

Aster Medical Journal

FEBRUARY 2020
VOL. 1 / ISSUE 4



www.theamj.org

Global Health

The Checklist
Manifesto for Surgeons

Clinical Medicine

PELD - Prospective
Study of 230 Cases

Conversation

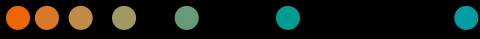
The Contrarian Who
Cures Cancers



HOW PERSONALISED MEDICINE IS CHANGING HEALTHCARE

We are at a pivotal moment in healthcare history. Healthcare is shifting from standard care to personalised care. Ever wondered what we could achieve if we bring together the best expertise in molecular biology, genomics, modern diagnostics and smart analytics? How might patients' lives be changed for the better?

Shaping the future of healthcare



SIEMENS
Healthineers

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Photograph By Elizabeth Conley

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After cancer took his mother, his uncles and his brother, **Dr James Allison** pioneered a treatment that unleashes the immune system to fight cancer.

Allison says immunotherapy is quickly becoming the “fourth pillar” of cancer therapy, joining long-established treatments such as surgery, radiation and chemotherapy.

Conversation



“We have about 100 hospitals, in Holland, and the number of beds is decreasing very rapidly. So, patients are coming in the morning and leaving in the afternoon. We have almost no long stays.”

Dr Peter Schneeberger

“Irrational use of antibiotics is two-fold. One is they are often wrongly prescribed. The flip side is when they are needed they are not prescribed.”

Dr Rajeev Jayadevan



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In many poor countries, older surgeons resist being questioned, and operations are more often emergencies, which leaves less time to review checklists.

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Cover Styling:
VK Haris

GO GREEN

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Prologue



The Growing Burden of Cancer

On the occasion of World Cancer Day, 4 February 2020, the World Health Organization (WHO), and the International Agency for Research on Cancer (IARC), the specialized cancer agency of the WHO, released two coordinated reports. Unfortunately, this critical information has all but sunk under the immediate global priority of the Coronavirus outbreak. The alarming findings revealed in the reports have not triggered the urgency they deserve or the discussions that they should have.

The 'Emperor of All Maladies', as Dr Siddhartha Mukherjee described cancer in his iconic Cancer Biography, is a devastating disease, and touches almost every human on the planet. Each of us has a close one or at least a known one, fighting 'the Big C', or one who has lost the battle to it. High-income countries have optimistic things to report on their cancer pages; the cancer mortality rates there are indeed falling. But this is not the case with the many low and middle-income countries (LMIC). Cancer mortality rates are on the rise here. Even now, the LMIC are grappling with facilities for cancer treatment, including timely and quality diagnosis, and comprehensive treatment.

The WHO warns that, if current trends continue, the world will see a 60% increase in cancer cases over the next two decades. The highest increase (an estimated 81%) in new cases will occur in LMIC, where survival rates are currently the lowest. In 2018, worldwide, approximately 10 million deaths from cancer had been reported. The same year threw up 18.1 million new cases. The latter figure is anticipated to double, to 29-37 million new cancer cases, by 2040. And this, in the LMIC, where more than two-thirds of the world's cancers will occur. The unfortunate situation

of a cancer patient having the stigma of being afflicted by a terminal illness continues even now in some LMIC countries. Even though cancer affects vast populations in the highly productive and income-generating age group, the lack of accessibility and affordability of quality cancer care leads to a tremendous amount of morbidity and mortality.

Yes, there indeed has been innovation and improvement in diagnosing cancer and treating it over this decade. But the distribution and uptake of these services, medicines and technologies have been profoundly inequitable and inefficient. High income countries are better placed to handle cancer, and they have adopted prevention, early diagnosis and screening programmes, which together with better treatment, have contributed to an estimated 20% reduction in the cancer mortality between 2000 and 2015. Still, low-income countries only saw a decrease of 5%. Obviously, there is inequality in cancer care.

As the WHO director-general Dr Tedros Adhanom Ghebreyesus said, "At least 7 million lives could be saved over the next decade, by identifying the most appropriate science for each country's situation, by basing strong cancer responses on universal health coverage, and by mobilizing different stakeholders to work together", Being diagnosed with cancer shouldn't be a death sentence just because you are born in a low-income country where there is no access to health care or the means to pay for it. Together, let's all work towards reversing the tide of cancer. The first logical step to know the size of the Emperor of Maladies is to have a cancer registry established in all LMIC countries as soon as possible.

Dr Azad Moopen, MBBS, MD
Founder & Chairman, Aster DM Healthcare

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CONTRIBUTORS
Dr Heather Robinson
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Jisha George
Nirupama
BrandPub
Editage / Cactus
Quintype Technologies

PLACE OF PUBLICATION

Aster DM Healthcare Limited
IX/475L, Aster Medcity, Kuttisahib Road,
Near Kothad Bridge, South Chittoor P.O.,
Cheranelloor, Kochi, Kerala- 682 027, India
T: +91 484 66 99 999

INTERNATIONAL ADDRESS

Aster DM Healthcare
33rd Floor - Aspect Tower
Business Bay, P.O.Box: 8703
Dubai - U.A.E
T: +971 4 454 6001

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The publishers regret that they cannot accept liability for omissions contained in this publication, however, caused. The opinions and views contained in this publication are the authors' and not necessarily those of Aster Medical Journal, Aster DM Healthcare or Members of the Editorial Board.

IMPRINT LINE

Printed and published by Dr Harish Pillai on behalf of Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O., Cheranelloor, Kochi, Kerala- 682 027, India and printed at Anaswara Offset Pvt Ltd, Perandoor Junction, Elamakkara, Kochi - 682 026 and published at Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O., Cheranelloor, Kochi, Kerala- 682 027. Editor: Dr Harish Pillai.

RNI No: KERENG/2019/77520 | Price: 150 INR



"Like many in my field, I worry that if and when the emergent virus takes root in poorer countries that are already tackling outbreaks of other pathogens, it could wreak havoc of an even larger magnitude." – Page 28

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Editorial



Driving a better future for patients

It's oft-quoted among the medical fraternity, "it is quite as important for the doctor to know what kind of patient the disease has for host, as to know what sort of disease the patient has for guest". A century and a quarter later, the statement stands validated, in the face of the current developments in personalised medicine.

Medicine today is generally based on a "one-size-fits-all" approach. Patients who suffered from a broad category of diseases were once treated with the same medication, leaving physicians to puzzle over why they worked for some people and not others.

Tailoring treatments start with highly specific diagnosis based on data integrated from various sources; adding genomics and radiomics enables a holistic understanding of the individual. These unique characteristics steer the personalization of treatment.

At the same time, molecular-level understanding of diseases with an amplified capacity of data analysis by AI-based algorithms enables a physician to deliver the best outcomes. For instance, we are now aware of more than 300 types and subtypes of cancer and cancer is not just one disease, but the result of a myriad genetic mutations.

This issue of AMJ brings you in-depth stories on personalised medicine concerning genomics, and precision-medicine in relation to radiomics.

We are also publishing the full-length transcription of the AMJ Roundtable held at Aster Medcity, Kochi on antimicrobial resistance. This would offer you a multi-stakeholder perspective on antimicrobial stewardship and antimicrobial resistance.

And then we bring you a read on two great minds in medicine - Dr James Allison an American immunologist and Nobel laureate whose discoveries have led to new cancer treatments for the deadliest cancers; and Dr Sanduk Ruit a Nepalese eye surgeon who has devoted most of his career to restoring sight and has brought back vision to more than 120,000 people.

I am certain you will be delighted with the diverse and rich stories we have showcased in this issue of AMJ.

Happy Reading!

Dr Harish Pillai
Editor & Publisher



Ayushman Bharat 2.0:

Incentives to get private hospitals to rural India

The Indian government has set aside a viability gap funding (VGF) under its massive insurance scheme to finance building hospitals in small towns. Two years after announcing the 'largest health insurance scheme', the government has been able to get nearly 10,000 private hospitals to partner out of over 31,000 in India. Some Indian private hospitals are hopeful that viability gap funding (VGF) can help sustainably operate hospitals in underserved areas. The VGF, which is proposed to come out of proceeds from the tax on medical devices, is meant for building hospitals in India's most disadvantaged 112 districts—primarily across Uttar Pradesh, Bihar, Chhattisgarh and Jharkhand—where there are no private hospitals or they're not empaneled with the government's scheme.



Healthcare Leak: Over 10 mn Patient Data Left Exposed

In the latest data leak related to users in India, over a million medical records and 121 Mn medical images of Indian patients, including X-rays and scans, have been leaked online to be freely accessible by anyone. According to German cybersecurity company Greenbone Networks, the patient records and scans and images from India also include details such as the name of the patient, their date of birth, the national ID, name of the medical institution, their medical history, physician names and other details that are meant to be classified. Among the leaked data are medical records belonging to Mumbai's Breach Candy Hospital as well as Utkarsh Scans, a medical imaging provider. The leak is a result of bad password practices at these hospitals and medical service providers.

Dubai Hospital reaches 88.5 per cent cure rate in child cancers



Dubai Hospital achieved a 88.5 percent cure rate on childhood cancers in 2019, which is on par with the world paediatric cancer cure rate of 85-90 percent, according to a statement issued by its paediatric oncology department. This reflects the UAE's rapid journey towards its goal of an overall cancer reduction by 18 per cent by 2021 in keeping with its National Health Agenda, the statement said. The UAE National Health Agenda 2021 has included cancer as one of the Key Performance Indicators (KPIs) to assess the nation's health-care goals being on track. According to the 2013 figures provided by the World Health Organisation (WHO), cancers in UAE claim 78 deaths per 100,000 of the total population. The target is to reduce the numbers to 64.2 deaths per 100,000 by 2021.

Coronavirus cases spike after changes to diagnosis method

A sudden spike in new coronavirus cases in China this week shocked researchers. But the huge bump in

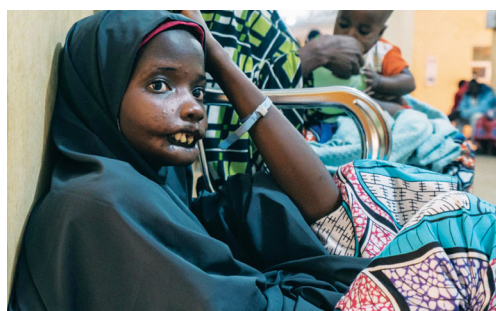
numbers isn't a sign that the epidemic is worsening, say researchers, it is instead the result of authorities changing how cases are confirmed. On 12 February, Hubei province reported nearly 15,000 new cases of COVID-19, the disease caused by the coronavirus, representing a 33% jump in total infections worldwide in a single day. But most of the Hubei cases — about 13,000 — are the result



of a new policy in the province that means physicians can diagnose suspected cases of COVID-19 on the basis of chest images, rather than having to wait for genetic tests to confirm the presence of the virus, which can take days. The new classification was listed in updated disease reporting guidelines issued last week, only applies to Hubei, where the virus originated in the city of Wuhan.



Restoring Dignity



Dr Hafiz Muhammed from Kozhikode, India, went to Nigeria as part of the Médecins Sans Frontières (MSF) team, where he treated 27 survivors of the Noma disease, sharing his experience of providing life-changing reconstructive surgery.

Noma is an overlooked but devastating disease which affects children who are often already suffering from malnutrition, malaria and other poverty-driven factors. I had only a faint memory of the name of the disease I had heard during my medical schooling. It starts as a small ulcer in the mouth but rapidly invades the soft tissue and the bones. Ninety per cent of the victims die. The rest who survive have big gaps in their cheeks and lips, and parts of their

nose would be lost. It is a grim sight. Poverty is, of course, at the root of the problem.

I had my apprehensions at first. I have never been exposed to the disease before. One week was spent on travel to reach Sokoto. And then we screened the patients to choose those we could perform the surgeries on. Some had malaria and could not be operated on.

Detailed literature regarding this disease is also fairly limited – a

small textbook by the Dutch Noma Foundation shared with me by a previous surgeon became my bible for understanding the disease. As

days passed by, my apprehensions died down as I realised that I could depend on my fundamental skills as a reconstructive surgeon at most times. We treated 27 patients, and the vast majority of them showed fair to excellent healing. My two-week assignment flew past in the blink of an eye. I hope to return soon!



COVID-19: China Turns to Cell Phones & Drones in Fight Against Virus

A Chinese man who had taken a trip to Wuhan— was amazed when cops turned up at his door after he returned, asking to inspect his temperature level.

The man had quarantined himself at his home in Nanjing, eastern Jiangsu district, and stated he had not informed anybody regarding his current journey to the city. But by trawling travelling data from Wuhan, neighbourhood authorities were able to zero in on him and also send off police officers to his residence.

Apps to check for coronavirus travellers

If you're worried, you travelled with someone with the coronavirus, get these apps. Chinese internet company Qihoo 360 has partnered with a Chinese tech firm to introduce a platform that lets users check if they have recently travelled with someone who contracted the coronavirus. By entering the date of their journey, together with flight or train numbers, users can find out if they were travelling with someone who has been infected with the virus. According to local media reports, more than 21 million people used the service within two days of its launch.

Mapping to Avoid Infected Neighbourhoods

Chinese citizens have now moved on to use mapping programs and travel trackers to avoid neighbourhoods with the Coronavirus infection. The data mapping company



QuantUrban and a third-party WeChat mini-program developer have created platforms that collect official information on the Coronavirus-infected communities and map it geographically so that users can gauge how close they are to infection sites. A Chinese search-engine and mapping provider has produced an online map that allows users to track the final destination of outbound car trips from Wuhan in the days leading to the city's shutdown.

Tracking Travelers from Hubei

The authorities are using people's cellphones to determine if they have been to the Hubei province - the epicentre of the outbreak. At a high-speed rail station in the eastern city of Yiwu, officials demanded that passengers send the text messages and then show their location information to the authorities before being permitted to leave the station. Those who had passed through Hubei were unlikely to be allowed entry.

In January, a person infected with the coronavirus used public transportation to crisscross the eastern Chinese city of Nanjing, potentially exposing those along the way to the highly contagious pathogen. By using this digital-surveillance, authorities were able to track-down to the minute, the sick person's exact journey through the city's subway system. Officials then published the details of the person's movements on social media and warned residents to get themselves checked if they had been in the vicinity at the time.

Drone to check the temperature.

A neighbourhood in China's eastern city of Nanjing has a novel solution to check the temperature of people under home quarantine without actually going to visit: Drones. A DJI Mavic 2 Enterprise Dual equipped with a thermal sensor has been used to check the temperatures outside windows. Through a speaker attached to the top of the drone, an operator on the ground asks people to open their windows and stand by while it checks in public.

In a town in Chengdu, a drone piloted by government officials busted a gathering of people who were playing a game of mahjong in an alley. Although mahjong is a popular holiday pastime for many Chinese people, the government managed to disperse the group by shaming them in public with a megaphone. Similar events of public shaming are seen in many cities and villages across China, albeit often in a more humorous way.

To contain the spread of the virus, drones are also used to monitor activities such as traffic and waste disposal. In Shanghai, drones have been deployed at inter-city roads for monitoring while officials check travellers' temperatures. In Zhongshan, drones are used to oversee the disposal of medical waste coming out of hospitals.

In focus

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INTEGRATING GENOMICS INTO HEALTHCARE: A GLOBAL RESPONSIBILITY

Genomic sequencing is rapidly transitioning into clinical practice, and implementation into healthcare systems has been supported by substantial government investment, totaling over US\$4 billion, in at least 14 countries.

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EXPANDING PRECISION MEDICINE

How Healthcare is Deploying
Precision Diagnosis and
Individualized Treatment at Scale



Expanding
the scope
of precision
medicine can
deliver improved
patient outcomes
and mitigate cost
pressures.

Personalised Medicine



Integrating Genomics into Healthcare: A Global Responsibility

by **Zornitza Stark,^{1,2,3} Lena Dolman,^{4,5} Teri A. Manolio,⁶ Brad Ozenberger,⁷ Sue L. Hill,⁸ Mark J. Caulfield,⁹ Yves Levy,¹⁰ David Glazer,¹¹ Julia Wilson,¹² Mark Lawler,¹³ Tiffany Boughtwood,^{1,2} Jeffrey Braithwaite,^{1,14} Peter Goodhand,^{4,5} Ewan Birney,^{4,15} and Kathryn N. North^{1,2,3,4,*}**

¹Australian Genomics Health Alliance, Melbourne VIC ³⁰⁵², Australia; ²Murdoch Children's Research Institute, Melbourne VIC ³⁰⁵², Australia; ³Department of Paediatrics, University of Melbourne, Melbourne VIC ³⁰⁵², Australia; ⁴Global Alliance for Genomics and Health, ⁶⁶¹ University Avenue, Suite ⁵¹⁰, Toronto, ON M^{5G} ^{0A3}, Canada; ⁵Ontario Institute for Cancer Research, ⁶⁶¹ University Avenue, Suite ⁵¹⁰, Toronto, ON M^{5G} ^{0A3}, Canada; ⁶National Human Genome Research Institute, National Institutes of Health, Bethesda, MD ²⁰⁸⁹²⁻²¹⁵², USA; ⁷All of Us Research Program, National Institutes of Health, Bethesda, MD ²⁰⁸⁹²⁻²¹⁵², USA; ⁸National Health Service England, Skipton House, ⁸⁰ London Road, London SE¹ ^{6LH}, UK; ⁹Genomics England, Queen Mary University of London, Dawson Hall, London EC^{1M} ^{6BQ}, UK; ¹⁰INSERM (French National Institute for Health and Medical Research), ⁷⁵⁶⁵⁴ Paris Cedex ¹³, France; ¹¹Verily Life Sciences, ²⁶⁹ East Grand Avenue, South San Francisco, CA ⁹⁴⁰⁸⁰, USA; ¹²Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge CB¹⁰ ^{1SA}, UK; ¹³Centre for Cancer Research and Cell Biology, Queen's University Belfast, ⁹⁷ Lisburn Road, Belfast BT⁹ ^{7AE}, UK; ¹⁴Australian Institute of Health Innovation, Macquarie University, ⁷⁵ Talavera Road, Sydney, NSW ²¹¹³, Australia; ¹⁵European Molecular Biology Laboratory-European Bioinformatics Institute, Hinxton, Cambridge CB¹⁰ ^{1SD}, UK

* Correspondence: kathryn.north@mcri.edu.au

Genomic sequencing is rapidly transitioning into clinical practice, and implementation into healthcare systems has been supported by substantial government investment, totaling over US\$4 billion, in at least 14 countries. These national genomic-medicine initiatives are driving transformative change under real-life conditions while simultaneously addressing barriers to implementation and gathering evidence for wider adoption. We review the diversity of approaches and current progress made by national genomic-medicine initiatives in the UK, France, Australia, and US and provide a roadmap for sharing strategies, standards, and data internationally to accelerate implementation.

Introduction

Five years ago, genomic sequencing was restricted to the research environment. Now, it is increasingly used in clinical practice, and over the next 5 years, genomic data from over 60 million patients is expected to be generated within healthcare.¹ But are our health systems ready for the complexity, volume, and responsibility associated with genomic medicine and the imperative to share clinical, epidemiological, and genomic data on a global scale to optimize the benefits for the individual? Genomic sequencing is a transformative technology, and effective integration in healthcare requires system-wide change.² Beyond the technical requirements of establishing sequencing and bioinformatics capacity to process samples, the real barriers to widespread clinical implementation span diverse domains, include data integration and interpretation, workforce capacity and capability, public acceptability and government engagement, paucity of evidence for clinical utility and cost effectiveness, and ethical and legislative issues.^{3,4} Frameworks for implementing genomic-medicine programs in single institutions and multi-institution collaboratives are

in Switzerland, the Netherlands, Brazil, and Finland are primarily focusing on the development of infrastructure, such as common standards and data-sharing policies and platforms. These projects will potentially be dwarfed by the China Precision Medicine Initiative: a 15-year, CN¥60 billion (US\$9.2 billion) project aiming to sequence 100,000,000 genomes by 2030.

Here, we illustrate the diversity of approaches and current progress made toward meeting the challenges of integrating genomics into mainstream healthcare at a national level by focusing on the UK, France, Australia, and US, as well as provide a roadmap for sharing tools, strategies, data, and standards internationally to accelerate implementation.

United Kingdom

The UK has a single-payer national healthcare system: the National Health Service (NHS). Genomics England (GEL) was established in 2013 with £300M (US\$415M) in government funding and a mandate to sequence 100,000 genomes from patients with over 100 rare diseases and seven common cancers, as well as their family members.⁶

Since 2013, the governments of at least 14 countries have invested over US\$4 billion in establishing national genomic-medicine initiatives to address implementation barriers and transition testing from centers of excellence to mainstream medical practice

available,^{2,5} but information on translating this experience to transform whole healthcare systems is scarce.

This is an international endeavor.³ Since 2013, the governments of at least 14 countries have invested over US\$4 billion in establishing national genomic-medicine initiatives to address implementation barriers and transition testing from centers of excellence to mainstream medical practice (Figure 1 and Table S1). In countries such as the UK, France, Australia, Saudi Arabia, and Turkey, workforce and infrastructure development have been coupled with testing large numbers of patients with rare diseases and cancer, two applications of genomic sequencing expected to have immediate clinical benefits. These “proof-of-principle” programs are driving change and fostering adoption among stakeholders under real-life conditions while simultaneously gathering evidence for wider implementation. Other countries such as the US, Estonia, Denmark, Japan, and Qatar have invested in population-based sequencing projects with return of results to participants, whereas national initiatives

This sequencing target was met in December 2018. The majority of rare-disease testing (the exception being that for late-onset adult disease) uses a trio-based approach to optimize large-scale data interpretation. A separate pathogen sequencing project is underway at Public Health England, and Health Education England is delivering 700 person-years of education and training to increase workforce capacity and capability.

GEL has established centralized infrastructure for the delivery of diagnostic whole-genome sequencing (WGS) services, including an NHS Genomic Sequencing Centre in partnership with the Wellcome Trust and Illumina, a standardized bioinformatics and analysis pipeline, a biorepository, and a data center. NHS England has established 13 Genomic Medicine Centers to identify, acquire consent from, and enroll participants in the project; collect high-quality DNA samples, including the establishment of new pathways for processing fresh and fresh frozen tumor DNA; provide clinical information to facilitate data analysis; and be responsible for

the interpretation and clinical actionability of final results. Genomic data are linked to health records in partnership with NHS Digital and are available to researchers and industry through the Genomics England Clinical Interpretation Partnership (GeCIP) and the Discovery Forum. Genomic-medicine initiatives have been funded in Scotland, Wales, and Northern Ireland (£6M [US\$8M], £6.8M [US\$9M], and £3.3M [US\$4.6M], respectively) to establish local clinical and laboratory genomics infrastructure and recruit participants for the 100,000 Genomes Project.

The 2016 annual report of England's Chief Medical Officer ("Generation Genome") called for the transformation of patient care through the systematic use of genomics and made 24 recommendations addressing further changes needed in NHS infrastructure, data sharing, governance, research, and clinician training.⁷ The NHS Genomic Medicine Service (GMS) was launched in October 2018 with a mandated test directory linking WGS for defined rare diseases and cancers to reimbursement. A new national network of Genomic Laboratory Hubs is being established, and WGS provision, data, and informatics infrastructure are delivered in partnership with GEL. The recent UK Life Sciences Sector deal, the £65M (US\$92.5M) investment by Health Data Research UK in a UK-wide collaborative network to facilitate the integration of health and data science, and the recent government announcement of plans to sequence 5,000,000 genomes in the next 5 years in the clinical and research environments are expected to further strengthen UK's leadership in genomics.

France

France has a healthcare system based on government-funded national health insurance. The French Plan for Genomic Medicine 2025 (Plan France Médecine Génomique 2025) was commissioned by the prime minister in 2015 and developed by Aviesan (the French National Alliance for Life Sciences and Health) in 2016. It aims to integrate genomic medicine into healthcare and establish a national genomic-medicine industry that promotes innovation and economic growth. Of the €670M (US\$822M) invested in the first 5 years, around €230M (US\$282M) will come from industry. Genome sequencing will be performed by 12 ultra-high-throughput services, two of which will be launched in 2018. A national data-analysis facility (Collecteur Analyseur de Données) will interpret and store data and interface with other national and international databases. Based at academic centers of excellence, a reference center for innovation, assessment, and transfer

National Genomic-Medicine Initiatives: Collaborative "Cross-Country" Projects Currently Underway

- Align research protocols to enable discovery across larger datasets, as well as compare outcome measures such as diagnostic and clinical utility, cost effectiveness, and patient- and family-reported outcomes (Genomics England, Australian Genomics, NHGRI Newborn Sequencing in Genomic Medicine and Public Health)
- Evaluate new sequencing and computational methods for clinical use (Genomics England and French Genomic Medicine Plan)
- Harmonize collection of clinical and phenotypic data: define the minimum clinical dataset required for interpreting genomic tests and the health informatics infrastructure required for data capture and exchange (Australian Genomics and Genomics England)
- Improve understanding of variant- and gene-disease associations by sharing the curation effort, developing common data models to capture evidence, and contributing to public knowledge repositories (NHGRI ClinGen, Genomics England, and Australian Genomics)
- Develop an evaluation framework for assessing existing educational resources (Australian Genomics and Genomics England); enable broader access, particularly to early adopters in countries with emerging genomic-medicine programs
- Develop strategies and capture experience in engaging culturally and linguistically diverse populations, indigenous populations, the general public, patients, professionals, and funders (Australian Genomics, Genomics England, NHGRI, All of Us, and Japan Agency for Medical Research and Development [AMED])
- Compare national consent procedures: reduce unnecessary heterogeneity, identify common features that represent best practices to allow global data sharing, and explore new models such as dynamic consent platforms (Australian Genomics, Genomics England, Swiss Personalized Medicine Network, and Japan AMED)

(Centre de Référence, d'Innovation, d'Expertise et de Transfert [CReFI]) will develop procedures, tools, and technologies and will also be responsible for implementation, commissioning, and workforce training. CReFI is already operational and has launched the first clinical pilot projects in rare disease, cancer, common disease (diabetes), and a population cohort to test technological, clinical, and regulatory barriers to implementation. It is anticipated that 10,000 individuals will be recruited

Table S1. Summary of currently active national government-funded genomic medicine initiatives

AUSTRALIA  Australian Genomics 2014-2021 Focus: Infrastructure and clinical cohorts: rare diseases, cancer, infectious disease. A collaborative partnership of over 80 institutions, with research driven through 4 programs: National diagnostic and research network; National approach to data federation and analysis; Evaluation, policy, ethics; and Workforce and education. Rare disease and cancer flagships serve as models for the implementation of genomic medicine in clinical practice. Leverages state-based initiatives Melbourne Genomics Health Alliance, Sydney Genomics Collaborative, and Queensland Genomics Health Alliance. Government investment: AUD125M (USD95M). AUD500M (USD353) announced in 2018 for Genomics Health Futures Mission. BRAZIL  Brazilian Initiative on Precision Medicine 2015-2024 Focus: Infrastructure, population-based cohort,	rare and common disease cohorts. Collaboration between five Research Innovation and Dissemination Centres to develop shared genomic databases compliant with GA4GH standards. Initial focus on creation of reference datasets, anticipated to progress to clinical cohorts. DENMARK  Genome Denmark 2012- Focus: Infrastructure, population-based cohort, pathogen project. Consortium between four universities, two hospitals and two private companies that aims to establish a national platform for sequencing and bioinformatics. Two demonstration projects: Cancer and Pathogens and Danish reference genome. Government investment: DK86M (USD13.5M). FarGen Project 2011-2017 Focus: Infrastructure and population-based cohort Establish Faroese reference genome and biobank through sequencing 1,500 individuals; develop local	competencies in genome sequencing. Government investment: DK10M (USD1.6M) ESTONIA  Eesti biopangas Estonian Genome Project 2000- ongoing Focus: Infrastructure and population-based cohort. Genomic data from GWAS, whole genome and whole exome sequencing from 52,000 individuals is linked to information from questionnaires, health records and physical examination. Additional government investment of €5M (USD5.9M) in 2017 for a cohort of 100,000 individuals. FINLAND  National Genome Strategy 2015-2020 Focus: Infrastructure. Development of Finnish national reference database and IT infrastructure to enable data integration between genomic data, metadata and health records. Legal and ethics framework, workforce development, clinical decision-support tools, public engagement and education. Establishment of Genome Centre.	Government investment: €50M (USD\$59M) FRANCE  France Genomic Medicine Plan 2016-2025 Focus: Infrastructure and clinical cohorts: rare diseases, cancer, diabetes. Initial focus on sequencing patients with cancer, diabetes and rare conditions, with the establishment of a hub-and-spoke model of 12 sequencing platforms in the country, and two national centres for genomic expertise and analysis. Expected to be capable of processing the equivalent of 235,000 genomes a year by 2020, and it is anticipated that the program will be expanded to common conditions 2020 onwards. Total investment: €670M (USD\$799M), of which €230 (USD\$273M) is from industry. JAPAN  Japan Genomic Medicine Program 2015- Focus: Infrastructure, clinical and population-based cohorts, drug discovery. The Japan Genomic Medicine Program is one	of the strategic priority areas of the Japan Agency for Medical Research and Development (AMED). Five initiatives underpin the Genomic Medicine Program: Tailor-Made Medical Treatment (mapping disease susceptibility and pharmacogenomics in a cohort of 100,000 patients); Platform for Promotion of Genome Medicine (maximising the efficiency of clinical and research infrastructure, and undertaking a research program in ethics, legal and societal implications); an Integrated Database of Clinical and Genomic Information; a Platform for Genomics-based Drug Discovery; and the Tohoku Medical Megabank project (developing a cohort of 150,000 individuals with deep phenotyping and genomic analysis). Government investment in 2017: JPY10.2B (USD\$90.05M) NETHERLANDS  RADICON-NL 2016-2025 Focus: Rare disease Trialling new technologies such as rapid whole genome sequencing in small cohorts to determine utility.
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into the initial pilot projects, and France will be capable of sequencing 235,000 genomes per year by 2020, corresponding to 20,000 patients with rare disease and 50,000 patients with metastatic or refractory cancer.

Australia

Australia has a national health system, but clinical and laboratory genetics services are funded by the six state and two territory governments. Thus, the approach to implementing genomic medicine has been based on the “federation” of existing state-based services with the engagement of state and federal governments in the development of a National Health Genomics Policy Framework.⁸

Australian Genomics was established in 2014 as a research partnership of 78 organizations, including diagnostic laboratories, clinical genetics services, and research and academic institutions. It was awarded

AU\$25M (US\$19.2M) by the National Health and Medical Research Council in 2015 to demonstrate the value and practical strategies for implementing genomics into healthcare, and it leverages AU\$100M (US\$76.8M) from state-based funding for genomics programs.

Australian Genomics comprises four research programs: (1) national diagnostic and research network; (2) national approach to data federation and analysis; (3) evaluation, policy, and ethics; and (4) workforce and education. Currently over 40 rare-disease and cancer flagship projects across 30 clinical sites provide experiential learning while prospectively evaluating diagnostic and clinical utility, cost effectiveness, and new approaches to service delivery and comparing different sequencing modalities, including WGS, whole-exome sequencing (WES), RNA sequencing, and large capture panels. The majority of rare-disease testing uses a singleton approach to optimize resource use. Although sequencing,

Health-Research**Infrastructure 2015-****Focus: Infrastructure**

Establish single interconnected infrastructure to combine genomic and other health data from multiple sources.

QATAR**Qatar Genome 2015-****Focus: Infrastructure and population-based cohort**

Creation of large data sets of around 6,000 deeply phenotyped individuals with whole genome sequencing data, available to researchers. Workforce development. Development of a national policy on genomic research. Clinical genome interpretation reporting service to be introduced.

SAUDI ARABIA**Saudi Human Genome Program 2013-****Focus: Infrastructure, clinical cohorts (rare and common genetic conditions) and population-based cohorts.**

Aims to sequence 100,000 individuals and create a national network of 7 sequencing laboratories, catalogue Saudi-specific mutations in known disease genes,

catalogue normal genetic variation in the Saudi population, catalogue mutations for recessive and common genetic disorders of unknown cause. Government investment: SAR300M (USD\$80M).

SWITZERLAND**Swiss Personalized Health Network 2017-2020**

Focus: Infrastructure Development of a distributed federated network, integrating existing heterogeneous systems at partner institutions. Development of common data standards and semantics. Implementation of a general consent. Definition of a data sharing policy framework. Government investment: CHF68M (USD69M).

TURKEY**Turkish Genome Project 2017-2023**

Focus: Infrastructure, clinical cohorts (rare disease, cancer, neurological disease) and population-based cohort Establish Turkish reference genome and clinical genomics infrastructure. Plans to sequence 100,000 individuals.

UNITED KINGDOM
Genomics England 2013-2021**Focus: Infrastructure and clinical cohorts: rare diseases, cancer, infectious disease.**

100,000 Genomes project is driving the establishment of the infrastructure required for the delivery of diagnostic genomics services in England, including a centralized sequencing facility, standardized bioinformatics and analysis pipeline, biorepository and data centre. 13 NHS Genomic Medicine Centres recruiting participants and returning results. Health Education England delivering workforce training. Government investment: £300M (USD\$415M).

Scottish Genomes Partnership 2015-

Focus: Infrastructure, clinical cohorts (rare disease and cancer), population-based cohort Establishment of two sequencing laboratories, and four clinical genomics centres. Recruiting to 100,000 Genomes Project, and compiling reference genomic data. Government investment: £6M (USD\$8M).

Welsh Genomics for Precision Medicine Strategy 2017-

Focus: Infrastructure, clinical cohorts (rare disease and cancer), population-based cohort Establishment of Genomic Medicine Centre, recruiting to 100,000 Genomes project, and compiling reference genomic data. Government investment: £6.8M (USD\$9M).

Northern Ireland Genomic Medicine Centre 2017-

Focus: Infrastructure, clinical cohorts (rare disease and cancer), population-based cohort Establishment of Northern Ireland Genomic Medicine Centre, recruiting to the 100,000 Genomes project, and compiling reference genomic data. Government investment: £3.3M (USD\$4.6M)

USA**National Human Genome Research Institute (NHGRI) 2007-**

Focus: Infrastructure and clinical cohorts Identification of barriers to implementation of genomics in clinical care and development

of solutions and best practices for widespread dissemination. Landmark projects include the Undiagnosed Diseases Network (UDN), Clinical Sequencing Evidence-Generating Research (CSER) consortium, Electronic Medical Records and Genomics (eMERGE) Network, Implementing Genomics in Practice (IGNITE) Network and the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, and the Clinical Genomics (ClinGen) Resource. Government investment: USD\$427M.

Precision Medicine Initiative (All of Us) 2016-2025**Focus: Population-based cohort**

Aims to create one of the largest, most diverse biomedical datasets through engaging 1,000,000 volunteers and combining genomic data with information from electronic health records, questionnaires, physical evaluations and biosensors. Government investment: USD\$500M over first two years.

bioinformatic analysis, data interpretation, reporting, and storage remain the responsibility of diagnostic laboratories, Australian Genomics is developing frameworks for ordering tests, acquiring consent, and capturing phenotypes; developing a federated repository of genomic and phenotypic data compliant with Global Alliance for Genomics and Health (GA4GH) standards; and enabling global data sharing through Beacon,⁹ Matchmaker Exchange,¹⁰ and ClinVar.¹¹ There is active engagement with patient advocacy groups, and a joint committee has been established with the Australian Digital Health Agency to integrate genomic test results into the national electronic health record (MyHealth Record).

Evaluation data are already available from several rare-disease flagship projects, indicating that genomic sequencing not only increases diagnostic yield but also has the potential to reduce diagnostic costs while improving short-term patient management and longer-term

patient and family outcomes.^{2, 12, 13, 14, 15, 16} The Australian federal government has recently committed AU\$500M (US\$372M) over 10 years for a Genomics Health Futures Mission to support new and expanded clinical studies in rare disease, cancer, and complex conditions; early access to clinical trials; and community dialog to understand the privacy, legal, social, and familial affects of genomics. Two initial projects have been announced—a population reproductive carrier screening program and a cardiovascular disease flagship project—and an additional AU\$26M (US\$18.4M) of funding has been granted to Australian Genomics for these.

United States

The US has a mixed private and public healthcare system and has invested in genomic-medicine implementation since 2011 with the launch of the new strategic plan of the National Human Genome Research Institute

(NHGRI).¹⁷ NHGRI's genomic-medicine programs aim to identify barriers to implementation of genomics in clinical care and develop solutions and best practices for widespread dissemination. Many of these landmark projects have recently reported results, establishing evaluation frameworks and providing evidence on the diagnostic, clinical, and economic value of genomic sequencing in specific patient groups, such as healthy and acutely unwell newborns;^{18, 19, 20, 21, 22} individuals with complex, undiagnosed rare genetic conditions;^{23, 24} and those in specific healthcare settings, such as primary-care and cardiology clinics.^{25, 26, 27} NHGRI projects are also addressing specific evidence gaps in the clinical delivery of genomic testing, such as the return of secondary findings,^{28, 29, 30} inter-laboratory consistency in variant interpretation,^{31, 32} integration of genomic resources with electronic records,³³ and sharing implementation and evaluation experience more broadly.^{34, 35, 36, 37} Tools for electronic phenotyping (Phenotype KnowledgeBase), clinical decision support (Clinical Decision Support KnowledgeBase), and implementation in resource-limited settings (IGNITE SPARK Toolbox) are openly available, and ClinGen plays a central role internationally in curating and disseminating consensus information on clinically relevant genes and variants.^{38, 39, 40, 41}

The Precision Medicine Initiative All of Us Research Program, initially funded through a special congressional appropriation of US\$500M to the National Institutes of Health in 2016–2017, has now launched throughout the US and has an additional funding commitment of US\$1.455B. All of us is engaging 1,000,000 volunteers of all life stages, health statuses, races and ethnicities, and geographic regions, reflecting the human diversity of the US. Mobilizing rich and constantly evolving data—from electronic health records, biospecimens, and questionnaires to physical evaluations, sensors, and other technologies—the program will support research at the intersection of lifestyle, environment, and genetics to produce new knowledge, leading to the development of innovative prevention strategies and treatments. Both genotyping and WGS are being evaluated as testing modalities initially.

