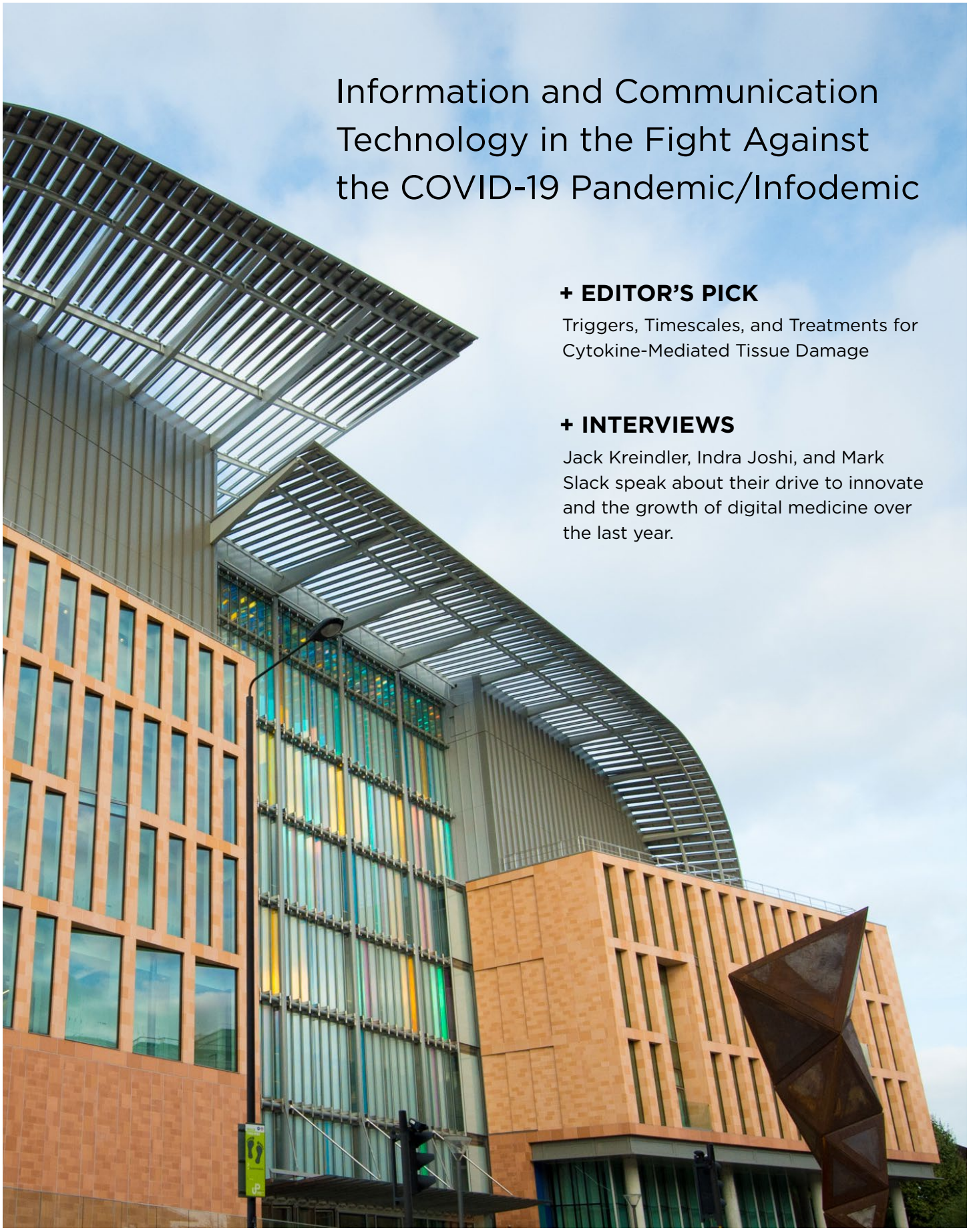
EMJ INNOVATIONS

Vol. 5.1 February 2021 emjreviews.com



Information and Communication Technology in the Fight Against the COVID-19 Pandemic/Infodemic

+ EDITOR'S PICK

Triggers, Timescales, and Treatments for Cytokine-Mediated Tissue Damage

+ INTERVIEWS

Jack Kreindler, Indra Joshi, and Mark Slack speak about their drive to innovate and the growth of digital medicine over the last year.

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"After 2020's impressive displays of worldwide collaboration and flexible adaptation in both clinical care and industry response, innovation in healthcare is taking centre stage."

Spencer Gore, CEO

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Aims and Scope

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

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

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

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This Publication

ISSN 2513-8634

EMJ Innovations is published once
a year. For subscription details please visit:
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EMJ Innovations 5.1

Welcome

Welcome to our latest issue of *EMJ Innovations* and our first journal issue for 2021. This year in particular, it is uplifting to be kicking off the year by highlighting innovations in medicine that focus on seeking solutions and new ideas in science, technology, and clinical care. After 2020's impressive displays of worldwide collaboration and flexible adaptation in both clinical care and industry response, innovation in healthcare is taking centre stage.

Sharing research via online and virtual formats, often for the first time, many medical congresses last year had to adapt their strategies to support collaboration, education, and research dissemination. Unsurprisingly, many of these congresses amplified innovative practices within their fields in dedicated congress sessions, and we have summarised several of these sessions in our *The Year in Innovations* review articles: 'Artificial Intelligence and Robotics in Endoscopy: Current and Future Perspectives,' 'Lithotripsy: Choose Your Laser,' 'Precision Medicine in Diabetes: The Road Ahead,' and 'Innovative Treatment Approaches of Inherited Neuromuscular Disorders'.

Here we share peer-reviewed original research and review articles, including a review of telemedicine by Seivert and Badowski, and an article considering the role for information dissemination to combat misinformation during a pandemic by Kobayashi. Our Editor's Pick by McBride et al. brings together evidence and understanding of cytokine responses in both infectious and autoimmune diseases, as we appreciate the current and future impact that addressing the activity of cytokines has in combatting severe illness.

We also had the pleasure of interviewing innovators in the provision of healthcare and the fascinating development of digital medicine: Dr Jack Kreindler, Founder and Medical Director of the Centre for Health and Human Performance; Dr Indra Joshi, Director of AI at NHSX and Founding Ambassador of One HealthTech; and Dr Mark Slack, consultant gynaecologist and urogynaecologist, and Chief Medical Officer and Cofounder of CMR Surgical.

Despite the hardships of the last year and the ongoing difficulties of combatting coronavirus disease (COVID-19), I remain amazed by the positive, solutions-focussed response across the health industry and clinical care. I am proud to share with you the insights from many of these disruptors and innovators in medicine and health technology in this latest issue of *EMJ Innovations*.

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Innovations in healthcare have undergone a remarkable renaissance in the past year, and humankind's ingenuity and resilience were demonstrated in response to the unexpected and influential coronavirus disease (COVID-19) pandemic. All contributions to this issue bear witness to the significant challenges that the pandemic has brought and how health systems have responded.

As societies went into lockdown, the potential of telemedicine was unleashed. While this is a major achievement, the ability to share data quickly is a double-edged sword; rapid access to knowledge improves patient care, but it can also produce 'fake news', as Kobayashi's paper, 'Information and Communication Technology in the Fight Against the COVID-19 Pandemic/ Infodemic' seeks to highlight. Even when telemedicine benefits can be demonstrated, as in Seivert and Badowski's paper, 'The Rise of Telemedicine: Lessons from a Global Pandemic', it is not a zero-sum game. Indeed, as Martin points out in 'General Practice Services in England During the COVID-19 Pandemic and Beyond: Patient Access and Barriers', access to consultation and the difference in behaviour that such a system produces has been a challenge.

As health services were inundated by the pandemic, Khan et al., in their paper, 'Rapid Reconfiguration of Paediatric Services in a District General Hospital During COVID-19, Addressing Challenges, and Seeing Opportunities', identified the reconfiguration needed in services to protect those most vulnerable children in society.

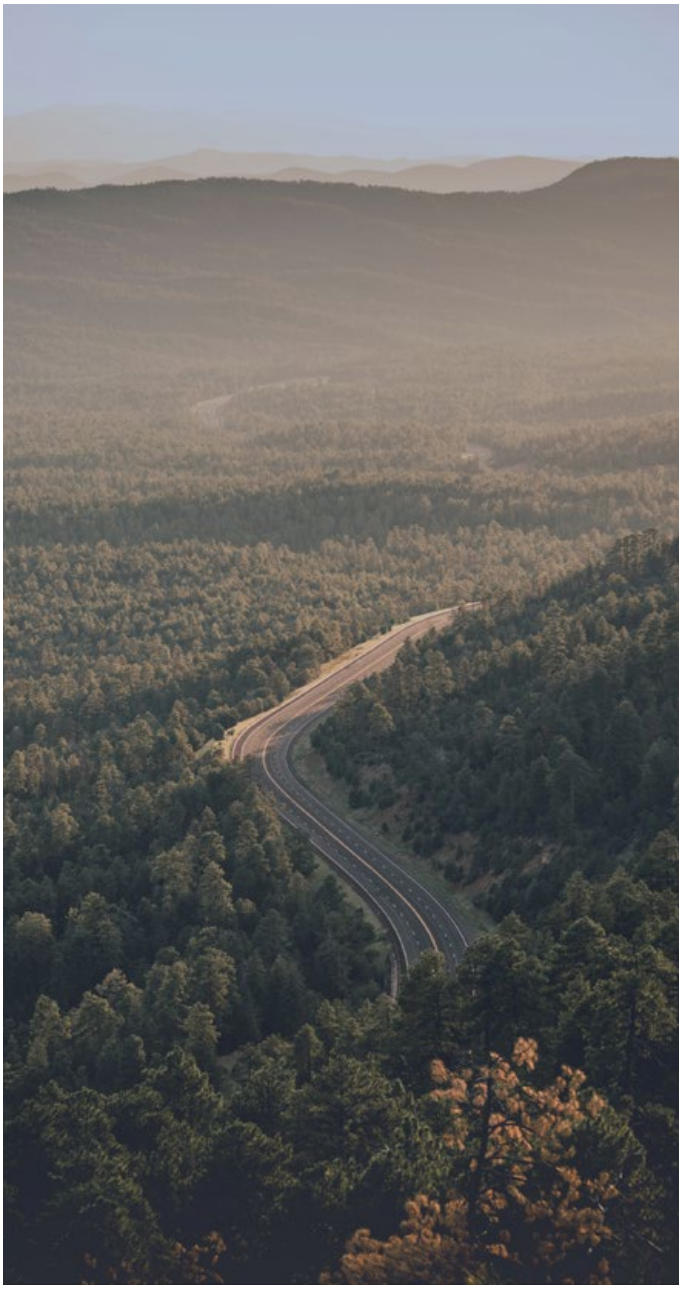
During the pandemic, many therapeutic interventions relied on prior knowledge of inflammatory processes, dexamethasone being a prime example. In the paper, 'Therapeutic Plasma Exchange Using Convalescent Plasma Replacement Therapy in Severe COVID-19 Infections: A Potential Therapeutic Option' by Varghese et al., early evidence of the use of this straightforward technique is presented. There is a long way to go before we can optimally manage cytokine-medicated inflammatory disease, but the paper by McBride et al., 'Triggers, Timescales, and Treatments for Cytokine-Mediated Tissue Damage', makes an excellent attempt at bringing this evidence together. I have chosen McBride et al.'s paper as my 'Editor's Pick' as it has such far reaching impact on how we manage patients with an adverse cytokine response, be it from viral or autoimmune disease.

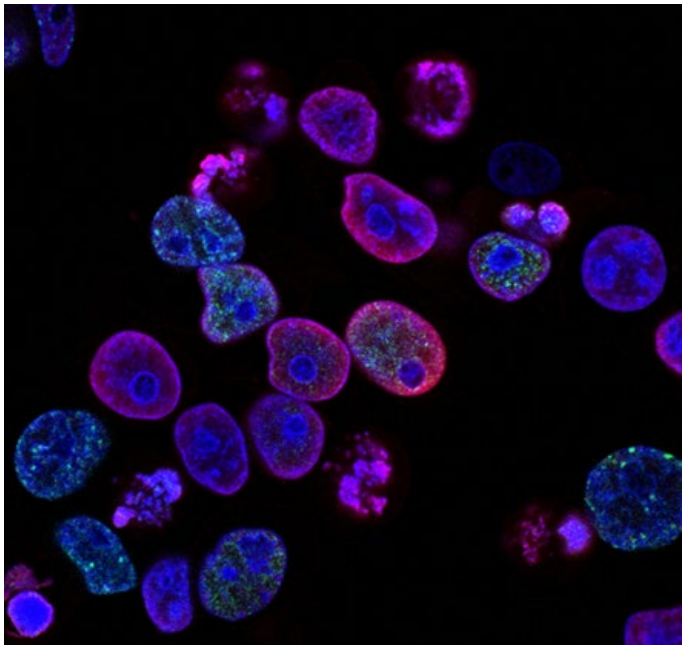
No doubt the analysis into best therapeutic interventions will be aided by the realisation of machine-learning, effective algorithms, and artificial intelligence in the next generation of therapeutics. We now have a glimmer of how these tools will be centre-stage in such infections and other areas of medicine such as inflammatory diseases and cancer. I wish you a thoughtful and happy 2021.

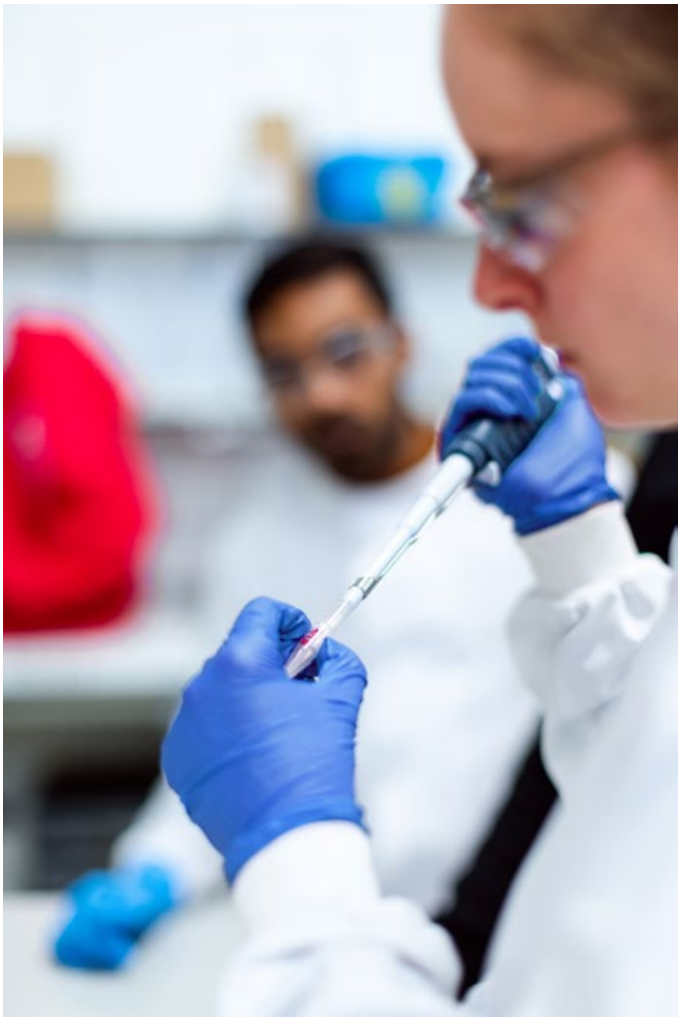
Dr Mike Bewick
Founder of IQ4U Consultants, London, UK

The Year in Innovations

In scientific approaches, clinical practice, and beyond, innovative practices continue to be accelerated. These feature articles review highlights from the past year, including the global efforts to develop a new vaccine to SARS-CoV-2.







COVID-19 and the mRNA Vaccine Legacy

Rachel Donnison
Editorial Assistant

FREQUENTLY pitted as the only way of eradicating the coronavirus disease (COVID-19) that arises from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the world is holding its breath as the first vaccination programmes of 2021 are rolled out in the UK, Germany, Italy, Poland, Denmark, and many other countries in Europe and further afield.

2020: A YEAR OF ACCELERATED VACCINE DEVELOPMENT

Of the 320 COVID-19 vaccine candidates in development,[1] the first to gain both U.S. Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA) approval was the BNT162b2 mRNA vaccine, produced jointly by the pharmaceutical giant Pfizer and biotechnology company BioNTech.[2,3] This was the first time an mRNA vaccine has ever received approval by either regulatory board. In another example of a pharmaceutical and institutional partnership, the FDA-approved SARS-CoV-2 vaccine produced by Moderna and the National Institute of Allergy and Infectious Diseases (NIAID) also utilises mRNA to generate immunity.[4] A more traditional form of a vaccine created against SARS-CoV-2 is the adenovirus vector-based ChAdOx1 nCoV-19 vaccine, developed by the joint efforts of the University of Oxford, Oxford, UK, and the multinational pharmaceutical company AstraZeneca.[5] This has recently been approved for use in the UK by the MHRA and is presently being rolled out across the country with the hope of vaccinating 15 million of those at highest risk by mid-February.

Imperial College London, London, UK, have also entered the race to end the current pandemic, offering their self-amplifying RNA vaccine, which is currently in Phase I clinical trials.[6]

Breaking away from traditional methods, COVID-19 vaccines have revolutionised vaccine development, as the use of mRNA has seen unprecedented uptake by developers. But how much do we know about these vaccines, and what efficacy and safety benefits do they offer over traditional vector-based vaccines?

HISTORY OF mRNA VACCINES

mRNA molecules carry the genetic code of a specific encoded protein from the DNA in the nucleus to the cytoplasm, where the protein is then formed. Manufactured as a potential vaccine, mRNA offer many safety advantages over their double-stranded counterpart; namely that they do not interact with the host's genetic material, excluding the potential negative effects of genomic integration. When used as a platform for vaccine development, their noninfectious, nonintegrating properties make the risks posed by infection or mutation low, and because it is degraded by natural cellular processes it can be easily regulated to lower immunogenicity.[7]

In 1989, the discovery of a successful method of mRNA *in vitro* transfection, whereby mRNA injected into mice resulted in the encoded protein's production, led to the first suggestions of using mRNA as a therapeutic.[8] Over the next 30 years, mRNA was largely side-lined because of technological issues with stability, induction

Breaking away from traditional methods, COVID-19 vaccines have revolutionised vaccine development

of host immune response (immunogenicity), and inefficient *in vivo* delivery.[7] Despite these barriers, mRNA offers high yields of *in vitro* transcription reactions, rendering them rapid, cost-effective, and scalable for mass production.[9] For context, DNA vaccines require producing cell lines and subsequent clinical grade protein production, which typically takes over a year, whereas nucleic acid mRNA vaccine manufacture can occur in a few weeks.[9]

mRNA VACCINES ARE NOT NOVEL

Though only two mRNA vaccines have been approved by the FDA, there are several in clinical trials for protection against Chikungunya virus,[10] HIV,[11] and rabies,[12] and there is much to be learnt from animal coronavirus vaccines.[13] The results so far are promising, though the only results to be published in the peer-reviewed literature, as of yet, are for the first rabies mRNA vaccine; the vaccine induced functional antibodies in all 101 participants when injected intradermally or intramuscularly, though many (78%) experienced limited systemic adverse events.[14]

Fast forward to 2019, and the chaos induced by COVID-19 forced many immunologists to rethink the DNA-based vaccine status quo; in the case of an emerging novel virus, it is not simply a question of therapeutic effectiveness, but also of rapid development and large-scale deployment.

However, despite the many immunological advantages, the necessity of storage at -70 °C has already caused issues with the Pfizer/BioNTech vaccine, particularly in low- and middle-income countries where such freezing facilities are limited. This has led to the development of the COVID-19 Vaccine Global Access Facility (COVAX), which aims to ensure fair allocation of vaccine supply; to end this pandemic, it is not enough to eradicate the virus locally, there must be a global approach.[15]

Clinical data have also been released on the Pfizer/BioNTech and Moderna/NIAID mRNA vaccines, as summarised below.

REGULATOR-APPROVED mRNA VACCINES AGAINST COVID-19

Pfizer/BioNTech BNT162b2

In response to the rising COVID-19 cases worldwide in early 2020, Pfizer and BioNTech initiated a joint co-ordinated programme of four potential RNA-based COVID-19 vaccine candidates. Following clinical studies in both Germany and the USA, two of the four were taken forward on the strengths of their ability to elicit high SARS-CoV-2 neutralising antibody titres:[16] the first was BNT162b1, which encoded the SARS-CoV-2 receptor–binding domain, and the second was BNT162b2, which encoded the SARS-CoV-2 full-length spike protein that is used by the virus to invade host cells.[16] In the Phase I trials of both variants, the BNT162b2 vaccine was selected for continuation to Phase II/III based on its associated lower incidence and severity of systemic reactions, particularly in older participants.[17] Phase III trials of the BNT162b2 vaccine, which enrolled 43,548 participants, showed a 95% effectiveness in preventing COVID-19 in a two-dose regimen, with similar efficacy across subgroups defined by age, sex, race, ethnicity, BMI, and comorbidities.[18] In terms of safety, the most reported systemic events were headache and fatigue: 59% and 52%, respectively, in those aged 16–55 years, compared with 51% and 39% in those aged >55 years; however, headache and fatigue were also reported by placebo participants (23% and 24%, respectively).[18]

Moderna/NIAID mRNA-1273

Also utilising the SARS-CoV-2 spike glycoprotein is Moderna/NIAID's mRNA vaccine contender. The lipid nanoparticle-encapsulated mRNA vaccine focusses on the SARS-CoV-2 pathway of viral entry: the spike protein is the major surface protein on the CoV virion, making it the logical primary target for neutralising antibodies.[19] After successful antigenicity by mRNA-1273 *in vivo*, human Phase I clinical trials began in March 2020, just 66 days after the SARS-CoV-2 viral sequence was published.[20] Tested in 45 volunteers, antibody responses were recorded in all participants and no trial-limiting safety concerns were identified; >50% of participants reported mild symptoms, such as fatigue, chills, headache, myalgia, and pain at the injection site.[20] With the regulator's permission, Phase II/III trials were approved and an interim analysis in November 2020 showed an effectiveness of 95% in the >30,000 USA participants enrolled.[21] In contrast to the Pfizer/BioNTech vaccine that needs to be stored at -70 °C, the Moderna/NIAID vaccine will remain viable after freezing in a conventional freezer for

up to 6 months, and once thawed can be placed into a standard refrigerator for 30 days.[22]

2021: ANOTHER UNPRECENDED YEAR?

Not only did both of the approved mRNA vaccines prevent symptomatic COVID-19 in their Phase III trials, but they also prevented severe cases of COVID-19; there were only 10 such cases with the Pfizer/BioNTech vaccine[18] and 11 with the Moderna/NIAID candidate.[21] Immunologically, both mRNA vaccines show similar efficacy (95%), though logistically the Moderna/NIAID vaccine is easier to store with current freezing systems. The results of the Imperial College London self-amplifying RNA vaccine trials will be much anticipated this year, and we can also expect to see results of DNA-based COVID-19 vaccine candidates, namely from Janssen/Johnson & Johnson, GlaxoSmithKline/Sanofi, and Altimmune. The challenge of emerging mutations in the genome of SARS-CoV-2 could potentially alter the efficacy of vaccines against COVID-19, although this is yet to be determined. "Unprecedented" has been a word used frequently since the onset of the pandemic, and the scientific innovation we have seen has been remarkable; we have seen the unprecedented speed of vaccine trials, unprecedented approval of an mRNA vaccine for human use, and unprecedented vaccine rollout. A process that can take more than 10 years reduced to just over 10 months will leave a legacy in vaccine development; the next time we are faced with an infectious disease of this scale, we will be thankful much of the leg work has already been done by those who came before us.

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Precision Medicine in Diabetes: The Road Ahead

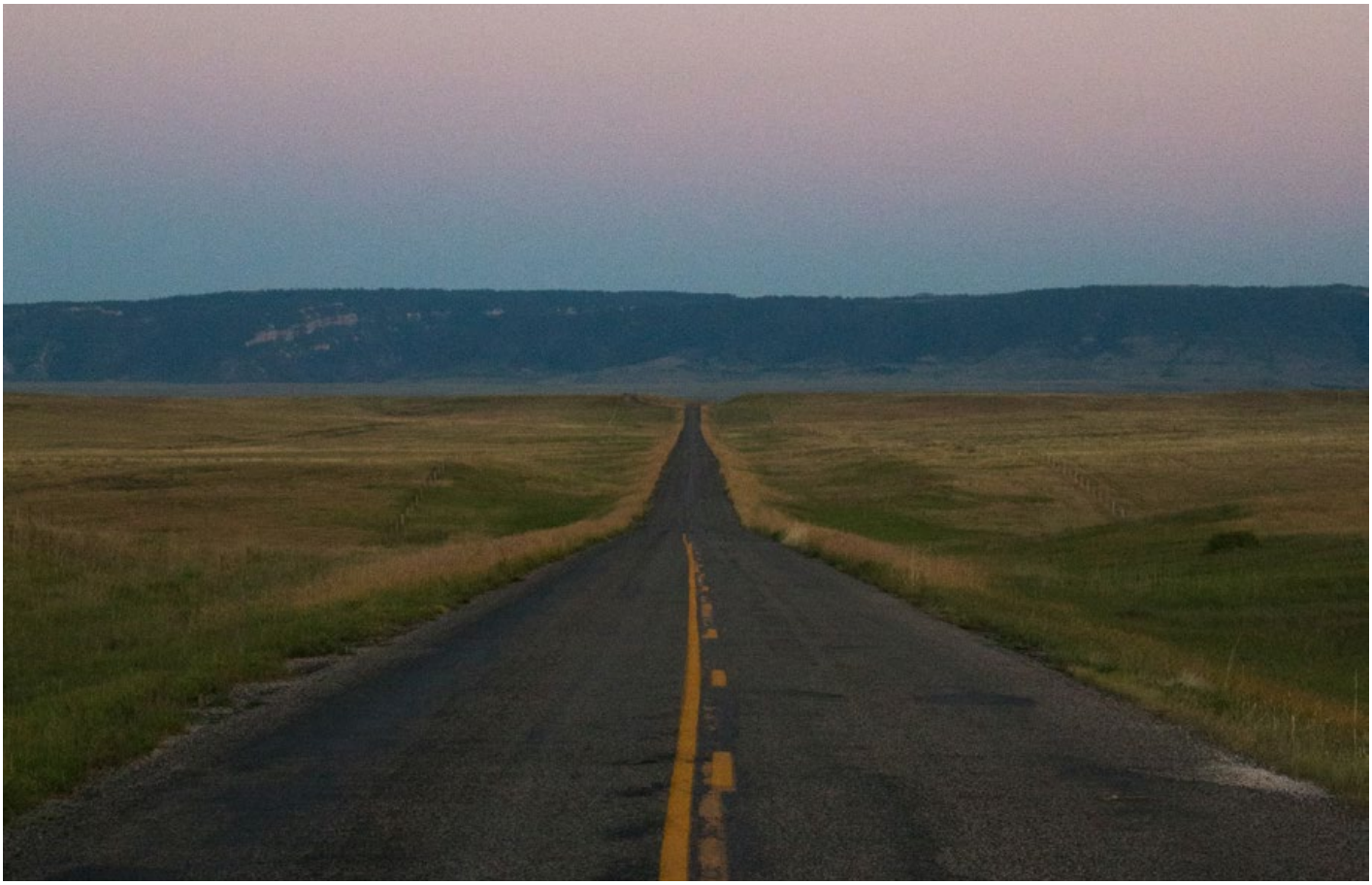
Anaya Malik
Editorial Co-ordinator

CONTRIBUTIONS to the European Association for the Study of Diabetes (EASD) Virtual Meeting 2020 included the far-reaching 'Precision Diabetes Medicine in Practice' held on 23rd September 2020. The virtual session considered the scope for precision medicine within diabetes care and outlined plans for forging a path ahead to incorporate precision medicine into medical training and patient care. The session was co-chaired by Dr Paul W. Franks, Lund University Diabetes Center, Lund, Sweden, and Prof Dana Dabelea, Lifecourse Epidemiology of Adiposity & Diabetes (LEAD) Center at the Colorado School of Public Health, Aurora, Colorado, USA. Prof Dabelea introduced Dr Louis Philipson, Director of the Kovler Diabetes Center, Chicago, Illinois, USA, a world-leading authority on diabetes, as the speaker for the presentation in which he discussed the recently published consensus report[1] for the Precision Medicine in Diabetes Initiative (PMDI) by the American Diabetes Association (ADA) and the EASD. Dr Philipson used the consensus report and other pertinent published works to explore what precision medicine is, what it could look like in practice, and the underlying signs needed to be part of a future effort.

