumours, reducing the effectiveness

of immune checkpoint inhibitor therapy. Indeed, baseline administration of supraphysiological doses of corticosteroids has been associated with adverse clinical outcomes in melanoma, non-small-cell lung cancer, and glioblastoma.[33] However, it should be noted that at least one study suggests that corticosteroids may impact the immune checkpoint inhibitor therapy differentially, depending on the tumour site.[34] Another found that corticosteroids only had a negative impact on overall survival when used for supportive care and not when used to mitigate adverse events.[19]

To improve the tolerability profile of the corticosteroids in CINV prophylaxis and to reduce immunosuppression, there has been growing interest in minimising the dose and frequency of dexamethasone without a loss of antiemetic efficacy.[35] Because of the COVID-19 pandemic, the ESMO highlighted that the use of antiemetic corticosteroids should be critically reviewed and a reduced dose of dexamethasone on Day 1 without additional use on the following days should be considered even in HEC treatment. In addition, clinicians may consider the long-acting 5-HT_3 RA, palonosetron, due to its potential better efficacy in the delayed phase of CINV specifically when sparing the dexamethasone dose.[36,37]

A recent randomised study demonstrated that dexamethasone sparing on Days 2–4 is an effective antiemetic option in patients receiving cisplatin-based HEC when associated with netupitant plus palonosetron (NEPA) plus single-dose dexamethasone on Day 1.[38] The dexamethasone-sparing regimen based on NEPA permits the administration of a simplified but guideline-consistent three-drug regimen before chemotherapy initiation in the challenging setting of CINV caused by cisplatin.

Neurokinin-1 Receptor Antagonists

The introduction of NK_1 RAs to the field of antiemetic prophylaxis has been considered the most significant advance in CINV control since 5-HT_3 RAs.[35]

The two oral NK_1 RAs marketed in Europe are aprepitant and netupitant.[6] Both are primarily metabolised through the cytochrome P450 3A4 pathway and block the binding of substance P at NK_1 receptors, which are expressed in the central and peripheral nervous system.[6,27] The available evidence supports a principal role for central NK_1 activation in delayed CINV.[27] The most common adverse effects of this drug class include headache, constipation, and hiccups.[6,27]

The standard 3-day treatment with oral aprepitant, though inferior to 5-HT_3 RAs in preventing acute CINV, is more effective against delayed CINV.[39] Aprepitant also increases the antiemetic effect of combined 5-HT_3 RA plus dexamethasone treatment.[40]

Netupitant was developed and investigated in combination with palonosetron as a single oral dose antiemetic.[6] Clinical studies have shown that the efficacy of oral NEPA was superior to palonosetron alone in terms of preventing both acute and delayed CINV associated with HEC/MEC therapy.[30,31] Intravenous NEPA was equally effective to oral NEPA and was not associated with injection-site or hypersensitivity reactions that can occur with other NK_1 RAs.[41-43]

The MASCC/ESMO guidelines recommend that patients receiving HEC are given a dose of 20 mg dexamethasone on Day 1 to prevent acute emesis; however, if the NK_1 RAs aprepitant or netupitant are also used, a reduced dose of 12 mg dexamethasone is recommended.[17] This dose reduction is due to the ability of both aprepitant and netupitant to inhibit the metabolism of dexamethasone leading to higher dexamethasone concentrations.[24]

By delivering both a 5-HT_3 RA and an NK_1 RA in a single dose before chemotherapy administration, NEPA can help simplify the antiemetic prophylaxis that patients must take at home. Therefore, it improves convenience and has the potential to improve the adherence to antiemetic therapy.[43,44]

Olanzapine

Olanzapine is an atypical antipsychotic drug approved for use for the treatment of schizophrenia and moderate-to-severe manic episodes.[45] However, it has also been investigated as an antiemetic drug in several clinical trials[6] and it has been used off-label for both acute and delayed CINV in combination with a 5-HT_3 RA and dexamethasone.[18,27]

Unlike other antiemetic drug classes, olanzapine acts on multiple receptors in the emetic pathway, blocking both dopaminergic and serotonergic neurotransmission.[27] It has been associated with several side effects, including sedation, dry mouth, hyperglycaemia, and diarrhoea, as well as an increased risk of extrapyramidal effects.[27]

A recent double-blind, randomised study demonstrated that a four-drug prophylaxis containing low-dose olanzapine (5 mg) is superior to a three-drug antiemetic regimen for CINV control in patients receiving cisplatin.[46] Despite the lack of a randomised study comparing the two doses of antiemetic olanzapine (10 mg or 5 mg per day on Days 1–4 post-chemotherapy), low-dose olanzapine has a high profile of tolerability in terms of drug-induced sedation.

Use of Neurokinin-1 Receptor Antagonists with Moderately Emetogenic Chemotherapy Agents in Patients with Increased Chemotherapy-Induced Nausea and Vomiting Risk

The MEC category of chemotherapeutic agents covers drugs associated with a broad risk of CINV (affecting 30–90% of patients). Current MASCC/ESMO guidelines do not recommend the use of NK_1 RAs as prophylaxis with MEC agents, though they do recommend dexamethasone as an optional agent for delayed CINV when oxaliplatin, anthracycline, and cyclophosphamide chemotherapy are used.[22]

However, healthcare providers may consider using an NK_1 RA in patients receiving MEC agents for whom CINV is a particular concern (Supplementary Table 4). This approach is supported by a recent placebo-controlled randomised study that evaluated the efficacy of a three-drug prophylaxis regimen, including an NK_1 RA in patients with gastrointestinal cancer receiving oxaliplatin- or irinotecan-based chemotherapy (both MEC).[47]

The study enrolled patients who were at increased risk of CINV due to patient-related factors, with eligibility criteria including female sex, age <50 years, and a history of little or no alcohol use. Patients were randomly assigned to receive palonosetron and dexamethasone plus either placebo or aprepitant.[47]

Results indicated that a statistically significant improvement in the control of emesis was achieved with the inclusion of an NK_1 RA versus placebo in the acute phase (92.7% versus 75.8%; p=0.001), the delayed phase (88.6% versus 70.0%; p=0.001), and overall (primary endpoint: 87.0% versus 66.7%; p<0.001). The incidence of adverse events was similar between the two prophylactic treatment groups.[47]

Multiple-Day Chemotherapy Regimens Containing Cisplatin

Chemotherapy regimens in which cisplatin is administered for multiple consecutive days (typically 5 days) represent a challenging setting of CINV control because acute and delayed CINV overlap.[24]

Current MASCC/ESMO guidelines recommend that patients receiving multiple-day cisplatin (HEC) should receive a combination of a 5-HT_3 RA plus aprepitant plus dexamethasone in the acute phase, and dexamethasone in the delayed phase.[17] Guidelines also recommend that while first-generation 5-HT_3 RAs should be administered at Days 1–5, palonosetron should be administered on Days 1, 3, and 5 only.[22,24] Similarly, the NK_1 RA inhibitor netupitant, which has a much longer half-life than aprepitant, may be administered on Day 1 only in this setting.[8]

EMETOGENICITY OF CHEMOTHERAPY REGIMENS FOR SOLID TUMOURS AND HAEMATOLOGIC CANCER

The estimated emetogenicity of commonly used combination chemotherapy regimens in the treatment of non-haematologic and haematologic malignancies are listed in Supplementary Table 5 and Supplementary Table 6, respectively.

Patients undergoing chemotherapy for haematologic malignancies are at particular risk of CINV because of their young age, exposure to HEC agents at high doses over multiple days, and the heavy psychological burden of such intensive treatments.[48]

High-dose chemotherapy is widely used as a conditioning regimen prior to autologous stem cell transplant (ASCT) in patients with the haematologic malignancy multiple myeloma.[49] Although any high-dose chemotherapy regimen

is classified as HEC, research into the incidence of CINV and the efficacy of antiemetics in patients treated with high-dose chemotherapy and ASCT can be confounded by the emetogenicity of antibiotics and opioids prescribed for mucositis management in this population, and by the use of irradiation therapy.[25] The most widely used high-dose chemotherapy regimens used prior to ASCT are listed in Supplementary Table 7.

Following a Phase III clinical trial,[50] the American Society of Clinical Oncology (ASCO) published an update to their antiemetic guidelines, recommending olanzapine as an optional addition to a triple-drug regimen in this population.[51] The use of NEPA has also been shown to be effective in preventing CINV in adult patients with multiple myeloma receiving high-dose melphalan and undergoing ASCT, even without the concurrent use of dexamethasone,[49] suggesting again that NEPA may have the potential to support corticosteroid-sparing treatment strategies.

CONCLUSION

Nausea and vomiting are two of the most feared side effects of chemotherapy in patients with cancer, and current management of CINV still remains sub-optimal. Effective prevention of CINV requires an understanding of the emetogenic risk of a chemotherapeutic regimen as well a patients' individual risk factors. Adherence to evidence-based guidelines for antiemetic prophylaxis is needed to reduce the incidence of CINV, improve patients' quality of life and treatment adherence, and ultimately improve outcomes.

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Demystifying the Discussion of Sequencing Panel Size in Oncology Genetic Testing

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Abstract

Clinical laboratories worldwide are implementing next-generation sequencing (NGS) to identify cancer genomic variants and ultimately improve patient outcomes. The ability to massively sequence the entire genome or exome of tumour cells has been critical to elucidating many complex biological questions. However, the depth of information obtained by these methods is strenuous to process in the clinical setting, making them currently unfeasible for broader adoption. Instead, targeted sequencing, usually on a selection of clinically relevant genes, represents the predominant approach that best balances accurate identification of genomic variants with high sensitivity and a good cost-effectiveness ratio. The information obtained from targeted sequencing can support diagnostic classification, guide therapeutic decisions, and provide prognostic insights. The use of targeted gene panels expedites sample processing, including data analysis, results interpretation, and medical reports generation, directly affecting patient management. The key decision factors for selecting sequencing methods and panel size in routine testing should include diagnostic yield and clinical utility, sample availability, and processing turnaround time.

Profiling by default all patients with late-stage cancer with large panels is not affordable for most healthcare systems and does not provide substantial clinical benefit at present. Balancing between understanding cancer biology, including patients in clinical trials, maximising testing, and ensuring a sustainable financial burden for society requires thorough consideration. This review provides an overview of the advantages and drawbacks of different sizes NGS panels for tumour molecular profiling and their clinical applicability.

NEXT-GENERATION SEQUENCING

NGS, also known as massively parallel sequencing, has revolutionised cancer research and treatment, providing sensitive and accurate high-throughput platforms for large-scale genomic testing.[1] The outstanding development of sequencing technologies has led to a rapidly growing body of pioneering research exploring the genomic landscape and molecular mechanisms of various cancer types, as well as the discovery of numerous genetic drivers of neoplastic growth (i.e., mutations that confer a selective growth advantage, thereby promoting cancer development). These genomic aberrations are single nucleotide variants, small insertions and deletions, copy number variations, and large gene structural variants, which accumulate in the genome during tumour development. While some mutations are already present at the time of diagnosis, others arise through clonal evolution during disease progression and are directly involved, for example, in mechanisms of treatment resistance.[2] The abundance of genomic and transcriptomic sequencing data generated allows us to address a variety of previously impossible questions and offers numerous potential applications in precision medicine and drug discovery. Examples include transcriptomic studies that have been used to identify predictive disease-related expression patterns or expression differences due to drug side effects,[3-5] as well as extensive genomic databases with curated information on DNA variants with clinical implications (e.g., OncoKB), which are often used as references for annotating observed variants.

In recent years, an increasing number of clinical laboratories worldwide are implementing NGS to detect genomic variants affecting the cancer genome. The main goal is to improve patient stratification strategies while supporting subsequent treatment decisions.

NGS strategies to identify genomic variations at the DNA level can be broadly divided into three main types: whole genome sequencing (WGS), whole exome sequencing (WES), and targeted sequencing (Figure 1). Sequencing cells' whole genome or exome has been critical for answering complex biological questions. However, these methods provide a depth of information that is difficult to analyse and process in a clinical setting,[6] making them currently unsuitable for broader application. The growing knowledge of the molecular alterations that initiate and drive tumour growth and metastasis has led to the development and the introduction of a variety of targeted gene panels that are used in routine clinical settings. Targeted sequencing, which typically involves analysis of a selection of genes with clinical significance, is by far the most widely used approach that best balances accurate identification of genomic variants with high sensitivity and a good cost-effectiveness ratio. Depending on the number of genes covered by the assay used, the targeted approach can be further subdivided into entry-level sequencing, characterised by the use of small- to medium-sized panels (i.e., up to 50 genes or similar) or comprehensive profiling based on large panels (in the range of hundreds of genes).[6] Information obtained from targeted gene panels can inform diagnostic classification, guide therapeutic decisions, and/or provide prognostic insights for a given tumour.[7] In addition, the use of targeted gene panels accelerates overall sample processing,[1] including data analysis, interpretation of results, and generation of medical reports, which directly affects downstream patient management.

Targeted NGS can be performed using a variety of molecular methods to select for genomic regions of interest. The most common are hybridisation capture and PCR amplicon enrichment. The technologies behind these methods are different and bring their own advantages and challenges (Figure 2). The hybridisation capture-based approach is most commonly used for wide screening of genomic variants, often involving WGS and WES, and combined with high throughput sequencing. In contrast, the PCR amplicon-based approach has a simpler and faster workflow and is mainly suitable for targeted sequencing. The PCR amplicon-based method is of great utility for low sample volume input and is, therefore, commonly used in routine clinical testing.[4]

This review provides an overview of the advantages and drawbacks of NGS panels of different sizes for tumour molecular profiling and their clinical applicability. Molecular profiling using NGS, including current guideline recommendations is discussed here in the context of lung cancer, a pivotal example of precision medicine for disease diagnosis and treatment.

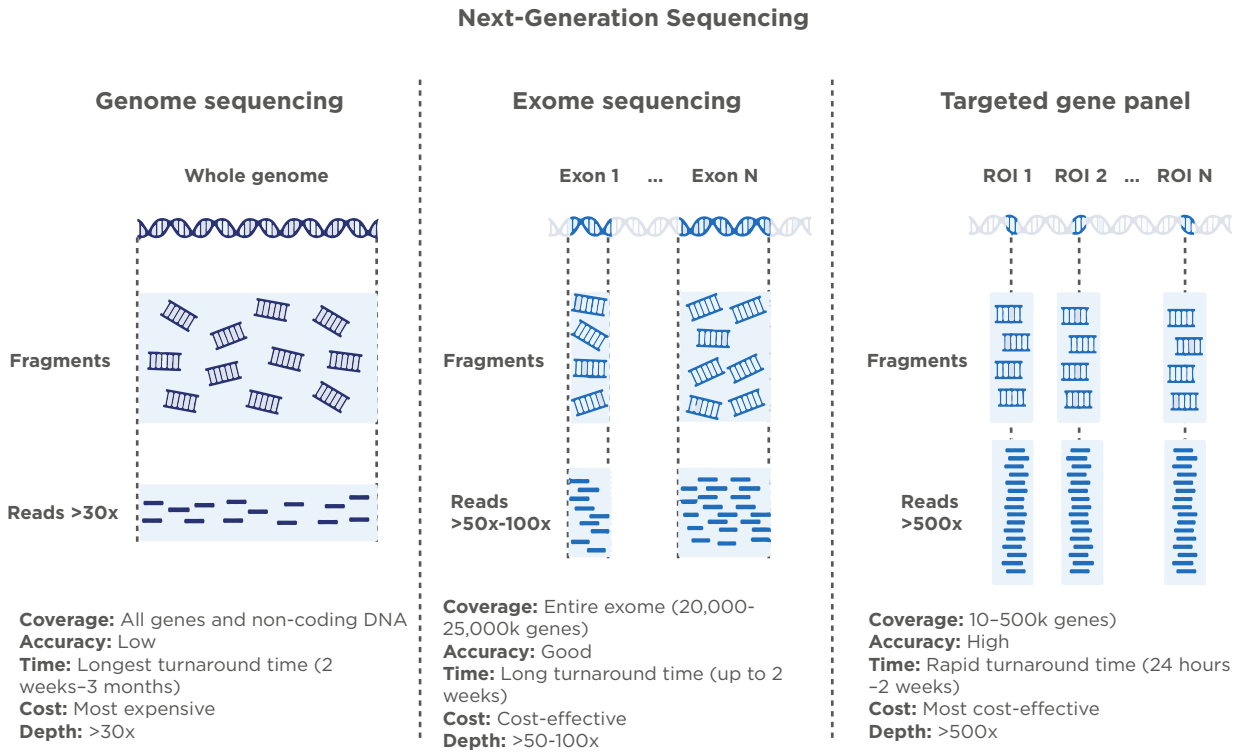


Figure 1: Comparison of next-generation sequencing techniques.

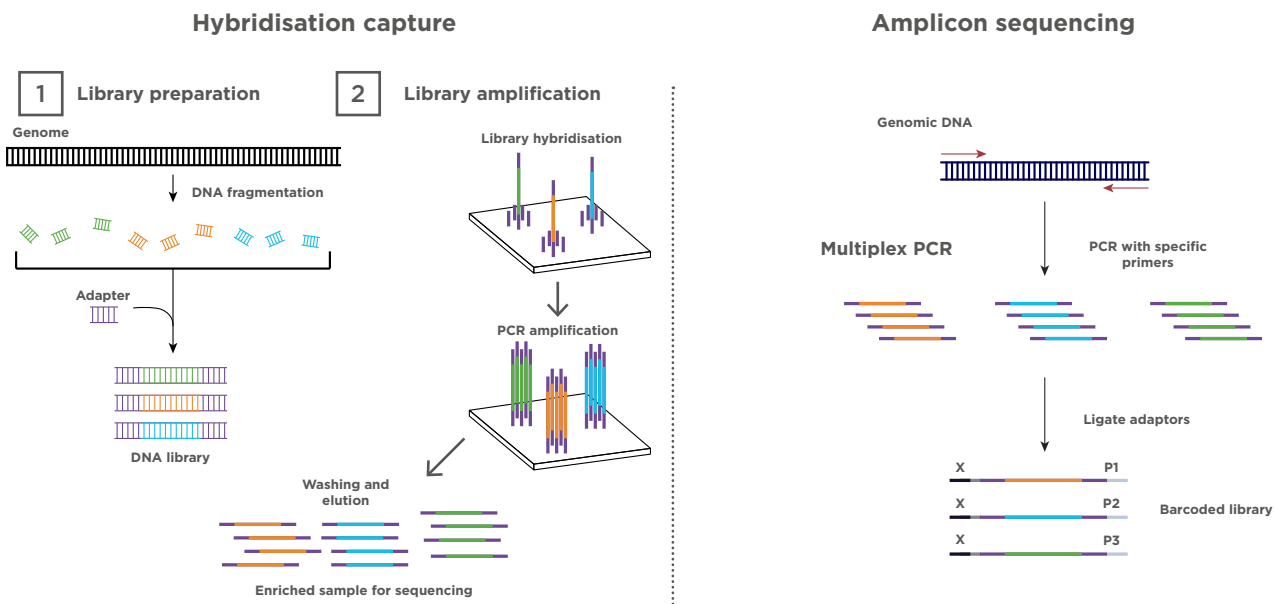
Different features of WGS, WES, and sequencing using targeted gene panels. The depth values shown are consistent with the established general recommendations for the sequencing approaches summarised here.

Image created with BioRender.com.

ROI: regions of interest; WES: whole exome sequencing; WGS: whole genome sequencing.

TUMOUR MOLECULAR PROFILING USING TARGETED NEXT-GENERATION SEQUENCING PANELS

Currently, molecular profiling of tumour samples plays a crucial role in the clinical management of patients with cancer. Rapid identification of genomic aberrations not only enables better stratification of patients for subsequent treatment with effective targeted therapies, but may also enable efficient disease monitoring and more accurate prognosis in the near future. Targeted NGS panels have been instrumental in this paradigm shift.[2] When designing an NGS panel, it is important to understand the intended use. For example, if the goal is to screen for therapeutic targets and also to enrol patients in clinical trials for investigational therapies, large panels that allow testing for complex biomarkers such as tumour mutation burden or genomic instability (e.g., homologous recombination deficiency), are usually the preferred option. Depending on whether a test is designed for initial disease screening, which requires high sensitivity and high coverage, or for disease monitoring, which focus on specific mutations, the panel size used may also vary.[8] Overall, the selection of the number and type of genes in a given NGS panel requires careful consideration. The size of the panel (number of genes and extent of gene coverage); type of samples to be tested; turnaround time and sensitivity required; type and complexity of variants to be determined; extent of bioinformatics support, including infrastructure and laboratory resources; and available technical expertise must be considered by the testing laboratory before selecting an NGS solution for routine clinical service.[7] Some of these parameters and the advantages and disadvantages of choosing different panel sizes (Table 1) are discussed in the following sections.



- Complex and laborious workflow
- Larger gene content (>50 genes)
- Virtually unlimited panel size
- Higher DNA or RNA input
- Lower on-target efficiency (higher DNA input)
- Higher turnaround time and cost
- Higher bioinformatics support
- Comprehensive profiling of all variant types

- Simple and fast workflow
- Smaller gene content (usually <50 genes)
- Fewer than 10,000 amplicons
- Low DNA or RNA input (>10 ng)
- Target and enrich low complexity regions
- Fast turnaround time and more cost-effective
- Built-in bioinformatic pipelines
- Detection of fusion oncogenes and hypervariable regions

Figure 2: Types of next-generation sequencing-based assays.

Target enrichment for NGS can be performed using a hybridisation capture-based method or a PCR amplicon-based method.

Hybridisation capture can be performed either in a solution or on a solid substrate such as a microarray. Both methods require the use of synthetic oligonucleotide probes complementary to the genetic sequence of interest. The target regions are then amplified and washed to obtain the desired isolated regions for sequencing.

Amplicon-based enrichment uses carefully designed PCR amplicons to flank the target regions and specifically amplify the regions of interest. The amplified products are then purified from the sample and used for sequencing, eliminating the need for enrichment by hybridisation. Image created with BioRender.com

Sample Quality and Quantity Requirements

Regardless of the NGS approach and methodology to be used, the feasibility of molecular profiling depends on the quality and quantity of the sample to be tested. The use of NGS to detect low allele frequency somatic variants in nucleic acids extracted from formalin-fixed paraffin-embedded tumour tissue is challenging for clinical molecular diagnostic laboratories, because these types of samples often yield low quantities of degraded, poor-quality genetic material.[10,11] It is estimated that molecular profiling fails in 5–30% of tested patients due to insufficient material or poor sample quality,[12,13] with the hybridisation capture method being the most affected by this issue. Thus, correct preservation and handling of clinical samples are critical for the application of panel testing in daily practice. The quality of nucleic acids extracted from formalin-fixed paraffin-embedded samples is negatively affected by several factors, including tissue age, fixation time, and tumour lesion size (i.e., large tumour masses often have hypoxic areas leading to high cell death).[11] In addition, the quantity of nucleic acids may be limited by the tumour sampling methods (e.g., fine-needle aspiration) and the tumour cellularity.[14,15]

Table 1: Comparison between small or hotspot, and large next-generation sequencing-based gene panels.