Genomic Medicine in the Private Sector

The increased integration of genomics into public healthcare systems is mirrored by an explosion in the use of genomics in the private sector, particularly in the US. Geisinger Health System's MyCode project, which began as a partnership with Regeneron Pharmaceuticals

to perform exome sequencing in 100,000 Geisinger patients and use the results for drug discovery and clinical care,⁴² has recently expanded to all consenting Geisinger patients. Foundation Medicine has developed a number of genomics-based tests in the domain of precision cancer medicine while also contributing to public databases, such as the National Cancer Institute's Genomic Data Commons. Direct-to-consumer (DTC) testing companies, such as 23andMe and Ancestry, capture significant health-related genomic information, but public and clinician responses to DTC genomics have been variable.^{43, 44, 45}

International Collaboration to Accelerate the Implementation of Genomics into Healthcare

The above-mentioned implementation approaches and priorities of genomic-medicine initiatives in high-income countries might not necessarily be applicable to low and middle-income countries.⁴⁶ Yet, broad implementation will be crucial in building representative population reference datasets that improve variant interpretation globally⁴⁷ and in accelerating the discovery of genes associated with rare disease, particularly in populations where consanguinity is common.⁴⁸ Implementation in a range of economic and social contexts will also help address health priority areas with a major contribution to global disease burden, including host-pathogen interactions in infectious diseases; common monogenic disorders, such as sickle cell disease and thalassemias; and complex conditions, including hypertension, dyslipidemia, diabetes, stroke, and kidney disease. The Global Genomic Medicine Collaborative is working to identify and share genomic-medicine implementation activities around the globe, including those in under-resourced areas. National initiatives, even in resource-limited settings, can often move more quickly in response to specific local health needs.⁵ The Southeast Asian Pharmacogenomics Research Network, for example, is a multinational collaboration focused on pharmacogenomic risk alleles present at high frequencies in Southeast Asian populations.⁴⁹ The Human Heredity and Health in Africa initiative, a large-scale multinational sequencing project that pools infrastructure and human resources, harmonizes data collection, and accelerates capacity development, provides another successful implementation model in low-resource settings.⁵⁰

All of these large-scale initiatives have the opportunity to transform healthcare systems by integrating genomic technologies into clinical care. However, with this comes the responsibility to do so efficiently and effectively and

to share knowledge and experience. Concerns about overpromising (“genohype”)⁵¹ and the perceived desire to exempt genomic testing from requirements for robust evidence, leading to misallocation of healthcare resources,⁵² have been raised. Delays in program evaluation mean that clinical implementation and policy development proceed uninformed by evidence, potentially resulting in inappropriate testing, poor-quality data interpretation, siloed data, and funding arrangements that entrench existing healthcare inequalities. Healthcare systems are already struggling with evidence-based medicine, and the absorptive capacity of frontline clinical teams looms large as a key challenge.⁵³ Almost all of the initiatives discussed here are subject to time-limited funding, with the danger of creating momentum for genomic medicine, without the guarantee of sustainable healthcare resource allocation.

The scale of the implementation challenge is formidable. Sharing data, tools, experience, and knowledge to create a global “learning health system” is essential if we are to effectively accelerate and sustain the integration of genomics into healthcare. Collaborations across multiple areas are already under way (Box 1), but here we will focus on discussing two key priorities: evidence generation and data sharing.

Building the Evidence Base for Implementation of Genomics in Healthcare

The paucity of evidence for the clinical utility of genomic testing, and the resultant lack of alignment of reimbursement methods to drive transformational change in healthcare, remains a principal barrier to implementation.^{3, 5} National-level initiatives have an important role in presenting a unified voice to governments to inform future policy development and service planning. Outcome evaluation of patient cohorts is a key priority to inform policy decisions but is hampered by a lack of consensus on standard criteria against which the effectiveness of genomic interventions should be evaluated and reported.^{54, 55} There is a need to develop and share evaluation methodologies specific to different disease groups,⁵⁶ funding contexts, and healthcare systems. Although some data are already available on diagnostic yields, short-term clinical utility, and cost effectiveness in small cohorts,^{12, 13, 15, 16} more data are needed on longer-term health outcomes following genomic testing, including measures such as the development and progression of disease, quality-adjusted life years gained, patient empowerment, impact on families, and

downstream cost effects on healthcare systems^{14, 25} and society. National genomics initiatives also provide the opportunity to assess the evidence for and against particular approaches for effective, sustainable implementation.⁵⁷ The framework developed by NHS England in conjunction with Genomics England to commission WGS for routine care provides an early example of integrating the clinical evidence base with operational and financial considerations.

Genomic Data Sharing

The importance of breaking down data silos to accelerate the development of knowledge databases that directly improve patient outcomes cannot be underestimated.⁹ Genomic data generated within healthcare settings are subject to strict national regulatory frameworks that are unlikely to allow large-scale data migration, and innovative solutions are necessary to enable federated data analysis without data movement across geographical borders⁵⁸ while maintaining public trust.⁵⁹ National genomic-medicine programs have the opportunity to resource and promote best practices in data sharing by structuring data access and consent processes, collecting clinical and genomic data in interoperable formats, committing to global data sharing, and informing public debate and policy development. GA4GH recently launched a 5 year strategic plan—GA4GH Connect—that focuses on the development of standards for responsible sharing of clinical-grade meta-, genomic, and phenotypic data. GA4GH toolkits provide a framework to enable transparent, responsible, and accountable data sharing, as well as practical specifications for genomic data formats and standards for interoperable exchange. Genomics England, Australian Genomics, and All of Us serve as early Driver Projects for GA4GH to inform the iterative development of tools and policies for data sharing, test them under real conditions, and disseminate best practices.

Conclusions

It takes an average of 17 years for research evidence to be implemented in clinical practice.⁶⁰ We have a global responsibility to accelerate the implementation of genomic medicine and enable the timely realization of the benefits of genomics for individual patients, families, and healthcare systems. Technical standards and policy guidance are high priorities at this crucial inflection point to enable a shift in the global community toward more responsible and effective sharing of genomic, epidemiological, and clinical data and facilitate evidence-based implementation. National genomic-medicine

initiatives, in partnership with GA4GH and other regional and global alliances, have an important role in strengthening an international collaborative network and creating a global learning healthcare system to enable rapid translation.

Acknowledgments

The Australian Genomics Health Alliance is supported by the Australian National Health and Medical Research Council (GNT1113531). The 100,000 Genomes Project is managed by Genomics England (a wholly owned company of the Department of Health). It is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK, and Medical Research Council have also funded research infrastructure. The 100,000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support. M.L. is funded by Health Data Research UK.

Declaration of interests

E.B. reports consultancies to Oxford Nanopore, GlaxoSmithKline, and Dovetail Genomics; M.L. reports personal fees (unrelated to the current work) from Pfizer.

Web Resources:

- All of Us Research Program, <https://allofus.nih.gov>
- Australian Genomics, <https://www.australiangenomics.org.au>
- French Genomic Medicine Plan, http://solidarites-sante.gouv.fr/IMG/pdf/genomic_medicine_france_2025.pdf
- Geisinger Health, <https://www.geisinger.edu/research>
- Genomics England, <https://www.genomicsengland.co.uk>
- Global Alliance for Genomics and Health, <http://www.ga4gh.org>
- Global Genomic Medicine Collaborative, <https://g2mc.org/>
- Health Education England, <https://www.genomicseducation.hee.nhs.uk>
- NHGRI Clinical Decision Support KnowledgeBase, <https://cdskb.org/>
- NHGRI Genomic Medicine, <https://www.genome.gov/27551170>
- NHGRI IGNITE Spark Toolbox, <https://ignite-genomics.org/spark-toolbox>
- NHGRI Phenotype KnowledgeBase, <https://phekb.org/>

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Precision Medicine



Expanding precision in medicine is opening the door to improving outcomes and reducing healthcare costs unlike anything before. The twin goals of more precise diagnoses and more individualized treatments are clearly within reach.

by **Dr Luis Lasalvia & Reto Merges**

EXPANDING PRECISION MEDICINE

How Healthcare is Deploying Precision Diagnosis and Individualized Treatment at Scale

How is it possible to improve patient outcomes in the face of relentless pressure to contain costs? As populations continue to age and advanced therapies continue to grow more expensive, scaling up precision in medicine is a recommended approach that can help healthcare executives to add value, reduce costs and improve clinical results. .

The age of precision medicine – tying pinpoint diagnoses to individualized treatment – has already begun. The trick now is to find cost-effective ways to scale up this potential game changer so its transformative power can be unleashed on a larger scale.

Doing so requires four things: improving the accuracy of diagnoses, reducing unwarranted

variations in diagnosis, personalizing treatment when it can make a difference, and finally, taking advantage of today's progress in advanced therapy intervention to maximize outcomes.

Achieving these four goals – known as the Four Pillars of Expanding Precision Medicine – is the recipe for enabling healthcare executives to fulfill the promise of implementing precision in medicine and empowering its adoption at scale around the world.

WHY PRECISELY DO WE NEED PRECISION MEDICINE?

The answer is simple: medicine, for all its advances, is still hobbled with inconsistency in both diagnosis and treatment. Although it is a cost problem, this is a human problem as well. Suboptimal precision in medicine is visible across the continuum of care. Diagnoses that are not precise, timely, or accurate negatively affect patients' results.

Even when the appropriate diagnosis is being made, unwarranted variations can add at least 25% to the cost of healthcare, with negative

impact in outcomes too. Medically justified treatments that aren't individualized or unnecessary invasive procedures put people's health at risk.

Lack of precision exacts a price both clinically and financially. A study by U.S. News and World Report found that in some regions of the U.S., Medicare patients underwent 450% more coronary artery angioplasty procedures than in other parts of the country.¹ Many of those patients, the article noted, had unnecessary invasive procedures that can be both risky and costly.

THE RIGHT TREATMENT AT THE RIGHT TIME FOR EVERY PATIENT

As a goal, it sounds simple. In practice it's one of healthcare's biggest challenges, with systemic effects on medicine around the world.

Thanks to the explosion of clinical data available from new technologies, it is easier to tailor treatments that take a patient's unique phenotype and genetic makeup into account.

Contextually relevant data is gold when it comes to reducing inaccuracies in diagnosis. It's one of the reasons the National Institutes of Health's All of Us Research Program is now gathering lifestyle, environmental, and biological data from one million U.S. volunteers. While All of Us is a user-friendly name, it's worth noting that it used to be called the Precision Medicine Initiative Cohort Program – a government commitment to advancing the field. Similar initiatives have been launched in the private sector. Healthcare companies and institutions such as Geisinger, Kaiser Permanente, and Johns Hopkins Hospital are leading the way in the U.S.

Researchers in Europe are also taking up the challenge of using data to scale up healthcare's ability to more fully characterize the determinants of health and disease. U.K.'s Biobank has a study that is looking at ways to clarify the specific roles that an individual patient's imaging and genetics make up, together with lifestyle and environmental factors, in the development of disease. In Germany, the Study of Health in Pomerania (SHIP) is currently assessing the "prevalence and incidence of common risk factors, subclinical disorders and clinical diseases" and using data to investigate associations and reactions between them.² In addition, in 2016, the Chinese government started the China Precision Medicine Initiative, pledging to invest 9.2 billion USD between now and 2031.

When massive datasets such as these are analyzed with the help of AI technologies, connections and patterns begin to emerge. The medical community is then able to determine optimal therapeutics based on an individual's phenotype, disease subtype, tumor signature, and other biomarkers so that the best therapy can be implemented as soon as possible. Just as exciting is the ability to use predictive analysis to enable earlier, more effective intervention.

Scaling up these capabilities will give healthcare providers significantly enhanced capabilities to diagnose based on synthesizing all relevant patient data and insights at the point of decision. Then the most appropriate treatment can be chosen.

SCALING UP THE FOUR PILLARS OF PRECISION MEDICINE

The promise of precision medicine is founded on four pillars:

- ▶ Improve Diagnostic Accuracy
- ▶ Reduce Unwarranted Variations
- ▶ Personalize When It Matters
- ▶ Advance Therapy Outcomes

The first two are about increasing precision in diagnosis; the second two focus on choosing the right therapy individualized for each patient. Expanding precision medicine to scale means scaling up both categories – all four pillars, and for all patients.

Let's examine these one by one.

IMPROVE DIAGNOSTIC ACCURACY

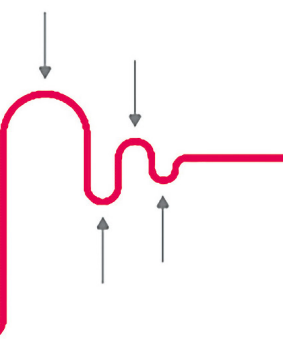
It is not possible to choose the right treatment with the wrong diagnosis. Accurately pinpointing what's wrong with a patient is the starting point for everything. Yet, in their 2015 report "Improving Diagnosis in Healthcare," The Institute of Medicine and The National Academies of Sciences, Engineering, and Medicine found that 5% of U.S. adults who received outpatient care that year – millions and millions of patients – had errors in their diagnoses. Those errors led to 10% of patient deaths and accounted for as much as 17% of adverse events in hospitals.³

It doesn't have to be that way. Today's advanced laboratory and imaging technologies can yield significantly more actionable information than ever before. And this information has the power to yield rich patient insights at the point of decision.

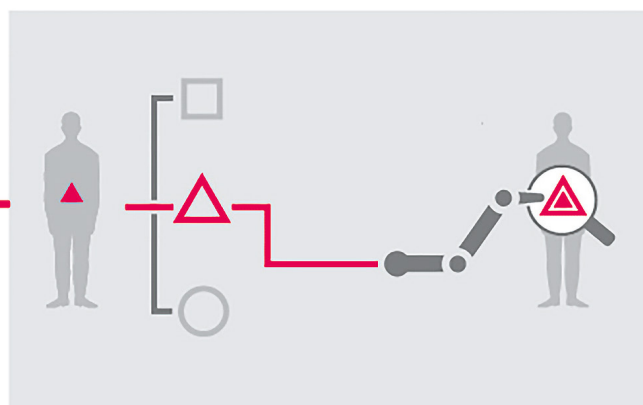
The Four Pillars



Improve diagnostic accuracy



Reduce unwarranted variations



Personalise when it matters

Advance therapy outcomes

In neurology, current imaging technologies with high resolution, for instance, can help in making the differential diagnosis between multiple sclerosis lesions and other inflammatory and non-inflammatory conditions.

In cardiology, suboptimal diagnosis can lead to non-adequate use of implantable defibrillators. More precise identification of patients at risk for sudden cardiac arrest can help make sure the right patients receive these life-saving devices at the right time. Running diagnostic processes based on imaging and laboratory tests can allow people who actually need defibrillators to get them – and people who don't need them don't wind up with them unnecessarily.

In oncology, rich clinical insights drawn from advanced imaging technologies are already improving the screening and diagnosis of many kinds of cancers. Multi-parametric Magnetic Resonance Imaging (mpMRI), for example, allows for more precise identification of prostate cancer versus standard transrectal ultrasonography-guided biopsies. The U.K. National Health Service estimates that “between 33% to 40% of patients who have an mpMRI scan will find out on the same day that they don't have prostate cancer.” That means they can avoid an unnecessary biopsy.⁴

In lung cancer, emerging radiomics digitally extract and analyze disease-related data from images. It can make lung cancer screening faster and more accurate by using machine learning when applied to the right set of high-risk patients.

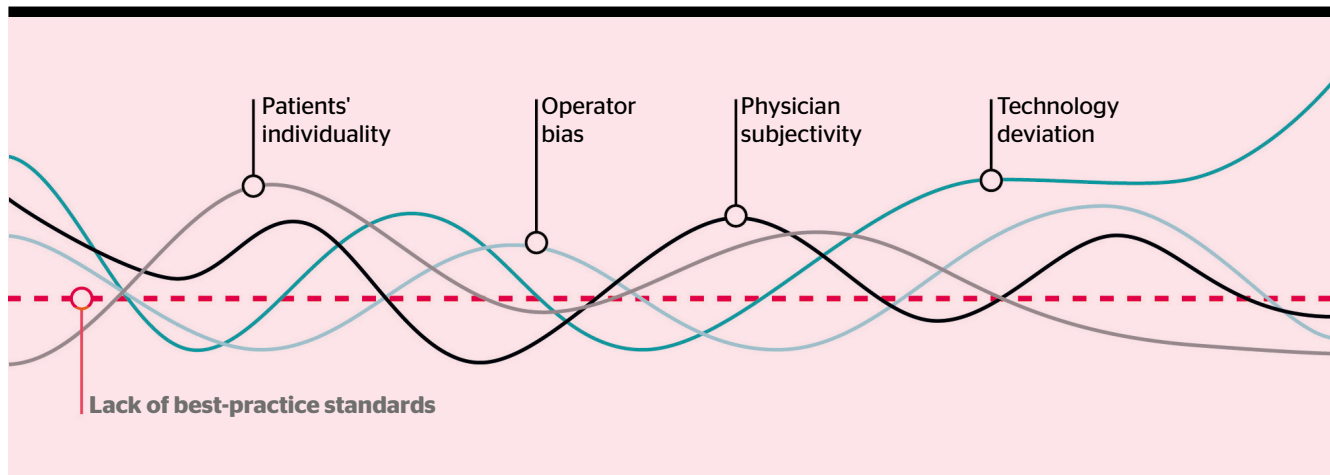
Laboratory tests have become more sensitive and precise in the vast majority of clinical conditions. Standardization allows for additional consistency in their interpretation. On top of that, automation in the laboratory adds accuracy by removing operation and manual handling risks.

One of the most fertile avenues for scaling up diagnostic accuracy lies in leveraging the power of digitalization and artificial intelligence. Technologies driven by quantified markers and machine learning are able to process vast sets of data from imaging, laboratory, socio-determinants, and other sources. That gives healthcare providers an expanded ability to pinpoint parameters that define subgroups of patients or disease states. The integration of data and artificial intelligence can be used in decision support systems to make suggestions for next steps. Add to that the ability of new networked medical technologies that enable physicians to share data from peers around the world, and you have a recipe for significantly more accurate diagnoses.

The bottom line is more precise diagnosis can be achieved for a broad range of conditions.

REDUCE UNWARRANTED VARIATIONS

Accuracy is clearly important. But without consistent accuracy – accuracy independent of who's doing the testing, who's reading the results, and where and when the testing occurs – the notion of “precision medicine” becomes meaningless. One of the biggest opportunities to improve outcomes while reducing costs is the reduction of unwarranted



Sources of unwarranted variations in diagnosis: Improving diagnostic consistency is possible through standardization, adaptation to the patient, automation, clinical decision support, and ensuring reliable and comparable results, when technology is applied.

ranted variations. Precision medicine can only expand when clinicians and patients can count on consistent results across different operators and institutions.

Unwarranted variations are the variations in medical practices that cannot be explained by illness, medical need, patient preferences, or the recommendations of evidence-based medicine.

We all pay a price for these unwarranted variations. Twenty-five percent of hospital costs are wasted due to variations, and some estimates even go up to 65% of HC costs, based on the “Five steps every hospital CEO should start today”.⁵

In the U.K., for example, the 2017 Diagnostic Atlas of Variation for England found a nine-fold variation in the acquisition of brain imaging for stroke patients within an hour of arrival at the hospital.⁶ In the U.S., the Dartmouth Atlas of Health Care found a greater than two-fold variation in per capita Medicare spending across the country driven by the rate of care utilization rather than price. And at least three groups have concluded that 30% of U.S. spending on health-care is unnecessary.⁷

Building best-practice standards along the continuum of care is a prerequisite for consistent, evidence-based care. The key levers for reducing variations are adapting to patients' individual needs and reducing the subjectivity of operators and physicians. Correspondingly, automation and assisted decision-making based on reproducible technology activate these levers to create consistent diagnostic results. Steady, iterative improvements using this approach effectively reduce unwarranted variations.



Dr Luis Lasalvia, MD, Vice President and Global Medical Officer, Siemens Healthineers. He has submitted a number of patents in the U.S. and Europe, and has authored numerous papers and articles in peer review journals and other prestigious publications.



Reto Merges, is Global Head of Expanding Precision Medicine, Siemens Healthineers. He has authored many publications, while submitting multiple patents.

Efforts to reduce unwarranted variations are beginning to bear fruit. Mercy Health in St. Louis, Mo., USA, was able to improve patient outcomes after total knee replacement (TKR) by analyzing a wide variety of data associated with the procedure. TKR patients with the shortest hospital stay, it turns out, had all been administered pregabalin prior to surgery based on published data that it can improve post-op pain management. Mercy Health, as a result, was able to improve patient outcomes for TKR patients, including reducing length of stay, for a total savings of more than \$1 million per year in direct costs.

PERSONALIZE WHEN IT MATTERS

Medical treatments are best when they're custom tailored to individuals and their conditions. Today, advances in biomarkers, genomics, proteomics, metabolic science, and AI-assisted data processing are enhancing the ability of healthcare providers to offer genuinely personalized care.

High-quality imaging technologies, for example, now allow for personalized radiation planning for patients undergoing radiation treatment based on their unique anatomical and functional imaging profile. Companion diagnostics – tests to determine which patients are likely or unlikely to be helped by a particular drug – are now required by the U.S Food & Drug Administration for drugs designed to work on a specific genetic or biological target typically present in small portions of the population. Herceptin, a HER2/ neu inhibitor, is a good example of a therapy that takes this model.⁸

In oncology, liquid biopsies (using simple blood samples instead of the more invasive traditional biopsy) combined with genomic analyses are able to identify the genomic makeup of circulating DNA or cancer cells, thus helping physicians to identify precise and effective individualized treatments, even in cases when tumors are not directly accessible.

The quantitative analysis emerging in radiology – known as radiomics – also shows promise in giving physicians greater insights into tumor biology and genetic diversity that can correlate with tumor aggressiveness and response to treatment.

The move to personalized treatment has begun. Deploying such personalized approaches at scale is a clear requirement for improving clinical and financial outcomes for patients and hospitals around the world.

ADVANCE THERAPY OUTCOMES

Today, physicians performing minimally invasive surgeries are able to turn to image guided therapies for unprecedented accuracy over traditional surgeries. The results: shorter hospital stays and less post-operative pain.

Many opportunities to enhance therapy precision lie in the integration of imaging and treatment delivery. Therapeutic procedures from surgery to radiation oncology rely on integrated real-time or multimodal image guidance and robotic assistance. This facilitates minimally and non-invasive interventions that support faster recovery with fewer complications. This enables healthcare providers to advance therapy outcomes and make treatment safer, faster, and less costly.

New advances in medical technology and imaging modalities such as ultrasound, magnetic resonance, CT, endoscopic cameras, and robotic technology are rewriting the rules for precise procedures and improved patient outcomes. Today's leading surgeons regularly rely on computed tomography and angiography systems for high-res images.

Real-time imaging is also finding a home in cardiovascular care, oncology, orthopedics, vascular procedures, and the surgical removal of tissue. Constantly improved outcomes at scale are likely to accelerate as these new technologies and procedures continue to mature.

CONCLUSION

Expanding precision in medicine is opening the door to improving outcomes and reducing health-care costs unlike anything before. The twin goals of more precise diagnoses and more individualized treatments are clearly within reach.

Expanding precision medicine to a global scale will be further enabled by the continued collaboration of healthcare providers, medical technology companies, and clinical partners to let precision diagnosis and individualized treatment become the default paradigms. The capability is clearly there to improve outcomes and reduce costs. All that's needed now is the will to bring it to scale so that 21st century precision medicine is available to everyone.

© This article previously published in the Journal of Precision Medicine Volume 5 Issue 3.

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CORONAVIRUS

Global fight depends on the health system of vulnerable countries



Dr Nahid Bhadelia, MD, MA

An infectious-diseases physician at the Boston University School of Medicine and the medical director of the Special Pathogens Unit (SPU) at Boston Medical Center.

The 2019 novel coronavirus has caused a public-health emergency in China, a global economic superpower. Like many in my field, I worry that if and when the emergent virus takes root in poorer countries that are already tackling outbreaks of other pathogens, it could wreak havoc of an even larger magnitude.

I am a physician who concentrates on outbreak preparedness against new infectious diseases, both in the United States and in countries with far fewer resources. I worked as a clinician in West Africa during the Ebola outbreak, and in New York City hospitals during the H1N1. My work—currently in western and equatorial Africa and previously in Asia and Latin America—has convinced me that global defenses against new infectious diseases are only as strong as the health systems in the poorest communities all around the world. The specifics of new diseases matter less than whether those communities can, with international support, build the resilience to face common (and uncommon) threats.

When I landed in Uganda a couple of weeks ago, the airport in Entebbe was screening for Ebola virus disease, because of the continuing outbreak in the neighboring Democratic Republic of Congo, and also for the novel coronavirus. That same week, a number of other diseases also threatened people living in the region. The Ugandan public-health authorities were simultaneously dealing with outbreaks of Crimean-Congo hemorrhagic fever and yellow fever.

Last week, WHO identified 13 African countries at high risk for transmission of 2019-

nCoV due to direct links or high-volume travel from China. The damage the new epidemic might cause in Africa is not only a function of the disease itself, but also of how it could combine with other health threats and disrupt trade, travel, and educational endeavors on the continent.

The last two Ebola outbreaks—in West Africa from 2013 to 2016 and now in the Democratic Republic of Congo—have devastated the affected countries. If any good has come of those events, it's that they have also led to improvements in many African countries' capacity to tackle emerging infectious diseases, bringing in investment in diagnostic capacity and national coordination.

Nigeria, for example, has improved its national laboratory that tests infectious-disease specimens. That nation's improved detection capabilities have improved surveillance not just of Ebola, but also of Lassa fever and of the growing incidence of monkeypox and other infectious diseases. There is greater regional leadership; the Africa Centers for Disease Control and Prevention—a.k.a. Africa CDC—has emerged as both a coordinator of and advocate for more resources and has led the efforts to conduct diagnostic testing for 2019-nCoV in multiple countries across the continent.

If the 2019-nCoV epidemic spreads around the world, rich countries may decide to test incoming travelers. In poor communities, identifying those carrying the virus will be even harder.

Nearly 90 previously unknown human pathogens have been discovered since 1980. Emergent diseases sometimes bring new attention and new resources; the Bill and Melinda Gates Foundation, for instance, recently made a major contribution to help tackle the novel coronavirus. Still, the central lessons of 2019-nCoV and Ebola are the same: Temporary support in the aftermath of an epidemic is not a substitute for much greater investment by the international community in health care in the most vulnerable countries all around the globe. The advent of 2019-nCoV should push us to look beyond specific diseases and toward how we can improve health care more generally—and contain the next pandemic before it starts.

Nearly 90 previously unknown human pathogens have been discovered since 1980.

Conversation

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Conversation with *Dr James P. Allison*:
The Contrarian Who Cures Cancers

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AMJ Roundtable:
**Antimicrobial Resistance
(AMR): A Battle Lost or a
Challenging Conquest?**



“We have about 100 hospitals, in Holland, and the number of beds is decreasing very rapidly. So, patients are coming in the morning and leaving in the afternoon. We almost have no long stays.”

– Dr Peter Schneeberger



Claudia Dreifus

The Contrarian Who Cures Cancers

Dr James P. Allison believed that unleashing the immune system was a way to beat cancer when almost no one else did. A Nobel Prize and a growing list of cancer survivors vindicate him.

by **Claudia Dreifus**

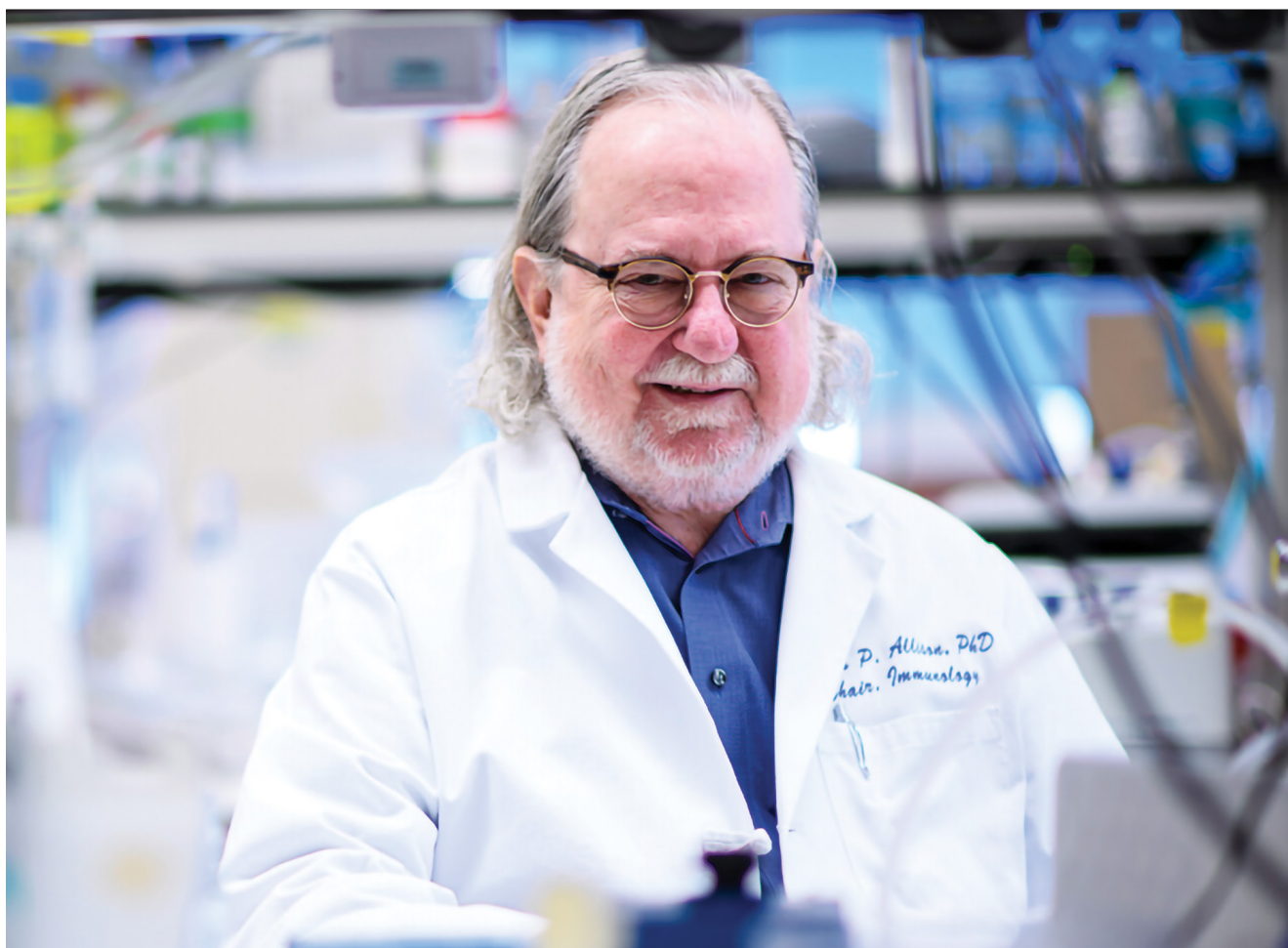
When I first met the immunology researcher James P. Allison in 2014, he was just becoming an icon. Columbia University had brought him to their campus to present him with the Louisa Gross Horwitz Prize for the new type of cancer therapy he had developed. Instead of trying to burn, poison or surgically remove malignant cells from the body, his treatment mobilized a patient's immune system to destroy them.

During his talk at the award ceremony, Allison explained that three years earlier, the Food and Drug Administration had approved the antibody drug he had developed, ipilimumab, for use against late-stage metastatic melanoma, which is among the deadliest of cancers. Some of the terminal patients who had participated in earlier trials, he reported, had gained a decade of life. As he described how his drug had changed the prognosis for some of these patients — it was effective for about 20% of them — tears came to his eyes.

In all my years on a science beat, I'd never seen a researcher cry. Allison, with his long gray hair and his loose-fitting clothes, struck me as among the most interesting figures in the scientific world. Speaking with him later, I sensed that he was someone deeply original, extremely confident of his intellectual powers and unafraid to go where they took him — the exact qualities it takes to invent a paradigm-shifting cancer treatment.

Allison's drug wasn't the first or only form of immunotherapy; scientists have worked on anticancer vaccines, for example, for decades. What made Allison's "immune checkpoint therapy" unique was that it used antibodies to unlock the immune system's potential to kill cancer cells.

This approach is the culmination of Allison's highly accomplished immunology career. In the early 1980s, he identified the receptor that allows the immune system's T cells to recognize the antigens of infected or abnormal cells. A decade later, he showed that T cells also need a



signal from a “costimulatory” molecule to launch their attacks. Then Allison and his colleagues discovered that a molecule called cytotoxic T lymphocyte antigen-4 (CTLA-4) acts as a checkpoint, or built-in brake, on T cells. They could remove the brake and set T cells loose against cancer cells with an antibody — ipilimumab — that inhibited the CTLA-4 checkpoint.

Work on immunotherapy has become a major trend in biotech research in the past decade. Variants and extensions of immune checkpoint therapy, often in combination with other drugs, are the basis for many treatments under development for cancers of the brain, lung, bladder and kidneys. None of these immunotherapy drugs are yet effective for all patients or all cancers, but when patients respond — as many metastatic melanoma patients do — their longevity is significantly improved.

Allison, now 71, was emphatic in his assessment of those outcomes when I spoke with him in his office at the University of Texas MD Anderson Cancer Center,

where he is the chairman of the department of immunology and the executive director of its Immunotherapy Platform. “You don’t just get an increase in median survival,” he said. Thousands of patients treated with immunotherapy have lived cancer-free for 10 or more years. “These people have been cured.”

Such results have brought Allison not a few honors, including the Paul Ehrlich and Ludwig Darmstaedter Prize and the Lasker-DeBakey Clinical Medical Research Award in 2015 and the Wolf Prize in Medicine and the Balzan Prize in 2017. Then, in 2018, Allison shared the big one with Tasuku Honjo of Kyoto University: the Nobel Prize in Physiology or Medicine (Honjo had independently found a different cancer checkpoint).

At MD Anderson, Allison’s colleagues were so thrilled that they held a victory parade for him. In Houston, Allison has become a major celebrity: a sought-after guest at fundraising galas, an advocate with the Texas legislature for research dollars, and the target of countless autograph hounds and selfie seekers. It hasn’t

hurt his celebrity-standing that on occasion he also plays harmonica on stage with Willie Nelson and that a documentary about him and his work, *Jim Allison: Breakthrough*, was released last year.

Allison and I spoke in person and over the phone, and also corresponded by email in the course of this reporting. The interview has been condensed and edited for clarity.

We met five years ago, before all the acclaim and honors. At the time, you seemed overworked and exhausted. Today, you are looking slimmer, tanner, rested. Does winning a Nobel Prize improve one's health?

[Laughs.] Yeah. Five years ago, I was eating too much, drinking too much, traveling too much. I decided that it was time to quit doing that. I started eating better, drinking less and saying no to some demands. I've never been good at saying no.

You know where all that started? A year ago, in Stockholm, when we went for the Nobel Prize. The celebrating started every morning at 11 with champagne. It would go until midnight — except on the night of the ceremony, when it went till 6 a.m. I gave out at 5.

That's when I decided it was time to take better care of myself.

Aside from pushing you to embark on a wellness campaign, how has winning the Nobel Prize changed your life?

Well, I get a lot more invitations to do things than I used to. I try to accept the ones where there'll be an audience that would be useful to talk to. I want them to know immunotherapy is working.

On the other hand, I'm learning how to say no to nonessential invitations more often. A lot of the Nobel laureates tell me this can become a problem. But the truth is, I like talking about immunotherapy. I like

spreading the word. I'll say yes to school groups or if I'm needed to talk to Congress about more money for cancer research.

Has the Nobel made you a bit of a celebrity?

Oh, yeah. For a while, right after the ceremony, I couldn't get into my office because in the morning people would be waiting for me so that they could take selfies and get autographs and stuff.

But I've got to say this: For better or worse, the Nobel and the other prizes have validated immunotherapy — specifically, the checkpoint-blockades way of treating cancer. The Nobel and the other awards have validated the notion that cancer can be cured. That wasn't the paradigm before. For the longest time, what we were doing was sort of at the edge of credibility.

What do you mean?

Well, even after "ippy" — ipilimumab, the first immunotherapy drug, which I developed — was approved by the FDA for melanoma, there were colleagues naysaying it. There's one person — I won't say his name here — who all along insisted it would never work. Then in 2011, after ipy was approved by the FDA for melanoma, he went, "Well, it'll be a good melanoma drug, but it won't work in anything else."