DRIVING PRECISION MEDICINE IN DIABETES CARE

Dr Philipson is a member of the task force that orchestrated the consensus report; the task force played a key advisory role, holding meetings with larger groups that led to the joint consensus statement. The initiative relies on expertise and collaboration from many stakeholders garnered through a hub-and-spoke model of working groups reporting to a steering committee, with the overall initiative managed by an executive oversight committee. The approach to precision medicine in diabetes has been to incorporate and build evidence for its use in diabetes practice to achieve quantifiable, implementable, and probabilistic outcomes based on aetiology and risk scores. The team are currently in the process of establishing data for a second set of evidence-based reviews.

The effort began in 2018, when key experts supplied a definition for precision medicine in diabetes: "An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." The concept of precision medicine is not unconventional. Clinicians have always assessed a patient for their illness, reviewed their ailments and symptoms, recognised patterns, and provided the most appropriate therapy. The visibility of detailed characteristics of human biology is now clearer owing to innovations in biomarkers, bioimaging, wearable technology, and big data from electronic



medical records, health insurance databases, and other platforms. Rapidly evolving computational power and bioinformatics methods are creating unprecedented opportunities to better understand diabetes and other complex traits. Beyond that, identifying hidden structures in datasets and linking these structures to outcome data will help to yield insights into the management of this disease. Consequently, it can be argued that bigger data pools and technological advances have driven precision medicine to provide greater opportunities in practice than previously experienced. Physicians, however, are lacking in experience, training, and time to align increased knowledge of lifestyle and environmental risk factors in diabetes.

Diabetes remains a serious condition and affects one in 11–12 people worldwide, although they may be unaware. There is a gap in the understanding of the molecular and environmental principles of diabetes that prevent repair of pathophysiological mechanisms in individual people to ultimately prevent disease progression. The increasing numbers of people with diabetes incurs greater healthcare strains and cost owing to the predisposition they face for microvascular end-organ and other severe complications. Ongoing development of drugs to control blood glucose levels, the main parameter for diabetes diagnosis, may alleviate aspects of disease outcome but does not cure the disease. According to Dr Philipson, drug development in the USA is slow, expensive, and often faces failure: development of the average prescription drug costs approximately $2.6 billion USD; the drugs take 11–14 years to come into market; just one in every 10,000 compounds get approval from the U.S. Food and Drug Administration (FDA); and the conditional probability of getting a compound to the market from the Investigational New Drug Application is <1%. Dr Philipson explained that several studies have demonstrated that lifestyle modifications can have a greater effect than drugs such as metformin in treating diabetes, but these changes are challenging for patients to engage in and sustain long-term. There is additional difficulty in determining diabetes strategies that work for different populations across the globe.

People with diabetes are disproportionally affected by coronavirus disease (COVID-19). This disparity has highlighted that parts of the

"The growing burden of the disease worldwide has provided the need to pave a path for the future, one that considers all aspects of a patient-centred approach and can be adapted to specific cultures, geographies, and individuals"

world struck most significantly are those with the fewest resources and least equipped to counter the overwhelming burden of the disease and its complications; therefore progress, and new approaches to it, are urgently needed. The taskforce responsible for the PMDI has partnered with authoritative parties to show that minority groups are at a higher risk of disease.

THE VEHICLES OF PRECISION MEDICINE

Executing precision medicine for diabetes care is a concept that is all-encompassing. Dr Philipson shared that genetics, typically hailing much attention in precision medicine, is helpful but is only part of the larger vision of precision medicine. He introduced the key areas in precision diabetes medicine: precision diagnostics, prevention, treatment, monitoring, and prognostics. Each of these concepts has been identified and detailed in the consensus report. A precision diagnosis was defined by Dr Philipson as "a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state."

Dramatic applications of precision diagnostics in monogenic diabetes have included transcending genetics to provide insights into specific therapy choices that specifically target the underlying aspects that used to be considered rare, but are now seen in 2–3% of the total population of younger adults or children with diabetes. Ideal approaches to prevention of diabetes require more innovative, evidence-based reviews. Precision prevention of diabetes should determine the likely responses to health interventions and risk factors, optimise interventions, and minimise risk factor exposure for an individual. Precision monitoring includes an array of concepts including measuring blood sugar, biological markers, diet, sleep, and psychological and physiological states; understanding of these factors provides a better projection for the practical approach in treating a patient. Precision prognostics is the notion "to improve the precision and accuracy with which a patient's disease-related outcomes are predicted using information about their unique biology, environment, and/or context." Dr Philipson explained that, if a disease-related outcome such as hypoglycaemia can be predicted based on likelihood, they may be able to provide key insights and predictive power in patient-centred outcomes.

THE FINISHING LINE AND FUTURE PLATFORMS

The future stages of the initiative are visualised in four key phases. The next phase, Phase 2, projected to take place between 2020–2023, will include publishing a second consensus report, seeking research funding, completing systematic reviews of evidence, and disseminating findings via research and educational symposia. In Phase 3, the team expect to continue this long-term research and implement clinical guidelines for practicing precision diabetes medicine. Phase 4 will begin in the year 2025 and continue beyond, when the team and the constructed guidelines will be instrumental in physician and patient education.

Dr Philipson reminded the virtual audience that genetics is only one part of the vision that the team is working toward. Precision and personalised medicine have achieved worldwide and enthusiastic acclaim by healthcare professionals and people with diabetes. The growing burden of the disease worldwide has provided the need to pave a path for the future, one that considers all aspects of a patient-centred approach and can be adapted to specific cultures, geographies, and individuals.

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Artificial Intelligence and Robotics in Endoscopy: Current and Future Perspectives

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PRECISION when imaging or performing minor surgical tasks is crucial for all endoscopists. The progresses in artificial intelligence (AI) and collaborative robots will undoubtedly be key in helping surgical practices move towards a higher level of accuracy. Presented at the special symposia 'AI and Robotics in Endoscopy: Hype or Reality?' at the United European Gastroenterology (UEG) Week 2020, Prof Philip Wai Chiu, The Chinese University of Hong Kong, Shatin, Hong Kong, shared his assessment of the current status of this technology and the outlook for the future.

MAN VERSUS MACHINE

Prof Chiu introduced the topic by explaining that "when we talk about AI, we always face the challenge of it being posed as man versus machine; however, I believe that the application of AI should be in collaboration with clinicians and endoscopists." He went on to express his hope that over the next 20 years, the efficacy and quality of diagnostic endoscopy will improve, predicting that robotics will be increasingly applied to enhance its therapeutic potential.

RECENT ADVANCES IN ARTIFICIAL INTELLIGENCE FOR ENDOSCOPY

The current development of AI in endoscopy is focussing on the standardisation of endoscopic examination, detection, and characterisation of gastrointestinal (GI) pathology. The human brain's performance can be altered by stress, fatigue, and limited experience. AI technology can compensate these limitations, decrease interoperator variability, enhance accuracy of diagnosis, and reduce the time, cost, and burden of endoscopic procedures.

Artificial Intelligence in Endoscopic Examination: Cerebro

Prof Chiu proceeded to explain that his institution, in collaboration with the start-up company Endovision (Hong Kong, Hong Kong), has developed a standardised AI-driven protocol for endoscopic examination entitled Cerebro, which provides enhanced screening and surveillance adherent to standard protocols.[1] Clinical trials of Cerebro examined the efficacy of application of the AI-driven assistance device to examine the GI tract (oesophagus, stomach, duodenum). The AI in the protocol has standardised the capturing of imaging and timing for the examination of each of the positions; therefore, if any position is missed the system will alert the endoscopist. Results

"I believe that the application of AI should be in collaboration with clinicians and endoscopists"

from 100 patients have shown a 95% accuracy with high sensitivity (95%) and specificity (95%), and 100 more patients are in the study pipeline. The AI of Cerebro can be regarded as an inspection completeness and quality control tool that ensures an endoscopic procedure is performed with the highest quality, and provides an example of the collaboration AI could offer.

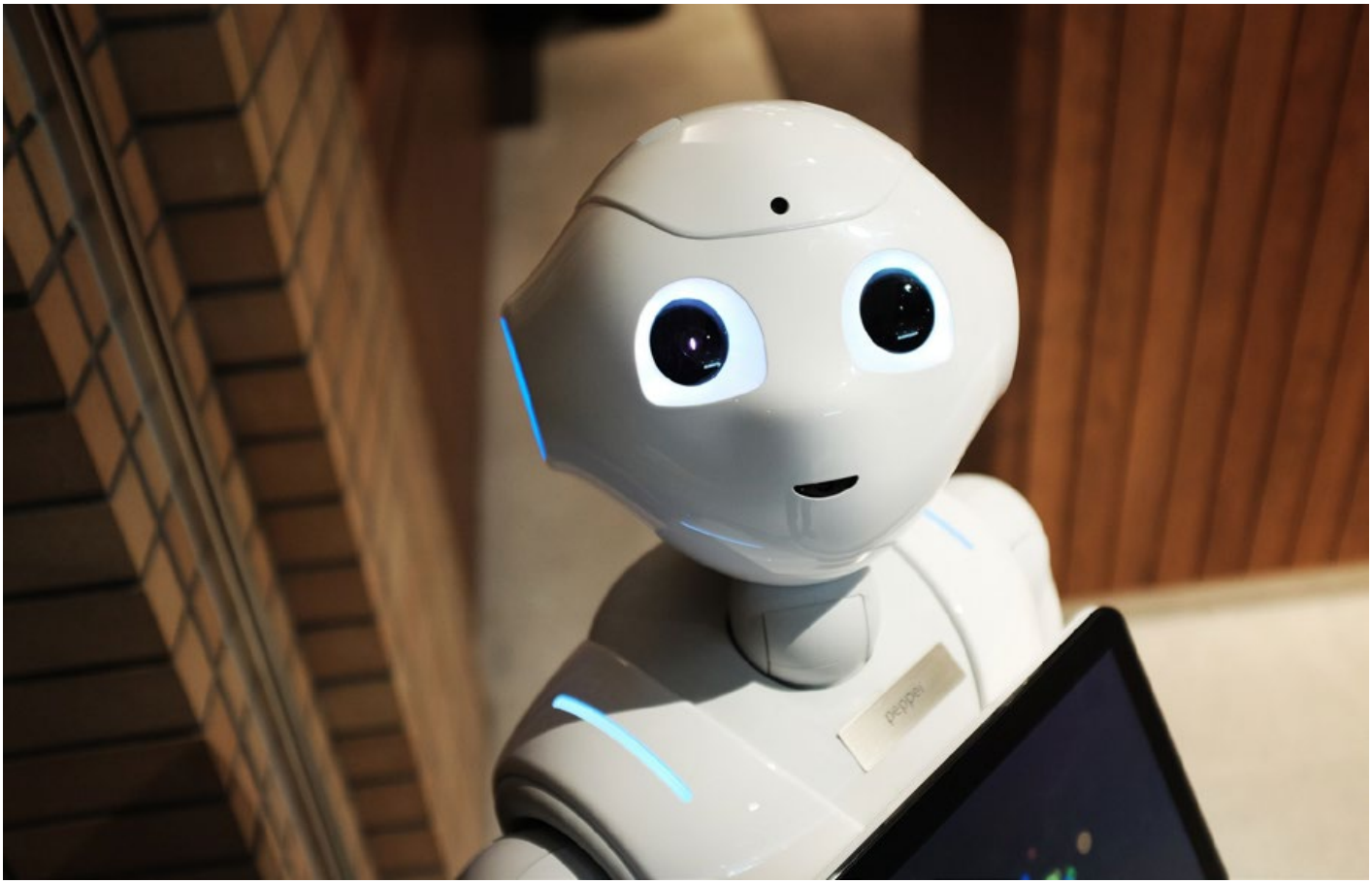
Artificial Intelligence in Endoscopic Detection: ENDOANGEL

Another AI protocol being applied clinically is the ENDOANGEL system (Wuhan, China) for the detection of GI pathology. The ENDOANGEL system utilises deep neural networks and perceptual hashing. In a recent study, patients aged 18–75 years (N=704) were assigned 1:1 to either the ENDOANGEL system (n=355) or unassisted colonoscopy (control; n=349). The results showed that the primary endpoint of adenoma detection rate was significantly greater in the ENDOANGEL group compared with the control group: 16% of 355 patients allocated ENDOANGEL-assisted colonoscopy had ≥1 adenoma detected compared with 8% in the 349 patients assigned to the control colonoscopy group (odds ratio: 2.30; 95% confidence interval: 1.40–3.77; p=0.0010).[2]

Artificial Intelligence in Endoscopic Characterisation: EndoBRAIN

The recently approved AI-assisted system EndoBRAIN has been shown to significantly improve the specificity and sensitivity in GI neoplasia diagnosis. In a Japanese multicentre study between 2017 and 2018, the EndoBRAIN system was trained using 69,142 endocytoscopic images, taken at 520x magnification, from patients with colorectal polyps who underwent endoscopy at five academic centres in Japan.[3] Retrospective, comparative analysis of the diagnostic performance of EndoBRAIN versus 30 endoscopists (20 trainees and 10 experts), in the ability to distinguish neoplasmatic from non-neoplasmatic tumours, highlighted that across all the results (sensitivity, specificity, accuracy, positive predictive value, and negative predictive value), EndoBRAIN had a much better diagnostic accuracy (96.9%, 94.3%, 96.0%, 96.9%, and 94.3%, respectively) compared with the trainees.[3] However, compared with the experts, only the sensitivity and negative predictive value of EndoBRAIN were significantly higher and all other values were comparable.

When questioned on how this technology could be used clinically, Prof Chiu responded that it is important to maintain collaboration between machine and humans. He believes that within their training period, trainees would still require



a mentor but that the AI system could provide telementoring for continuation of observation and guidance and enable the trainees to achieve a high diagnostic yield. This technology has now been authorised for clinical use by the Japanese regulatory agency and in a collaborative manner is assisting doctors in detecting lesions in the clinical setting.

Prof Chiu emphasised: "With this increasing application of AI detection and characterisation, I believe that there is a much higher demand for therapeutic endoscopy."

"In the future, I believe that the robotic technology will be combining with AI to increase the detection of early GI neoplasia"

RECENT ADVANCES IN ROBOTICS FOR ENDOSCOPY

The last 40 years have shown an increasing development in therapeutic endoscopy, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), natural orifice transluminal endoscopic surgery (NOTES), and peroral endoscopic myotomy (POEM). Similar to robotic-assisted surgery, robotics in endoscopy are being developed to enhance the interventional capabilities of endoscopists. Currently, robotics are capable of/assisting in polypectomy, mucosectomy, and ESD, with the latter technique being the most suitable to become the gold standard for endoscopic robotics.[4]

Robotics and Endoscopic Mucosal Resection: EndoMaster

The performance of ESD for early GI cancers allows for local, curative-intent treatment; organ preservation, including preserved organ function, fewer postgastrectomy syndromes, and improved quality of life; as well as better postoperative outcomes, such as decreased hospital stay and early return of GI function. However, the performance of ESD is particularly challenging because of the design and use of the endoscopic knife attached to the

"with the use of AI technology combined with the recognition of imaging, we will be able to automate some of the endoscopic procedures for ESD"

endoscope. On the other hand, the lessons we have learned from the use of robotics in general surgery have provided hope that the quality of dissection can be enhanced with robotic surgery.

With this in mind, the endoscopic robotic platform EndoMaster (Master And Slave Transluminal Endoscopic Robot) was developed by Prof Chiu's team in collaboration with researchers at Nanyang Technological University and National University Singapore, Singapore. The EndoMaster consists of two robotic arms attached to a conventional endoscope and, in 2012, was tested on five patients to perform the submucosal dissection portion of ESD. The EndoMaster was successful in all five patients and complete resection was completed in a short period of time, on par with that seen in similar cases performed through standard ESD techniques.

EndoMaster EASE

Limitations of EndoMaster led to the development of the second-generation EndoMaster Endoluminal Access Surgical Efficacy (EASE) system, which includes an independently designed flexible robotic platform, built-in endoscopic imaging system, independent water-jet system, and a channel passage to extrude and retract the two robotic arms.

This new system differs from conventional ESD as the versatility of movement the robotic arms provide allows for lifting and visualisation of the submucosa, making the system more stable. Currently, the EndoMaster EASE System is the first robotic-assisted system that can effectively remove GI tumours endoscopically without the need for surgical incisions.[5] The clinical trial for EndoMaster EASE for the treatment of patients with colorectal neoplasms started in May 2020 and is estimated to be completed by December 2021.[6] If approved, the system would enable minimally invasive surgery in the body with increased precision and reduced surgery time, and spearhead the future of robotic surgery.

FUTURE OUTLOOK

Prof Chiu went on to explain that this robotic technology can be used in the future to enhance endoscopic suturing, especially in the confined GI lumen. The technology may potentially also be clinically applied in GI emergencies, such as bleeding ulcers, GI fistula/perforation, and anastomotic leakage. The utility further extends to cases of morbid obesity and can aid in endoscopic sleeve gastrectomy and the management of pouch dilation.

"In the future, I believe that the robotic technology will be combining with AI to increase the detection of early GI neoplasia. Then we will be able to apply more of the endoluminal robotics for the treatment of GI neoplasia," Prof Chiu stated. He further imagines that eventually "with the use of AI technology combined with the recognition of imaging, we will be able to automate some of the endoscopic procedures for ESD." In his concluding remarks, Prof Chiu echoed that AI and future improvements towards three-dimensional and 4K imaging in robotic endoscopy and novel devices for suturing and dissecting will yield tremendous developments in endoscopic surgery.

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Innovative Treatment Approaches for Inherited Neuromuscular Disorders

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Editorial Assistant

INHERITED neuromuscular disorders (NMD) provide a great challenge to the treating clinician owing to their characteristically chronic and progressive nature. Historically, it has been difficult to find effective treatments for these disorders because their pathogenesis is of a genetic nature. Over the last decades, however, gene and RNA-based therapies have gained enormous interest, leading to a collection of such therapeutics now being approved for conditions affecting a variety of bodily systems. In a session at the 2020 European Academy of Neurology (EAN) Virtual Meeting, four experts in NMD discussed the rapid progression in new pharmacological technologies that have occurred as a result of improved understanding of pathophysiological and genetic mechanisms of NMD.

GENE THERAPEUTIC APPROACHES FOR NEUROMUSCULAR DISORDERS

During the first presentation, Dr Teresinhaas Evangelista, Hôpital Pitié-Salpêtrière, Paris, France, introduced the concept of a gene therapy as a biological medicinal product containing RNA, capable of inducing the regulation, replacement, addition, or deletion of a genetic sequence. Two main delivery systems for gene therapies currently exist: 1) *in vivo*, in which the gene is introduced directly into the patient; and 2) *ex vivo*, in which cells are isolated from the patient, genetically modified, and then reintroduced back into the patient. *In vivo* gene therapy is commonly used for monogenic disorders in post-mitotic tissues, and hence is the popular choice for NMD, Dr Evangelista explained. Using engineered plasmids or viruses, copies of functional genes can be delivered into patients with genetic diseases, whereby the vector will produce a functional version of the missing protein. Gene expression can also be modulated by small synthetic fragments of single-stranded nucleic acid sequences called antisense oligonucleotides (ASO), which can be administered without the use of a vector. ASO can be designed to either promote exon skipping or splicing of precursor mRNA, or to promote degradation of mRNA for gene knockdown. Dr Evangelista concluded her presentation by highlighting current hurdles that exist for these therapeutics from a clinical standpoint, namely that "gene therapy approaches are presumably irreversible, potentially providing sustained benefits but also raising the spectre of long-term untoward effects."

"Gene therapy approaches are presumably irreversible, potentially providing sustained benefits but also raising the spectre of long-term untoward effects"

THE EVOLVING LANDSCAPE OF RNA-BASED THERAPIES

Antisense Oligonucleotides

Prof Giuseppe Vita, University of Messina and NeMO Sud Clinical Centre, Messina, Italy, discussed the mechanism of actions and summarised key clinical data for innovative ASO therapies for NMD that have reached the market in recent years. Spinal muscular atrophy (SMA) is a rare disorder caused by a loss-of-function mutation in the *SMN1* gene, which results in the inability to code the survival motor neuron (SMN) protein and presents as the loss of motor neurons and progressive muscle wasting. *SMN2* is a gene that is also capable of producing SMN, but it differs to *SMN1* by a single nucleotide substitution that leads to the exclusion of exon 7, rendering 80–90% of its transcripts to be truncated, unstable, and of no biological function, whereas the remaining 10–20% are still functional. Dr Vita explained that the ASO drug nusinersen can bind to *SMN2* precursor mRNA and thereby modify the splicing of it, functionally converting it to *SMN1* and therefore increasing the production of the full-length SMN protein. Initial clinical trials were prematurely halted because the drug showed clear benefit to patients, with real-world data also reflecting this. After 6 months of treatment, an increase of more than 2 points in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND; an evaluation of motor skills) occurred in 56% of patients, and an increase of more than 4 points occurred in 28% of patients older than 2 years and 30% of patients older than 10 years.[1]

Eteplirsen is another ASO that has been approved by the U.S. Food and Drug Administration (FDA) to treat an NMD, but its target and action on RNA differs to that of nusinersen. Duchenne muscular dystrophy (DMD) is characterised by progressive muscle weakness that manifests as a result of various mutations to the dystrophin gene, including the deletion of exon 51, which leads to a disruption of the reading frame. To counter this deletion, explained Dr Vita, eteplirsen binds to the mutated exon 51 so that when the gene is translated from the mature mRNA, the exon is skipped over and therefore the disrupted reading frame is restored, creating a truncated but functional dystrophin protein. Clinical trial data showed that eteplirsen stabilised the 6-Minute Walking Test (6MWT) initially, then improved scores after 48 weeks, versus 6MWT deterioration observed with placebo.[2] However, the European Medicines Agency (EMA) are yet to approve the therapy due to concerns over the robustness of the data. A dystrophin exon 53 skipping agent, golodirsen, was recently approved by the FDA for DMD, but again is yet to be approved by the EMA.

Hereditary transthyretin amyloidosis (hATTR) is a neurodegenerative disorder for which the pathogenesis can be one of more than 130 mutations of the *TTR* gene. Normal transthyretin (TTR) proteins bind to form tetramers, but mutations in the *TTR* gene interfere with this tetramer formation and stabilisation. As a result, the proteins misfold and exist as monomers, which aggregate to create fibrils that accumulate across the body, including the peripheral nerves, cardiac muscle, and kidneys. Inotersen is an ASO to TTR mRNA, which it selectively binds to trigger its degradation through RNAase H1, leading to the reduced production of TTR and thereby reducing the accumulation of the protein fibrils. A Phase I study demonstrated significant reductions in circulating TTR. In Phase III trials, inotersen demonstrated good efficacy, with significant reductions in the change in modified Neuropathy Impairment Score+7 (mNIS+7) and patient-reported Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaires seen at 14 months versus placebo.[3] Dr Vita added: "Inotersen is also effective in the cardiomyopathy, which is a clinical challenge of TTR amyloidosis. It is able to decrease left ventricular mass, interventricular septal thickness, and increase motor performance measured by 6MWT."[4] A recent open-label Phase III study confirmed that inotersen slows disease progression and reduces quality of life deterioration.

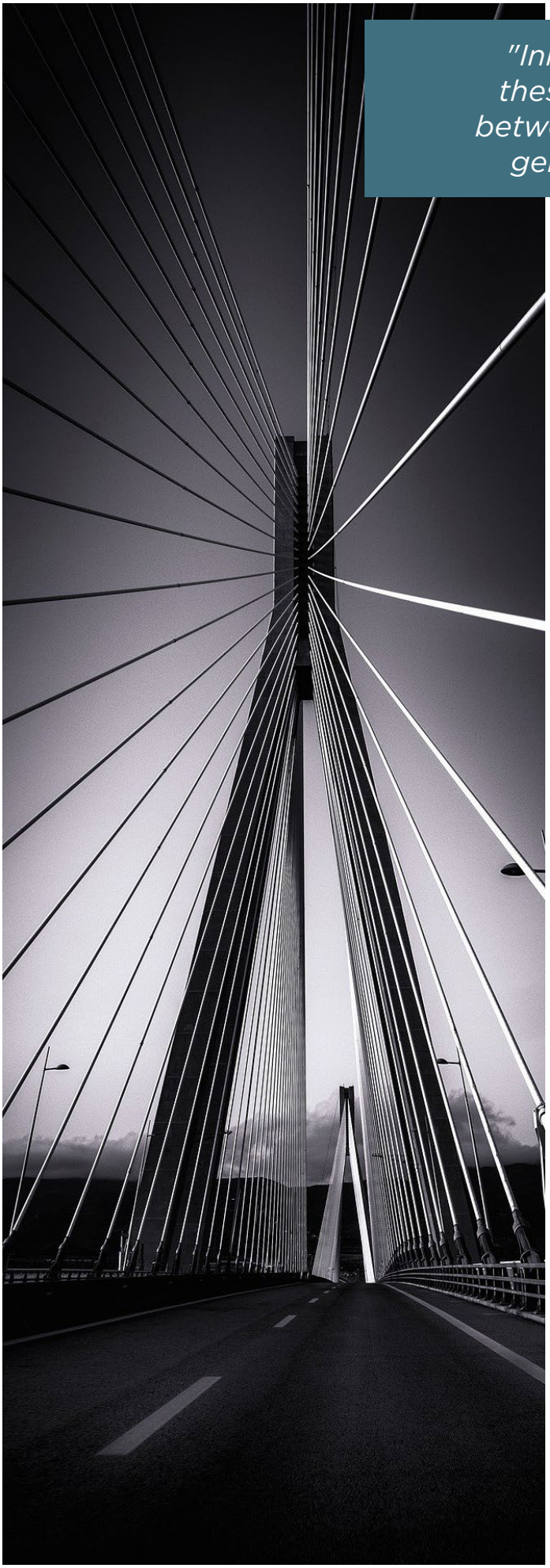
RNA Interference

Patisiran is another RNA therapy for hATTR that has shown remarkable Phase III results, and is the first small interfering RNA-based drug to receive approval from the FDA. Utilising the endogenous RNA interference pathway, patisiran selectively binds to the TTR mRNA, triggering its degradation and therefore suppresses its translation and production of the TTR protein. In the Phase III APOLLO trial, patisiran was able to induce a mean maximum serum TTR reduction of up to 90% over 18 months versus placebo.[5] There was a stabilisation and an unexpected improvement in mNIS+7 and quality of life over 18 months of patisiran versus placebo, potentially suggesting that it halts and possibly reverses the progression of amyloidotic polyneuropathy.[6] While both inotersen and patisiran have shown significant reductions in circulating TTR by targeting the liver, where 85% of TTR is produced, neither of the therapies can cross the blood–brain barrier (BBB), an important factor for a complete resolution of symptoms as 12% of TTR is synthesised in the brain. Strategies to allow such molecules to cross the BBB are currently under investigation, including intrathecal administration, viral vectors, and agents that temporarily disrupt the BBB, such as mannitol and bradykinin.