Feature	Small or hotspot panels (<50 genes)	Large panels (>50 genes)
Input amount	Smaller DNA or RNA input (10–100 ng)	Higher DNA or RNA input (50–1,000 ng)
Turnaround time	Yields faster results	More time-consuming
Data analysis	Fewer data generated Easier to interpret	Higher amount of data More difficult to interpret
Cost	Best value for money Better reimbursement policies available	More expensive Reimbursement of larger NGS-based panels is limited
Best-suited applications	Detection of specific and targeted disease-associated variants Detection of germline inherited SNPs, indels, and gene fusions	More comprehensive molecular profiling of tumours Detection of rare variants Clinical trials or basic oncology research
ESMO recommendations[9]	Lung adenocarcinoma, prostate cancer, and cholangiocarcinoma to access Level I alterations Ovarian cancers to determine somatic *BRCA1/2* mutations Colon cancer as alternative to PCR if it does not result in additional cost	Larger panels can be used based only on specific agreements with payers, considering the overall cost of the strategy (drug included) and if they report accurate ranking of alterations Carcinoma of unknown primary To determine tumour mutation burden

ESMO: European Society for Medical Oncology; NGS: next-generation sequencing; SNP: single nucleotide polymorphism.

Another aspect to consider is that most patients with cancer are only diagnosed at advanced stages, when the available sample material is often limited.[16] This situation *per se* hampers the use of large gene panels, an approach that may require a large amount of sample material to provide fully reliable results. The minimum sample input requirements for NGS depend on the enrichment technique, sequencing method, and depth of sequencing required. In particular, when using small- to medium-sized targeted gene panels, successful profiling is possible with as little as 5–10% of neoplastic cell sample content and 10 ng of DNA or RNA.[17] This is particularly relevant when the amount of biopsied tissue is reduced, as in the case of fine-needle aspirates.

The desired limit of detection must also be considered to determine the minimum amount of DNA or RNA required to perform a test and the lowest frequency of mutant alleles that can be detected.[18] This is important for all oncology assays, where tumour percentage and heterogeneity affect mutation allele frequencies.[19]

Bioinformatics and Interpretation of Variants

The large amount of raw data generated by NGS-based assays requires a bioinformatics pipeline capable of converting nucleotide sequences into meaningful biological and clinically actionable results. In addition, such an analysis must meet several analytical requirements and ensure the accuracy and reproducibility of the results obtained.

A typical pipeline for analysing NGS data can be divided into four main operations: base

calling, read alignment, variant identification, and variant annotation.[20] The larger the region of the sequenced genome, the greater the likelihood of encountering rare or novel variants that require complex interpretation. As the size of diagnostic panels increases, the likelihood of detecting incidental findings also increases.[19] The available interpretation software is extensive and is constantly updated as new biomarkers are discovered and NGS assays are introduced to the market.[18,21,22]

Another challenge is deciding which genes to test in a given clinical scenario. Although there are guidelines that define the most common mutations or genes of interest (tests that are usually reimbursed), the literature and clinician interest may propose other genes (tests that are usually not reimbursed) that may be medically useful.[19,23] To standardise the reporting and interpretation of clinically relevant genomic data in the management of patients with cancer, the European Society for Medical Oncology (ESMO), led by the ESMO Translational Research and Precision Medicine Working Group, developed the Scale for Clinical Actionability of molecular Targets (ESCAT) ranking system.[24] ESCAT defines six levels of evidence as Tier I: targets ready for implementation in routine clinical decisions; Tier II: investigational targets that likely define a patient population that benefits from a targeted drug but magnitude of benefit is unknown; Tier III: clinical benefit previously demonstrated in other tumour types or for similar molecular targets; Tier IV: preclinical evidence for actionability; Tier V: evidence supporting co-targeting approaches but without clinical benefit; and Tier X: lack of evidence for actionability. In addition, organisations such as the Association for Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP) have also developed classification systems to rank the clinical utility of variants based on the level of evidence.

In particular, for WGS and WES, performing the entire workflow from DNA or RNA extraction to bioinformatics analysis, requires trained personnel with extensive expertise and considerable hands-on laboratory work. On the other hand, several targeted solutions with fully automated end-to-end workflows are commercially available. They offer optimised solutions for data analysis and reporting that can be easily handled by a certified technician with a minimum of NGS-specific training.

Diagnostic Yield and Clinical Utility

The diagnostic yield is an important selection criterion for determining the performance of any assay, including those for genetic testing. It is primarily defined as the likelihood that a test will provide the required information for a genetic diagnosis. For example, laboratories can use this parameter to decide whether to switch from one particular test method to another (e.g., fluorescence *in situ* hybridisation for gene fusion detection versus RNA-based NGS). The same is true when deciding between sequential testing for single genes and NGS, as in the example reported by Pósafalvi et al.,[25] showing that using a targeted panel of 55 cardiomyopathy genes significantly improved the percentage of patients in whom disease-causing mutations were found (15–50% in more than 250 patients tested), demonstrating the benefits of adopting NGS-based methods in clinical diagnostics.

In another study, Garg et al.[26] compared the clinical diagnostic yield of a targeted sequencing panel (Trusight Tumor 26 [Illumina, San Diego, California, USA]) in melanoma, colorectal, and gastrointestinal stromal tumours with non-NGS assays. Overall, 79% of melanomas and 94% of colorectal tumours were positive on panel testing, demonstrating that NGS increases diagnostic yield by 24% and 36%, respectively, for routinely tested variants in melanoma and colorectal cancer. No additional benefit was observed in gastrointestinal stromal tumours. Nevertheless, these results demonstrate the impact of NGS-based assays on diagnostic yield in cancer.[26]

In a study aimed at understanding the appropriate size of a solid tumour sequencing panel to identify clinically actionable variants, Vail et al.[27] directly compared the results of a large gene panel (315 genes, reference laboratory assay [Foundation Medicine, Cambridge, Massachusetts, USA]) with those of a medium-sized panel (161 genes, Oncomine™ Comprehensive Assay [Thermo Fisher Scientific, Waltham, Massachusetts, USA]) and a small hotspot panel of 50 genes (Oncomine™ Precision Assay [Thermo Fisher Scientific, Waltham, Massachusetts, USA]).[27] While the larger panel detected more variants, the additional variants

beyond those included in the medium panel had no impact on patient management. The data indicate that any variant identified by the larger panel in the context of an U.S. Food and Drug Administration (FDA)-approved therapy would also have been identified by the medium panel. Even more remarkably, nearly all variants (88.5%) would have been identified by the 50-gene panel. Overall, this comparative analysis of the clinical utility of gene panels of different sizes shows that small and medium-sized optimised gene panels are as informative as larger panels when the primary goal is to identify clinically actionable mutations.[27]

The use of diagnostic yield as a criterion also implies that genes included in a panel should be carefully selected (i.e., only genes for which sufficient data are available to demonstrate their involvement in the disease of interest).[28] Considering the ESCAT ranking, prevalence of alterations, number of patients to be tested with NGS, and matching of an effective drug in routine clinical practice, ESMO reported that there was no proven public health impact if actionable alterations were detected beyond ESCAT Level I.[24] In light of this, ESMO recommends larger panels to be used only based on specific agreements with payers, taking into account the total cost of the patient treatment strategy (including drugs) and when they provide an accurate ranking of mutations.[28] Overall, ESMO suggests that from a public health perspective, targeted small- to medium-sized NGS panels should be the primary choice in patients with the following metastatic cancers: advanced lung adenocarcinoma, prostate cancer, ovarian cancer, and cholangiocarcinoma (Table 1).[9,29] Patients with other cancers could decide with their physician to order NGS for a large panel of genes, provided that there is no additional cost to the public healthcare system and the patient is informed of the relative likelihood of benefit (patient-centric perspective). Similarly, large gene panels should be used in academic reference centres where clinical and translational research is conducted.[9,29]

Turnaround Time and Cost-Effectiveness

One of the most critical components of clinical testing where rapid decisions must be made is the turnaround time of the test. Oncologists need to start treating patients quickly, especially if the cancer is aggressive or refractory.[30] Larger gene panels are more time consuming as they may require a more complex data analysis workflow. In contrast, small hotspot panels (<50 genes) or medium-sized panels are best suited to achieve faster results because they are less 'sequencing intensive' and their analysis is based on a limited number of clinically valuable targets.[16] Any solution that can deliver fast and reliable results should ideally be considered for routine testing. The consequences of a long testing turnaround time can have a negative impact on the clinical management of patients with advanced-stage cancer, with reduced outcomes, and should be avoided (2022 ASCO Annual Meeting abstract, unpublished data in press).

Another important component of diagnostic testing is cost, which is directly influenced by several components, such as the choice of enrichment strategy used (hybridisation capture versus PCR amplicon), size of the genome targeted, and labour and equipment required for data generation and analysis.[19] The cost of library preparation and overall sequencing also depends on samples' batching. With current NGS platforms, the data yield is high enough to barcode multiple samples and sequence them together (i.e., multiplexed). However, the size of a targeted gene panel (i.e., the number or size of genes targeted) determines the degree of multiplexing that can still achieve good coverage per sample (i.e., large panels have a low degree of multiplexing and small panels have a high degree).[30] Sequencing solutions are now available that allow cost compression to combine small- to medium-sized targeted panels with optimised sample batching capabilities.[31]

THE PARAMOUNT EXAMPLE OF NEXT-GENERATION SEQUENCING TESTING UTILITY: LUNG CANCER

Lung cancer remains one of the most commonly diagnosed cancers and the leading cause of cancer mortality worldwide.[32] Among histologic types, non-small cell lung cancer (NSCLC) is the most common and accounts for approximately 80–85% of all cases, of which about 40% are adenocarcinoma, 25–30% are squamous cell carcinoma, and 10–15% are large cell carcinoma.[33]

Recent advances in characterising the molecular biology of lung cancer, particularly the discovery of genetic driver mutations in non-squamous NSCLC, have led to the development of unique targeted therapies that often achieve remarkable success in patients with these genetic alterations.[29]

Current guidelines published by AMP, CAP, and the International Association for the Study of Lung Cancer (IASLC) recommend testing for mutations in four to eight specific genes for each patient with NSCLC.[27,34] This may result in the need for multiple tests using different techniques (e.g., fluorescence *in situ* hybridisation, immunohistochemistry, and Sanger sequencing), each with different tissue requirements and demanding different expertise.[27] In this context, NGS panels have gradually replaced these techniques in clinical laboratories and allowed simultaneous analysis of multiple genes.[20] The use of hotspot testing in advanced NSCLC, particularly through PCR amplicon-based methods that focus on unique gene alterations such as single nucleotide variants, indels, or gene fusions associated with effective targeted therapy, has been shown to be a cost-effective approach that can achieve high success rates (above 90%) even with low input material.[35-37] In addition, extremely fast turnaround times (within 3 business days) have been reported, even for tests performed in a community hospital.[38] Although the utility of large-panel NGS sequencing as an initial testing approach for all patients with NSCLC remains to be demonstrated,[39] it is important to consider this testing option for patients who are driver-gene negative, as this may increase their chances of enrolment in clinical trials.

Clinical Practice Guidelines for the Use of Next-Generation Sequencing

The National Comprehensive Cancer Network (NCCN) Clinical Practice[40] and ESMO guidelines[41] for advanced NSCLC recommend molecular testing for clinically relevant biomarkers such as *EGFR*, *BRAF,* and *KRAS* mutations; *ROS1*, *ALK,* and *NTRK1/2/3* fusions; *MET* exon 14 skipping mutations; and programmed death-ligand 1 expression. Emerging biomarkers include *MET* amplification, *RET* fusions, and *ERBB2* (*HER2*) mutations.[41]

ESMO has proposed three levels of recommendations for the use of NGS in advanced non-squamous NSCLC based on the ESCAT ranking. It is recommended that a tumour (or plasma) sample from a patient with advanced non-squamous NSCLC could be profiled using NGS technology to detect ESCAT Level I alterations (i.e., targets suitable for implementation in routine clinical decisions such as *EGFR*, *MET*, *BRAF*^{V600E}, *ROS1,* and *ALK*). In addition, the ESMO guidelines state that there is no evidence that panels detecting genes with a lower level of evidence add value from a public health perspective and should only be considered from a translational research perspective.[9]

CONCLUSIONS

NGS has become a robust, reproducible, and cost-effective technology to screen tumours for genetic alterations. The democratisation of NGS (i.e., its broad application from large academic centres to community hospitals) is critical to fully unleash the promise of 'precision medicine'. Nevertheless, there are many approaches to perform NGS testing today, encompassing large to small sequencing assays, and several aspects must be considered when selecting a gene panel. Choosing the best panel size for clinical practice has sparked intense debate among researchers and clinicians. For routine patient testing, diagnostic yield and clinical utility, along with technical aspects such as sample availability and turnaround time, should be the main guiding principles to make the most appropriate sequencing method and panel size decisions. A cost-effectiveness analysis should be carefully considered, as testing per default all patients with late-stage cancer with large panels is not affordable for most healthcare systems worldwide, nor does it currently provide substantial clinical benefit for all patients. The need to advance our understanding of cancer biology and provide patients with the opportunity to participate in clinical trials, while ensuring that the financial burden remains reasonable, requires a thorough consideration of what panel size will best serve the target population of patients. Equally, considering the evolution of the 'hub and spoke' model in the context of current trends in social medicine, it is reasonable to think that the backbone of decentralised testing in regional and

community hospitals could be represented by an NGS panel of smaller size, whereas testing in major reference hubs should include broader use of comprehensive genomic profiling.

To date, as there is no 'one size fits all' solution for either small- to medium-sized or large NGS panels, flexibility remains key. Nevertheless, the improvement in cancer knowledge achieved by wide mutation panels performed on a large scale could help prioritise some alterations for the design of 'pragmatic' and cost-effective panels for daily oncology practice in the future. Ultimately, what really matters is that as many patients with cancer as possible are tested effectively and reliably.

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Sodium-Glucose Co-transporter-2 Inhibitors in Heart Failure with Preserved Ejection Fraction: A Breakthrough in Improvement of Clinical Outcomes?

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Abstract

The conventional conception of the therapy of heart failure (HF) with reduced ejection fraction has been recently modified by adding sodium-glucose co-transporter-2 (SGLT2) inhibitors to the combination consisting of beta blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors, with the aim of improving clinical outcomes. It remains unclear whether other sub-populations of patients with HF, having either HF with preserved ejection fraction (HFpEF) or HF with mildly reduced ejection fraction, are relevant candidates for the effective therapeutic intervention that includes SGLT2 inhibitors.

The purpose of the narrative review is to elucidate plausible perspectives for the clinical implementation of SGLT2 inhibitors into optimal medical therapy in patients with HFpEF. The authors searched the bibliographic databases (Embase, Medline, and the Web of Science) and the Cochrane Central to find English-written publications satisfying the purpose of this study. The authors included eight studies and two meta-analyses that have been reported as completed and found that there were high heterogeneous data regarding the fact that SGLT2 inhibitors had strict resemblance in their efficacy among patients with HFpEF with and without Type 2 diabetes. Due to the use of unpublished data and findings from the trials ended early, there is a lack of upper left ventricular ejection fraction threshold levels to identify inclusion criteria and no agreement in heart failure with reduced ejection fraction determination. However, the results of the meta-analysis, especially come from subgroups' analysis, appeared to be relevantly optimistic for use of SGLT2 inhibitors in HFpEF therapy.

INTRODUCTION

Despite a moderate trend of the incidence of new cases of heart failure (HF) and HF with reduced ejection fraction (HFrEF) to decline, mainly in developed countries, the estimated absolute number of prevalent HF with preserved ejection fraction (HFpEF) seems to steadily increase in both developed and developing countries as the result of ageing and the comorbid conditions

of the population.[1,2] Rising costs for medical care and the implementation of several modern technological innovations into routine clinical practice sufficiently increased the burden of HF.[3,4] The American Heart Association (AHA) has reported that the real total of direct medical costs as a result of HF is said to increase from 21 billion USD in 2012 to 53 billion USD in 2030 in the USA.[5] Moreover, these expenditures seem to be projected without double counting the direct costs that are attributed to several comorbid conditions related to HF development.[5] In fact, guideline-directed medical therapy in patients with HFrEF is based on using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors, which has been shown to be suboptimal due to low target drug dose achievement and respectively high discontinuation rate over 12 months.[6]

In addition, event rates for HF hospitalisation or premature death remain unacceptably high and strongly associated with a disproportional growth of expenditures on medical services.[6-9] Obviously, traditional treatment of patients with HF requires improvement. Moving away from the old conception (mentioned above) to new four pillars treatment scheme including angiotensin receptor-neprilysin inhibitors, beta blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors (particularly dapagliflozin and empagliflozin), the authors have received new data from several large clinical trials and meta-analyses, which have demonstrated remarkable improvement of prognosis and noticeable attenuation of cost-efficacy in patients with HFrEF compared with standard therapy.[10-12] However, it remains unclear whether other subpopulations of patients with HF, having either HFpEF and HF with mildly reduced ejection fraction, are relevant candidates for the effective therapeutic intervention that includes SGLT2 inhibitors. The purpose of the review is to elucidate the plausible implementation of SGLT2 inhibitors into optimal medical therapy in patients with HFpEF.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND CARDIOVASCULAR BENEFITS IN PATIENTS WITH AND WITHOUT DIABETES

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, luseogliflozin, and ertugliflozin) combined with the SGLT1/2 inhibitor sotagliflozin are modern innovative drug classes, which were initially designed as antidiabetic agents.[13] They have demonstrated beneficial effects on fasting and postprandial hyperglycaemia through decreasing glucose reabsorption as a result of a blockage of SGLT2 proteins, which are abundantly expressed in the proximal convoluted tubule of the kidney and ensure re-absorption of about 90% of all glucose.[14] Indeed, these agents being administered as a monotherapy and in combination with other glucose-lowering therapies, including metformin and insulin, which have shown significant reductions in HbA1c and fasting glucose without an adverse impact on cardiovascular (CV) safety compared with placebo.[15]

In addition, SGLT2 inhibitors exerted a sufficiently lower risk of hypoglycaemia compared with sulphonylureas and similarly low risk as metformin, pioglitazone, or sitagliptin.[15] In patients with Type 2 diabetes (T2D), the SGLT2 inhibitor canagliflozin provided a remarkable reduction of body weight, which contributed to a decrease in systolic blood pressure.[16] However, previous clinical studies have yielded strong evidence regarding the tissue-protective activity of SGLT2 inhibitors.[17] Along with it, SGLT2 inhibitors were found to be able to attenuate CV and renal outcomes in long-term studies in patients with T2D with known CV diseases, including myocardial infarction, chronic kidney disease, and HF, as well as in individuals with traditional CV risk factors.[18-20]

The meta-analysis of 40 clinical trials by Benham et al.[21] revealed that SGLT2 inhibitors led to a much more pronounced reduction of total CV events in patients with T2D compared with placebo, but there was no significant association between the risk of CV events and decrease in blood pressure. Another meta-analysis of 27 studies (N=7,363) has shown that the administration of SGLT2 inhibitors was associated with lowered HbA1c coupled with blood pressure, body

weight, and albuminuria in patients with T2D and chronic kidney disease.[22] Therefore, SGLT2 inhibitors exhibited a significant reduction in the risk of CV death, non-fatal myocardial infarction or non-fatal stroke, and HF without an effect on all-cause death.[22] Consequently, SGLT2 inhibitors have been initially approved by highly reputed medical associations for the therapy of T2D and then they went on to turn in HFrEF regardless of the presence of T2D.

The first SGLT2 inhibitor that received approval by the U.S. Food and Drug Administration (FDA) for treatment of HFrEF, with the aim of reducing the risk of CV death and hospitalisation in patients regardless of the presence of T2D, was dapagliflozin. Shortly after, the FDA approved another SGLT2 inhibitor, empagliflozin, for the same indication.[23] Current clinical guidelines recommend both dapagliflozin and empagliflozin for the therapy of HFrEF, but not HFpEF due to limiting solid evidence.[24-26] However, exact molecular mechanisms that are involved in the beneficial impact of SGLT2 inhibitors on CV outcomes in HF continue to remain to be uncertain.[27]

PLAUSIBLE MECHANISMS OF ACTIONS OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS

Although a broad range of pleiotropic effects of SGLT2 inhibitors have been previously found and thoroughly investigated, the interrelation between direct hypoglycaemic effects and indirect pleiotropic effects requires additional explanation.[28] Figure 1 illustrates a large variety of opinions about the role of several molecular pathways contributing to the effects of SGLT2 inhibitors.

The most simple assumption that is considered to be realistic is a decrease in sustained systolic and diastolic blood pressure, resulting in natriuresis and sympathetic tone, which can translate into improvement of CV prognosis and slowing kidney disease progression. Perhaps, bodyweight reduction can be a potential mechanism in the alleviation of CV risk.[29] Apart from this, it has been hypothesised that SGLT2 inhibitors can be involved in the regulation of the sodium–hydrogen exchange in the heart and kidney leading to both cardiac and renal protection. Through their stimulating effect on diuresis and natriuresis, these agents can decrease the interstitial osmotic gradient, pre- and after-load, and thereby potentially improve vascular structure and function.[30] Acting as stimulators of erythropoiesis due to the 'mimicking' effect of systemic hypoxia on the kidney, SGLT2 inhibitors seem to be powerful triggers for non-specific tissue protection.[31,32] In addition, they may modulate the production of a wide spectrum of adipokines (leptin, visfatin, adiponectin), myokines (apelin, irisin), and inflammatory cytokines (TNF-α, IL-6) acting through the sirtuin-related signalling pathway.[33] This signalling pathway is also responsible for the turnover of myocardial energy homeostasis from glucose utilisation to oxidation of other substrates, such as ketone bodies, free fatty acids, and branched-chain amino acids, which appear to be a powerful modulator for mitochondrial function playing a pivotal role in pre-conditioning and oxidative stress.[33] Finally, the sirtuin-1 pathway seems to be a central player in SGLT2-related regulation of reducing cardiac cells necrosis and cardiac or kidney fibrosis.[34]

BENEFITS OF THE SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

There is data about 19 clinical trials that have been initially designed with the aim of elucidating the effect of SGLT2 inhibitors in patients with HFpEF, with and without T2D, on clinical outcomes and the surrogate points (mainly the levels of cardiac biomarkers), but only eight from these had a completed status along with available results to evaluate (Table 1). In addition, nine randomised clinical trials have been reported as permanently completed, but the study design provided for the possibility to enrol patients with T2D for whom HF was not determined as inclusion criteria (EMPA-REG, CREDENCE, DECLARE-TIMI-58). However, post-hoc analysis was frequently performed with the aim of elucidating the impact of SGLT2 inhibitors on either cardiac biomarkers or HF-related outcomes.