For whatever reason, there's sometimes been a lingering skepticism. But the situation for immunotherapy is much different from 15 years ago. In those days, 90% of people I encountered thought it was not worth doing because it wouldn't work.

I'd go, "I've got something that can cure cancer," and they'd go, "What kind of cancer would you use it for?" I'd say, "I don't think the [specific] cancer matters much," and that would be the end of the meeting. There had been a lot of failures with attempts to make vaccines for cancer. No one wanted to go there.

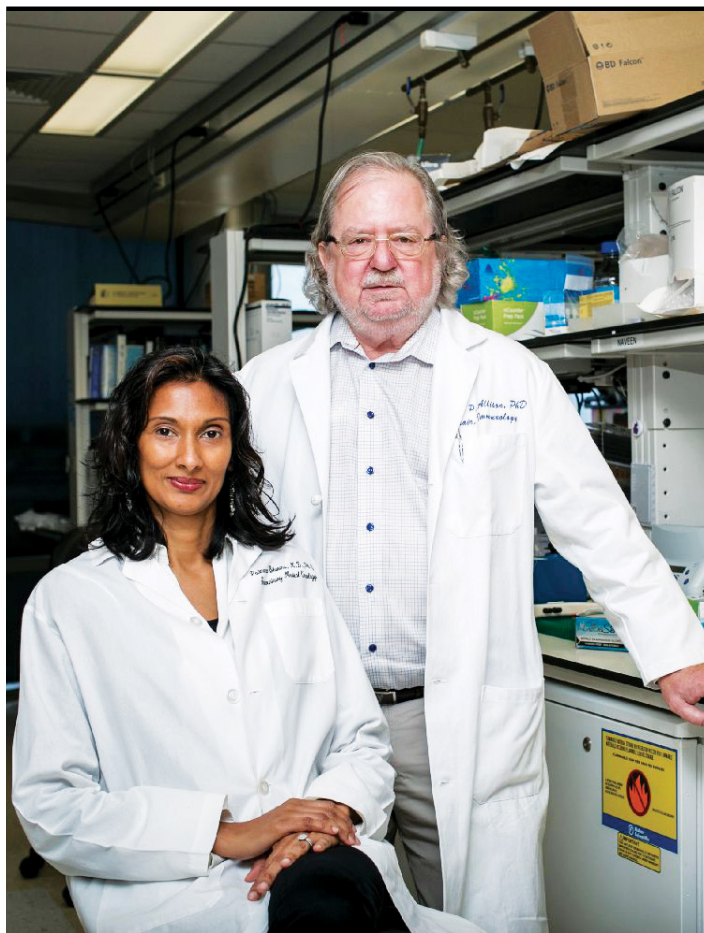
I went to the various pharmaceutical companies for two years, and only one small company, Medarex, was eventually interested. Medarex was later [in 2009] bought by Bristol-Myers Squibb, which took ipy through the approval process and to market.

Immunotherapy is said to be the first major change in cancer treatment in 100 years. Do you think some of the skepticism had to do with how different it is from what had become the standard treatment — usually some combination of surgery, radiation and chemotherapy?

That may be part of it. These drugs target the immune system, not the cancer. They unleash the immune system so that it will destroy the cancer. The drugs are based on the idea that our adaptive immune system can recognize and destroy our own abnormal cells.

And the treatment works! More than 20% of the

“For the longest time, what we were doing was sort of at the edge of credibility.”



metastatic melanoma patients who get it achieve a long-lasting response. It used to be that with metastatic melanoma, the average time between diagnosis and death was something like four months. We're seeing some melanoma patients living 10, 20 years after being diagnosed. There's a woman who was in on the very beginning of the phase 1 trials with ippy. She's 19 years out now.

After the trials were expanded, thousands of others received it, and a lot of them have lived 10-15 years so far, with no recurrence.

Is 20% good enough?

No. It's not an endpoint. The research is continuing. We're still in the early days of immunotherapy.

With metastatic melanoma, right now, with ipilimumab alone, the response is, as I mentioned, 20-something percent. With a drug that acts on PD-1 [programmed cell death protein 1], a different immune checkpoint found independently by Tasuku Honjo of Kyoto University, it's in the 30 percents. If you offer the two in combination, there's a 55% response.

With the monotherapies, which target one immune checkpoint, the response rate on kidney cancer is at about 30%. If you combine the two therapies, it's probably going to be closer to 50% in both kidney and bladder cancer.

Researchers say that the immunotherapy breakthroughs are likely to come with the combination treatments. Do you agree?

Absolutely. Because cancer has certain vulnerabilities. In fighting it, we've got to think not just about the cancer cells but the whole tumor microenvironment. That's a complicated thing. If you want to eliminate the tumor, you just have to take on multiple issues.

For example, there's a trial underway right now for pancreatic cancer. It involves a chemotherapy drug, plus three different immunotherapy antibodies. They'll probably add a little radiation to that. In the end, they'll be giving patients five or six different agents. But with pancreatic cancer being pretty impervious to any single therapy, hitting it this way could get a response.

You have to remember that before ippy, the five-year survival rate after a diagnosis of metastatic melanoma was essentially zero. We started trials on the melanoma combination treatments five years ago. Half of these melanoma patients are alive today. The trick now is to find the combinations that can get us to 60, 70, 80%. It's never going to be 100%, but it's better than no hope at all.

Where did the underlying idea for immune checkpoint therapy come from?

It's been around for a long time. The first person to propose using immunotherapy in a way close to what we're doing now was Paul Ehrlich [one of the founders of modern immunology]. He worked out antibodies and structure and how they worked. When I was in Germany a while ago, I saw his 1906 data book, and there was a drawing of an antibody interacting with a cancer cell.

Listen, it's been known for decades that cancer somehow thwarts the T cells — which are the attack cells of the immune system. So to get anywhere with a therapy, the question that had to be answered first was: How does it do that?

My team and other groups showed that with cancer, there were molecules on the surface of T cells that acted like an off switch, shutting down the immune response. They are called immune checkpoints. I wondered whether we could block the off switch that was shutting down the immune response and keep the T cells turned on.

What I did was find an antibody that inhibited the CTLA-4 immune checkpoint, shutting it off and allowing the T cells to go into the tumor and kill it. I termed the process immune checkpoint blockade.

Independently of my group, Tasuku Honjo of Kyoto University — I'd later share the Nobel Prize with him — found another immune checkpoint on T cells. His discovery was the PD-1 molecule that I mentioned

earlier. The two are the basis of most of the currently approved immunotherapy drugs.

For many years, you were a kind of contrarian in the research world, an outsider. Have the Nobel and all the other prizes transformed you into an insider?

Well, maybe. Rather than me being outside, maybe everybody else has come inside to my house. [Laughs.]

What do you mean?

As we speak, there are something like 3,000 different immunotherapy trials underway.

The FDA has approved checkpoint inhibitor therapy for non-small cell lung cancer, small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin lymphoma, some kind of diffuse large B-cell lymphoma, esophageal cancer, and some colorectal cancer that has defects to DNA damage. In fact, immunotherapy has been approved for any cancer type that has a defect in DNA damage repair called microsatellite instability.

The big pharmaceutical companies are now all players. Many, many early biotech firms are also trying to gain a presence. What you see, though, is that a lot of companies with patents on older, more conventional drugs are experimenting by combining them with checkpoints, just because they have the drugs. This is being done, in my opinion, without a lot of thought. A lot of them fail, but that information is usually lost because there's no requirement for reporting. That's still important information. So many combinations that are being tried are duplicative. It's just a mess.

Are these trials being done on actual cancer patients?

Oh, yeah. They're wasting patients. By that, I don't just mean a large number of patients are not getting the treatments most likely to provide them benefit. Because we have a limited pool of patients, the most promising trials are not accruing sufficient patients fast enough to get these drugs to the clinic as quickly as we can.

“It’s never going to be 100%, but it’s better than no hope at all.”

Is that ethical?

I think it's unethical. I think there shouldn't be any trial where you don't learn something.

Padmanee Sharma, who's a clinical oncologist, and I have an operation here at MD Anderson called the Immunotherapy Platform. We're currently involved in something like 117 different trials. We get tumor tissue from patients before and after treatment. We dissect it, looking for changes in cells, gene expression and structure. This can tell us something about what has happened.

If you are just looking for a clinical signal that a drug has worked or not, and that's all you are doing, we might not learn anything.

A personal question. Padmanee Sharma is your second wife. One of the legends about you is that when you proposed to her, you said that the two of you ought to marry because nobody else could stand either of you.

What I meant was, nobody liked either one of us, because we were both too intense about T cells.

Now that you're married, do you talk about T cells all day long?

On and off, yeah. It's what we're keen on. We also talk about music, and we have some fun every now and then. But not a day passes when we don't talk about something relating to T cells, especially because of our work together on the Immunotherapy Platform.

Can we backtrack a little here? I'm wondering what drew you to doing scientific research in the first place. Were you one of those people who always knew this was what you wanted to do with your life?

No. When I started college, I knew I wanted to do some sort of biology — either that or be a doctor. My father had been a country doctor.

While at college — I was pre-med at the University of Texas — I saw that medical training involved filling your head full of stuff. Your job is to just pack your head with so many goddamn facts that if someone comes to you with a problem, you can make a diagnosis. And you'd better be right! Because if you're wrong, you could hurt your patient.

Now as a research scientist, you're supposed to be wrong. You have an idea about something that nobody understands and you're trying to figure it out. And the only way you can do that is to have a hypothesis and do an experiment that says, “No, that's not it.”

Why did you choose cancer research? Cancer is quite prevalent in your family. Your mother, father and brother died of it. Was that part of your motivation?

My motive was a complicated thing. I'm a basic scientist at heart. That's what drove me. I can't say I was

driven to do cancer research. I got into science because I was interested in science.

You did your doctorate on the immune system?

No, it was on a cancer issue, but at the same time I did some immunology. I had this vague idea, “Maybe we can get the immune system to treat cancer.”

One time, just for the hell of it, I did an experiment. There’s an enzyme called asparaginase that’s still being used to induce remissions in kids with some kinds of leukemia. I had these mice I had cured with the enzyme, and I had another group of new mice I was giving tumors to. I thought, “Well, I’m just going to see if I can challenge these other guys that I’ve already cured with the asparaginase.”

I gave them the tumor. Well, it wouldn’t take! I gave ’em 100 times more of the tumor and it still wouldn’t take. They were immune. They rejected the tumor, whereas the untreated mice got sick and died unless I treated them with this enzyme.

I thought, “Wow, this is interesting. File it away.” To me, “interesting” has always been the most important thing. I can’t work on something that doesn’t fascinate me.

Back when you were doing your early research, immunology was not a particularly hot field. It was certainly not the place where a smart guy could make a reputation for himself. Given that, why go there?

You’re right. When I first came to Berkeley in the 1990s, for example, they were in the midst of trying to redefine modern biology, and certain very powerful people there did not even want there to be a department of immunology. They felt that immunology was not a real discipline because it didn’t deal with the static, fundamental processes of biology that apply to everything. To be a real biologist, they believed you needed to study things like how DNA replicates, how to make a protein, or how to make RNA. I thought they were silly.

Why silly?

Because there are certain key elements of immunology that immunologists pay attention to that people in other fields don’t. T cell biology, where the main principle is the recognition of the nonself, is an example. I wanted to know about how the immune system recognizes the nonself. How do you get to that? What regulates that? What are the cells and molecules involved? What helps you or stops you from recognizing the self? All these things are unique to the immune system.

Those were the questions that intrigued me. I eventually ended up identifying the T cell antigen receptor, which is the way T cells recognize anything at all.

So how did you battle against the conventional scientific wisdom?

After my postdoc at Scripps, I moved to what was then a new MD Anderson campus in Smithville, Texas. It was very new and very isolated. There were only six faculty members. I was the only immunologist there, so there was nobody to tell me I was wrong.

Sometimes, you just have to get away from everybody. I take some pride in the fact that I don’t think I read as many journal papers as other people. There was a period when I was working on the T cell receptor and I made a determined decision not to read a damn thing about T cell receptors because the papers were so confusing and contradictory. Some of the experiments weren’t even understandable.

I’d think, “Either I’m too stupid to understand this, or nobody knows what they’re talking about. I’m just going to sit down and figure out something logical to me, making certain assumptions and predictions, and just do it.”

Why did you have enough faith in yourself to go it alone?

Because I could make certain minimal assumptions, based on a little bit of data. I know what science is. I know how to use it.

If somebody shows me that I’m wrong and has some data that’ll convince me of that, then I’ll admit I’m wrong. I mean, I’ve had to do that a few times. [Laughs.] Not too often, thank goodness.

When we met five years ago, you told me about one of the big moments in your life. In your off-hours, you’d been a country musician, and once, while you were still a postdoc, you got to play with Willie Nelson. Do you still see him?

I do. If he’s playing anywhere around here, his people call me. I played with them on Austin City Limits. It was a pretty big deal — there were 70,000 people there.

The last time I played with him, it was at his ranch. He had a party, and Mavis Staples was singing with him. So we did a gospel medley with Mavis Staples and Willie’s band, and me playing the harmonica. That was fun.

I once asked you whether you’d like your tombstone to read “Jim Allison, he played with Willie,” or “He cured cancer.” Since you can now say that you’ve done both, let me ask that again.

Either one. [Laughs.] I think I would like to just have something that says that the world is a better place because I was there.

Antimicrobial Resistance: A Battle Lost or a Challenging Conquest?



Aster Medical Journal held its inaugural AMJ antimicrobial resistance roundtable in Aster Medcity Kochi. Roundtable brought together clinicians, healthcare professionals, policymakers, pharmaceutical companies, academic researchers and NGOs. The expert panel discussed the wide range of issues that affects the antimicrobial resistance response.

**Dr Sonali Dighe**

Country Medical Director,
Pfizer Biopharma Group,
India

**Dr Geetanjali Kapoor**

Senior Research
Fellow- CDDEP.

**Dr Harish Pillai**

Chief Executive
Officer - Aster DM
Healthcare India

**Dr Aravind R**

Lead - Anti Microbial
Stewardship Program,
Government of Kerala

**Dr Peter Schneeberger**

Medical Microbiologist -
S Hertogenbosch,
Netherlands

**Dr Satish Rath**

Global Chief of
Innovation and
Research, Aster DM
Healthcare

**Mr. Sampath Kumar**

Assistant Manager,
Scientific Education,
Medical Affairs, bioMer-
ieux India

**Dr Rajeev Jayadevan**

Gastroenterologist,
Sunrise Hospital Kochi
& the President of the
Indian Medical Associa-
tion (IMA) Kochi Chapter

**Dr Willemien Maathuis**

de Haan Gelre Hospitals
Infection Prevention
Expert - Netherlands

**Dr T R John**

Psychiatrist & Chief of
Medical Services -
Aster Medcity

MODERATOR

**Dr Anup R Warriar**
Lead - AMS Program, Aster
DM Healthcare India

Dr. Anup R Warriar: Before I start, I would like to take a poll. The title of this roundtable is “AMR - A Battle lost or a Challenging Conquest”. How many of you would go with the first term? The whole exercise is a battle lost? Anyone for that?

Mr. Sampath Kumar: Not yet

Dr. Anup R Warriar: Zero? Can I conclude that all of you are thinking of it as a challenging conquest? It is great to know we are optimistic. Since we represent a multitude of stakeholders, I am trying to take this from bottoms up. I want to start the discussion with **Dr. Rajeev** because he is a practising physician, besides holding the added responsibility of the Presidentship of the Indian Medical Association (IMA), at Kochi, which is a large association of practising doctors. He also has administrative responsibility in his hospital. So, he is the apt person to start off this discussion.

My first question to **Dr Rajeev** is, what are your observations regarding the awareness about the Antimicrobial Resistance? Does the “Antimicrobial Stewardship Program” come across as a solution among the doctors, especially among your IMA & Hospital colleagues, and various other people you come to face in your fraternity?

Dr Rajeev Jayadevan: Well, we are located in the town of Kochi, the academic capital of the State of Kerala; in a sense, we have a medical education program happening practically every day. Practising doctors meet in rooms like this and discuss academic topics. From that standpoint, the doctors in this part of the State are no strangers to the term Antibiotics Stewardship. Kochi is a

town buzzing with academic activities, but that doesn't represent the rest of India. So, I want you to keep in mind that distinction very clearly. Thus, the standard of practice around this area could potentially be of a higher standard than in the rural segments of the country where there is no access to CMEs.

I represent the Indian Medical Association as the President of the local chapter. We have several initiatives to reach out to doctors who are in practice. When I say the CME program,

there is a set group of doctors who attend these programs. And there is a vast majority who never comes for these programs. That is our target. That is the group of people we need to be addressing. I always say that there is something called the seminar paradox. The seminar paradox is - that the people who attend the seminar are not the ones who need the seminar. The ones who need the seminar are always outside the seminar. So we must make ways for the ideas to reach the grass-root level.

Dr. Anup R Warriar: What do you believe are the challenges in managing this problem? What are the challenges in handling or managing AMR and getting proper compliance with the AMS initiatives and strategies in your hospital?

Dr Rajeev Jayadevan: Rational use of antibiotics is twofold. One side, they are often wrongly prescribed. The flip side is when they are needed; they are not prescribed. So, we need to address both sides. From a practising doctor's standpoint, I would equate it to the garbage case in the country. I am sure

you have travelled widely enough to see garbage piling up on the roadside. That is because; it is multifactorial. If you take a look at an area where garbage is piling up; you see one person going and depositing his junk, then you see another person seeing this person depositing junk, and says "Okay. Let me go and put mine as well". Now you have two pieces of garbage. A third guy says, "Well, that is the official place to dump garbage!", so, this is a self-fuelling process. Bad prescribing patterns work like this. Seeing your colleague prescribing or talking about antibiotic use for a mild condition or you see their notes. We see our patients, and we share similar notes, we learn passively seeing that an antibiotic is prescribed. We may not be learning actively. We learn the practice from other people. So when we see wrong practices around us, we tend to copy them. And we don't have corrective measures often enough. We don't have audits often enough to stop this copying process. So, this results in a large pile of garbage because when everybody thinks the

"Kerala has taken the lead in the AMR activities across the nation because Kerala was the first State to launch this."

other person is doing the right thing, then collectively, we are all doing the wrong things. That is the way I would equate the antibiotic prescribing practice in our country.

Dr. Anup R Warriar: Do you believe that good audits on the antibiotics prescription practices where you provide feedback to the prescribers would be some part of the solution?

Dr Rajeev Jayadevan: Yes, but again, audits will affect only a small segment of the prescribing physicians. Because audits are typically in academic settings, but the vast majority of practice does not happen in an academic setting. If you ask me, what is the best way to reach out to them? When I say 'them', I do not mean somebody who knows less than me. It could be me sitting alone in a clinic somewhere. The best way, in my opinion, is to create a list of the most commonly prescribed situations, what are the situations where you do not need antibiotics!. Educate them from what I would say, the wrong end of the equation. Rather than telling them what is right, tell them what is wrong. Often *Antibiotics Stewardship* meetings talk about the transfer of resistance, plasmids, horizontal transmission etc. The practising physician doesn't care about mechanisms of resistance, he cares for a sore throat in a patient coming his way, a patient having a fever or a woman who is having dysuria. We need to create easy solutions, workable solutions for these

people so that they will know that for uncomplicated sinusitis I don't need antibiotics.

Each of them has a reason for over-prescribing; each of us has a patient's case that did not go right. I have an uncle who died because his chest infection was treated with a low-grade antibiotic. He died at the age of 59. He should have been alive and well in his 80s at this moment. And that happened in Trivandrum in one of the largest hospitals. He had total lung destruction because of progressive pneumonia. That is another example of antibiotic use which is underprescribed. All doctors have experiences like this, so when a patient comes in front of them, they don't want to take a chance. They are not bad people; they just want their patient to get better.

Dr. Anup R Warriar: Dr Aravind has visibility at the Kerala government level. Kerala has taken the lead in the AMR activities across the nation because Kerala was the first state to launch this. Please explain the various steps taken by the Government of Kerala to fight AMR?

Dr Aravind R: From 2013 onwards, unofficially, the Government of Kerala has been tracking resistance. It was mainly through microbiology departments in the major medical colleges in the State as well as from the NABH accredited hospitals. In 2017 the *National Antimicrobial Resistance Program (NARP)* came into force in India, the states were invited to a workshop, and were given the task of developing their *Action Plan* in a five year time. Kerala

took the cue and became the first state in India to release its own *Action Plan*. That is "KARSAP" – Kerala Antimicrobial Resistance Strategic Action Plan, which was released by the honourable Chief Minister, on October 25, 2018.

Why the Chief Minister is the crux of the question. Because AMR is managed under multiple ministries. When the Delhi declaration came in 2017, 11 ministries came together with the AMR declaration, because it is not only the health department alone which is concerned. We need to have different ministries as; Animal Husbandry Department, Environment, Aquaculture and Fisheries. We want the Ministry of Finance to support us. At the National level, there are around 11 ministries. So ideally it should be the Prime Minister who is heading the national program. But unfortunately, it is the Health Minister who usually heads the program. So the Environment Minister may not listen to the Health Minister. So in Kerala, the initial aim of the state was to have the Chief Minister to head the program, and that happened. So all the other departments are working under the Chief Minister of Kerala even though it is coordinated by the Department of Health and Family Welfare. What we are following is the 'One Health' approach.

We have the six strategic priorities under the KARSAP.

First, is knowledge and awareness building. Second, is knowledge and evidence, that is, through surveillance. Third, is infection prevention and control. Fourth, is antibiotic stewardship. Fifth, is research; for which the *Rajiv Gandhi Centre*, which is a Central Government Institute, is our partner. And the sixth is the most important one: public-private collaboration. All these six strategic priorities cut across all the aspects of the 'One Health' approach. When we speak of knowledge and awareness, it is not about creating awareness among doctors alone; we tackle the farmers, horticulturalists and aquaculture persons.

Additionally, India has not banned over-the-counter-selling of antibiotics. Even though we do have *Schedule H1* as well as *Redline* campaign, the ground reality is that all the antibiotics are still available over the counter. Even though the situation is far better in Kerala compared to other states, it is still a reality. So, we cannot just blame the doctors. We need to engage the public as well because antibiotics are readily available at the pharmacies. In 2019, the objective of the state was to educate everyone; All the consumers, all the pharmacists, as well as the public. And the Kerala Health Minister declared that by the time of '*Antibiotics Awareness Week*' next year (November 18, 2020), Kerala would become an antibiotic literate or aware state where everyone in Kerala will be aware of 10 basic facets.

Regarding the second aspect, the surveillance looks at the ground level resistance data. Where we started, in 2018, we had around ten labs reporting to the nodal centre, that is the Department of Microbiology, Trivandrum Medical College, and we had an NCDC site that we reported to. And from there our data is being reported to GLASS, that is a global surveillance system. Then we came with some interesting observations because the ten labs which were reported happened to be the medical college hospitals as well as a District Hospital Ernakulam. The resistance rates, even between the medical colleges, were entirely different. Trivandrum having more critical care support had more resistance rates. Small medical colleges like Alleppey, Kottayam the resistance rates were pretty low. So we decided not to have a state-level antibiotic policy or guidelines like the national guidelines, it may drive up the resistance if you are following the guidelines based on data only from the tertiary care centres. It was like a microbiologist paradox. If you follow the guidelines, we may drive up the resistance rates. So, the Kerala government decided not to have an antibiotic policy or guideline for the state; instead, we said that all hospitals should have their own AMR guidelines.

Then, we started with the second aspect of this KARSAP. To come up with KARSNET - 'Kerala Antimicrobial Resistance Surveillance Network' where we incorporated 17 other hospitals as well as the labs so that we can get data from the ground level representing the primary health centre, as well as the secondary health centre. And so now we do have the

data representing all levels of care in the State of Kerala. That is KARSNET.

Third, is the Infection Prevention and Control. Our focus is really on Infection Prevention and Control. People who were on the frontline fighting Nipah, in Calicut, were people who got training under KARSAP. That actually can be counted as one of the successes of KARSAP, because Infection, Prevention and Control were given such support by the state government.

Fourth, is about Antibiotic Stewardship, not only on the human side but also in animal husbandry and aquaculture. We are addressing the low-hanging fruit. All the hospitals cannot have a restriction or a prospective audit and feedback; thus, we do insist on certain things only to start with, except in the tertiary health centre.

The research aspect is going on in all fields. Animal Husbandry, Agriculture, everywhere it is going on. All the data is being collected by the Rajiv Gandhi Centre.

Sixth is the public-private collaboration where we are working closely with an NGO - Centre for Science and Environment - to help us with environmental surveillance aspect, chart out the good farm management practices, as well as ensure the biosecurity guidelines and waste management practices in farms.

One advantage of Kerala is that we don't have that much of big pharmaceutical industry, so the affluence from the pharmaceutical industry is not a major problem for Kerala, but the affluence from the hospitals are. Those aspects are being taken care of with the help of CSE.

These are the initiatives taken under KARSAP.

Dr. Anup R Warriar: In infection control, what kind of capacity building has been done? I know that posts are being used as infection control officers. Can you give us more details?

Dr Aravind R: Even before the KARSAP materialised in 2017, an examination was conducted in almost all the government hospitals to select five to six nurses and were given a 7-day training by the Director of Medical Education, and they were designated as infection control officers in their respective hospitals. A major problem with the hospital is that the Trivandrum Medical College has around 3500 beds. So ideally, we should have around 35 infection control nurses. This is practically impossible, and we have only two infection control nurses. Another system is that we have link nurses and mentor nurses. They double up as infection control nurses. And this link nurses system has been spread across the state, and all the hospitals now have link nurses. Infection control nurses their function is only infection control, auditing and all those things. Link nurses do their job and double up as infection control nurses.

In a resource limited space, this is the only thing which works. As far as infection prevention and control, Nipah was

a blessing in disguise. Everyone became aware of the importance of infection prevention and control. Our hospitals are very crowded, the situation has not changed much, but the situation in ICU has improved a lot. The situations in the ward, OP, and casualty are still out of control, but what we have observed is that the resistance is more of a problem in the ICU. So we are focusing our work on the ICUs.

Dr Rajeev Jayadevan: What are link nurses? What does that mean? Is it as in L-I-N-K?

Dr Aravind R: Yes. L-I-N-K. We are doing surveillance on three fronts under the KARSAP. One is the healthcare associated infection surveillance where we look at the VAP rates, CLABSI rates, CAUTI rates, SSI rates etc. Link nurses are the ones who collect the data from the ground level – that is the ICU levels, and they have a computerized system. Otherwise, they would write it down and convey it to the infection control officer who in turn will convey it to the Infection Control Committee.

Dr. Anup R Warriar: The sixth point mentioned was a public-private partnership. What are the opportunities existing as of now, where is the private partner with the government in this program, and what kind of partnerships have already occurred? What are the things you are looking for, for partnering with private institutes?

Dr Aravind R: For KARSAP there is no split between private and public because AMR is not my problem or your problem, it is our problem. KARSAP is headed by Amrita hospital, the private sector in collaboration with IMA is looking after creating awareness and all aspects of AMR in the private sector, and we do have six other partners. We have signed an MOU with the Government of Kerala BD, Beckman Coulter, BioMerieux, DSM Sinochem CSE; and recently, a group of ID physicians and microbiologists in Kerala came up with an app to help the students. So the contents are verified by the KARSAP committee and also are a part of it. Anyone in the private sector who is contributing to AMR is welcomed to be a part of this program because our aim is to make Kerala an antibiotic literate state by next year.

Dr. Anup R Warriar: Thank you Aravind. Moving on to Dr. Geetanjali from CDDEP. CDDEP has a tremendous amount of surveillance data from the national level, as well as through its visibility at the global level. When looking at the website of CDDEP, we see that it is very rich in data. You have a lot of prevalence studies, incidence studies, and coming on MDR and AMR data.

Despite this much data available in the sphere, just as Dr Aravind just said, when it comes to local implementation, the first thing we say is that we don't have local data. So, let us wait and try to generate local data. Do you think it is essential for every unit at the local level to generate enough data? And do you think data will be vastly different from what you have accumulated from across the nation?

Dr Geetanjali Kapoor: CDDEP is a public health research

organisation incorporated in 2010, headed by Prof. Ramanan Laxminarayan. CDDEP has various flagship programmes. One of them is the resistance map; that is an interactive tool that provides the data across different countries for AMR and AMU. AMR data reaches us through various networks across countries. So we cover over 70 countries, and the data reaches us. For example, in India, we have data coming from the Fortis SRL Labs, Vietnam, it comes from the Vietnam network. When we receive the AMR data from the labs, and we do a second-level run on that data before publishing it as a map on the CDDEP website. So everybody can view that. It's not representative of the entire country for sure. It does not mean that we need to wait for data to come from everywhere. We don't have as much time as we know because we say a "battle lost". I would say that it's lost if you do not take action now, with whatever data we have, yes, we do press for more data, we are encouraging our partner hospitals to share the data with us.

Dr. Anup R Warriar: Do you have any plans to have a map for infection prevention control or hospital-acquired infections?

Dr Geetanjali Kapoor: I think you have raised a perfect point. We shouldn't restrict to either AMR or AMU. We should map as much data on hospital-acquired infection, devices associated, even community-acquired infections. However, the data collection has to be done as per stringent quality standards, because if you have data on your records or on your registers, that is not through a proper quality system. That collected data will not be useful in the end.

Dr. Anup R Warriar: Willemien, we will come to you now. From an international perspective, in the Netherlands, as we know, the per capita consumption of antibiotics is quite low. What do you think is the contribution of infection prevention to achieving the lowest per capita consumption in the whole world?

Dr Willemien Maathuis: Standard precautions in the hospital.

Dr. Anup R Warriar: Do you think you have the best infection control compared to the US & UK?

Dr Willemien Matheuis: Oh No, I don't think we are the best. We have the same problem that you have here in India. This morning when I was talking to the infection prevention control team in Aster Medcity, I heard that infection prevention and standard precaution is so simple. Everyone can do it, you have to do it. And that's the problem. You see, nurses mostly do it well. But other people in the hospital don't do so well. And we all know it. We have the measures, we have the guidelines, but the change of behaviour. That's the most important thing.

Dr. Anup R Warriar: Did you structure the program there so that it works, and how?

Dr Willemien Matheuis: Yes, when your basic hygiene is

in order, then the hospital-acquired infection gets lower. The compliance is higher, and the infection gets lower. So, infection prevention control is simple, but everyone has to do it. And that's the problem. And the change in behaviour is very problematic.

Dr. Anup R Warriar: When we visited the Netherlands, there was this session on change management & changing behaviour. That's very new because in our regular curriculum it's not there.

Dr Willemien Matheuis: It begins with educating doctors and the nurses, in the first year we have infection prevention education. The knowledge, the risk you take for the patient, and for yourself, it's a part of our curriculum.

Dr. Anup R Warriar: The doctors mostly drive the antibiotic stewardship as of now, what do you see the role of nurses and pharmacists? In the Netherlands do you have the involvement of the nurses and pharmacists as some decision makers anywhere in this whole structure of AMS?

Dr Willemien Matheuis: Yes, nurses play a significant role. They even change or regulate the antibiotics as per the patient improvement. Nurses decide to change antibiotics from IV to oral. The active involvement of nurses in monitoring and promoting the best governance plays a crucial role.

Dr Anup R Warriar: Peter, Netherlands has the lowest per capita consumption of antibiotics for humans,

but has the highest per capita consumption of antibiotics among animals. Nowadays, we hear this from clinicians when we discuss antibiotics, 80% is used in animals, so why are you coming and talking to us! Does this mean that heavy use of antibiotics in animal husbandry and fisheries doesn't directly contribute to AMR rates in the community? Or is it that food hygiene is so good that it does not translate into human resistance?

Dr Peter: We indeed have very high antibiotic use in livestock. So how come it doesn't reflect on the human situation in hospitals? I think AMR is a very complicated problem, and you only address it looking at 'one health'. 'One health' means you have to look at the communities where you live, and you have to look at hospitals, and you have to look at livestock. You also have sanitation, hygiene and quality control, like in hospitals we have infection control, in livestock you have the control of the food whether it is safe or not. Of course, you have waterways and waste problems, so it's a very complicated thing. Now if you think, for instance, Holland and Kerala are almost equally large. If you consider this as a country, we are almost similar. We have abundant water areas, we live in a delta, and you have a lot of water, and you live in a delta. Why

it's different in Holland, and why high antibiotic consumption in livestock does not reflect on hospitals!

We have about 100 hospitals in Holland, and the number of beds is decreasing very rapidly, so patients come in the morning and leave in the afternoon. We almost have no long-stays. We have renovated all our hospitals in the last 15 – 20 years, they are all quite modern, this may be an essential factor. I don't know. If you look, for instance, the emergence of MRSA, in the 90s, Netherlands and Great Britain had the same problem of low resistance levels, and what we did in Holland was aiming at fighting MRSA right from the beginning. So anyone with MRSA was placed in isolation and treated, and we got rid of MRSA.

In England, they did not do this. So, ten years later, there was more MRSA per capita in England compared to the Netherlands. They were very alarmed about this. It took them ten years to take general precautions to come back to the level

“It's true that we have very high antibiotic use in livestock. So how come it doesn't reflect on the human situation in hospitals?”

that we have in Holland. So this explains the power of just general infection control. Maybe targeted to specific situations.

After that, we started to use a lot of antibiotics in livestock. I live in the south of Holland, and that's where we have the most livestock in Holland. What we saw was a tremendous increase in livestock-associated MRSA. This came directly from pigs; they were given antibiotics as a growth factor. They developed resistance, and because a lot of people were working in farms in our area, they got infected, or rather contaminated, with LA MRSA from pigs directly.

They came to the hospital, and we didn't find many infections, what we saw a steep rise in the prevalence of LA MRSA. This caused a lot of public resistance, and they executed a new law, that bans giving antibiotics as a growth factor. When antibiotics are given to livestock as a growth factor, the animals grow better and have less disease, so it's very profitable economically. So they said we want to stop this, and what we see now is that five-six years later the prevalence of LA MRSA is going down.

If in Holland, we see a patient with NDM, we are almost sure that it's someone coming from India. So how come? If

we have someone with NDM we get alerted, we had a large outbreak in our hospital with NDM, probably you have read about it I am not sure, because we never had NDM before, we started an outbreak control. What did we do? We just said we have to do general infection control practice. Nothing extra, just what's usual, but we have to adhere to it, as we had 30 patients with NDM all of a sudden. Only doing that stopped the epidemic.

But interestingly we found that the NDM gene was not only in *E. coli* but also in *Klebsiella* and *Enterobacter*. So if we had not genotyped at the laboratory, we would have fought three different epidemics. What happened is that the resistant gene plasmid was able to go from one to the other species. This can be very confusing. In Holland, there are only a few epidemics, and we know we can fight them very effectively by simple infection control measures.

Dr. Anup R Warriar: From being a medical microbiologist,

“At the smaller nursing home, the main problem is that they do not have an antibiotic policy specifically.”

how important do you think it is for a country like us to invest in molecular diagnosis. As you said, you had an outbreak, and you used molecular diagnosis. Nowadays it is all about molecular epidemiology, so being in an endemic setting, and even for diagnostic stewardship part, for faster diagnosis and more accurate diagnosis etc., do you think that introduction of molecular technology in India, in infectious diseases, will help us or complicate things more?

Dr Peter: It will help on a national level to understand what's going on. If you know where the clones are going, and what the drivers are, if you see a particular gene, very prevalent intakes, you know you have to go there. If you see it's in the community, you have to go there. On a national level, it's vital. I would look at the hospital level, and I think a quick and accurate diagnosis of infections is crucial. That's life-saving and cost-saving. We had a large epidemic in Holland of Q fever, all these patients were treated with beta-lactams because nobody knew it was Q fever. Hundreds of patients got the wrong antibiotic which resulted in an average length of stay which was double than usual. If we had a proper diagnosis, we could have saved lives, and we could have saved a lot of money. I believe molecular tests will help us in quick and accurate diagnosis for sure.

Dr. Anup R Warriar: We have two industry partners with us from BioMerieux and Pfizer. Can you share with us some of the initiatives from BioMerieux? What are your contributions or initiatives in controlling AMR?

Mr. Sampath Kumar: Thank you so much for inviting us to this Roundtable. I represent BioMerieux. Navjeet Singh is the head of our medical affairs and Asia Pacific lead for AMR. And I am here on his behalf. First of all, the philosophy of BioMerieux is that diagnosis is power. That drives us. As we know, the diagnosis has played an important role in isolating and curbing down the infection rates. What we hear is that 70% of medical decisions are based on laboratory results. But how much is being invested in the labs is like less than 10%. As a structured program for our customers; not only for our customers as such, for anyone in the industry to join this global point prevalence survey - with the help of the University of Antwerp in Association with Biomerieux . Only as monetary

support. And it's a purely voluntary basis - customers can go into this program - it's a one day point prevalence survey. It started in 2015, and around 17 hospitals across India participated in this and shared the data with us - and they were given an individualized report on their way of antimicrobial prescriptions and their resistance rates.

If there was any need for improvement, it was shared with them. It turned out to be an excellent tool for

them to analyse themselves - the way they are doing their antimicrobial stewardship. This year we have targeted 75 hospitals, 50 we were able to achieve. Fifty are there - as a part of this global point prevalence survey. And it is entirely free of cost. That is one structured way of involving in the antimicrobial stewardship. We also support world antibiotic awareness week every year.