TOWARDS A BETTER UNDERSTANDING OF ENZYME REPLACEMENT THERAPIES

Inborn errors of metabolism (IEM) are disorders that usually occur from defects in enzymes involved in metabolic pathways. Such defects stop a specific substrate being converted into its product, for which symptoms can occur because of either an accumulation of the substrate and/or a deficiency of the product. Enzyme replacement therapy (ERT) is a treatment that aims to replace the deficient enzyme so that the metabolic process can occur. Although individually rare, more than 1,000 different IEM are thought to exist, meaning that collectively they are common and are estimated to affect between one in seven and one in 10 of the population.

Dr Mark Roberts, Salford Royal NHS Foundation Trust, Salford, UK, showcased the use of ERT in IEM with Pompe disease, a rare genetic disorder caused by a mutation in the gene encoding α-glucosidase, an enzyme that breaks down glycogen in the lysosome to release glucose back into the cytosol. This enzyme deficiency causes accumulation of glycogen in the lysosome, which leads to the lysosome rupturing, releasing their hydrolytic, and therefore potentially destructive, enzymes into the cytosol. The severity of this disease's progression means that infants often die at just 8 months old, despite clinical presentations being well defined and



"Innovative adjustments such as these are likely to bridge the gap between today and the sought-after genetic therapies of tomorrow"

including significant weakness, head lag, and hypotonia. Adults can also present with Pompe disease due to the variability in levels of enzyme deficiency. Myozyme is a humanised analogue of α-glucosidase that binds to the M6P receptor on cells and is internalised by endocytosis before being trafficked to the lysosomes where it degrades glycogen, preventing accumulation, and releases glucose back into the cytosol. Myozyme was approved by the FDA and EMA following the results of an open-label study in which 18/18 infants treated with myozyme were still alive at 18 months of age versus just 1/62 in the untreated controls.[7] Limitations to myozyme do exist however: in many infants, immune reactions to ERT can occur and therefore medications, often a cocktail of drugs including rituximab, are needed to induce immunotolerance; myozyme does not cross the BBB, so symptoms such as deafness and cognitive dysfunction are still manifested; and for the adult patients, the progression of disease is only delayed and not entirely halted, which Dr Roberts stated is a way of buying essential time for patients until new therapeutics, including gene therapies, are discovered.

A very-high dose of myozyme is required to elicit a response, owing to just 1% of the enzymes reaching the lysosomes. To address this shortfall, NeoGAA, an enhanced enzyme with increased binding to the M6P receptor, has been developed and was successful in Phase I and II trials and is now in Phase III, in which it is being compared to myozyme. Another enhanced enzyme is ATB200, which, in addition to increased M6P binding, has additional glycans to enhance entry into the cells. ATB200 is also administered with a chaperone, which has been shown to stabilise the ERT in the blood and maintain catalytic activity, increasing delivery of active enzyme to the lysosome. Innovative adjustments such as these are likely to bridge the gap between today and the sought-after genetic therapies of tomorrow, studies for which are likely to start soon.

THE ROLE OF SMALL MOLECULE APPROACHES TREATING INHERITED NEUROMUSCULAR DISORDERS

The therapeutic pipeline for countless diseases has been flooded with biologics and RNA therapies, but during her talk, Dr Maria Molnar, Semmelweis University, Budapest, Hungary, reminded the audience that small molecules are still a very promising therapeutic approach for inherited NMD, and represent around 40% of newly approved orphan drugs. Small molecules dominate the field because of certain characteristics, such as their ability to be designed to target and reach intracellular targets and cross the BBB, which biologics are unable to achieve; they can be orally administered; and are able to be distributed via the blood circulation compared with the blood and lymphatic system seen in biologics, meaning that peak concentrations can be reached faster. However, drawbacks to using small molecules do exist, such as an increased number of off-target sites and more drug–drug interactions compared with biologics.

Repurposing already approved drugs can be a resourceful approach to finding a therapeutic that can ameliorate symptoms of rare diseases

A small molecule that has exemplified the targeting of RNA as a therapeutic approach is ataluren, which is indicated for DMD caused by nonsense mutations in the dystrophin gene. Ataluren makes ribosomes less sensitive to the premature stop codons, which allows for the readthrough and the synthesis of the full-length, functional protein. Risdiplam is indicated for SMA and works in a similar manner to nusinersen by binding to the *SMN2* precursor mRNA and thereby modifying the splicing of *SMN2* to include exon 7 and increase the production of functional and stable SMN proteins. One key difference between the two therapies is that risiplam can cross the BBB.

Since the number of patients affected by a single genetic disease is very low, the incredible cost to research and develop a drug means that pharmaceutical companies can be hesitant to investigate potential therapeutics. Repurposing already approved drugs can be a resourceful approach to finding a therapeutic that can ameliorate symptoms of rare diseases. Among such repurposed drugs include mexiletine, a sodium channel blocker that was developed as an antiarrhythmic, to reduce myotonias; deflazacort, a glucocorticoid that has numerous applications, can be used in DMD to improve muscle strength in the short term; and PXT3003, a combination of baclofen, naltrexone, and sorbitol, is being investigated for use in Charcot-Marie-Tooth Disease Type 1A.

SUMMARY

This session from the 2020 EAN Virtual Meeting showcased that the current and prospective treatment landscape for inherited NMD is one full of hope and innovation. Interest in and development of RNA therapies is thriving, and many have proven to be the out-reaching hand patients have been grasping for. The price tags that accompany these innovative therapies, however, can severely limit patient access and is a paramount challenge that needs to be addressed to secure these lifelines for patients. As RNA therapies and biologics grow exponentially, the small molecules should not be forgotten, as they continue to demonstrate their value in the NMD field.

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Lithotripsy: Choose Your Laser

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FOR THE PAST two decades, lithotripsy strategies for the treatment of nephrolithiasis have been dominated by the development and optimisation of holmium lasers. Holmium lasers have become the gold standard in interventional management of renal stones as the safest, most versatile, and most effective approach. However, alternatives for stone ablation are now emerging, including thulium lasers as a direct competitor to holmium lasers, and ballistic or pneumatic devices offering alternative ablation strategies. At the 35th Annual European Association of Urology (EAU) Congress, expert presenters discussed these alternatives for lithotripsy on Sunday, 19th July 2020 in a plenary session, titled 'Stones: The Role of Innovation'.

HOLMIUM LASERS

In his presentation, Dr Khurshid Ghani, Ann Arbor, Michigan, USA, outlined the mechanism of ablation performed by holmium lasers, described factors impacting their efficacy in lithotripsy, and highlighted recent advancements improving their use in clinical practice.

Current Practice

Holmium lasers predominantly use a photothermal ablation mechanism to fragment renal stones, maximising energy transfer to the stone by laser contact. A photoacoustic effect causes additional fragmenting of the stones, but this effect is minimal and mainly plays a role in the 'popcorning' or 'pop-dusting' approaches to laser lithotripsy. Three factors affect successful fragmentation by photothermal ablation with holmium lasers: pulse duration, stone absorption and fragmentation, and fluid absorption. Modern development of holmium lasers has favoured longer pulse duration for finer fragmentation and dusting; however, the risk for collateral and thermal damage from longer pulse durations needs to be considered. The level of stone absorption of laser energy has a maximum threshold, beyond which less fragmentation occurs. Finally, holmium is not well-absorbed by fluid, so it operates best when in direct contact with renal stones. Optimising these three factors has been the focus of the advances in holmium laser systems over the past two decades.

Advances in Holmium Lasers

Next-generation holmium laser systems deliver higher energies and allow surgeons to use higher frequencies for a dusting technique. A significant advance in holmium laser systems was the development of MOSES™ technology (Lumenis, San Jose, California, USA), which delivers a short, low-energy pulse to create a vapour bubble before delivering the actual ablative energy pulse. By manipulating the wave form over two pulses, MOSES 'distance mode' improves fragmentation by 28% when in contact with renal stones, and by 100% when at 1 mm distance from the stone, compared with short pulses of holmium laser.[1] This provides a clinical benefit in improving dusting techniques, as a study of dusting techniques determined that only 23% of dusting occurs when within 0.5 mm of the stone;[1] therefore, for effective dusting, advancements

in laser systems should be optimised to work at distance and not only in direct contact.

Pulse modulation has also been developed for holmium lasers and this was shown to deliver better quality dusting. This results in finer fragments for clearer vision during the procedure, and is valuable for effective clearance and suction techniques, both in current practice and in development. Pulse modulation also results in less retropulsion for easier utility of the laser device.

Multipulse sequencing has improved the quality and speed of fragmentation, with better results than long-pulse techniques. Future holmium laser technologies aim to optimise this effect, with the development of 'pulse trains' of rapidly repeated, similar-energy pulses that aim to avoid the risks of prolonged energy durations without sacrificing the efficacy of high power.

THULIUM LASERS

Thulium lasers represent the leading competitor to holmium lasers for laser lithotripsy, with an emergence of studies in recent years supporting their efficacy and comparing their clinical utility to their holmium laser predecessors. During his presentation, Dr Peter Kronenberg, Amadora, Portugal, highlighted studies comparing both practical and clinical considerations, to determine the scope for thulium lasers to join the field for the interventional management of renal stones.

Practical Comparison

The holmium laser apparatus utilises a resonance chamber for energy amplification, and requires a large cooling mechanism, thus resulting in bulky machinery, weighing up to 300 kg. The thulium laser amplifies within the fibre itself so it does not require a resonance chamber, and can be cooled with a simple fan; this results in an apparatus that is much smaller and lighter, weighing 35–40 kg, 7–9 times lighter, and 8 times smaller than the holmium machine. The holmium laser also requires high power to operate, needing a specialised 46 amps power outlet and consuming 10,000 W of energy. By comparison, the thulium laser can run off a standard power outlet as it consumes only 800 W of energy, which allows for more practical incorporation into pre-existing operating theatre infrastructure.

Clinical Comparison

In comparing the clinical results of the two lasers, it is evident that the fragmentation capability of the thulium fibre laser is faster than that of the holmium laser; the thulium laser fragments stones twice as fast as the holmium laser and completes dusting up to four times as fast.[2,3] Study results found that the thulium laser had faster ablation on every setting and for all stone types.[4] The thulium fibre laser was also found to produce a higher quantity of smaller dusting particles during ablation, which contributes to clearer field of view and ease of suction clearance.

During operation, the thulium fibre laser generates less retropulsion than the holmium laser. As explained by Dr Kronenberg: "Reduced retropulsion makes the thulium fibre much easier to handle, without the need to constantly reposition the fibre tip in relation to its target." The settings available for use with the thulium laser exceed that of the holmium laser, in energy,

"Study results found that the thulium laser had faster ablation on every setting and for all stone types."

frequency, and pulse duration. Much lower energies are available with the thulium laser (0.025–6.00 J versus 0.200–6.00 J with the holmium laser), allowing for precision dusting. The maximum frequency of the thulium laser reaches 2,400 Hz compared with the holmium laser maximum of 100 Hz, and the pulse duration available extends up to 40 times longer (200–50,000 µsec versus 150–1,300 µsec with the holmium laser). These available settings may offer improved dusting performance in lithotripsy, however, further research analysis and clinical experience is needed to assess the safety profile and real-world impact on intervention for renal stones compared with the well-established holmium laser.

THERMAL INJURY

Recent research has highlighted the impact of collateral thermal injury from the use of lasers in renal stone ablation. In his presentation, Dr Evangelos Liatsikos, Patras, Greece, outlined findings clarifying the risks associated with both holmium and thulium laser systems in lithotripsy. Higher energy, while contributing to speed and efficacy of ablation, generates higher heat, particularly in the presence of low irrigation. The threshold for cellular injury is 43 °C; this threshold is reached within the first 1 second of laser use and returns to normal temperature levels over 5 seconds following laser cessation. Dr Liatsikos highlighted the surgical circumstances associated with greatest risk of thermal injury: low irrigation (passive or gravity irrigation), higher laser energies, and instrument use without an access sheath. For clinical safety, he reported that research analysis recommended that irrigation should be >100 mL/min for powers >30 W and that laser power >100 W cannot be recommended.

Using an access sheath increases irrigation inflow by 35–80% compared to flexible scope alone;[5] therefore, use of an access sheath is recommended to reduce risk of cellular injury. However, increased irrigation poses risk of injury via raised intrarenal pressure, including risk of renal extravasation, haematoma, urinoma, sepsis, postoperative pain, and long-term risk of renal scarring. To reduce the risk of these significant complications, pressure must be maintained <30 mmHg. Use of an access sheath (with a diameter ≥10/12 Fr) increases irrigation but lowers intrarenal pressure, compared to forced irrigation in the absence of an access sheath,[5] helping to reduce the risk of these complications. Newer irrigation tools and surgical technologies in development appreciate the importance of continuous monitoring of both temperature and pressure and are incorporating sensors into their designs.

WHAT'S THE VERDICT?

Holmium lasers balance stone and water energy absorption to be safe and effective for fragmentation of renal stones, when in both direct contact and at distance. Thulium pulse lasers show excellent promise for more efficient renal stone ablation and have practical improvements over bulky holmium lasers; however, the thulium alternative does not have the foundation of evidence and experience that the holmium laser systems have established over the past two decades. Both laser systems present risks of thermal injury that have been historically underappreciated but are important, immediate clinical considerations and are influencing the technological advancements of the lithotripsy systems in development.

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Interviews

Medical innovation has transformed at a remarkable pace. We spoke to the experts pushing the revolution at the forefront. Drs Jack Kreindler, Indra Joshi, and Mark Slack share their drive to innovate, the growth of digital medicine in the UK, and the future of the discipline.

Dr Jack Kreindler

Founder and Medical Director, The Centre for Health and Human Performance, London, UK

Q1 **In your specialty of emergency and high-altitude medicine, and specifically your work in extreme environment physiology, which diseases or conditions do you manage?**

So obviously, the mountains and very remote places very seldom have the same level of equipment as you can imagine is just down the road with an ambulance being able to take you there. So an old answer to that question is that in remote and extreme environments, everything is a serious condition sometimes. Even a cut that might look innocuous could well become something that stops you from climbing the mountain. A blister, for instance, that goes completely pear-shaped can be a disaster for a whole expedition. But clearly there are classic things, which in my area of interest are quite unusual to find at normal altitudes and in normal situations. They include, quite specifically in the extremes of altitude, acute mountain sickness, high altitude pulmonary oedema (meaning high-altitude lung fluid build-up), high-altitude cerebral oedema (which is swelling and fluid build-up in the brain because of altitude), general problems with hypoxia (like people getting confused and becoming unconscious), and the environmental things (which you know if you're wearing enough sun cream at sea level) and they're not really much of a problem, but they can cause profound burns exposure, you can get heat stroke, you can get hypothermia, or your blood sugar can get dysregulated; there are many things that simply do not happen, except in the rarest circumstances, at sea level. That is mainly what we learn to deal with, but without the hospital around. We have to deal

with that with the bare bones of equipment and medicines with us, so it's challenging in many ways.

Q2

How has your passion for your work been sustained over the years? How did this lead to the founding of the Centre for Health and Human Performance (CHHP)?

Being able to practise medicine in an environment that is utterly astounding, in remote places that are of outstanding natural beauty and sometimes savagely remote but equally beautiful, is hardly a bad office view or environment. So it makes me chuckle when you say 'how have you maintained your passion' because even just the thought of practising or teaching or researching in environments where there are fewer people, perhaps, that have stood on those places than stood on the moon, for me is automatically intriguing and brilliant. It's an adventure.

Having said that, for 10 years I did practise as an associate specialist in emergency medicine in the NHS at The Whittington Hospital, London, UK, and I suppose the other side of it is not the environment, but who you're working with and who you're working for. I just have never, ever got bored of being stimulated by and learning from patients and colleagues. There is never a day where you can't learn from someone's story, someone's tragedy, someone's miraculous recovery, and I generally have a rule, which is to work with people that are cleverer than you so that you can always learn.

I know that many of my colleagues, having met them after 20 years of qualifying from University College London, London, UK, some of them feel as if they need something else now to remotivate them, but I have never had a shortage of satisfaction and stimulation from my work. And bear in mind that my research isn't in a laboratory and it isn't doing the conventional clinical trials that other people might do. My work in medical technology and remote patient monitoring, both for extreme environments, but also for people who have extremely severe physiological problems like chronic obstructive pulmonary disease and congestive heart failure, are areas of research that have kept me very much at the forefront of technology. And when you're at the front of technology, nothing bores you. I mean, it's pretty amazing stuff. And the winnings from the technology work is what funded the CHHP. So I put all my winnings towards my little not-for-profit institute, which was founded in 2007, and that continues to be a source of the same kind of inspiration from patients and colleagues and exploring what technology can do.

Q3

If you had not chosen medicine as your profession, what career path do you think you would have taken?

I would be sitting on the banks of the Grand Canal in Venice, painting beautiful domes made by architects who are my heroes. I am not actually a scientist natively: I am an artist. I studied art, probably with more passion than any science. In fact, I still believe that I am the first person and only person in the history of UK medical school to be allowed to study medicine with art as the third A-level. It took a lot of arguing that folk like da Vinci and even Russian vorticists had something that could contribute to the medical world. And why is that? I think it's because basically in medicine we are given superpowers but also handcuffs with respect to evidence base and science: building the evidence base and sticking to it, and then renewing it when new evidence comes along. It's a very scientific process, but actually medicine is also an art: it's an art of observation, an art of interpretation, and an art of communication. There are a lot of interpersonal politics and diplomacy, and things that have nothing to do with Henderson–Hasselbalch equations or other kinds of chemistry. I love that aspect of medicine, and if I didn't qualify, I would have still stuck to those things and probably have done something in the creative world, connected to science but not practising medicine.

"There is never a day where you can't learn from someone's story, someone's tragedy, someone's miraculous recovery, and I generally have a rule, which is to work with people that are cleverer than you so that you can always learn."

Q1 COV-CLEAR is a platform for coronavirus disease (COVID-19) case reporting, launched earlier this year by yourself and a team of medical professionals in the UK. Are you able to share some of the main successes of this platform so far?

COV-CLEAR was founded as an entirely voluntary initiative by doctors, scientists, some policy makers, technologists, and pure mathematicians and logicians and so forth as a response to the COVID-19 crisis. Not as an official advisory to government, but we ended up writing a lot of white papers with a lot of very clever people around the world, mainly around common standards and open-source tools for data to be better shared between different research groups, and for personal results to be better shared among recipients who need to trust in the results.

So, if you get a vaccine have you really been given that vaccine? Was it you that was given that vaccine? Was the vaccine the vaccine? Have you still got antibodies? Have you got COVID-19? When were you tested? Who tested you? Did you test yourself? And can we preserve the patient's identity, and privacy around their identity and their medical test results with privacy-preserving solutions? You can have a look at it on online,[1] but we published the world's first open standard for how to ask questions in symptom surveys.

We accidentally acquired about 5,000 responses from our prototype survey. We were astounded at the number of people that had symptoms, and we noticed that a lot of people wrote in an extra symptom (this is in March/early April by the way): they started writing in that they'd lost their sense of smell. This is weeks before it was actually noted, and we thought 'this is weird, about one in three people are writing that they lost their sense of smell.'

Then we got a group of mathematicians to build a new kind of statistical method around improving the reliability of all these tests. Every question is a test, like every blood test is a test, and every swab test is a test. And if you can glue together all these different types of tests to get a better reliability and diagnostic power, without spending lots of money in very expensive labs, could you glue together the questions that are asked by doctors or asked in a questionnaire with a self-reported antigen test, or even antibody test, and can we then better understand if you really had COVID-19 or not or when you had it? Are you still infectious or are you not? And all of these kinds of things have evolved into a computational model, which can plug in laboratory or point-of-care or even home remote testing to better reduce the risk of people coming together in large crowds for things like the live events industry to avoid 'super spreader' events.

So, we are now taking the COV-CLEAR group into a series of trials sponsored by Live Nation Entertainment, Beverly Hills, California, USA, the largest live events production company in the world. They are sponsoring a series of five trials (capacity one, two, three, four, and five), starting in Estonia with 1,000 people, under the University of Tartu, Tartu, Estonia, and the Estonian government. We're not allowing anyone under 50 to go in because we don't want to have any risk of hospitalisation, but we will be studying how economically we can get to a predictable and acceptable level of COVID-19 transmission risk reduction. You can't do it for a £100 a go; it's got to be less than £10. So can we get them to be trustable? Can we get the people who do the tests to be witnessed cheaply that they're doing it right and not cheating (because you will cheat if you can go to a concert, especially in lockdown). And can we predict mathematically the prior probability of spread, hospitalisation, and death? The ultimate goal of COV-CLEAR is to not only provide open-source questionnaires and digital certificate architectures, but open-source protocols approved by national governments for the whole industry to adopt, not for us to own, but for the whole industry to adopt in order to help culture, media, and sport happen at scale again.

Q5 In a TEDx Talk that you delivered in September 2019,[2] you implored the audience to "not underestimate the power of data and exponential technology." Since then, there have been rapid advancements in digital innovation in response to the COVID-19 pandemic. Do you think that healthcare professionals, and the wider industry, had been underestimating the value of digital technology and data?

My view on it is slightly different to others: I don't think people underestimated the power of digital, they just overestimated the power of analogue and face-to-face. There was a kind of mantra around 'nothing can beat a face-to-face contact.' The pleasure, enjoyment, and improvement in noticing subtle vital signs about somebody, the way that they feel those kinds of cues, emotional and otherwise, and body language: it's all a bit harder over a phone. I think people were 100% convinced that you should only use telemedicine, for instance, in the rarest of circumstances if needs be.

But actually now, once you've gotten used to it, and we had to get used to it, we had to do all of our consults remotely, we had to master Zoom or whichever platform you're using as a general practitioner. The reality is that once you've been trained, you suddenly realise the benefits of the other way of doing it too. And there are enormous benefits to doing it, which will never replace face-to-face but you realise that actually there are lots of things that you can do a lot more quickly with a much better patient experience in terms of booking, waiting, travelling, paying for car parks in the hospital, getting a parking ticket in the hospital; all of these things really hurt the patient, both from a time and resource perspective. Do you need a secretary to book an appointment with the doctor? You can just say 'my next appointment is here,' press the button on your screen, and boom: you've got another Zoom link. And things like messaging to remind people to turn up to something or to take their medication has become so much more widely appreciated now. I think we overestimated how brilliant analogue was, and we never had the chance to really feel comfortable about digital and now that we have, the whole thing has changed.

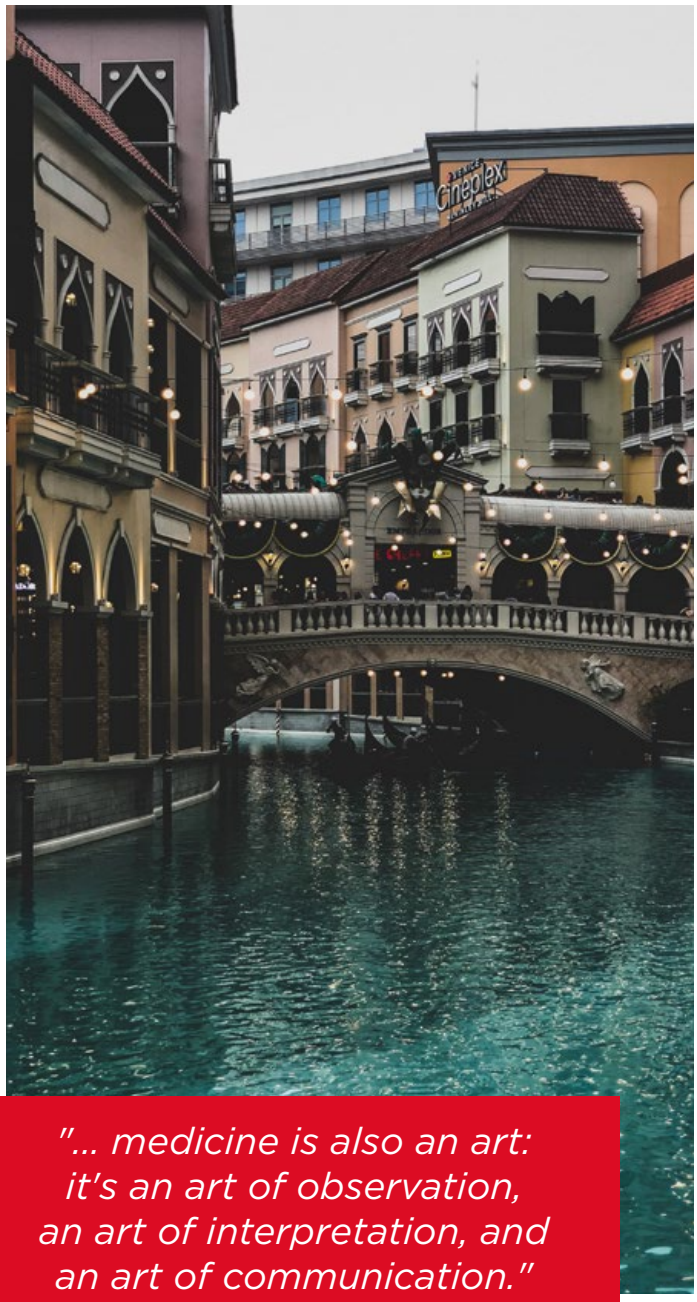
Q6 What can clinicians do to promote transformative innovation in healthcare and empower hesitant patients to support advancements in medical technology to manage their health?

Meet people where they are. I think that's the bottom line. You have to ask the question "would you like to see me in person, or would you like to see me from the comfort of your home?" Let the patient drive it. That's my view.

I know we're a not-for-profit institute but we couldn't be luckier to be on Harley Street: it's a beautiful place in Marylebone, we've got every single thing you could possibly want at your fingertips in terms of being able to order anything for patients who rapidly need things. If they need them, it's there. It's nice to see people in our laboratory, put them in on our cardiopulmonary exercise testing rig, and see them do their best and wobble out. But they also like to be at home and they also like to fit in a really important

conversation within the half hour they've got between one meeting and the next. And you can do that remotely. So, you've got to ask the patient, 'what is the best experience for you?' and then have both options for them.

I think there will be some people that just refuse to feel comfortable in the digital world. I don't know if it's the doctor's job to train them or not. But what lockdown has done is forced everyone, not just the medical profession but clearly every area of life, work, family, personal, professional, doesn't really matter, everyone has had to use teleconferencing. I mean, just imagine what this lockdown would have been like for work, business, socialising, dating, you name it, without these devices that we can talk on. You can see my face. You can hear my voice. There's a camera. It's bonkers! We could be thousands of miles away from each other and still be having this conversation. This is Star Trek! If you think about it, compared to 20 years ago. And there are maybe four or five billion people, maybe less, who can do this! It's bonkers!



"... medicine is also an art: it's an art of observation, an art of interpretation, and an art of communication."

And I think that we've been forced to do it and it's all given us 'School of Hard Knocks' training in it, but most of us are comfortable with it, most of us see the benefit now. I don't think there's that much more to do. It's been thrown in at the deep end out of deep necessity. We are talking about the digital telemedicine thing quite specifically here. There are lots of other things around digital that we haven't talked about, but the big thing staring us in the face is clearly the ability to talk and communicate and see each other in teleconferencing set-ups. That's the biggest thing that I think has changed in medicine.

Q7

Where can we expect to see your focus lie in coming years? Has the COVID-19 pandemic shaped or affected these plans?

The application of extreme environments physiology to helping the sickest patients with the hardest-to-treat cancers hasn't changed. That is still a huge area of passion and interest for me. We founded my charity 'ACT for cancer' with Tessa Jowell and her daughter. Before Tessa died of glioblastoma, she wanted a charity to be set up and it's been my work for a decade. But I decided to turn that compassionate care work that we did to try to help people navigate their way through access to trials and expanded access to treatments, which otherwise are given as standard care. That work continues.