Nassif et al.[35] evaluated 324 patients with HFpEF (left ventricular ejection fraction [LVEF]: >40%) who were randomly included in the groups of

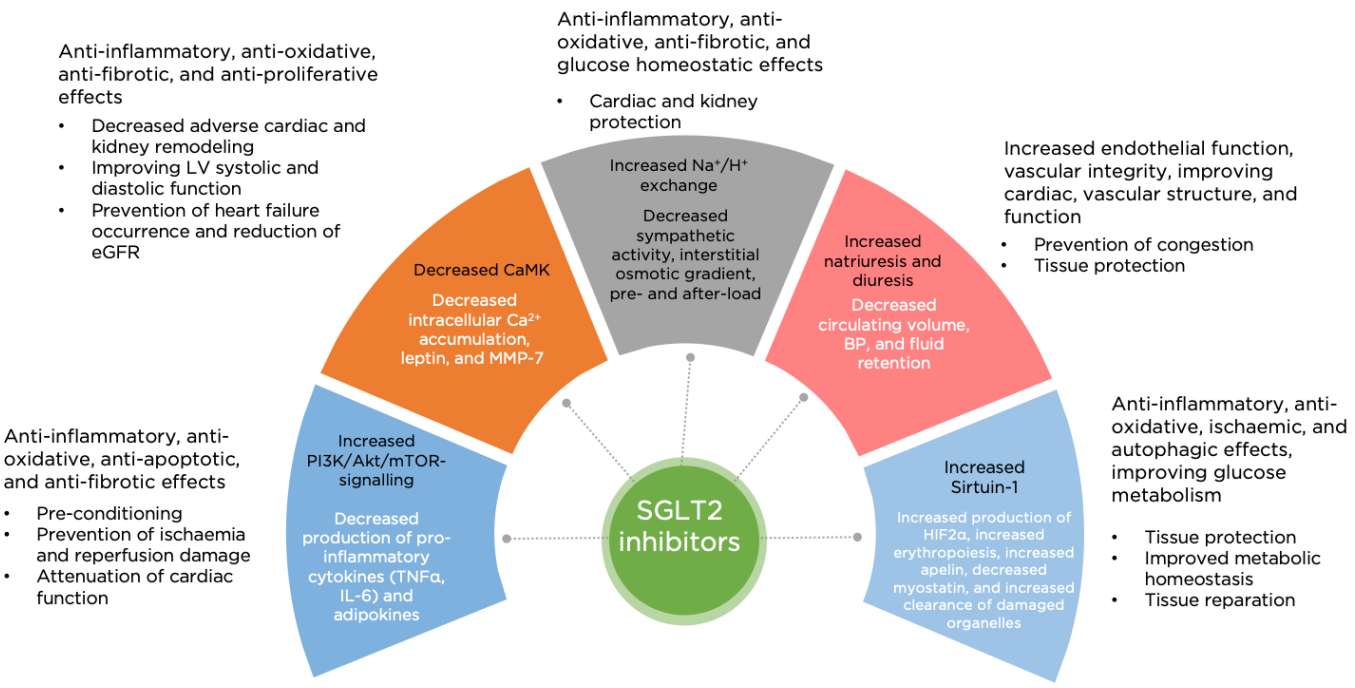

Figure 1: Plausible molecular mechanisms contributed to the beneficial effects of SGLT2 inhibitors in patients with heart failure.

Akt: serine/threonine-specific protein kinase; BP: blood pressure; Ca^{2+}: calcium; CaMK: Ca^{2+}: calmodulin-dependent protein kinase; eGFR: estimated glomerular filtration rate; HIF: hypoxia inducible factor; LV: left ventricular; PI3K: phosphatidylinositol 3-kinase; MMP: matrix metalloproteinase; mTOR: mammalian target of rapamycin; SGLT2; sodium-glucose co-transporter-2.

Table 1: Completed randomised clinical trials dedicated the impact of sodium-glucose co-transporter-2 inhibitors on clinical status of patients with heart failure with preserved ejection fraction.

Study acronym or NCT number	Number of participants	Intervention	Duration of follow-up	Primary outcomes
PRESERVED-HF (NCT03030235)[35,36]	324 (with and without T2D)	Dapagliflozin or placebo	12 weeks	Increased KCCQ-TSS and 6MWD, decreased body weight
EMPEROR-Preserved (NCT03057951)[37,38]	5,988 (with and without T2D)	Empagliflozin or placebo	26.2 months (median)	Decreased CV death and HF hospitalisation
VERTIS CV (NCT01986881)[39,40]	8,246 with T2D	Ertugliflozin or placebo	3.5 years	Similarity in a reduction of a risk of HF hospitalisation in those who had LVEF: ≤45% and LVEF: >45%
MUSCAT-HF[41]	173 patients with T2D and HFpEF	Luseogliflozin 2.5 mg once daily or voglibose 0.2 mg 3 times daily	12 weeks	No difference between groups in the reduction in BNP levels
CANDLE[42]	233 patients with T2D and stable chronic HF	Canagliflozin or glimepiride	24 weeks	No differences between groups in the levels of NT-proBNP

Table 1 continued.

DECLARE-TIMI-58 (NCT01730534)[43-45]	14,565 patients with T2D and at high CV risk	Dapagliflozin or placebo	4.2 years	No effect on all-cause and CV mortality and HF hospitalisation in patients without HFrEF Decreased risk of CV death and HF hospitalisation in patients with higher levels of NT-proBNP
SCORED (NCT03315143)[46,47]	10,584 patients with T2D and eGFR between 25–60 mL/min or 1.73 m^2	Sotagliflozin or placebo	16 months	Decreased risk of CV death, HF hospitalisation, and urgent visits for HF
SOLOIST-WHF (NCT03521934)[48,49]	1,222 patients with T2D and recent worsening HF	Sotagliflozin or placebo	9 months	Decreased number of CV deaths, HF hospitalisations, and urgent visits for HF

BNP: brain natriuretic peptide; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; KCCQ-TSS: Kansas-City Cardiomyopathy Questionnaire-Total Symptom Score; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro–B-type natriuretic peptide; NCT: National Clinical Trial; T2D: Type 2 diabetes; 6MWD: 6-minute walk distance.

dapagliflozin (10 mg daily) or placebo.[35] The authors reported that dapagliflozin noticeably improved Kansas-City Cardiomyopathy Questionnaire (KCCQ)-Clinical Summary Score, six-minute walk distance, and reduced body weight compared with placebo over 12 weeks, whereas there were no significant differences between both groups in systolic blood pressure and the levels of natriuretic peptides and HbA1c.[35,36]

The EMPEROR-Preserved trial has been enrolled 5,988 patients with class II–IV HFpEF (LVEF: >40%) to receive empagliflozin 10 mg/day or placebo added on optimal therapy for HF and comorbidities.[37,38] Eligible patients had either the levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP) of ≥300 pg/mL without atrial fibrillation or >900 pg/mL with atrial fibrillation due to established structural heart disease within 6 months prior to study entry or hospitalisation within 12 months before being included in the trail.[37] Therefore, 49% of the patients had T2D. An estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 was found in 50% of eligible patients and atrial fibrillation was diagnosed in 51% of all recruited individuals.[37] The primary outcome (CV death or HF hospitalisation) occurred in 13.8% and 17.1% for empagliflozin group and placebo group, respectively (hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.69–0.90; p<0.001).[37] The authors emphasised that the benefit was noticed to be similar in patients regardless of the presence of T2D, but patients with HFpEF and LVEF of ≥60% exerted less advantage in composite clinical outcome. However, amongst secondary outcomes, total hospitalisations, and change in mean eGFR slope per year were found to be significantly reduced in empagliflozin group when compared with placebo group (p<0.001 for all cases), whereas improvement in all-cause mortality, composite renal outcome, new onset T2D among patients with pre-diabetes were not remarkably changed during the study.[37] In addition, the meaningful improvement in KCCQ-Clinical Summary Score was more likely to notice in empagliflozin versus placebo.[37] Thus, the results of the study have yielded that superiority of empagliflozin to placebo was associated with a reduction in HF hospitalisations and quality of life, but not with all-cause and CV mortality and renal outcomes.[37]

VERTIS CV was specially designed to elucidate whether ertugliflozin reduces HF hospitalisation and CV death in patients with T2D and atherosclerotic CV disease.[39,40] Unlike in EMPEROR-Preserved trial, this study has been included 8,246 patients with T2D, 1,958 of which had a history of HF (HFrEF: n=959; HFpEF: n=999). All patients were allocated into two groups (ertugliflozin 5 mg or 15 mg daily [n=5,499] or placebo [n=2,747]) and followed for a mean of 3.5 years.[39] The results of the study have ascertained that ertugliflozin reduced the risk of first HF hospitalisation and the total number of HF admission to hospitals with strict similarity in patients with HFpEF and HFrEF. In addition, the authors noticed a remarkable decrease in the combined outcome (total HF hospitalisation or CV death) in eligible patients.[39]

Novel SGLT2 inhibitor luseogliflozin has been investigated in a small study called MUSCAT-HF, in which 173 patients with T2D and HFpEF (LVEF: ≥45%; BNP: ≥35 pg/mL) were included.[40] All eligible patients were allocated to receive luseogliflozin (n=83) 2.5 mg once a day or voglibose (n=82) in 0.6 mg daily for 12 weeks. The authors reported that there was no remarkable difference between groups in the reduction in the plasma levels of BNP.[41]

Tanaka et al.[42] elucidated the impact of canagliflozin on the changes in circulation on the levels of cardiac biomarkers such as NT-proBNP in patients with T2D and chronic HF. They included 233 patients having a mean LVEF value of 57.6% (standard deviation: 14.6%), so 71% of eligible patients had been diagnosed with HFpEF (LVEF: ≥50%).[42] All patients were randomised to receive canagliflozin 100 mg or glimepiride (initial daily dose was 0.5 mg with follow-up titration) and followed for 24 weeks. Unfortunately, the levels of NT-proBNP were not found to show a sufficient reduction during the observation period in both groups. Moreover, the authors did not find significant differences between groups in this parameter at the end of the study.[42]

In the DECLARE-TIMI-58 trial, dapagliflozin (10 mg daily) exerted a significant risk reduction of the composite outcome (CV death or HF hospitalisation) compared with placebo in patients with T2D, while the study was not designed as HF trial.[43-45] Indeed, only 1,464 patients (10.1%) from the 14,565 who were selected had a history of HF, mainly HFrEF, which was defined as LVEF: <45%, but not as LVEF: <40%.[43] Therefore, 1,316 (7.7%) had HF without known reduced LVEF.[40] Zelniker et al.[43] measured baseline NT-proBNP levels in patients who were enrolled in the study and found that the mean values were 75 pg/mL (interquartile range: 35–165 pg/mL]. Importantly that dapagliflozin reduced the risk of the composite outcome regardless of NT-proBNP levels, although the effect of the agent was found to show greater absolute risk reductions in patients with T2D having higher baseline NT-proBNP concentrations compared with those who had lower ones.[40] Kato et al.[44] reported that dapagliflozin remarkably reduced all-cause mortality in patients with HFrEF (HR: 0.59; 95% CI: 0.40–0.88), but not in those who had no HFrEF.[44]

SCORED was a multicentre double-blind randomised clinical trial that enrolled patients with T2D and chronic kidney disease and then allocated to receive sotagliflozin (n=5,292) or placebo (n=5,292).[46,47] The median of the observation was 16 months; however, the trial was ended early due to loss of funding and might have affected the results. To note, the majority of eligible patients had HFpEF defined as LVEF: ≥50%. The authors found that sotagliflozin was superior to placebo in a reduction of CV death, HF hospitalisation, and urgent visits for HF, but was associated with numerous adverse events, such as diarrhoea, genital mycotic infections, volume depletion, and diabetic ketoacidosis.[46]

The SOLOIST-WHF trial depicts to elucidate the impact of sotagliflozin on CV death, HF hospitalisations, and urgent visits for HF in patients with T2D and recent worsening HF.[48,49] A total of 1,222 patients with T2D with either HFpEF (LVEF: ≥50%) or HFrEF (<50%) were randomised to receive sotagliflozin (n=608) or placebo (n=614) after reaching haemodynamic stability and then were followed for 9 months.[48] Participants had elevated BNP levels (≥150 pg/mL for patients without atrial fibrillation and ≥600 pg/mL for those who had atrial fibrillation). The results have yielded much more pronounced reduction of primary endpoints in the sotagliflozin group compared with the placebo group (HR: 0.67; 95% CI: 0.52–0.85; p<0.001).[48] All these data reflect a favourable trend to lower NT-proBNP/BNP levels and/or

quality of life in patients with HFpEF treated with SGLT2 inhibitors. Along with it, the benefit of the agents in keeping with CV outcomes and HF-related complications remained uncertain. Perhaps it relates to short follow-ups, unknown HF phenotypes and upper LVEF limit for inclusion at the baseline, and high variety in age and gender in different studies.

A recent meta-analysis of nine randomised clinical trials (n=19,741) by Singh and Singh[50] yielded the significant risk reduction in composite endpoint ([CV death and/or HF hospitalisation] HR: 0.74; 95% CI: 0.69–0.79; p<0.001), with CV death (HR: 0.86; 95% CI: 0.78-0.95; p=0.003) and HF hospitalisations (HR: 0.68; 95% CI: 0.62-0.74; p<0.001) with SGLT2 inhibitors in patients with chronic HF. Analysis of the subgroup did not show a benefit in the composite of CV death or HF hospitalisation in patients with HFrEF or HFpEF, so these findings require more investigations in the future.

Another meta-analysis of eight large clinical trials by Lu et al.[51] confirmed these conclusions (mentioned above) and demonstrated that SGLT2 inhibitors noticeably decreased the risk of composite end-point (CV death or HF hospitalisation) by 23% (HR: 0.77; 95% CI: 0.72–0.82), HF hospitalisations by 32% (HR: 0.68; 95% CI: 0.62–0.75), and CV death by 15% (HR: 0.85; 95% CI: 0.76–0.94) in patients with known HF, regardless of its phenotype. Obviously, the results of both meta-analyses are based on the hypothesis that the proportion of patients having HFpEF in the studies enrolled to the investigations and the qualification of clinical outcomes have been thoroughly possessed; however, innate restrictions such as the use of unpublished data and findings from trials that ended early, a lack of upper LVEF threshold levels to identify inclusion criteria, and no agreement in HFrEF determination are limitations for them.[50,51]

However, the effect of SGLT2 inhibitors being independent from T2D status is considered to be clearly elucidated in specifically designed trials dedicated to outcomes in patients with known HFpEF. In order to compare the results of these studies and prevent misunderstanding, the universal definition of HFpEF is used to stratify patients at risk and diagnose HF phenotype for all studies that are going to conduct. Whether dapagliflozin and empagliflozin are effective in prevention of CV death or worsening HF in patients with HFpEF, independent of their T2D status, will hopefully be discovered when two new large clinical trials are will be completed in the near future. The DELIVER[52] and EMPERIAL-Preserved[53] trials are now in progress.

GAPS OF KNOWLEDGE AND FUTURE PERSPECTIVES

Nowadays the definition of HFpEF is an object of scientific discussion and several previous studies that are considered to have been dedicated SGLT2 inhibitors in HF have, in reality, been provided in a wide range of patients who not only had HFpEF but also HF with mildly reduced ejection fraction, unconfirmed HF phenotype, and those with LVEF: ≤60%. There are serious concerns that the data obtained cannot be an attribute of the bias and high variability in the effects. This means, in particular, that it will be difficult to extrapolate data received from placebo-controlled trials into actual clinical practice, even if studies with relatively small sample sizes had been shown positive effects of SGLT2 inhibitors on surrogate endpoints in HFpEF (LVEF: <40%). This is particularly true if some patients with HFrEF might have serious benefits in terms of increasing LVEF until the threshold is over 49%. Although this fact is not considered to be a cause to change a phenotype of HFrEF to HFpEF during SGLT2 inhibition, new values of LVEF should be pondered in case of interpreting the results. The next concern relates to uncertainty in the decision-making of the regulatory authorities in many countries because the prescription of SGLT2 inhibitors according to new indications such as HFpEF is still restricted by them and requires solid approval. In addition, there is no consent on how the metabolic phenotype influences the drugs' efficacy in HFpEF. Animal studies have clearly revealed that SGLT2 inhibition can attenuate cardiometabolic dysregulation of cardiac function and modify the altered myocardial structure, but there is a serious deficiency in clinical evidence. However, these clinical findings might represent as novel therapeutic targets for the treatment of HFpEF with SGLT2 inhibitors associated with reduced all-cause and CV mortality.

CONCLUSION

Recent clinical studies for SGLT2 inhibitors exhibited heterogeneous data regarding the fact that these agents had a strict resemblance in their efficacy among patients with HFpEF with and without T2D. However, the results of meta-analysis, especially come from subgroup analysis appeared to be relevantly optimistic for use of SGLT2 inhibitors in the therapy of HFpEF, because of a lack of difference in dynamics of cardiac biomarkers amongst patients with HFrEF and HFpEF and there was a steady trend to improve HF hospitalisation. The DELIVER trial and the EMPERIAL programme, including the EMPERIAL-Preserved trial, are addressed to the question whether SGLT2 inhibitors are powerful agents to reduce all-cause and CV mortality in HFpEF.

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Perspectives on Treatment of Inflammatory Bowel Disease in Older Patients: Applying Gut-Feeling in an Evidence-Based Era?

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Abstract

Background: The older inflammatory bowel disease (IBD) population is challenging to treat because of heterogeneity in characteristics related to frailty. The authors aimed to study factors contributing to the difference in treatment between older and younger patients with IBD and the relation between frailty and therapy goals, from the perspectives of both professionals and patients with IBD.

Methods: Semi-structured interviews in 15 IBD professionals and 15 IBD patients aged ≥65 years.

Results: Professionals had 1–20 years of experience, and three practiced in an academic hospital. Patients were aged 67–94 years and had a disease duration between 2 years and 62 years. The authors found that professionals aimed more often for clinical remission and less often for endoscopic remission in older compared with younger patients. Older patients also aimed for clinical remission, but valued objective confirmation of remission as a reassurance. Professionals sometimes opted for surgery earlier in the treatment course, while older patients aimed to prevent surgery. Professionals' opinion on corticosteroids in older patients differed, while patients preferred to avoid corticosteroids. In professionals and patients, there was a shift towards goals related to frailty in patients with frailty. However, professionals did not assess frailty systematically, but judged frailty status by applying a clinical view.

Conclusions: Many therapy goals differed between older and younger patients, in both professionals and patients. Professionals did not assess frailty systematically, yet aspects of frailty influenced therapy goals. This underlines the need for clinically applicable evidence on frailty in IBD, which could aid tailored treatment.

INTRODUCTION

Inflammatory bowel diseases (IBD), comprising Crohn's disease and ulcerative colitis, are chronic diseases occurring as a relapsing and remitting inflammation of the intestines. Patients experience disabling symptoms such as abdominal pain, diarrhoea, and fatigue.[1,2] The prevalence and incidence of IBD is increasing, especially in the older patient population.[3,4] IBD treatment is often challenging in older patients because this population is heterogenous in their functional, mental, and social capacities, and sometimes live with frailty.[5,6] Moreover, it has been established that older patients with IBD are often undertreated compared with younger patients.[7] Corticosteroids are only suitable for remission induction and not for maintenance therapy due to their unfavorable safety profile.[8-12] However, longer courses of corticosteroids are prescribed to older patients and step-up towards maintenance therapy, such as immunomodulators or biologicals, is less frequently initiated.[7-13] This difference in pharmacologic treatment between older and younger patients is not necessarily because of a milder disease course in older patients.[7]

Guidelines do not differ between older patients aged ≥65 years versus younger patients with IBD. The European Crohn's and Colitis Organisation (ECCO) advises gastroenterologists to assess an individual's frailty when making treatment decisions in older patients.[14] Meanwhile, evidence on the prevalence of frailty and the role of frailty in treatment safety and effectiveness in older patients with IBD is scarce.[15-18] It is unclear which patient characteristics are deemed important by professionals and patients in the management of IBD in older patients, and which therapy goals are currently being pursued. Furthermore, it is unclear if and how frailty is accounted for in current clinical practice.

In this article, the authors aimed to study factors contributing to the difference in treatment between older and younger patients with IBD and the relation between frailty and therapy goals, from the perspectives of both professionals and IBD patients.

MATERIALS AND METHODS

Study Design

This was a semi-structured interview study consisting of 34 face-to-face, in-depth interviews with professionals and patients. The study is reported following the checklist of the Consolidated Criteria for Reporting Qualitative Research (COREQ)[19] and was conducted in two parts. Initially, professionals were interviewed between May and July 2019. Next, older patients with IBD were interviewed between June and October 2020.

Participants

Professionals

Professionals were defined as either gastroenterologists with a focus on IBD or nurses specialised in the treatment of IBD working in the Netherlands. Professionals were approached for inclusion by email. Purposive sampling was applied to ensure a heterogeneous population,[20] and professionals were included based on differences in age, sex, geographical location of practice, nature of hospital of practice (referral versus general hospital), and possession of a PhD title. Professionals were included after signing informed consent and agreeing to having the interview audio taped. The authors aimed to include at least 15 professionals (10 gastroenterologists and five IBD nurses).

Patients

Patients were recruited at the Leiden University Medical Center (LUMC), the Netherlands, and were eligible if they had a confirmed clinical, endoscopic, and/or histological diagnosis of Crohn's disease, ulcerative colitis, or IBD unclassified. Patients were approached for participation using a letter written on behalf of

their treating physician. The authors aimed to include 15 patients aged ≥65 years. To ensure a heterogenous population, purposive sampling was applied by selecting older patients from the authors' cohort study on geriatric assessment in older patients with IBD.[21] In this way, the authors could select patients based on information in the electronical medical record, such as age, sex, IBD disease history, disease duration, IBD medication, and place of living, and based on frailty, comorbidity, and educational level. All patients were included after signing informed consent and agreeing to having the interview audio taped.

In addition, to explore if new themes were generated, the authors aimed to interview five younger patients aged 18–65 years with IBD.

Data collection and setting

Interviews were conducted face-to-face and consisted of two parts. In Part A, the authors conducted a semi-structured interview. In Part B, the interviewer presented prewritten cards. The interviews with professionals were conducted at their workplace, and interviews with patients were performed at their location of preference (hospital or at home). A caregiver or family member was allowed to be present during the patient interviews, and to participate in the interview. Interviews were conducted by two female Master of Medicine students who both had completed their clinical rounds (professionals were interviewed by SW, patients by CV). The interviewers did not know the professionals or patients beforehand, and the interviewers introduced themselves by providing the above information prior to the interview. Both interviewers conducted three practice interviews. Field notes were made during and after each interview. During interviews with professionals and patients, the authors performed interim analyses. Consultation was also performed with members of the research team. No repeat interviews were carried out.

Part A was conducted according to a predefined interview scheme with open-ended questions, and a list of potential additional questions to create more in-depth responses. The interview scheme was developed by the research team (VA, AP, SM, and PM). At the start of the interview, the interviewer introduced herself and collected information about the participant's baseline characteristics.

In Part B, the authors presented two sets of cards to the participants. First, the interviewer presented a series of cards that each depicted one specific patient characteristic, such as characteristics regarding disease activity and frailty. Professionals and patients were asked to create a hierarchy from most to least important in making treatment decisions in older patients with IBD. Participants were then presented with a series of cards that each featured one specific therapy goal regarding older patients with IBD, such as measures of disease control and preservation of functional status. For both the patient characteristics and therapy goals, participants were allowed to place more than one card in the same hierarchy level. Next, the authors asked professionals if their hierarchy of patient characteristics and therapy goals would be different if applied to younger patients. Finally, both professionals and patients were asked if and how impairments regarding each of the six geriatric characteristics would change the hierarchy of the therapy goals. In each interview, the authors also presented some empty cards to allow participants to add patient characteristics or therapy goals to the list.

In addition, the authors asked professionals if they were reticent in prescribing certain IBD medications in older patients. Initially, only an open-ended question regarding this topic was asked. However, after having performed six interviews, the authors added questions about specific medications. This was either because opinions on these medications (corticosteroids and methotrexate) differed, or because the authors were specifically interested in recently approved medications for IBD care (tofacitinib). Further, after having completed the interviews with professionals, the authors found that there was a difference in the therapy goals and treatment strategies considered to be applied to older patients compared with younger patients. Therefore, a question was added to the patient interviews that highlighted this finding and asked patients for their opinion on it. Moreover, patients were asked about characteristics of frailty. However, after having performed four interviews, the authors noted that this question was hard to answer, and consequently made

it more personal by asking: "Do you think that you are frail at the moment?", "Why do you or do you not think you are frail at the moment?", and "What would make you (more/less) frail?" Furthermore, the authors added some additional cards in the interviews with patients. After three practice interviews, "Worries about family or loved ones" was added to the set of cards on patient characteristics, and "Decrease in inflammation in the blood ([C-reactive protein] CRP)" was added to the set of cards on therapy goals. After seven interviews, the authors added "Inflammation in the stool ([faecal calprotectin] FCP)" to the former set of the cards. When no new ideas or themes emerged in three successive interviews, the authors concluded that data saturation had been reached.