Dr. Anup R Warriar: What does BioMerieux understand about the QC & standardisation of microbiological reporting? Do you have any program focusing on the smaller lab which caters to a huge group of private practitioners on standardization of culture reports and in terms of reporting and background?

Mr. Sampath Kumar: We do a lot of educational activities where we target lab technicians, nurses, and also the clinicians on various aspects. For example, for clinicians, we harp upon the number of blood culture bottles. For nurses, the volume of blood and the aseptic collection aspect. For the technicians, how fast he should process samples to reduce the turnaround time for the patient, these aspects we harp upon. When it comes to antimicrobial resistance, we speak to the doctors about the importance of having the way of doing the right antibiotic prescriptions. For example, with the

help of the culture. So what we have been harping upon is to inculcate the concept of prescribing culture because in many places, it is in the OP setting; straight away, the antibiotics are prescribed without doing any diagnostic test. This leads to a lot of antimicrobial resistance.

Dr. Anup R Warriar: What are Pfizer's initiatives to Address the AMR and AMS issue?

Dr Sonali Dighe: Globally, Pfizer has been doing a lot of things in this space of AMR. Right from an earlier time, as well, but they have become more serious about this after the science declaration, the diverse declaration where about close to 100 pharmaceutical companies have come together and sort of pledged their support to curbing AMR in the world. Even there if you see the roadmap for reducing AMR, the aspects, the pillars are very similar to what you had mentioned. We start with AMS, the Antimicrobial Stewardship. There is surveillance. There is also this bit about prevention, and I will talk a little bit more about prevention.

As far as AMS is concerned, there are several initiatives at different levels that are going on. For example, at the tertiary care level, the initiatives are more around education; having training modules that are being used for educating the clinicians, even the pharmacists based on the need. There is also this capability building initiatives like infectious disease fellowship. There are these international partnerships like the Academy of Infection Management where there is a certification program that the doctors can take up.

If you look at the smaller nursing home, the secondary care, at the smaller nursing home, the main problem is that they do not have an antibiotic policy specifically. So Pfizer has been working with these nursing homes to work on their own antibiotic policy. Everyone will have slightly different data based on their susceptibilities in their hospitals plus their prescription data. Based on this, they plan their antibiotic policy, and we hope that they can see before, after, and actually see the difference and hence will continue to use antibiotic policy. Because we believe that we can do one intervention, second intervention, but after that, the nursing homes will have to take it ahead by themselves.

In India, a nursing home is a smaller hospital with about 15-20 beds. And then at the public level, there is our association with ICMR where we did have a public awareness campaign about the misuse of antibiotics. Because there is a lot of OTC antibiotics usage in India, which all of us are aware of. So there was this campaign about not using it until prescribed by the doctor, and once prescribed also, taking the right dose for the right duration etc.

So that is something we are currently doing from the AMS perspective. Coming to surveillance again, there is a global program; we are calling it ATLAS, where there are more than 70 sites in the world, a few sites in India as well - surveillance from susceptibility data for different molecules has been looked upon over the years.

The third bit and again I would think that is an important bit that often gets missed out - prevention. Prevention in terms of vaccination. That's one of the important aspects of AMR according to us.

Again, vaccination at the paediatric level. We are aware of it because the paediatrician is the one who asks to go for vaccination. There is a very clear national immunization program there. Going ahead, what we want to do is also to talk about adult vaccination, which is at a very rudimentary level in India. Then you avoid infection in the first place, and hence AMR.

The last bits I would say R&D, while there are a couple of molecules we would be launching. All of us know that the pipeline is not very great, but at the global level Pfizer is working with the regulator in terms of how can we get molecules, how can we work on the real-world data and hence get new molecules. And there are those aspects that Pfizer is working at the global level. So this is broadly about what we have been doing.

Dr. Anup R Warriar: The second question is about the poor quality of drugs. Organisations, including the World Health Organisation, have mentioned the poor quality of antibiotics as being one of the drivers which drive antibiotic resistance. So what are the regulatory and compliance structures which are in place in India to address this issue as of today and how far has this been successful?

Dr Sonali Dighe: And that actually reminds me of the importance of good manufacturing practices. I think India, from a few years from a regulator's perspective, gained a lot of awareness about the importance of manufacturing practices. So what we know is that - not just OTC prescription and the H1 Schedule, the drugs under the H1 Schedule that the Indian regulatory bodies have got into. But also there is a push to increase inspections. There are drug inspectors who actually visit the manufacturing sites, and they can take samples from any manufacturing site. They can take samples from the pharmacies and get them tested at central laboratories. The government has increased the number of drug inspectors as well as the central laboratories. If they are sub-standard, then they get back to them. The medicine may have to be withdrawn from the market. And in fact, they do publish the data on the website as well. So there is this awareness among everyone about the importance of substandardization of medication.

Dr. Anup R Warriar: What about the approval level? Just last week I saw promotions for meropenem, sulbactam and meropenem & EDTA Combinations by good companies. If you look at WHO list, there is a whole lot of medicines which are in the non-approved list in the World Health Organisation schedule, and there are many companies which are launching this non-approved combination by World Health Organisation to the market as recently as you know this month and last month. Are there any regulatory frameworks at the ap-

proval? If somebody comes out with an A-plus B combination or antibiotics B or C, is there a system where the government or the Drugs Controller looks at?

Dr Sonali Dighe: Actually there are. By the Drug Controller General of India through the subject expert committee, there is a very clear process of approving the drug. So when I have to apply for marketing authorisation, there is not just the clinical trial data, but data of Indian patients has to be submitted and also data of manufacturing practices has to be submitted. And you know API level data has to be provided. They go through this data. As some of you might be aware, now our regulators insist on Indian patient data.

Dr. Anup R Warriar: How did those combinations come into the market?

Dr Sonali Dighe: I don't know. Probably they have shown Indian patient data. I would not know to that extent. If you look at the framework, there is definitely a framework. A very stringent framework to see through that there are the right molecules, and the right products come into the market.

Dr Geetanjali Kapoor: I would like to comment. We also need to address the fact that some of these drugs are coming not from within India but from the borders, especially spurious drugs. There are markets which are outside India, and the borders are so porous, I think till we have an international agreement and international strict regulations, all that you do, it would be a failure because the drugs are coming from China, from Vietnam, from Nepal, from other countries. I think the porous borders and regulations need to be tightened even at those levels. Apart from this, 68% of the fixed-dose combinations are not registered with the Central Drugs Standard Control Organisation, the CDSCO. So that's a huge number. 68% are not registered, but they are available in the market. This was in the year 2017, so I don't know the latest figures. But a huge number of FDCs are still unfortunately in the market.

Dr Rajeev Jayadevan: Dr Sonali talked about substandard medication. I am sorry to say, but in India, with all the heterogeneity in the health sector, we also have some substandard prescribers. A large number of prescribers from a healthcare provider is not from an MBBS doctor. And that is a fact. In some of the larger towns outside of Kerala, I am told that the majority of general practitioners are not MBBS graduates. MBBS is a basic medical degree. And these individuals control the market. I don't know what kind of standards they are practising with. So when we talk about substandard medicine, we must also talk about substandard prescribers.

Dr Geetanjali Kapoor: Even the online pharmacies are openly selling drugs though they are not supposed to be sold over the counters.

Anup R Warriar: Now I am going to invite Dr Harish Pillai. When you sit around with other CEOs of other hospitals in the country, does this thing come at all? Do CEOs talk about Antimicrobial Resistance?

Dr Harish Pillai: You are trying to strip me naked. Honestly.

Anup R Warriar: There is a specific reason why I asked you because the UN is saying that the GDP will drop by 3.8% by 2050 because of AMR.

Dr Harish Pillai: Like many of us, for the right reasons, we start questioning Donald Trump and his theory on climate change, where many Americans, especially those in the Trump faction think that climate change is a hoax, and is not based on science. Unfortunately, the reality is that the CEOs around the world, especially in the private sector, their priorities are entirely different. And these kinds of discussions in a hospital set up, even in large enterprises are learnt from the clinical leadership level. I would not say it is the management level.

Anup R Warriar: What would be the roadmap ahead for Aster DM looking at the focus of AMR and antibiotic use. Where do you see in another five years the Aster DM doing in the field of AMR or infectious prevention or AMS?

Dr Harish Pillai: For Aster, because we are a multinational Indian healthcare entity. We are presently there in nine countries. Our presence in India is rather small compared to our presence in the GCC. We are the largest primary health providers in the GCC region with extensive investment in primary and secondary care because demographics in countries such as UAE, especially in the city of Dubai, is such that it is mostly a clinic and ambulatory practice.

But in India, the spectrum is different. All our hospitals are focussed on tertiary and quarterly care. The institution where you are sitting right now, the Aster Medcity, is a classic example of what Aster would like to do in India. We have a big portfolio of hospitals across five states, and the way we have set up Aster Medcity is to create a certain benchmark of best practices across the spectrum.

Just to give you a snippet about that, this hospital is the result of an epidemiological study of the state of Kerala where we realised the rapid ageing of the population and extensive prevalence of type II diabetes. We established the centres of excellence which are just focussing on eight to nine spectrums. So from NCD point of view, what is really necessary for our community in Kochi or in the larger state of Kerala is cardiac, orthopaedics, neurosciences, gastroenterology, oncology, women health, metabolic diseases, critical care, multi-organ transplantation, so that is the focus of this tertiary care hospital.

And the resource planning, whether in terms of capital allocation of resources or the manning plan, all support the larger epidemiological data that flowed through when we set up this hospital. I would say this was the easy part. The tougher part was to set the culture. And many of you mentioned behaviour as a critical part of sustainable programs. When we started this hospital, in fact, I was the first CEO of the hospital, it was left to us to ensure that we hire right. And we built the concept of a collaborative team. The idea was to deploy clinicians who knew their limits. We didn't want to

have cowboys in the system. We ensured that algorithms and evidence are set from Day 1.

Like Dr Warriier, I had the privilege of hiring him. He was from Day 1 the single point of contact for infection control and infectious diseases. And it was very obvious, even though you have senior colleagues in Internal Medicine, or the subspecialties of medicine, when they have a moment of doubt, the question has to be raised to Dr. Warriier for an expert second opinion. So that culture was built in from Day 1.

The second aspect, in addition to behaviour, was the investments we made in IT systems. We had a very robust electronic recording system from Day 1. We said there would be no paper medical records in this hospital. Ambulatory and inpatient data will be entirely electronic medical records. And you have a decision support system embedded into that. And the conversation which all of you had on nursing. We have a very empowered team of nurses. We used to encourage the nurses to pull the chain. If they had a doubt, whether in terms of prescription or anything else. Nurses are highly empowered.

The third important aspect I think is the clinical pharmacy, the whole cadre of clinical pharmacists. Aster Medcity has a total of 13 clinical pharmacists. I know that this is probably one of the few hospitals in the state of Kerala and even in South India, wherein one institution has 13 clinical pharmacists.

We have a large number of education programs. We have about a hundred postgraduate students being trained in this hospital, both from the national board of exams and they have a very interesting program accredited by the three royal colleges of physicians for IMT - Internal Medicine Training. All these postgraduates also get to have that element of the important role of AMR, the other aspects, the cultural aspects are embedded into them.

We are also generating a new generation of clinicians who would hopefully have altered behaviour compared to the set rate. The beauty of running a hospital in Kochi and I would say, I would dare say in Kerala also, is the quality of other hospitals. Like we have a large representation of public sector as well the private sector. It is a real pleasure where people do not hesitate to reach out and share knowledge just because you are a competitor hospital. Between societies, we have a strong bond. You have a lot of these societies, for example, the Gut Club in Kochi. Many of these societies have a lot of fraternal relationships across the state of Kerala. There is a symbiotic aspect to spreading knowledge, and that elevates the practice structure in the State overall.

Answering Dr Warriier's question is that, the good things which we have done in Aster medcity, we are trying to spread

across Aster India because I have a benchmark in Kochi. So I ask my colleagues either from infection control or from quality, from the rest of India to come to Kochi and learn from their colleagues; because they have already been doing that for the past six years. Ultimately the way forward is, this hospital is already doing a joint commission accreditation and all the joint accreditations; I am also trying to get all the other hospitals in India to go through the same path, the same path as Kochi hospital.

We are also now investing in the database in software where the clinical outcomes, for about 15 specialities, would be published and also shared with Institutions overseas. We can benchmark our clinical outcomes—both for specialities and for physicians.

Dr Anup R Warriier: Dr Satish, What are the technological innovations that we can look forward to? At two levels. One, the technological innovations which are out there in the world, but may or may not be financially feasible for us. Second, what are the innovations which you think you can bring down to our or-

“68% of the fixed dose combinations are not registered with the Central Drugs Standard Control Organisation, the CDSCO. So that's a huge number.”

ganisation and we can look forward to using in the near future?

Dr Satish Rath: We have two technologies understanding biology, infection and genomics well. It's a semiconductor technology that we can call lab-on-a-chip. You put any fluid, and you can analyse it at a very cheap cost. We were always able to analyse this. But the computation power was very high. Maybe a computer of this-sized room. What we used to do in 2003 or 2002 has come down to a tiny fraction of things.

And the cost of computing has also come down drastically. So we have chips for everything, and we have the power to compute it at the point of care which is making a lot of start-ups coming into local diagnostics.

On the other side, we have a lot of data exploding - the power of AI, which has improved over the last four to five years. You put any data, and you can churn out the real insights. Why do people prescribe even when they are not sure about something? They do not want to miss out. An antibiotic need might be there, and there might be a bacterial infection. I don't have a diagnostic to tell me whether this is a bacterial infection or a non-bacterial infection. I believe these kinds of technology

which can quickly diagnose it's bacterial or non-bacterial that would be a real game-changer. The good thing is that its happening. The technology is coming very fast from countries like the US, Israel, Australia, Singapore and some parts of Europe.

The second piece is, as we understand in Biology as the doughnut model. As a scientist, you see the doughnut with the middle portion, which is empty, that is microbiomes. The microbiomes are controlling the NCD'S, the infections, the immunity and the inflammation. There is gut-brain access. So how we are thinking, how we are handling the external pathogens, is contributing a significant part into it.

If I have taken a certain kind of food, I am particularly vulnerable of being exposed to certain types of microbes, and my susceptibility to infection and infection resistance power. It would be beneficial if the government takes it up to have a microbiome database. So that we understand this is the microbial pattern of people who are resident in Kerala or say migrant from Kerala. And you can then correctly prescribe what kind of antibiotics they should be taken based on the microbial pattern.

There is a start-up in Israel called k2, which has started this area, and they already have two publications in nature. Before you are prescribed antibiotics or NCD drugs, your microbial analysis is going to be done, which is a very cheap thing. Because the sample is the stool, and you are going to be prescribed personalised antibiotics. This reminded me of one of our researches when I was in xerox lab. We invented something based on normal cellulose, paper, what is used for printing, and we can print it with wax, and this can act as a lab-on-a-chip. So, the cost of a lab-on-a-chip is just the cost of your paper. We had worked with WHO to make it widely available, we had samples for E.coli, and salmonella, shigella and work is still going. Why I am citing this is because technologies are available, which can make it available at the doorstep of each and individual patient before they are prescribed anything.

When we say all kind of data, real-world evidence data becomes very very important. You have data which is getting generated, if you have real-world data, what we call real-world data is citizen data plus enterprise data. Consider citizen data as whatever my online data, my behaviour is there, from my phone, there is a humongous amount of data which is out there. There are good companies which can mine it, through Artificial Intelligence, and then you know there is the enterprise data, which is the AMR data or PHR data, let's say surveillance data. When you combine these two, citizen data is up to 70%, and enterprise data is up to 20%, you have a remarkable amount of specificity in the insights. This is seen as the next big thing.

When you use AI in unsupervised learning, an area where we throw any data, AI identifies which are the closest patterns, what we call as clustering. Now we have started to understand what are the older antibiotics which have been put out of use, can be used to treat particular infections. And this is a signifi-

cant discovery where we are having the falling of the pipeline of the antibiotics. If you ask any of the pharmaceutical companies they will say, they are apprehensive about not having the new molecules not coming up. Still, here we have an opportunity where we can identify which antibiotic might work for which demographic, which localisations, and entirely for a newer indication, which was not identified. So, if we use lab-on-a-chip we can have a diagnosis part, and this is very much possible, we should not think that this is very much expensive. And the entrepreneurship should be driven by both government and private partnership. Birac, DBT, other funding agencies are supporting things like that, and this should be done. I would see this is the best part of a public, private partnership.

Dr John: Dr Harish was saying that driving AMR is a clinical activity. I will fully agree with him. When I took over as Chief of Medical Services at Aster Medcity two years back, this was one of the issues and I had able support from Dr. Warriier. I can give you a simple example, it was the surgical site infections that was a battle we won. And we did not go for anything hitech. we knocked off 95%. From where we stood, we have come down to 1.

Dr. Anup R Warriier: We had about 15-20 every month, now it has come down to 1-3.

Dr John: Yes, we came down to 1. Regularly we are hitting it. The battle is not lost. We have to start with the basics. Education. Educating the public in a language they understand. That's what we did. We took groups, nurses, paramedics, doctors, and gave them feedback. Retrain, retrain, give them feedback. And it took some time. One and a half years almost. But we did it. And that is what I think. I fully say that it is a challenging conquest which we are going to win. That's what my final remark will be.

Dr Harish Pillai: Dr Anup, please, allow me to add to what Dr John just mentioned.

Dr. Anup R Warriier: Yes, Dr Harish

Dr Harish Pillai: In our group of hospitals in India, this institution - Aster Medcity receives the largest volume of international patients. Which adds one more dimension to the challenge of antimicrobial resistance. These groups of patients are mostly coming in from the Middle East and Africa. What he just was talking about, the 2-year cycle of surgical site infection rate, the same period also showed a quantum increase in the number of international patients. So, despite that surge, I think, what he said is something pretty good. In India, we also see this as a national challenge, because India is positioning itself as a medical value traveller's destination to the world, as we discussed today unless Indian hospitals (especially those who are NABH accredited) get this act together; instead of being a solution to the world, we might become a headache. It's critical that hospitals that cater to international and domestic patients have very robust AMR and AMS systems in place.

Research

Role of Susceptibility-weighted Imaging in Grading of Gliomas Compared to Perfusion MRI, with Histopathology as the Gold Standard

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PELD (Percutaneous Endoscopic Lumbar Discectomy): Prospective Study of 230 Cases, Indications, Patient Satisfaction and Recovery

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Proper surgical indications and a good working channel position are important for successful PELD. The “surgeon factor” is critical, as each endoscopic surgeon needs to possess a wide range of surgical experience and skills to determine the procedures and techniques that work best.

Role of Susceptibility-weighted Imaging in Grading of Gliomas Compared to Perfusion MRI, with Histopathology as the Gold Standard

Praveen Mathew¹, KG Ramakrishnan²

^{1,2} Department of Radiodiagnosis, Aster MIMS, Kozhikode, Kerala, India

Keywords:

Glioma, ITSS, rCBV, Perfusion MRI, Susceptibility

Financial Support And Sponsorship:

Nil.

Conflicts of Interest:

There are no conflicts of interest.

ABSTRACT

BACKGROUND: Perfusion MRI is considered one of the best available methods in grading of gliomas and studies have shown it to be superior to conventional MRI sequences in this regard. Due to its high sensitivity to tumor microvasculature and hemorrhagic products, susceptibility-weighted imaging (SWI) is a promising imaging tool for evaluating angiogenesis, which in turn can help differentiate low grade from high grade gliomas.

AIMS: This study aims to compare the accuracy of SWI with Perfusion MRI in the grading of gliomas.

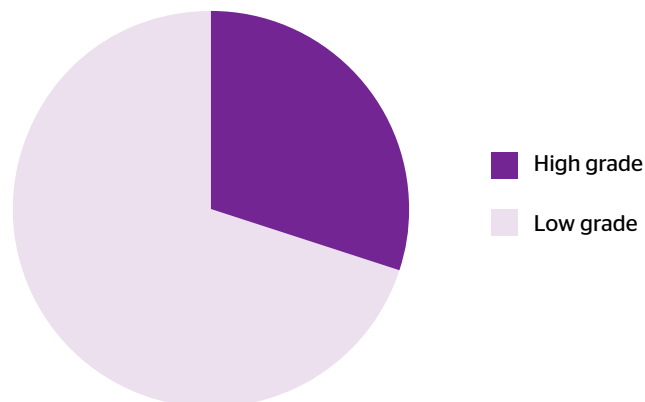
METHODS: In this prospective study on 40 patients with gliomas of different grades diagnosed based conventional MRI sequences (confirmed later on biopsy), SWI and perfusion MRI images were acquired by a 1.5 T MRI machine. rCBV (Relative cerebral blood volume) values were obtained by Perfusion MRI and ITSS (Intratumoral susceptibility signal) magnitude denoting the number of linear or dot like hypointensities within the tumor, was assessed from SWI images. Receiver operating characteristic (ROC) curve analysis was used to determine the individual diagnostic performances of rCBV and ITSS in

grading of the gliomas. Reliability of both diagnostic tests was assessed by kappa statistic along with its 95% CI (confidence interval) and p Value.

RESULTS: High ITSS magnitude on SWI (5 and above) had sensitivity of 100% and specificity of 91.7% in predicting High grade gliomas. Positive and negative predictive values were 96.6% and 100% respectively. The overall diagnostic accuracy was 97.5% and the Kappa statistic was 0.94. Similarly a high rCBV value (Above 1.75) on perfusion MRI had sensitivity of 85.7% and specificity of 91.7% in predicting High grade gliomas. Positive and negative predictive values were 96% and 73.3% respectively. The overall diagnostic accuracy was 87.5% and the Kappa statistic was 0.72. p values for all the above results were <0.05.

CONCLUSIONS: The findings in our study show that non-invasive grading of gliomas based on their ITSS magnitude on SWI has a diagnostic accuracy comparable to rCBV values obtained by Perfusion MRI. These findings imply that visual assessment of the degree of intratumoral susceptibility signals in a glioma can predict its grade similar to Perfusion MRI, which has generally been considered the gold standard noninvasive method of grading gliomas.

Figur 1. Pie diagram of high grade and low grade glioma percentages.



INTRODUCTION:

Magnetic resonance imaging (MRI) is the gold standard in non-invasive diagnosis and grading of gliomas. Conventional MRI techniques may provide less than optimal information by assessing only the anatomic characteristics of the tumor. New complementary MRI techniques have been developed that provide quantitative parameters which provide functional or physiologic data, thereby improving their accuracy in grading these tumors^[1].

Perfusion MRI is one such technique that has become a powerful tool by giving insight into angiogenesis, a critical component of gliomas of higher grade, thereby potentially helping to differentiate low grade from high grade gliomas. Studies have shown that it improves the accuracy in grading of gliomas and is generally considered superior to conventional MRI in this regard^[2-4].

Due to its high sensitivity to tumor microvasculature and hemorrhagic products, susceptibility-weighted imaging (SWI) has recently been included as a potential imaging tool for evaluating angiogenesis and thereby help in grading gliomas. SWI has potential advantages in that it is a non-contrast technique and does not have some of the technical limitations and pitfalls in diagnostic interpretation present in perfusion MRI^[5]. This study aims to compare the accuracy of SWI compared to perfusion MRI in grading gliomas.

MATERIALS AND METHODS:

Data collection:

A total of 40 patients with subsequently histopathologically proven gliomas of different grades were analysed from June 2017 to May 2018 by MRI. Perfusion MRI and SWI images were used to obtain rCBV and ITSS values respectively from each of the gliomas.

Imaging analysis:

All patients with suspected gliomas based on conventional MR imaging features were graded based on Perfusion MRI as low grade or high grade (using an rCBV value of 1.75 as the cut off for differentiation, based on previous valid studies)^[2,4]. The rCBV value was calculated from the site of maximal blood volume in the lesion, compared with a contralateral area of normal white matter. Quantitative assessment of intratumoral susceptibility signals (ITSS) was performed in the

selected imaging slice that visually showed the highest frequency of ITSS within the tumor. This did not include hypointense lines and dots seen on the other conventional sequences, but only those hypointense foci seen only on the SWI sequence. Results were then be compared with the histopathological grade of the tumor obtained by surgery or stereotactic biopsy.

Statistical analysis:

Data was analyzed using SPSS 22.0. Comparison of continuous variables was assessed using independent sample t test. Susceptibility weighted imaging using an ITSS value and Perfusion MRI imaging using an rCBV value were compared with histopathology in distinguishing low grade (grade I and II) and high grade (Grade III and IV) gliomas. ROC curve analysis was used to define the cut off value for ITSS. The pre-fixed cut off value for rCBV based on previous studies as mentioned in the review of literature was 1.75^[9]. Sensitivity, Specificity, Positive and Negative predictive values were used to interpret the accuracy of SWI and Perfusion MRI with respect to Histopathology. Reliability of both diagnostic tests was assessed by kappa statistic along with its 95% CI (confidence interval) and p Value. For all tests a p value of < 0.05 was considered as statistically significant.

RESULTS:

In the study of 40 patients, majority of the gliomas (57.5 %) were grade IV on histopathology (23 patients). Grade I gliomas accounted for 10% of the patients. Grade II and Grade III gliomas accounted

Table 1 : Area under the ROC curve for rCBV value

Area Under the Curve (AUC)	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	
0.921	0.056	0.812	1.000	<0.001

Table. 2: Comparison of Perfusion MRI grade with Histopathological grade

Grade based on rCBV value on perfusion MRI	Histopathologic grade		Kappa statistic (95%CI)
	High grade (N= 28)	Low grade (N=12)	
High grade (≥ 1.75)	24 (85.7%)	1 (8.3%)	0.72 (0.5 -0.95)
Low grade (< 1.75)	4 (14.3%)	11 (91.7%)	

Table 3 : Area under the ROC curve for ITSS

Area Under the Curve (AUC)	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	
0.990	0.012	0.966	1.000	<0.001

Table.4: Comparison of ITSS magnitude on SWI with histopathological grade

ITSS magnitude on SWI	Histopathologic grade		Kappa statistic (95%CI)
	High grade (N= 28)	Low grade (N=12)	
High (5 and above)	28 (100%)	1 (8.3%)	0.94 (0.82- 1.0)
Low (up to 4.99)	0 (0%)	11 (91.7%)	

Table 5: Comparison of Validity of SWI and Perfusion MRI in predicting High grade glioma

Parameter	SWI statistic (95% CI)	Perfusion MRI statistic (95% CI)
Sensitivity	100% (89.7 – 100)	85.7% (72.7 – 98.7)
Specificity	91.7% (76.1- 100)	91.7% (76.1 – 100)
Positive Predictive Value	96.6% (90- 100)	96% (88.3- 100)
Negative Predictive Value	100% (74.1 – 100)	73.3% (50.9- 95.7)
Area under Curve (ROC)	0.99 (0.97 – 1)	0.92 (0.81 – 1)
Kappa Statistic	0.94 (0.82 – 1)	0.72 (0.5 – 0.95)

for 20% and 12.5% of patients respectively. Grade I and II gliomas are classified as low grade gliomas and grade III and IV are classified as high grade gliomas by convention. By this classification, 70 % (28 cases) of the gliomas in this study were high grade and 30% (12 cases) were low grade.

The mean rCBV value (on perfusion MRI) of high grade gliomas was 3.61 ± 3.02 and low grade gliomas was 0.99 ± 0.78 , and the mean difference (2.62) between the two groups was statistically significant (P value 0.006).

The rCBV value of the tumor had a good predictive validity in predicting histopathological high grade gliomas, as indicated by area under the curve of 0.921 (95% CI 0.812 to 1.00; p value <0.001). Out of the histopathologically proved high grade gliomas, 85.7% were shown to be high grade on Perfusion MRI as well, using an rCBV cut off value of 1.75, giving it a sensitivity of 85.7%. Out of the histopathologically proved low grade gliomas, 91.7% of the lesions were low grade on Perfusion MRI as well, giving it a specificity of 91.7%. Positive predictive value was 96.0% and negative predictive value was 73.3%; the overall diagnostic accuracy was 87.5%. The kappa statistic was 0.72 with a 95% CI of 0.5 to 0.95.

The mean ITSS magnitude on SWI of histopathological high grade gliomas was 16.25 ± 6.54 and low grade gliomas was 2.67 ± 2.84 , and the mean difference (13.58) between the two groups was statistically significant (P value<0.001).

Based on the ROC curve analysis, an ITSS value of 5 was chosen as the cut off between high grade and low grade gliomas, as it was the point of maximum sensitivity and specificity.

In our study population, SWI showed better validity parameters than Perfusion MRI in predicting glioma grade, with the greatest difference being in the sensitivity and negative predictive value, in which SWI had values of 100% .The difference

was however statistically insignificant with a p value of 0.1 and overlap in the 95 % confidence intervals of all the validity parameters between the two tests.

DISCUSSION

The present study was conducted with the objective of comparing the accuracy of Susceptibility-weighted Imaging (SWI) with Perfusion MRI in non-invasive grading of gliomas, using an optimal Intratumoral Susceptibility Signal (ITSS) cut-off value derived from the study.

The prospective study included 40 patients with histopathologically proved gliomas, of which 70% (28 in number) belonged to the high grade group and 30% (12 in number) belonged to the low grade group.

The accuracy of Perfusion MRI in predicting high grade gliomas was determined based on an rCBV threshold value of 1.75 (from previous studies); the accuracy of SWI was determined using an ITSS threshold value of 5, derived from the ROC curve analysis in this study.

The findings in our study show that grading of gliomas based on their ITSS magnitude on SWI has a diagnostic accuracy (sensitivity of 100 % and specificity of 91.7 %) comparable to that of Perfusion MRI based on their relative cerebral blood volume (rCBV) measurements (Sensitivity of 85.7% and specificity of 91.7%). Perfusion MRI has generally been considered the gold standard non-invasive method of grading gliomas and this study shows SWI to be an equally accurate alternative, the advantage being it does not require contrast administration and is free from software related technical pitfalls often present in perfusion MRI.

In our study, there was a statistically significant difference between the mean ITSS magnitude of high grade and low grade gliomas, with a mean value of 16.25 ± 6.54 for high grade gliomas and 2.67 ± 2.84 for low grade gliomas. This result is

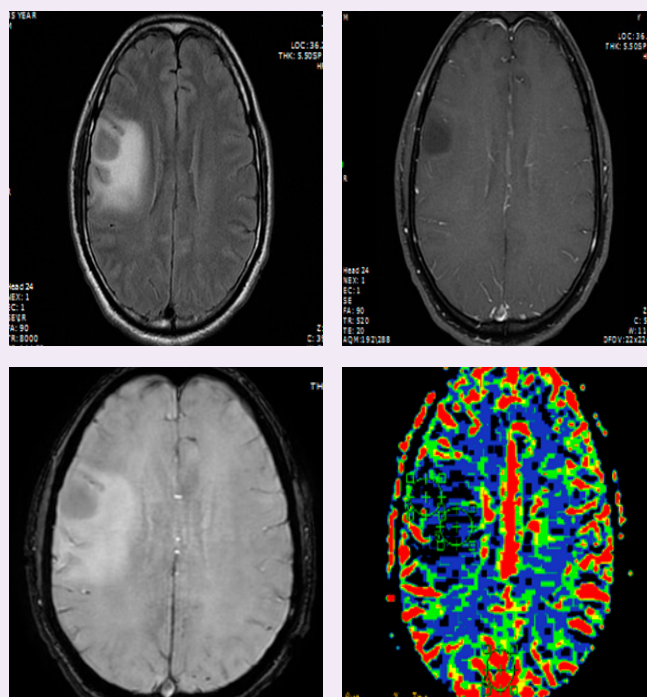


Figure 3

Representative case 1: Axial FLAIR, Post contrast T1, SWI and CBV perfusion images (Images from top left to bottom right): Non-enhancing right frontal lobe lesion showing no ITSS signals on SWI and mildly reduced rCBV on the perfusion map. Histopathology: Grade II Astrocytoma

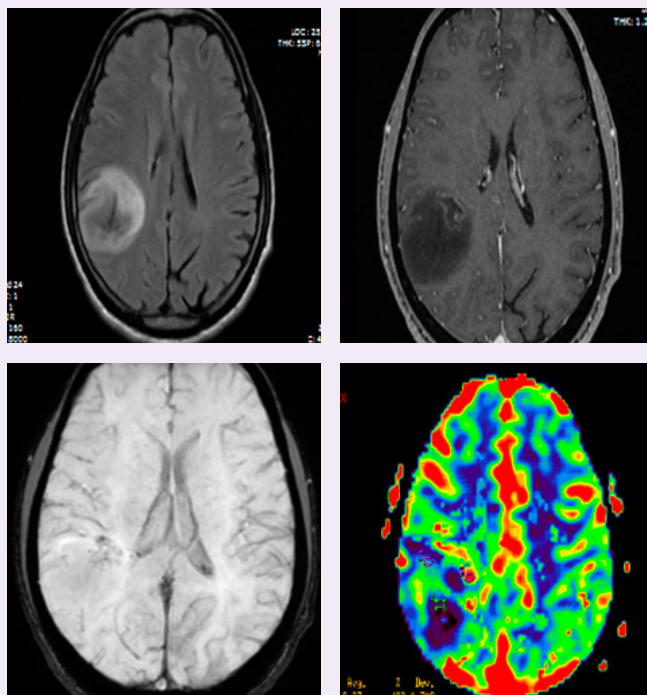
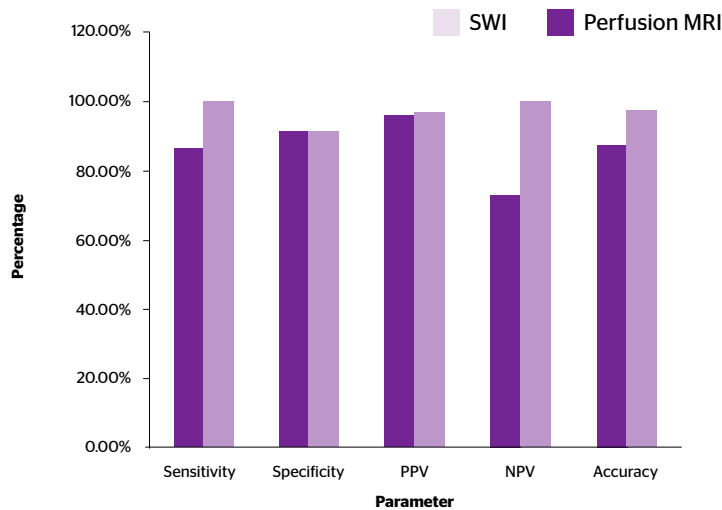


Figure 4

Representative case 2: Axial FLAIR, Post contrast T1, SWI and CBV perfusion images (Images from top left to bottom right): Small area of enhancement in the anterior aspect of the lesion shows multiple punctate ITSS signals on SWI and significantly elevated rCBV on the perfusion map. Histopathology: Grade III Astrocytoma

Figure 2. Cluster bar comparison of Validity of Perfusion MRI and SWI in predicting High grade glioma



similar to previous studies by Park et al^[5], Zhang et al^[6] contrast enhanced T1WI (CE-T1WI, Li et al^[7] 9 of which were grades I-II, and 13 were grades III-IV. All examinations were performed on Signa DEx 3.0 T MRI scanner. Conventional imaging techniques (T1WI, T2WI, T2FLAIR, CE-T1WI and Wang et al^[8] and there was also a significant correlation between rCBV and tumor grade ($r=0.77$; $P < 0.001$. For example, the study by Li et al^[7] 9 of which were grades I-II, and 13 were grades III-IV. All examinations were performed on Signa DEx 3.0 T MRI scanner. Conventional imaging techniques (T1WI, T2WI, T2FLAIR, CE-T1WI in 22 gliomas showed an ITSS magnitude of 17.7 ± 12.71 in high grade gliomas and 7.9 ± 7.62 in low grade gliomas with a statistically significant difference.

In our study, using an ITSS magnitude of 5 as the optimal threshold value based on the ROC curve analysis, the sensitivity and specificity in predicting high grade gliomas was found to be 100% and 91.7% respectively. Positive and negative predictive values were 96.6% and 100% respectively. These results are similar to those of the previous study by Park et al^[5], who also used the value 5 as their ITSS threshold in a study population of 41 gliomas (29 high grade and 12 low grade) and obtained a sensitivity of 85.2%, specificity of 92.9%, and positive and negative predictive values of 95.8% and 76.5% respectively.

Similar to perfusion MRI, the role of SWI in grading gliomas is also based on evaluating the

process of neoangiogenesis that occurs more in high grade gliomas. However, unlike perfusion MRI, HR-SWI evaluates the anatomical aspect of the vascularity by assessing the number of tiny new vessels within the tumor, with their accompanying microhaemorrhages because of the leakiness associated with these immature new vessels. These are significantly higher in high grade gliomas than those of low grade.

CONCLUSION

ITSS quantification on the SWI sequence has a diagnostic performance comparable to Perfusion MRI in the grading of gliomas and is easier to perform and interpret with fewer technical limitations and pitfalls compared to Perfusion MRI, with an added advantage being non-requirement of contrast administration.

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Original Study

PELD (Percutaneous Endoscopic Lumbar Discectomy): Prospective Study of 230 Cases, Indications, Patient Satisfaction and Recovery

Dr Faizal M Ikbal MS^{1*}, Dr Hassan Muhammad MS¹, PhD, Dr Kadavil R Shaji MD²

Patient satisfaction was defined as a maintained reduction in pain and absence of recurrence within a 24 month period, with no further surgery being necessary.