I suppose the stuff that changes now is how much of the very face-to-face, multidisciplinary, everyone in a room together kind of stuff that we did for athletes and cancer patients and so on, and on the preventive side too, how much of that can we push out to many more people through technology? So, do I have to really do an hour's worth of questions and answers? Or can I do three-quarters of that as a patient outside of a consult using an incredibly well-crafted logic-based questionnaire. Can I automatically generate a report with beautiful English, but from structured rule sets or maybe in future more sophisticated language-generation systems that can help me as a doctor to write a report in five

minutes rather than an hour? Can we take the stuff we started with COV-CLEAR and build a full-blown, trust at scale service for any kind of test that could be as trusted as going to an expensive doctor, in an expensive clinic, with an expensive lab, and expensive electronic record system giving you the result? Not just for COVID-19, but for anything. I think that's the bit that changes for me really.

The profound other thing is that my little institute has been in its location now for 13 years. We've loved working there and we have a great team and we have a great setup at CHHP in London. Is that the model for care? Is it physical infrastructure or is physical infrastructure a fraction of what we need? Do we really need 3,500 square-feet, or do we only need 1,000? That's another question that I've got. I think that for digitising interactions and scaling the trust fabric of getting people to do things, and writing and recording it in the right way, does that really need physical infrastructure? I think that's going to be a fundamental change. Like what has happened to banks; I mean, do you very often physically go to the bank anymore? Clearly, they still need somewhere to store the gold, if that exists, but do you actually need a bank? Do you actually need as much clinic space as you had before? I think that things that are really important that you clearly cannot do digitally are imaging equipment, beds for acute stuff, intensive care units, and maternity; there are certain things that you just can't do without. But I just wonder how much of it can be done so much more efficiently, making that space then more available for the things that we're now seeing we don't have enough of, such as intensive care beds. So, it will be interesting.

Q8 What advice do you have for medical colleagues who may also be seeking less usual clinical career paths?

I've always been in a nontraditional path, so for me this is well-trodden ground. What I would say is that I sense that there were almost three things that you could do when I qualified: you either were a full-time medic, or you chucked in some research, or you went into industry, which invariably meant medical devices or pharma. But now there are myriad health technology companies, and innovative different models of practising medicine and of scaling care. The world has gone bonkers, in a good way, around more rapid development of drugs or getting trials to run more efficiently as a result of using technology to do things. Either at the artificial intelligence (AI) discovery end, or the less AI but equally important decentralised, distributed trials end of things. There are so many things where people with medical degrees are vital in the new digitised health economy. And I say that broadly digitised: there are no longer just human brains involved. There are a lot of robots, machines, technology, software, and so on.

And that, I think, is vast and the only real way to navigate it is to plunge into the technology and healthcare technology innovation world, where there are lots and lots of conferences where you'll meet lots and lots of people. Even now, they happen online all the time. On the farthest end of it, you've got things like Exponential Medicine that will completely blow your mind and you might end up coming back to London to go to ward round, having a bit of an existential crisis thinking, 'no, I want to be a Californian; I want to be the chief medical officer for SpaceX and go to Mars.' Through to things that are a lot more industry-focused but equally as inspiring, like Collaborating for Novel Solutions (CNS) Summit, which happens every October/November time. There's HLTH. There's the J.P. Morgan Healthcare Conference where everyone got COVID-19 in January/February. And there's tons of stuff in the UK as well. If you search online 'health technology conference' or 'health innovation conference' or 'future of medicine conference,' you will undoubtedly find people in places talking about stuff that you haven't heard about, which will inspire you and give you some ideas about what to do next. That would be my advice. That's how my world expanded, where I realised I wasn't the only person in the UK doing this stuff, I wasn't the only doctor trying to still practise and also build things. And nowadays, instead of being frowned upon, it's lauded. There were lots of frowns when I was doing it, put it that way!

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Dr Indra Joshi

Director of AI at NHSX; Founding Ambassador of One HealthTech, London, UK

Q1 You have built an atypical medical career, holding roles that did not exist 10 years ago, such as the Director of AI at NHSX, UK. What led you to pursue a career in health technology and artificial intelligence (AI) in healthcare, and what elements of your medical training and experience have served you well in forging this path?

I have always been interested in technology and how it might be used to improve health and outcomes. Working in a busy emergency department and understanding who the different users of the health and care system were helped me a lot when I transitioned into a more policy-focussed role. Also being able to navigate the many acronyms in use was extremely helpful.

Q2 How do you think AI in healthcare should progress? Should clinicians take the lead, health policy strategists, or those with a background in technology and data?

For healthcare in AI to progress, it's important that all of these professionals come together. Different sectors working in isolation can disrupt the life cycle of AI technologies; developers and policymakers need to understand clinicians' needs and clinicians need to understand the rationale behind technologies and regulation. Having a variety of people around the table gives a far better understanding of the challenges and opportunities. This reflects a major role of the NHS AI Lab[1] in convening a range of expertise in order to accelerate the safe and effective adoption of AI technologies.

Q3 As AI takes on a bigger role in healthcare in the coming years, should clinicians and patients have a better understanding of data, machine learning, and the processes and ethics of using AI?

Ensuring that those who will be impacted by the use of AI technologies have an understanding of the rationale for their use is central to building trust in their adoption in health and care settings. Part and parcel of safe and effective deployment of AI in healthcare is ensuring that clinicians and patients feel comfortable and well-informed. This raises the question of how we can best provide this education and who should oversee it. Following on from the Topol Review, HEE are working towards addressing some of the recommendations.

Q4 What obstacles are facing the growth of AI in healthcare? How can we combat these to improve patient care and health service delivery?

There are lots of challenges to contend with. Firstly, the rate of innovation is outpacing regulation and policy. This means we risk having a bottle neck where clinically useful tools are not being deployed in a timely manner. This is one of the areas the NHS AI Lab is focussing on, working alongside regulatory bodies to create a safe and supportive ecosystem. This ties into a second challenge: the need for joined up systems. Developers need to have a clear path to bring their products to market and deploy them in health and care settings. Our AI in Health and Care Award is one of the ways we are trying to guide innovators through this process. Thirdly, I think there is a wider agenda around trust and understanding when it comes to AI for health. Clear guidance and communication wherever possible will help people understand the benefits and risks of these technologies.

Your appointment to the role of Director of AI at NHSX came shortly before the coronavirus disease (COVID-19) pandemic. How have your priorities shifted this year to face the challenges of the pandemic? What impact do you think COVID-19 will have on the future of AI in healthcare?

COVID-19 has been a massive accelerator of innovation across health and care. Like everyone, we have adapted our work to support the pandemic response. NHSX set up the National COVID-19 Chest Imaging Database (NCCID), a centralised UK database containing chest X-ray, CT, and MRI images from hospital patients across the country to better develop technology to optimise care for hospitalised patients with severe infection. This has inspired us to look further into whether the NHS could benefit from having a national imaging platform to facilitate improved development and deployment of AI technologies. Looking to the future, I think COVID-19 has made us all very aware of our own health, there is an opportunity for AI to help us manage our own health more easily and feel empowered to do that.

Q5 As AI applications aid accuracy and speed in clinical management over the coming years, how do you think we can maintain the human connection of care in health?

The purpose of AI in health and care is not to replace health and care workers, but to support them so they have more time and energy to focus on those all-important human connections which we know are at the heart of providing excellent care. Used appropriately, AI technologies have huge potential to improve the personalisation and precision of healthcare. The NHS and social care workforce are our greatest assets: our job is to harness the power of technology to support them. In some instances, AI can reduce the burden on the workforce, and in others it can directly improve patient care. For example, the 'e-Stroke suit' by Brainomix, which was prized with funding in our first round of awards, not only uses AI to help interpret brain scans and get patients the best possible treatment but also allows doctors to share information across hospitals in real-time, avoiding all too common delays in the systems which can impact on patient care.

Q6 Your advocacy work for inclusion and representation in technology and AI extends beyond the NHS to your role as a founding ambassador for One Healthtech, what strategies do you think are needed to ensure better representation of people of different backgrounds in both the technology field and the data used to build AI systems for healthcare?

AI technologies need to be trained on large amounts of data that represent the whole population. Accessing this level of data is often a real challenge, which is one of the reasons why we're looking into the possibility of creating representative data platforms to help validate models. In terms of ensuring diversity within the technology workforce, people need to see themselves represented. This needs meaningful inclusivity of people from diverse backgrounds in senior leadership. We need to be scouting out the best talent, making it clear that we need a really diverse skill set and challenging any misconceptions about what it means to work in technology and AI. It's important to inspire the next generation to realise the exciting opportunities in health technology.

Q7 As AI and health technology explodes into more common clinical practice, what advice do you have, or further training or education do you recommend, for clinicians or medical students interested in this field?

There are lots of ways people who are interested in AI and health technology can build their knowledge and experience! Reading recent reports and blogs and listening to a range of the fantastic podcasts out there is a good place to start. There are some great postgraduate opportunities to study AI and health for those who want to pursue a specialist career. I would also encourage people to get involved with groups like One Healthtech and other communities for health innovation. The NHS AI Lab has some great resources on our website, and a new AI Virtual Hub to facilitate a growing community of practice.

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Dr Mark Slack

Consultant Gynaecologist and Urogynaecologist, Chief Medical Officer and Cofounder, CMR Surgical, Cambridge, UK

Q1 What were your motivations for starting CMR Surgical, and what goals do you have for the business?

Despite having been around for 30 years, keyhole surgery has failed to penetrate the majority of surgeries. In this time multiple advantages have been demonstrated over conventional open surgery like less wound infections, reduction in pain, and fewer incisional hernias. In total, minimal access surgery (MAS) has a 50% lower complication rate; despite these many advantages, the uptake remains relatively poor because of the difficulties in mastering keyhole surgery.

I believe that robotic surgery can provide the bridge for surgeons to transition from open surgery to MAS more easily than with conventional manual (handheld) MAS.

Q2 What are the biggest obstacles that are impeding patient access to MAS, and how can they be overcome?

MAS is technically very difficult. Many surgeons struggle to adapt to the techniques for MAS. Even with training, many surgeons struggle to attain the competencies required to perform MAS fluently and well; consequently, they revert to open techniques. Complex manoeuvres like suturing and knot tying are difficult to master with conventional unwristed MAS instruments. The addition of robotic wristed instruments, three-dimensional magnified vision, and better control and precision offered by the robot will help surgeons master these otherwise difficult techniques. This will allow more surgeons to perform keyhole surgery therefore getting it to more patients with all the benefits it gives.

Q3 How has the coronavirus disease (COVID-19) pandemic affected surgical developments?

It has released the brakes on the monopoly held by major companies. There is now an accelerated process for trial development, which has already shown results with the sped-up process for vaccine development. The pandemic has highlighted many outdated practices in surgery that are brakes to efficient delivery of service. It has shown that admission for same day surgery and the use of enhanced recovery to speed up discharge are important aspects of efficient safe and economical surgery.

Q4 With the ongoing COVID-19 pandemic having significant impacts on performing surgical procedures, what role could robotic surgery have in ensuring that patients are still able to undergo surgery?

Robotically assisted surgery can help to reduce the number of people in direct contact with the patient for prolonged periods of time. It reduces the number of surgeons and assistants at the bedside as well as the number of people in the theatre. Indeed, the surgeon can be behind a protective screen or even in an adjacent room for most of the surgery. As the pandemic has progressed, we have realised that the risk to operating theatre staff is small, so this has not really made a huge difference; however with less pain and lower complications there will be a reduction in the time spent in hospital for patients, reduced readmissions, and reduced reoperations.

Q5 What do you think have been some of the major medical breakthroughs of the past year? Have any particularly resonated with you?

2020 has been a miraculous year in medicine. In under 12 months, scientists have characterised the genetic profile of COVID-19, understood the disease process leading to the introduction

of different management techniques leading to marked reduction in complications and mortality, developed a number of vaccines (both traditional and novel), and started administering them to patients. The mRNA vaccines have a very high effectiveness and also work in the elderly. In addition, it looks like these techniques may also have a role in tumour immunology.

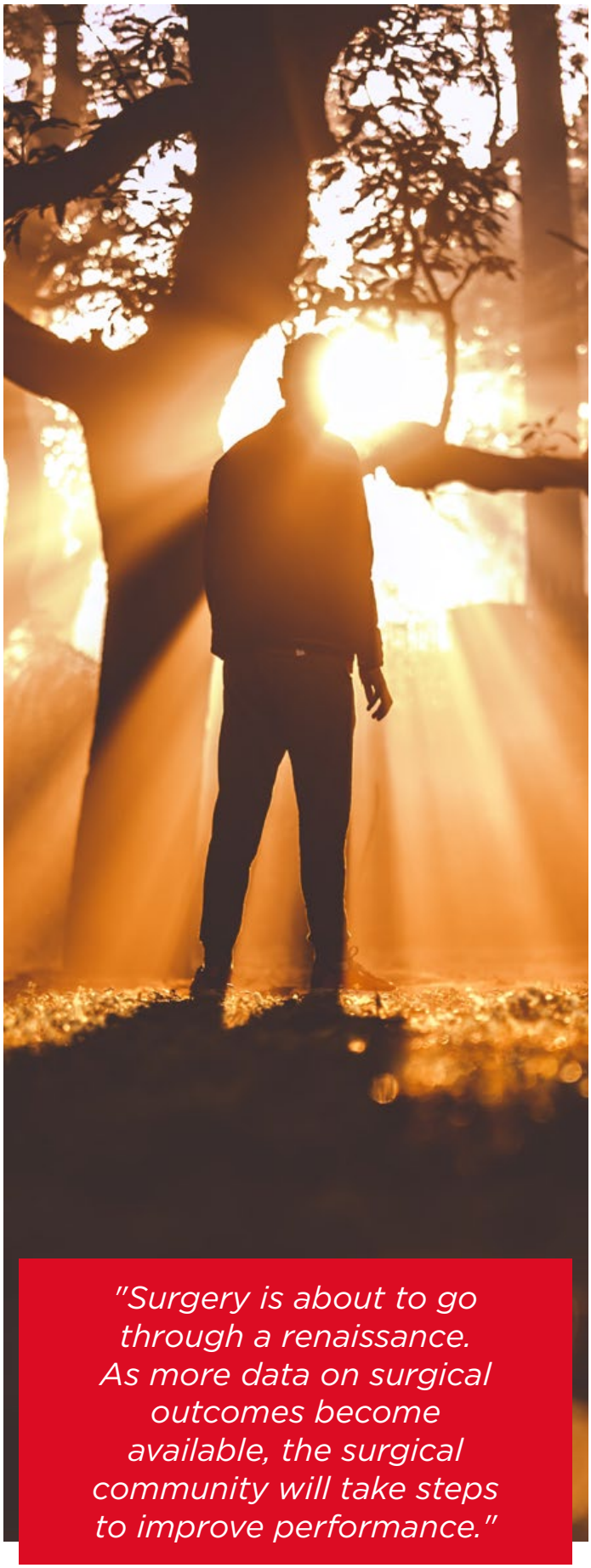
The 2020 Nobel prize was awarded to the developers of the CRISPR technique: a development likely to have a similar impact on healthcare as the discovery of antibiotics. Finally, Demis Hassabis (London, UK) and his team have developed an algorithm to decipher the 3D structure of proteins, which could change the rate and number of new developments of drug discovery and disease management.

Q6 You recently gave a presentation at the Association of Surgeons in Training (ASiT) Surgical Summit, what were the main messages from this talk?

I wanted to inform them about my vision of the future of surgery. I also wanted to show them the proven scientific evidence of why we believe robotics is the way forward. More importantly, I wanted to motivate them about their chosen career path. To remind them that they are in a wonderful profession and to remind them of their responsibilities to the pursuit of good science and to always remember that the ethical approach to medicine is the only one.

Q7 What do you envision the future of surgery to be, and what ongoing innovations are you most excited to see in surgical practice?

Surgery is about to go through a renaissance. As more data on surgical outcomes become available, the surgical community will take steps to improve performance. The use of data bases to monitor outcomes will become widespread. A robot introduces a system between the surgeon and the patient that makes the capture of data much easier. This also allows the correlation of outcome data with the systems telemetry and the possibility of monitoring performance through objective metrics. The gradual introduction of artificial intelligence with advanced hyperspectral imaging, image overlay, and autonomous functions will all contribute to better and better surgical outcomes. So much to look forward to and so much to do.



"Surgery is about to go through a renaissance. As more data on surgical outcomes become available, the surgical community will take steps to improve performance."

Information and Communication Technology in the Fight Against the COVID-19 Pandemic/Infodemic

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Disclosure: The author has declared no conflicts of interest.

Received: 31.08.20

Accepted: 17.11.20

Keywords: Coronavirus disease (COVID-19), eHealth, information and communication technology (ICT), technology.

Citation: EMJ Innov. 2021;5[1]:42-45.

INTRODUCTION

A new coronavirus infection named coronavirus disease (COVID-19) was discovered in Wuhan, China at the end of 2019, and has rapidly progressed. The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020. COVID-19 was characterised by the rapidity of the outbreak that was accelerated by transportation networks worldwide. Researchers have attempted various approaches to manage COVID-19, such as genome analyses, diagnostic methods, treatments, and prevention. An 'infodemic' situation has developed, whereby misinformation has caused logistical disruptions and resulted in health hazards and shortages of supplies. In Japan, face masks became difficult to find and toilet paper temporarily disappeared from stores because it was thought that it was made from the same paper as masks.[1] Similar panic buying and stockpiling has occurred worldwide, disrupting logistics. In Iran, a false rumour circulated that methanol was effective against COVID-19, which led to nearly 500 deaths.[2] In the USA, the President Donald Trump made comments about injecting disinfectant, leading to several people drinking the disinfectant and causing them health problems.[3] The International Telecommunication Union (ITU) released a statement to make it known that there is no scientific basis for the claim that 5G network accelerated the COVID-19 pandemic.[4] Social unrest has increased the stigma attached to those of Asian ethnicity, people who have recovered from COVID-19, and health care workers.[5] Even before the COVID-19 outbreak, smartphone apps were being utilised to combat infectious diseases, and more apps have since been developed to tackle COVID-19. Though information and communication technology (ICT) have the capacity to cause an infodemic, ICT has been widely applied as a tool against the COVID-19 crisis. The Taiwanese government disclosed that their advanced information technology capacity helped them to achieve far greater control of COVID-19 than other countries.[6] In this article, the author has reviewed the features of successful ICT approaches against COVID-19 and discussed their effects.

INFORMATION AND COMMUNICATION TECHNOLOGY APPLICATIONS FOR COVID-19

The ICT applications for the COVID-19 pandemic/infodemic have been categorised into patient registry, clinical decision support, telemedicine, contact tracing, and digital quarantine. Each category is outlined below (Figure 1).

Patient Registry/Geographical Information System

The tracking of patients and their contacts is imperative to public health in the fight against infectious diseases. Johns Hopkins University Department of Public Health, Baltimore, Maryland, USA, developed an interactive geographical information service (GIS) that was developed using ArcGIS (Esri, Redlands, California, USA) to display the number of confirmed cases of and deaths caused by COVID-19 on a map.[7] This GIS publishes epidemiological data worldwide, as well as the country and regional trends in patient numbers. Comprehensive information is available on maps and graphs (Figure 1). The World Health Organization (WHO) also built a similar website[8] and, in Japan, the Tokyo Metropolitan Government commissioned a website to visualise data related to COVID-19 (confirmed patients and related deaths).[9]

Clinical Decision Support

It has also been reported that machine learning of medical images, such as chest radiographs and CT scans, can be used to accurately diagnose COVID-19-associated pneumonia.[10] Much of the available data related to COVID-19 are open access, and machine learning models to support clinical decision making have made use of such data. The creation of electronic clinical guidelines has also been reported, whereby implemented data sets have aided diagnosis and treatment of COVID-19.[11]

Telemedicine

The use of telemeeting and teleworking systems using ICT became popular because of the many regional lockdowns that acted as a countermeasure to the pandemic. In Japan, telemedicine had not previously been adopted widely but now many healthcare providers utilise it for outpatient management and the initial treatment of patients with COVID-19. Various medical conferences have been held as teleconferences using video calling technologies, which has contributed to the spread of the latest medical information, including the latest developments in COVID-19 research.

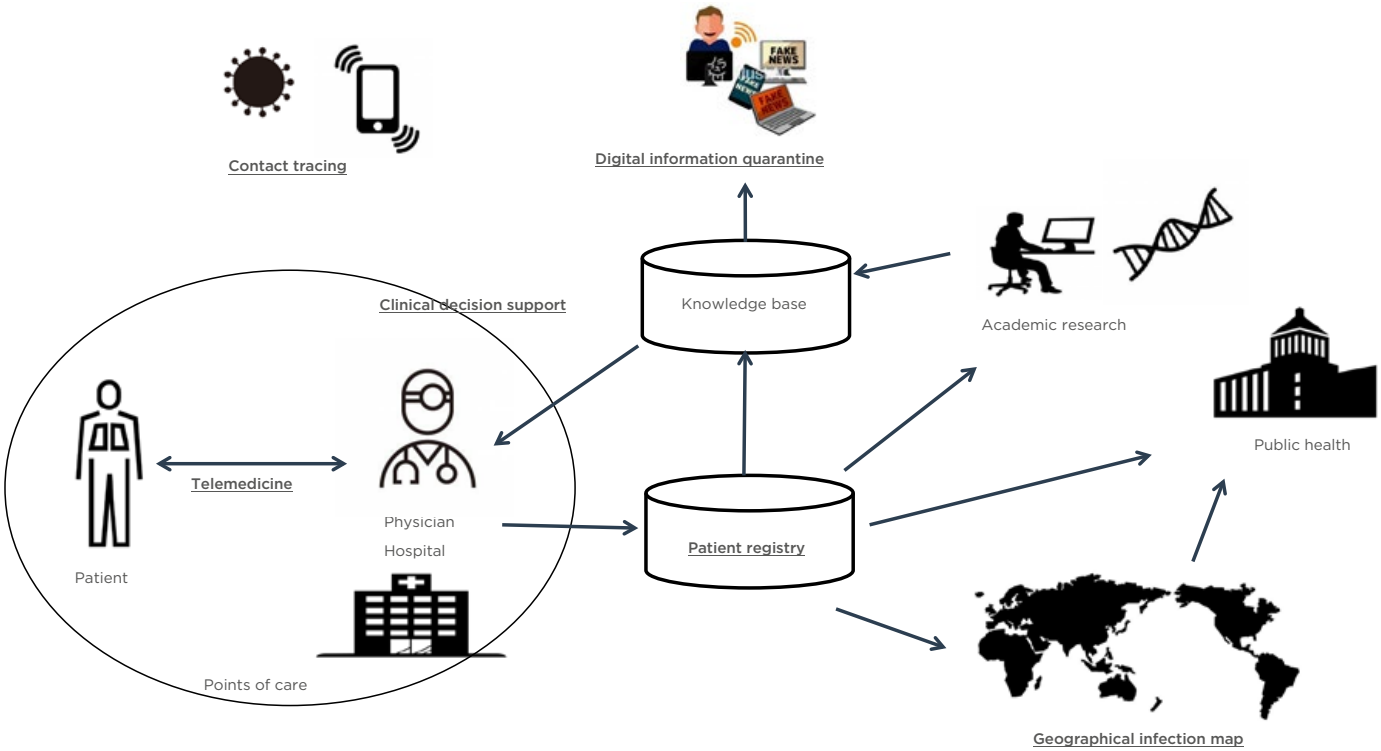

Figure 1: Information and communication technology tools for the coronavirus disease (COVID-19) pandemic/infodemic.

Contact Tracing

Digital contact tracing was suggested as a means to help control COVID-19 transmission following both real-world experiences in Singapore and mathematical models.[12] Both Apple and Google provide a contact tracing application programming interface (API) on their iOS (Apple, Cupertino, California, USA) and Android (Google, Mountain View, California, USA) products. Both companies limited access to the representative agency in the user's country to protect user privacy. Japan and Germany have also developed contact tracing software using Google/Apple API and have shared it with the public as an open-source software.

Digital Quarantine Against Misinformation

To counter COVID-19-related misinformation, the WHO and other health organisations of many countries have ensured that accurate information is published. They have also blocked misinformation shared on social media and guided public information. Social media platforms also banned many accounts that propagated conspiracies related to COVID-19.

DISCUSSION

There are many advantages and disadvantages of utilising ICT in a pandemic, the disadvantages mainly concerning privacy issues and ICT investment. Various ICT tools are being used to fight the current COVID-19 pandemic. The data related to COVID-19 are available as open data, and volunteers have been using it to help control the spread of disease. It is helpful to understand the current epidemic status using websites that visualise the 'heatmap' of patient numbers and graphs (Figure 1). Trials using data for clinical support are underway, and there are high expectations regarding the potential of ICT tools to fight COVID-19.

In contrast, the privacy of infected patients has the capacity to be violated by a breach of the ICT software. Contact tracing could divulge private information, such as the whereabouts of a user and their relationships, to an unintended audience. There is also scepticism about its effectiveness in tracking infection; for example, a contact tracing app was released in Norway but was discontinued because of the low numbers of people infected and the suspicions about privacy implications. The WHO published a statement in 2016 about ethical considerations during the epidemics of infectious diseases, aiming to avoid the stigma directed at patients by protecting personal privacy.[13] Germany and Japan are developing their contact tracing app as open-source software in order to improve transparency and manage private information.

Nevertheless, ICT has been widely adopted to fight COVID-19, despite the suspicions the public may have about the technology. Misinformation has generated panic in relation to disasters throughout human history, long before the ICT era. ICT has accelerated the speed of information and misinformation spread and caused an infodemic, a new type of information panic. However, ICT has also delivered authentic information about COVID-19 and become a modern weapon in the fight against the pandemic. Telemedicine has already become part of the healthcare infrastructure to combat COVID-19, and will be the 'new normal' when the pandemic is over. More ICT tools are needed to keep fighting COVID-19, which could not only help in this pandemic but the next one too. In the near future, artificial Intelligence based on machine learning could be utilised to detect early stages of outbreaks, though privacy issues in training data for machine learning could cause problems.

CONCLUSION

Various ICT tools have been implemented and used to block misinformation, guide authentic information, support clinical decisions, and enable contact tracing, among other applications. Although ICT has become indispensable in the fight against COVID-19, there are still many suspicions regarding its effects. Further research and development should be performed for the next pandemic.

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Catheter-Based Local Delivery of Therapeutics to the Lungs for Severe or Critically Ill Patients with COVID-19

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors contributed equally to this work.

Received: 27.04.20

Accepted: 04.01.21

Keywords: Acute respiratory distress syndrome (ARDS), catheter interventions, coronavirus disease (COVID-19), local drug delivery, respiratory infections, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Citation: EMJ Innov. 2020;5[1]:46-51.

INTRODUCTION

Currently, the majority of treatment strategies reported for coronavirus disease (COVID-19) involve the systemic administration of drugs, in addition to other approaches including convalescent plasma.[1,2] The pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was believed to be largely localised in the lungs. Retrospective observational studies from Wuhan, China have shown subgroups of patients with symptoms affecting the cardiovascular, renal, nervous, and digestive systems.[3,4] Yet the most critical cases largely encompass those suffering from acute respiratory distress syndrome (ARDS). Therefore, the authors propose a combination of local delivery of therapeutics directly to the lungs and adjunct systemic administration (i.e., intravenous infusion).

SARS-CoV-2 Pathogenesis

Building on initial clinical and serological reports, SARS-CoV-2 appears to mainly infect the upper and lower respiratory tract. Hoffmann et al.[5] demonstrated that the virus requires two host cell factors for successful viral entry: angiotensin-converting enzyme 2 (ACE-2) and transmembrane proteases, serine 2 (TMPRSS2). Previous studies have indicated the expression of both factors in human lung tissue.[6,7] Wang et al.[8] analysed specimens taken from the lower and

upper respiratory tract, faeces, blood, and urine samples of laboratory-confirmed COVID-19 cases, in which a majority of live virus was obtained from the lower respiratory tract in bronchoalveolar lavage fluid (93%). Therefore, if viral replication is primarily occurring in the lungs, a localised therapeutic approach could prove to be just as, if not more effective than, a systemic approach. Similarly, proinflammatory cytokines (i.e., IL-6 or TNF-α) activated by a viral infection in the lungs will proliferate mainly in the lungs. Radiological studies have demonstrated bilateral interstitial lung inflammation and fibrosis, characterised by ground glass opacity, crazy-paving pattern, and consolidation in lung CT scans.[9] Drugs candidates that target these proinflammatory cytokines (IL-2, IL-6, TMPRSS2) would again benefit from a localised delivery to counteract the damaging effects of ARDS. Considering that COVID-19 primarily affects the lungs, the authors propose a transcatheter approach to locally deliver pharmaceutical therapies (Table 1) as an adjunct to systemic therapy.