Data Analyses

All interviews were transcribed verbatim using Amberscript software (Amberscript, Amsterdam, the Netherlands), and transcripts were not returned to participants. The data from Part A were analysed based on the grounded theory approach.[22] Two coders coded each interview independently. VA and SW coded the interviews with professionals; VA and CV coded the patient interviews. The two coders frequently met during the coding process to compare codes until consensus was reached. Open coding was performed, and a code list was developed inductively. Codes were renamed and reordered in Excel whenever the coders agreed this was necessary. The code list was used for all subsequent interviews in the same sample of interviewees. In parallel to open coding, axial coding took place, in which the coders performed classification of the codes into categories and themes. This categorisation was completed and revised whenever necessary during and after the interview rounds. To apply structure to the themes that were found, selective coding was applied, and themes were categorised into disease-related (such as IBD symptoms or IBD complications); treatment-related (such as IBD medication or surgery); and geriatric themes, related to daily functioning (such as functional or cognitive status).

The data from Part B were analysed by listing the hierarchy of cards provided by each participant in a separate Excel file. During the analysis, the authors focused on each participant's top three; most participants included more than one card per hierarchy level. These were analysed independently by the same two coders as in Part A (VA and SW, and VA and CV, respectively). During the analysis, both coders read the considerations that the participants mentioned while ordering the cards, and listed them per card. To create order and to enhance the ability to recognise patterns between different participants, the authors categorised the cards and applied colours to each category. In patients, the authors looked at whether the presence of geriatric impairments, found during a geriatric assessment, seemed associated with patterns in hierarchy. Participants did not provide feedback on the findings.

Ethical Considerations

The study protocol was declared not subject to the Medical Research Involving Human Subjects Act by the Medical Research and Ethics Committee at the LUMC, Leiden, the Netherlands (Protocol number: N19.026), and was approved in all participating centres in which professionals had their practice. Written informed consent was obtained from all participants.

RESULTS

Participants

In total, 34 interviews were conducted in 15 professionals, 15 older patients, and four younger patients. For the interviews with professionals, the authors approached 15 gastroenterologists and 10 IBD nurses, of whom 10 and five, respectively, participated. Three gastroenterologists did not want to participate due to lack of time, and two gastroenterologists and three nurses did not respond. Two nurses wanted to participate but could not be included for logistical reasons. The interviews with professionals lasted between 27 minutes and 51 minutes. Gastroenterologists had a median age of 45 years, ranging from 39 years to 61 years. IBD nurses had a median age of 41 years, ranging from 34 years to 54 years. The years of experience in IBD care in professionals ranged from 1 year to 20 years (Table 1).

For the interviews with patients, 20 older patients with IBD were approached, of whom 15 participated. Two older patients were not willing to participate, one patient did not speak Dutch, and two patients could not be

reached. Eight patient interviews took place at the LUMC, one interview took place over the telephone due to COVID-19 restrictions, and the remaining interviews took place at the patients' homes. During three interviews, a spouse or child was present. Interviews took between 37 minutes and 69 minutes. Patients had a median age of 74 years, ranging from 67 years to 94 years. Disease duration ranged between 2 years and 62 years, and patients used different IBD medications at the time of the interview. Four patients had a high comorbidity level as measured by the Charlson Comorbidity Index (CCI), 10 patients had two or more impaired geriatric domains in their geriatric assessment, and were therefore classified as frail (Table 1). Five younger patients with IBD were approached and included. However, one patient withdrew consent due to disease severity. Sociodemographic and disease characteristics of younger patients are presented in Table 1.

Professionals

Therapy goals in treatment of older patients with inflammatory bowel disease according to professionals

The authors asked professionals what goals they aim for in the treatment of older patients with IBD, and whether these goals differ from those for younger patients. Some professionals said they aim for the same goals in older versus younger patients with IBD. However, other professionals stated that they aim for different therapy goals in older patients with IBD.

Regarding disease-related goals, a number of professionals stated that clinical remission was often more important, whereas endoscopic remission and mucosal healing were reported to be less important in older patients. The prevention of long-term complications was considered to be less important in older patients, and some participants tended to treat older patients with IBD less aggressively. This was motivated by some professionals' belief that disease course is more indolent in older patients. "Free of symptoms, with the least possible amount of immunosuppression, yes that's it. And the presence of biochemical remission or mucosal healing, that really doesn't matter much to me," said one gastroenterologist (number 6)

Second, other treatment-related goals in older patients with IBD were named. Professionals reported to aim more towards remission with as little immunosuppression as possible in older patients, and to prescribe medication with as few adverse events as possible. When remission is achieved, a couple of professionals declared to stop maintenance therapy sooner in older patients. Sometimes, professionals tended towards surgery earlier in the treatment course in older patients compared with younger patients. One professional mentioned to aim for as little burden for the older patient as possible by reducing hospital visits. Third, goals related to daily functioning were identified. Professionals put more focus on functioning in daily life, preventing social isolation and immobilisation, and retaining physical activity in older than in younger patients. An overview of therapy goals is depicted in Figure 1.

All professionals included clinical remission or corticosteroid-free remission in their top three therapy goals. More than half of the professionals did not put endoscopic remission in their top three. For younger patients, most of the professionals would rank endoscopic remission higher. Some professionals would rank corticosteroid-free remission higher in younger patients versus older patients. In contrast, other professionals would rank it lower.

"Corticosteroid free remission, it depends on the case. In younger patients it would be number one priority, in older patients we will sometimes accept low doses," stated one gastroenterologist (number 3).

"Definitely no [corticosteroid] maintenance therapy. I think that is just not right," said another gastroenterologist (number 8).

When looking at therapy goals related to daily functioning, preservation or restoration of independence and mobility was most often chosen for the top three hierarchy. Next, the authors asked if and how the presence of geriatric impairments in an older patient, such as impaired functioning in daily life, cognition, and independence, or the presence of multiple comorbidities, would change their ranking of goals. Clinical remission remained the most important therapy goal for most of the professionals, regardless of geriatric impairments.

Table 1: Participant characteristics.

Professional		
Characteristic	**Gastroenterologist (n=10)**	**IBD nurse (n=5)**
Sex, female	4	4
Age*	45 (39–61)	41 (34–54)
Years of experience in IBD*	10 (3–20)	6 (1–10)
Practicing in academic medical centre	2	1
PhD title	7	0
Contacts with IBD patients in last 2 weeks*†	43 (12–160)	80 (40–500)
Contacts with IBD patients aged ≥65 years in last 2 weeks*†	6 (1–53)	10 (2–125)
Patient		
Characteristic	**Older patients with IBD (n=15)**	**Younger adult patients with IBD (n=4)**
Sex, female	6	2
Age*	74 (67–94)	30 (25–45)
Educational level (high)	4	1
CCI ≥3	4	N/A
High frailty level (≥2 impaired geriatric domains)	10	2‡
IBD type, CD	8	2
Disease duration*	34 (2–62)	4 (3–12)
Current IBD medication		
None	4	0
5-ASA	7	2
Corticosteroid	3	0
Immunomodulator	2	0
Biological	4	3

*Median (range).

†At outpatient or inpatient department, during telephone consultation or supervision.

‡Considers itself frail.

CD: Chron's disease; CCI: Charlson Comorbidity Index; IBD: inflammatory bowel diseases; NA: not applicable; 5-ASA: 5-aminosalicylates.

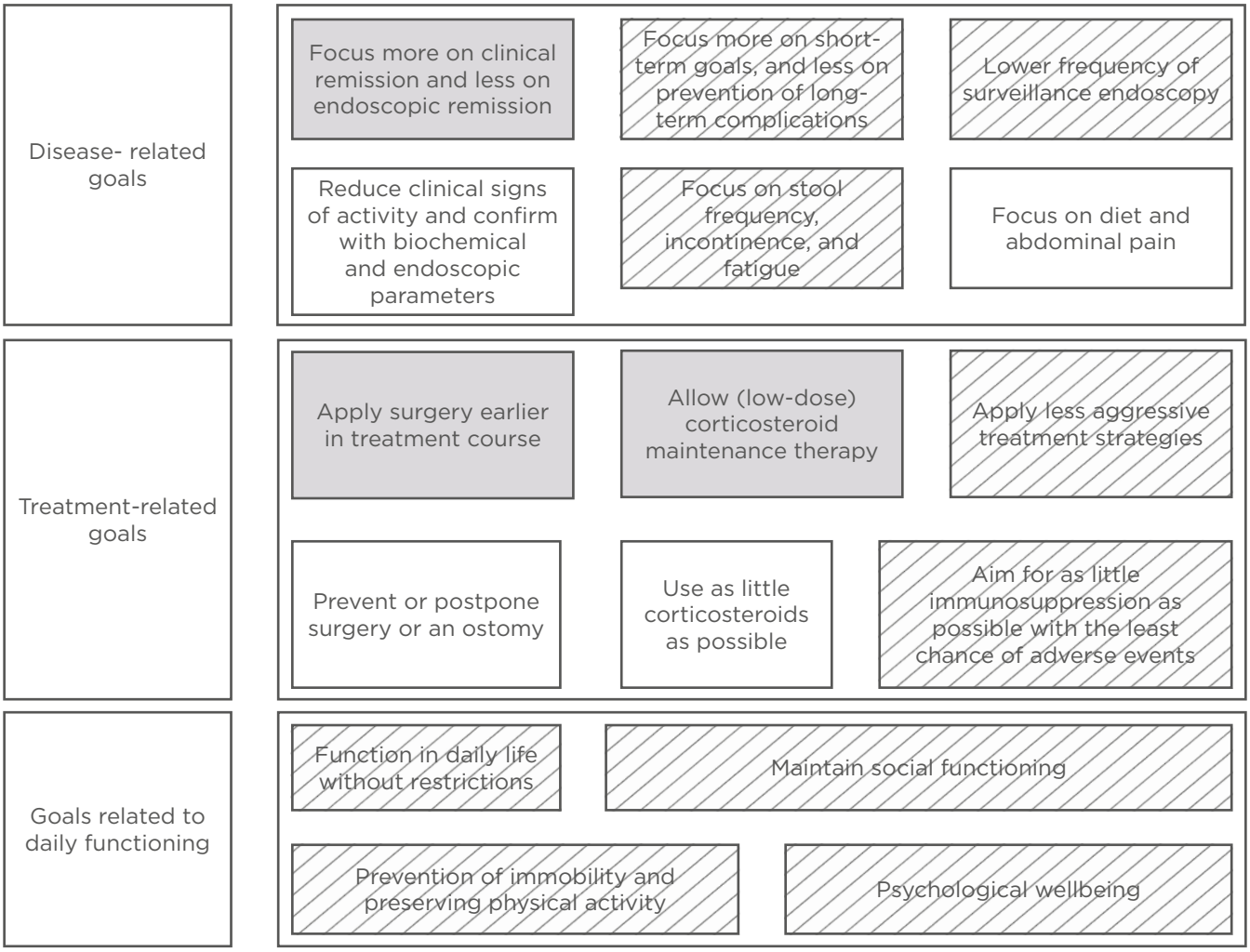

Figure 1. Conceptualisation of therapy goals in the treatment of older patients with inflammatory bowel diseases as compared to younger patients, according to professionals and patients.

Regarding patients' answers, both quality of life goals and therapy goals were incorporated in this figure.

Grey: named by professionals; white: named by patients; grey and white shaded: named by both professionals and patients.

Professionals said that this is the goal they can influence the most. Some professionals chose to strive more towards preservation or restoration of independence and mobility if those were impaired in patients. One professional said that impairments in mobility or functional status could be a reason to choose an ostomy, as incontinence could be more disabling in those patients. A few professionals said that corticosteroid-free remission was less important to them in an older patient with geriatric impairments. However, other professionals said to aim for corticosteroid-free remission, no matter which impairments were present. Some said they put even more emphasis on corticosteroid-free remission when there were multiple comorbidities or an impaired cognition.

"If a patient has dementia and it's all about maintaining quality of life, and we achieve quality of life with clinical remission, then I won't worry about whether this patient does or doesn't use corticosteroids," revealed one gastroenterologist (number 1).

Preferences in inflammatory bowel disease medications among professionals

After asking about patient characteristics and therapy goals, the authors asked professionals if they were reticent in prescribing certain IBD medications in older

Table 2: Reticence in prescribing medication in older patients with inflammatory bowel diseases.

IBD-medication	Reticence	No reticence
5-ASA	*	• Not reticent
Corticosteroids	• No high doses • Only short courses • No maintenance therapy • High risk of infection • Risk of osteoporosis • High risk of adverse events in patients with diabetes or high blood pressure	• Good short-term solution • Long-term adverse events are less important • Accept low-dose maintenance when comorbidities are present • Low-dose is best solution in some patients • Low-dose maintenance budesonide when history of malignancy is present
Methotrexate	• Out of fashion • No methotrexate in older patients • Only when combining with rheumatoid arthritis treatment • Route of administration • Coadministration of folic acid	• Good option or solution for some patients • Milder adverse events compared to thiopurines • First opt for methotrexate in older-onset instead of biologicals
Thiopurines	• More careful in older patients • Stop earlier in older patients • Start with lower dose in older patients • High risk of lymphoma, malignancy, and infections • More alert to adverse events in older patients	• We try thiopurines a lot after corticosteroid induction
Biologicals	• High risk of infections in older patients • More alert to adverse events in older patients • Tend to prescribe biologicals more in younger than in older patients • Logistical challenge due to route of administration	*
Anti-TNFα	• Reticent with infliximab • High risk of adverse events and malignancy • Reticent in patients with cardiovascular problems • Logistical issues when patient is immobile • Afraid for low medication adherence in adalimumab	• Monotherapy is safe in older patients • I prescribe standard dose

Table 2: Reticence in prescribing medication in older patients with inflammatory bowel diseases. (Continued)

Ustekinumab	• The fact that it is relatively new	• A good option • Safe feeling to prescribe • More often prescribe as first choice
Vedolizumab	*	• A good option • Rather opt for vedolizumab instead of anti-TNFα or thiopurine • Less systemic infections • Safe feeling to prescribe • More often prescribe as first choice • Prefer vedolizumab in case of history of malignancy • Less severe adverse events compared to ustekinumab or tofacitinib
Tofacitinib	• Careful with new medications in older patients • Risk of opportunistic infections • Risk in patients with history of cardiovascular or thromboembolic events • High risk of adverse events • Only when you have no other options • Risk of herpes zoster infection	• Oral route of administering is an advantage • It is an option in older patients
Combination therapy	• More reticent to prescribe in older patients • Higher risk of infections	*

Table reflects the answers of professionals (gastroenterologists and inflammatory bowel disease nurses) to the question: "Are there IBD medications you would prefer not to prescribe in older patients with IBD, and if so, which and why?" After 6/15 interviews, the authors started asking professionals specifically about corticosteroids, methotrexate, and tofacitinib.

*When no comments were made about reticence or preference in older patients columns were left blank in the table.

5-ASA: 5-aminosalicylates.

patients. The results of this question are displayed in Table 2.

Aspects of frailty in older patients with inflammatory bowel disease according to professionals

First, the authors asked professionals if they make a distinction between fit and frail patients in daily clinical practice. Thereafter, the authors elaborated on how this distinction was being made and whether this influenced choice of treatments or therapy goals. A couple of professionals mentioned paying attention to frailty. The way frail patients were identified varied from applying a clinical view to estimating biological age or life expectancy. None of the professionals reported to assess frailty in older

patients with IBD systematically, or to apply validated frailty screening tools. Somatic aspects of frailty were most often mentioned, primarily comorbidity but also polypharmacy and malnutrition. Furthermore, a lot of professionals acknowledged functional status, such as living in an assisted home facility and not being able to perform activities of daily living, as an important aspect of frailty. A few professionals stated that therapy goals should be based on the presence of frailty; for example, preventing surgery in older patients with frailty. However, others said that patients with frailty presenting with a flare-up of IBD should be treated the same as other patients.

"Therapy goals will be different and they depend on how many aspects of, yes, frailty are present. We don't ask specific questionnaires regarding frailty yet; I think actually we should do it in older patients," commented one gastroenterologist (number 3).

Patients

Quality of life and therapy goals according to older patients with inflammatory bowel disease

First, the authors asked patients about factors determining quality of life. Aspects of functional status were mentioned most often; patients considered their ability to function in daily life and mobility to determine their quality of life for a large part. Second, patients were asked about their therapy goals in IBD. Therapy goals were again specified into disease-related goals, treatment-related goals, and goals related to daily functioning. Disease related goals were mostly absence of inflammation, in general or as seen during endoscopy, and decrease of IBD symptoms, of which stool-related symptoms (stool frequency, incontinence, and diarrhoea) and abdominal pain were named most often.

"I mean, he didn't dare to go anywhere, not even to a birthday party. He was just too scared he could not make it to the toilet and would be incontinent in front of his friends. So tha t is what really made live a very solitary life," commented the daughter of patient (number 8).

Themes identified as treatment-related goals were mostly surgery- and medication-related. Surgery-related goals included preventing or postponing surgery and preventing an ostomy. The patients who already had an ostomy reported to strive towards good functioning of the ostomy. Medication-related goals were finding the most effective medication with the least possible adverse events, aiming for no medication or as little medication as possible and a treatment without corticosteroids. Themes related to functional status, such as being able to function as normally as possible, were mentioned most often when looking at goals related to daily functioning. Younger patients added therapy goals related to the ability to work and the ability to have a successful pregnancy.

When asked to rank the cards with therapy goals, almost all patients ranked clinical remission in their top three. Patients stated that reducing IBD complaints was important because this leads to less disability, more independence, and a better quality of life. Almost all patients also ranked a decrease in inflammation assessed by blood or stool tests or endoscopy in their top three. Considerations mentioned here were the fact that a decrease in inflammation as seen by objective markers led to an in increase in general health and a decrease in IBD complaints. Moreover, patients said that having certainty about the severity of inflammation as measured by objective parameters or the presence of polyps was important to them. A large proportion of the patients strived towards goals related to daily functioning, such as preservation or restoration of independence, good memory, positive mood, and social contacts. Patients selecting those goals as most important were of advanced age, frail, and had multiple comorbidities. Conversely, patients selecting disease-related goals as their top priority were often of lower age, less frail, and had little comorbidities. Almost half of the patients put striving towards remission without the use of corticosteroids in their top three therapy goals. Their considerations included negative experiences with corticosteroids in the past and the high risk of adverse events. Younger patients mainly prioritised objective markers of disease; only one younger patient selected "Reducing IBD complaints" in their top three hierarchy. Younger patients who considered themselves frail more often selected goals related to daily functioning.

Aspects of frailty in inflammatory bowel disease according to patients

Almost all older patients had a positive experience with the geriatric assessment performed during the authors' cohort study. One patient said she felt fooled when undergoing the cognition questionnaire. Many patients thought that a geriatric assessment should be part of standard care. Reasons were first because it could add to the early detection of geriatric impairments. Second, patients thought it would be helpful to optimise therapy goals. Third, it could help tailor individual care, such as by providing written explanations when cognitive impairment is present. Suggestions for further extension included repeating the assessment every couple of years to monitor functional decline. Younger patients did not undergo a geriatric assessment; however, suggestions were given by them to perform a geriatric assessment not only in older patients but also in younger patients, as younger patients could also be frail.

"Someone who is physically very weak and tells a story about what he cannot do anymore, for me, it would be a very big decline, but for someone else it could be a very reasonable way of living. I think this can differ a lot per person," noted one patient (number 10).

The aspects of frailty that were identified by patients with IBD were largely related to functioning in daily life, such as being able to do everything yourself and being able to walk and move without falling. Also, aspects of comorbidity were often mentioned, such as having other diseases, having pain in general, or having a hearing impairment. Polypharmacy was named as being an aspect of frailty because medications could lead to adverse events. Impaired mental status, namely depression and anxiety; impaired cognition; and the inability to cope with negative events was also supposed to influence frailty in a negative way. The presence of social support and informal caregivers was deemed to affect frailty in a positive way. Being of advanced age was mentioned by a couple of patients. Many patients mentioned their IBD as an aspect of frailty, especially in case of a flare-up, incontinence, or diarrhoea, or when they have to pay attention to what they can and cannot eat. Also, feeling fatigued was mentioned as an aspect of frailty. The two patients who had an ostomy at the time of the interview mentioned their ostomy as an aspect of frailty. Patients mentioning functioning in daily life and being able to do everything yourself were all frail, while patients mentioning IBD-related aspects of frailty were mostly less frail. The interviews in younger patients did not yield new aspects of frailty.

DISCUSSION

Current evidence in IBD points towards different treatment regimens being used in older patients compared with younger patients.[7-13] Therefore, the authors aimed to study factors contributing to the differences in treatment between older and younger patients with IBD, and the relation between frailty and therapy goals, from the perspectives of both professionals and patients with IBD. To the authors' knowledge, this is the first study allowing for perspectives of both professionals and patients, thereby creating a comprehensive conceptualisation of the treatment of IBD in an older population.

In both professionals and patients, the authors noted that therapy goals in older patients differed from those in younger patients. A variety of themes were generated on this topic and are presented in Figure 1. Firstly, a lot of professionals mentioned to aim more for clinical remission in older patients compared with younger patients, and put lower priority on endoscopic remission. Although older patients themselves were also focused on clinical remission, a lot valued confirmation of remission by objective markers as a reassurance. Secondly, the authors noted a discrepancy regarding surgery. Some professionals stated that they opt for surgery earlier in the treatment course of older patients, while older patients themselves strived towards postponing or preventing surgery and an ostomy. A couple of patients explained that they believed themselves to be too old for surgery and were afraid of becoming dependent on caregivers or nursing aid after surgery. Thirdly, in professionals, the authors found diverging opinions on the use of corticosteroids in older patients with IBD. Some stated to allow low-dose maintenance therapy in older patients, while others were reluctant to even prescribe them short courses of corticosteroids. These views were in contrast with those of patients, who were quite uniform in preferring to avoid corticosteroids. Patients

explained that this was mainly based on their earlier negative experiences with corticosteroids. This finding is in line with a study by Asl Baakhtari et al.,[23] who investigated factors making patients with IBD less willing to take corticosteroids.

Furthermore, the authors found a lot of considerations in professionals regarding reticence or preferences in prescribing IBD medications in older patients, as depicted in Table 2. Interestingly, little to no reticence with regards to prescribing ustekinumab or vedolizumab in older patients was present. This finding is in agreement with the results from a case-based survey, which found that vedolizumab was the preferred first-line agent in the treatment of older patients with steroid-dependent, moderate-to-severe UC.[24]

Both the above-mentioned differences in therapy goals and the experienced reticence in prescribing IBD medications are factors contributing to the use of different treatment regimens in older versus younger patients.

Some professionals said to account for frailty, but none of the professionals assessed frailty systematically. At the same time, professionals reported that the presence of aspects of frailty influences therapy goals and treatment modalities. Professionals said to prioritise functional-related goals, such as maintaining self-dependence and mobility, in older patients with a low level of dependence or impaired cognition. In older patients with aspects of frailty, some professionals put higher priority on corticosteroid-free remission and others lower priority compared with older patients without aspects of frailty. Some said to aim more for the prevention of surgery, while others said that in older patients with frailty, they would opt earlier for an ostomy. The fact that frailty status influenced therapy goals and treatment was in line with considerations provided by patients, as patients with frailty more often gave priority to goals related to frailty, which was also found in younger patients who considered themselves frail. This could suggest that frailty status is more important than age in the treatment of IBD.