¹ Department of Orthopaedics, Aster MIMS Hospital, Kottakkal Malappuram District, Kerala, India.

² Department of Neurosurgery, Aster MIMS Hospital, Kottakkal Malappuram District, Kerala, India.

*corresponding author

Key words

Low backache, keyhole-surgery, daycare-surgery, Discectomy, Endoscopic Indication, Inter-laminar, Transforaminal.

Conflicts of interest

No conflicts of interest have been declared.

ABSTRACT

Background

Low back pain is a major clinical problem that results in an important socioeconomic burden. The percutaneous endoscopic lumbar discectomy technique developed by Yeung, also known as PELD, is currently the flagship of minimally invasive transforaminal decompression. Kambin and Gellman first introduced PELD in 1983. PELD has been further developed with the Yeung endoscopic spine system and transforaminal endoscopic spine system.

Statement of Problem

Patient apprehension towards open surgery and risk of complications with anaesthesia in patients with multiple comorbidities have led us to conduct a review on how the endoscopic technique differs from conventional open lumbar discectomy in terms of patient satisfaction.

Objective

PELD surgery- short term results and follow-up of 230 patients, reporting patient satisfaction, in terms of duration of surgery and early recovery.

Methods

A prospective study was performed on all 230 patients who had undergone PELD between September 2018 and July 2019 at Aster Mims Kottakkal. This included patients who presented with intervertebral disc prolapse, both central and paracentral disc herniation, or radiculopathy. A narrative review was conducted to outline the basic principles, surgical techniques, and clinical outcomes of lumbar and cervical disc herniation.

Results

PELD allows intra-operative protection of the nerve roots, and communication with the patient under local anaesthesia. However, the learning curve for PELD is steeper than that of conventional

microsurgery, and proper surgical indications and a good working channel position are important. PELD approaches should be tailored to remove disc fragments specific to various types of HD.

We observed 184 successful cases (80%) and 3 infected patients (1.3%) with discitis, one of which relapsed, the other two being converted to open surgery. We observed 2 cases of impending cauda equina syndrome and 10 cases of degenerative lumbar canal stenosis. Radiculitis patients (n=7, 3%), were effectively treated with oral steroids. The complication rate was <5%, similar to that of conventional open techniques.

Conclusions

PELD may be an ideal surgical technique for LDH. Preliminary results demonstrate a high efficacy rate, with few surgical complications. Given recent technical advancements, surgical indications for endoscopic spine surgery are still expanding and the clinical results have become more practical and reliable.

INTRODUCTION

Low back pain is a major clinical problem, that results in an significant socioeconomic burden.¹ Its incidence appears to be increasing, despite technical and therapeutic advances in diagnosis and treatment. Surgery is advantageous over conservative treatment in most cases of back pain caused by lumbar spinal stenosis.² Over recent years, various percutaneous, minimally invasive intra-discal techniques have been developed, directed at the mechanical process of discus herniation, with the underlying aim of capitalizing on the advantages of operative therapy, with as few of the disadvantages as possible.

Posterolateral Selective Endoscopic Discectomy (SED) and radiofrequency (RF) thermal annuloplasty, a percutaneous endoscopic technique developed by Yeung,^{3,4} also known as PELD, is currently the flagship of minimally invasive transforaminal decompression. Kambin and Gellman first introduced PELD in 1983 to remove affected disc material under local anaesthesia, for direct neural decompression.⁵ PELD was further developed with the Yeung endoscopic spine system (YESS) and transforaminal endoscopic spine system (TESSYS)

Table 1

	Total patients (%)
All cases	230 (100)
Male	156 (67.8)
Female	74 (32.2)
Mean age, yrs (SD)	(45.1±13.6)
Cauda equina	2 (0.9)
Degenerative lumbar canal stenosis	10 (4.3)
Epidural + local anaesthesia	65 (28.3)
MAC + local anaesthesia	165 (71.7)
PELD right side	116 (50.4)
PELD left side	108 (47.0)
PELD bilateral	6 (2.7)
PELD L5-S1	73 (31.7)

techniques, and thereby became a feasible alternative for lumbar disc herniation (LDH) treatment.

In contrast to traditional open surgical techniques, PELD involves a lateral rather than midline approach, introducing an endoscope to the disc space through the foramin, thus avoiding damage to the vital lumbar structures. The annulus is cut and prolapsed disc material retrieved through the annular tear, keeping the dural tube free from compression, and therefore providing immediate relief to the patient.

Patient apprehension towards open surgery, and the complications of anaesthesia associated with patients with multiple comorbidities (including CAD, CKD, diabetes and reliance on antiplatelets), for whom open surgery and regional and general anaesthesia pose a risk, yet we can easily perform endoscopic surgery under local anaesthesia, have led us to conduct a review on how the endoscopic technique differs from conventional open lumbar discectomy.

Here, we analyse the short term results of percutaneous endoscopic transforaminal lumbar discectomy in terms of patient satisfaction, based on a cohort of 230 patients treated at Aster Mims Kottakkal during the period of September 2018 to July 2019.

OBJECTIVE

To review the results from short term follow-up of 230 patients receiving PELD surgery, reporting patient satisfaction in terms of duration of surgery and likelihood of early recovery.

MATERIALS AND METHODS

A prospective study review was performed on all 230 patients who underwent PELD between September 2018 and July 2019, performed by a team of 5 doctors. This included patients who presented with intervertebral disc prolapse, or both central and paracentral disc herniation. All patients had radiculopathy, which was resistant to medical treatment. The height and width of the foramen, LDH type, and positional relationship between LDH and the foramen were radiologically evaluated prior to surgery.

All cases underwent PELD on a single vertebral level, based on standard indications, with patients in the prone position. Chart review was carried out, and preoperative, intraoperative, and post-operative radiographic reviews were performed. Patient satisfaction was defined as a maintained reduction in pain and absence of recurrence within a 24 month period, with no further surgery being necessary.

A literature search of the transforaminal approach to LDH was carried out, with a focus on surgical indications for percutaneous endoscopic discectomy and corresponding clinical outcomes in the lumbar region and spine, in cases involving percutaneous or full endoscopic discectomy, carried out with a working channel endoscope.

Statistical comparisons of proportions were performed using Fisher's exact test. P values less than 0.05 were considered statistically significant.

RESULTS

Review of reported Outcomes of PELD

There are a range of studies available which indirectly or directly compare open surgical patient outcomes to PELD and other endoscopic outcomes. Five such studies were systematically reviewed in 2016 by Peng *et al.*,⁹ which report similar clinical outcomes across a range of different measures, yet greater patient satisfaction with PELD, with 91% of patients being satisfied with their surgeries.

Among more recent studies, a single centre

study of 10,228 patients by Choi *et al.* over a 12 year period showed a successful post-operative outcome rate of 95.7%.¹⁰ Positive outcomes were judged by indications for reoperation within 6 weeks. The most common cause of failure was incomplete removal of the herniated disc, with a third of these cases the result of incorrect positioning of the working channel, highlighting the importance of tailoring the PELD approach in each case based on pre-operative indications.

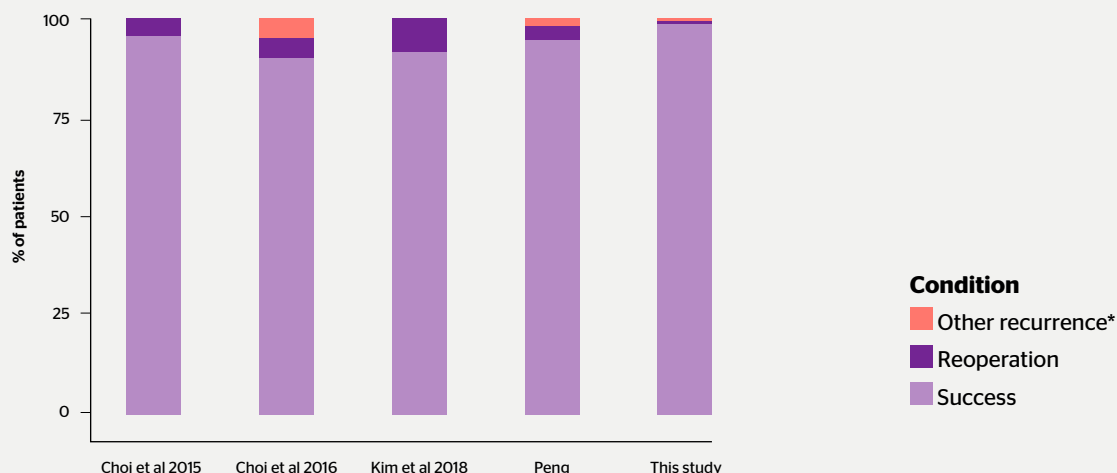
A study by Choi *et al.*,¹¹ comparing satisfaction in 23 patients with large LDH (>50% of spinal canal occupied) undergoing open lumbar microdiscectomy (OLD), and 20 receiving PELD, measured significantly higher patient satisfaction in the PELD group, as reported using a pain and movement questionnaire. Additionally, a loss of disc height in the OLD group was avoided with PELD. The frequency of recurrence or reoperation within 24 months was 10%. However, a longitudinal study made in Korea showed no difference in the reoperation rates observed with OLD and PELD between 1973 and 2018.¹²

Song *et al.* compared PELD outcomes of 30 patients to those of 30 patients receiving micro-endoscopic discectomy (MED), which also uses an endoscope, but does not integrate radiofrequency technology.¹³ Clinical markers of operative success were similar across both groups, with the PELD group having a faster post-operative recovery.

Indications for PELD were as follows- Song *et al.* included patients with MRI and MR imaging indications, differential pain in the waist and lower limb(s) in conjunction with positive results for either the femoral or sciatic nerve stretch tests,¹³. Choi *et al.* also included patients with MRI imaging

A prospective study review was performed on all 230 patients who underwent PELD between September 2018 and July 2019, performed by a team of 5 doctors. This included patients who presented with intervertebral disc prolapse, or both central and paracentral disc herniation.

Figure 1. Summary of patient satisfaction outcomes reported in prior studies comparing PELD patient outcomes to other control groups.



*recurrence without reoperation statistics not available across all studies.

indications,^{10,11} and used imaging results used to infer the optimal approach. Wildermuth et al. demonstrate similar accuracy with MRI imaging and functional myelography in identifying measurements of the lumbar dural sac.¹⁴

Hirano et al. suggest inclusion of patients with recurrent disc herniation after microdiscectomy, who are high risk for general anaesthesia, have LDH at L3-4 or above, or are emergency cases.¹⁵ They do not recommend PELD with limited accessibility to the disc space, bony canal stenosis, large and hard herniated nucleus pulposus (HNP), or HNP with a vertical migration of more than 10 mm.

A steep learning curve is described for PELD, as explored by Lee et al;¹⁶ Hirano et al also describe lessons learned from early procedures, in which 16% of patients experienced unfavourable outcomes,^{6,15} yet these became rare events with increasing surgical experience. Specifically, Hirano et al. describe the following difficulties regarding PELD training⁶: (1) Posterior procedures have been performed for decades by spine surgeons, so they are familiar with posterior anatomy. However, PELD is a posterolateral approach, and the intervertebral foramen anatomical structure is relatively new to surgeons; (2) Anatomical landmarks are absent, and (3) tissue differences between the annulus fibrosus and posterior longitudinal ligament (PLL), or the PLL and dura matter, are vague.

Case post-surgical outcomes

The demographics and surgical approaches of case patients are shown in Table 1. Two patients presented with impending cauda equina syndrome and 10 with degenerative lumbar canal stenosis.

80% of patients who returned for one and two-year follow-ups reported successful outcomes requiring no further treatment, with an average 90% reduction in reported pain, and early ambulation. Three patients had an infection (discitis), of which one had a relapse. The other two cases were converted to open surgery. Sterilization methods were revised, and all instruments autoclaved. These patients were managed post-operatively with IV antibiotics for 24 hours, followed by oral antibiotics for 1 week. On the initial post-operative follow up, we recorded no permanent complications.

The overall complication rate was <5%, including transient dysesthesia, the most common postoperative complaint, which occurred in approximately 5%-15% of cases. Dysesthesia is almost always transient. Three patients had post-surgical radiculitis, which was effectively treated with oral steroids. With these exceptions, all patients were satisfied with their results, received relief of pre op pain and experienced early recovery. Our rates of reoperation, and combined reoperation and recurrence, are similar to those of other studies

reporting results from earlier years of PELD implementation ($P>0.05$, Figure 1), and are congruent with the 95.7% of 10,228 patients considered to have had successful outcomes by Choi et al. at 6 weeks post-surgery ($P>0.05$), although this study includes all negative outcomes reported within 24 months.

Based on the observations of this study and the literature, we propose the following inclusion and exclusion indications for PELD surgery:

Include:

- 1) Single level disc prolapse, ideally with unilateral radiculopathy.
- 2) Foraminal stenosis with claudication.
- 3) Revision cases- in this study, patients seeking consultation following a transient successful or partially successful or unsuccessful trans-laminar discectomy were offered endoscopic discectomy.

Exclude:

- 1) Multilevel bilateral foraminal stenosis- for such cases, the procedure must be staged, with an inter-surgery interval varying from 3 weeks to 3 months.
- 2) Patients with psychomotor symptoms (even if they are indicated to be under adequate cover of antidepressants and are receiving suitable counselling).
- 3) Central bony-canal stenosis is an absolute contraindication to the procedure.

DISCUSSION

Preliminary results with PELD surgery demonstrate a high efficacy rate, with few surgical complications.^{6,9,10,11,13} The indications for operative discectomy are larger disc protrusions,

and extrusions that show signs of nerve root compression on MRI. Smaller, focal protrusions, without nerve root compression, appear to be less apt to spontaneously resorb, and have a less favorable natural resolution. In comparison with open surgery, minimally invasive spinal surgery has repeatedly shown short-term benefits, including shorter operation and lower complication rates.⁹⁻¹¹ By preserving paraspinal muscle, and avoiding iatrogenic facet injury, PELD gives superior patient outcomes in comparison with conventional OLD, in terms of a shorter hospital stay,^{9,10} often with same-day discharge, less postoperative pain,¹⁰ and reduced intraoperative blood loss.⁹

Proper surgical indications and a good working channel position are important for successful PELD.^{6,8,15,16} The “surgeon factor” is critical, as each endoscopic surgeon needs to possess a wide range of surgical experience and skills to determine the procedures and techniques that work best, limited only by their own surgical experience and ability. The learning curve of PELD is perceived to be longer and steeper than that of conventional microsurgery,^{6,15,16} due to the unfamiliarity of most surgeons with the anatomy of the intervertebral foramen. Despite these complications, some studies report an acceptable PELD learning curve with sufficient preparation and pre-operative training, such as attending seminars, hands-on training, or learning at advanced surgical centres.¹⁷

PELD has a number of advantages over OLD. Firstly, that it can be performed under local anaesthesia, which supports communication between patients and surgeons during the operation and is beneficial to intraoperative protection of the nerve root and rapid mobilization postoperatively. Secondly, approach-related complications, such as dural tear and cerebrospinal fluid fistulas,⁷ are minimised in patients receiving PELD. Finally, PELD retains the motor segment, and thus decreases the incidence of fusion diseases such as adjacent segment disease.

Some patients are particularly suited to PELD. PELD is the simplest way to remove foraminal stenosis when encountered, removing the need for fusion. In this study, foraminal stenosis was present in 4.3% of patients, and the benefits of PELD are likely to be greater in this subgroup. Most patients suffering from LDH are elderly, with various medical comorbidities. A shorter operative

Proper surgical indications and a good working channel position are important for successful PELD. The “surgeon factor” is critical, as each endoscopic surgeon needs to possess a wide range of surgical experience and skills to determine the procedures and techniques that work best.

time and reduced blood loss have been demonstrated to help in reducing potential complications in such cohorts.⁶ PELD has also shown promise for treating serial multilevel LDH.¹⁹

Theoretically, PELD is assumed to be superior in terms of postoperative low back pain, because normal paraspinal structures are more likely to be preserved.¹⁸ However, PELD also poses several challenges, such as higher incidences of postoperative chronic low back pain and recurrence. Within a 12 month follow-up period, two patients underwent reoperation at the operated level or another lumbar level after PELD. No further reoperation was required within 24 months, suggesting the follow-up period was sufficient to capture most complications. The rate of reoperation was similar to that seen with conventional procedures, and to that reported across similar single and multi centre studies. We therefore consider that PELD for recurrent disc herniation yielded favorable outcomes within our centre.

CONCLUSION

Our results suggest that PELD that avoids the occurrence of iatrogenic normal-tissue injury may be an ideal surgical technique for addressing LDH. The procedure is effective for preservation of the facet joint. Based on the preservation of normal anatomic structure, its usefulness could be maximized in patients with serial multilevel LDHs. Given recent technical advancements, the number of surgical indications for endoscopic spine surgery are increasing, and clinical results have become more practical and reliable. PELD techniques should be tailored to remove disc fragments in various forms of HD.

PELD allows a short hospital stay, which reduces total costs and results in a direct economic advantage. As most patients suffering from LDH are elderly, with various medical comorbidities, a shorter operative time and reduced blood loss are clear advantages.

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Views & Reviews

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There are many ‘non-epileptic’ episodes which can mimic an epileptic seizure and are not uncommon in children including neonates. Most of these conditions have favorable prognosis. Hence, clinicians should be aware of such differential diagnosis, as incorrect diagnosis of epilepsy has huge ramification on the child as well as their families.

Dr Vivek Mundada is Consultant Pediatric Neurologist, Medcare Women and Children Hospital, Dubai and Aster Hospital, Al Qusais, Dubai, UAE

ABSTRACT

Diagnosis of epilepsy is like a jigsaw puzzle and can often take time if important pieces of the information are missing. The first step in the multiaxial classification of epilepsy is to make sure that the paroxysmal episode which a child had was epileptic or non-epileptic. This step is almost always clinical and relies on the history-taking skill of the clinician. Videos of such episodes are extremely helpful and occasionally investigations can help. However, there is no investigation to 'rule out' or to 'confirm' epilepsy as many times; an EEG can be ordered after a single suspected seizure episode.

There are many 'non-epileptic' episodes which can mimic an epileptic seizure and are not uncommon in children including neonates. Most of these conditions have favorable prognosis. Hence, clinicians should be aware of such differential diagnosis, as incorrect diagnosis of epilepsy has huge ramification on the child as well as their families. In uncertain situations, such children should be referred to a child neurologist

BACKGROUND

A 6-month-old, ex-preterm male infant was referred to the author by a pediatrician with history of suspected epileptic spasms. He was already started on an antileptic medication by the same pediatrician. On the very next day, the infant was seen. Fortunately, the parents also had videos of the episodes, which these days all epileptologists find quite useful. In the first instance, the author was not convinced that those paroxysmal episodes were epileptic spasms. Moreover, going through the detailed history, it was thought that those episodes were 'non-epileptic'.

On examination, the infant had generalized dystonia as well as spasticity. His weight was under 0.4th centile for age and sex. The episodes were more in numbers after the feeds and after witnessing them in the ward, it was confirmed that they were in fact due to severe gastro-esophageal reflux disease. Eventually, the episodes plummeted in severity and frequency once the anti-reflux medications were started. The antiepileptic medication was stopped as it was not needed. Clearly, no EEG was needed here as it would have been misleading or not helpful in "ruling out" epilepsy as the diagnosis.

This is not an unusual story for many of the pediatric neurologists. Just like a surgeon should know when 'not to operate', a neurologist should also know when a seizure is not an epileptic one. This is because, the rate of misdiagnosis is very high especially in the pediatric population. Almost one in three children are misdiagnosed with epilepsy and the consequences are not just on these children but are also on their families (1). The rate of misdiagnosis is even higher in children with severe intellectual impairment (2)

Confident diagnosis of non-epileptic seizures in children is often more challenging than making a positive diagnosis of epilepsy. However, this challenge must be overcome to avoid parental anxiety, unwarranted investigations and potentially harmful and unnecessary treatments. In addition to this, there is a risk of missing another serious diagnosis such as Long QT syndrome that can be life threatening because of the risk of ventricular tachyarrhythmias (Torsades de pointes) (3) The diagnosis of epilepsy is mainly a clinical one. Hence it depends on the good history taking skill.

What is an epileptic seizure and epilepsy?

An epileptic seizure by definition is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (4) whereas, epilepsy is called when

1. At least two unprovoked (or reflex) seizures occur greater than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome can be made even after the first seizure

So, any seizure which is not due to the abnormal electric activity in the brain is "non-epileptic". Such episodes are often stereotyped and most of them tend to occur within the same context or environment.

Some of the common non-epileptic episodes seen in children are discussed below.

1. Breath holding episodes

These can be either blue (prolonged expiratory apnea) or pallid breath-holding spells. Typically, these are triggered by an initial emotional or physical provocation which then leads to crying and then followed by a silent pause. This results in either a blue

or pale color change. The attacks typically terminate with a sudden gasp and rapid return of consciousness. Prolonged and severe episodes can lead to loss of consciousness with increased tone in the limbs.

They are more common in children between 6 and 12 months of age. Typically, an increase in their frequency is seen by the age of 2 years. Nearly half of children grow out of these by 4 years of age (5)

Parental education and reassurance are needed in such cases. Also, treatment with iron for any iron deficiency is recommended (6). EEG is not required but a standard 12-lead ECG and a referral to pediatric cardiology should be considered. In pallid breath holding spell with bradycardia, a pacemaker implant may be considered in some cases. (7)

2. Reflex anoxic seizure

This is an episode which is triggered by a painful stimulus. Such stimulus, by vagal stimulation causes pronounced bradycardia or even cardiac arrest and relative cerebral ischemia leading to an 'anoxic seizure'. A careful history will always identify the triggers in such episodes, as these are almost always the provoked episodes. The most common trigger is pain or fright such is venipuncture, trapping fingers in a door or minor head injury etc. (8)

During an episode, children can become stiff and can have cyanosis along with few brief myoclonic or clonic movements affecting some or all the four limbs. The eyes can be deviated upwards. Urinary incontinence can occur as well. This particular phase can be misinterpreted as an epileptic seizure

Reflex anoxic seizures (RAS) are common in children between 6 months to 2 years of age; although it can happen in adolescents and even in adults. They are more common in girls than boys.

The successful management involve correct diagnosis of RAS and making sure that there is no underlying cardiac arrhythmia; reassurance of the parents and the avoidance of any unnecessary investigation like EEG. Cardiac pacing may be considered in frequent and severe RAS which affects the child and the family's quality of life (9)

An useful website for the parents is the Syncope Trust and Reflex Anoxic Seizures website ('STARS'; <http://www.stars.org.uk>)

3. Daydreaming episodes

Such episodes are commonly mistaken as 'absence seizures'. Daydreaming episodes are commoner in children with learning difficulties. They are more commonly seen in the primary school age children. Children during such episodes can be interrupted by a stimuli like touch

Table 1

Common non-epileptic events in neonatal age and infancy

- Jitteriness
- Benign sleep myoclonus of infancy
- Breath holding spells
- Benign paroxysmal torticollis of infancy
- Paroxysmal dyskinesias
- Sandifer syndrome
- Infant gratification
- Shuddering
- Benign paroxysmal vertigo
- Hyperekplexia
- Alternating hemiplegia of childhood

or tickle. They do not manifest during any interesting activities and are very situational. Unlike typical absence seizures, they are not frequent in numbers and cannot be induced by hyperventilation (10).

4. Benign myoclonus of early infancy

These episodes involve clusters of myoclonic movements involving various body parts like head, trunk, neck, limbs, eyes and head nodding episodes. They typically have onset between 3 to 9 months and tend to disappear by 3 years of age. Several episodes can occur during a single day.

These infants are neurodevelopmentally normal and the EEG is also normal. An EEG may be considered, especially to rule out myoclonic epilepsy of infancy or epileptic spasms when there is such suspicion (11)

5. Infantile gratification disorder and shuddering

This is often under-recognized or under-diagnosed in children. These episodes are self-stimulating behavior and hence were called has infantile masturbation. These are self-limiting and tend to disappear by 2 years of age

Such episodes can easily be misdiagnosed as epileptic seizures. Usually, a child is sitting in a high chair or a car seat with a strap between the legs. The episode happens when the child is bored. The child can stare into space rocking back and forth with the legs crossed and making grunting noises. Such episode can stop with distraction, although the child can be annoyed with such distraction. Videos of such episodes can often facilitate the diagnosis (12).

Shuddering episodes are characterized by tremors of the head, arms and shoulders as if the infant is shivering. An episode can last for few seconds and can come in clusters. Spontaneous resolution is the norm.

6. Tics

Tics are sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations usually appearing in bouts while waxing and waning in frequency and intensity. Tics occur predominantly in children and mean age of onset is around 5 years. These can be either motor or vocal. Motor tics are common in face, neck or shoulder group of muscles. Some of the common motor tics are eye blinking, nose, mouth twitching and shoulder jerks; whereas common vocal tics are throat clearing, grunting and sniffing like sounds. Coprolalia (uttering socially inappropriate words) can occur in up to 20% of individuals. Motor tics usually start in the face and tend to extend caudally and are more common than the vocal tics. They typically can disappear during sleep (13).

The severity of the tics is dependent on factors such as anxiety and stress. They can even be more evident during relaxation like while watching television.

More than two third of the cases can have associated comorbidity. Attention deficit hyperactivity is the most common association followed by obsessive compulsive disorder. Other comorbidities include sleep impairment, learning difficulties, anxiety disorders, conduct disorders etc. (14)

7. Night terrors

Night terror can occur in up to 1-6% of children. They are more common in children between 3 and 12 years of age, with a peak between 5 and 7 years of age. During a typical episode, a sudden arousal from non-dreaming sleep occurs, usually about one and half hours or so after falling asleep. The child wakes up suddenly from sleep, sits or even jumps out of the bed and usually screams with fear. The child appears frightened and confused. These episodes can be associated with tachycardia, tachypnoea, flushed face, bed wetting or dilated pupils (15). Such episodes can be easily be mistaken for nocturnal frontal lobe epilepsy. In case of dilemma, a sleep study or video- EEG telemetry like investigations can be useful.

8. Syncope

Syncope is a transient loss of consciousness resulting from an insufficient supply of oxygen to the brain (16). There is usually a sudden decrease in cerebral perfusion as the result of reduction in cerebral blood flow.

Up to 15% of children can experience such episode before they turn 18. Such episodes are more common in females in their adolescence.

Syncope can be sudden or gradual in onset and can be associated with various different motor phenomenon like hypotonia, extensor spasm like movement of the upper limbs or hypermotor movements like jerking of the limbs. Urinary incontinence can be associated in syncope and hence is not a pathognomonic sign of epileptic seizure. The key to diagnosis is the history immediately preceding the attack and the occurrence of pallor during the attack.

There are various different types of syncope. A reflex syncope is triggered by some stimulus, like pain or shock; orthostatic syncope happens on standing up quickly from sitting or lying position; convulsive syncope is when there is associated abnormal postures or a convulsion; sudden syncope is when there is no warning sign (and hence carries a risk of injury) whereas gradual onset syncope has some pre-syncopal symptoms such as dizziness, nausea, feeling cold or sweaty etc. (17)

9. Psychogenic Non-Epileptic Seizures (PNES)

These episodes mimic epileptic seizures and hence it is important to correctly diagnose such episodes so that the correct management can be provided to the affected individuals. People with PNES usually present to the same clinicians who deal with individuals with epilepsy. Nearly one in ten children with suspected epilepsy referred to a secondary care clinic actually has PNES (18)

The estimated prevalence of such seizures is around 50 per 100,000. There is however no best terminology available to describe such episodes and these are called by various different names like pseudo seizures, psychogenic seizures, functional/hysterical, dissociative or conversion seizures. Most of these terms are often confusing.

Table 2

Common non-epileptic events in children

- Syncope
- Long QT syndrome
- Migraine including benign paroxysmal vertigo
- Tics
- Motor stereotypies
- Pseudoseizures
- Night terrors and sleep walking
- Fabricated induced illness

Table 3**Common non-epileptic events in children with special need or intellectual impairment**

- Self-stimulation
- Secondary motor stereotypies
- Dystonic posturing
- Status dystonicus
- Choreoathetosis
- Spasticity
- Severe gastro-esophageal reflux and constipation
- Hyperventilation

Children can have both- epileptic as well as PNES coexisting together which can make the diagnosis a challenge. In such cases, the outcome usually is less favorable. In adults, there is often a history of physical or sexual abuse or associated mental health issues like complex personality disorders, anxiety or depression. Moreover, the quality of life can be equally affected like in the patients with epilepsy (19).

The treatment should always be focused on psychological rather than medical issues for better outcome.

Some of the features which can differentiate a PNES from an epileptic seizure are-

- Eye closure during the attack
- Tremors and shaking of limbs rather than actual tonic and clonic jerks
- Easy distractibility from the episode
- Variability in motor symptoms such as jerking or shaking
- Side-to-side head movements or thrashing movements
- Self-protective mechanisms to avoid injuries
- Prolonged periods of lying without actual loss of consciousness or awareness
- Preserved corneal reflex during the episode along with responsive pupils

Associated features like a history of aura, urinary incontinence, an abnormal or normal standard EEG, associated or prior diagnosis of epilepsy, response to anti-epileptic medication, family history of epilepsy are never helpful and should not point out towards the diagnosis of epilepsy. A video of the episode along with detailed history and in some cases, video-EEG telemetry like investigations are often helpful for establishing the accurate diagnosis.

10. Motor stereotypies and other movement disorders

Motor stereotypies are common, repetitive, rhythmic movements with typical onset in early childhood. They are most often described in children with autism spectrum disorder (ASD) and intellectual disability

(ID). Such movements are usually bilateral with a fixed pattern. Common motor stereotypies are hand flapping, waving, or rotating. They can usually be stopped by distraction such as by calling one's name. (20)

They are classified as primary (physiological and common examples are pencil tapping, hair twisting, nail biting) and secondary (pathological and depending upon the presence of additional signs or symptoms). Nearly half of the children with ASD can have secondary motor stereotypies.

The biggest differential features from motor tics is the absence of premonitory urges prior to the motor stereotypies. Also unlike tics, stereotypies can have onset before the age of 3 years. ADHD, ASD and OCD are the commonest comorbidities found with complex motor stereotypies (21)

Children with dyskinetic cerebral palsy can have various dyskinesias which often can mimic epileptic seizures. For example, repetitive twisting movements of dystonia, status dystonicus or choreoathetoid movements can be mistaken as an epileptic seizure.

APPROACH

Never forget the basics- history, history and history!

Accurate diagnosis sometimes cannot be possible in the first consultation itself and often more information- such as good description or video of the episodes are needed. Sometimes, the clinician can imitate the episode in the clinic to get the clear picture of them. Even after these, investigations like video-EEG telemetry might be needed. It is hence necessary not to order unnecessary investigations or start any treatment like anti-epileptic medications before confirmation of the diagnosis.

The health professional should be prepared to say 'I do not know' in situations where insufficient evidence is present and more information is needed to come to the conclusion. Also, avoiding terms like 'seizures' or 'convulsions' can be helpful as their usage can project a biased opinion. Instead, they can be referred as 'events' or 'episodes'. Often, a detailed history itself can solve the mystery in nearly half of the patients (19). Often such children are 'labelled' with epilepsy and are started on anti-epileptic medication even before referring to a pediatric neurologist. So, in a tertiary hospital clinic, the pediatric neurologist can face challenges in expunging the given label of 'epilepsy'.

Investigations are to support the clinical diagnosis of epilepsy and not to rule out epilepsy! A video of the episode can be the first sought investigation. Such video can be also shared with another health professional

with the parent's consent where another opinion is needed.

The diagnosis of an epileptic seizure is mostly clinical one and there is no single best diagnostic test for it. Interictal EEG lacks both specificity and sensitivity. Patients with epilepsies can have normal EEGs and patients without epilepsy may show electroencephalographic abnormalities (22). Video-EEG telemetry can be a useful investigation in certain cases if such facility is available in the hospital. Alternatively, ambulatory EEG can be considered.

ECG should be obtained in all 'convulsive' seizures and in cases where cardiac cause is suspected. These children should be referred to a pediatric cardiologist so that appropriate cardiovascular investigations can be arranged.

Neuroimaging has limited role and brain MRI can be considered only in cases like benign paroxysmal torticollis of infancy, paroxysmal tonic upgaze of infancy and spasms nutans.

Other investigations like impedance study (e.g. in Sandifer syndrome), genetic investigations (e.g. in paroxysmal dyskinesias, hemiplegic migraine and hyperekplexia), electrolytes (e.g. in jitteriness), sleep study and polysomnography (e.g. in narcolepsy and cataplexy) should be considered and used judiciously depending on the clinical suspicion

CONCLUSION

Paroxysmal non-epileptic seizures can be result of number of neurological, cardiac, psychogenic and other miscellaneous conditions. As they can mimic epileptic seizures, misdiagnosis is common in such patients. Clinicians, hence should be aware of such differential diagnoses to avoid psychological, physiological and socio-economic consequences to the children and their parents.

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Liver Elastography: The latest ultrasound breakthrough

Ultrasound Elastography is perhaps the most important breakthrough in the evolution of ultrasonography in the last 15 years.

Elastography is an advanced imaging technology which uses a surface ultrasound for non-invasively assessing the elasticity and stiffness of various tissues in the body. Elasticity of the tissues actually describes the resistance to deformation of a tissue to an applied stress.

In quantitative ultrasound elastography the stress is applied via shear wave propagation generated by ultrasound transducer. The underlying concept in the shear wave speed is related to tissue stiffness and travels faster in stiff tissues and slower in soft tissues.

Liver Elastography is by far the best tool for assessing and evaluating Liver Fibrosis non-invasively. It can evaluate the stiffness of the liver tissue and thus finds out the extension of the liver damage and correctly identifies the stage of fibrosis.

The liver tissue responds to any kind of damage by depositing fibrous tissue and the end results are Liver Cirrhosis and Portal Hypertension, and Hepatic Insufficiency and Hepato-cellular Carcinoma.

Until recently it was the invasive procedure of liver biopsy

that was used to do the staging of liver fibrosis.

Now with the advent of Liver Elastography, we can non-invasively stage the liver cirrhosis and can detect the severity of the underlying chronic liver disease and also assess the disease outcome and evaluate the response to therapy.

MODES OF LIVER ELASTOGRAPHY

TE - Transient Elastography or Fibroscan – uses a mechanical wave generated by a special transducer.

ARFI – Acoustic Radiation Force Impulse Imaging

SWE – Shear Wave Elastography or Supersonic Imaging – uses sound waves.

Other newer modalities are also being developed, but TE and ARFI and SWE are the techniques currently in use.

Ultrasound Procedure

Now with the newer advanced ultrasound machines, Liver Elastography is a totally painless and non-invasive procedure and takes only 10 -15 minutes to perform the scan. Ideally 2 – 4 hours of fasting is required prior to the scanning, and after the procedure, which is purely an OPD procedure, the patient can immediately leave the scanning department and do all his normal activities.

Interpretation of the scans have to be done by an experienced Radiologist who has super specialized in Ultrasound Scanning.

Measurement of Liver Stiffness:

The most commonly used units are Kilopascals (it is actually the measurement of Shear Stiffness) and measurement of the Shear wave speed – (Meter/second).

Normal measurement is less than 5.7 kPa (<1.37m/s)

Mild to Moderate Fibrosis is 5.7 kPa to 15 kPa (1.37m/s to 2.2 m/s)

Severe Fibrosis/Cirrhosis is more than 15 kPa (>2.2m/s)

Elastography techniques can be used to distinguish patient with no or minimal fibrosis (METAVIR STAGE F0 and F1) and differentiate them from those with severe fibrosis or cirrhosis (METAVIR STAGE F3 and F4) with no need to biopsy these groups.

As scar tissue accumulates, the liver loses some of its elasticity and becomes stiffer. Liver elastography involves the use of a surface ultrasound probe that delivers a low frequency pulse or shear wave to a small volume of liver tissue under the rib cage. The transmission of the sound wave is totally painless.

Indications for Liver Elastography

1. Non-alcoholic fatty liver disease.
2. Alcoholic liver disease
3. Non-alcoholic steatohepatitis
4. Chronic Hepatitis B and C
5. Cirrhosis
6. Unspecified Thrombocytopenia
7. Biliary disease (Primary Biliary Cirrhosis & Primary Sclerosing Cholangitis)
8. Persistent Unexplained Abnormal LFTs.

Advantages:

1. Absolutely painless and non-invasive
2. Relatively inexpensive
3. Available easily
4. Both Quantitative and Qualitative assessment of the liver is possible.
5. Long Term follow-up is possible

Conclusion:

Detection of significant liver fibrosis and cirrhosis is important for diagnosing, determining the treatment, prognosis and follow up of chronic liver disease.

Ultrasound Liver Elastography techniques have developed into accurate methods for quantitative non-invasive diagnosis of liver fibrosis.

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IN MANY POOR COUNTRIES, OLDER SURGEONS RESIST BEING QUESTIONED, AND OPERATIONS ARE MORE OFTEN EMERGENCIES, WHICH LEAVES LESS TIME TO REVIEW CHECKLISTS.



As researchers learn more about how exercise fights chronic ills like heart disease and diabetes, doctors may soon be able to treat physical activity as the powerful medicine it is

THE WORKOUT DRUG



Exercise is good for you. That's hardly news: People who exercise tend to have longer, healthier lives. But until recently, researchers have tallied its benefits only in narrow slices: Exercise lowers your cholesterol and blood pressure; it keeps you from getting fat. Now it's becoming clear that those known slices don't add up to the full pie.