Table 1: Drug candidates for local delivery in the treatment of patients with coronavirus disease (COVID-19).

Mode of Action	Class	Drugs
Antiviral	Nucleotide prodrug	Remdesivir
	Protein	Human recombinant soluble ACE2 (hrsACE2)
	Photosensitiser	LS11
	Polysaccharide	Pentosan polysulfate
Anti-inflammatory	Immune modulator	Colchicine
	Glycosaminoglycan	Low-molecular-weight heparin
		Unfractionated heparin
	mTOR inhibitor	Sirolimus
Antithrombotic	Glycosaminoglycan	Danaparoid
		Sulodexide
	Synthetic oligosaccharide	Fondaparinux
Bradykinin storm inhibitor	Immune modulator	Icatibant
Cytokine storm inhibitor	Monoclonal antibody	Sarilumab
		Tocilizumab
		Baricitinib
		Risankizumab
		Lenzilumab
	Hormone	Prednisolone
		Dexamethasone
	Interferons	Interferon β-1a
Endothelial protectant and vasculoprotective	Nucleic acid-based drug	Defibrotide
	Oestrogen	17β-oestradiol
Thrombolytic	Protein	Tissue plasminogen activator
	Plasminogen activator	Urokinase
	Enzyme	Streptokinase
ADP receptor inhibitor	Antiplatelet drug	Cangrelor

ACE2: angiotensin-converting enzyme 2; ADP: adenosine diphosphate.

RATIONALE FOR LOCAL THERAPEUTICS

Drug Delivery Methods

There are numerous drug candidates being investigated for COVID-19 treatment that either target the virus lifecycle (entry, replication, or exocytosis) or modulate the host immune response (stimulate viral interferons or inhibit cytokine storm).[10] Regardless of the candidate, these therapeutics can be administered as a tablet, intravenous infusion, or subcutaneous injection. Orally administered drugs may be affected by first-pass metabolism, in which a majority of the therapeutic is metabolised by the liver. Once it passes the liver, the bioavailability of the drug may be greatly reduced at which point the drug circulates systemically. Intravenous administration typically overcomes issues regarding bioavailability, though the drug again circulates systemically once it passes the lungs. A localised delivery of therapeutics (Figure 1) could increase the bioavailability at the site of action (i.e., the lungs).

LOCAL DRUG DELIVERY APPROACHES

Pulmonary Artery Delivery

One possible solution is to administer drugs locally using a Swan-Ganz catheter and administering the drug through the pulmonary artery. This could be performed bedside. Some intensive care units or COVID-19 treatment floors may already have catheterised their patients with triple-lumen internal jugular sheaths, in which case a Swan-Ganz approach would be easy. Two large, multicentre, randomised controlled studies looked at the use of pulmonary artery catheters (PAC) in patients with shock and ARDS.[11,12]

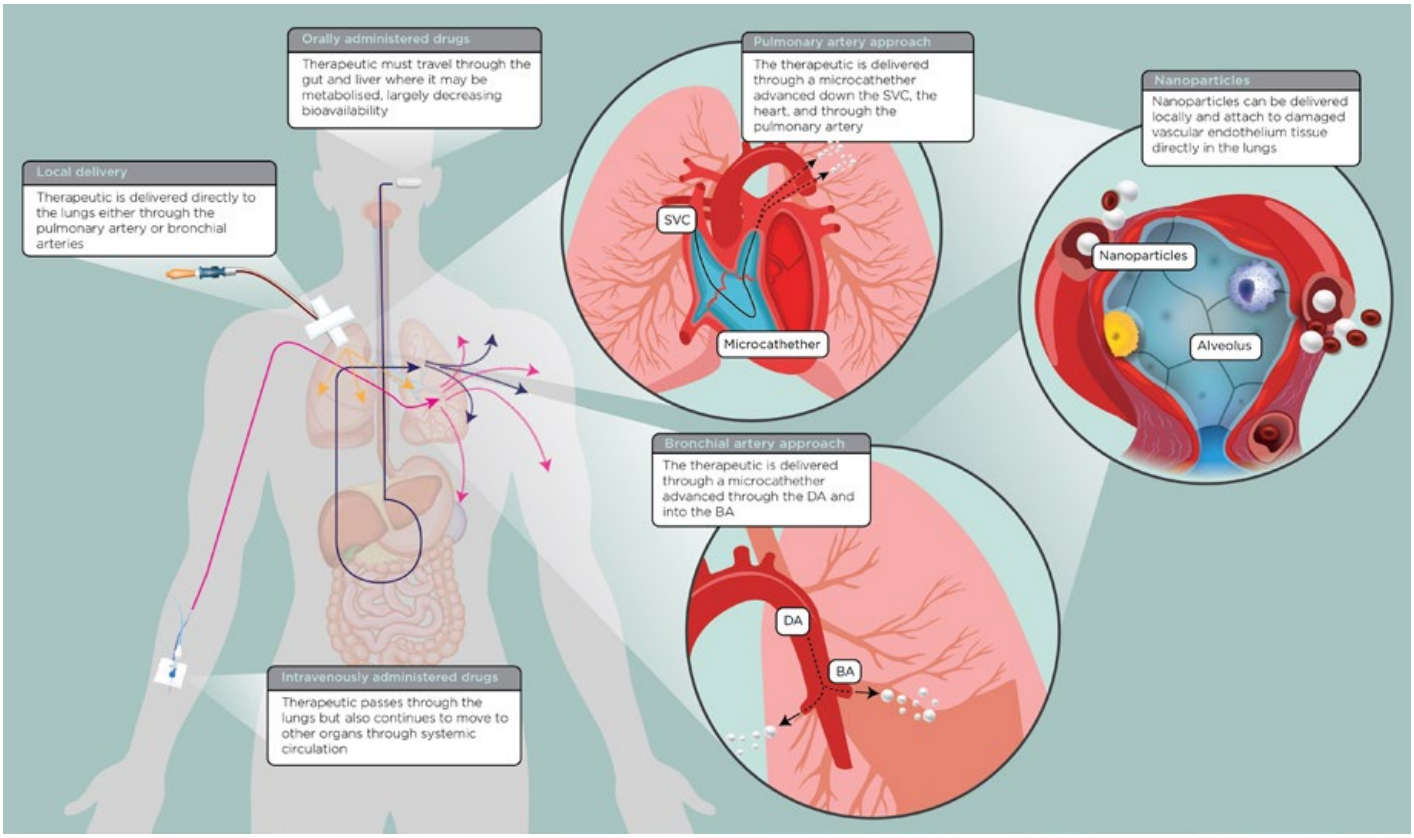

Figure 1: A simplified overview of orally administered (i.e., pill or oral suspension), intravenously administered, and locally delivered drugs for patients with coronavirus disease (COVID-19).

Blowout panels describe two local delivery approaches: the pulmonary artery and BA. The third panel describes the use of nanoparticles, which can be used with any local delivery approach.
BA: bronchial arteries; DA: descending aorta; SVC: superior vena cava.

PAC in the context of these trials were used to measure ventricular filling pressures, cardiac output, and other haemodynamic data, which the clinicians then used to guide treatment decisions. While there was no significant benefit shown in the use of PAC to guide decision-making, there was no difference in mortality between the groups who did and did not receive a PAC. This may indicate that the use of PAC in patients with ARDS or acute lung injury does not pose an increased risk for mortality. Both studies indicated PAC-associated arrythmias as the most common complication. In the French PAC study, additional complications included arterial puncture and haemothorax. No deaths were attributable to ventricular fibrillation or arrhythmia. Several patients developed positive bacterial cultures following PAC insertion.[12] In the National Heart, Lung, and Blood Institute (NHLBI) study, the rate of complications was no different between groups, and no deaths were related to the insertion of a catheter.[11] In the setting of COVID-19, the risk of PAC-acquired bacterial infection could be low because most hospitalised patients requiring central catheter insertion are being given antibiotics prophylactically to protect against secondary infections.[13,14] Local delivery of antibiotics in the form of aerosol inhalations are approved for two antibiotics in the USA (aminoglycoside and monobactam), with numerous ongoing clinical trials assessing the efficacy of aerosolised antibiotics or antibiotics reformulated as nanoparticles for chronic pulmonary infections or cystic fibrosis.[15,16] In COVID-19, the drugs that target proinflammatory cytokines common in ARDS can be administered locally and several times if needed.

Transarterial Local Delivery

Transarterial local delivery is a well-established procedure, including local lung therapy via the bronchial arteries using microcatheters.[17-19] With a localised therapeutic approach for COVID-19, the treating physician could administer drugs through the bronchial artery. However, given the complexity, a transarterial approach would require the clinician to perform the intervention using imaging. Yet, administering therapeutics through the bronchial artery may provide the greatest increase in bioavailability in comparison to other methods.

CATHETER-DIRECTED THROMBOLYSIS

There is growing evidence of viral coagulopathy developing in a subgroup of patients with COVID-19. Viral coagulopathy is not uncommon in other respiratory viruses, including infection from SARS-CoV-1 and 2009 pandemic H1N1 (pH1N1). Patients affected by SARS or pH1N1 developed intravascular thrombi, microthrombi, intra-alveolar haemorrhage, fibrin deposition in the lungs, and diffuse alveolar damage.[20-22] Several clinicopathologic reports on COVID-19 have reported postmortem findings of venous thromboembolism and thrombosis of small and midsized pulmonary arteries, as well as diffuse alveolar damage, oedema, hyaline membranes, and proliferation of pneumocytes and fibroblasts.[23-25] Catheter-directed thrombolysis (CDT) could prove to be another powerful therapeutic to treat COVID-19-associated pulmonary embolism. CDT can be performed using a PAC positioned in the pulmonary artery proximal to the location of the thrombus or thrombi. Following successful positioning, a thrombolytic agent is infused through the positioned PAC, such as tissue plasminogen activator, streptokinase, or urokinase.[26] CDT could reverse the hypercoagulable condition demonstrated in COVID-19 ARDS, resulting in improvements in the cardiovascular and pulmonary function. Systemic thrombolysis in the context of therapy to treat pulmonary embolism is associated with an increased risk of adverse effects, including major bleeding and stroke.[27] Two previous trials assessing the efficacy of CDT versus systemic thrombolysis demonstrated improved cardiovascular haemodynamics following CDT administration of tissue plasminogen activator, with no increased risk of intracranial haemorrhaging in CDT.[28,29] Moreover some investigators support catheter-directed treatment as a potential first-line therapeutic approach for Covid-19.[30] However, large studies are warranted to determine the optimal dosing regimen of systemic thrombolysis and CDT with or without therapeutic anticoagulation in COVID-19 ARDS .

Targeted Delivery Using Microparticles

Local therapeutic administration can be buttressed by using different types of drug delivery vehicles (nanoparticle drug carriers,

liposomes, viral vectors, or microbubbles). The latter adhere to sites of damaged vascular endothelium and thus may be a method of systemically targeting delivery of therapeutics to lungs damaged in SARS-CoV-2 infection. For example, perfluorobutane gas microbubbles with a coating of dextrose and albumin efficiently bind to different pharmaceuticals. These 0.3–10.0 µm particles bind to sites of vascular injury.[31] Further, the perfluorobutane gas is an effective cell membrane fluidiser. The potential advantages of microbubble carrier delivery include none to minimal (additional) vessel injury through delivery, no resident polymer to degrade and lead to eventual inflammation, rapid bolus delivery, and repeated delivery. Microbubble carriers were successfully used in different animal models and clinical trials to deliver antisense oligonucleotide and/or sirolimus to the injured vascular bed.[32,33]

LIMITATIONS

There are several logistical and clinical challenges one must consider when planning a local therapeutic approach. During the severe and/or critical period or period of illness, patients with COVID-19 are highly contagious, at which time the virus may spread via droplets or become aerosolised during intubation or other aerosol-producing conditions. Therefore, the physical movement and intervention of these patients in catheterisation laboratories need to be highly controlled to minimise the risk of transmitting disease to uninfected patients, healthcare providers, or hospital staff. However, with growing evidence for significant damage to the cardiovascular system including heart failure, stent thrombosis, and acceleration of atherosclerosis of coronary arteries, percutaneous coronary interventions are unavoidable and warranted. Sensitivity to contrast media in these patients is not documented and the use of contrast should be approached with caution.

CONCLUSIONS

Despite the possible challenges, local drug delivery could prove to be a powerful tool in treating patients with severe or critical cases of COVID-19. Feasibility studies will help to determine the safety and preliminary efficacy of this approach.

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Triggers, Timescales, and Treatments for Cytokine-Mediated Tissue Damage

EDITOR'S PICK

While nearly all of the papers highlight the complexity of managing the pandemic and the ability to communicate effectively with patients when the system is in crisis, I have chosen McBride and colleagues' paper as my 'Editor's Pick' as it has such far reaching impact on how we manage patients with an adverse cytokine response, be it from viral or autoimmune disease. This paper makes an excellent attempt at bringing this evidence together and offers hope that the understanding we already have can give a more nuanced approach to the management of these diseases.

Dr Mike Bewick

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Disclosure: The authors have declared no conflicts of interest.

Received: 06.08.20

Accepted: 06.10.20

Keywords: Cancer immunotherapy, coronavirus disease (COVID-19), cytokines, cytokine release syndrome, cytokine storm, inflammation, sepsis, T cells.

Citation: EMJ Innov. 2020; DOI/10.33590/emjinnov/20-00203

Abstract

Inflammation, an essential cytokine-mediated process for generating a neutralising immune response against pathogens, is generally protective. However, aberrant or excessive production of proinflammatory cytokines is associated with uncontrolled local and systemic inflammation, resulting in cell death and often irreversible tissue damage. Uncontrolled inflammation can manifest over timescales spanning hours to years and is primarily dependent on the triggering event. Rapid and potentially lethal increases in cytokine production, or 'cytokine storm', develops in hours to days, and is associated with cancer cell-based immunotherapies, such as chimeric antigen receptor T-cell therapy. On the other hand, some bacterial and viral infections with high microbial replication or highly potent antigens elicit immune responses that result in supraphysiological systemic cytokine concentrations, which manifest over days to weeks. Immune dysregulation in autoimmune diseases

can lead to chronic cytokine-mediated tissue damage spanning months to years, which often occurs episodically. Upregulation of IL-1, IL-6, IFN-γ, TNF, and granulocyte macrophage colony-stimulating factor frequently coincides with cytokine storm, sepsis, and autoimmune disease. Inhibition of proinflammatory molecules via antagonist monoclonal antibodies has improved clinical outcomes, but the complexity of the underlying immune dysregulation results in high variability. Rather than a 'one size fits all' treatment approach, an identification of disease endotypes may permit the development of effective therapeutic strategies that address the contributors of disease progression. Here, the authors present a literature review of the cytokine-associated aetiology of acute and chronic cytokine-mediated tissue damage, describe successes and challenges in developing clinical treatments, and highlight advancements in preclinical therapeutic strategies for mitigating pathological cytokine production.

INTRODUCTION

Cytokines are essential regulators of the immune response that mediate protective inflammation, but uncontrolled production by hyperactivated immune cells induces toxicity and adverse conditions. Pathologies that arise from excessive inflammation driven by a 'cytokine storm' are observed in cytokine release syndrome (CRS), systemic inflammatory response syndrome (SIRS), and sepsis.[1,2] The severity can vary substantially, ranging from mild symptoms to potentially life-threatening conditions. Mild symptoms are temporary and include fatigue, muscle and joint pain, headache, fever, and rash. In more severe cases, immune hyperactivation may lead to acute respiratory distress syndrome, haemophagocytic lymphohistiocytosis, disseminated intravascular coagulation, and multiorgan failure.[3,4] These symptoms are driven by local and systemic hyperphysiological concentrations of one or more cytotoxic effector cytokines, which include IL-6, IL-1, granulocyte macrophage colony-stimulating factor (GM-CSF), IFN-γ and TNF.[4] Innate immune cells, primarily monocytes and macrophages, as well as T cells of the adaptive immune system, are key participants and often work in concert to amplify cytokine production, which results in the characteristic symptoms (Table 1).[5,6]

Aberrant cytokine production by hyperactivated immune cells may be triggered by infections, immunotherapies, and autoimmune conditions. The manifestation of excessive cytokine production may be immediate, delayed, and/or persist as a longer-term organ- or tissue-specific chronic inflammatory condition.[7] Rapid development of CRS over a few hours to days has been documented in monoclonal antibody (mAb) therapies designed to promote graft acceptance or cancer clearance, as well as post-infusion of engineered T-cell therapies (Figure 1A).[8-11]

On the other hand, infection by microbes that elicit a particularly intense immune response or that have a high replicative potential may result in SIRS-associated sepsis that manifests over several days to weeks (Figure 1B).[12] Exemplary SIRS-like pathology is observed in some patients with acute manifestations of coronavirus disease (COVID-19), in which elevated serum IL-6 correlates with respiratory and organ failure, with adverse clinical outcomes.[13] The use of immunosuppressive drugs has had limited success in managing SIRS-like pathologies. For example, the use of corticosteroids to treat inflammation arising from severe acute respiratory syndrome and Middle East respiratory syndrome did not improve mortality but delayed viral clearance.[14,15] Conversely, dexamethasone treatment lowered mortality among COVID-19 patients receiving respiratory support but not among those who did not receive respiratory support, suggesting that the benefit of glucocorticoid-modulated inflammation to mitigate lung injury may be nuanced and depend on disease severity.[16] Other long-term and episodic inflammation is associated with autoimmune conditions and spans weeks to years, such as that observed in rheumatoid arthritis (RA), systemic lupus erythematosus, or chronic graft-versus-host disease (cGvHD) (Figure 1C). For such conditions, broad immunosuppressive drugs increase susceptibility to opportunistic infections.

Common features associated with the hyperproduction of cytokines permit the development of therapies that might be applicable across different forms of CRS that

have similar aetiology. A widely used strategy is to block the activity of the cytokines or their cognate receptors, an approach with origins in the management of rheumatic disease. As a participant in RA, TNF was the first cytokine to be fully validated as a therapeutic target.[17]

Clinical trials using a combination of mAb targeting TNF (adalimumab) and methotrexate have an established record of safety and clinical efficacy for effectively reducing cytokine-mediated tissue damage in RA.[18] However, in RA refractory to TNF inhibition, alternative therapeutic targets are necessary to induce remission. IL-6 is a participant in both RA and more acute forms of CRS, and the administration of mAb against the IL-6 receptor (tocilizumab) is frequently used to treat RA that is refractory to methotrexate or TNF inhibition.[19] Tocilizumab is also clinically approved by the U.S. Food and Drug Administration (FDA) for the treatment of chimeric antigen receptor T (CAR-T) cell-induced CRS, with proven efficacy, minimal side effects, and without negatively affecting response to therapy.[20] More recent developments in RA focus on inhibiting GM-CSF using mavrilimumab, an inhibitor of GM-CSF receptor α. In clinical Phase II RA trials, GM-CSF antagonism has efficacy similar to that of TNF blockade in mitigating tissue destruction.[21] Early clinical data from GM-CSF inhibition in patients with COVID-19 pneumonia suggests potential efficacy in improving clinical outcomes, and a follow-up of randomised controlled trial is underway (COMBAT-19).[22,23] Siltuximab, an FDA-approved IL-6 agonist for use in multicentric Castleman disease, is undergoing Phase III clinical trials for the treatment COVID-19-associated immune hyperactivation.[24,25] However, the complete cytokine profile of CRS is diverse, involving the monocyte and macrophage-associated cytokines IL-8, IL-10, IL-12, TNF, IFN-α, monocyte chemotactic protein-1 and macrophage inflammatory protein-1α, in addition to the aforementioned cytokines.[26]

Table 1: Key cytokines, their sources, and physiological effects.

Cytokine	Source cells	Physiological effect
IL-1	Macrophages, DC, endothelial cells	Fever, haematopoiesis Activates innate immune cells
IL-6	Macrophages, monocytes	Fever, capillary leakage, coagulation, hypotension, and complement pathway activation Promotes granulo- and haematopoiesis
IL-2	T cells	Promotes T-cell proliferation and cytokine production
IL-12	Macrophages, DC, B cells	Drives T-cell differentiation, and T- and NK-cell activation
IFN-γ	T cells, innate lymphoid cells	Flu-like symptoms and macrophage activation
TNF	Macrophages, DC, endothelium, lymphocytes, myocytes	Flu-like symptoms and cell death in some cell types, which plays a role in capillary leakage, cardiomyopathy, and lung damage
GM-CSF	T cells, macrophages, endothelium, fibroblasts, NK cells	Enhances innate and immune cell activity and is linked to neurotoxicity in severe CRS
IL-10	Lymphocytes, macrophages, DC	While IL-10 upregulation is consistent in CRS, it is classically thought to have anti-inflammatory properties and its role in CRS remains unclear
IL-17	T cells	Promotes innate immune cell recruitment and activation

CRS: cytokine release syndrome; DC: dendritic cells; GM-CSF: granulocyte macrophage colony-stimulating factor; NK cells: natural killer cells;

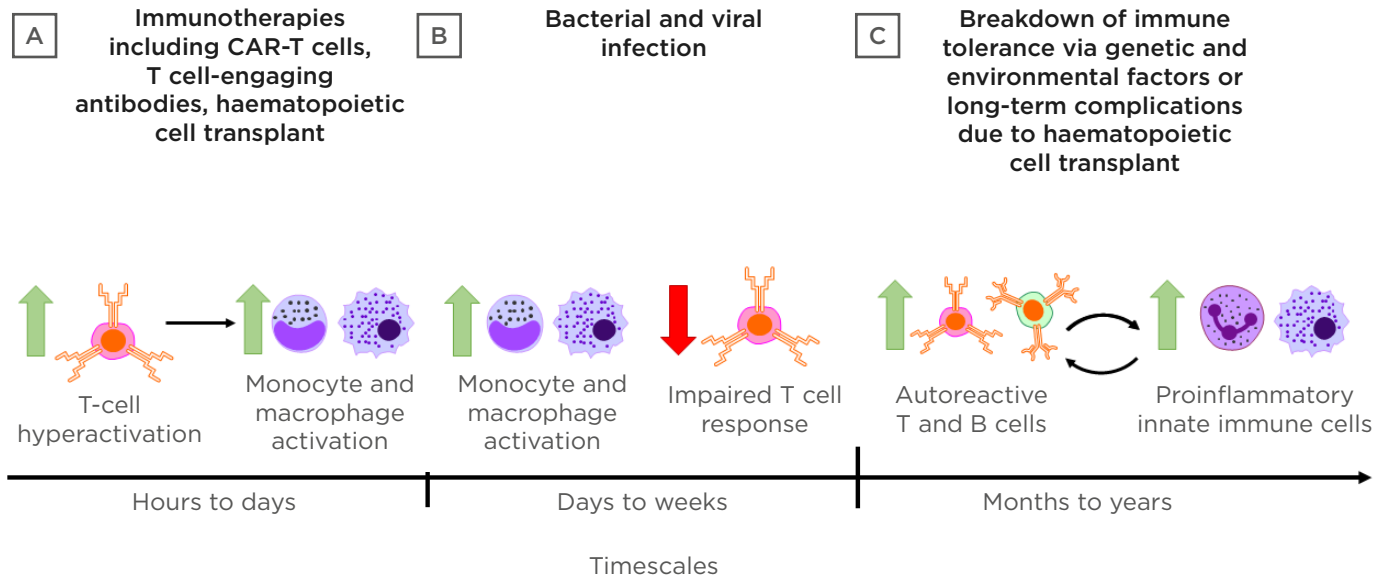

Figure 1: Triggers and timescales in the development of cytokine-mediated tissue damage.

Cytokine-mediated tissue damage may manifest in different forms across a range of timescales depending on the triggering events. **A)** Immunotherapies, including CAR-T cells, T cell-engaging antibodies, and haematopoietic cell transplant can all drive rapid T-cell hyperactivation and subsequent activation of innate immune cells that may result in cytokine release syndrome within hours. **B)** Microbial infections with high replicative potential or particularly virulent antigens may result in hyperactivation of innate immune cells over days to weeks. Delayed viral clearance leading to sepsis may also be associated with impaired T cell responses. **C)** Genetic factors and environmental triggers can combine to result in the breakdown of immune tolerance mechanisms, leading to chronic autoimmune disease in which autoreactive adaptive immune cells mediate cyclic cytokine-driven inflammation and tissue damage.

CAR-T cells: chimeric antigen receptor T cells.

Therefore, while targeted cytokine inhibitors mitigate aberrant cytokine-mediated tissue destruction, the effectiveness of cytokine-targeted therapeutics is difficult to predict because of the complex network of cytokines and disease heterogeneity.

This review discusses recent work that has advanced the understanding of cytokine-mediated tissue damage with distinct onset profiles arising from cancer immunotherapy, infection, and autoimmune disease. The authors describe the contributions of cytokines in disease pathogenesis, and how existing mAb therapies are repurposed to treat cytokine-mediated tissue damage. Lastly, the authors describe recent preclinical work developing new therapeutic options to mitigate damage from hyperactivated immune cells.