Both professionals and patients emphasised that clinical remission remained important, independent of non-IBD characteristics. This is because professionals can influence this goal the most. Moreover, for patients, a decrease in complaints automatically leads to an increase in independence, especially regarding decrease of stool incontinence.

Many different aspects of frailty were identified, thereby illustrating that frailty is a heterogenous concept. It was remarkable to see that a lot of patients mentioned disease-related aspects, such as the presence of a flare-up or incontinence. This underlines the importance of IBD symptom control in older and frail patients with IBD. Frailty is a concept best measured by performing validated screening questionnaires[25,26] or a complete geriatric assessment.[6] The lack of implementation of frailty measurements in current daily practice is illustrated by the ways frailty is currently measured. Indeed, current studies on frailty in IBD retrospectively assess frailty using International Classification of Diseases (ICD) codes and not by clinically applicable measurements.[15,27-29] Therefore, the gap between scientific evidence and daily practice is still present. In older patients who are candidates for intensive treatments such as chemotherapy or major surgery, implementation of a routine clinical care pathway provides the opportunity to study associations between characteristics of frailty and treatment outcomes.[30] In older patients with IBD, applying such standardised frailty screening prior to starting therapy could also guide decision making and support individualised treatment.

A couple of qualitative studies describing patient perspectives on IBD treatment have been performed,[33-35] and also in other autoimmune diseases.[34,35] However, this study is the first to investigate the opinion of both gastroenterologists and older patients on IBD treatment and the concept of frailty. Involving older patients with multiple conditions or frailty in the decision-making process could be challenging because of the potential for competing outcomes.[36] Nevertheless, Fried et al.[37] found that it was feasible for older patients to prioritise preferences in health outcomes by asking older patients to rank outcomes on a visual analogue scale. The resulting conceptualisation of the authors' study therefore delivers important lines of approach for further research and treatment of older patients with IBD. By using semi-structured interviews, open questions allowed in-depth exploration while the use of cards yielded additional information and considerations. A couple of studies have been

published on the association between frailty and readmissions, infections, and mortality.[27,29] In this study, the authors explored current modalities of frailty measurements and what both professionals and patients consider to be aspects of frailty.

This study delivers important lines of approach for both daily practice and further research on IBD in older patients. Goals named by professionals and patients could be used in research including older patients with IBD. Likewise, considerations regarding different treatment strategies in older patients could be used in surveys to assess current opinions on a larger scale.

This study also has some weaknesses. All participating patients were under treatment in an academic hospital, and could therefore have a more severe IBD history. However, this effect was minimised by applying purposive sampling and thereby reaching maximum variation. Participant size of the authors' study was small, which is inherent to the qualitative study design. Because of the small sample size, certain themes could have been missed. The authors tried to prevent this by assessing data saturation. When no new ideas or themes emerged in three successive interviews, the authors concluded that data saturation had been reached. Both professionals and patients could have given socially acceptable answers during interviews. This response bias was minimised by the fact that the interviews were conducted by medical students who had no prior relation with the participants, and participants were not informed on the questionnaires beforehand.

CONCLUSION

The authors found that many therapy goals differed between older and younger patients, in both professionals and patients. Besides, professionals did not assess frailty systematically, yet aspects of frailty influenced therapy goals, thereby exposing the gap between current evidence and daily clinical practice. The authors believe that the variation in professionals' therapy goals found in this study reflects the lack of evidence on most effective treatment strategies in this heterogenous population. The results of this study further underline the need for a systematic assessment of frailty in individual patients and collection of evidence on optimal treatment of frail patients.

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Lymphoepithelial Cysts of the Pancreas: CT and MRI Features

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Abstract

Objective: Describe CT and MRI features of the lymphoepithelial cyst (LEC) of the pancreas.

Methods: The authors identified 13 cases of LEC by searching their institutional electronic medical archives from 2004 to 2020. All of the patients had CT scans and six patients had both a CT and MRI. The final diagnosis was established either by fine-needle aspiration with cytopathology (n=6) or surgical resection (n=7).

Results: The mean diameter of the cysts was 36 mm (range: 6–93 mm). Almost all of the cysts were exophytic (92%) and solitary (85%), favouring the tail (54%) or body (38%) of the pancreas. LECs were either oval (62%) or round (39%) and had well-defined contours. All LECs showed T2 hyperintensity and T1 hypointensity; however, the signal was heterogeneous. Diffusion-weighted imaging showed restricted diffusion in all cases. On CT, LECs commonly showed complex fluid density (>15 HU) with no visible septation, enhancement or calcification.

Conclusion: LECs have a distinguishing feature on MRI, which is restricted diffusion on diffusion-weighted imaging. This is presumably secondary to the presence of keratin, which can be a helpful feature differentiating LECs from other pancreatic cystic neoplasms. Besides this, LECs predominantly appear as solitary and exophytic lesions, with complex fluid density on CT and heterogeneous hypointense T1 and heterogenous hyperintense T2 signal on MRI.

INTRODUCTION

As the list of cystic pancreatic lesions grows, so does the importance of accurate characterisation and recognition of the various entities that form this differential diagnosis. A lymphoepithelial cyst (LEC) is a rare benign lesion of the pancreas of uncertain pathogenesis that occurs almost exclusively in males.[1] LECs comprise an important category in the differential diagnosis of cystic lesions of the pancreas. Histologically, these cysts contain keratin and are lined by mature stratified squamous epithelium surrounded by dense lymphoid tissue.[2] The imaging appearance can mimic other cystic neoplasms; therefore, distinguishing LECs from other benign, premalignant, or malignant cystic lesions is important.

The radiology literature is limited to a small number of case series of CT and case reports of MRI of this entity.[3,4] Definitive diagnosis has traditionally relied on histopathologic evaluation following resection. It is important to differentiate benign cysts from premalignant cysts to prevent unnecessary surgery.[5] In this study, the imaging features of 13 cases of pancreatic LECs are presented and its differential diagnosis from other cystic lesions is discussed.

MATERIALS AND METHODS

Case Selection

Ethics Committee approval has been obtained. The institutional review board waived the requirement for obtaining a written consent form for this study. Radiology, gastroenterology, surgical, and cytology archives from 2004 to 2020 were searched retrospectively to identify patients with LEC. A total of 13 cases were identified and the diagnosis was established either by fine-needle aspiration (FNA) with cytopathology (n=6) or surgical resection (n=7).

Imaging Studies

A CT scan was performed on the multi-slice CT scanner, with post-contrast study after evaluating each patient's serum creatinine and glomerular filtration rate. Approximately 100–120 mL of Isovue-370 and portal-venous phase (45–60 sec) scanning was performed from the dome of the diaphragm to pubic symphysis. An MRI was performed with basic T1-weighted, T2-weighted, T1-weighted in and out phase imaging, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map. DWI was used (b values used were 50, 400, and 800) and performed in 3T MRIs. The T1-weighted post-contrast phase of MRI study was performed in arterial, portal-venous, and delayed phases.

Image Data Collection

A fellowship-trained pancreas radiologist with 21 years of experience reviewed the imaging studies. The radiologist noted cyst location (head, body, or tail), size (in mm), exophytic or endophytic, shape (oval or round), and contour (smooth or lobulated). On CT images, CT density was measured in all cases. If the fluid was less than <15 HU, it was labelled as simple fluid and if it was >15 HU, was labelled as complex fluid. Presence of calcification and enhancement was noted. On MRI images, the radiologist recorded the presence of septations, T2-weighted signal (hyperintense or hypointense, homogenous or inhomogeneous), T1-weighted signal (hyperintense or hypointense, homogenous or inhomogeneous), and finally recorded the ADC signal (decreased, increased, or iso signal).

Histopathologic Evaluation

Cytology results were reviewed and confirmed by an experienced cytopathologist. The presence of nucleated and/or anucleated squamous cells. admixed with a variable number of lymphocytes on FNA smears, was considered diagnostic of LEC. In cases where FNA cytology was non-diagnostic, the diagnosis was established by a histopathologic evaluation of the surgical resections. The diagnosis was confirmed by surgery in seven cases, while the remaining cases were diagnosed by FNA cytology.

RESULTS

LECs were found in 12 males and 1 female, with a mean age of 56 years (Table 1). All patients had CT scans, and six patients had an MRI. The indication of the study included a pancreatic cyst in five patients, abdominal mass in three patients, abdominal pain in two patients, two evaluations of an incidental finding, and one for a liver lesion. These lesions were exophytic 92% of the time and

Table 1: Macroscopic features of lymphoepithelial cysts.

Sex	Location	Age (years)	Size (mm)	Exophytic	Shape	Contour
Male	Tail	37	26	Yes	Oval	Smooth
Male	Tail	75	94	Yes	Round	Lobulated
Male	Body	49	35	Yes	Oval	Lobulated
Male	Body	58	27	Yes	Oval	Irregular
Female	Tail	43	52	Yes	Oval	Lobulated
Male	Body	65	25	Yes	Round	Smooth
Male	Tail	73	27	No	Oval	Lobulated
Male	Tail	40	8	Yes	Round	Smooth
Male	Body	65	29	Yes	Oval	Lobulated
Male	Body	62	52	Yes	Round	Smooth
Male	Tail	50	28	Yes	Oval	Smooth
Male	Tail	54	26	Yes	Round	Smooth
Male	Head	56	32	Yes	Oval	Smooth
Summary of findings						
Male: 92%	Tail: 54% Body: 38% Head: 8%	Mean: 56	Average: 36	Exophytic: 92%	Oval: 61% Round: 39%	Smooth: 54% Lobulated: 38% Irregular: 8%

predominantly located in the tail (54%), followed by the body (38%) and head (8%). The mean size was 36 mm (range: 8–94 mm). The shape was oval in 61% of cases and round in 39%. The contour of the cyst was smooth in 54% of cases, lobulated in 38%, and irregular in 8%.

CT imaging features of LEC are listed in Table 2. There were no septations or enhancement in 92% of the cases (Figure 1). Most cases (62%) measured complex fluid (density: >15 HU). None of the cases showed calcification.

MRI features of LEC included T1, T2, internal septation, and ADC signal on DWI, which are listed in Table 3. All patients showed inhomogeneous hyperintense signal on T2-weight imaging and the majority (83%) showed inhomogeneous hypointense signal on T1-weighted imaging. Septations were seen in 50% of MR cases and were enhancing in two-thirds of cases. Diffusion restriction was seen in all three cases when the diffusion images were performed (Figure 2).

DISCUSSION

A LEC is a rare but benign cyst of the pancreas.[6] There are several hypotheses about histogenesis of the LEC, including squamous metaplasia of the pancreatic ducts with subsequent cystic transformation; ectopic pancreatic tissue included in a peripancreatic lymph node; epithelial remnants with peripancreatic lymph nodes; and ectopic remnants of a brachial cleft cyst that are misplaced and fused with the pancreas during embryogenesis.[7,8] These cysts contain caseous, cheesy, or curd-like material and are lined by squamous epithelium containing keratin, surrounded by lymphoid tissue with rare follicles.[2]

The pathological diagnosis of a LEC is usually straightforward; however, the imaging features on CT or MRI are not well known. A LEC is a benign entity; therefore, if the imaging characteristics of a cystic pancreatic lesion are highly suggestive of a LEC, unnecessary surgery can be avoided.[9]

Table 2: CT imaging features of lymphoepithelial cysts.

Septation	Density	Enhancement	Calcification
No	Complex fluid	No	No
No	Simple fluid	No	No
No	Simple fluid	No	No
No	Complex fluid	No	No
No	Complex fluid	No	No
No	Complex fluid	No	No
No	Simple fluid	No	No
No	Complex fluid	No	No
No	Complex fluid	No	No
Yes	Complex fluid	Yes	No
No	Simple fluid	No	No
No	Simple fluid	No	No
No	Complex fluid	No	No
Summary of findings			
No septation: 92%	Complex: 62% Simple: 38%	No enhancement: 92%	Calcification: 0%

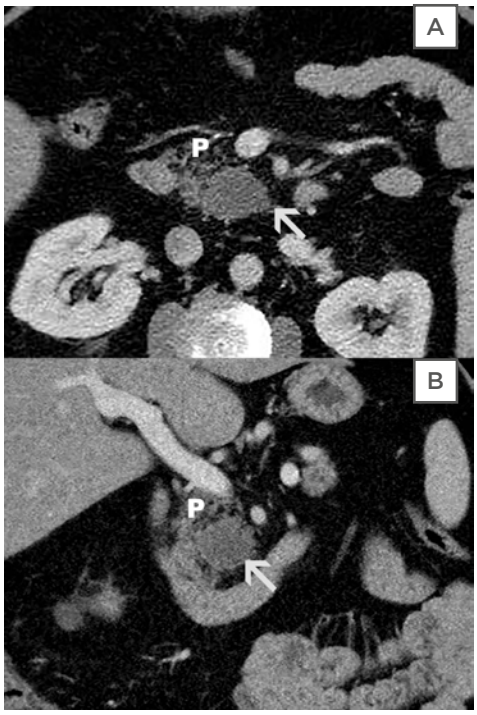

Figure 1: CT images of a lymphoepithelial cyst found in a 65-year-old male.

A) This is an axial contrast-enhanced CT image of an incidentally found LEC in a 65-year-old male. The cyst was oval, had sharply demarcated margins, and the CT density measured 32 HU (arrow). There are no visible internal septations or nodularity. **B)** This is a coronal reformat of the same cyst (arrow) and shows the exophytic location in the pancreatic head (P).

LEC: lymphoepithelial cyst; P: pancreas.

Table 3: MRI features of lymphoepithelial cysts.

Enhancement	T2 Signal	T1 Signal	Septation	ADC signal*
Septal	Hyperintense, inhomogeneous	Hypointense, inhomogeneous	Yes	N/A
No	Hyperintense, inhomogeneous	Hypointense, homogeneous	No	Decreased
No	Hyperintense, inhomogeneous	Hypointense, inhomogeneous	Yes	Decreased
No	Hyperintense, inhomogeneous	Hypointense, inhomogeneous	No	N/A
Septal	Hyperintense, inhomogeneous	Hypointense, inhomogeneous	Yes	N/A
No	Hyperintense, inhomogeneous	Hypointense, inhomogeneous	No	Decreased

* DWI was performed in three cases.

ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; N/A: not applicable.

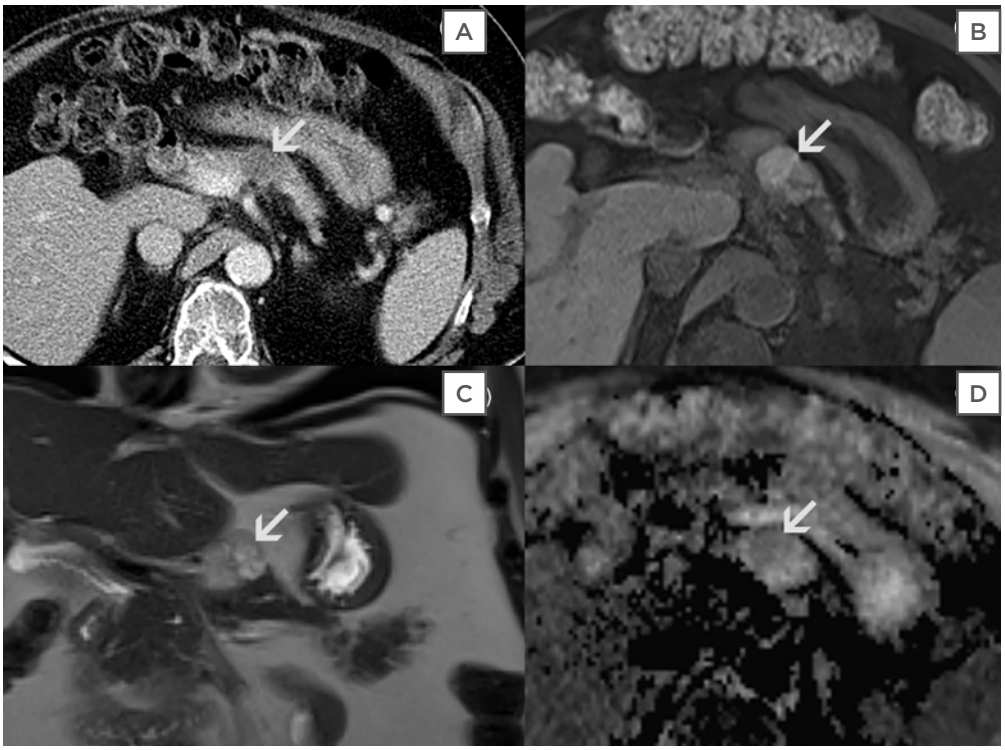

Figure 2: Diffusion restriction as seen three cases when diffusion-weight imaging was performed.

A) This is an incidentally found LEC seen in a 56-year-old male. An axial CT image with contrast showed an oval low-density lesion (arrow) in the pancreatic body. CT imaging features are non-specific; therefore, further evaluation with MRI was performed. **B)** This is an axial unenhanced T1-weighted image with fat suppression of the same cyst. There was a heterogeneously mixed signal intensity indicating complex nature of the cyst. **C)** This is a coronal T2-weighted image without contrast or fat suppression. LEC had septations and shows an inhomogeneous hyperintense T2 signal (arrow). **D)** This is an axial ADC map image of the same cyst in the pancreatic body (arrow). There is a hypointense signal that indicates restricted diffusion. This was presumably secondary to keratin content, seen with LECs, and is a useful differentiating feature from other pancreatic cystic neoplasms.

ADC: apparent diffusion coefficient; LEC: lymphoepithelial cyst.

In the authors' data series, LECs were predominantly seen in middle-aged males (mean age: 56), with a male to female ratio of 12:1. Yanagimoto et al.[10] reviewed 106 cases of LECs, and the mean age of presentation was also 56 years, with a 4:1 male to female ratio. Most of the lesions in the authors' study were located in the body or tail and were exophytic, similar to prior reports.[11] Previous studies reported CT scan findings as a simple or complex cyst, septations, papillary projection, or solid component, which may enhance and wall calcification.[12] However, in the authors' case series, septations were seen in 50% of cases with MRI and 8% with CT. This discrepancy in septations is probably due to the insensitivity of CT in showing internal architecture (Figure 2). The authors measured complex fluid density in 62% by CT and inhomogeneous T1 and T2 signal in almost all cases.

The most distinguishing imaging feature of LEC was seen on DWI (Figure 2D). LECs showed restricted diffusion (i.e., hypointensity) in all three cases on the ADC map. This was probably due to the presence of keratinised material in these lesions and can be a useful distinguishing feature of LEC.[13-15] This characteristic feature was also reported on prior case reports.[4] T1-weighted images showed heterogeneous hypointensity in patients (five out of six) and T2-weighted images showed heterogeneous hyperintensity in all (six out of six) cases. Heterogeneous T1 and T2 signal are presumably due to the presence of cholesterol and keratin within the cyst.

The authors' study was limited by the low population size. However, this is expected in rare cases such as LEC. There was not a big enough sample size to generate inter-observer variability using multiple readers.

In summary, a LEC is a rare, predominantly solitary, and exophytic lesion commonly found in the body or tail of the pancreas. On DWI imaging, all LECs showed restricted diffusion secondary to presence of keratin, which can be a distinguishing imaging feature from other pancreatic cystic neoplasms. Otherwise, CT and MRI findings are non-specific. They commonly showed complex fluid density on CT or heterogeneous hypointense T1 and heterogenous hyperintense T2 signal on MRI.

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A Retrospective Database Cohort Study Evaluating the Association Between Immune Suppressive Therapy and the Development of Cancer in Patients with Atopic Dermatitis Within UK Primary Care

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Abstract

Introduction: First-line regular systemic treatment for atopic dermatitis (AD) in the UK consists of methotrexate, azathioprine, ciclosporin, or mycophenolate (immune-suppressive therapies [IST]). ISTs have been associated with malignancy, hence the need for evaluation for the relationship to the risk of developing cancer.

Method: This retrospective cohort study utilising the Clinical Practice Research Datalink (CPRD) followed two cohorts with moderate or severe AD: one prescribed ISTs and one without. A total of 222,978 patients were included. The index date was the date of first IST prescription within primary care for the IST cohort, and the date of first potent topical steroid prescription from January 2001 to May 2021. Cohorts were propensity matched 1:1, resulting in 17,556 patients per cohort. Cox proportional hazard models were used to model the hazard of a cancer diagnosis. A secondary analysis was carried out on a restricted population, excluding patients with other comorbidities where ISTs were commonly prescribed. A further analysis explored the relation between the dose and the association with the risk of cancer.

Results: Both the primary (hazard ratio: 1.01; 95% confidence interval: 0.94–1.08) and secondary (hazard ratio: 1.03; 95% confidence interval: 0.93–1.14) analyses did not show a significant difference in the hazard of a cancer code in the IST and non-IST cohorts. The exploratory dose–response analysis showed a higher risk of cancer associated with more prescriptions of IST per year.

Conclusion: This study shows that amongst patients with moderate or severe AD, overall IST prescription in primary care is not associated with the onset of a cancer code. However, there is a trend with a higher risk of cancer coding with more prescriptions of IST.

INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin condition, affecting 11–20% of children and 5–10% of adults.[1] The pathophysiology of AD involves both skin barrier defects and immune dysregulation.[2] The universal initial treatment for AD includes

topical treatments, such as emollient to support the skin barrier, and topical corticosteroids to manage the immune dysregulation.[3] Common further treatment in primary care includes the prescription of more potent topical corticosteroids or intermittent and short-term use of systemic corticosteroids.[4] Upon referral to secondary care, patients can be treated with topical calcineurin inhibitors, ultraviolet light therapy, and systemic immune-suppressive therapy (IST) before consideration for biologic or JAK inhibitor therapy. Current further management includes potent topical corticosteroids; systemic steroids; tacrolimus; systemic IST, such as methotrexate, azathioprine, ciclosporin, and mycophenolate; biologics; and JAK inhibitors. The majority of the diagnoses of AD in the UK are carried out by a general practitioner in primary care.[5] Severity of AD can be assessed through various methods, including patient-orientated scoring of AD (PO-SCORAD), patient-orientated eczema measure (POEM), and patient global assessment (PGA). Depending on the patient reported outcome measure, approximately 53–68% of patients have moderate-to-severe AD.[5] Although there is no consensus definition for moderate and severe AD, within database and claims research, potent and very potent topical corticosteroids, systemic corticosteroids, and IST have been used as surrogates.[6]

The use of systemic immune modifiers is associated with numerous adverse events, and requires close monitoring. Ciclosporin is associated with nephrotoxicity, hypertension, infection, hypertrichosis, headache, and malignancy.[7] Methotrexate is associated with bone marrow suppression, pulmonary fibrosis, skin cancer, and lymphoma.[8] Azathioprine has been associated with an increased risk of bone marrow suppression, infection, lymphoma, and non-melanoma skin cancer development.[9] Mycophenolate is associated with infection, gastrointestinal events, and lymphoma.[10]

Prior studies have shown inconsistent results with respect to the background risk of AD. A 50% increased risk of any cancer was observed in patients with AD compared with controls.[11] In two large cohort studies in England and Wales, no evidence was found of an increased risk of most cancers among people with AD compared to those without AD. However, within this study, there was an increased risk of lymphoma, with risk increasing with greater severity.[12] This result is partially explained by a statement in the American Academy of Dermatology (AAD) guidelines: "An increased risk of skin cancer and lymphoma may be observed with use of immunosuppressive drugs in AD."[13] An increased risk for cutaneous melanoma was found in patients treated with methotrexate for their psoriasis.[14] A follow-up study in this same population found no dose–response association with cancer risk among users of methotrexate.[15] A systematic review of randomised clinical trials for moderate-to-severe AD up to February 2020 identified three trials featuring 140 patients evaluating azathioprine; three trials with 179 patients evaluating methotrexate; and 19 trials featuring 820 patients evaluating ciclosporin.[16] Follow-up varied from 12 weeks to 5 years for azathioprine, identifying myelosuppression as an adverse event. Follow-up for trials evaluating ciclosporin varied between 6–52, with nephrotoxicity reported. Follow-up for trials evaluating methotrexate varied from 12 weeks to 5 years. Malignancy did not feature as an adverse event in these studies. A 5-year follow-up study featuring patients prescribed azathioprine and methotrexate included 35 patients, of which only 27 completed the 5-year follow-up. One malignancy featured in each of the treatment cohorts, which was considered not statistically significant.[17] The small numbers of patients and short follow-up in these studies make drawing associations of malignancy risk difficult.