"When people totaled up those effects, they only account for about half the benefit," says Michael Joyner, an exercise physiologist at the Mayo Clinic in Rochester, Minnesota. "So what's contributing to the biomedical dark matter?"

To solve that mystery, researchers are now digging deeper into the mechanisms that underlie the benefits of physical activity. They are finding that exercise is both powerful and wide-reaching, affecting not just muscles and the cardiovascular system, but almost every part of the body, from the immune system to the brain to the energy systems within individual cells. And as scientists understand more precisely which levers exercise pulls to improve our health, clinicians are on the verge of being able to change their practice. The goal is to think of exercise as a medicine — a therapy that they can prescribe in specific doses for specific needs.

"It's like your own personal regenerative medicine," says Joyner.

Brain gains

Scientists have long known that some of the benefits of exercise are a simple matter of plumbing. Exercise makes blood vessels bigger and keeps them functioning smoothly, which makes them less likely to plug up and cause a heart attack or stroke. There have been hints that this may also mean more blood flow to the brain, which could help prevent cognitive decline. For example, studies have linked exercise to a reduced risk of Alzheimer's.

Now researchers are making a more explicit connection between exercise and brain health. They are discovering that the full benefit of exercise comes not from mere physical movement but from actual physical fitness, the body's cardiovascular health. A long-term study of Norwegian military recruits, for example, found that their aerobic fitness at age 18 was highly predictive of their risk of dementia in old age. And Swedish women who were highly fit in middle age had an eight times lower risk of dementia over the next 44 years than women of only

moderate fitness, researchers reported in 2018 in *Neurology*.

Another recent study, led by K. Sreekumaran Nair, an endocrinologist at the Mayo Clinic, found that after just 12 weeks of a high-intensity exercise regimen, participants' brains showed increased glucose uptake and higher metabolic activity, particularly in regions that usually show decline in Alzheimer's disease. High-intensity exercise was found to have a similar effect on the parts of the brain most affected by Parkinson's disease, in research led by Marcos Bamman, an exercise physiologist at the University of Alabama at Birmingham.

Benefits of brawn

Exercise doesn't just build bigger blood vessels; it also builds bigger muscles. That benefits health in a number of ways, from minimizing the risk of diabetes to enhancing the body's immune response to ills such as cancer.

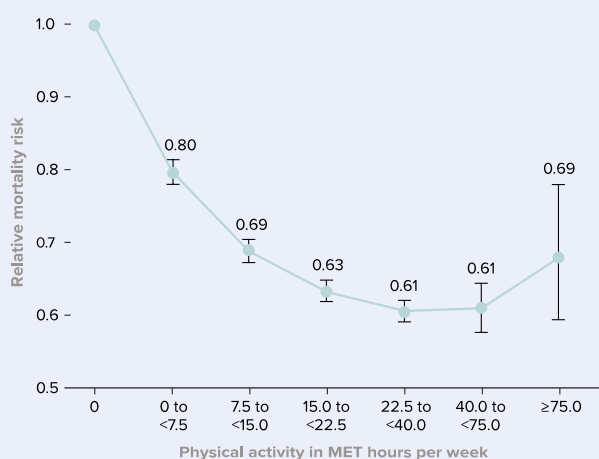
Muscle is the largest consumer of all the glucose that floods into the bloodstream after a meal. More muscle means quicker removal of this glucose surge, says Bamman — and therefore, less exposure to the harm caused by elevated blood sugar, a serious health issue for people prone to diabetes.

The muscle-building aspects of exercise also help reverse a key change associated with aging: a decline in the function of mitochondria, our cells' energy generators. This decline, often seen in sedentary individuals, can leave the mitochondria unable to completely burn the cellular fuel and that can lead cells to generate more oxidants, the oxygen-rich, reactive molecules that damage proteins and DNA.

Muscles are chock-full of mitochondria and exercise can help avoid this oxidative damage. Nair's studies show that aerobic exercise, alone or in combination with strength training, improves people's mitochondrial function, reduces the production of oxidants and forestalls oxidative damage. High-intensity aerobic exercise also encourages mitochondria to produce more of the proteins they use to burn fuel.

Muscle has another important role: Its abundant proteins serve as reservoirs of amino acids for the rest of the body. Usually, when other organ systems need amino acids, says Bamman, "those are drawn from muscle." That's especially important when someone is sick because the immune system needs lots of amino acids to make antibodies that fight infection.

A little makes a big difference



Source: American Medical Association 2015

Just getting the minimum recommended amount of exercise (7.5 metabolic equivalent (MET) hours per week) reduces mortality risk by 20 percent compared with no exercise at all. Exercising a little more than that minimum continues to reduce the risk, but such benefits taper off after about three times the recommended minimum. (MET is the ratio of a person's working metabolic rate relative to their resting metabolic rate, 1 MET is the rate of energy expenditure while at rest, walking at 3 to 4 miles-per-hour is considered to require 4 METs.)

The biggest benefit from building muscle, though, may come from the signaling molecules it pumps into the blood. Bente Klarlund Pedersen, an exercise physiologist at the University of Copenhagen, identified the most-studied of these signaling molecules back in 2000, and later coined a term for them: myokines. Since then, she and other researchers have found hundreds more, many of which are activated by exercise. These molecules, which are released in response to muscular exertion, help regulate muscle growth, nutrient metabolism, inflammation and a host of other processes. "I think for most people it's difficult to understand why muscle work can influence my liver or be good for my brain or bones," she says. Myokines serve as the link between muscle activity and these other organs.

One of the most important myokines in this crosstalk is interleukin-6. Released in response to muscular exertion, IL-6 has several effects, including suppressing hunger and enhancing the immune system's response to cancer. Another signaling molecule, cathepsin B, triggers beneficial changes in the brain, including the production of new brain cells. Other signaling molecules can help moderate depression.

Inflammation extirpation

Exercise, of course, also helps keep you thinner — and especially, it forestalls the accumulation of ab-

dominal fat, a particularly harmful sort. One reason abdominal fat is so bad for you is its partnership with inflammation. "If we take out visceral fat and study it in the lab, we see that visceral fat is more inflamed than subcutaneous fat," says Pedersen. "This inflammation will spill over into the blood, causing chronic systemic inflammation."

Chronic inflammation, Pedersen suggests in the 2019 Annual Review of Physiology, may be the underlying reason why inactivity contributes to so many different diseases. "We know that being physically inactive increases the risk of approximately 35 different diseases or disorders," she says. "And if you have one of these diseases — let's say you have type 2 diabetes — you have increased risk of others, like cancer or heart disease. If we tie it all together, one feature of all these diseases is physical inactivity, and the other is chronic inflammation."

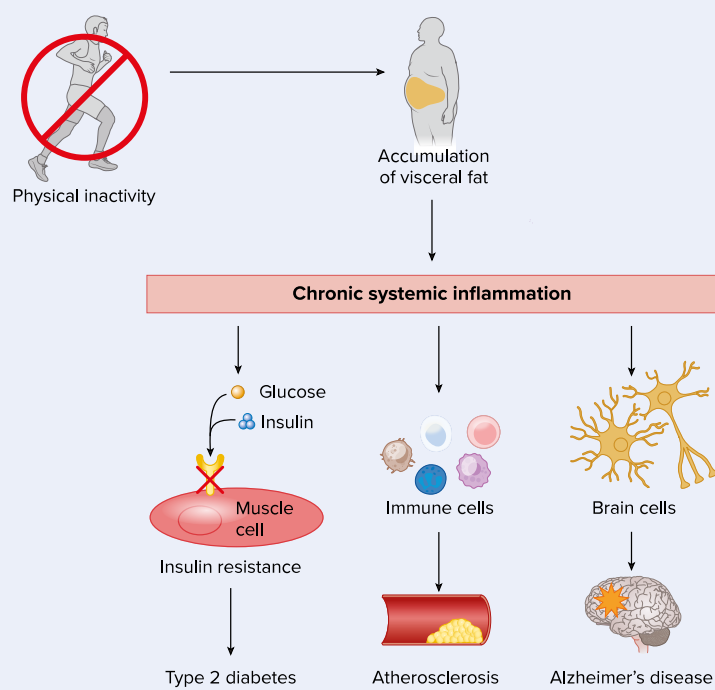
About a decade ago, Pedersen conducted an experiment in which she had healthy young men reduce their daily step count from about 10,000 steps per day to just 1,500. Within two weeks, the men showed a 7 percent increase in abdominal fat mass. Along with this change, the men showed hints of reduced insulin sensitivity, a change also seen in type 2 diabetes.

Interleukin-6 appears to be at the heart of exercise's effect on visceral fat and inflammation. In a recent experiment, Pedersen and her colleagues put 27 potbellied volunteers on a 12-week exercise-bike program, while 26 other volunteers remained inactive. Half the participants in each group also received a drug that blocks the action of IL-6. At the end of the 12 weeks, the exercisers had lost abdominal fat, as expected — but only if they had not received the IL-6 blocker. (Oddly, IL-6 is generally thought of as a pro-inflammatory molecule, because it is more abundant in obese people with systemic inflammation. But Pedersen has some evidence that in these people, elevated IL-6 is an effect, not a cause, of the inflammation.)

Rx for movement

As researchers tease out more of the details about how physical activity benefits health, the moment is fast approaching when exercise becomes not merely "a good thing to do," but a medicine in its own right, just like pharmaceutical drugs. Several studies already point in this direction. For example, more than half of 64 adults with type 2 diabetes were able to stop taking medication to lower their blood sugar within a year of beginning a regular exercise program, Pedersen and her team found. And a survey of more

Abdominal fat's insidious effects



Even a few weeks of inactivity can cause fat to accumulate in the abdomen, which spurs chronic inflammation throughout the body. This inflammation contributes to a range of ailments, including type 2 diabetes, cardiovascular disease and Alzheimer's disease.

Source: Adapted from B.K. pedersen / AR physiology 2018

than 300 randomized controlled trials found that exercise was just as effective as drugs for people at risk of heart disease and diabetes, and was more effective than drugs for rehab after a stroke.

But if exercise is to truly become a medicine like any other, clinicians will need to learn how much to prescribe to maximize its benefits. “Just saying ‘be physically active’ is like telling people ‘eat better’ — it doesn’t tell us what we should be doing,” says Kirk Erickson, an exercise psychologist at the University of Pittsburgh. But developing more precise dosing recommendations is difficult, because there are so many ways to exercise, which vary in duration, intensity, frequency and kind. (Tailoring to individual disease risks — telling one person to do X because they’re at risk of diabetes, and another person to do Y because of a family history of dementia — is an even more distant goal.)

Researchers are still working out what matters in this complex arena. Exercises that involve more muscle groups generate more IL-6, so full-body exercises like running have a greater anti-inflammatory effect than exercises that target just a few muscle groups, says Pedersen. And the benefits go away within a couple of days, suggesting that exercising frequently is important. “If it’s been 48 hours since you exercised, it’s time to do it again,” says Jill Barnes, an exercise physiologist at the University of Wisconsin–Madison.

A series of upcoming randomized trials may soon bring more certainty to the dosing question. One of the largest, which Bamman is involved with at the University of Alabama, will have nearly 2,000 volunteers undertaking either 12 weeks of endurance exercise, 12 weeks of weight training or no exercise program. Researchers will measure gene activity, molecular signaling and other changes within the body, which could allow them to pin down exactly how these two modes of exercise differ in effect. Because the study is so large, researchers should also be able to explore why some people respond more strongly than others to the same dose of exercise.

Another large study that Bamman is participating in, funded by the US Department of Defense, aims to compare genes activated by moderate exercise to those activated by high-intensity exercise in young, healthy volunteers.

Erickson is trying to parse the specifics with a study that will assess the effect of exercise volume

on brain aging. Researchers will measure inflammation, signaling molecules, body composition and other markers, as well as mental acuity, on more than 600 volunteers ages 65 to 80, both before and after a year of exercise. Some of the volunteers will do 150 minutes per week of supervised moderate exercise, others will do 225 minutes per week, while a third group will do light stretching instead.

Of course, even after the results of these and other forthcoming trials are in, the “right” amount of exercise for a particular person is likely to depend on their individual circumstances. “For someone with diabetes who wants to improve blood-sugar control, even 10 minutes is probably great,” says Barnes. “But for cardiovascular risk or brain health, that may be different.”

Bamman agrees. “There’s not a single organ system in the body that isn’t affected by exercise,” he says. “Part of the reason the effect of exercise is so consistent and so robust is that there isn’t a single molecular pathway — it’s going to be a combination of all these things. So at the end of all these trials, we’re going to look back and list off not just one or two mechanisms, but a number of them. It’s going to be a complicated answer in the end.”

Where Surgeons Don't Bother with Checklists



Gordon Yuill/Lifebox

IN MANY POOR COUNTRIES, OLDER SURGEONS RESIST BEING QUESTIONED, AND OPERATIONS ARE MORE OFTEN EMERGENCIES, WHICH LEAVES LESS TIME TO REVIEW CHECKLISTS.



Ten years ago, checklists for surgeons were all the rage. Inspired by the preflight routines of airline pilots, surgical checklists were shown to prevent tragic errors, reduce infections and save lives. Dr Atul Gawande, a Harvard-trained surgeon, championed them in *The New Yorker* and wrote a book about them, “*The Checklist Manifesto: How to Get Things Right.*”

A two-minute, 19-item checklist was eventually endorsed by the World Health Organization, which advocated its use by every hospital in the world. The checklist is even available as a cell-phone app from the United Nations Institute for Training and Research.

It includes many simple steps for surgeons who are preparing to operate, some as basic as ascertaining that the right patient is on the table and the incision site correctly marked, and that anesthetics, oxygen and transfusion blood are on hand.

Now that a decade has passed since the W.H.O.’s recommendation, a nonprofit founded by Dr Gawande has surveyed almost 1,500 hospitals in 94 countries to see how often a surgical checklist is used.

Adoption has been spotty, according to the report released on Wednesday by the nonprofit, Lifebox, and by Ariadne Labs, a joint venture of the Harvard T.H. Chan School of Public Health and Brigham and Women’s Hospital, both in Boston. (Both institutions seek to improve surgery and anesthesia in poor and middle-income countries.)

In wealthy countries, a list is used in 90 percent of surgeries, the report found. But in poor countries, a checklist is used only about a third of the time.

The study blamed many factors: surgeons who resent the implication that they may make dangerous mistakes, lax enforcement by hospital administrators and the powerlessness of nurses in some cultures.

In poor countries, most surgeries are emergencies, such as cesarean sections, appendectomies or trauma repair after a car crash. Rushed surgical teams are less likely to use a checklist.

In poor countries, there are often failures in support systems intended to ensure the availability of oxygen, blood transfusions and postoperative antibiotics, and sometimes even just clean operating rooms.

When checklists are strictly adhered to, missing even one of those elements can prevent the operation from beginning. Instead, some hospitals just avoid the checklist.

There is enormous room for improvement, the study found.

For example, up to 95 percent of Africa’s population does not have access to safe and affordable surgery, and African patients are twice as likely to die after an operation, compared with the global average, said Dr Bruce M. Bickard, an anesthesiologist at the University of Cape Town and a leader of the African Surgical Outcomes Study, which produced some of the data used in the new report.

In countries where doctors and nurses do not speak one of the six official languages of the United Nations — Arabic, Chinese, English, French, Russian or Spanish — a checklist is less likely to be used. Also, cultural barriers have hindered its adoption.

The checklist includes requirements that doctors and nurses introduce themselves and confirm that all have the same understanding of how the operation will ideally proceed. But teamwork can be difficult to introduce, both in traditional cultures based on hierarchy and obedience and in intensely competitive environments like those in American medical schools.

Even hospitals that faithfully used a checklist often adapted it to local circumstances, the report found. Some translated it into Tagalog and Amharic, for example. A West African surgi-



Outside influences can be powerful, the report noted. It singled out the charity Mercy Ships as instrumental in introducing the checklist to Africa.

cal team added a requirement that the hospital's generator be working. A Guatemalan team added pain-control medication to the list of requirements.

A decade ago, as a young surgeon in Ethiopia, Dr Abebe Bekele, the dean of the University of Global Health Equity in Rwanda, tried to introduce the checklist to the hospital where he worked in Addis Ababa, after seeing it when he trained in Seattle.

"No one else was on board," Dr Bekele, who was a consultant on the Lifebox report, said in a telephone interview. His own team used it when he insisted, but

not when working with other surgeons, who were usually much older than their nursing staffs.

"I had the momentum but not the wisdom on how to implement it," he said.

Two years later, however, after studies showed the checklist reduced deaths by 24 percent and major complications by 60 percent, he had more success "by bringing everyone into a single room to discuss and write down the checklist."

Since then, younger surgeons have become more receptive, Dr Bekele said, and now the checklist is taught in the rapidly expanding medical schools in Ethiopia.

Outside influences can be powerful, the report noted. It singled out the charity Mercy Ships as instrumental in introducing the checklist to Africa. Mercy Ships has a hospital ship that docks for months in various port cities in Africa, performing thousands of surgeries.

At each port of call, it also trains dozens of local medical practitioners.

When the Africa Mercy was docked in Cotonou, Benin, from 2016 to 2017, for example, it sent teams to 36 hospitals to lead workshops in using a surgical checklist.

Before the training, only about 30 percent of surgeries performed incorporated checklists. Afterward, nearly 90 percent did — and compliance was still at 86 percent during follow-up visits a year later.

Case Reports

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Anatomical and physiological differences between pediatric and adults require special attention when imaging pediatric patients. Before performing a pediatric CT examination, it is essential to fully evaluate the risks radiation dose and benefits of the requested examination.

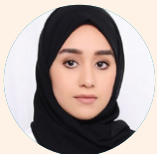
Ultra-Low Dose Free-Breathing Pediatric CT Imaging

Technologies has developed and would continue to develop innovations that follows the ALARA principles. Here we are showcasing some novel clinical examples that achieved the dose as low as possible.

Badriya Mohammed Hassan & Hashim Al-Awadhi

Dubai Hospital, United Arab Emirates

Medical Imaging Team



Badriya Mohammed Hassan
Senior Principal Radiographer
CT - Team Leader
Dubai Hospital, UAE



Hashim Al-Awadhi
Consultant, Radiographer
Dubai Hospital, UAE

INTRODUCTION

Anatomical and physiological differences between pediatric and adults require special attention when imaging pediatric patients. Before performing a pediatric CT examination, it is essential to fully evaluate the risks of the radiation dose and benefits of the requested examination. Systematic efforts can be used to drive process and quality improvement in terms of optimizing CT radiation dose while maintaining image utility. The other challenge was the imaging without sedation and breath hold. Image quality is a key factor because of these images are routinely used for clinical evaluation as well as preoperative surgical planning. Technologies has developed and will continue to develop innovations that follow the ALARA "As Low as Reasonably Achievable" principle.

PROSPECTIVE

Technologies has developed and would continue to develop innovations that follows the ALARA principles. Here we are showcasing some novel clinical examples that achieved the dose as low as possible while using the technologies like care dose 4d and care kv, turbo flash, sub second rotation and ADMIRE iterative recon algorithm.

PEDIATRIC CASE STUDY #1

DLP: 4 mGy x cm. Achieved effective dose level of 0.12 msv

History – 7-month-old male infant presented for follow up study of invasive fungal infection treated with 6 weeks of antifungals

Examination Protocol - • 70 kV • 10 mAs/rot • Dedicated single acquisition

ultra-fast pediatric protocol for chest, abdomen and pelvis • CARE Dose4D and CARE KV • DLP: 4 mGy x cm. Achieved effective dose level of 0.12mSv (Conversion Factor abdo pelvis $k=0.030$) with superior image quality.

Diagnosis - Follow up CT imaging depict the appreciable therapeutic response. Resolution of the previously seen right para tracheal and retro caval lymph nodes. The mid bilateral basal pleural effusion and basal atelectatic bands are no longer visible in the current study. The liver is still seen mildly enlarged with resolution of the previously seen enhancing hepatic focal lesion showing residual hypodensity.

PEDIATRIC CASE STUDY #2

DLP: 8 mGy x cm. Achieved effective dose level of 0.2mSv

History – 9-month-old female child presented for CT scan chest with right upper zone haziness a query of mediastinal mass. Suspecting hepatoblastoma and further evaluation of staging.

Examination Protocol – • 70 kV • 18 mAs/rot • Dedicated single acquisition ultra-fast pediatric protocol for chest two phase (P+C) • CARE Dose4D and CARE KV • DLP: 8 mGy x cm. Achieved effective dose level of 0.20 mSv (Conversion Factor chest 1 year $k=0.026$) superior image quality.

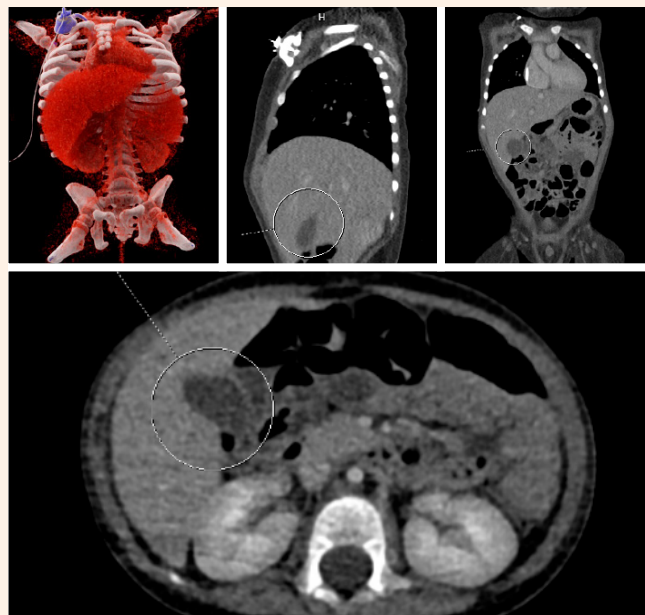
Diagnosis – CT evidence last heterogeneously enhancing mass like lesion involving the upper and lower lobes of right lung. The lesion shows air bronchogram and multiple low attenuation areas. The features most likely represent infective etiology (necrotizing pneumonia)

PEDIATRIC CASE STUDY #3

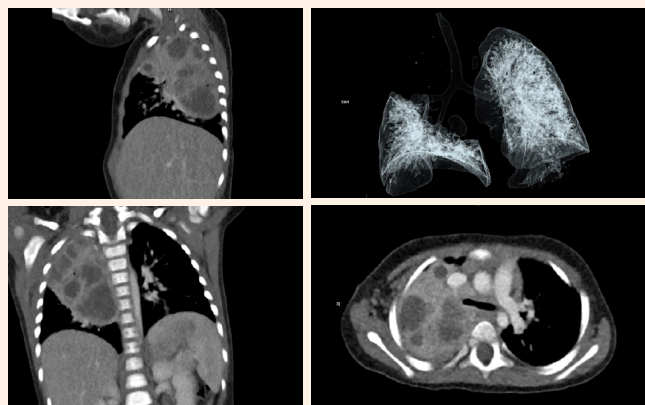
DLP: 15 mGy x cm. Achieved effective dose level of 0.73 mSv

History – 6-month-old boy presented for CT scan chest and abdomen with a query of pulmonary nodule and hepatic mass. Suspecting hepatoblastoma and further evaluation of staging.

Examination Protocol – • 70 kV • 24 mAs/rot • Dedicated single acquisition ultra-fast pediatric protocol for chest and abdomen • CARE Dose4D and CARE KV • DLP: 15 mGy x cm. Achieved effective dose level of 0.73 mSv (Conversion Factor abdo pelvis 0-year $k=0.049$) superior image quality.

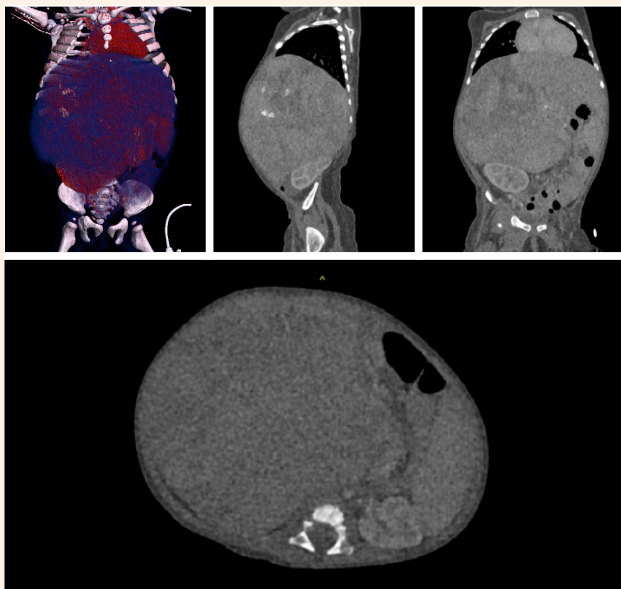


MPR image with VRT clearly delineating hepatic focal lesion showing residual hypodensity

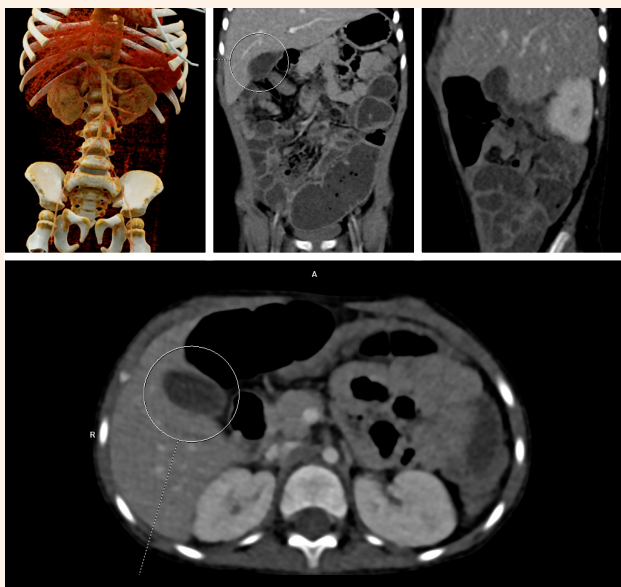


MPR image with VRT clearly delineating heterogeneously enhancing mass like lesion involving the upper and lower lobes of right lung

Diagnosis – Both the lung field appears to be normal and no evidence of sizable pulmonary nodule large hepatic infiltrative neoplastic mass lesion. Likely hepatoblastoma.



MPR image with VRT clearly delineating heterogeneously enhancing mass like lesion involving the upper and lower lobes of right lung



MPR image with VRT clearly delineating the large hepatic infiltrative neoplastic mass lesion

PEDIATRIC CASE STUDY #4

DLP: 19 mGy x cm. Achieved effective dose level of 0.38 msv

History – 5-year-old boy presented for CT scan Follow up study of Burkitt's lymphoma post chemo

Examination Protocol – 70 kV • 30 mAs/rot • Dedicated single acquisition ultra-fast pediatric protocol for chest two phase (P+C) • CARE Dose4D

and CARE KV • DLP: 19 mGy x cm. Achieved effective dose level of 0.38 msv (Conversion Factor abdo pelvis 5-year k=0.020) with superior image quality.

Diagnosis – Post CT Compared images are evidence of B cell lymphoma showing residual short segmental small bowel mural thickening with significant proximal small bowel dilation. mild hepatomegaly and sub centimetric mesenteric lymph nodes are visible.

CONCLUSION

Adapting new CT technologies opens doors to a decisive factor in critical emergency situations and complex pediatric imaging. It helps us to perform CT studies without the need for breath-hold with high-quality diagnostic imaging. This is the case for trauma patients as well as for very young or elderly patients who are unable to hold their breath either at all or for longer periods of time. Here, fast scans eliminate the potential need for sedation or intubation, and thereby save additional costs. For those patients who still require an anesthetic, fast scans also reduce the associated risks. Somatom force CT scan can scan the entire thorax in sub seconds, and it can scan the thorax, abdomen, and pelvis in 1 second in high-pitch mode. This leads to significantly reduced motion artifacts.

Pediatric imaging presents specific challenges that range from reducing X-ray doses to creating an anxiety-free environment during imaging procedures. Innovative concepts and new technologies can help address all these challenges.

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Case Report

Looks Can Deceive: An Interesting Case of Furuncular Myiasis

Furuncular myiasis should be considered in a patient who has traveled recently to a botfly-endemic area and who has a furuncular lesion.

Dr Aishani Shah

Department of Dermatology, Aster Clinic, Al Nahda, Dubai.

A 31-year-old male, presented to the out patient department with a 2 week history of a gradually enlarging painful boil on right arm. He gave a history of occasional serosanguinous discharge from the lesion. He was systemically well, and had no recollection of an insect bite. He had no history of any topical or systemic treatment. He gave history of recent travel to Africa.

Examination revealed a 2.5cm furuncle (fig 1A & B) with a central pore. When the lesion was manipulated to extract the discharge/pus to send for further examination, a whitish soft tube like projection was seen extending through the central pore. On close examination it seemed like a breathing tube and body of an insect larva.

The protruding larva was grasped immediately with forceps and

completely extracted with gentle, continuous tension together with manual pressure exerted on the sides of the nodule. Complete extraction of the larva was possible (fig 2 A & B).

The area was cleaned, and the patient was started on oral antibiotics to prevent any secondary bacterial infection. Oral as well as topical ivermectin was also given along with the antibiotics.

We referred the patient for an ultrasound examination to rule out possibility of multiple larvae. The examination did not reveal any further larvae. Myiasis is the infestation of human tissue by fly larvae. Forms of infestation include wound myiasis, furuncular myiasis, plaque myiasis, creeping dermal myiasis, and body cavity myiasis.¹

The human botfly, *Dermatobia hominis*, is a common cause of furuncular myiasis in the neotropical regions of the New World. The female glues its eggs to the body of a mosquito, stablefly, or tick. When the unwitting vector punctures the skin by biting, the larva emerges from the egg and enters the skin through the puncture wound. Over several days, a painful furuncle develops in which the larva is present.²

Removal of the maggots of furuncular myiasis can be accomplished by injection of a local anesthetic into the skin, which causes the larva to bulge outward. The opening of the furuncle can also be occluded with hair gel, surgical lubricant, lard, petrolatum, or bacon, causing the larva to migrate outward.² Removal of the intact larva is curative, although infestation may be complicated by secondary bacterial infection.³

A close examination of all furuncular lesions is a must so that the diagnosis is not missed. Furuncular myiasis should be considered in a patient who has traveled recently to a botfly-endemic area and who has a furuncular lesion. The furuncle has a central pore that intermittently exudes a serosanguinous discharge (the feces of the larva), and protrusion of the breathing tube of the larva frequently can be observed with the aid of a hand lens.⁴

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Figure 1 A

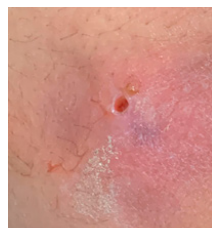


Figure 1 B



Figure 2 B



Figure 2 A

A High-risk Ambulance Transfer and Management of a Critically-ill Patient with Severe Acute Pancreatitis in Oman

This case report is regarding a young gentleman whom we transferred to our center from a Ministry hospital located 150kms away, a while ago; who was critically ill and was on mechanical ventilation, with unstable haemodynamics owing to severe necrotizing pancreatitis.

Dr Ashik Sainu Mohiyadeen - Sr Consultant Gastroenterologist.

Dr Dilip Abdul Khadar - Specialist physician (Intensivist).

Aster Al Raffah Hospital, Muscat, Oman.

Mr. H, a 30 year old gentleman had complaints of severe abdominal pain and was admitted to Ministry Hospital, Nizwa. He was admitted at MOH there with Severe acute pancreatitis and was subsequently intubated and mechanically ventilated since the day of admission due to haemodynamic instability, MODS. He was managed there on ventilator for a whole week.

He was found to have severe hypertriglyceridemia. He was also an alcoholic. His CT done there has features of severe necrotizing pancreatitis.

Our Gastroenterology team was approached by his family to take over the case since he was deteriorating and after deciding to take over the case our Aster hospital team went to undertake this high risk in ambulance

to Aster Al Raffah Hospital, Muscat for further care.

On arrival at the hospital of transfer, the ICU patient was on ventilator SIMV mode, sedated with Midazolam, Fentanyl and Propofol. On high dose Iontrope support with Dopamine at 15 mcg/kg bodywt/min on flow, barely maintaining a systolic BP of 90/50, tachycardic with a heart rate of over 140/min.

His output was maintained with 40mg IV BD Furosemide. He had a central venous catheter (right internal jugular vein) in place (Day 8), on ventilator (Day 8) with paralytic ileus, with hugely dilated abdomen, with pancreatic ascites not tolerating RT feeds, no bowel sounds, started on Day 1 of TPN, empirically initiated on Carbapenem (Day 8) and IV Fluconazole (Day 1) in Moderate ARDS (PaO₂/Fio₂) -114, able to ventilate. Blood culture results- awaited.

He was thus assessed by our Critical Care Physician and found to be a deteriorating patient. He was jaundiced and diagnosed as severe acute pancreatitis in shock possibly due to Infected abdomen, diaphoretic, spiking high grade fever with Paralytic Ileus, in Moderate ARDS, SIRS. A hemodynamically compromised patient with circulatory collapse due to MODS and in respiratory distress on ventilator, able to ventilate and attain adequate saturation. His last done ABG there had a PH- 7.45, PO₂- 80.5, PCO₂- 43.5, HCO₃- 29.6 with a lactate of 2.5 and Fio₂ of 70% O₂. He had skin peeling on sacral region and scrotal skin peeling while receiving the case.

Accepting this challenge, the team took over after getting handover from the team in care there. After signing in the register that transfer is done at own risk of the Intensivist they were willing to permit transfer. There was

a general sarcasm all round by the staff on duty regarding the transfer to such an extent, that one nursing staff uttered openly that she would refuse the transfer if she was in the receiving team's shoes as it had a high chance of spiralling down.

The ambulance transfer was initiated at 11:00pm by our team. The team consisted of the Intensivist, OT technician, Male nurse and a ER attender. It was for the first time such a transfer was attempted. It took 1 hour 15 minutes at night for the transfer and it was a adrenaline high experience for the entire team as the risks and consequences involved in such a transfer in a foreign country is huge if things go wrong. Giving no room for errors, after multiple checks and paralyzing the patient on ventilator with Rocuronium, sedation on flow, with an FiO₂ of 100%. Dopamine infusion continued on flow at 15 mcg/kg bodywt/min the journey began and the transport went smooth and was uneventful except few runs of Dopamine induced tachyarrhythmia. Since it was night there were no road blocks at signals and it was a straight nonstop run by road to our ICU at Aster Al Raffah Hospital, Muscat.

After receiving at our ICU at 12.30am a new central venous catheter (right sub clavian vein) was immediately secured. CVP was transduced which was 14. Blood cultures were send from peripheral line and the old central line after which it was immediately removed being Day 8 and continued on Dopamine at 10mg/kg bodywt/min maintaining an ideal MAP. A femoral arterial line was secured for invasive hemodynamic monitoring. PETCO₂ was 45. His foleys catheter was Day 8 and was changed into silicon catheter and urine routine and cultures were send.

He was toxic, diaphoretic and was spiking fever of 38 C. Meropenem was

continued. Metronidazole was initiated alongside considering pancreatic penetration. Fluconazole and TPN was stopped. He was sedated well and continued on volume-controlled mode of ventilation with a tidal volume of 400 and a PEEP of 10, with Fio₂ of 70% and a RR of 20/min maintaining a plateau pressure of 22 well below 30 cmH₂O thereby optimizing ventilation.

ABG was repeated which had a similar picture as last one with metabolic alkalosis possibly due to diuretic given earlier. SCVO₂ was done from CVC which was 71.5% and fluid was optimised. Blood panel was repeated. He was kept NPO until next day. He was suspected to have abdominal compartment syndrome.

On the next day he was reassessed in detail by our gastro team. His WBC was 31.5×10^9 , CRP-301 mg/L, LFT- Total Bilirubin- 55.4 umol/l and Direct bilirubin- 40.3 umol/l, Hb- was 8.1 g/dL. LDH was elevated 729.71 U/L, Peripheral smear was normal. Other parameters including coagulation profile, PLT count, RFT, serum electrolytes were normal. Ionotrope was changed from Dopamine and a MAP of 65mm Hg was attained using Noradrenaline infusion at 0.3mcg/kg bodywt/min with which his tachycardia settled and better BP control was attained. He continued to be toxic with high grade fever and diaphoresis. His chest X-ray had features suggestive of left pleural effusion. Urine routine had plenty of bacteria and pus cells for which urine culture was sent and awaited. His screening swabs for MRSA were negative. His Lipase level was 135.6 U/L.

He was initiated on Movicol sachet and Dulcholax suppository and he started passing stool and flatus. RT feeds were started at 30cc/hr and slowly uptitrated with IV prokinetics. He tolerated RT feeds. Potassium was

always maintained above 4.0 mmol/l. He was initiated on aggressive chest and limb physio. He was started on DVT prophylaxis using mechanical prophylaxis and LMWH. Bedside ultrasound-guided therapeutic paracentesis was done, draining about 1.2 litre from both drains and was send for routine labs and cultures which showed a TC of 980 hence diagnosing Spontaneous Bacterial Peritonitis. Our cardiologist did a bed side echo and his LV function was found to be normal.

He was adequately fluid resuscitated with CVP guidance and serial SCVO₂ every day.