CYTOKINE-MEDIATED TISSUE DAMAGE ON SHORT TIMESCALES

Immunotherapies

Acute cytokine release is associated with cell-based cancer therapies such as engineered T cells, and T cell-activating immunotherapies. It is well recognised that abrogating cytokine-mediated off-target toxicity is a critical step in their widespread application. These therapies derive their efficacy, in part, from nonphysiologic T-cell activation that permits rapid and sustained production of effector cytokines. While such behavior is programmed to promote antitumour efficacy, it also leads to the unintentional consequence of notable toxicity in some cases, which typically develops within a few days after infusion and, if left untreated, may lead to death. Serum IL-6, IL-10, and IFN-γ are among the core cytokines that are consistently found to

be elevated in serum CRS, which is initiated by the release of IFN-γ by activated T cells or the tumour cells.[4] Generally, a higher tumour burden at the time of infusion and a greater peak in the expansion of CAR-T cells increases the risk of severe CRS. Conversely, an improved clinical outcome is not predicated on the development of severe CRS, and an effective antitumour response may be induced in the absence of this toxicity.[27]

While initiated by T cell-produced cytokines, CRS in CAR-T cell therapy is also dependent on the engagement of the innate immune system.[6] CAR-T cell-produced IFN-γ and GM-CSF activate macrophages and monocytes, resulting in upregulation of IL-1 and IL-6 signaling. In a murine leukaemia model treated with CAR-T cells infused intraperitoneally, it was observed that macrophages in the peritoneal cavity, and not the spleen, had upregulated activation, suggesting that localised macrophage signaling plays a key role in the pathogenesis of CRS.[6] Because of the involvement of macrophages, the inducible nitric oxide synthase, an enzyme indicative of macrophage activation, has been identified as a potential biomarker of CRS, in addition to IL-1 and IL-6. Current therapeutic options for CAR-T cell-associated CRS involve the blocking of inflammatory cytokine-mediated signalling. IL-6 receptor (IL-6R) blockade has generally been accepted as the front-line treatment for CAR-T-mediated CRS. The IL-6R blocker tocilizumab has been shown to reverse CRS in some patients, though some patients manifest tocilizumab-refractory CRS.[28] Furthermore, early clinical results suggest that successful ablation of CRS symptoms with tocilizumab may not be sufficient to prevent delayed neurotoxicity.[29,30] The pathology of CAR-T cell-induced CRS was studied in a humanised mouse model, and the upregulation of IL-1 preceded IL-6 upregulation. Treatment with an IL-1 receptor antagonist (anakinra) successfully inhibited both short-term CRS-mediated tissue damage and long-term neurotoxicity, while tocilizumab only mitigated short-term CRS, indicating that IL-1 signalling may be the initiator of CRS.[31] This was further corroborated by successful treatment of CRS-like pathology in mice by inhibiting IL-1 signalling via an IL-1 receptor antagonist.[6]

While high IL-6 and IFN-γ are associated with CRS in CAR-T cell-based therapy, CRS may also manifest at lower levels of IL-6 and IFN-γ, and instead present as a higher concentration of IL-2 and GM-CSF.[32] Because IL-2 is necessary for CAR-T cell activity, approaches that inhibit GM-CSF may be preferable to mitigate this form of CRS.[33] Ibrutinib, a drug which inhibits the IL-2-induced tyrosine kinase activity, has been shown to reduce serum cytokine levels in mice.[34] GM-CSF neutralisation with lenzilumab prevents CRS and neuroinflammation in mouse models of acute lymphoblastic leukaemia. Additionally, mice treated with lenzilumab and CD19-targeted CAR-T cells had enhanced antitumour efficacy compared to those treated with CAR-T cell therapy alone. When engineered with a GM-CSF knockout gene, CAR-T cells had enhanced survival rates and tumour control. These results suggest that among the inflammatory milieu, GM-CSF may be one of the crucial mediators of CRS-associated complications and could be an effective therapeutic target for controlling CRS.[35]

CYTOKINE-MEDIATED TISSUE DAMAGE ON INTERMEDIATE TIMESCALES

Viral and Bacterial Infections

Excessive cytokine production is associated with complex interactions between bacterial or viral pathogens and the host, inducing hyperactivation of immune cells.[36] The immune response is typically characterised by an initial intense inflammatory response that rapidly peaks to increase local coagulation and thereby restrict tissue damage.[37] However, an overwhelming production of these proinflammatory cytokines can result in infection-induced SIRS, termed sepsis; disrupt regulation of the immune response; and induce pathological inflammatory disorders, such as capillary leakage, tissue injury, and lethal organ failure. Generally, a high infection burden, superantigens, virulence factors, resistance to opsonisation and phagocytosis, and antibiotic resistance lead to sepsis progression when the host cannot inhibit the infection. In addition, serum concentrations of the anti-inflammatory cytokine IL-10 have been shown to parallel the sepsis score, and a high IL-10:TNF-α ratio is a predictor of severity and fatal outcomes in sepsis.[38]

In contrast to CRS in T cell-engaging therapies, sepsis caused by persistent bacterial and viral

infection develops primarily via the innate immune system.[39] Innate immune cells are activated upon recognition of exogenous and endogenous pathogen-associated molecular patterns. High microbial replication may induce hyperactivation of innate immune cells, and additional off-target tissue destruction may result in a positive feedback loop of tissue destruction and immune activation. E.g., in H5N1 human influenza A, high viral load and excess cytokine production were associated with fatal outcomes, even with low T cell counts.[40] In addition, genetic polymorphisms contribute to excess cytokine production and impaired resolution of inflammation, and contribute to the variability in sepsis pathogenesis. A single nucleotide polymorphism on the IL-1 receptor antagonist gene is associated with lower plasma levels of IL-1β and improved sepsis survival, while specific alleles of the *TLR4* and *TLR1* genes have negative impacts on sepsis outcomes due to enhanced signaling and cytokine production.[41,42] While these and several other polymorphisms relating cytokine signalling to sepsis and severe infection outcomes have been identified, clinical trials targeting individual cytokine pathways related to identified polymorphisms have demonstrated limited efficacy.[39]

Colonisation of barrier tissues by bacterial biofilms elicits an immune response that may lead to localised and potentially systemic cytokine-mediated tissue damage, of which periodontitis (PD) is exemplary. Although periodontopathic bacteria are the aetiological agents in PD, the primary determinant of disease progression and clinical outcome is the host immune response, which involves the generation of cytokines, and recruitment of inflammatory cells.[43] While the ideal outcome of inflammation is resolution, uncontrolled inflammation, mediated by IL-17, TNF, IL-6, and IL-1 in PD, upregulates matrix metalloproteinases and the receptor activator of NF-κB ligands (the primary activation factor for osteoclasts), leading to tissue injury and scarring, fibrosis, alveolar bone destruction, and tooth loss.[44-47] Surgical intervention may be necessary in severe forms of PD. However, in the face of uncontrolled inflammation, reconstruction of periodontal tissues is significantly hampered.[48-50] Furthermore, chronic PD may lead to increased systemic inflammation either via locally produced cytokines entering systemic circulation, or via translocation of pathogenic bacteria to lung or heart tissues from the initial gingival ulcers.[51]

Severe and often lethal clinical outcomes of COVID-19 infection are associated with CRS-like symptoms that affect multiple organs, including the lungs. In a murine model of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a delayed hyperproduction of IFN-β was linked to high levels of inflammatory monocyte-macrophage (IMM) infiltration to the lungs, resulting in mortality.[52] Early administration of intranasal IFN-β or depletion of IMM improved survival and T-cell response. Early clinical results testing IFN-β for the treatment of severe COVID-19 suggest a lower 28-day mortality, consistent with results from the murine model of SARS-CoV.[53] Delayed hyperproduction of IFN-β also induced T-cell lymphopenia in mice, which may further contribute to increased viral load and IMM hyperactivation, as virus-specific T cells are required for viral clearance.[54,55] Similar to cancer immunotherapy-associated CRS, high levels of IL-1 and IL-6 were correlated with disease severity. However, while early results suggested that using tocilizumab alone to target IL-6R might be an effective therapeutic target to suppress hyperactive inflammation in CRS, a recently concluded Phase III clinical trial (COVACTA)[56] did not meet its primary endpoint of improved clinical status in patients with COVID-19-associated pneumonia, or the key secondary endpoint of reduced patient mortality, underscoring the complexity of the cytokine network underlying the disease.[57] Results from ongoing clinical trials testing single-target cytokine inhibition for the treatment of severe COVID-19 are awaited, with additional testing planned for antibody cocktails targeting one or more of IL-6, IL-1, TNF, and GM-CSF.[58]

CYTOKINE-MEDIATED TISSUE DAMAGE ON EXTENDED TIMESCALES

Autoimmune Diseases and Autoimmune-like Conditions

In autoimmune diseases and autoimmune-like conditions, immune dysregulation contributes to episodic elevation in cytokine production and chronic inflammation that may last over a lifetime. In contrast to acute CRS, which is associated with multiorgan failure, damage

from autoimmune diseases are primarily tissue-specific, and chronic conditions contribute to long-term collateral damage of organs such as the skin, eyes, lungs, and heart. Proinflammatory cytokines drive pathogenesis in RA as well as systemic lupus erythematosus, and flares of disease activity are associated with increased cytokine production.[59] Comprehensive efforts have developed a high resolution map of the hierarchical position of distinct cytokines, which mediate the overlapping innate and adaptive immune responses associated with disease onset and persistence in RA pathogenesis.[60] Preclinical and clinical studies, along with the success of cytokine-targeting drugs, such as anti-TNF and anti-IL-6R, have validated the pivotal contribution of cytokines in the pathogenesis of RA. In RA, cytokines regulate cellular phenotype, localisation, activation status, and longevity in the synovial and lymphoid microenvironments, supporting a role for cytokines in the licensing of cell function in RA rather than simply as strict differentiation factors. However, in contrast to a specific antigen or pathogen, the immune response in RA is not thought to be synchronised by a specific initiating event; therefore, the usual innate and adaptive cellular responses are unlikely to operate in the rheumatoid joint. The net effect of this cellular profile is the generation of tissue-destructive enzymes, reactive oxygen and nitrogen intermediates, prostaglandins and leukotrienes, and a broad range of effector cytokines, outside their normal homeostatic 'on–off' regulatory cycle, often following an unpredictable schedule. The result is that the therapy needs for each patient may be distinct and an ad hoc combination is often employed to induce disease remission.

In cGvHD, cytokine production by autoreactive donor T cells drives immunological dysregulation and tissue damage. IL-17-producing T helper (Th17) cells are thought to drive the pathogenesis of cGvHD, and targeting the Th17 axis has been shown to ameliorate cGvHD in preclinical models.[61,62] A mAb targeting the p40 subunit found on both IL-12 and IL-23 reduced the production of both IFN-γ and IL-17 and reduced tissue damage in the skin and salivary glands in a preclinical model of cGvHD.[61] In a retrospective analysis, tocilizumab has shown potential in treating cGvHD, as IL-6 signalling is necessary for Th17 differentiation; however, more comprehensive clinical studies may be necessary to establish clinical efficacy.[63] Furthermore, the contributions of cytokines in cGvHD is complex and may be source-dependent. Host and donor cytokines may play opposing roles, and cytokines may be protective in some tissues but damaging in others, which may drive the selection of which cytokines to suppress. For example, recipient IL-22 has demonstrated protectivity for intestinal stem cells in cGvHD, whereas donor-derived IL-22 plays a critical role in driving cutaneous cGvHD.[64] Therefore, while broadly targeting IL-22 may alleviate cGVHD symptoms, it may not represent the optimal cytokine for inducing disease remission.

To date, there is no single successful strategy to manage cGvHD in the clinic. The clinical gold standard of using combination cyclosporin and methotrexate, which has remained unchanged for decades, is only partially effective.[65] In addition to lengthening the period of immune deficiency, in the order of several years or even the lifetime of the individual, some patients may develop steroid-resistant cGvHD. A strategy that has demonstrated promise in controlling cGvHD is the selective expansion of T_{regs}, mediated by systemic IL-2 infusions.[66,67] However, in clinical trials daily injections were needed for therapy, and patients experienced symptoms of cGvHD immediately following cessation of treatment. mAb, such as the anti-CD20 antibody rituximab, have been shown to be useful in several clinical trials for the treatment of cGVHD; however, these therapies are administered over the lifetime of the patients, significantly impacting the immuno-competence of an individual and thereby limiting its applicability.

INNOVATIVE TREATMENTS IN THE CLINICAL AND PRECLINICAL PIPELINE

While current frontline mAb treatments for specific cytokines are effective at mitigating CRS in some patients, targeting multiple pathways may improve efficacy and applicability (Figure 2A). One method employed is broad-spectrum cytokine absorption with biomimetic nanoparticles to reduce undesired cytokine signalling (Figure 2B). Nanoparticles coated with neutrophil membrane have been shown to reduce proarthritogenic factors such as IL-1β, TNF-α, and matrix metalloproteinase-3, and ameliorate

experimental arthritis in both a collagen-induced arthritis model as well as in a TNF-transgenic mouse.[68] Dendrimers, which are highly branched macromolecules with polyvalent adsorption capabilities, have been demonstrated to mitigate adverse cytokine-mediated tissue damage. In a rhesus macaque model of *Shigella dysenteriae* infection, orally administered dendrimer glucosamine significantly reduced colonic levels of IFN-γ, IL-1β, IL-6, and IL-8, and conferred protection against neutrophil-mediated vasculitis and gut wall necrosis.[69] A hydroxy dendrimer, termed OP-101, has been shown to inhibit multiple macrophage cytokine pathways and is currently undergoing Phase II clinical trials for the treatment of patients with severe COVID-19 (PRANA).[70] Such nanoparticle medicines have the advantage of being able to simultaneously target multiple pathways while still providing rapid clearance and off-the-shelf convenience.

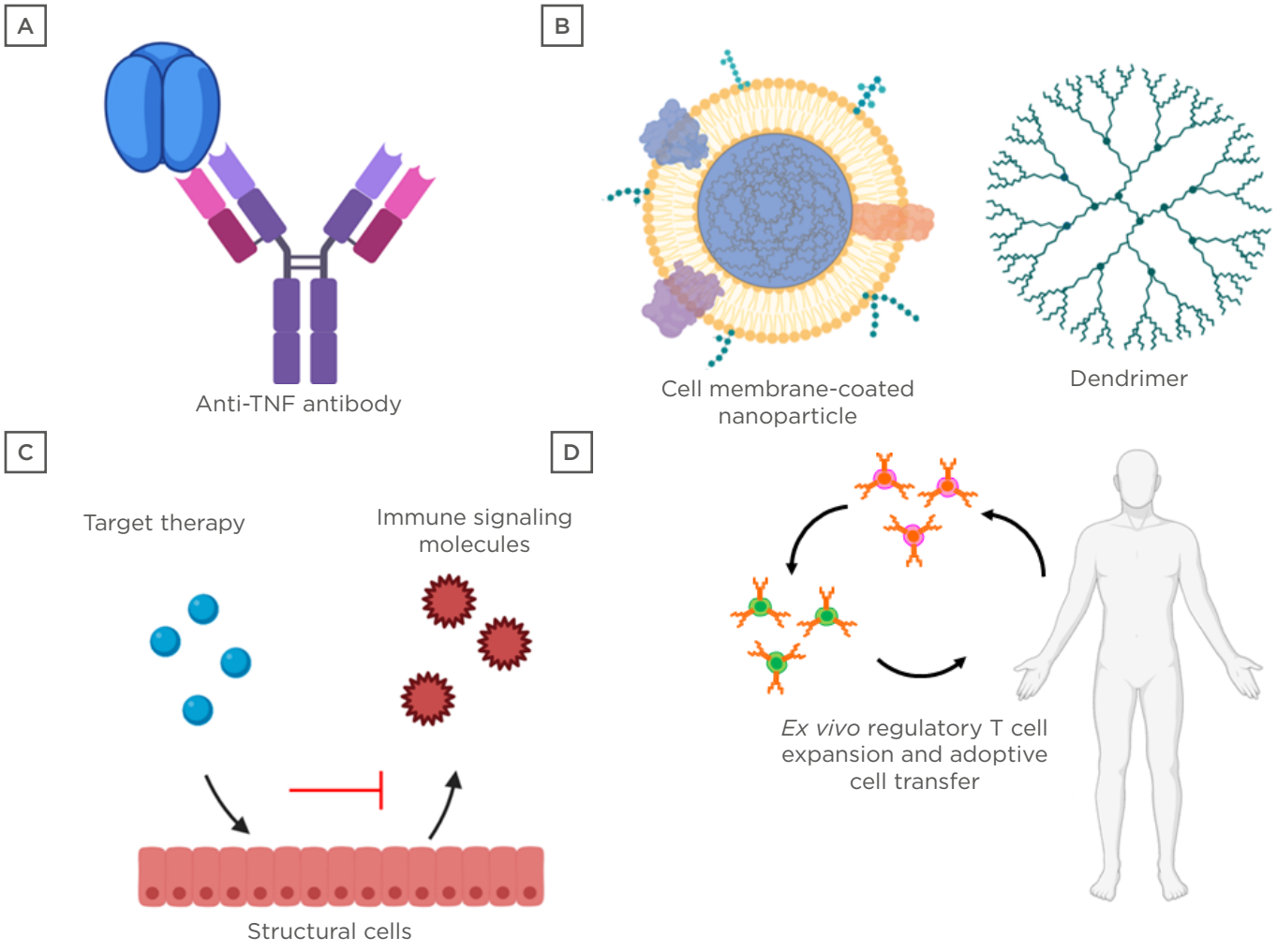

Figure 2: Treatments for cytokine-mediated tissue damage.

A) Monoclonal antibodies and broad-spectrum immunosuppressive molecules, such as steroidal anti-inflammatory medications, are current front-line therapeutics for the mitigation of cytokine-mediated tissue damage. **B)** Nanomedicines offer the advantage of targeting multiple pathways via a single platform and may be engineered with enhanced targeting capabilities to minimise off-target immune suppression. **C)** Advanced omic profiling has shed light on the involvement of structural cells, such as endothelial, epithelial, and stromal cells, in orchestrating immune responses, and preclinical therapies targeting these cell types have shown promise in mitigating cytokine-mediated tissue damage. **D)** Immunomodulatory tolerogenic vaccines and cell therapies to enhance the number and function of regulatory immune cells may hold the key to restoring immune homeostasis in chronic diseases with complex underlying cytokine networks, such as chronic graft-versus-host disease and autoimmune diseases.

Alternatively, directly targeting cells affected by CRS may prove useful to reduce tissue damage (Figure 2C). Recent multiomics profiling of endothelial, epithelial, and stromal cells demonstrated that these structural cells play critical roles in immune regulation in a tissue-dependent manner.[71] In a murine model of influenza infection, agonism of sphingosine-phosphate-1 reduced chemokine production by pulmonary endothelial cells and mortality due to cytokine storm.[72] Additionally, the Slit2/Robo4 signalling in endothelial cells may be a therapeutic target, as Slit2 inhibits ICAM-1 expression on endothelial cells that promote monocyte adhesion, as well as reducing lipopolysaccharide-induced production of proinflammatory cytokines by endothelial cells.[73]

In addition to treatments for acute manifestation of cytokine-mediated tissue damage, several treatments for chronic conditions are currently being explored (Figure 2D).

Preclinical models of tolerogenic vaccination to enhance regulatory immune cell subsets and promote antigen-specific tolerance show promise and have been reviewed extensively elsewhere.[74,75] Cell-based therapies to restore immune homeostasis in autoimmune disease have shown great promise.[76-80] Clinical trials evaluating the efficacy of transfusion of autologous tolerogenic dendritic cells and regulatory T cells are underway for Type 1 diabetes mellitus, as well as RA.[78,81] While clinical outcomes and efficacy are awaited, the prospect of cell-based therapy, combined with front-line therapies targeting cytokines for debilitating chronic inflammatory disease, may be a promising strategy for patient-specific long-term disease remission.

CONCLUSION

Cytokine-mediated inflammation is an essential component of the natural course of an immune response. However, immunological dysregulations that arise from immunotherapies, persistent or highly immunogenic microbial infection, and underlying genetic predisposition, can result in the supraphysiological production of cytokines that results in harmful toxicity. Common features associated with the hyperproduction of cytokines have resulted in therapies that are transferable and effectively manage symptoms, independent of disease aetiology. Current treatments for these pathologies using mAb to inhibit key inflammatory cytokines have shown promise, but patient-to-patient response can be highly variable, in part because of the complex underlying cytokine network. Therefore, therapies targeting multiple pathways may improve outcomes and management of CRS. Identifying the key cellular and molecular determinants of immune tolerance and their role in immune dysregulation will characterise differences between distinct manifestations of CRS, as well as classify patient subsets and better predict therapeutic targets.

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The Rise of Telemedicine: Lessons from a Global Pandemic

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Disclosure: The authors have declared no conflicts of interest.

Received: 30.09.20

Accepted: 14.12.20

Keywords: Coronavirus disease (COVID-19), pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), telehealth, telemedicine.

Citation: EMJ Innov. 2020;5[1]:64-69.

Abstract

Telemedicine has been available for healthcare systems to assist patient care for many years; however, it was not until recently that the field of telemedicine exploded. Inconsistent coverage of telemedicine services as well as a general level of unfamiliarity with the technology required to perform telemedicine services contributed to the lack of its widespread use. The coronavirus disease (COVID-19) pandemic drove the institution of telemedicine in all areas of healthcare. Healthcare institutions around the world adapted both inpatient and outpatient services in order to utilise telemedicine. The implementation of telemedicine can partly be attributed to the expansion of insurance coverage as well as the relaxation of technology requirements to avoid Health Insurance Portability and Accountability Act (HIPAA) violations. During the global pandemic, telemedicine helped to preserve personal protective equipment during a worldwide shortage, protect healthcare workers from being infected, and allowed the monitoring of patients' chronic conditions without putting them at risk by attending medical settings. The COVID-19 outbreak has highlighted the advantages that telemedicine has to offer and has served as the push many health systems needed to implement telemedicine services more widely across these institutions. This article highlights the role of telemedicine during the ongoing COVID-19 global pandemic.

INTRODUCTION

Telemedicine has developed how healthcare practitioners interact and provide medical care to patients. Overall, telehealth includes a variety of tools and technology resources that effectively deliver care to a patient. Telemedicine is a subset of telehealth which refers to a direct interaction between a healthcare provider and the patient. Telemedicine can be useful in providing follow-up care in patients for the management of diseases that require frequent monitoring.[1] Aside from the outpatient setting, telemedicine has also proved effective for monitoring patients in an intensive care setting.[2] Telemedicine has a multitude of benefits for the patient, the healthcare system, and the provider (Table 1).[1,3,4] With the various benefits available to each participating party, it is clear that the use of telemedicine could completely change the way medicine is practised.

Table 1: Advantages of telemedicine for patients, providers, and healthcare systems.

Patient	Provider	Healthcare system
Increased continuity of care leading to better patient outcomes	Capability to work from anywhere	Ability to provide care to underserved populations/areas of the community
Access to medical professionals outside of typical clinic hours	Reduced commute time	Possibility to expand clinical services even when space does not permit expansion
Reduced travel burden	Ability to provide care to rural areas without having to move there or commute long distance	Reduction in clinic congestion
Cost savings (vehicle parking, loss of wages from time off work)	Increase in job satisfaction with the implementation of telecommuting	Decrease in in-person staff burnout with additional support from remote-staff
More likely to return for follow-up visits when it is convenient for the patient		

Adapted from American Medical Association (AMA),[1] Barnett et al.,[3] and Martin et al.[4]

PAST

Telemedicine has been available to clinicians for many years; however, it was not until recently that telemedicine has truly been embraced. According to data from OptumLabs Data Warehouse[3] (Optum, Eden Prairie, Minnesota, USA), the use of telemedicine has increased between 2005 and 2017; however, overall use was still low and use within the health system was infrequent.[3] While the use of telemedicine for mental health services grew steadily between 2016 and 2017, its use for other specialties, or even primary care, was still not universally implemented.[3] A survey conducted by the American Hospital Association (AHA) reported the use of telehealth within the hospital system increased from 35% in 2010 to 76% in 2017. As of 2017, 61.2% of hospitals in the USA used telehealth for remote patient monitoring.[5] Telemedicine was seen by many as a last resort to treat their patients rather than an equally effective alternative to face-to-face patient care.[6]

Prior to the coronavirus disease (COVID-19) pandemic, many barriers to the widespread implementation and use of telemedicine existed. Logistics of training staff on the use of a new electronic platform for telemedicine was seen as a considerable obstacle to implementing its use across healthcare systems. In addition to the lack of desire to train staff on a new skill set, there was also a general unwillingness from clinicians to convert their current practices and learn a new way of providing medical care since the current mode of practice had been working sufficiently for many years.[7,8]

Prior to 2016, the European Union (EU) lacked synchronised regulations regarding the use of telemedicine across European countries, which limited its development.[9] Both patients and physicians became comfortable with the way things were and showed little interest in making drastic changes.[10] Many healthcare professionals were not familiar with the endless technological possibilities that then became available to facilitate patient care via telemedicine. The lack of consistent reimbursement for telemedicine services also discouraged many health systems from implementing telemedicine on a wider scale.[10] Another prevalent barrier to implementation of telemedicine was the misconception that it was only beneficial to help patients living in rural areas, leaving healthcare providers and systems without the sense of urgency to change current practices.[8]

PRESENT

The COVID-19 pandemic forced rapid implementation of telemedicine into everyday practice. What once seemed like a lofty, futuristic goal became reality within the blink of an eye as various levels of telemedicine were globally transformed into practice.[10] The large-scale conversion to telemedicine visits over in-person visits was fueled by fear of the unknown as health systems entered the heart of a global pandemic. Firstly, the use of telemedicine in nonurgent cases would ensure continuity of care while patients and healthcare staff were able to remain socially distant. In addition, the conversion to telemedicine also helped to reduce the risk of exposure to COVID-19 for healthcare workers thanks to less contact with potentially infected patients. Exposure and infection of healthcare workers had the potential to place a serious strain on the rest of healthcare staff and essential resources. An employee who had been exposed to an infected patient would be required to quarantine meaning one less healthcare professional able to work with the increased patient load.[7] In addition, not only would the employee need to quarantine, early on in the spread of COVID-19 there was no consistent data on how long self-quarantine should last. Finally, healthcare societies began publishing more guidelines on ways to properly implement telemedicine while still maintaining optimal patient care.[11] In Western China, the telemedicine infrastructure was used to educate healthcare workers about COVID-19. Information on methods to standardise the diagnosis of COVID-19, approaches to control the spread of COVID-19 through the hospital, and ways to effectively protect hospital workers were provided to healthcare workers across the country.[12] Telemedicine had never before been implemented on such a wide scale and each day brought new challenges and strategies to overcome the obstacles to provide optimal patient care.