In UK primary care, IST prescription for patients with AD is initiated in secondary care by dermatologists, and followed up via a shared care protocol where the primary care practitioner provides prescriptions and blood monitoring. Although the initial prescriptions to titrate the IST dose are provided by the dermatologist, the follow-ups provided by the primary care prescription are recorded within the Clinical Practice Research Datalink (CPRD).[18] The accuracy of recording cancer diagnoses in CPRD was compared with hospital episode statistics, with a concordance of 94%.[19] Given the number of patients within primary care treated with ISTs, there was opportunity to study the association of IST prescription in primary care with the risk of cancer; this was undertaken utilising the CPRD database.

METHODS

Study Design

This was an historical matched cohort study encompassing a baseline period prior to the index date for the characterisation of patients for matching, and an outcome period to identify time to cancer outcomes. Only cancer codes appearing outside this window were considered, so as to disregard cancer that may be investigated at the consultation at index period.

The index date was defined in the IST group as the date of the first prescription of an IST, or in the control group as the date of the first prescription of a potent topical therapy (potent topical corticosteroid, very potent corticosteroid, or tacrolimus), or oral corticosteroid. A substudy was carried out, excluding patients with baseline comorbidities where ISTs were prescribed. The study adopted a per protocol approach; thus, patients who were prescribed an IST after prescription of a potent topical therapy entered the control cohort at time of topical therapy, and were censored on the date of their first IST therapy.

Data Source

The authors' retrospective cohort study used CPRD Aurum,[18] an ongoing primary care database of anonymised medical records from general practitioners, which is comprised of over 40 million research-acceptable (permanently registered with sufficient data quality) records.[18,20] The database is broadly representative of the general population in England in terms of age, sex, and ethnicity, and covers over 20% of the UK population. The CPRD primary care database is, therefore, a rich source of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours, and referrals to secondary care. Each year, CPRD must obtain Section 251 regulatory support through the Health Research Authority Confidentiality Advisory Group (HRA CAG). All requests from researchers to gain access to linked data must be approved via the CPRD Research Data Governance (RDG) Process.

Exposure Studied

IST was a composite of prescriptions for methotrexate, ciclosporin, azathioprine, and mycophenolate.

Methotrexate is an antimetabolite most commonly used in chemotherapy and as an immunosuppressant in autoimmune diseases.[21]

Azathioprine is a medication used in the management and treatment of active rheumatoid arthritis and the prevention of kidney transplant rejection.[22]

Ciclosporin is an immunosuppressive agent used to treat organ rejection post-transplant. It also has use in certain other autoimmune diseases; treatment of organ rejection in kidney, liver, and heart allogeneic transplants; and rheumatoid arthritis when the condition has not adequately responded to other drugs.[23]

Mycophenolate mofetil is an antimetabolite and potent immunosuppressive agent used as adjunctive therapy in prevention of allograft rejection, and in the treatment of serious autoimmune diseases.[24]

All dosages and routes of ciclosporin, methotrexate, azathioprine, and mycophenolate medication documented within primary care records were included in this study.

Inclusion Criteria

Patients included had a diagnostic code for AD or eczema. Codes for nummular, discoid, contact, dyshidrotic, and varicose eczema were excluded. Patients with no relevant AD diagnostic codes ≥15 years old were removed, as childhood AD is frequent and can resolve in adulthood. Patients with documented allotransplant of bone marrow or liver, renal, pancreas, lung, or heart transplant, or metastatic cancer prior to the index date were excluded, as these conditions are frequently treated with ISTs. Alternative subanalysis was carried out excluding patients with a documented condition at or prior to the index date (rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, and multiple sclerosis) where ISTs may be prescribed.

OUTCOME ASSESSMENTS

The primary outcome of this study was the time to coding of malignant cancer.

Matching and Weighting

Patients prescribed an IST were propensity score matched 1:1 with no replacement for patients without an IST prescription.

Initially, a characterisation of all baseline demographics, comorbidities, and patient variables was carried out for each cohort. The difference between treatment groups was quantified using a p-value of a hypothesis test of difference using a Wilcoxon Rank Sum Test or a Pearson's Chi-squared test. Additionally, the standardised mean difference was calculated. Variables with missing data were encoded into categorical variables, with a category for the missing value, enabling matching to be performed.

As the treatment pathway is typically the use of a potent topical therapy prior to IST prescription, there was a necessity to match by age at the index date. Other variables that were matched included inflammatory bowel disease,[25] BMI,[26] smoking status,[27] rheumatoid arthritis,[28] sex,[29] diabetes,[30] gastritis,[31] chronic liver disease,[32] tacrolimus prescription, index year, chronic renal disease,[33] and gastro-oesophageal reflux disease.[34] Tacrolimus was also included as a matching criterion despite recent evidence that it was not associated with cancer due to historical warnings around its carcinogenic potential.[35,36] The age of the first AD consultation was also determined, so that patients who had AD codes as a child which subsequently resolved could be excluded. Matched characteristics are shown in Table 1.

An exploratory analysis for patients with different prescriptions per year post-initial prescription was also carried out, with the comparator being patients with no prescription of IST to establish a dose relationship. The number of prescriptions per follow-up year including index date were categorised into <3 prescriptions/year, 3–<6/year, 6–<9/year, and ≥9/year.

STATISTICAL ANALYSIS

In determining a significant margin to define excess risk of cancer, the authors referred to Mansfield (2020).[12] It is stated that a hazard ratio (HR) for cancer of 1.04 (99% confidence interval [CI]: 1.02–1.04) was not appreciably significant, whereas the HR for non-Hodgkin lymphoma was significant at 1.19 (99% CI: 1.07–1.34). Based on this, the authors have assumed that a margin of 10% is clinically relevant. Equal cohort sizes and an α value of 0.05 provided 80% power to detect a difference of 10%, and this required 3,456 patients in each group.

Wilcoxon Rank Sum Test or a Pearson's Chi-squared test was calculated to identify differences between characteristics during the baseline period. Variables demonstrating a >0.05 standardised mean difference were considered for matching. The propensity score was generated using a generalised logistic model. The calliper used for the propensity score was 0.25 of its standard deviation. For the outcome, 10 matching runs with different random patient orders were made to select the best combination of matched patients and balance statistics.

The intention was to adjust for variables with residual confounding post-matching if the standardised mean difference >0.05, and for cumulative prescriptions for topical corticosteroids and oral corticosteroids.

Conditional proportional hazards regression compared IST to no IST for time to the presence of a cancer code.

During the authors' preliminary exploration of the data, it was noted that psoriasis and AD were frequently coded in the same patient. Although the prevalence ranged from 0.3% to 12.6%, the pooled prevalence was 2.0%, which was considerably lower than their initial findings. Hence, a secondary study without patients with a history of conditions where IST prescriptions may feature, such as psoriasis, was carried out.

All statistical analyses were performed using R Statistical Software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Table 1: Matched characteristics of patients for primary analysis.

Characteristic	Non-IST cohort N=17,566*	IST cohort N=17,566*	p†	Standardised mean difference
Demographic information				
Gender	7,686 (44%)	7,464 (42%)	0.017	0.0256
Age	48 (33, 63)	48 (33, 62)	0.300	0.0122
Age at first AD presentation >15 years	37 (24, 55)	39 (24, 55)	0.016	0.0215
BMI	27 (23, 31)	27 (23, 31)	0.900	N/A
Missing BMI	1,827	1,905	N/A	N/A
Categorised BMI (p>0.9)				
10–<15	31 (0.2%)	33 (0.2%)	N/A	0.0026
15.0–<17.5	183 (1.2%)	179 (1.1%)	N/A	0.0023
17.5–<20.0	1,218 (7.7%)	1,188 (7.6%)	N/A	0.0068
20.0–<22.5	1,574 (10.0%)	1,600 (10.0%)	N/A	0.0051
22.5–<25.0	3,211 (20.0%)	3,251 (21.0%)	N/A	0.0059
25.0–<27.5	2,427 (15.0%)	2,355 (15.0%)	N/A	0.0120
27.5–<30.0	2,658 (17.0%)	2,654 (17.0%)	N/A	0.0006
30.0–<32.5	1,267 (8.1%)	1,268 (8.1%)	N/A	0.0002
32.5–<35.0	1,308 (8.3%)	1,282 (8.2%)	N/A	0.0057
35–<40	1,111 (7.1%)	1,105 (7.1%)	N/A	0.0014
40–<45	476 (3.0%)	464 (3.0%)	N/A	0.0043
45–<50	150 (1.0%)	162 (1.0%)	N/A	0.0071
≥50	125 (0.8%)	120 (0.8%)	N/A	0.0035
Smoking status				
Missing	119 (0.7%)	104 (0.6%)	0.6	0.0005
Non-smoker	6,806 (39%)	6,832 (39.0%)	N/A	N/A
History of smoking	10,641 (61%)	10,630 (61.0%)	N/A	N/A
Follow-up time	1,808 (816, 3,266)	2,068 (998, 3,541)	<0.001	N/A
Comorbidities				
Neurological condition‡	1,222 (7.0%)	1,150 (6.5%)	0.130	0.0166
Rheumatoid arthritis	3,111 (18%)	3,424 (19%)	<0.001	0.045
Systemic lupus erythematosus	612 (3.5%)	635 (3.6%)	0.500	0.007
Ankylosing spondylitis	128 (0.7%)	133 (0.8%)	0.800	0.0033
Psoriasis	3,469 (20%)	3,337 (19%)	0.075	0.0192
Diabetes	1,374 (7.8%)	1,381 (7.9%)	0.900	0.0015
Gastritis	1,058 (6.0%)	1,108 (6.3%)	0.300	0.0117
Gastro-oesophageal reflux disease	560 (3.2%)	548 (3.1%)	0.700	0.0039
Chronic liver disease	558 (3.2%)	495 (2.8%)	0.049	0.0217
Chronic renal disease	317 (1.8%)	272 (1.5%)	0.061	0.0207
Inflammatory bowel disease	1,702 (9.7%)	1,948 (11%)	<0.001	0.0446

Table 1 continued.

Characteristic	Non-IST cohort N=17,566*	IST cohort N=17,566*	p†	Standardised mean difference
Categorised index year (p=0.002)				
2001–<2003	762 (4.3%)	851 (4.8%)	N/A	0.0236
2003–<2006	1,247 (7.1%)	1,352 (7.7%)	N/A	0.0224
2006–<2009	2,066 (12.0%)	2,114 (12.0%)	N/A	0.0084
2009–<2012	2,847 (16.0%)	2,925 (17.0%)	N/A	0.0119
2012–<2015	3,588 (20.0%)	3,622 (21.0%)	N/A	0.0048
2015–<2018	4,183 (24.0%)	4,016 (23.0%)	N/A	0.0226
2018 onwards	2,873 (16.0%)	2,686 (15.0%)	N/A	0.0296
Pharmacological information				
Time on topical steroids	2,026 (921, 3,597)	3,533 (1,985, 5,586)	<0.001	N/A
Not on topical steroids	127	1,454	N/A	N/A
Tacrolimus prescription	946 (5.4%)	794 (4.5%)	<0.001	0.0417
Methotrexate	0 (0%)	9,646 (55%)	<0.001	N/A
Ciclosporin	0 (0%)	3,496 (20%)	<0.001	N/A
Mycophenolate	0 (0%)	1,587 (9%)	<0.001	N/A
Azathioprine	0 (0%)	5,850 (33%)	<0.001	N/A
Types of IST (p<0.001)				
0	17,566 (100%)	0 (0%)	N/A	N/A
1	0 (0%)	14,980 (85.0%)	N/A	N/A
2	0 (0%)	2,201 (13.0%)	N/A	N/A
3	0 (0%)	343 (2.0%)	N/A	N/A
4	0 (0%)	42 (0.2%)	N/A	N/A
Number of topical corticosteroid prescriptions	2 (1, 6)	4 (1, 14)	<0.001	N/A
Patients prescribed potent topical corticosteroids	16,851 (96%)	13,561 (77%)	<0.001	N/A
Patients prescribed oral corticosteroids	6,985 (40%)	12,132 (69%)	<0.001	N/A
Mean prescriptions of IST/year	0.0 (0.0, 0.0)	2.7 (0.7, 7.2)	<0.001	N/A
Mean prescriptions of potent topical corticosteroids/year	0 (0, 0)	10 (2, 33)	<0.001	N/A
Patients without potent topical corticosteroid prescriptions	127	1,454	N/A	N/A
Median oral corticosteroid prescriptions/year	0.6 (0.3, 2.0)	1.0 (0.4, 3.1)	<0.001	N/A

Table 1 continued.

Characteristic	Non-IST cohort N=17,566*	IST cohort N=17,566*	p†	Standardised mean difference
Patients without oral corticosteroid prescriptions	10,581	5,434	N/A	N/A
IST prescriptions/year				
<3	0 (N/A)	9,231 (53%)	N/A	N/A
3–<6	0 (N/A)	2,959 (17%)	N/A	N/A
6–<9	0 (N/A)	2,182 (12%)	N/A	N/A
≥9	0 (N/A)	3,194 (18%)	N/A	N/A
None	17,566	0	N/A	N/A

*n (%); range; median (IQR).

†Pearson's Chi-squared test; Wilcoxon Rank Sum Test; Fisher's exact test.

‡Includes myasthenia gravis and multiple sclerosis.

AD: atopic dermatitis; IQR: interquartile range; IST: immune suppressive therapies; N/A not applicable.

PATIENT DEMOGRAPHICS

After applying the inclusion and exclusion criteria, 17,566 patients prescribed ISTs and 222,978 patients not prescribed ISTs were identified. The authors noted that 6% of patients in the non-IST cohort and 19% of patients in the IST cohort had a diagnostic code for psoriasis.

In the unmatched IST cohort, approximately 55% had been prescribed methotrexate, 20% had been prescribed ciclosporin, 33% were prescribed azathioprine, and 9% had been prescribed mycophenolate. The authors noted that 15% of patients had been prescribed more than one type of IST.

Following matching, the study population consisted of 17,566 patients in each cohort. The median ages of the matched treatment groups were 48 years and 49 years in the IST and non-IST cohorts, respectively.

Age, BMI, categorised BMI, smoking status, and categorised age were balanced. Matched characteristics of these patients are presented in Table 1. Standardised mean difference was lower than 0.05 across all covariates used within the matching, indicating sufficient balance. Forty-two percent of patients were male in the IST compared with 44% in the non-IST cohort. Patients with rheumatoid arthritis were higher in the IST cohort (19% versus 18%). Similarly, there was a higher proportion of patients with inflammatory bowel disease in the IST group (11.0% IST versus 9.7% non-IST). Fewer patients in the IST group had a code for tacrolimus prescription (4.5% versus 5.4%).

In the matched group, median follow-up was 5.7 years in the IST group, and 5.0 years in the non-IST group.

The exploratory analysis cohort of patients without psoriasis, inflammatory bowel disease, rheumatoid arthritis, myasthenia gravis, and multiple sclerosis consisted of 8,175 patients in each of the IST cohort and non-IST cohort.

For the additional analysis of patients with different mean prescriptions per year of IST, matched comparisons were made between patients with <3 prescriptions/year, 3–<6 prescriptions/year, 6–9 prescriptions/year, and ≥9 prescriptions/year, compared with patients with no prescriptions of IST.

PRIMARY ANALYSIS

Patients initiating IST therapy versus patients without IST therapy both had a rate of 2.1 cancers per 100 patient years.

Results of the Cox proportional hazards model indicated that the risk within patients prescribed IST were similarly likely to develop cancer, compared with the patients without a prescription of IST. After adjusting for cumulative potent steroids and oral corticosteroid prescription, the HR was 1.03 (95% CI: 0.93–1.14; p=0.56).

Exploratory Analysis

In the exploratory analysis, patients initiating IST therapy versus patients without IST therapy both had a rate of 1.8 cancers per 100 patient years.

The effect sizes in the additional analyses, where patients with conditions where ISTs are commonly prescribed were excluded, showed that there was no evidence that the risk of cancer in patients with ISTs was higher than in patients with no IST prescription, after adjustment for cumulative potent steroid and oral corticosteroid prescription. The adjusted HR was 1.01 (95% CI: 0.94–1.08; p=0.85).

Additional Dose–Response Analysis

For the additional analysis, a trend of increasing HR was seen for both the primary and exploratory populations with an increasing category of IST prescriptions/year, as illustrated in Figures 1 and 2. The distributions of the bins containing patients with a set number of prescriptions/year was chosen after visualisation of the distribution among the patients. Given that comparing predefined bins may result in selection bias, a logistic regression was carried out for the occurrence of a cancer code against the number of IST prescriptions/year, showing a unit increased risk of 0.103 per prescription/year.

A descriptive analysis was also taken of the locations of cancer for the non-IST cohort and the IST cohort. The most common cancer within the IST group was skin cancer, followed by breast, prostate, lung, then lymphoma. Within the non-IST group, colon cancer replaced lymphoma as the fifth most common cancer.

DISCUSSION

The results of this large historical cohort study indicated that prescription of one or more of methotrexate, ciclosporin, azathioprine, or mycophenolate in patients with moderate or severe AD in primary care was not associated with a greater risk of being coded for cancer, as compared with no IST prescription. However, there was evidence that higher prescription numbers per year was associated with an increased risk of cancer, both with prescriptions within defined categories, and on a prescription/year basis. Caution must be applied to this interpretation, as patients who are prescribed ISTs will have increased vigilance from both primary care and secondary care, with frequent blood tests compared to patients on topical therapies, and will be more likely to be diagnosed through monitoring of white cell count, liver function, and other markers for cancer. In addition, within the main analysis cohort, treatment decisions around other comorbidities requiring ISTs may not take into account a patient having AD.

Further study is required to explore the association of cancer risk to IST use. Lymphoma[37] and skin cancer have been associated with methotrexate[38] and azathioprine use, and examination of particular types of malignancy may show stronger signals. The findings by Mansfield et al.[12] identified lymphoma as a particular pathology associated with IST use. The authors noted that a descriptive ranked analysis showed that lymphoma displaced colon cancer as the fifth most common cancer code, but requires further analysis to determine significance. Additionally, differentiating between the different types of ISTs will provide further guidance to which may confer a higher malignancy risk. The authors also noted that in the baseline characterisation of patients, the prevalence of psoriasis was 6%. Since psoriasis and AD are considered as opposite poles of T helper activity, it would also be worth exploring the diagnostic pathway of these patients.

The authors also noted that the mean age at IST prescription may be considered to be higher than expected, from a disease that is traditionally considered to be a disease of childhood with some persistence until adulthood.[39] However, it has been reported that one in four adults report adult-onset disease, and AD typically follows a relapsing pattern, which can emerge in later adulthood.[40,41] The proportion of adults with moderate or severe AD is consistent with figures of 1–3% of total patients within CPRD. Another possibility for this higher age could be the influence of conditions such as rheumatoid arthritis or inflammatory bowel disease,

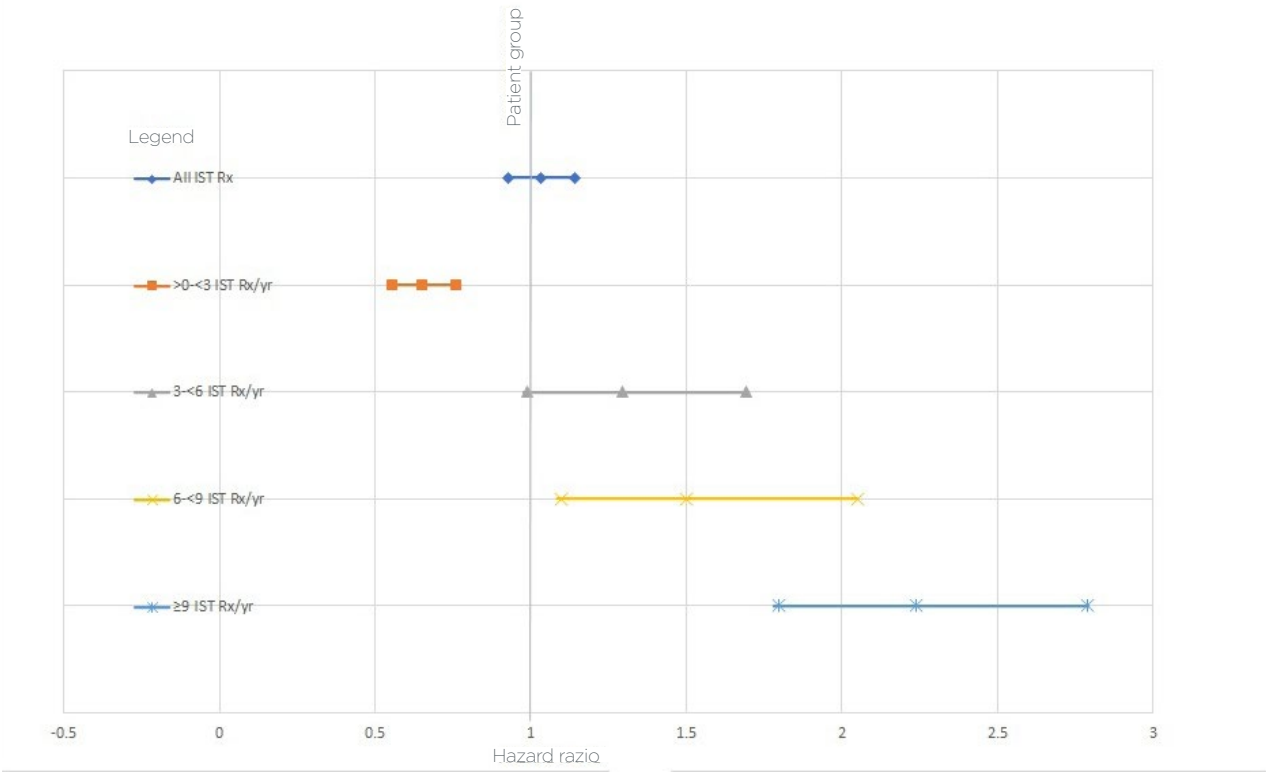

Figure 1: Hazard ratios of cancer for cohorts prescribed/not prescribed immune-suppressive therapies.
IST: immune-suppressive therapy; Rx: prescription; Yr: year

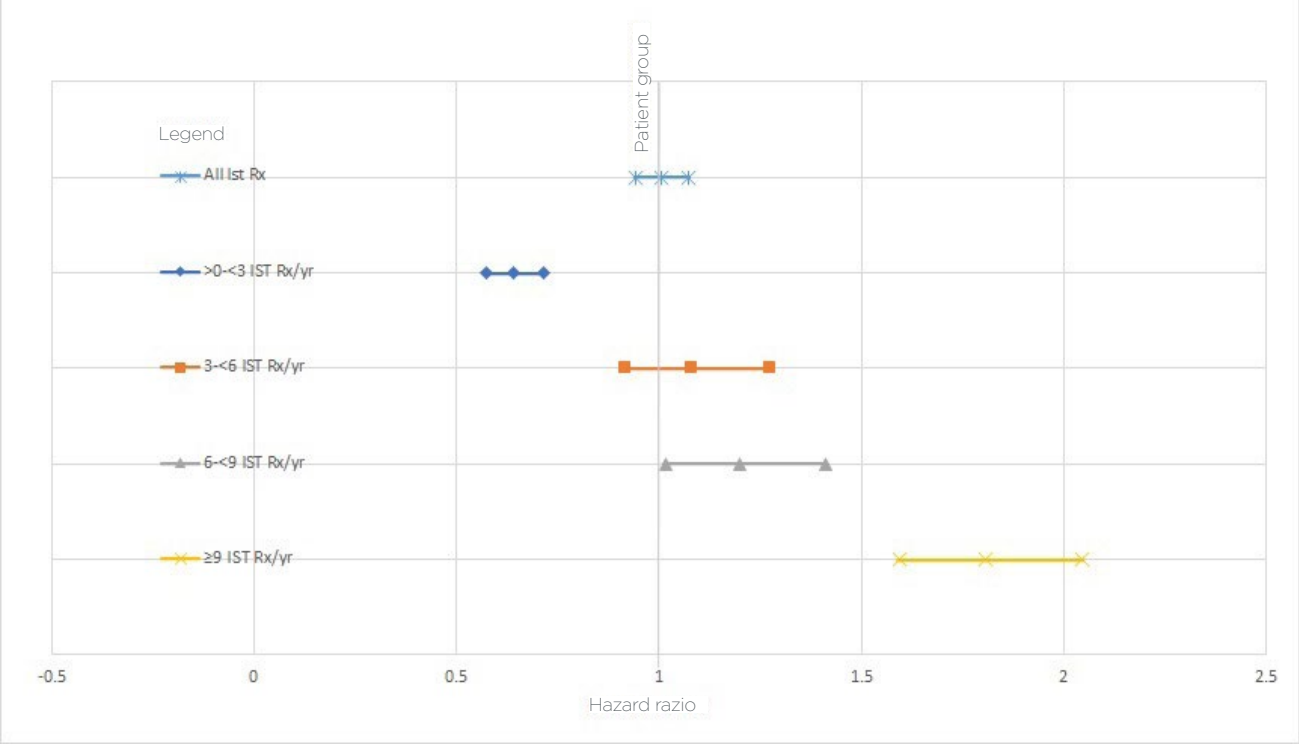

Figure 2: Hazard ratios of cancer for cohorts with restricted comorbidities, prescribed/not-prescribed immune-suppressive therapies.

commonly treated with ISTs. However, in the non-IST cohort, the median age of patients with AD was 44 years, at the time of potent, very potent, oral corticosteroid or tacrolimus prescription. The additional analysis examining patients without comorbidities still showed a median age of 43–44 years, indicating that AD presentation in adulthood was not uncommon.