Input and Output were optimised. He was transfused one packed red blood cell and Hb was optimised. His urine culture had Staph Haemolyticus and antibiotics were optimised according to sensitivity pattern. His Blood cultures didn't yield any growth. His CRPs continued to be elevated. He underwent one more USG guided paracentesis for the distended abdomen. His LFT values started coming down and his jaundice regressed. His repeat LFT showed a total bilirubin of 32.4 umol/l and direct bilirubin of 24.4 umol/l. His albumin was low (27.4g/L) and was started on albumin as replacement and for volume expansion and continued for 5 days.

He was shifted for CT the next day which showed evidence of necrotic pancreatitis with pancreatic ascites. He had abdominal distention and significant abdominal ascites despite multiple attempts at paracentesis.

That evening under aseptic precaution and USG guidance two pig tail drains were inserted were inserted and peri pancreatic collection and ascitic collection were drained by our Interventional Radiologist bedside. Ascitic fluid was again send for routine and cultures. The total

counts came as 3550 & 1250 for peri pancreatic drain and ascitic drain. An add-on agent Levofloxacin 750 mg IV was added. Cultures and gram stain did not yield any growth. He was continued on Meropenem. The pig tail catheters drained about 750ml from peri pancreatic drain and 550ml from ascitic drain on first day.

He continued to be in sepsis-induced encephalopathy. His repeat labs showed total counts have a downward trend to 14.1×10^9 , LFT has normalized but CRP continued to be 298 mg/L. With time and taking one day at time he started haemodynamically stabilizing and after a week of stay at our hospital the ionotropes were tapered, stopped and arterial was removed.

By now sedation breaks were given and he was initiated in SIMV/VC mode of ventilation. He continued to have high grade fever with diaphoresis. Surveillance cultures were repeated for bacteria and fungus. The drains were regularly draining. The abdominal distension was significantly reduced.

His sensorium improved and he was initiated on weaning. Post multiple drainage his abdominal distension decreased. He tolerated CPAP, T piece trail and was extubated on the 9th day at our hospital. The ET tube tip and non-bronchial lavage was sent for culture. Post extubation he was agitated and pulled out the central venous catheter. A left-sided subclavian line was secured subsequently.

He tolerated extubation for 6 hours and then became tachypneic, developed desaturation despite adequate pain control. He was reintubated and mechanically ventilated again in volume control. His PaO₂/FiO₂ was 154. Xray had B/L infiltrates. In view of his ascites, abdominal pain and drains he was not an ideal candidate

for proning. The family was not in favour of tracheostomy.

He was tolerating RT feeds well by now. He was empirically started on Fluconazole. His Xrays started clearing and haemodynamics stabilised. His sensorium improved. He was transfused one more packed cell. Hb was 9.2. His ET tip culture and Non BAL grew MDR Klebsiella and Stenotrophomonas maltophilia sensitive to Fluroquinolones. By then his total counts were 15.7×10^9 , CRP has reduced to 47.35mg/L, Chest Xray cleared, and secretions were minimal, with less bouts of fever - so was continued on same antibiotics. His sensorium totally improved. The earlier send fungal culture reports came as negative for 7 days growth-first interim report. A negative balance was attained for next few days.

He was attempted to wean once more after 2 week ventilator stay at our hospital (3 weeks in total) with the plan if weaning failure to come out with a tracheostomy on the same day, after convincing the family with great difficulty and obtaining consent for the same. He tolerated CPAP, 2 hours t-piece trail and was finally extubated and tolerated extubation well. He was active and alert.

His potassium was low in the subsequent days so correction was given along with magnesium and was optimised. He was extubated and was managed with nasojejunal feeds and hydration. His silicon catheter was removed.

MRI done subsequently showed acute pancreatitis with necrosis, moderate loculated inflammatory ascites, bi basal atelectasis with mild left pleural effusion.

His central line was removed after MRI after establishing a peripheral line. Two sets of surveillance cultures were repeated again, one from central

line prior to removing and one from peripheral line which did not yield any growth. He was shifted out of the ICU.

He improved clinically and symptomatically then onwards. His bed sores have by now healed well. His antibiotics Metronidazole was discontinued on Day 12, Levoflox after 10 days. Meropenem to be continued till discharge in view of SBP/ Sepsis. Fluconazole discontinued after a week.

He was initiated on peripheral TPN for 4 days after for improving nutritional status along with oral feeds. His repeat albumin was 34.2 g/L.

The drain continued to have high output of around 500 ml from both drains, which persisted despite the nasojejunal feeds. So, he was initiated on Inj. Octreotide as infusion and over a period of time the drain settled down and both pigtail catheters were removed and he was fed orally with recurrence of collection seen.

An MRCP did not reveal any disconnect of the ducts and hence an ERCP was deferred. He was advised that he would require an endoscopic ultrasound and possibly an ERCP if the pancreatic ascites as well as peripancreatic collection persists.

Pancreatitis is a multi-system disease especially a case such as this which had almost all complications of severe pancreatitis. In management of pancreatitis the first few days are extremely critical especially with regards to fluid resuscitation and interventions. This patient had abdominal compartment syndrome which was very effectively managed with pigtail drainage enabling effective ventilation and hydration. He was subsequently discharged after 4 weeks of stay. This case could not have been managed without the excellent teamwork and communication across all the subspecialties concerned.

Case Report

A Case Report on Pulmonary Tuberculosis with Penicillium Co-Infection in a Patient Without HIV Infection

A case report of coinfection with *Penicillium marneffe* and *Mycobacterium tuberculosis* in a 29 year old male patient who was diagnosed with Immune Thrombocytopenic Purpura and received oral Prednisolone since 6 months.

***Dr Anjaly K.C, Dr Jacob Baby¹, Dr Praveen Valsalan², Dr Elizabeth Sunila C.X³, Dr Michelle Lolly⁴, Dr Nabil Ahamed⁵**

Department of Pulmonology, Aster Medcity, Kochi, Kerala

Conflicts of Interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding Authors

¹Dr Jacob Baby, HOD and Lead Consultant, Department of Pulmonary Medicine

²Dr Praveen Valsalan, Consultant Pulmonologist

³Dr Elizabeth Sunila C.X, Consultant Pulmonologist

⁴ Dr Michelle Lolly, Senior Specialist, Department of Pulmonology

⁵ Dr Nabil Ahamed, Specialist, Department of pulmonology

Keywords:

Penicillium marneffe, *Mycobacterium tuberculosis*, immunocompromised host

* 2nd year DNB-PG registrar

ABSTRACT:

A case report of coinfection with *Penicillium marneffe* and *Mycobacterium tuberculosis* in a 29-year-old male patient who was diagnosed with Immune Thrombocytopenic Purpura and received oral Prednisolone since 6 months. Patient was successfully treated with Inj Amphotericin B and oral Itraconazole and completed concomitant anti-tuberculous therapy. To the best of our knowledge this is the first case of *Penicillium marneffe* and *Mycobacterium tuberculosis* co infection reported in a HIV negative host. The current case report highlights the importance of clinician awareness of concurrent infections with *Penicillium* and other pathogens in immunocompromised patients.

INTRODUCTION:

T. marneffe, a temperature-dependent dimorphic fungus previously known as *Penicillium marneffe*, is an important pathogen of HIV-associated opportunistic infection in endemic areas. It was first isolated from liver of the bamboo rat (*Rhizomys sinensis*) in 1956, and subsequently from an HIV-infected human in 1988. In endemic areas, which include Southeast Asia, Southern China, Hong Kong, north east India, and Taiwan, *T. marneffe* can cause fatal disseminated infection in immunocompromised hosts by inhalation of fungal conidia into the lungs.

Concomitant infection with *T. marneffe* and other opportunistic pathogens is plausible because the majority of cases of severe mycosis due to *T.marneffe* occur in patients with advanced HIV infection with CD4+ T cell count below 100 cells/microlitre. But in a non HIV patient *T. marneffe* infection is very rare with concomitant tuberculous infection. The diagnosis and treatment is challenging in the clinical setting. In the current case report, a concurrent infection with *T.marneffe* and *Mycobacterium tuberculosis*-isolated from bronchial

wash, in a young male patient who was HIV negative. A literature review was performed to provide new insight into treatment of this rare concurrent infection.

CASE REPORT:

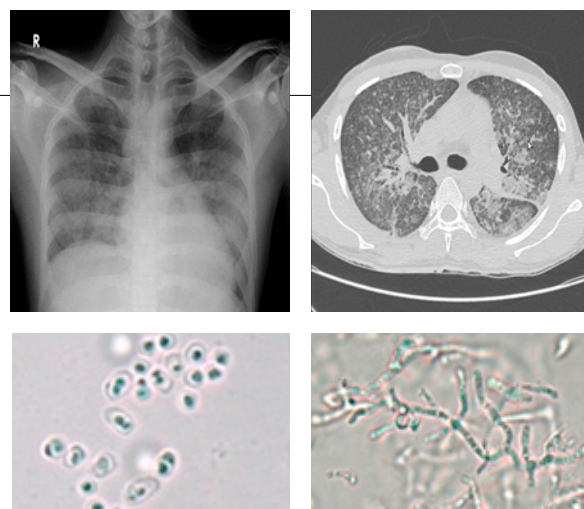
A 29-year-old gentleman, working as a salesman at a Maruti showroom, presented with fever of 1-month duration with evening rise of temperature, cough for 1 month, which was productive with mucopurulent sputum, breathing difficulty for 1 month, initially grade 1 mMRC and later progressed to grade 3 in 1 week, with history of loss of appetite and loss of weight. 10 years back he had an episode of Cerebral Venous Thrombosis and was treated with Warfarin at that time and later discontinued treatment. 6 months back he had an episode of focal seizure and was started on Sodium Valproate since then and also found to have high homocysteine level and he was started on tab Dabigatran. At that time he was diagnosed with ITP and since then he is taking tab Wysolone 30mg. The patient had no recent or direct contact with specific plants including rotten sugar canes nor has a recent travel history. On presentation patient was febrile, conscious oriented, had hypotension and bilateral pedal oedema, on auscultation of chest there were coarse inspiratory crepts on right infra scapular and infra axillary areas, all other system examinations were unremarkable. Initial investigations showed CRP:154.3mg/ litre, Total Count :10k/micro-litre, Platelet count:130K/micro litre, LFT: Total bilirubin: 1.20/SGOT:101/SGPT:73, Protein 5.1, Albumin:2.7, RFT was normal, PT INR - 1.41. Initial chest Xray and HRCT Thorax showed bilateral miliary nodules.

He was started on Inj Cefoperazone sulbactam empirically and other supportive measures. His blood pressure was not maintaining at steady level, he was put on 100mg Hydrocortisone stress dose of steroids after consulting with Endocrinologist. As his LFT was deranged Sodium Valproate was changed to Levetiracetam after consulting with Neurologist. His blood and sputum culture showed no growth. So, it was decided to do Bronchoscopy and TBLB 3 days following admission after stopping oral anticoagulants.

BAL smear was positive for Acid Fast Bacilli and in GENE EXPERT MTB was detected(low) with no Rifampicin resistance. BAL CYTOLOGY showed Acid Fast Bacilli in the cell block sections and fungal elements on special stain, which showed yeast cells and hyphae.

TRANSBRONCHIAL LUNG BIOPSY:

Showed chronic granulomatous inflammation; consistent with Tuberculosis. He was started on Modified ATT as his LFT was deranged. But after 2 days of starting ATT, patient's condition deteriorated, he had frequent fever spikes and



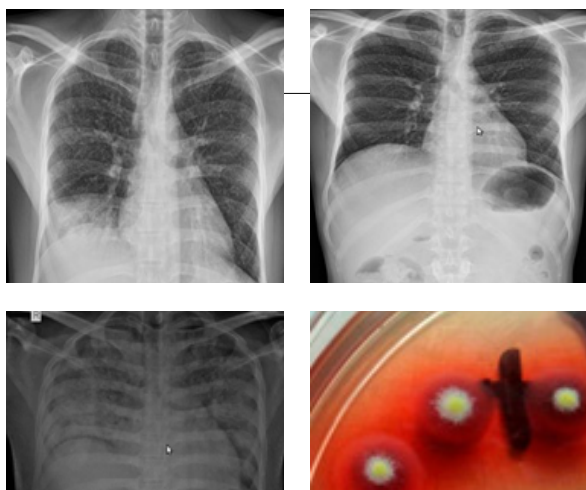
there was drop in saturation level to 85% at room air. ABG was done which showed Type 1 respiratory failure. Due to suspicion of secondary infection a repeat CRP was done which was increased to -188. Then he was started on Inj Meropenem and steroid dose was reduced to 20 mg. Repeat chest Xray showed bilateral diffuse infiltrates. He started coughing out yellowish mucopurulent sputum with brownish specs. At that time the bronchial wash fungal culture report came and it showed growth of *Penicillium*.

So, it was decided to start Inj Amphotericin B 150mg iv once daily in 500ml (due to financial constraints liposomal amphotericin was not given). After 2 days of amphotericin B, patient improved clinically, fever spikes decreased and oxygen saturation improved. Serial RFT monitoring was done and amphotericin injection was continued for 14 days. His LFT improved and there was reduction in CRP. Repeat chest Xray showed some clearance with right side minimal pleural effusion.

He was discharged with modified antitubercular drugs (Tab R-Cinex 300/450 mg od/Tab Levofloxacin 750mg od/Tab Ethambutol 800 mg od) and Tab Wysolone 10 mg. He was advised to continue Itraconazole 200 mg tid (higher dose to counter interaction with Rifampicin) for 2 months. Patient continued ATT with serial LFT monitoring and his chest Xray showed complete resolution after 1 month of treatment.

DISCUSSION:

Although coinfection of *T. marneffii* with other opportunistic pathogens is plausible as *T. marneffii* infection mostly occurs in immunocompromised hosts, reports of co infection are scarce. In a case series that reviewed 24 patients with *T. marneffii* infection, two HIV-negative patients were coinfecting with disseminated *M. intracellulare* and *M. fortuitum*, respectively. Clinical presentation of these disseminated infections may mimic each other, and a proper diagnostic approach is necessary to avoid insufficient treatment. From this point of view, we think that the present case is clinically



informative. On thorough literature search we could not find any case of *Mycobacterium tuberculosis* and *Penicillium marneffei* co infection in a non HIV patient. Some investigators have demonstrated that non-HIV hosts without any immunosuppressant may have impaired cell-mediated immunity, resulting from the derangement of cytokine cascades, including overproduction of suppressive cytokine, interleukin (IL)-10, and cytokine deficiency in the IL-12/interferon- γ pathway.

There is a significantly seasonal variation in infection rates of *Penicillium*, with an increased incidence in the rainy season. Some investigators have suggested that soil exposure, especially during the rainy season, is a critical risk factor associated with infection by *P. marneffei*.

The most common presentation of *T. marneffei* infection is fever and weight loss, occurring in more than 75% of patients. Other manifestations are anaemia, skin lesions, lymphadenopathy, hepatomegaly, and pulmonary disease, in decreasing order of frequency. Skin lesions are seen in 71% of patients, and include generalized papules, central umbilicated papules, and acne-like lesion. In our case there was lung and liver involvement. Patient also had hypoalbuminemia and anaemia.

Here we reported a case involving a healthy host without HIV infection but who was on steroid therapy for ITP developed *Penicillium* coinfection with TB.

P. marneffei grows as yeast bodies inside phagocytes. Immunosuppression after infection is a commonly encountered problem in affected patients. Causes of immune depletion may include prednisolone therapy, initial misdiagnosis, and disease progression. Because of the long duration of prednisolone therapy in the present case, the *P. marneffei* infection is associated with high mortality because it is commonly misdiagnosed in the early stages.

P. marneffei is identified by culture and pathological examination. *P. marneffei* grows as a yeast at 37°C, but as a mold at 25°C on Sabouraud dextrose agar, exhibiting a soluble red pigment that diffuses into the medium. The yeast form of PM has a characteristic morphology, including a transverse

septum and sausage-shaped organisms that can be demonstrated by pathological and cytological examination.

Tuberculosis is the most common misdiagnosis for the following reasons: (i) relevant literature and research on PM are limited; (ii) PM has been strongly emphasized as a common opportunistic infection of patients with AIDS; (iii) the signs, lung imaging findings and pathological examination results are similar to those of tuberculosis; and (iv) in the early stages, there is a low concentration of viable lesions and a low culture positive rate.

PM infection in normal hosts is characterized by an insidious onset, various clinical manifestations, and common misdiagnosis, leading to high mortality rates. Fortunately our patient was a young male with no HIV infection and with only lung and liver involvement and he was successfully treated with antifungals and he completed 6 months of ATT without further worsening of LFT and eventually he was cured.

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Multiple Sclerosis: Experience in a Single Center in the UAE

We describe the experience in a single-center of managing the condition in the local population. In the period between January 2019 and October 2019, six patients (5 women) were diagnosed with definite MS.

Dr Rahashekher Garikapati, Neurologist, Aster Hospital, Mankhool

Dr Mahendra Ramadas, Neurologist, Aster Clinic, Bur Dubai, Dubai

Dr Amit Arora, Neurologist, Aster Clinic, Al Muteena, Deira, Dubai

Dr Pawan Kumar Maniyar, Radiologist, Aster Hospital, Mankhool, Dubai

Dr Naveen Bhardwaj, Radiologist, Aster Hospital, Mankhool, Dubai

CASE REPORTS:

CASE 1: A 56 - year old lady of Scottish extraction, living in Dubai for many years, working as director of company, presented with right upper and lower limb stiffness, paresthesia and difficulty walking of 6 weeks' duration. (Clinically Isolated Syndrome).

CASE 2: A 48 - year old Indian housewife presented with sudden onset of bilateral lower limb sensory symptoms, with dysesthesia, cutaneous allodynia, pain and sensory level at D4. (Clinically Isolated Syndrome).

CASE 3: A 28 - year old Myanmar lady working as restaurant staff presented with visual blurring, ataxia, and hemisensory symptoms. (Relapsing - Remitting MS, previously unrecognized).

CASE 4: A 32 - year old Lebanese man, working as hotel staff, already on bi - weekly treatment with Interferon since two years, presented with symptoms of ataxia. (Relapsing - Remitting MS, previously recognized).

CASE 5: A 49 - year old Filipina, working as supermarket assistant, presented with atypical facial pain and non - neurological symptoms, found incidentally on MRI to have lesions fulfilling criteria for MS. (Radiologically Isolated Syndrome).

CASE 6: A 21 - year old Egyptian lady, working as office assistant, presented with recurrent episode of blurring of vision, hemisensory loss, and ataxia; she had previous episodes not recognized to be MS. (Relapsing - Remitting MS, previously unrecognized).

ABSTRACT

Multiple Sclerosis is a common neurological condition among younger people in the UAE. Diagnosis and management of MS and its complications remain difficult and are evolving. We describe the experience in a single-center of managing the condition in the local population. In the period between January 2019 and October 2019, six patients (5 women) were diagnosed with definite MS. Three were started on oral Disease Modifying Therapy (DMT), FINGOLIMOD, one was started on bi-weekly Interferon (PLEGRIDY). We describe here the experience and discuss the pros and cons of early versus delayed treatment.

All the patients fulfilled the Modified McDonald (2017) criteria for Dissemination in Time (DIT) and Dissemination in Space (DIS) at the time of diagnosis. At the time of presentation, two patients presented with Clinically Isolated Syndrome (CIS), one patient presented with Radiologically Isolated Syndrome (RIS), and two others presented with relapse of a recognized (one) and unrecognized Relapsing - Remitting form of MS. Confirmation of definite MS in most of the patients was done by identifying CSF Oligoclonal bands. MRI scan

of brain and spine with and without Gadolinium enhancement was done for all patients to fulfill McDonald's criteria, using Barkhoff's criteria for typical MS lesions. Patients with MS need to be followed up for several years to identify the benefits of DMT. In patients presenting with CIS, the presence of spinal cord lesions may indicate higher risk of future relapse and conversion to Relapsing-Remitting form of MS; hence, early treatment with DMT may be of greater benefit in these patients. The patients in this series will be followed up on a long-term basis to observe the benefit.

INTRODUCTION

Multiple Sclerosis is one of the commonest serious neurological conditions to affect young people. It is commoner among females, and shows ethnic predilection. Practitioners of clinical neurology newly exposed to a rich ethnic mix of population in the UAE are highly likely to encounter higher numbers of patients with this condition. The diagnosis of MS is not without its challenges; even on date there are many patients treated with expensive and potentially toxic medications over long periods of time before alternate diagnoses are discovered. This not only burdens the patients and the system but also exposes the clinician to litigation. Familiarizing oneself with the latest in the field then becomes of paramount importance.

We summarize in this case series the experience in a single centre of patients presenting either with a Clinically Isolated Syndrome, a Radiologically Isolated Syndrome, or with a relapse of a previously recognized or unrecognized Relapsing - Remitting MS. We describe the clinical presentation, the diagnosis, the radiological findings, the initial management, and the plan for long - term management. We discuss also the rationale for early vs late treatment for patients with CIS who will benefit with Disease Modifying Therapy (DMT).

DETAILED CASE HISTORIES

CASE 1:

This patient, a 54 - year old lady of Scottish extraction, working as director of a hotel designing company, and doing mostly a desk job, noticed difficulty in walking, with the right leg becoming stiff and a tendency to drag the right foot; there



Figure 1
Sagittal FLAIR images (Case 1): Multiple hyperintensities seen in this sagittal image in the cervical spine.

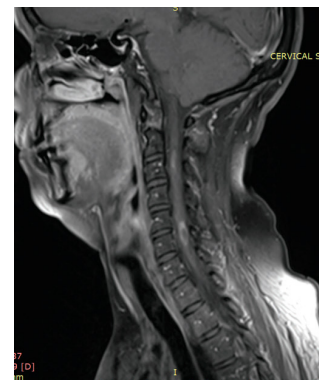


Figure 2
Sagittal Contrast - enhanced images, Cervical spine in Case 1; two lesions show contrast - enhancement.

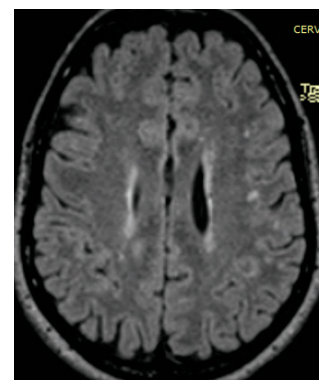
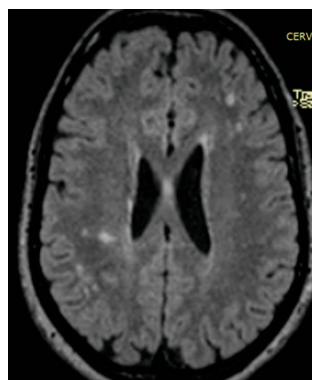
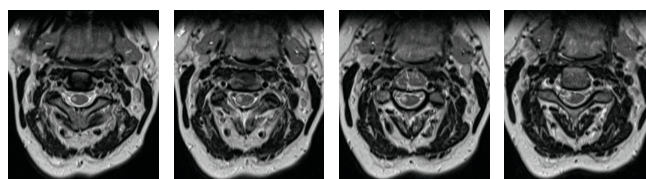


Figure 3
Screening of Brain showed multiple, bilateral periventricular and juxtacortical lesions on T2 / FLAIR images (Axial images shown above), with lesion number exceeding 9 in total, fulfilling Barkhoff's criteria, as well as McDonald's criteria (modified, 2017).



is in addition, a difficulty in writing with the right hand. She has mild pain in the right side of neck and some low back pain as well. There is no history of trauma accident fall or injury.

She has been on analgesics since then, and also treated with physiotherapy and chiropraxy;

she had some benefit with physiotherapy, and intermittently felt better with the treatment.

There is no h/o diabetes mellitus, hypertension, thyroid disease, arthritis, coronary artery disease, stroke, renal, hepatic or any other illness. About 8 years before this, she was living in Malaysia, and recalled an episode of visual blurring in one of her eyes, which was not completely evaluated, and which recovered spontaneously. She has brother who is 6 years younger to her, who has been on treatment for MS with Interferons for many years, and is currently wheel - chair dependant.

PHYSICAL EXAMINATION:

At the time of presentation, the patient was conscious, alert, oriented; higher mental functions were normal. Speech was normal. Cranial nerves were normal. Fundus examination was normal. Examination of the motor system revealed increased tone on the right side with ankle clonus and bilateral upgoing plantars. All deep tendon reflexes were brisk with MRC Grade 3+ bilaterally. There was mild distal weakness for fine motor actions in the fingers of the hands. There was reduced vibration sense distally on the right side with sensory level at D6 dermatome. Rhomberg's test was negative, and there was spasticity during gait testing.

Examination of other systems did not yield any findings.

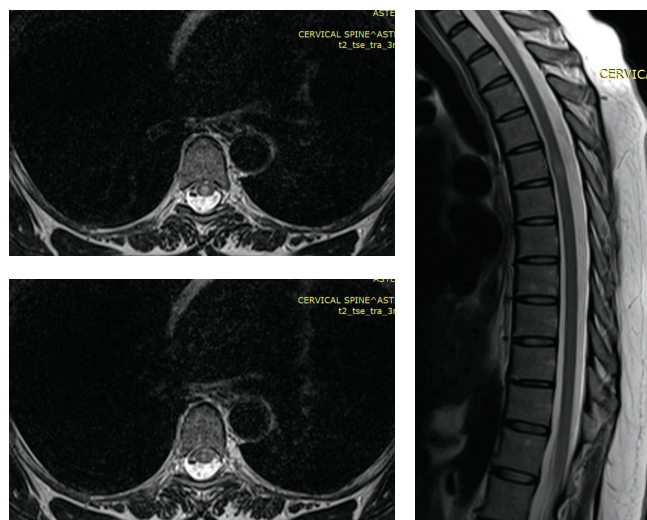
The patient was subjected to Lumbar Puncture; routine CSF evaluation showed no cells, normal protein (41.7 mg/dL; range, 15 - 45 mg/dL), and normal glucose (65.6 mg/dL). CSF and serum NMO Ab was negative, whereas Oligoclonal antibodies were positive in both CSF and Serum

Thyroid function tests, liver function tests, renal function tests were all within normal limits.

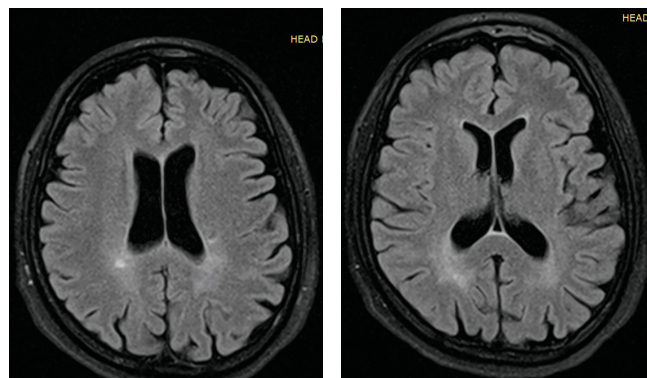
The patient was started on a 5 - day course of Inj Methyl Prednisolone, which was followed by Inj PLEGRIDY. She has been on this injection once every two weeks for the last 10 months.

CASE 2:

A 48 - year old Indian housewife, living in Dubai for the last twenty years, presented to Emergency Room with complaints of stiffness and lack of sensation of lower extremities for the last one week. She had been seen in one of the clinics, when she first noticed abnormal sensations in the outer aspects of both feet simultaneously 7 days prior to



Axial T2/FLAIR sequences of MRI brain showed two lesions in the periventricular white matter which were non - enhancing with Gadolinium.



admission. Though treated symptomatically initially, the abnormal sensation along with numbness ascended into the legs and thighs up to the lower abdomen along with feeling of stiffness in the legs over the next few days. She had difficulty in standing with lack of feeling in the feet and difficulty in sitting on the commode, though she had normal control of bladder and bowel. There was no history of trauma, accident, fall or injury. There was no previous history of any significant medical or surgical illness. Specifically, there was no history of joint pains, rashes, any recent visits

to any new places, any vaccinations. There was no fever, cough, breathlessness, headache, vomiting, visual symptoms, swallowing difficulties, cognitive difficulties, or memory difficulties. She had history of thyroid disease, well-controlled on hormone replacement therapy, gastro-esophageal reflux disease, and occasional palpitations for which no specific treatment was being taken. She had no history of diabetes mellitus, hypertension, heart disease, liver, kidney, or any other systemic illness.

Physical Examination: At the time of admission showed a conscious, alert, and oriented patient. She had normal speech, cranial nerves, and fundus. Her higher mental functions were intact, and she had normal memory and cognition. Upper limbs showed normal power, tone, and reflexes. Lower limb showed mild spasticity, evident when she was made to stand and walk. Knee deep tendon reflexes were reduced bilaterally, while ankle jerks were increased, and bilateral plantars were upgoing. Sensory system examination showed reduced vibration sense with a level at D6. Coordination was normal.

She underwent extensive evaluation with MRI of cervical, dorsal, and lumbar spine; only one lesion was found in the dorsal spine.

Two non-enhancing lesions were found in the supra-tentorial cerebral white matter on the right side, adjacent to the lateral ventricle in the trigonal area. Her CSF was positive for Oligoclonal bands. She was treated with 5 doses of Inj Methyl Prednisolone 1 gm daily, and then followed up with oral Prednisolone, tapered over three weeks, and her symptoms gradually improved.

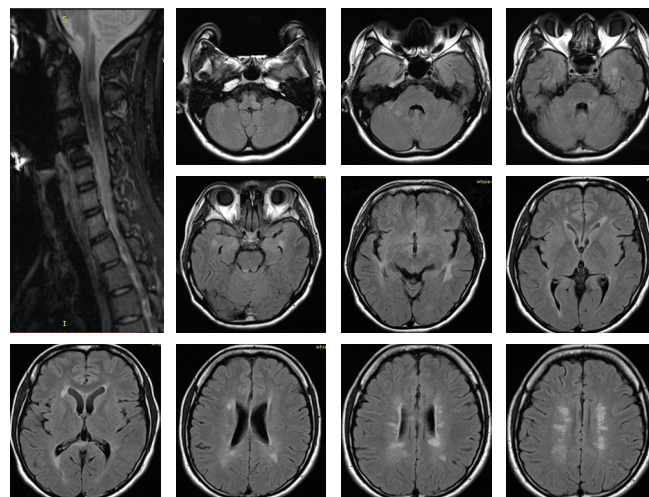
She was treated with Inj Methyl Prednisolone 1 gm daily for 5 days; recovery took a prolonged time. CSF studies showed the following findings: CSF: Cell count: nil; Protein: 29.5 mg/dL (normal range: 15 - 45 mg/dL); Glucose: 83 mg/dL; Gram stain, AFB stain, Fungal stain, pan-cultures: negative; CSF and serum NMO Antibody: negative; CSF and serum Oligoclonal antibodies positive.

She is on follow up at present.

This patient is on follow up for the last 6 months, and not on any specific disease - modifying therapy for Multiple Sclerosis, even though by McDonald's criteria, she had Definite MS.

CASE 3:

A 28 - year old Myanmar lady, working as



catering staff with a major company in the UAE, presented to Neurology clinic at Aster Hospital, with complaints of progressively increasing blurring of vision, difficulty in walking with unsteadiness, and abnormal feeling in the hands and legs. She had travelled in her native place in the Philippine a month ago, and felt mild bilateral blurring of vision soon after returning to work in Dubai, which she initially ignored. This increased gradually, and three weeks before presentation, she noticed pins and needles in her hands; a week later, these intensified and spread to the feet, and were associated with stiffness in the legs. This was associated with some difficulty in walking. She was brought to the OPD in a wheelchair because the combination of stiffness in the limbs and visual difficulty made it hard to walk, though she was able to walk independently. There was no double vision, no difficulty swallowing, no falls, no loss of consciousness, no seizures, loss of memory or other cognitive difficulties.

She had past history of blurring of vision about two years ago, for which she attended hospital locally in Dubai, was evaluated with MRI and was informed that she had some neurological illness; there had been no follow up, hence she was not on any treatment. There was no history of thyroid disease, arthralgias, skin rash, liver, kidney, heart, pulmonary diseases, diabetes mellitus or hypertension.

Physical Examination at the time of admis-

sion showed mild visual blurring, with impairment of both central and peripheral vision. Extraocular movements were normal. Fundus showed bilateral pale discs. There were no other cranial nerve abnormalities. She had normal memory and cognition. She had spasticity in both lower limbs; all her deep tendon reflexes were pathologically brisk and plantars were bilaterally upgoing. There was mild distal ataxia, in the form of finger - nose inco-ordination. Sensory examination was normal. Examination of other systems was normal.

COMPLETE BLOOD COUNT

WBC Count 7.49 $10^3/\mu\text{L}$ (4 - 10)
 RBC Count 5.31 $10^6/\mu\text{L}$ (3.8 - 4.8)
 Hemoglobin 11.6 g/dl (12 - 15)
 Hematocrit 36.6% (36 - 46)
 MCV 68.9 fl (83 - 101)
 MCH 21.8 pg (27 - 32)
 MCHC 31.7 g/dl (31 - 37)
 Platelet Count 214 $10^3/\mu\text{L}$ (150 - 410)
 RDW-CV 14.7% (11.6 - 14)
 MPV 10.7 fl (7.6 - 10.8)

DIFFERENTIAL COUNT

Neutrophil 63.4 % (40 - 80)
 Lymphocytes 31.5 % (20 - 40)
 Monocytes 3.3 % (2 - 10)
 Eosinophils 1.5 % (1 - 6)
 Basophil 0.3 % (0 - 1)

Total Iron Binding Capacity (Fx) 387 ug/dl (250 - 400)

Transferrin Saturation (Fx) 29.46 % (16 - 50)

Ferritin levels 47.8 ng/mL (range 12 - 150)

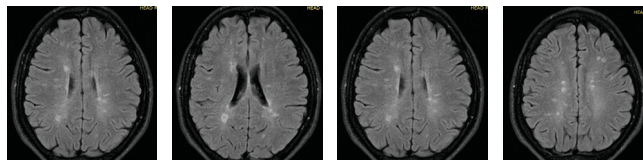
Hemoglobin electrophoresis showed 94.7% HbA, 2.3% HbA2 and HbF <1%, and HbD was absent (against diagnosis of Beta thalassemia trait). Hence microcytic anemia may be due to iron deficiency anemia, secondary to excessive menstrual loss and inadequate dietary iron intake. Vitamin B12 and Folic Acid levels were not checked.

Thyroid function, Renal function, hepatic function were within normal limits. Chest Xray and ECG were both normal.

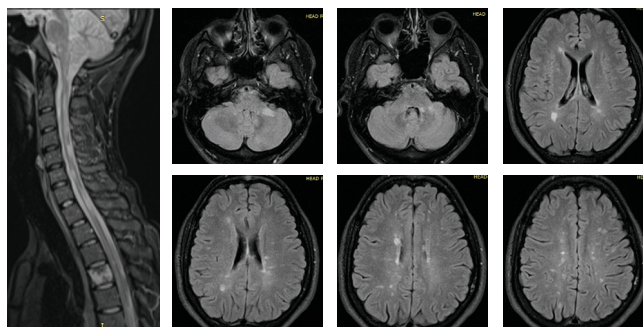
CSF:

Cell count: 0 cells; Protein: 22.9 mg/dL (15 - 45);
 Glucose: 75.6 mg/dL

CSF and serum Oligoclonal bands positive, with



FLAIR Axial Images from MRI done in July 2019 at the time of admission with current relapse.



extra Bands observed in CSF : Demonstrates both Intrathecal & Systemic IgG synthesis.

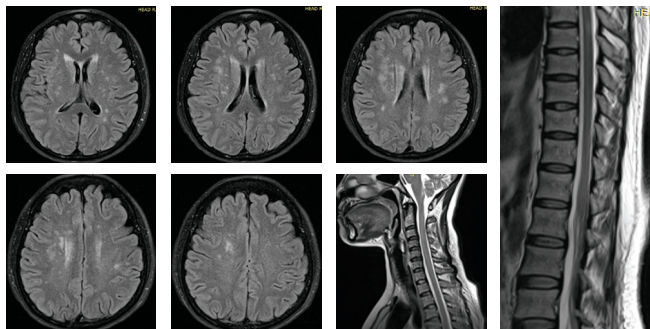
TREATMENT:

She was started on a 5 - day course of Inj Methyl Prednisolone 1 gm daily, with which she improved, and following this, has been started on oral disease modifying therapy with Fingolimod 50 mg daily. She is on regular follow up.

CASE 4:

This 32 - year old Lebanese man works as hotel staff in Dubai. He presented in 2017 with right sided weakness. Evaluation with MRI at that time showed multiple demyelinating lesions, and CSF showed positive Oligoclonal bands. Since then he has been on weekly Inj Interferon (Avonex, 30 mcg weekly, subcutaneously), till 3 weeks before presentation, when he had a relapse in the form of abnormal painful burning paresthesia in both hands. In addition, he gets burning pain when he bends his neck; he has been getting pain in the low back as well. He has noticed difficulty in walking with tendency to sway to the left since the last 12 days which is progressively getting worse.

Physical Examination at the time of admission showed reduced sensations in both upper limbs, and reduced motor power in both upper limbs,



up to MRC Grade 4/5 proximally. The deep tendon reflexes in the upper limbs, including bilateral triceps and brachioradialis were reduced; left biceps jerk was brisk; both knee jerks were brisk, ankle jerks were normal. Bilateral plantar reflexes were upgoing. Distal vibration and joint position sense were lost in both feet. Tandem walking was impaired, but Romberg's test was negative (no sensory ataxia).