Hospital workflow changed drastically as COVID-19 spread across the world. Many changes were implemented to preserve personal protective equipment (PPE) during the global shortage. The use of telemedicine for nonurgent visits allowed PPE to be reserved in more urgent patient situations which required on-site management. At Baylor Scott & White All Saints Medical Center (Fort Worth, Texas, USA), the emergency department began using telemedicine communication techniques so that physicians could communicate with patients who tested positive for COVID-19 without ever having to enter the patient's room.[13] Remote monitoring of inpatients in the intensive care unit also allowed hospitals to conserve PPE with less frequent trips to isolation rooms that would have required new PPE with each new entrance.[2] Elective procedures and appointments were postponed so that staff could focus on the influx of patients resulting from the virus and reduce the risk of exposure to healthy patients. The number of hospital staff working in person was reduced to decrease potential spread of the virus and forced clinicians to find a new way to provide care.[6] At University Rey Juan Carlos (Madrid, Spain), telemedicine was used to triage patients presenting to the emergency department in an effort to determine which patients could be cared for virtually to reduce traffic and preserve resources.[14]

Telemedicine was incorporated into inpatient care in many hospitals to balance the supply of clinical services with the increasing demands. The aim was to limit contact with potentially infected patients to reduce the spread of the virus, decreasing the risk of hospital staff becoming infected. The conversion to telemedicine within the inpatient setting allowed higher-risk hospital staff, whether immunocompromised or elderly, to work remotely and still manage the increased patient volume without compromising their own health. Videoconferencing applications were also used by hospitals to help patients in isolation to communicate with family and friends who were restricted from visiting.[2,6]

Another serious implication of restricting access to hospitals not often discussed was the training of upcoming medical professionals including nurses, doctors, and pharmacists. Many had their training postponed when there was an increased need for healthcare staff. Telemedicine has allowed these students to participate in training activities, such as patient rounding, without putting them in high-risk situations where they could be exposed to COVID-19.[2] Telemedicine created an environment in which healthcare trainees were included in and learnt from the healthcare team without entering the hospital.[2]

Tongji Hospital (Wuhan, China) used telemedicine services to supplement their typical inpatient workflow using a new system by monitoring patients with COVID-19 who were self-quarantined at home. As hospitals across the world encouraged patients with mild illness to stay home and self-quarantine rather than flood the emergency departments, this strategy was not without risks of its own. The condition of these patients could change rapidly, and the patient's condition could quickly develop into a critical situation, which would require inpatient care. Self-quarantine of patients delayed time to proper care and led to potential adverse patient outcomes. One team from Tongji Hospital conducted a retrospective study to evaluate patient outcomes when self-quarantined patients were monitored from home using telemedicine. Between 6th January and 31st January 2020, patients suspected of having COVID-19 were given an initial questionnaire to determine if their case required inpatient care or could be monitored at home in self-quarantine. If the patient was deemed eligible for self-quarantine, they were set up with the electronic counselling system. The system allowed for two-way communication between the patient and an interdisciplinary team with two physicians, three nurses, a rehabilitation physician, and a psychologist. The patient updated their condition daily by answering questions regarding their health on an electronic counselling app on their phone. The health team then assessed the patient's temperature, heart rate, and oxygen saturation and provided feedback to the patient. At the end of the study, 74 patients who were diagnosed with COVID-19 had been eligible for self-quarantine. Sixty-eight participants effectively recovered during their self-quarantine without requiring inpatient care; however, six of the 74 patients had a worsening of their status and required hospital admission. All six patients were eventually discharged, and no deaths were reported during this study. With the help of telemedicine, 74 patients diagnosed with COVID-19 were effectively treated by only seven healthcare workers without any risk of transmission to hospital staff, other patients, or the general public.[15]

In contrast to the implementation of telemedicine in the inpatient setting, outpatient settings became the most common use of telemedicine prepandemic and continue to serve a vital role as the pandemic continues. Conversion of outpatient visits to telemedicine allowed patients to continue care of their chronic conditions while not having to travel to clinic and risk exposure. The deferment of care of these chronic conditions caused by fear from the providers or the patients could have led to future health complications. It was essential that a patient's chronic conditions continued to be monitored and cared for in a timely fashion to prevent potential decline in their condition as a result of COVID-19.[2] Prior to the pandemic, Duke University Health System (Durham, North Carolina, USA) had telemedicine practices in place; however, they were not widely used. Over a 4-week period (12th March–9th April 2020), Duke University Health System's telehealth visits increased from <1% of total visits to 70% of total outpatient visits. At the peak of the pandemic in April, the Duke University Health System performed over 1,000 telehealth visits per day via phone and videoconferencing.[2]

New York University (NYU) Langone Health (New York City, New York, USA), was another institution that used telemedicine prior to the pandemic; however, not in a widespread manner. Prior to the coronavirus outbreak, telemedicine was only used in approximately 25 of over 500 ambulatory clinics in NYU, with fewer than 100 telehealth visits per day. On 19th March 2020, NYU Langone Health expanded telemedicine to all of its ambulatory clinic locations. Within 10 days, more than 7,000 telemedicine visits were performed, accounting for >70% of the total ambulatory visit volume. Patient satisfaction remained unchanged throughout this transition based on surveys administered to the patients.[10]

West Tennessee Health (Jackson, Tennessee, USA), contrastingly, had plans to implement telemedicine practices prior to the pandemic; yet, they had not performed a single telemedicine visit. The COVID-19 outbreak pushed West Tennessee Health to rapidly carry out their telemedicine plans to keep healthy individuals out of waiting rooms. Throughout March 2020, the health system had a 1,300% increase in telemedicine visits conducted throughout the month.[16]

Italy was one of the first European countries to shut down in response to the rapid increase in COVID-19 cases. In some Italian cities, a complete lockdown was implemented leading to a drastic

decrease in the number of patients attending outpatient appointments. The Outpatient Rehabilitation Institute at IRCCS Istituto Ortopedico Galeazzi, Milan, Italy, transitioned all face-to-face visits to telemedicine visits on 16th March 2020.[17] A face-to-face visit was only deemed necessary, if at all, after a telemedicine consultation was performed. Within a few days, the institute developed emergency protocols to make the swift transition. Between 16th March and 3rd April 2020, the Rehabilitation Institute conducted 1,207 telemedicine outpatient visits. Only one out of every 200 patients were required to complete a face-to-face appointment following a telemedicine consultation, attributed to the inability to effectively care for the patient via telehealth.[17] While the Rehabilitation Institute fully transitioned to telemedicine visits, provider satisfaction surveys were distributed to assess the efficacy of the transition. Mean satisfaction of telemedicine visits was 2.8 out of 3 and physicians indicated that they were "overall happy" with their experience using telemedicine. Even physicians who were not comfortable with technology prior to the transition reported being surprised with the high level of satisfaction they had while using telemedicine for outpatient visits.[14]

FUTURE

With the seemingly successful conversion to telemedicine, the question remains: How were the barriers to telehealth overcome so rapidly, and what does this mean for the future? One of the biggest barriers to telemedicine prepandemic was insurance regulations and lack of reimbursement for services. During the pandemic, telemedicine regulations were relaxed, and most telemedicine services were covered. Many insurance companies implemented temporary approval of telehealth services, which led to increased use.[6,10] In the USA, 'Medicare' patients were offered the same telemedicine coverage as the Medicare 'Advantage' patients. There was also an increase in state and federal government funding in an effort to promote telehealth in low-income areas in addition to the provision of necessary technology to complete remote visits.[6] Perhaps the biggest change came on 17th March 2020, when the Office of Civil Rights, U.S. Department of Health and Human Services, announced that potential Health Insurance Portability and Accountability Act (HIPAA) violations for using everyday communication technology for patient care would be waived.[16] This vastly increased the virtual platforms that clinicians were able to use to provide patient care.

As a healthcare system, many lessons have been learned since the start of the COVID-19 outbreak. One of the biggest accomplishments realised from the pandemic is that many outpatient visits can be effectively managed via telemedicine without compromising patient care.[7] The pandemic forced the use of telemedicine allowing patients, providers, and healthcare systems to appreciate the advantages of telemedicine, which included optimising patient care virtually and using it as a means to provide nonurgent follow-up visits. In many instances, the wireless connectivity and technology capabilities were already in place, it was just a matter of maximising their use. The COVID-19 pandemic has demonstrated that healthcare staff can quickly adapt to the new technologies needed to implement telemedicine.[7,8,16] In the case of Duke University Health System, the hospital-wide use of telemedicine was started in mid-March and by 1st May 2020, staff, physicians, nurses, care specialists, pharmacists, and other healthcare professionals had been fully trained and were able to provide telemedicine in both the inpatient and outpatient setting.[2]

Previously, telemedicine was typically only adopted for specialised care; however, in light of COVID-19, healthcare workers have been able to recognise that telemedicine can also be utilised for routine patient care.[2] Moving forward from the global pandemic, further implementation of telemedicine into everyday practice will require switching from crisis mode to sustainability. Ensuring that providers and healthcare workers are fully trained in telemedicine is essential. Healthcare providers are still required to follow both institution protocols and best practice guidelines to provide optimal patient care. No matter what platform a healthcare provider is using to treat a patient, they should always be practising at the top of their licence and providing the same standard of care to all patients whether face-to-face or virtually. Proper documentation and follow-up are still essential in the practice of telemedicine and the safety of the patient should never be jeopardised.[7] It is also important to minimise the risk of physicians

abusing the telemedicine system solely as a way to increase revenue.[7] Other things to consider when moving forward with telemedicine is the ability of low-income or elderly individuals to access the device or network that is required for the use of telemedicine. Telemedicine is available to increase access to care. It should not be seen as a barrier that would prevent patients from accessing proper medical care.[6] In addition to ensuring adequate access to necessary technology and resources for telemedicine, insurance coverage for telemedicine services is essential postpandemic.[11]

CONCLUSION

While the COVID-19 pandemic produced a feeling of mass chaos in many aspects of life, one positive impact of the pandemic has been the widespread implementation of telemedicine. Without the push from the pandemic, many health institutes would have continued to avoid the widespread implementation of telemedicine and may never have come to realise all the benefits telemedicine has to offer.

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General Practice Services in England During the COVID-19 Pandemic and Beyond: Patient Access and Barriers

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Disclosure: The author has declared no conflicts of interest.

Acknowledgements: The author would like to thank Dr H. Devitt, A. Nelson, Dr S. Matharu, M. Dalton, J. Woods, and L. Durno for their contributions to gaining the survey data.

Received: 29.07.20

Accepted: 05.10.20

Keywords: Coronavirus disease (COVID-19), general practice, health services accessibility, remote consultation, technological innovations.

Citation: EMJ Innov. 2021;5[1]:70-77.

Abstract

Background: During the coronavirus disease (COVID-19) pandemic, primary care services have been forced to operate differently, limiting face-to-face consultations and relying on telemedicine. This has impacted the care received by patients in need of primary care. The aim of this article was to assess the patient needs during the pandemic, their perspectives on current interactions with primary care, and the readiness for change in operating general practices in the future.

Method: A survey was conducted among patients in Leeds, UK, that explored whether patients had health needs during the pandemic, the decisions that were then taken if so, their use of online information and resources, and their satisfaction with primary care website portals and consultations.

Results: Over 75% of patients gathered information online before deciding to consult. The main effect of the pandemic was that among those whose health needs remained, 37% did not consult, preferring to wait to see if their symptoms resolved by themselves. There was a significant statistical difference depending on age groups: among those patients aged <30 years, 48% did not consult a primary care physician.

Conclusion: The primary care response during the pandemic led to a large number of patients to withhold their concerns, and careful consideration is needed to access how to improve accessibility in future crises.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic has changed the way general practitioners (GP) are assessing patients, as they have avoided face-to-face consultations and instead used telephone calls, video calls, and other digital solutions.[1] This situation has forced clinicians to work differently and patients to receive care in a limited way, breaking with the traditional, person-to-person interaction.

The city of Leeds, with a population of around 870,000 people, is served by 94 GP practices. In the current National Health Service (NHS) structure, the practices are expected to work together serving natural communities of about 30,000–50,000 patients in what are called Primary Care Networks (PCN). In Leeds, there are 19 PCN, and among them is the Bramley, Wortley, and Middleton (BWM) PCN. The population served by this PCN numbered at around 30,000 and had slightly more children and fewer elderly citizens. The majority of these patients lived in the second most deprived area of Leeds, and a large number are in the most deprived area. The majority of patients were considered white British and the levels of long-term conditions (chronic obstructive pulmonary disease, asthma, heart disease, and minor and severe mental illness) were above the Leeds average.

To provide a better service, the BWM PCN discussed the use of a survey to gather patients' concerns on the available accessing services. The aim was to assess concerns as to whether patients were accessing services when needed, as well as whether the current process was affecting trust in primary care and if this was an indication of a permanent change in the way consultations in the future would occur. It was considered not only the responsibility of clinicians to asses whether or not to continue with any changes introduced during the crisis;[2] it was deemed a coproductive effort, needed to reshape practices to make them stronger after the pandemic.

Assessing the patients' decisions in the lead up to booking a consultation, as well as gathering information on their own health, was the first step. It was accepted that many patients access the internet for health information before a GP consultation.[3] It is also known that a proportion of patients in the UK access their own electronic clinical records as a result of the strong governmental push to provide digital access to patients,[4] and this could be facilitated by using the same clinical software as their GP (all the practices use systmOne/SystmOnline),[5] or by using the NHS app.[6]

Assessing consultation needs and types was needed next. The push to replace face-to-face consultations over the last few years has not been very successful,[7] but it has become an urgent necessity as a consequence of the COVID-19 pandemic. Telephone and video consultations could easily replace and be more convenient than face-to-face consultations for conditions that do not require physical examination.[8] However, the following questions needed to be answered: would patients agree to virtual consultations? Would they expect more examinations? Would they be less satisfied with remote consultations?

METHOD

The survey was created in Google forms and designed to follow a possible patient journey in primary care, starting with the need to satisfy a healthcare need, finding information online ("Would you look for information online before booking an appointment?"; "Have you used our website and its links to other NHS sources of information?"), deciding to seek attention or not ("Did you get the answers you were looking for? What did you do then?"), and the format of the service they interacted with ("What type of consultation have you had during the lockdown?"; "Did you feel safe coming to the practice?").

The survey was designed to be completed in one sitting and in a short time, and there were two types of questions: closed questions (e.g., the percentage of patients looking for information online before a consultation or preferring not to consult when a symptom or health need was present), allowing for the measuring of quantitative differences in responses; and open questions ("If you had symptoms and needed help, what prevented you from contacting NHS services?"), as this allowed a more in-depth assessment of the situation, to find themes representing the behaviours, concerns, and barriers patients perceived.

The invitation was sent via SMS to patients aged >18 years with a mobile phone number on file. Clinical software allowed for the creation of reports to identify candidates with the inclusion criteria and to send the agreed SMS. The survey was also available on the practices' websites and posted on their social media channels. Data were collected between the 7th of May 2020 and the 5th of June 2020.

A mandatory question at the end of the survey asked if the patient's responses could be used

for research purposes. Only data from patients who had agreed to this secondary purpose were included in this paper.

RESULTS

The survey analysed access to online information before consultations, decisions made after information gathering, and types of consultations and satisfaction, as well as how future primary care pathways and interactions could change. Although the invitation was sent to around 10,000 patients, there were only 1,246 responses. However, the number of responses still allowed for a valuable analysis.

This paper focusses on the findings among those who gave consent for the use of their data for research purposes (1,183 patients, 94.9% of the total); there is a variation in response numbers depending on the journey taken by the patient (Figure 1) and whether they answered all the questioned presented.

Descriptive statistical analysis indicated sex (male: 34.2%; female: 65.3%; 'other': 0.2%; and 'prefer not to say': 0.3%), age group (aged <30 years: 12.0%; aged 30–65 years: 69.9.%; and aged >65 years: 18.1%). It should be noted these values do not represent the population served, but simply those who responded to the survey. Respondents were also asked if they were told to 'shield' during the pandemic ('no': 76.3%; 'yes': 11.5%; and 'maybe': 12.2%); shielding was a new concept for patients that followed guidelines introduced by the UK government in March 2020 in preparation for the country's 'lockdown', the term used to describe the requirement for people to stay at home and avoid outdoors activities. These guidelines have been regularly updated since their initial introduction.[9]

Access to Online Information

Not all patients accessed their records, even though they were available to them; in this study's sample, 501 patients (42.3%) accessed their own clinical records, mainly using the practice's clinical software (420 patients, 35.5%), while 23 (1.9%) used the NHS app and 58 (4.9%) used both software available to them. 903 patients (76.3%) accessed online health information before deciding to request a consultation, while 280 (23.7%) did not.

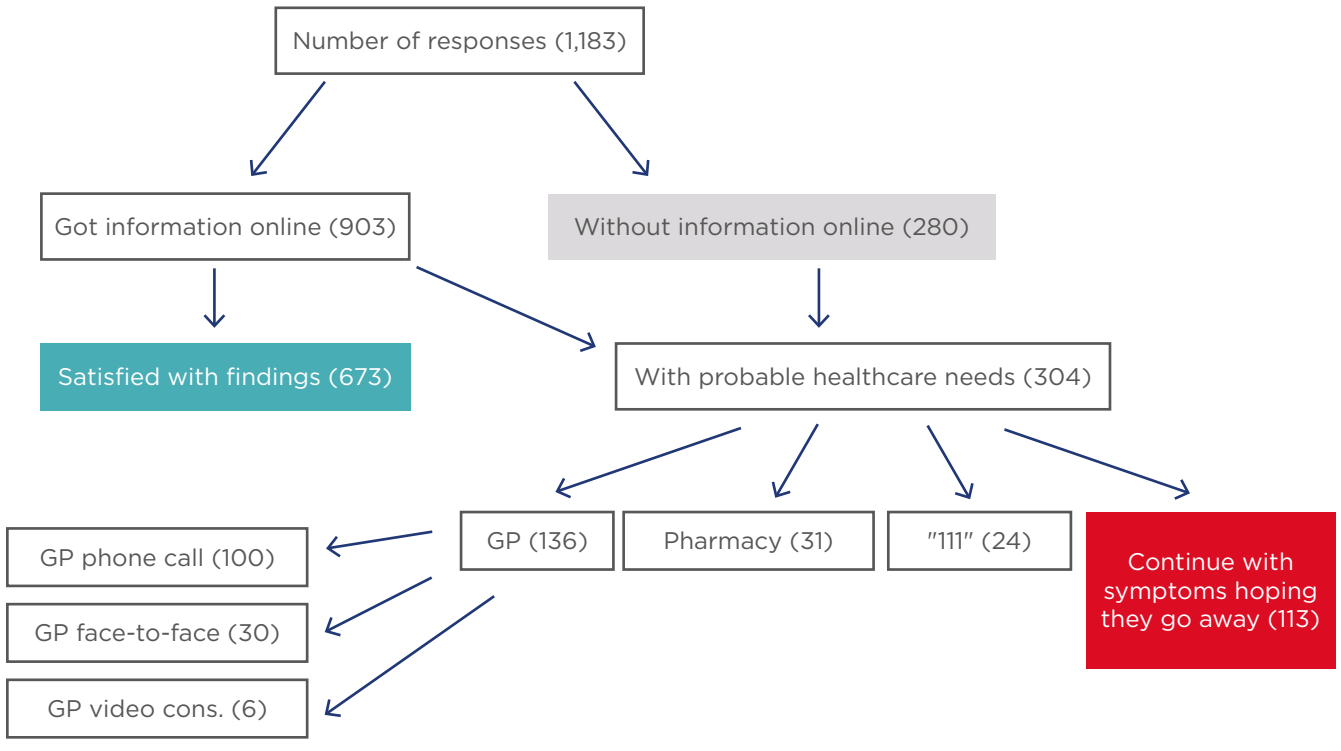

Figure 1: Flow of patients through the survey.

Regarding the use of the primary care practices' websites to search for information, among the 848 respondents, 384 patients (45.3%) reported using it.

Pearson chi square test of independent analysis indicated that the relationship between age groups and accessing information online was significant (X^2 [2, n=1,183]=54.6; p<0.001), confirming that older patients used the internet less.

Among the 369 responses to the question "Is there anything we need to change on the website?", 276 patients considered it to be 'okay' or did not make any suggestions. The following themes were identified among the 71 participants who considered changes were needed:

- Access: patients were eager to have more of their information available online (e.g., "blood test results from specialists" and "full test results"), but also wanted easier access to online forms and to the clinical software itself. There were concerns about difficulties in resetting passwords for the clinical software and the lack of a "facility to register other members of the household."
- Appointments: participants wanted an easier to book, clearer system, "to see previous appointments and be able to filter by available slots and by doctor," with more appointments available online.
- Functionality: patients asked for access to a messaging service with doctors/healthcare professionals for nonurgent needs and the ability to request sick notes and prescriptions on the same site.
- Information: requests were made for more updates and more details on specific conditions such as diabetes and Ehler-Danhlos Syndrome, because links to NHS pages did not seem to provide the desired information for them to decide when to call for an appointments.
- Navigation: Nine respondents did not like the websites, considering them "messy," "too long winded at times," "hard to follow," and needing to be easier to use for the older generation, with larger print and more clarity.

Among other resources used and the reasons for doing so, 402 respondents either did not use other sources (189 cases), 90 used NHS websites, 49 used Google, and several others used specific online providers such as medical sites (PubMed, The Royal College of General Practitioners [RCGP], WebMD), support sites (Mumsnet, Asthma UK), and UK government websites. A minority also reported asking family, pharmacists, or colleagues at work for advice. The reasons for searching online were not solely to find information, but to also obtain clarity, to get "more detailed information" before "bothering the GP," and "to prevent doctor's appointment."

The information online was treated with caution, as observed by one respondent: "The internet isn't always a good tool as some things can be so similar that you self-diagnose incorrectly as sometimes you can be met with five possible answers."

The final outcome, considered by the 903 respondents who consulted the internet, was that the healthcare need was resolved in 74.5% of cases, while 25.5% felt they still needed some help.

Unresolved Healthcare Needs

When asked what action was taken regarding the patient's needs once they had consulted the internet to provide clarify on their symptoms, among the 304 respondents, 136 patients (44.7%) booked an appointment with a primary care physician but 113 patients (37.2%) opted to continue with their symptoms, in the hope that they would go away. Going to the pharmacy was an option considered by 31 patients (10.2%), while 24 (7.9%) phoned NHS 111 number (provides urgent health advice out of hours when GP practices are closed) (Figure 2).

For statistical analysis, the actions taken by the three age groups were condensed into three options: booking an appointment, continuing with symptoms, and other support (including phoning 111 or going to pharmacy). The Pearson Chi square test of independence was then performed. There was a significant association between age group and the action taken in this patient sample (X^2 [4, n=304]=27; p<0.001).

Older patients were more likely to book an appointment rather than leave symptoms alone (66%), while younger patients would do the opposite (37% for those aged <30 years old, and 35% for those aged 30–65 years) (See Table 1).

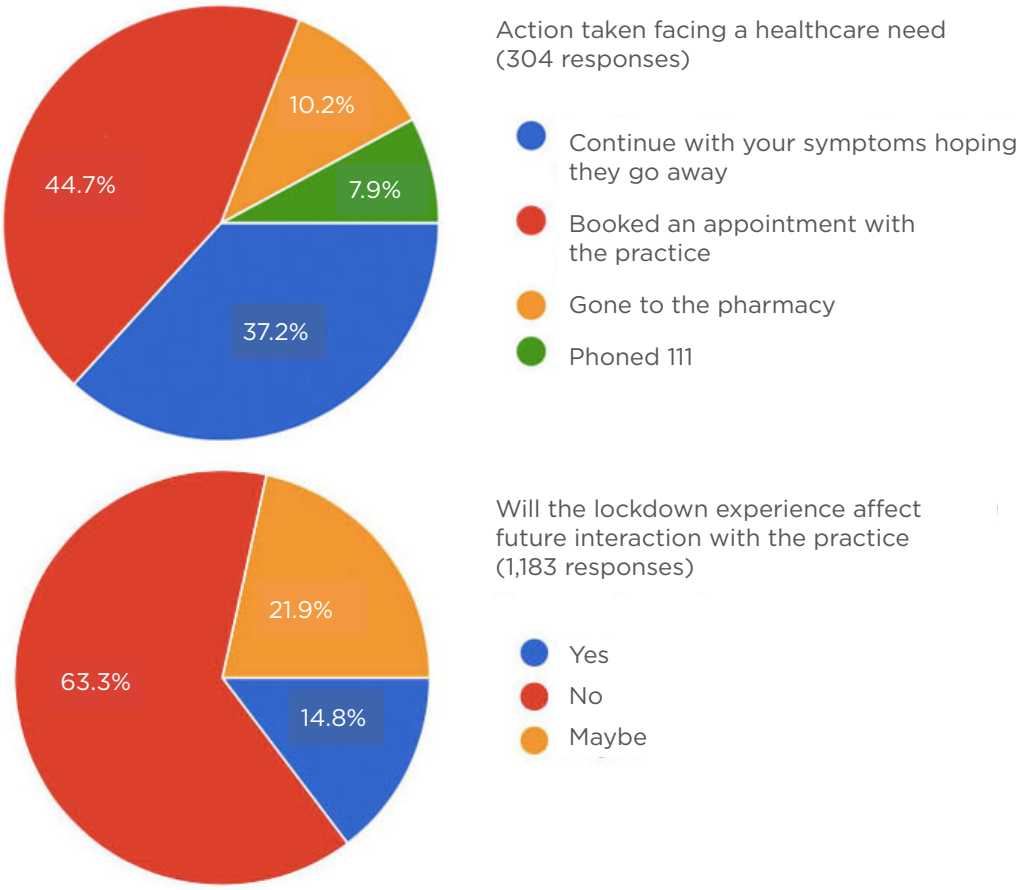

Figure 2: Visual representation of actions taken during the coronavirus disease pandemic and views on future interaction with primary care.

When considering the statistical analysis of those who were shielding, the actions were condensed into two groups depending on whether the individual sought medical attention or not. The Pearson Chi square test of independence was subsequently performed (See Table 1). The relationship between these two variables was significant (X^2 [2, n=304]=6.3; p=0.0042), although it was weaker than the age-related association. Patients who were uncertain about their shielding status were more likely to seek help (73%), compared to those who were shielding (58%) and those not shielding (62%).

When patients were asked "If you had symptoms, what prevented you from contacting NHS services?" the themes identified were:

- Access limitations: an inability to book appointments online or to get an appointment soon enough, and several responded that "anything that would need outside referral has been put on hold/telephone only," or "I want to see somebody, not talk over the phone."
- Burden: comments such as "I don't want to burden the NHS," "I feel bad imposing on NHS at this time," or "the NHS have a lot going on at the moment," were made.
- COVID-19: whether the patients suffered from it, at higher risk, or simply concerned about contracting it, prevented patients to contact services.

Consultations During Lockdown

The UK Government adopted the slogan "Stay at Home, Protect the NHS, Save Lives", which triggered a belief among 34.5% of patients that primary care was not open as usual. Additionally, among the 447 respondents, 15.7% of individuals considered that NHS 111 and pharmacies were not offering their regular services.

Patients during the lockdown had been offered telephone calls or video consultations as their first-line of contact in the primary care setting and, when required, face-to-face follow-up consultations ensued. Among the survey

respondents, 136 patients had a consultation; 100 (73.5%) had a telephone call, 30 (22.1%) had a face-to-face discussion, and six (4.4%) had a video consultation. Among the 30 patients that came to the practice, 28 (93.3%) felt safe coming, while two (6.9%), when asked if they would feel safe, responded "maybe."

When patients were asked if the type of consultation received was sufficient to assess their needs, 27 of the 30 that were seen face-to-face agreed (90%) and three responded with "maybe." In contrast, among the 100 patients who had telephone consultations, 79 (79%) agreed that it was sufficient, nine responded "maybe," and 12 (12%) believed it was not sufficient.

PRIMARY CARE IN THE FUTURE

When people were asked if the lockdown experience would affect the way they interact with their primary care practice in the future, 749 patients (63.3%) considered it would not, 259 (21.9%) thought it might, and 175 (14.8%) reflected that they believed it would (Figure 2).

When given the option to comment, the following themes were noted:

- Avoidance: "I am worried about using up GP time," "I am nervous regarding doctors waiting rooms and other patients," and "I come in to the practice less" or "only going when I absolutely have to."
- Business as usual: "go back to using them as normal as face-to-face meetings are more effective," "I think doctors need to see you face-to-face for mental health problems," and "I prefer to speak to a person."
- COVID-19-related: being more "alert," "aware," "more cautious of keeping distance from people," and avoiding "going into the surgery where possible." These issues will probably return to normal once the pandemic is over.
- Digital changes: more online access, more video consultations and electronic communications ("I liked that I could send a picture"), and more website use.
- Pharmacy use: "I will use the chemist more."
- Telephone appointments: most believed it was likely they would be used more often;

Table 1: Action taken by patients depending on age group and shielding status.

	Action taken (%)			
Age group	Booked an appointment with the practice	Waited for symptoms to improve	Other support (NHS 111, pharmacy)	**Total**
<30 years old	10 (37%)	13 (48%)	4 (15%)	**27**
Between 30–65 years of age	63 (35%)	80 (44%)	39 (21%)	**182**
>65 years old	63 (66%)	20 (21%)	12 (18%)	**95**
Total	**136**	**113**	**55**	**304**
Shielding status	Sought help	Waited for symptoms to improve		**Total**
Maybe	33 (73%)	12 (27%)		**45**
No	132 (62%)	82 (38%)		**214**
Yes	26 (58%)	19 (42%)		**45**
Total	**167**	**113**		**304**

NHS: National Health Service.

"Maybe telephone consultations will become more prevalent rather than face-to-face appointments?"

Also of note, one participant commented: "I do not use computers and I have not got one. I struggle with the new phones also; this is the first time I have managed something like this," as a reflection on digital literacy.

DISCUSSION

Summary

This survey has demonstrated that patients have not been addressing their health needs during the pandemic appropriately, as a considerable proportion refrained from seeking attention when it might have been needed. There was a statistical difference in behaviour between younger individuals, who were more likely to wait for symptoms to improve, compared with older patients, who were more likely to consult. It could not be attributed to younger people accessing more online health information. Another area of probable confusion was the shielding status, and that individuals who were uncertain on their shielding status were more likely to seek attention.

Though clinicians are making decisions about changing consultation formats in the future, the patients in this study believed that long-term access to primary care would not be affected by the pandemic, and that telephone calls were generally rated as less effective at solving their health needs. There was certain resistance to moving from face-to-face consultations, despite the participants also being interested in using digital tools, if possible. If telephone consultations were to become the norm, many patients would probably oppose.

Strengths and Limitations

The survey data from this small sample obtained important information to consider regarding who is statistically more likely to seek help (patients with unclear shielding status, older patients) and the fact that a large proportion of patients appear to consult the internet before deciding to approach primary care.

The invitation to the survey by SMS limited the type of patients able to access it, although it may have focussed on the type of patients most likely to use telemedicine. This is suggestive of health inequality increasing if views of those who are not digital literate are not taken into account. The PCN population, with a considerable level of deprivation, may have reduced smartphone use compared to other communities. The survey also has limitations in that open questions were used, which tend to encourage short answers.[10] It should also be noted that more female patients took part in the survey, which may be reflective of females tending to interact more with general practice; for example, in the study by Wang et al.,[11] the crude consultation rate was 32% lower in males than females.