STRENGTHS AND WEAKNESSES

The study has several important strengths relative to prior work. This study utilises a large primary care database covering 20% of the UK population, with a 5-year follow-up period exceeding the follow-up period of prior randomised control trials. Previous work examining malignancy considered patients without consideration of IST prescription.

The limitation of this study is inherent to its nature as an historical study. Despite extensive quality control and validation, records collected in CPRD were collected for routine clinical purposes. As such, some degree of inaccuracy and incompleteness may be present, and the inability to control for potential confounders and variables not recorded in the database.

The authors noted that secondary care prescribing is not captured in CPRD. Patients are initiated on IST by their dermatologists prior to primary care prescribing until the dose is stabilised, typically within 2–8 weeks of initiation, meaning it is likely that the index date for IST prescription is delayed, and time to cancer events underestimated. Other treatments in secondary care, such as ultraviolet light therapy, may also increase the risk of cancer, and are not well documented within CPRD.

The focus of the study was on patients who have relevant dermatitis codes at or after 15 years of age. Many patients with moderate or severe AD will present and may resolve prior to this age, and were not included in this study.

Amongst the practices where CPRD collect data, there are those who do not participate in shared care; thus, the authors did not capture any of their IST prescriptions, and they appeared within this study as part of the non-IST cohort.

As data on medication usage were not captured in CPRD, the current study was unable to control completely for adherence to prescribed ISTs.

Prescriptions for ISTs may not have been specifically for AD. The authors controlled for this by matching on comorbidities where ISTs are prescribed in primary care, and through the secondary analysis where these conditions were excluded.

ETHICS

This study complied with all local and international laws and regulations, including ICH E6 Guidelines for Good Clinical Practices, and the study protocol was approved by the Independent Scientific Advisory (ISAC) committee.

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Varicella Zoster Reactivation Following mRNA Vaccination: Two Case Reports and a Review of Cutaneous Adverse Events of COVID-19 Vaccines

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Abstract

Cutaneous reactions following the COVID-19 vaccination, in particular mRNA vaccines, have been increasingly reported in literature. The most common morphologies were delayed large local reactions, local injection site reactions, urticaria, and morbilliform reaction. The purpose of this report is to review the cutaneous manifestations of COVID-19 vaccines and to report two cases of COVID-19 mRNA vaccine-induced varicella zoster reactivation along with the possible pathogenesis.

These two cases are of an 80-year-old female patient with multiple comorbidities and a previously healthy 57-year-old male patient who experienced varicella zoster reactivation post-COVID-19 mRNA vaccine (Pfizer, New York City, New York, USA) following the first and second dose.

INTRODUCTION

Cutaneous reactions following COVID-19 vaccination, in particular mRNA vaccines, have been increasingly reported in literature. The most common side effects encountered during the worldwide administration of the various type of COVID-19 vaccinations ranged from mild local injection site reactions to more severe urticaria and morbilliform reactions. The less common side effects included varicella zoster reactivation post-vaccination.[1]

Here, the authors report two cases of varicella zoster reactivation after a COVID-19 mRNA vaccine.

CASE 1

An 80-year-old female patient with hypertension, Type 2 diabetes, hypothyroidism, dyslipidaemia, history of a gastrointestinal stromal tumour, and overactive bladder presented with 3 days history of a painful erythematous vesicular eruption on the left thigh. The patient reported that they began to experience generalised myalgias and fatigue 4 days after the first dose of their COVID-19 vaccine (Pfizer [New York City,

New York, USA] and BioNTech [Mainz, Germany] vaccine), and low-grade fever followed 1 day later by the eruption of multiple fluid-filled vesicles on their left thigh, which were painful and itchy. A review of system was negative. The patient was not on any immunosuppressive drugs, had no recent trauma or surgery, had no previous history of varicella or shingles, and was not exposed to anyone with varicella or zoster infection.

A physical exam revealed the presence of a cluster of clear, pus-filled vesicles that were surrounded by erythema and covered an area on the left thigh corresponding to the L2 and L3 dermatomes in a linear distribution (Figure 1A).

A clinical diagnosis of herpes zoster (HZ) was made, and the patient was started on valacyclovir 500 mg, two tablets thrice a day for 7 days, with daily antiseptic wash and painkillers.

The patient presented for follow-up after 1 week with slight improvement; some of the vesicles were dried out while others were still filled with pus (Figure 1B). The patient was started empirically on cefadroxil 500 mg, two tablets twice daily for 3 days, and then one tablet twice daily for 6 days. Tzanck smear (Figure 2), PCR, and bacterial cultures were completed from the fluid- and pus-filled vesicles. The smear results were positive for Tzanck cells and varicella zoster virus (VZV) was detected on PCR, while the bacteriological cultures were negative.

Follow-up after 6 days showed an improvement of the symptoms, with the vesicles crusting.

The patient was advised to delay the second dose of the vaccine until full resolution of the rash.

CASE 2

A 57-year-old male patient, with no known medical conditions, presented with a 5-day history of a vesicular eruption on the left thoracic area along the T3–T4 dermatomes.

The patient reported that 2 days after receiving their second dose of the COVID-19 vaccine (Pfizer Inc. and BioNTech vaccine), they noticed the appearance of multiple clusters of vesicular lesions on their chest in a linear distribution over T2–T4 dermatomes (Figure 3), which was associated with a burning pain and stinging sensation. The patient denied the presence of any associated symptoms. They were not on any immunosuppressive drugs, had no recent trauma or surgery, had no previous history of varicella or shingles infection, and were not exposed to anyone with varicella or zoster infection. After the appearance of the vesicular eruption on the chest area, the patient followed up with their physician and a clinical diagnosis of HZ was made. The patient was started on valacyclovir 500 mg, two tablets thrice a day for 7 days, with a daily antiseptic wash.

On follow-up 7 days later, the patient reported that the lesions had crusted over, and the pain associated with the rash was substantially improved.

DISCUSSION

The cutaneous manifestations of COVID-19 are increasingly being reported in the literature.[2]

The VZV is responsible for the development of varicella and shingles. It is transmitted either by the airborne route or through direct contact with the vesicles.[3]

Following primary infection, the virus remains latent in the sensory dorsal root ganglion. Reactivation of the virus can be triggered by various factors, including stress, old age, immunocompromised status, as well as various immunosuppressive drugs.[3]

After the introduction of COVID-19 vaccines and the rapid spread of vaccination campaigns, light is shed on the cutaneous manifestations associated with the COVID-19 vaccines. To date, three main types of vaccines are being utilised in the world for COVID-19 and these include mRNA-based vaccines: mRNA-1273 (Moderna, Cambridge, Massachusetts, USA) and BNT162b2 (Pfizer and BioNTech); adenoviral vector vaccines: ChAdOx1 nCOV-19 (Oxford–AstraZeneca, Cambridge, UK), Sputnik V or Gam-COVID-Vac (Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia), and Ad26.COV2.S (Janssen, Beerse, Belgium); and inactivated whole virus vaccines: BBIBP-CorV (Sinopharm, Beijing, China) and CoronaVac (Sinovac, Beijing, China).[4]

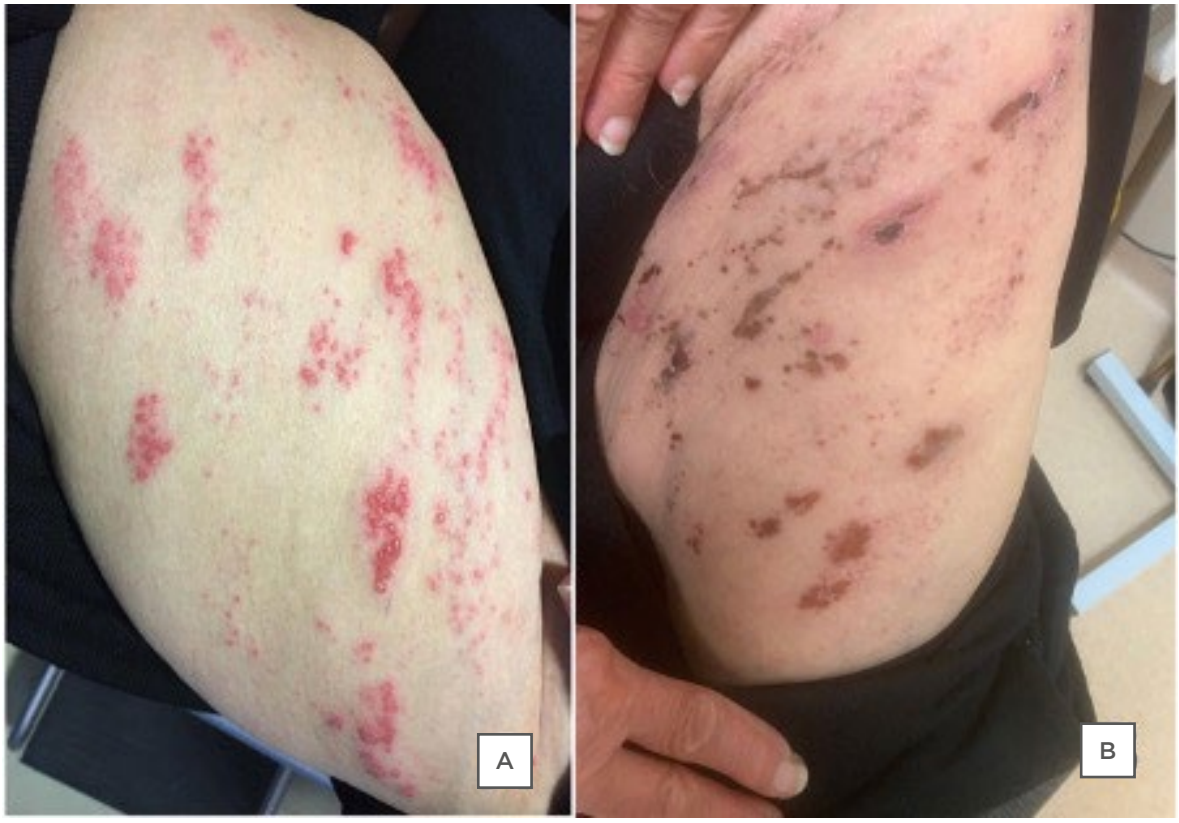

Figure 1: Fluid-filled vesicles on the left thigh (L2–L3 dermatomes) of an 80-year-old female as a result of varicella zoster.

A) Shows the patient before and B) shows the patient after their treatment.

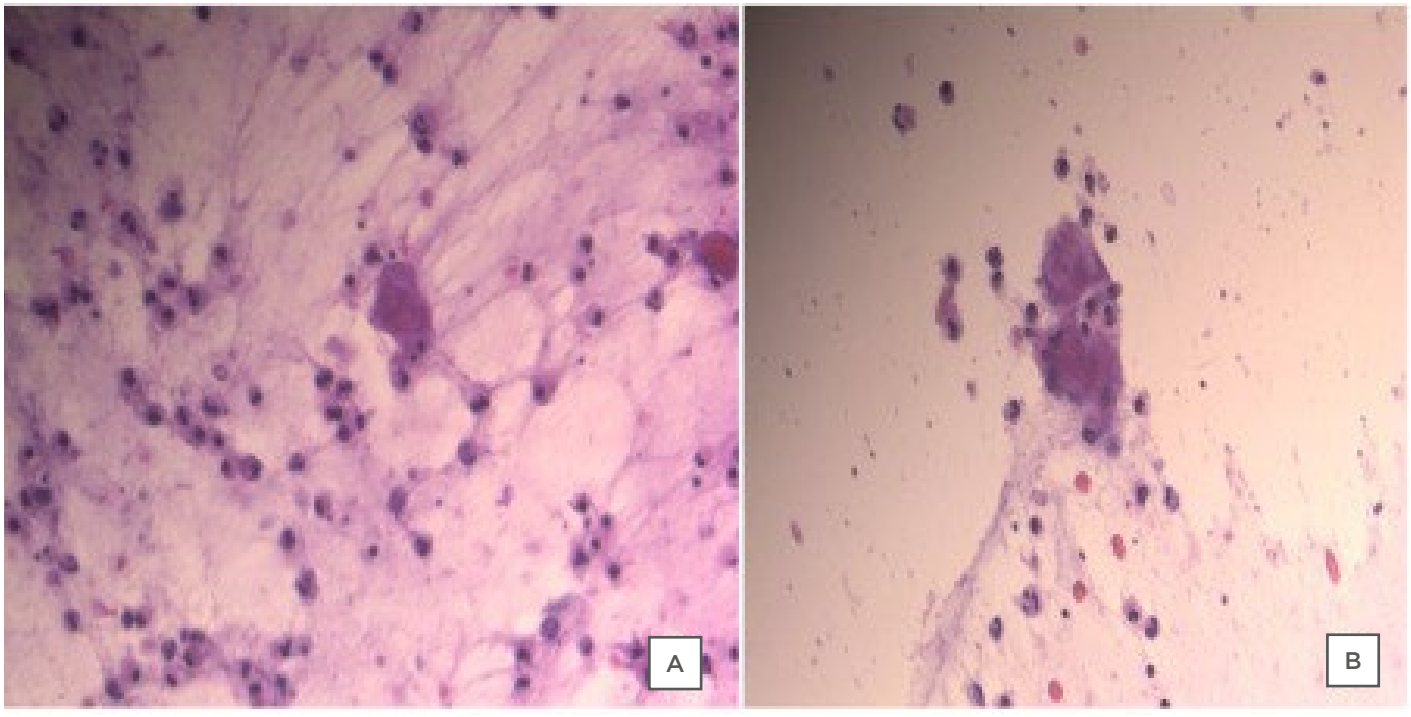

Figure 2: Tzanck smear from vesicles of a female patient, showing the presence of multinucleated giant cells.

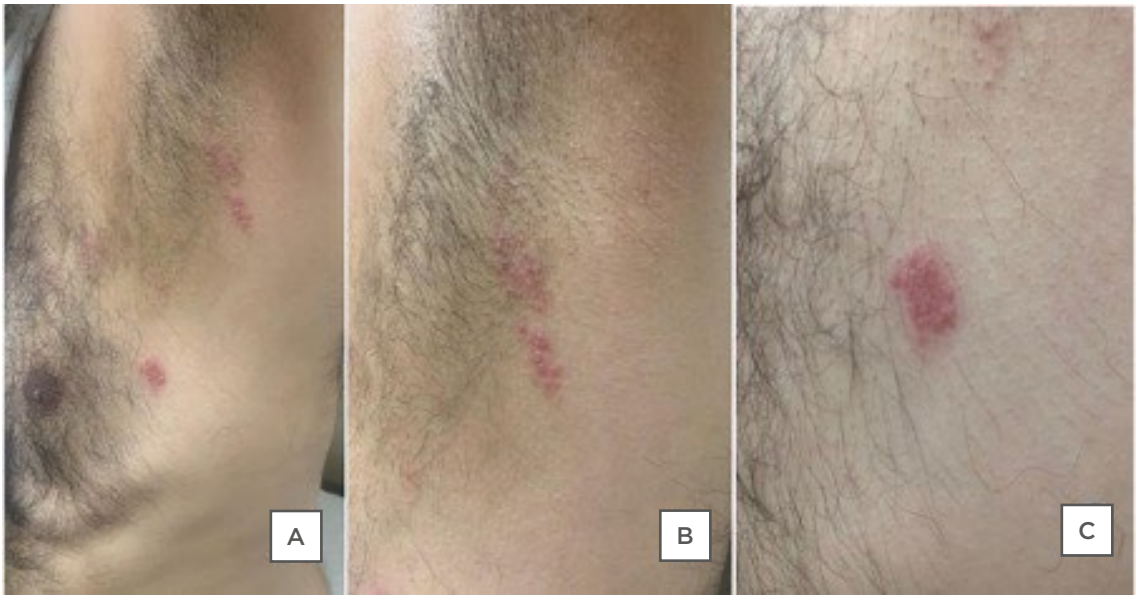

Figure 3: Multiple vesicular lesions on the chest of 57-year-old male.

Injection site reactions were the most frequent side effects described in all three types of vaccines. They were due to non-specific stimulation of inflammation. These reactions ranged from mild injection site reactions, redness, and swelling, to injection site urticaria and maculo-papular dermatitis.[4] The underlying mechanism causing vaccine-related reactions are thought to be a Type 1 IgE-mediated hypersensitivity reaction to various excipients of the vaccines.[4] Other than the acute injection site reaction, a delayed Type 4 hypersensitivity reaction can also occur with the vaccines. This is seen with the mRNA vaccines, where erythema, tenderness, and induration appear after a week on average post-vaccine. Both the acute and delayed hypersensitivity reactions are non-severe and can be managed symptomatically.[4] Anaphylactic reactions are the more serious adverse events that can be associated with the vaccines. In the case of the mRNA vaccines, such reactions are induced by polyethylene glycol and macrogol.[4] For the other types of vaccines, including the AstraZeneca and Janssen ones, cutaneous reactions have linked them with the possible vaccine-induced prothrombotic immune thrombocytopenia. Vaccine-induced prothrombotic immune thrombocytopenia can manifest with petechial eruption or erythema along with the associated systemic symptoms involving the nervous, cardiovascular, and the gastrointestinal systems.[4] Other reported skin findings associated with the AstraZeneca vaccine include injection site reaction, pruritic erythematous maculopapular eruption, and one case of cellulitis.[4]

As for the Russian vaccine, Sputnik V, an adenoviral-based two-part vaccine, reactions ranged from mild injection site reactions to hives in one patient. Other reactions included petechial rash, extremity abscess, acneiform dermatitis, eczema, and alopecia.[4]

The Chinese vaccine, CoronaVac, an inactivated vaccine, mostly showed injection site reactions. Other rare events include non-infectious gingivitis, buccal ulcerations, oral herpes simplex virus, and lymphadenopathy.[4]

A few reports emerged linking the COVID-19 infection to HZ reactivation in adults, some of whom presented with severe necrotic zoster.[5-8] On the other hand, there are very scarce reports of HZ reactivation post-vaccine, despite the high rate of vaccination worldwide. Seven cases were reported after an mRNA vaccine (one case report and six patients in an observational study), temporally linking the COVID-19 vaccine with the development of HZ.[9,10]

To date, no clear mechanism has been identified for the development of HZ post-COVID-19 infection or vaccination. The proposed mechanism underlying reactivation of HZ in patients infected with COVID-19 is secondary to a drastic decrease in the number of lymphocytes, mainly with reduced numbers of cluster of differentiation 4 positive T cells, cluster of differentiation 9 positive T cells, B cells, and natural killer cells, as well as eosinophils and monocytes.[11]

Concerning the link between HZ reactivation and COVID vaccine, van Dam et al.[12] also reported lymphopenia to occur in a dose-dependent manner in vaccinated patients, reaching its peak a few days following vaccination, then progressively returning to normal 6–8 days post-vaccination; it has therefore been proposed that, during this window, a VZV reactivation could take place. Other factors that might be implicated include both physical and psychological stress.[12] Other plausible mechanisms that have been suggested are attributed to immune dysregulation.[10] According to Furer et al.,[9] mRNA COVID-19 vaccines stimulate the innate immunity through toll-like receptors, which are essential for reactivation of herpes viruses. Several studies have reported that toll-like receptor reactivation can function as a signal that triggers lytic replication of viral particles within the host cells and, thus, cause the reactivation of the virus.[13] This theory of immune dysregulation has been observed and speculated with VZV reactivation after vaccines such as hepatitis A, hepatitis B, and influenza, with the exact mechanism not clearly elucidated.[14]

Multiple risk factors have been implicated in the reactivation of HZ infection, including older age, immune compromise, and stress.[3] In the authors' cases, the only risk factor was older age in the first case. The absence of immunosuppression or a clear trigger factor, as well as the temporal association of the symptoms and vaccine receipt, allowed the authors to presume the presence of a connection between virus reactivation and the vaccine in both cases.

As for whether the authors' patients should receive the second dose of the vaccine or not, this remains a subject of debate. In the literature, 43% of patients who received the mRNA vaccine experienced cutaneous adverse effects after the second dose, such as delayed large local reactions, local injection site reactions, morbilliform rash, and urticaria. Those cutaneous reactions were reported to be similar to the initial reaction after the first dose of vaccine in 28%, milder in 28%, and more robust in 45% of these patients.[1] As HZ reactivation was not the consequence of a direct immune-mediated reaction to the vaccine in these cases, the authors encouraged the patients to take the second dose; however, they refused to do so.

CONCLUSION

In conclusion, with the rapid administration of COVID-19 vaccines worldwide, recognition of its possible dermatological side effects should be recognised. The authors' cases represent one of the possible cutaneous manifestations associated with the COVID-19 vaccine, in particular the mRNA vaccine.

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Diabetic Ketoacidosis Precipitated by COVID-19: A Case Report

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Abstract

Introduction: Diabetic emergencies such as diabetic ketoacidosis (DKA) are life-threatening complications, often precipitated by infections or illnesses such as COVID-19.