A clinical diagnosis of relapse of Multiple Sclerosis was made, and patient was admitted for Inj Methyl Prednisolone, and MRI evaluation.

MRI images of the patient at the time of first presentation in October, 2017, showing extensive lesions in the supratentorial periventricular, juxtacortical, posterior fossa, and spinal cord location, fulfilling criteria McDonald's and Barkhof's MRI criteria for diagnosis of Multiple Sclerosis. This was further confirmed with positive CSF Oligoclonal bands.

TREATMENT:

Since the patient had a relapse while on Avonex (Interferon), a plan was made to change the disease - modifying therapy, as the patient preferred one of the oral drugs. A choice was made to start him on oral Fingolimod, and the patient has been on this therapy for the last 3 months.

CASE 5:

This 49 year old Filipina was referred by physician for evaluation of possible diagnosis of Multiple Sclerosis. She had recurrent admission in the previous month for abdominal complaints. She presented with dizziness, vomiting, loose motions, and upper abdominal discomfort and pain in the month of

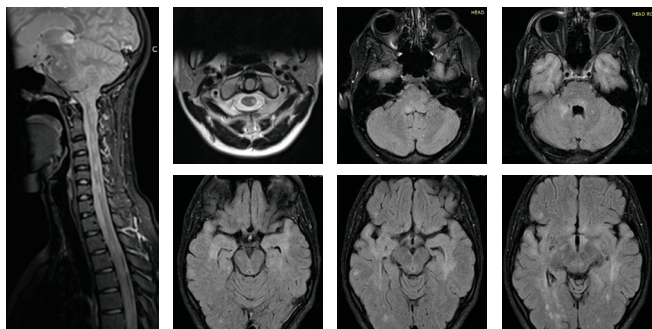
July, 2019. She was found to have cholelithiasis, and calculous cholecystitis was diagnosed, and laparoscopic cholecystectomy was performed. She was readmitted a week later with the same complaints, hence she was referred for evaluation to Neurologist and Gastroenterologist for possible other causes of her symptoms. On detailed history taking, she revealed that she had been admitted with similar complaints in 2017, for which she had gone to the government hospital. At that time, she had burning facial pain as well, but this was not completely evaluated at that time. When the facial pain persisted, she visited a private hospital, who evaluated her with MRI brain scan. Some lesions were seen on the scan, and lumbar puncture was performed, but the results were not conclusive, hence the patient was discharged on Gabapentin for the facial pain. She continued this for a month, after which she stopped it and did not continue follow up. She had past history of Type 2 Diabetes mellitus and was on oral hypoglycemic drugs, and over the next few months, she developed right shoulder pain as well as left flank pain, all of which were attributed to diabetes and treated with medicines.

She was asked to visit the out-patient department with her previous reports, and was seen again 1 week later. The MRI images showed periventricular lesions highly suggestive of, but not pathognomonic of MS; CSF report was available, but the report for Oligoclonal bands was not available. Antinuclear antibody was positive at 3+, but dsDNA and SmDNA were both negative. As per these records, the diagnosis considered was Trigeminal neuralgia, and patient was discharged on Gabapentin.

FLAIR Axial MRI images showed multiple periventricular and juxtacortical lesions in the supratentorial compartment; screening MRI of the spine suggested additional lesions in the cervical and dorsal spinal cord. The lesions in the brain did not enhance with Gadolinium. Additional study of the spine with Gadolinium, as well as CSF study for Oligoclonal bands was planned, but could not be completed due to insurance issues.

CASE 6:

A 21 - year old Egyptian lady was referred in the last week of October to the OPD at Aster Hospital with the complaints of increasing double vision and ataxia. She first noticed double vision in last



week of September, and initially ignored it. In early October, she noticed unsteadiness while walking, which she ignored for a further one week. Since about a week prior to presentation, she started feeling abnormal sensation in the left side of the body especially the left leg and left flank from the chest down, and had a lack of sensation on the left thigh and leg; she occasionally couldn't feel the left thigh even on scratching it deeply when it itched. With these complaints she approached a neurologist at Aster Clinic who then referred her to OPD at AHM as possible MS.

She had h/o left facial numbness a few years ago that remained undiagnosed, and in 2016, she had an episode of left sided double vision that was not fully evaluated.

Physical Examination: At the time of admission, her visual acuity was recorded as follows:

VISUAL ACUITY (UNAIDED)

OD : 6/60p

OS :6/36

NVN :N6 OU

Detailed eye examination revealed the following:

ANT SEGMENT: No abnormality found in either eye

PUPIL - Normal size, reacting to light - both Direct and Consensual

FUNDUS both eyes - media clear; Disc vertically oblong with hazy margins with water marks and old inflammatory pigments around disc; cup normal / disc pallor ++ /more temporally

Fundus: No abnormality detected; Intraocular pressure: 15 and 17 mmhg by nct

DETAILED NEUROLOGICAL EXAMINATION

She had reduced movement in the left eye (lateral rectus weakness); other cranial nerves

were normal. Motor system showed normal power and tone in the muscles. Deep tendon reflexes were brisk at the knee and ankle; upper limb deep tendon reflexes were reduced. Plantars were bilaterally upgoing. There was loss of vibration sense on the left side in the lower limb with sensory level for vibration at D6 on the left side. There was no limb or gait ataxia.

The MRI findings of lesions in the various locations including juxtacortical, periventricular, posterior fossa, spinal cord, along with few lesions of more than 6 mm size, were considered sufficient to diagnose Definite Multiple Sclerosis in this 21 - year old patient who had previous history of undiagnosed neurological illness at age 18 years and one more episode prior to this; based on the clinical history and MRI picture, there was evidence of dissemination in time as well as space.

TREATMENT:

She was treated with an initial 5 - day course of Inj Methyl Prednisolone 1 g daily, with which she improved, and has been started on oral Fingolimod, and is on regular follow up.

DISCUSSION

The diagnosis of Multiple Sclerosis can be straightforward if dissemination in time and space can be established at any point of time. The difficulty arises when a patient of appropriate age presents for the first time with a neurological illness, and the MRI criteria are not sufficient to confirm Definite Multiple Sclerosis. In our series, this situation prevailed in Patient 2, a 48 year old Indian housewife, who presented with sensory symptoms localizing to the dorsal spine; initial imaging showed a symptomatic lesion in the dorsal spinal cord, and few non - specific lesions in the brain. When all the other tests were normal, only CSF Oligoclonal bands were the means to establish the diagnosis. This patient went for further opinions from other neurologists in India, and, being reluctant to start any treatment, was satisfied when there was divided opinion among neurologists. Only long - term follow up can resolve this issue.

In the other patients, the issues were easier since the number of lesions on MRI scans were sufficiently large for the diagnosis to be seriously considered. Even then, diagnosing MS solely on

imaging criteria is fraught with risk if there are no clinical events; this is exemplified by our Patient number 5, who never clearly reported an episode which could be considered a relapse. Her MRI brain, however, is quite similar to those of other patients who have been diagnosed with definite MS. We could not complete the evaluation, unfortunately, though MRI of the spine and CSF studies were planned, due to insurance issues. The problem of Radiologically Isolated Syndrome continues to plague MS care givers.

In the case of Clinically Isolated Syndrome, by definition, the patient presents with the first episode of neurological illness which may be considered as Possible MS, and the clinician then has to look for additional evidence to support the diagnosis of Definite MS, as defined in the 2017 Modification of McDonald's criteria. In our small series, Cases 1 and 2 can be considered to be CIS, if the old history of visual blurring in Case 1 8 years prior to presentation with current illness is not considered as the initial event. While Cases 3 and 6 had clear history of prior episodes which could be classified as MS relapses, in Case 4, the diagnosis was already established by prior CSF Oligoclonal bands.

Except in Case 4, all the other patients were diagnosed de novo; hence the burden of diagnosis as well as initiating long - term, potentially toxic, and definitely expensive disease-modifying therapy lay with us.

There are two schools of thought in this regard: those who advise early institution of disease-modifying therapy, and those who advocate that we should wait at least till the first or second relapse, so that we don't treat all those MS patients who have few or no relapses, as also all those non - specific demyelinating syndromes that get mis-labelled as MS. While this is an area of intense, ongoing debate, there are a few studies which have pointed out clinical and MRI features that may help us to decide which candidate deserves early treatment, and which factors do not help us to decide this.

For example, among patients who present with CIS or RIS, detection of asymptomatic lesion in the spine is considered to increase their chance of conversion into full-blown MS within the next 5 years. The sensitivity of this finding is 87.5, specificity is 91.5%, while the positive predictive value is 84% (Okuda et al, 2011, Neurology). Factors

that do not predict such conversion include: gender, number of T2 lesions on MRI, Oligoclonal bands, and IgG index. Other factors that have been more commonly associated with later conversion to Clinically Definite MS include VEP findings, younger age, and Gadolinium - enhancing lesions on follow - up MRI.

In the two patients who presented with CIS, Case 1 had spinal cord lesions as well as enhancing lesions on MRI; these factors predict progression to Clinically Definite MS, hence she should be started on DMT, and has been placed on a regimen of bi-weekly PLEGRIDY.

In Case 2, there is one spinal cord lesion, but this is the symptomatic lesion; there are no enhancing lesions. VEPs were normal, and her age (48 years) puts her in a slightly older age bracket. Based on these criteria, the chances of progression to CDMS are somewhat lower in her; she has been placed on long - term follow up.

Cases 3 and 6 had previous episodes which were suggestive of MS; their MRI findings fulfilled McDonald's 2017 criteria for Definite MS; and in Case 3, this was further confirmed with CSF OCB. Both had spinal lesions; neither showed enhancing lesions; both had abnormal VEPs, and both are young (in their 20s); based on these criteria, the chances of frequent future relapse are higher in these individuals, hence they have been started on DMT (both on Fingolimod).

Case 4 had already been diagnosed previously with MS, was on Interferon, and had a relapse while still on DMT, hence he was changed to oral Fingolimod at his own preference.

Case 5 is a RIS; in her case, the diagnostic study is not yet completed. It remains to be seen whether she has spinal lesions, and what her VEP findings will be. It would be interesting to follow up this patient to find out the natural history of some one who never had a relapse, to see if she develops a clinical relapse or the MRI findings show any evolution over time.

In conclusion, therefore, it may be said that the diagnosis of MS can be challenging despite all the advances made in medical science. With new therapies and new advances in investigational methods, it is imperative that a complete diagnosis be made in every patient. Patients have to be fully informed about the condition, along with the pros and cons of treatment or of withholding treatment.

Coital Headache Presenting as Linear Epicrania Fugax on Left Side

Headache associated with sexual activity has been referred to as sexual headache, benign vascular sexual headache, coital cephalalgia, coital headache, intercourse headache, (pre)orgasmic cephalalgia, and (pre)orgasmic headache. Orgasmic headache presenting as epicrania fugax on left side is rare.

Dr Harsha Bhatia, Aster Medical Centre, Neurology, Doha, Qatar

Dr Gireesh Kumar B, Aster Medical Centre, AH, Doha, Qatar

INTRODUCTION

Epicrania fugax (EF) is a primary headache whose main feature is the dynamic character of the pain. EF pain typically moves across different dermatomes in a linear or zigzag trajectory.

Headache associated with sexual activity has been referred to as sexual headache, benign vascular sexual headache, coital cephalalgia, coital headache, intercourse headache, (pre)orgasmic cephalalgia, and (pre)orgasmic headache. Orgasmic headache presenting as epicrania fugax on left side is rare.

CASE REPORT

48 years male presented with acute onset linear trajectory shaped headaches radiating anteriorly from back of head only when he reaches peak of his sexual activity, and this headache is persists 1-2 hours, partially relieved with analgesic, but soreness persisting over that area, no vomiting. This has been there since last 2 months, examination normal, BP 130/90mmhg CTSCAN HEAD NORMAL, MRI BRAIN AND ANGIO NORMAL, Patient started on beta blocker and gabapentin and pain was relieved.

DISCUSSION

This is a rare case of sexual headaches presenting as epicrania fugax, EF essentially consists of brief paroxysms

of pain describing a linear or zigzag trajectory across the surface of one hemicranium, commencing and terminating in the territories of different nerves. The pain of forward EF originates in a particular area of the occipital, parietal or temporal regions and moves anteriorly, whereas the pain of backward EF originates in the frontal area, the eye or the nose and moves posteriorly. Onset and termination points remain constant in each patient, with the pain strictly unilateral, although some patients have shifting sides. This combination of sexual headache with epicrania character is rare and could be attributed to haemodynamic changes.

CONCLUSION

This is a rare combination of headaches; sexual headaches may present differently but this is unique.

References

1. Epicrania fugax: 19 cases of an emerging headache Cuadrado ML Headache. 2013
2. Epicrania Fugax. Cuadrado ML, Guerrero AL, Pareja JA. Curr Pain Headache Rep. 2016

Living Donor Liver Transplantation for Acute Liver Failure Due to Hepatitis E in a Pregnant Patient - Challenges in Management

Hepatitis E virus belonging to the family Hepeviridae, is an important cause of enterically transmitted hepatitis in developing countries.

Dr Rakesh Babu, Senior Specialist, Anesthesia and Intensive Care, Aster MIMS, Kozhikode, Kerala, India

Hepatitis E virus belonging to the family Hepeviridae, is an important cause of enterically transmitted hepatitis in the developing countries. Hepatitis E can lead to acute liver failure in pregnant patients and in patients with pre existing liver diseases. The mortality rates increase especially in the third trimester of pregnancy¹. We describe a case of a 28-year-old female at 28 weeks of gestation who presented with acute liver failure due to hepatitis E virus.

CASE REPORT

A 28-year-old female at 28 weeks of gestation was referred from a peripheral centre with history of tiredness, jaundice of 6 days duration and altered sensorium for a day. She was investigated and found to be hepatitis E card test positive. Patient was admitted in the intensive care unit. Blood investigations revealed coagulopathy (INR- 6.76). Fetal ultrasound was done which showed appropriate results for gestational age fetus with good cardiac activity.

Patient was started on supportive management. Liver protective strategy in the form of NAC infusion started. Inotropes were started for hypotension. Coagulopathy worsened on the subsequent day, patient developed per vaginal bleeding, and encephalopathy worsened (grade 2). She met the King's College Criteria for transplantation and was reviewed by the transplant team. The spouse was identified as a suitable donor and all donor work up were initiated. She was simultaneously listed for cadaveric transplantation with the state registry (KNOS).

A multidisciplinary team decided to proceed for Liver Transplantation, with lower segment Caesarean section prior to transplant. Patient was shifted to the operating

room; IV access was done with wide bore cannula and multiparameter monitoring started. Right radial artery was cannulated for invasive pressure monitoring.

Rapid sequence induction was done and Intubated. LSCS was done and a live female baby was delivered. Baby was handed over to the neonatal intensive unit, where the baby was intubated and ventilated. Coagulopathy during surgery was corrected by use of fresh frozen plasma and platelet concentrate. Inotropes were increased in view of hypotension post cesarean section.

Once the LSCS completed, fresh drapings were made for Liver Transplantation surgery. Advanced venous access 9 F was done in the right IJV under ultrasound guidance. Triple lumen central venous catheter, 7 F was also secured to the Right internal jugular vein, one inch below the AVA insertion site. All lines were secured using sutures. Left sided radial artery was cannulated for sample collection and intraoperative coagulation monitoring.

ROTEM was used for coagulation assessment. Flotrac- EV 1000 (Edwards) was used for intraoperative hemodynamic monitoring. CVP monitoring was initiated during the entire surgery and to the post operative period. The dissection phase was accompanied by severe coagulopathy, the correction of which was done guided by the ROTEM values. Noradrenaline infusion, Phenylephrine infusion and Vasopressin infusion were started off early during the dissection phase due to hemodynamic instability.

Anhepatic phase blood gases showed acidosis which was corrected by Sodium Bicarbonate infusions. Correction of hypocalcemia was done during the anhepatic phase.

The implantation of the graft liver was done using IVC cross clamp. The total cold ischemia was 2 hour 11 minutes.

The reperfusion phase was marked by severe post reperfusion syndrome which was tackled by increased dose of inotropes, infusion of soda bicarbonate, Calcium Chloride 10% and a single bolus dose of Adrenaline (1:100000).

The immediate reperfusion phase showed a rise in cvp and worsening acidosis which settled within half hour post reperfusion. Clearing of acidosis in the ABG was noted one hour post reperfusion. The warm ischemia time was 56 minutes.

All the anastomosis were done and meticulous hemostasis was done. Closure done after checking instrument and mop counts. The total duration of surgery noted was 11 hours. The patient was shifted to the transplant ICU for elective postoperative ventilation. She was put on pressure support ventilation and sedation done by propofol and fentanyl infusions. Tapering of inotropes were done gradually.

Weaning from the ventilator was started 6 hours post surgery and was extubated after 12 hours post surgery. Her higher mental functions were intact and inotropes were tapered off 14 hours post transplant. The baby was put on elective ventilation for 48 hours, ECHO revealed PDA, which was managed medically. Liver function tests of the recipient started declining to normal level 24 hours post liver transplant. 72 hours post transplant immunosuppression was started and was titrated according to the enzyme values. Patient was discharged 20 days post surgery with no complication. The patient and baby is on regular follow up for the past one year with no post op surgical or medical issues.

DISCUSSION

Hepatitis E is an important cause of enterically transmitted hepatitis in developing countries. It can lead to acute liver failure especially in pregnant patients and in patients with pre existing liver diseases¹. The mortality rates increased in the third trimester of pregnancy and with increasing grades of hepatic encephalopathy. The frequency of infection and mortality rate increase with the gestational age.

The severe course in pregnant women is related to a reduction in the expression of progesterone-receptor, which led to a predominance of T-helper type 1 lymphocytes. This immunologic shift results in an exuberant cytotoxic T-cell reaction resulting in foetal and maternal injury.² Orthotopic Liver Transplantation (OLT) is a treatment option for patients with ALF.

To the best of our knowledge, doing a combined lower segment Cesarean section along with a Living Donor Liver Transplant for Hepatitis E induced ALF was a rare entity. Our case at the time of hospitalisation had worsening encephalopathy and a viable fetus.

The worsening encephalopathy, coagulopathy, viable fetus and availability of transplant facility in our centre favoured the decision for combined LSCS and a Living Donor Liver

Transplant. The mortality rates were higher as found in other studies when the transplant was done at a later stage of encephalopathy. So, we decided upon terminating the pregnancy with the hope of saving a viable fetus and following up with a Living Donor Liver Transplantation to save the mother.

A case where LSCS was done to terminate the pregnancy and later proceeding with transplant option with a successful outcome was available in the literature³. Our case had higher grades of encephalopathy and coagulopathy which made us to proceed for the transplant, without waiting for further worsening of the clinical condition of the patient.

Combined lower segment Caesarean section and liver transplantation is a rare entity. Timing of LSCS and liver transplantation is an always debatable topic. Various case reports are available in literature where LSCS was done and later transplantation was done. Centres have done induction of labour and then depending on the clinical condition, transplantation was done at a later stage⁴. Delaying the delivery of fetus will interfere with the immunosuppressive regimen as many of the immunosuppressive agents are not pregnancy safe⁵.

In our case we decided upon LSCS and liver transplant with the idea that a viable fetus could be saved and better hemodynamic control could be achieved in a controlled way and transplant offered in the same session could have a better prognosis for both the mother and the baby.

SUMMARY

Hepatitis E can cause severe hepatic failure in pregnancy. Early intensive care management is the key to survival. Termination of pregnancy depends on the viability of the fetus. Liver transplantation can be a suitable option where facilities are available. Combined liver transplant and Caesarean section or liver transplant followed by delayed delivery of fetus can be considered depending on the clinical situation.

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‘All it takes is five minutes and three dollars’, says Dr Ruit. He has proved it by doing approximately 1,20,000 cataract surgeries so far, in makeshift hospitals in the remotest of places where people have no access to affordable quality healthcare.



A BAREFOOT SURGEON WITH A VISION





by **Suneetha Balakrishnan**

Dr Ruit is the Founder & Executive Director of the Tilganga Institute of Ophthalmology, the implementing body of the Nepal Eye Program.

Poor and blind, what's a worse recipe for a miserable life? That too, in a region which is not exactly known for its medical facilities? Thanks to a 'Man with Vision', the ophthalmologist Dr Sanduk Ruit, many poor people with 'avoidable blindness' have been able to get back their eyesight. This, not just in his home country of Nepal, but also in other neighbouring Asian countries as well as in Mongolia, North Korea, Ethiopia, Vietnam, Cambodia and Kenya.

Dr Ruit is the Founder & Executive Director of the Tilganga Institute of Ophthalmology, the implementing body of the Nepal Eye Program. Tilganga has an international centre of excellence for ophthalmology training, and its surgeons have been conducting camps to train eye-surgeons elsewhere in the pioneering small-incision low-cost cataract micro-surgery technique using the innovative implanted intraocular lenses, which is sutureless and self-healing. Dr Ruit has perfected this technique from his mentor and renowned Australian eye-surgeon, Dr Fred Hollows. The 'Nepal Method' is also taught in the United States Medical Schools.

'All it takes is five minutes and three dollars', says Dr Ruit. He has proved it by doing approximately 1,20,000 cataract surgeries so far, in makeshift hospitals in the remotest of places where people have no access to affordable quality healthcare. He has been hailed with epithets like 'The Barefoot Doctor', 'Man with Vision', 'God of Sight' and many more. And been showered with honours ranging from the Magsaysay Award for Peace and International Understanding to the Padmsri from the Government of India and the National Order of Merit of Bhutan, and many many more. There's even an asteroid named after him, Asteroid 83362 Sandukruit.

But this was not always the picture. Dr Sanduk Ruit, his first name Sanduk means Sky Dragon, has come a long way from where he lived once. The remote mountainous village Ol-

angchunggola, located 11000 ft above sea level, right in the lap of Mt. Kanchenjunga, along the border with Tibet in northeast Nepal had no power, no school, or health centre, or communication facility. In fact, it's a snow-covered village for most parts of the year. A subsistence living from small agriculture, petty trading and livestock farming was all his rustic and illiterate parents had, to raise their six offspring. But Ruit's father knew the value of education, and sent his son to the nearest school, St. Robert's School, which was a whole 11-days' walk away, at Darjeeling.

At school, Sanduk was bullied and lonely. And on vacations, while most of his school mates left for home, little Sanduk almost always stayed back with the priest in charge. Home was too far away and too remote to visit. His education was the priority. But when the Indo-China war broke out, Sanduk had to go back, and he continued his high school education at Siddhartha Vanasthali School, Kathmandu. Sanduk had the ambition to become a pilot at one point. But something happened then, that changed his mind and his future. His little sister, his closest companion, Yang La, died of tuberculosis. He had already lost an elder brother and a younger sister before this. And his family had been too poor to afford treatment each time. Sanduk thence resolved to become a doctor, and to work for the poor.

He gained a scholarship to study MBBS at King George's Medical College at Lucknow, India and then went on to do a 3-year Ophthalmology residency at the All India Institute of Medical Sciences, New Delhi; the latter in the beginning of the 1980s. Once this was concluded, he then went back to Nepal.

In Nepal, Dr Ruit was working on the National Blindness Survey when he met the iconic and incomparable eye-surgeon, Dr Fred Hollows. Their passion for their work soon brought them close, and Dr Hollows became Dr Ruit's mentor,



The Barefoot Surgeon:
The Inspirational Story of Dr Sanduk Ruit, the Eye Surgeon Giving Sight and Hope to the World's Poor

by Ali Grippier

inspiring him to choose his life's vocation: viz. to restore eyesight to people who are blind, but need not remain so. Dr Ruit went on to the Prince of Wales Hospital, Sydney, Australia, to study with Dr Hollows.

Both Dr Ruit and Dr Fred Hollows were convinced that all people with 'avoidable blindness' have the right to reinstated vision. As also, that people in developing countries needed accessible and affordable quality healthcare at par with those in the developed world. Cataract surgery in the West is typically performed with complex machines, which poor countries can hardly afford. And in Australia Ruit learned about a cataract micro-surgery technique using implanted intraocular lenses. He understood that this was exactly the technique he needed to take home to help the poorest of the poor. And he did just that. In 1994, Dr Ruit helped found the Tilganga Eye Center at Kathmandu with the help of the Fred Hollows Foundation; where he became the first Nepali surgeon to do cataract surgery with intraocular lens implants. He then refined small-incision microsurgery to remove cataracts

The study declared that not only was Dr Ruit's method less expensive and quicker, it also had the same outcome as the machine-induced surgery in the West. The outcome was put at 98% success at a six-month follow up.

without sutures and went on to pioneer a high quality micro surgical procedure in eye camps at remote locations.

Indeed, there was plenty of scepticism in the medical field when the doctor set out on his life's mission. But Dr Ruit's ingenuity brought on a surgical procedure which was safe, of excellent quality, and had high volume outputs at a fraction of the cost in other places. And this at make shift camps, in places that was thought filthy by western counterparts. It was at this juncture that the *American Journal of Ophthalmology* brought on a study of a randomized trial of Dr Ruit's technique. The study declared that not only was Dr Ruit's method less expensive and quicker, it also had the same outcome as the machine-induced surgery in the West. The outcome was put at 98% success at a six-month follow up. The sceptics did not have anything more to say.

Tilganga hospital gets around 2500 patients a week. But not all of them need to pay. And for those poor patients who cannot come to Kathmandu, Dr Ruit travels to them; trekking into remote parts of the country and outside and setting up mobile eye-camps at wherever possible. He walks miles, wades through waist deep water, rides horseback and what not, to reach that bunch of patients; who are waiting for him to open their window to the world. The moniker The Barefoot Doctor comes from his preference for being barefoot while doing surgery, for improved management of machines he operates.

Now called the Tilganga Institute of Ophthalmology, the venture manufactures 450,000 micro lenses needed in cataract surgery, of excellent quality, and at a mere US \$3.50 as against the US \$ 200 in the West. These are exported to at least 50 countries.

Dr Ruit is now in his mid-sixties but has not let up in going out to remote eye-camps. His astonishing skill and speed in surgery would be in demand in the highest-paying medical establishments, but the good man is intent on one thing, bringing vision to those who cannot afford treatment. His best reward? The happy expression on his patients' faces as they get back their vision. Nothing can beat that, says he.

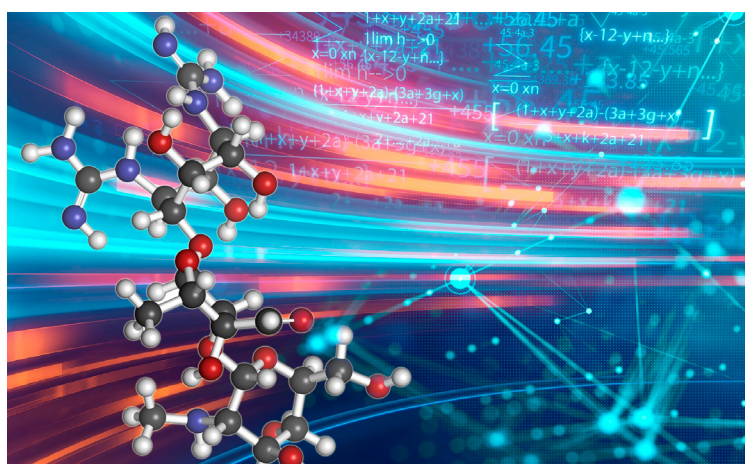
Dr Sanduk Ruit's biography, *The Barefoot Doctor* by Ali Gripper, lays out the life, trials and tribulations of this medical giant, in its truest essence.



by Ian Sample

AI Discovered a New Antibiotic for the First Time

Using a machine-learning algorithm, MIT researchers have identified a powerful new antibiotic that can kill many species of antibiotic-resistant bacteria.



A powerful antibiotic that kills some of the most dangerous drug-resistant bacteria in the world has been discovered using artificial intelligence. Although AI has been used to aid parts of the antibiotic-discovery process before, the researchers say that this is the first time it has identified completely new kinds of antibiotic from scratch, without using any previous human assumptions. The work, led by synthetic biologist Jim Collins at the Massachusetts Institute of Technology in Cambridge, is published in *Cell*.

Tests showed that the drug wiped out a range of antibiotic-resistant strains of bacteria, including *Acinetobacter baumannii* and *Enterobacteriaceae*, two of the three high-priority pathogens that the World Health Organization ranks as “critical” for new antibiotics to target.

“In terms of antibiotic discovery, this is absolutely a first,” said Regina Barzilay, a senior researcher on the project and specialist in machine learning at Massachusetts Institute of Technology (MIT).

“I think this is one of the more powerful antibiotics that has been discovered to date,” added James Collins, a bioengineer on the team at MIT. “It has remarkable activity against a broad range of antibiotic-resistant pathogens.”

To find new antibiotics, the researchers first trained a “deep learn-

ing” algorithm to identify the sorts of molecules that kill bacteria. To do this, they fed the program information on the atomic and molecular features of nearly 2,500 drugs and natural compounds, and how well or not the substance blocked the growth of the bug *E. coli*.

Once the algorithm had learned what molecular features made for good antibiotics, the scientists set it working on a library of more than 6,000 compounds under investigation for treating various human diseases. Rather than looking for any potential antimicrobials, the algorithm focused on compounds that looked effective but unlike existing antibiotics. This boosted the chances that the drugs would work in radical new ways that bugs had yet to develop resistance to.

Jonathan Stokes, the first author of the study, said it took a matter of hours for the algorithm to assess the compounds and come up with some promising antibiotics. One, which the researchers named “halicin” after Hal, the astronaut-bothering AI in the film 2001: A Space Odyssey, looked particularly potent.

Tests on bacteria collected from patients showed that halicin killed *Mycobacterium tuberculosis*, the bug that causes TB, and strains of *Enterobacteriaceae* that are resistant to carbapenems, a group of antibiotics that are considered the last resort for such infections. Halicin also cleared *C. difficile* and multidrug-resistant *Acinetobacter baumannii* infections in mice.

To hunt for more new drugs, the team next turned to a massive digital database of about 1.5bn compounds. They set the algorithm working on 107m of these. Three days later, the program returned a shortlist of 23 potential antibiotics, of which two appear to be particularly potent. The

scientists now intend to search more of the database.

Stokes said it would have been impossible to screen all 107m compounds by the conventional route of obtaining or making the substances and then testing them in the lab. “Being able to perform these experiments in the computer dramatically reduces the time and cost to look at these compounds,” he said.

This groundbreaking work signifies a paradigm shift in antibiotic discovery and indeed in drug discovery more generally.

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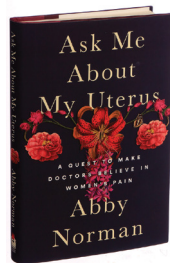
When Doctors Don't Listen to Women

Ask Me About My Uterus is an important addition to a long tradition of pain memoirs. Norman shares a particular tale of suffering but expresses a common frustration about the dearth of words to convey pain.

In the 1940s, in their quest to devise an objective pain scale, Cornell University researchers poked an increasingly hot metal rod into the hands of 13 women in the throes of childbirth. The volunteers were supposed to express how each level of heat compared with the others. But as labor progressed and the rod got hotter, they were in too much distress (and quite possibly distracted with other kinds of pain) to grapple with adjectives. Throbbing? Searing? A 7 on a scale of 10?

And therein lies the conundrum. Few of us can express our aches and hurts accurately, particularly when we are in the thick of them.

This quirky bit of medical history opens Abby Norman's vivid memoir, "Ask Me About My Uterus." But the focus of the book is really in the subtitle: "A Quest to Make Doctors Believe in Women's Pain." She builds a convincing case that women describing discomfort are more likely than men to be dismissed by physicians, but along the way tells a story that will resonate with anyone (man or woman) who has ever experienced pain.



ASK ME ABOUT MY UTERUS
A Quest to Make Doctors Believe in Women's Pain
Abby Norman

Written By:
Abby Norman

1272 pp.
Nation Books

Norman suffers from endometriosis — a chronic and debilitating illness triggered by uterine-like cells growing outside of the womb. Women with the disorder have heavy, agonizing periods along with a litany of other symptoms depending on where the rogue cells lurk. If they congregate near the bladder, urinating hurts; near the sciatic nerve, pain can shoot down the legs; inside the lung (a rare event), breathing can be stifled.

After one bout — "as sudden as a thunderclap. A stabbing pain in my middle" — Norman eventually got to an emergency room, where she was handed the typical 1-10 pain scorecard. She was still aching, but not in the original horrors of it all. So she didn't know how to assign a number to it: "Bad enough that I couldn't ignore it, which made it definitely higher than a four or five." She questioned whether she was a six or higher and whether the doctor would believe her anyhow.

Norman repeatedly told doctors that sexual intercourse ached "like a dull pinch, that resonated to my pelvis." No one paid attention until her

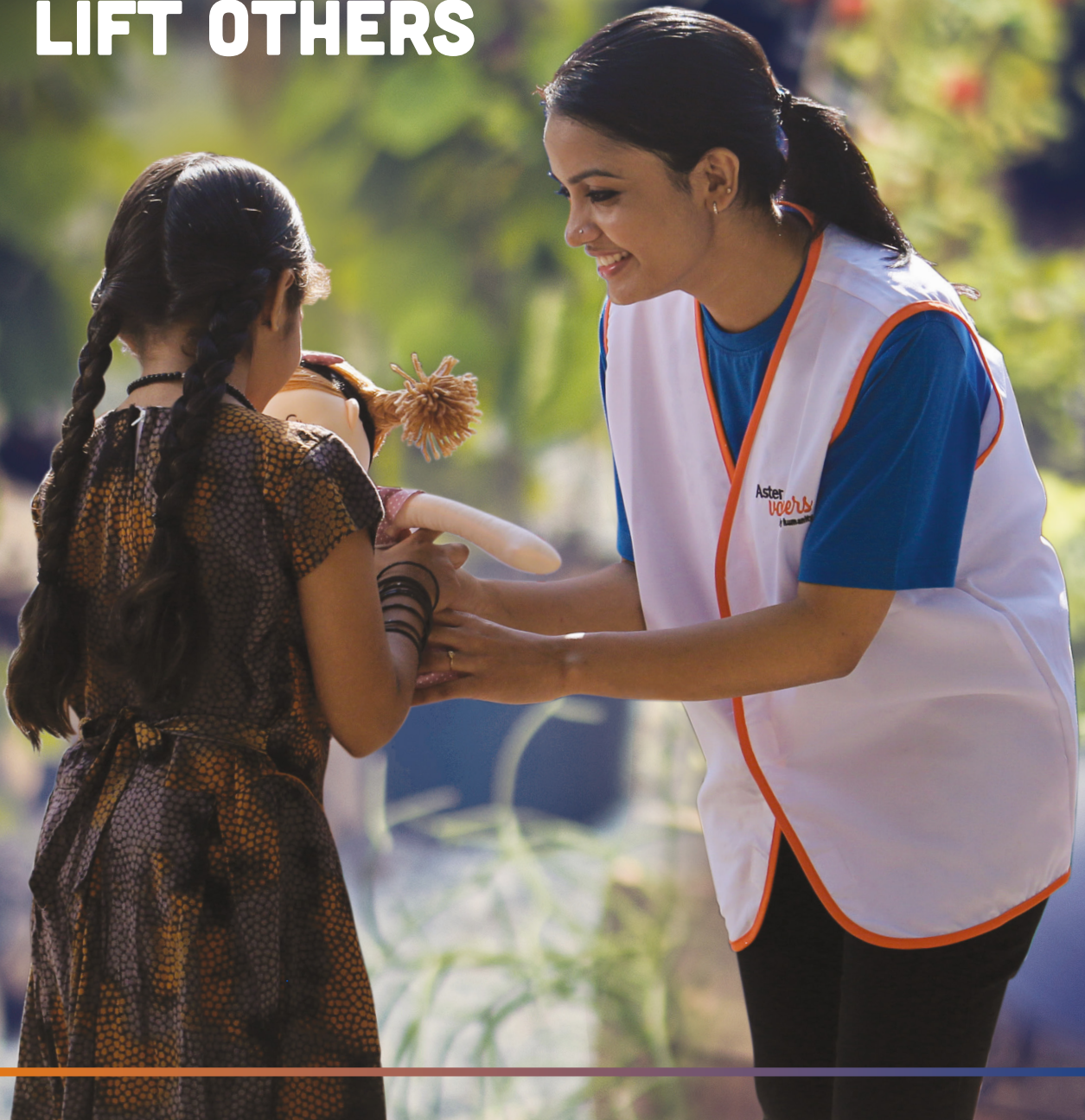
boyfriend accompanied her and mentioned his frustration. "Becoming a disappointment to a man," she writes, "seemed to do the trick."

Norman is a terrific storyteller with a gift for weaving memorable anecdotes, some drawn from medical history, others from recent scientific debates and most plucked from her own travails.

Norman's life is much more than a disease. She emancipated herself from her family at the age of 16 and sought solace in books, particularly scientific literature, to understand her symptoms. Many doctors chalked up her distress to physical expressions of a psychic trauma.

"Ask Me About My Uterus" is an important addition to a long tradition of pain memoirs. Norman shares a particular tale of suffering but expresses a common frustration about the dearth of words to convey pain. Any schoolgirl can talk about love, Virginia Woolf famously said, but "let a sufferer try to describe a pain in his head to a doctor and language at once runs dry."

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