Comparison with Existing Literature

This study confirmed that patient's access to online services decreases with age,[12] but the amount of healthcare need that was solved by access to online information and the proportion of patients who preferred to wait with their symptoms are both areas that have not been explored before, and are quite relevant in the current context. Concerns have been raised on the impact of not seeking medical attention for symptoms, which could lead to poorer outcomes in long-term conditions like cancer,[13] and the inequalities created by the shift towards telemedicine.[14] In the past, changes in consultation methods came from different pressures, and innovations like electronic consultations have had less impact than expected.[15] The current reality is an effect felt everywhere, and this burden needs to be assessed regularly at a national and local level.[16] The survey presented focussed on general access to services, and the learning from the results could help similar processes elsewhere. Other surveys have focussed on different aspects, such as the perception of digital healthcare,[17] the concerns of contracting COVID-19,[18] or the preparedness of primary care.[19] Together a clear picture is emerging of the pandemic's impact on all levels of healthcare.

CONCLUSIONS

Primary care, alongside many other health services, will undergo multiple changes following the current pandemic. Understanding

patients' perspectives, as well as clinicians' attitudes, could help to build a resilient and satisfactory consultation pathway. The impact of service digitalisation on patients who are not electronically literate needs to be explored further.

Ethical Approval Statement

Patients were asked at the end of the questionnaire if responses could be used for research purposes. Only those survey answers where the patient agreed for this secondary purpose were used.

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Therapeutic Plasma Exchange Using Convalescent Plasma Replacement Therapy in Severe COVID-19 Infections: A Potential Therapeutic Option

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Disclosure: The authors have declared no conflicts of interest.

Received: 24.07.20

Accepted: 08.12.20

Keywords: Convalescent plasma (CP), severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), plasma exchange.

Citation: EMJ Innov. 2021;5[1]:78-81.

Abstract

Currently, the coronavirus disease (COVID-19) pandemic, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), is a major global public health emergency. Cytokine storm is a key factor and plays a major role in disease severity and clinical outcome. Recently, the literature reveals the use of therapeutic plasma exchange to reduce the inflammatory markers. Evidence also exists for the use of convalescent plasma therapy in patients with severe COVID-19. This brief communication explores the advantages on therapeutic plasma exchange with convalescent plasma in patients with moderate-to-severe COVID-19.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is a positive-sense, single-stranded RNA virus that belongs to the coronavirus family, and it is the seventh in that family known to infect humans. It is responsible for the third pandemic disease in the past two decades. The disease caused by SARS CoV-2 is referred to as coronavirus disease (COVID-19).[1] COVID-19 manifests as a mild disease in approximately 80% of infected patients; the remaining would require hospitalisation, sometimes in intensive care with or without respiratory support. Death is often a result of multi-organ failure and is common amongst 'high-risk' populations, such as patients aged >60 years; presence of comorbidities including diabetes, hypertension, and associated chronic diseases; and those on immunosuppressants. Globally, scientists and researchers are in the process of discovering drugs, vaccines, and many other modalities to combat this virus.

CYTOKINE STORM

Huang et al.,[2] in a study on patients with severe presentations of COVID-19, found that

a 'cytokine storm' can occur, as evidenced by the presence of high levels of proinflammatory cytokines, such as IL-2, IL-7, IL-10, TNFα, IFNγ-induced protein 10, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α in sera of these patients.[2,3] There are several ongoing trials on targeted therapy to reduce this cytokine storm by inhibiting cytokine response at receptor level and its subsequent pathways.[4]

THERAPEUTIC PLASMA EXCHANGE

Currently, there are sufficient evidence from the literature to support the role of plasma exchange therapy in various cytokine storm-induced diseases, such as thrombotic thrombocytopenic purpura and cytokine release syndrome, and its effectiveness in reducing the inflammatory markers of a cytokine storm.[5-7] In 2015, Liu et al.[8] reported the efficacy of therapeutic plasma exchange (TPE) in severe avian influenza disease with a good survival benefit. They also showed that a combination of plasma exchange with continuous venovenous haemofiltration had a better outcome, the latter assisted in maintaining a haemodynamic stability in those with septic shock.

In China, during the present SARS CoV-2 pandemic, Xu et al.[9] used artificial liver blood-purification system in severe COVID-19 disease based on their previous experience in managing severe avian influenza with good survival benefit. As a consequence of the present and past experiences, the National Clinical Research Centre for Infectious Diseases in China has placed forthwith expert committee recommendations and guidelines for artificial-liver blood-purification system in the treatment of patients with severe COVID-19. Recent studies by Khamis et al.[10] and Shi et al.[11] revealed improvements in clinical outcome of severe COVID-19 infections by using TPE.

CONVALESCENT PLASMA THERAPY

One other salvage modality would be to transfuse plasma from patients who have recovered from COVID-19, i.e., convalescent plasma therapy (CPT) that contains high levels of neutralising antibodies to patients with severe presentations of the disease that require either oxygen therapy or those on ventilator support. This form of therapy was used as early as 1918 and 1957 during the 'flu epidemics' and more recently for SARS, Middle-East respiratory syndrome (MERS), and Ebola pandemics.[12,13] This form of therapy has also been used by the present authors in patients with liver disease who are undergoing liver transplantation and are positive for hepatitis B virus. Plasma rich with anti-hepatitis B virus antibodies, known as hyper immune plasma, was given in a dose of 2,000 IU/L to maintain adequate anti-hepatitis B virus antibody levels to prevent hepatitis B virus recurrence.[14]

In a press release from February 2020 (unpublished data), China reported that it used plasma of convalescent individuals in 245 patients with COVID-19 and reported good survival benefits. Zhang B et al.[15] published their first case series on effectiveness of convalescent plasma in four patients with severe COVID-19, who were on ventilator support with more than one organ failure and who did not show clinical or biochemical improvement after standard recommended therapy. Following CPT, SARS CoV-2 reverse transcription PCR was negative within 3–22 days, and anti-SARS CoV-2 IgG levels were detected 4 days post reverse transcription PCR negativity.

Another benefit forthcoming with use of CPT was the reduction in severity of entry of SARS CoV-2 by cross-neutralisation, further suggesting that convalescent sera of SARS CoV-2 had neutralising antibodies.[4] These virus-specific antibodies usually peak at 4 months and gradually taper over the next 24 months.[16] Studies in animal models have shown that anti-SARS CoV-2 IgG is likely to protect an individual from subsequent exposures too.[17] Possible mechanisms of convalescent plasma in COVID-19 includes direct neutralisation of virus; control of overactive immune system, such as cytokine storm; and immunomodulation of hypercoagulable state.[18]

COMBINED EFFECT OF THERAPEUTIC PLASMA EXCHANGE WITH CONVALESCENT PLASMA THERAPY

Based on the above literature evidence on the role of CPT as well as TPE in managing the cytokine storm, there is a case series of novel therapeutic approaches, such as TPE using SARS CoV-2 CP from recovered individuals in patients with severe COVID-19.[19] This will not only reduce the cytokine storm, but also provide the patients with virus-specific neutralising antibodies and thereby improve the overall survival of patients who have organ failure in one or more organ. This study emphasises the importance of the timing of immunomodulatory treatments. As IL-6 level will be peak in between 7 and 14 days after the onset of symptoms, early initiation of TPE with CP would be beneficial to patients with COVID-19 who are symptomatic. Interestingly, the literature review by Kesici et al.[19] revealed that no major adverse events have been reported by using TPE or CP or the combination of both in patients infected with SARS CoV-2, although it might increase procoagulant state of the patients because it involves 5% albumin or fresh frozen plasma. Moreover, Jaiswal et al.'s[20] study on patients with severe COVID-19 who required mechanical ventilator support showed significant clinical improvement with use of TPE with CP. Table 1 summarises the differences in the transfusion of CPT with and without TPE. There are case reports of TPE with intravenous Ig in a patient critically ill with COVID-19.[11]

CONCLUSION

Early intervention of CP as well as TPE has showed benefit to patients symptomatic with COVID-19. Combination of CPT with CP novel modality is likely to circumvent the imminent mortality in patients with severe COVID-19, while scientists and researchers are working on vaccines and other pharmacotherapeutic agents for preventing mass transmission in the community.

Table 1: Differences between convalescent plasma therapy, therapeutic plasma exchange, and the combination of convalescent plasma therapy with therapeutic plasma exchange in patients with severe coronavirus disease (COVID-19).

	CPT	TPE without CPT	TPE with CPT
Requirement	Ward	ICU	ICU
Vascular line	Peripheral line	Central line	Central line
Duration	30 min	2–3 hours	2–3 hours
Procedure	Manual	Automated	Automated
Cytokine removal	No	Yes	Yes
Neutralising antibodies	Yes	No	Yes
Side effects	Rarely, minor allergic reactions	Minor allergic reactions, hypocalcaemia, hypotension	Minor allergic reactions, hypocalcaemia
Absolute contraindications	None	Systolic BP <90 mmHg	Systolic BP <90 mmHg
Procedure safety	Yes	Yes	Yes
Cost of therapy	Less	High	High
Outcome	Good	Good	Better

BP: blood pressure; CPT: convalescent plasma therapy; ICU: intensive care unit; TPE: therapeutic plasma exchange.

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Rapid Reconfiguration of Paediatric Services in a District General Hospital During COVID-19, Addressing Challenges, and Seeing Opportunities

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Disclosure: The authors have declared no conflicts of interest.

Received: 22.09.20

Accepted: 21.12.20

Keywords: Accessibility, coronavirus disease (COVID-19), innovation, opportunities, technology, together, waiting list, whole team approach.

Citation: EMJ Innov. 2021;5[1]:82-87.

Abstract

The scale, speed, and impact of the coronavirus disease (COVID-19) pandemic disruption to healthcare services has been unprecedented, placing significant additional pressures on the National Health Service (NHS). COVID-19 presented exceptional challenges to vulnerable families and is placing increasing pressure on children's services. The child population does not seem to have been severely impacted by COVID-19; however, some will require hospital care in addition to the current caseload. It is imperative that steps are taken to ensure continued delivery of urgent and emergency paediatric services and the associated maternity and neonatal services at local levels throughout the pandemic. A rapid reconfiguration of services was necessary when the pandemic reached the NHS. Healthcare services had to rethink how to deliver care in the short and medium term, better preparing them for future demands and ensuring that safe and effective care was maintained.

INTRODUCTION

The Southern Health and Social Care Trust (SHSCT) has two acute hospitals: Craigavon Area Hospital (CAH) and Daisy Hill Hospital (DHH). Both hospitals deliver emergency department services and inpatient services for medical, surgical, paediatrics, obstetrician and gynaecology, and radiology departments, laboratory, and other support services. The paediatric ward in DHH has 13 inpatient beds and cots, predominantly single room, six elective surgical beds, a paediatric theatre, and four single rooms for Short Stay Paediatric Assessment Unit (SSPAU). There are an additional six cots in the Special Care Baby Unit (SCBU), which serves around 2,000 deliveries in the adjacent maternity unit each year. There is a three-tier medical rota with appropriate levels of nursing staff monitoring all shifts ensuring high-quality care. The SSAPU opens at 9 a.m. to 10 p.m. on weekdays, and receives referrals from primary care teams and supports the emergency department. In addition to this, the team also provides telephone advice via a paediatric advice line (PAL) to primary care teams and service users.

RECONFIGURATION

"The best defence against any outbreak is a strong health system," stated the Director-General of the World Health Organization (WHO), Tedros Adhanhom Ghebreyesus,[1] teaching the importance of exploring healthcare services and further strengthening them through necessary adaptations in the face of the pandemic. During the first wave of the coronavirus disease (COVID-19) pandemic, CAH was designated as a COVID-19 hospital site and DHH as a non-COVID-19 site. Some resources had to be relocated from DHH to the site of CAH; this included the temporary closure of the DHH emergency department, resulting in the greatest impact of service reconfiguration initially experienced by DHH.

Paediatric services in DHH commenced a rapid reconfiguration as per advice from Northern Ireland Child Health Partnership forum and COVID-19 Silver Command Centre. This was to support adult medical services because of increasing numbers of adult patients. Service delivery had to be proactive, responsive, and focussed on safe and effective patient care and staff wellbeing. A service improvement approach was adopted so that any changes made would be reviewed and acted upon, giving a continuous cycle of improvement and opportunity throughout the pandemic, recognising the benefits and challenges that lay ahead of the service: "Certain factors may help to foster an environment that is conducive to change and improvement. An organisation where there is strong leadership and everyone is focussed on improving patient care is more likely to develop motivated staff with a desire for continuous quality improvement," as stated in NHS Improving Quality guidelines.[2]

Any temporary reconfiguration of paediatric services had to ensure that (Table 1):

- Steps to mitigate the impact on vital children's services were taken while services responded to the pandemic.
- Reconfiguration was to be completed within 1 week.
- Children with non-COVID-19 conditions who required urgent and emergency care continued to receive appropriate general and specialist hospital care.
- Agreed clinical pathways were in place to ensure appropriate, timely, and safe care.
- Paediatric cover was in place to support obstetric services and neonatal units.

OPPORTUNITIES AND LESSONS LEARNT

Whole System Approach

The necessity and speed of the reconfiguration allowed recognition of a common, greater goal across regional, primary, and secondary care. Streamlined care pathways were agreed through positive and meaningful multidisciplinary engagements. Through positive engagement and working together, the COVID-19 pandemic broke down barriers and refocussed services. Collaborative working between primary and secondary care improved; these relationships still need nurturing and support to enhance shared learning. Such an approach can be effective in many settings and institutions throughout public services and healthcare, as long as there is a sense of a common goal and shared purpose.

Flexible Working Staff: Coming Together

Flexible working arrangements were afforded to staff to work onsite and offsite, with some virtual consultations completed offsite. Computer and technological support were crucial during this process. Staffing reductions from redeployment would have caused the middle- and junior-tier rotas to have been harder to fulfil without staff coming together with some possible solutions. Their active role in the process enabled solutions to be found rather than furthered challenges faced by the service. Consultants delivered onsite cover for the middle-tier rota, which provided shared responsibility. Skills, experience, and expertise were spread across the rota, ensuring safe and effective care of patients. The flexible working arrangements were beneficial in the shorter term; however, to be sustained in the long term, further exploration is required with regard to productivity and service delivery. As part of a service improvement cycle, this adaptation will continue to be reviewed and evidenced, ensuring that the needs of the service can be met and sustained.

Table 1: Reconfiguration of paediatric services, the challenges, and outcomes.

A

Structural and patient flow changes
Challenges
Maintaining communication with service users and the wider healthcare system in the hospital, primary care teams, and regionally.
The inpatient ward in DHH to close for all new paediatric patient admissions from 3rd April 2020.
An arrangement for streamlined patient care pathways was essential for the access to appropriate care for service users.
DHH ED was temporarily closed to strengthen CAH ED staffing levels; therefore, temporarily, there was no ED cover available in DHH.
Actions taken to mitigate the risk
A multidisciplinary team that included clinical and operational staff was formed to implement the rapid reconfiguration. It was a two-pronged approach including local and regional considerations to ensure effectiveness. Mechanisms for transparent and meaningful communication and collaboration were commenced and maintained throughout the pandemic, not only within the Southern Trust but also with other regional services.
Daily operational meetings were convened, ensuring that there were open and clear lines of communication, with opportunities for services across the organisation to support one another in their pressures, as well as learn from one another.
A regional approach to triggering, monitoring, and communication was agreed by the regional Child Health Partnership Forum to ensure the safe and effective care of patients across the region. This agreement allowed for consistency and collaborative working across all Trusts so that all children in need received the same high standard of care regardless of which area they resided in.
NMS forum established. This forum included paediatric and GP representatives to improve shared care responsibilities and meaningful communication through active stakeholder engagement.
The patient care pathway from primary care to hospital paediatric services was discussed and developed so that barriers were identified and addressed where possible. This enabled opportunities to tackle any delaying areas and work together to find resolutions, which facilitated more effective care provision. These were continuously reviewed and refined over the following months, allowing for continuous improvement to occur.
The patient flow pathway was adapted to address the deficiency of no ED and no inpatient ward in DHH. By doing so, there was a clear channel of how care provision would continue to be delivered without these components on site.
As the inpatient unit was closed for paediatric services, all remaining inpatients in DHH either transferred to CAH or discharged home with appropriate follow-up arrangements.
The inpatient ward was handed over to adult services to utilise space for the safe and effective care of adult patients during the COVID-19 pandemic. A sense of togetherness was reinforced between colleagues as paediatric services supported the pressures on adult services through this change.
Paediatric services were changed to SSPAU/ambulatory-based services. Clinical management was mainly delivered through the SSPAU and phone consultations to meet the needs of the patient.
Paediatric phone clinics started to utilise the virtual consultation platform, allowing for continued care of patients, reduction of waiting lists, and enhanced communication and relationship building with service users and their families. Virtual consultation operating procedures were developed so that there were clear protocols and guidelines for all users. Staff training was provided where necessary so that everyone was equipped with the skills needed to utilise this tool.
A paediatric resuscitation area was created within SSPAU for unexpected, unwell patients so that there was a contingency in place for all eventualities of patient safety measures in the absence of ED in DHH.
SIM training sessions were delivered for all staff for the management of sick children.
All ambulances to DHH were diverted to CAH. This arrangement was agreed after close consultation with Northern Ireland ambulance services; again, strengthening relationships and highlighting the importance of partnership working.

CAH: Craigavon Area Hospital; DHH: Daisy Hill Hospital; ED: emergency department; GP: general practitioner; NMS: No More Silo; SIM: simulatory; SSPAU: Short Stay Paediatric Assessment unit.

B

Staffing Changes
Challenges
A number of paediatric staff were redeployed to CAH acute medical department, therefore paediatric services had to manage patients with reduced staffing levels.
Anxiety levels among staff were particularly heightened due to professional and personal pressures faced throughout the pandemic. With changes to their workplace, routines, and a rapid reconfiguration to their service, some staff found themselves feeling additionally stressed.
Actions taken to mitigate the risk
Regular staff meetings were established to communicate with and listen to front-line staff and enable them to safely voice their concerns where appropriate, providing reassurance, guidance, and support under the strains faced in the pandemic. Front-line staff were active participants in the reconfiguration, keeping them involved and informed.
Working patterns were changed to allow safer staffing levels. This included collapsing three-tier rotas into two-tier rotas on DHH site. This was entirely new to the service and increased the sense of togetherness and teamworking in the face of adversity.
Consultants delivered onsite resident duties, which added to the sense of a shared workload in an already challenging environment. Consultants also completed middle-grade/registrar duties, providing senior decision-making at the front end of the services.
Some consultant staff offered their assistance to adult medical services, enhancing a sense of unity and togetherness across the organisation.
Given the potential risk posed to safe practice from potential reduced staffing levels as a consequence of sickness and self-isolation, a backup consultant rota was established for out-of-hours consultant shifts. This contingency offered assurance to the service when necessary.
Organisational staff support. Occupational health staff support sessions and psychological sessions were offered to all staff across the organisation, and a staff newsletter was provided regularly to all staff throughout the Trust. This was to offer health and wellbeing supports as well as a sense of value within the organisation.

CAH: Craigavon Area Hospital; DHH: Daisy Hill Hospital.

C

Risk management
Challenges
Clinical risk was higher because of rapid reconfiguration of services; therefore, it was vital to closely monitor risk management processes alongside any actions taken, which are noted within the table.
Actions taken to mitigate the risk
The senior management team held regular operational meetings to share information and provide updates.
Patient flow was monitored daily in MDT meetings to identify and address any areas of delay and note areas of progress.
Clinical incidents were closely monitored, and any learning disseminated throughout MDT engagement and clinical governance/patient safety forums.
Virtual patient safety and mortality and morbidity meetings started via Zoom (San Jose, California, USA).
An MDT handover commenced 3 times per day, every day. This incorporated patient safety briefs, which included unusual patient presentations, any patient on unusual medication, on intravenous fluids, same-name patients, any expected transfers, and any clinical incidents during the previous 8 hours. This utilised the handover communication tool for further enhancing patient care and assisting with decision-making: "Decisions should be individualised – this means that decisions must take into account patient's individual characteristics, preferences, and prognosis."[4]
Weekly operational/clinical group meetings were established to review and plan for the following week, allowing for forward planning and reducing the risk through a structured approach.
A paediatric and GP interface forum convened to discuss and mitigate any patient flow risks.
Daily regional paediatrics network forum meetings took place, giving a platform for shared learning across the region, assisting with mitigating any risks faced and creating an environment for safe learning even during a pandemic.

GP: General practitioner; MDT: multidisciplinary team.

Innovation Using Technology

Innovative work can offer organisations new ways of addressing current and future challenges, reaching their targets, and addressing backlogs, which may not have been achievable previously. Because of the current pandemic, face-to-face clinics and interactions decreased, replaced by virtual consultations and meetings, allowing for staff time to be more structured and focussed.

Virtual consultations were implemented, ensuring that patient medical needs continued to be met within a safe and controlled environment. The more effective use of resources had a positive impact on the clinic waiting lists. The PAL was extended from 9 a.m. to 10 p.m. and 4 hours on weekends with a senior decision-maker available to provide advice to primary care teams and service users.

Remote Access and Clinical Application

The current pandemic highlighted the requirement for clinical teams to have remote electronic access of resources. Innovative technology is being enthusiastically progressed within the service by the further development of a paediatric smart device app to enable remote information accessibility of clinical guidelines, care pathways, and services contact directory. Appropriate protocols and guidelines were developed for all when using these technologies so that this could become embedded in the future of service delivery, also keeping within organisational governance. With emerging evidence on the persistence of coronavirus on inanimate objects such as shared computers in the patient care environment, the app, available on personal devices, provides an alternative access point for information. The ambition is to roll this app out to both primary care teams and secondary paediatric services following a successful testing period. This in turn will continue to maintain and sustain communication between services and to improve care pathways.

Service User Engagement

To ensure service user engagement throughout the reconfiguration and adaptations, patient feedback was actively sought so that all stakeholders, not just those multidisciplinary partners, were consulted with. Those who received appointments additionally received a leaflet explaining the changes being made to the service. This information was also made available on the app as a full consultation with an explanation as to why service could not be commenced, attributed to the timescales involved in the reconfiguration: "Coproductive working relationship with children, care leavers, their families, and carers to establish what matters to them and to ensure they feel respected and informed. This includes explaining to children and families the ways in which the COVID-19 arrangements may impact on the provision of their care and support."[3] In recognition of patients being active stakeholders, a concerted effort to collect feedback was made to assist the shaping of future service delivery. Service users who attended the paediatric services during this time were sent feedback forms to provide input into the changes that were being made. This allowed service users to feel like they were active participants, and gain greater understanding of the restraints being put upon the healthcare system and the rationale for the reconfiguration. Service users were extremely positive about the increased sense of accessibility for advice, information, and care through the use of the PAL, the app, and virtual consultations. Families who would have struggled to arrange time off work, childcare, or travel arrangements to accommodate consultation had now been given the freedom of a less stressful appointment through the facilitation of virtual consultations. The service user feedback data collected will be collated and analysed in coming months to allow for shared learning with senior management team to convey the work achieved by the service and the value in learning from the opportunities identified throughout the pandemic. This piece of work will then be further shared across the Trust through the 'Learning from Experience' forum, which is attended by all directorates, facilitating further dissemination of the learning and a chance to reflect on the sense of achievement of overcoming the challenges faced.

Feedback and ongoing collaboration with service users can be repeated in any setting as long as there is honest and transparent communication and expectations are managed appropriately. The demand on services remains the same; however, the pandemic allowed the freedom to

make innovative progress in a safe, productive, and efficient manner with all stakeholders working together for the greater good.

THE WAY FORWARD

There is more that can be done when working in a whole system approach. The authors will continue to explore innovative solutions to improve patient outcomes and drive efficiency. This case study proved the value of taking measured, brave decisions to try new innovative methods, and taking a step back to reflect upon how best to provide safe, high-quality services using a collective and collaborative approach during a pandemic. Communication on every level with all active participants allowed for greater understanding, better informed decision-making, and reduced risk. The key themes of meaningful engagement, positive communication, teamwork, and support can be adopted into any organisation and any setting, developing a culture of continuous improvement, and ultimately service reward for the benefit of all.

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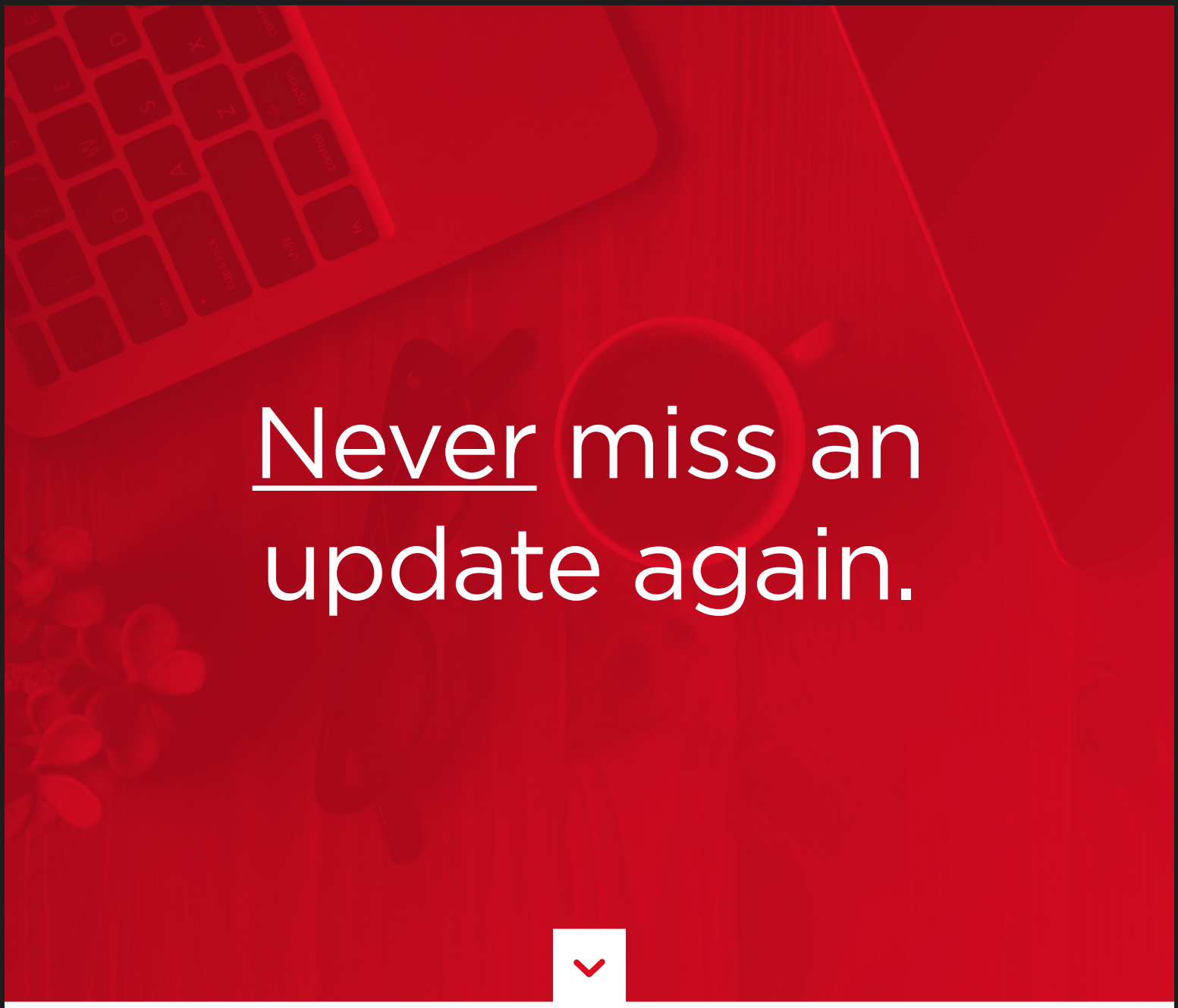

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