Case presentation: A 55-year-old African American female presented to their primary care physician, complaining of fatigue, dehydration, decreased appetite, hypersomnia, and sudden weight loss, and a past medical history of Type 2 diabetes. They had a glucose level of >15 mmol/L and ketone level of >16 mmol/L; they were immediately sent to the emergency department for assessment of DKA. There, the patient tested positive for COVID-19. They had a glucose level of 361 mg/dL, a pH of 7.11, a bicarbonate level of 10 mEq/L, a sodium level of 125 mEq/L, a potassium level of 3.9 mEq/L, a chloride level of 95 mEq/L, an anion gap of 20, and a positive ketone level. Over the next few days, the patient's condition got worse; their chest CT scan showed ground-glass opacities with consolidations in the middle and inferior lobes of the lungs bilaterally, along with interlobular septal thickening, which are consistent with an atypical infection, respiratory distress, and pneumonia. The patient was on intravenous fluids, insulin therapy and empirical antibiotics for the next few weeks, and eventually recovered.

Discussion: Factors precipitating DKA in patients with diabetes in the setting of COVID-19 are: the increased secretions of stress hormones that counter the effects of insulin and increase blood glucose levels, and the ways in which severe acute respiratory syndrome coronavirus 2 interacts with human cells, leading to pancreatic islet cell damage.

Conclusion: Diabetes and COVID-19 intensify each other's complications in patients diagnosed with both.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak began in China in December 2019, and the World Health Organization (WHO) declared COVID-19 as a pandemic in March 2020.[1] Since then, there have been 146,054,107 positive cases and 3,092,410 deaths globally to date in April 2021.[2] Recent COVID-19 studies have shown that individuals above the age of 60, or with underlying health conditions such as obesity, diabetes, chronic kidney disease, cardiovascular disease, and cancer, are at a higher risk of severe illness and mortality.[3] A study conducted in New York, USA, showed that the prevalence of diabetes was higher in patients with COVID-19 who were hospitalised (34.7%) versus recovering from home (9.7%).[4] Another study based in England, UK, revealed that among patients with COVID-19 who have passed away at hospital, 32% had Type 2 diabetes and a 2.03 times higher rate of mortality, and 1.5% had Type 1 diabetes and a 3.5 times higher rate of mortality.[5] Another study conducted in China showed that the prevalence of diabetes amongst the general population was 8.2%, and increased to 34.6% in patients with COVID-19.[6] Diabetic emergencies like diabetic ketoacidosis (DKA) are life-threatening complications, often precipitated by infections or illnesses.[7] Currently, there is limited data on the correlation between COVID-19 and DKA. The authors report a case of a 55-year-old African American female with COVID-19, who developed DKA.

CASE PRESENTATION

A 55-year-old African American female presented to her primary care physician (PCP), complaining of fatigue, dehydration, decreased appetite, hypersomnia, and sudden weight loss. They denied any fever, cough, sore throat, shortness of breath, headache, runny nose, vomiting, diarrhoea, and loss of taste or smell. Their past medical history included schizophrenia, Type 2 diabetes, hyperlipidaemia, and vitamin D and zinc deficiency. They were taking risperidone 25 mg intramuscular Q14, metformin 1,000 mg orally twice daily (PO BID), empagliflozin 25 mg once each morning (PO QAM), insulin glargine 25 units by single-carrier quadrature amplitude modulation rosuvastatin 40 mg orally at bedtime, vitamin D 2,000 units PO QAM, zinc gluconate 50 mg once daily (PO QD), and acetaminophen 325 mg every 4 hours, as needed.

Examination by the PCP showed that the patient's vitals were stable. They had a blood pressure of 132/82 mmHg, a heart rate (HR) of 82 bpm, a respiratory rate of 16 breaths/min, and an oxygen saturation of 98%. The urine dipstick test showed a glucose level of >15 mmol/L and ketone level of >16 mmol/L. The patient was immediately sent to the emergency department (ED) for assessment of DKA. Upon arrival at the ED, the patient's vitals remained stable. They had a blood pressure of 138/82 mmHg, an HR of 80 bpm, a respiratory rate of 16 breaths/min, and an oxygen saturation of 98%. A reverse transcription-PCR test was conducted as part of routine COVID-19 testing, and the patient tested positive for COVID-19. They were immediately moved into isolation, where further work-up was completed. Blood work and urinalysis were consistent with DKA; the former showed a glucose level of 361 mg/dL, a pH of 7.11, a bicarbonate level of 10 mEq/L, a sodium level of 125 mEq/L, a potassium level of 3.9 mEq/L, a chloride level of 95 mEq/L, an anion gap of 20, and the latter was positive for ketones. The patient was started on intravenous (IV) fluids, insulin therapy, and empirical antibiotics for the management of DKA and COVID-19. They were then transferred to the intensive care unit (ICU) for further care.

Over the next 3 days, the patient's condition worsened. The ECG showed sinus tachycardia, probable left atrial enlargement, and borderline T-wave abnormalities; the patient was persistently tachycardic with HRs ranging from 100–140 bpm. The CT scan without IV contrast showed ground-glass opacities with consolidations in the middle and inferior lobes of the lungs bilaterally, along with interlobular septal thickening, which are consistent with an atypical infection, respiratory distress, and pneumonia. The peripheral doppler ultrasound ruled out deep vein thrombosis and the CT pulmonary angiogram ruled out pulmonary embolism. The patient had nasogastric and endotracheal intubation. They continued on IV fluids, insulin therapy, and empirical antibiotics.

Eventually, the patient's DKA and COVID-19 resolved with standard management, and they were finally discharged home 1 month later. Their

discharge prescription included risperidone 25 mg intramuscular Q14, metformin 1,000 mg PO BID, linagliptin 5 mg PO QAM (new medication), insulin glargine 25 units by single-carrier quadrature amplitude modulation, rosuvastatin 20 mg orally each bedtime (lowered dosage), ezetimibe 10 mg PO QAM (new medication), bisoprolol 5 mg PO QAM (new medication), vitamin D 2,000 units PO QAM, zinc gluconate 50 mg PO QD, multivitamin with iron 1 tablet PO BID (new medication), and acetylsalicylic acid 81 mg PO QD (new medication). The patient was referred to a diabetes educator and an endocrinologist for further follow-up.

The day after discharge from the ICU, the patient visited their PCP, who reviewed their ED and ICU notes, discharge prescription, and referrals. The patient was feeling better and was not in any distress. The PCP noted that the patient had a case of DKA precipitated by COVID-19.

DISCUSSION

It has been established that patients with diabetes are at increased risk of COVID-19 infection, ICU admission, and mortality.[3-6] Multiple explanations have been postulated for this predisposition. Dysregulated immune responses in patients with diabetes lead to a higher susceptibility to infectious diseases.[8] Furthermore, *in vitro* and animal studies show that hyperglycaemia facilitates local viral replication in the lungs and impairs antiviral immune responses.[9,10] Conversely, fasting blood glucose levels are higher in patients with COVID-19. Additionally, higher levels of IL-6 seen in diabetes predispose these patients to a greater risk of a cytokine storm, which may lead to critical illness.[8] Thus, diabetes and COVID-19 intensify each other's complications in patients diagnosed with both.

The patient presented in this case was diagnosed with DKA that was likely precipitated by COVID-19. Although the patient did not present with typical COVID-19 symptoms, their reverse transcription-PCR test results prove the diagnosis. In addition, their chest CT scan results are consistent with typical COVID-19 pneumonia appearance, with a sensitivity of 73.5% and specificity of 82.8%, as per the Radiological Society of North America (RSNA).[11] A study from China highlighted 58 COVID-19 cases characterised by positive chest CT scanning in which the patients were asymptomatic.[12] Furthermore, the absence of other possible triggers for the development of DKA is suggestive that it was likely provoked by COVID-19.

DKA is a lethal complication of diabetes characterised by anion gap metabolic acidosis and the accumulation of ketone bodies due to uncontrolled blood glucose levels. This typically occurs in Type 1 diabetes but has also been seen in Type 2 diabetes, especially in the presence of an infection. The resistance or deficiency of insulin increases blood glucose levels to a range of 350 mg/dL (19.4 mmol/L) to 450 mg/dL (27.8 mmol/L), and up to 800 mg/dL (44 mmol/L).[13] Clinically, the patient will present with decreased alertness, nausea, vomiting, dehydration, Kussmaul breathing, and abdominal pain. The patient's blood glucose level on admission to the ED was 361 mg/dL, which was consistent with DKA. Furthermore, blood work showed a low pH, low bicarbonate level, and an elevated anion gap metabolic acidosis. The inability to use glucose due to insulin resistance and deficiency leads to enhanced lipolysis, and the primary source of energy shifts from glucose breakdown to fatty acid breakdown. Ultimately, there is an abundance of acetyl coenzyme A, which is converted to acetoacetic acid, and further reduced to β-hydroxybutyric acid. Both of these ketone acids contribute to anion gap metabolic acidosis and can be detected on urinalysis, as seen in this patient.

Since the beginning of the COVID-19 pandemic to date, some cases of DKA precipitated by COVID-19 have been reported. Multiple explanations to this pathophysiology have been proposed. One of the most common precipitating factors of DKA is infections or illnesses.[14] They cause increased secretions of stress hormones such as catecholamines and cortisol, which counter the effects of insulin and increase blood glucose levels.[15] Some studies have shown that patients with COVID-19 have significantly higher levels of cortisol, which may induce DKA if they are also diabetic.[16] Another factor precipitating DKA in patients with diabetes may be the ways in which SARS-CoV-2 interacts with human cells. The spike protein receptor binding domain on SARS-CoV-2 binds to the angiotensin converting

enzyme 2 receptors in humans; the host cell then internalises the receptor along with the bound virion, allowing it to become effective and cause cellular damage.[17,18] Angiotensin converting enzyme 2 receptors are found on multiple organs throughout the body, including the pancreatic islet cells; as a result, SARS-CoV-2 binds to these pancreatic islet cells, leading to insulinopenia and increased risk for DKA.[19]

CONCLUSION

The 55-year-old patient with a medical history of Type 2 diabetes developed DKA in the setting of COVID-19. Patients with diabetes are known to have an increased severity of COVID-19 infection and COVID-19 infection is known to precipitate DKA. Therefore, diabetes and COVID-19 intensify each other's complications in patients diagnosed with both.

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Total Plasma Exchange for Hypertriglyceridaemia Complicated by Acute Pancreatitis: A Case Report

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Abstract

Introduction: Hypertriglyceridaemia (HTG) is common and often precipitates into acute pancreatitis. Early diagnosis of HTG pancreatitis (HTGP) is essential for appropriate management to avoid recurrence of pancreatitis. Plasmapheresis was suggested as treatment modality to decline triglyceride levels, especially in critical patients with multiorgan failure. Few randomised studies are recorded regarding the value of plasmapheresis over classical therapy.

Objective: To evaluate the value of plasmapheresis in patients with HTGP with worrisome signs as fever, tachycardia, high inflammatory markers, and pancreatitis.

Methods: Clinical course and laboratory markers status after total plasma exchange (TPE) for HTG that is not responding to initial, traditional therapy by insulin infusion was reported.

Results: The authors' patient had an initial triglyceride level of 30 mmol/L, with a worsening clinical condition and acute pancreatitis. After TPE, there was a significant decline in their triglyceride serum levels (53%) after the first session, leading to marvellous recovery.

Conclusion: The authors suggest treatment with TPE for systemic inflammation and HTGP-induced multiorgan failure. However, further research is necessary.

INTRODUCTION

Hypertriglyceridaemia pancreatitis (HGTP) accounts for 1–35% of acute pancreatitis (AP) cases.[1] Acute pancreatitis is an acute inflammatory process of the pancreas. Hypertriglyceridaemia (HTG) is considered the third most common aetiology of AP, following gallstones and alcohol. It is responsible for 1–4% of AP cases and it seems to be more serious than AP caused by other aetiologies.[2]

The possibility of AP progressively increases when triglyceride levels are >500 mg/dL (5.6 mmol/L) and with levels over 1,000 mg/dL (11.3 mmol/L).[3]

Management of patients includes supportive treatment for AP and reducing triglyceride levels to less than 500 mg/dL (5.6 mmol/L), with the goal of preventing necrotising pancreatitis and organ failure.[4] The approach to initial therapy depends on the severity and scoring of AP and the presence of worrisome clinical signs.[5] In patients with severe HTG, it may be beneficial to lower the triglyceride (TG) levels without delay. Plasmapheresis has been shown in some cases to be effective in reducing the TG levels in patients with severe HTG.[6] This can be achieved by the rapid removal of TGs from plasma, leading to the reduction of free fatty acids, which can cause further damage to the pancreas.[7] Here, the authors present a case of severe HTG with AP, for which the trial of therapeutic plasma exchange modality was reported.

CASE REPORT

A 24-year-old female with no significant medical history nor history of alcohol intake presented at the authors' hospital with a complaint of a pain in her abdomen (pain scale: 8) and after vomiting for 2 days. They were diagnosed before referral as HTG, which was complicated by AP. They were transferred to the authors' facility for other intervention for HTG as they were not improving on insulin infusion after 48 hours.

On physical examination, the patient was well-oriented (Glasgow Coma Scale [GCS]: 15/15) and their blood pressure was within normal range; however, they had a high-grade fever, tachycardia, and tachypnoea. Their BMI was 20 kg/m^2. An abdominal examination showed diffuse abdominal tenderness but no guarding or rebound tenderness, while an abdominal ultrasound showed an enlarged liver and the bulky hypoechoic pancreas of AP. A laboratory investigation showed evidence of AP due to severe HTG as the patient had an elevated lipase value of 889 units/L and TG level of 2,654.87 mg/dL (30 mmol/L). There were no previous interventions that were relevant to the patient's condition, nor genetic history of familial HTG. An abdominal CT scan showed pancreatic oedema, suggesting AP. There was a small focal hypodense area at the lower pole of the spleen and right hepatic lobe (segments V and VI) due to infarction, mild pelvic ascites, and mild hepatomegaly.

On the first day of hospital admission, the patient was treated with aggressive hydration with lactated Ringer's solution; however, due to their worsened clinical condition and marked elevation of TG (30 mmol/L) with fever and leucocytosis, an alternative treatment was discussed with the patient on the second day of hospital admission. The patient consented to therapeutic plasma exchange as a therapeutic intervention.

The patient underwent a total plasma exchange (TPE). During each TPE, 1.5% plasma volume was exchanged and replaced with a 5.0% albumin, which added to a normal saline solution alternate with fresh frozen plasma. Anticoagulation during TPE was achieved with a low-molecular-weight heparin. A review of relevant literature showed many small studies that highlighted the usefulness of early plasmapheresis in this scenario.

A femoral venous catheter was inserted and TPE started within 24 hours of admission. Following the first plasma exchange, the patient's TGs decreased by 53% to 16 mmol/L (Figure 1).

On the third day of hospital admission, the second session of TPE was completed and decreased TG to 5.65 mmol/L. The patient's condition improved significantly over the following day: the abdominal pain decreased, and they started feeding orally. A threshold was set for apheresis if TGs were found to be >5.6 mmol/L and rising progressively; however, further sessions were not required.

On the sixth day of hospital admission, the patient started a fibrate therapy and omega-3 fatty acids. A decline in TGs was recorded during their hospital stay. A follow-up CT of the abdomen showed enhancing pseudo-capsulated peripancreatic fluid (12x5 cm), which was in the process of forming into a pseudo cyst. The patient was discharged on the eighth day, with a TG stationary level of 5.8 mmol/L and asymptomatic. The patient followed up on the phone and was doing fine.

DISCUSSION

TG level values of >1,000 mg/dL (11.3 mmol/L) occur in fewer than 1 in 5,000 people.[8] Elevated TGs have been reported in patients with underlying genetic predisposition to abnormal lipoprotein metabolism such as familial combined

Figure 1: Graphical representation of the biochemical trend over hospital admission, showing triglyceride level.

hyperlipidaemia, familial HTG, or other rare abnormalities, precipitating by secondary factors such as excessive alcohol ingestion, insulin resistance, diabetes, nephrotic or metabolic syndrome, and drugs. Uncommonly, a patient with familial HTG with no secondary precipitating factors may also be seen in clinical practice.[9]

The authors could not find any secondary factors in their patient's history, so it prompted clinical suspicion for a genetic predisposition. Unfortunately, the authors could not complete genetic study.

Pancreatitis occurs as the result of analysis of TGs into fatty acids by pancreatic enzyme lipases, which leak out of the acinar cells in the vascular bed of the pancreas. This is the probable reason for the accumulation of free fatty acids at high concentrations. Free fatty acids are toxic and they can destroy the acinar cells and capillary endothelium.[10] Furthermore, the marked elevation of chylomicrons increase the blood viscosity in the veins and the impaired pancreatic blood flow leads to ischaemia and acidosis in the pancreas.[11] Free fatty acids in acidosis activate trypsinogen and initiate acute oedema and necrosis of pancreases.[12] The severity of pancreatitis in patients with HTG is the effect of the inflammatory process caused by pancreatitis combined with lipotoxicity from TG hydrolysis.

Severe HTG and high lipase levels lead to high fatty acid levels and can be complicated by systemic inflammation and multiorgan failure from AP.[10] The initial treatment of a patient consists of supportive therapy, including fluid resuscitation and pain control that is followed by intravenous (IV) insulin as an infusion therapy, which was found effective in patients in some cases with marked HTGP.[13-15]

Therapeutic plasmapheresis was suggested and utilised as a possible therapy for HTG.[6,16] Evidence to support the value of plasmapheresis in patients with HTGP is from limited small observational studies; large randomised trials are absent.[6] One session of plasmapheresis was recorded to decrease TG levels by 50–80%;[16] therefore, plasmapheresis may be used in patients with HTGP with alarming parameters, including hypocalcaemia and evidence of systemic inflammation, which involves two or more of the following symptoms: temperature: >38.5 °C; heart rate: >90 beats/min; respiratory rate: >20 breaths/min or partial pressure of carbon dioxide: <32 mmHg; white blood cell count: >12,000 cells/mL or <4,000 cells/mL.[6]

The authors' case had fever 39 °C; a tachycardia heart rate of 140 beats/min; leucocytosis; neutrophilia; high inflammatory markers; mild hypocalcaemia; and a high serum lipase that was more than double the normal reference range, which indicated severe pancreatitis. Therefore, the authors started the patient on early TPE. In the authors' case, the decline in TG level was recorded at 53% following the first session, which suggests that plasmapheresis can be a helpful tool to rapidly and significantly reduce TG levels. Although there are no guidelines for management of HTG-AP, there is a literature review that showed that decreasing TG levels to <500 mg/dL (5.6 mmol/L) can prevent the evolvement of acute pancreatitis.[17]

The beneficial effects of plasmapheresis are the removal of TGs, active enzymes, and inflammatory plasma mediators, as well as the supplementation of free fatty acids, apolipoproteins, and lipoprotein lipase from a healthy donor plasma. However, accessibility issues in many centres and its high cost limits the use of plasmapheresis. The most recently established guidelines prepared by the American Society for Apheresis (ASFA) notes that HTG-induced AP as a Category III indication (in the case of disorders where the optimum role of apheresis is not established, individualised decision is necessary).[18] Fibrates, niacin, and omega-3 fatty acids are the cornerstone of pharmacological therapy.[17] Medical therapy, dietary modification, and dietitian counselling are for maintaining goal TG levels.[19]

CONCLUSION

HTG-induced AP treatment involves the restriction of oral intake; IV hydration; administration of pain medication; an insulin infusion with glucose treatment; and possible TPE. A lipid-free diet and drugs (fenofibrate, gemfibrozil, and omega-3 fatty acids) are utilised to reduce HTG. TPE could be a beneficial treatment modality for patients with HTG-induced AP. Appropriate candidates for apheresis could be patients with severe pancreatitis, who continue to have TG levels of >1,000 mg/dL after the 48 hours of IV insulin.

Further studies that compare the apheresis plus conservative treatment and only conservative treatment in patients with HTG-induced AP patients are required.

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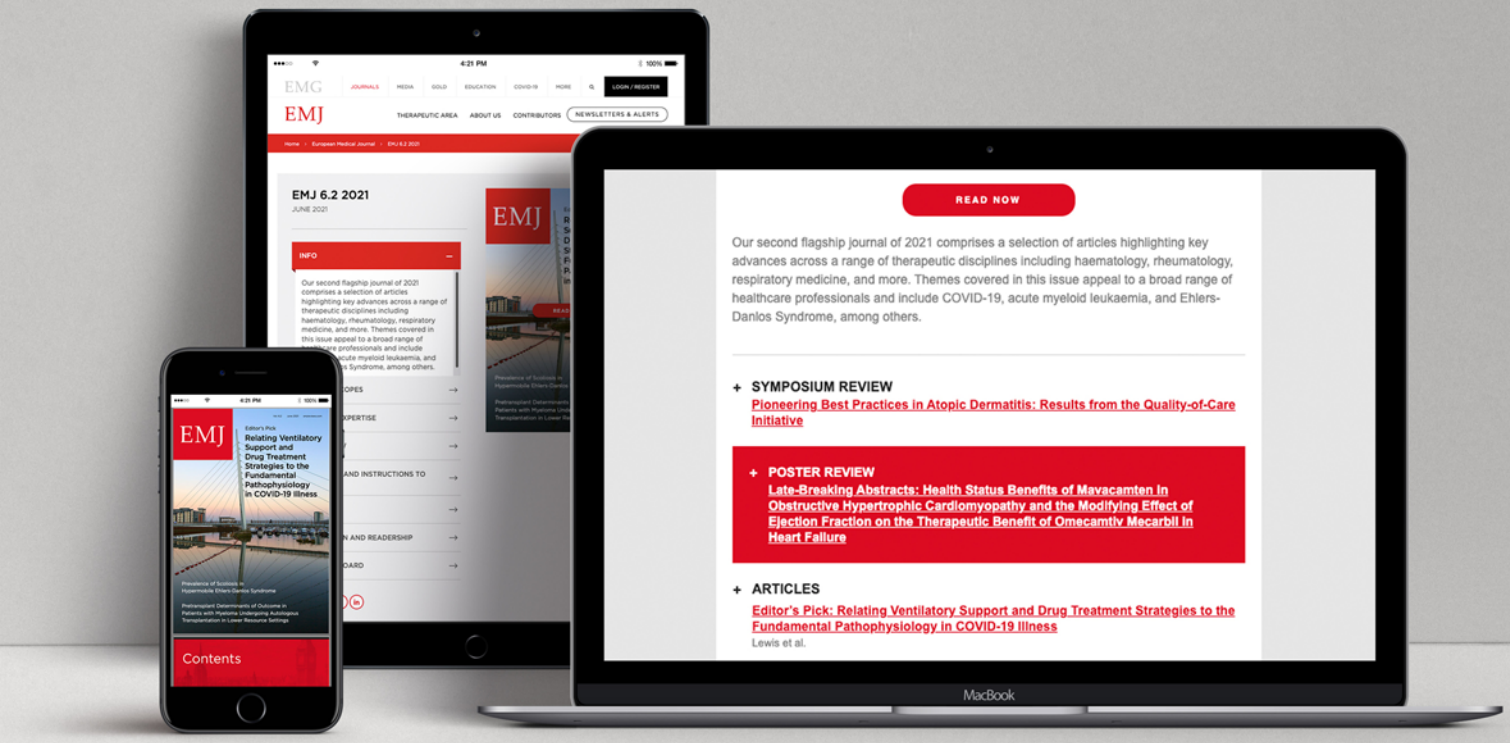

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