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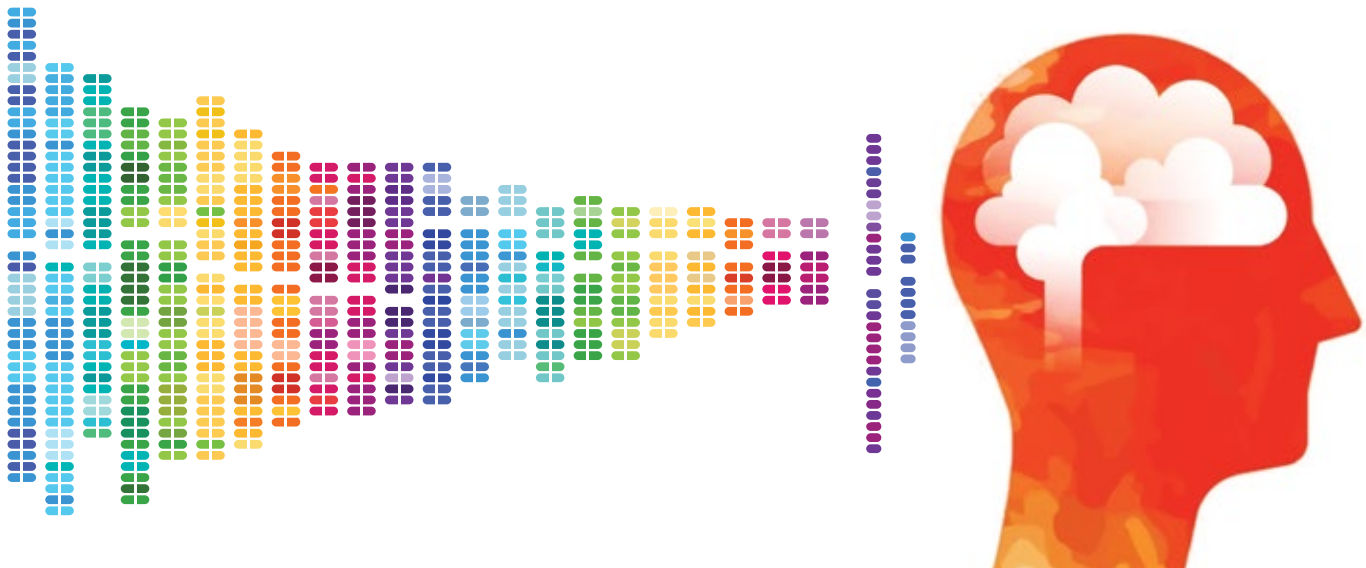
Cancer Deaths
India Ranks Second in Asia for Cancer Deaths, Study Reveals

Parkinson's
How Gut Bacteria Connect to Parkinson's Disease

TOP 10 Medical Breakthroughs of 2023

From revolutionary gene therapies that hold the potential to rewrite our genetic code to innovative treatments for Alzheimer's disease that offer a ray of hope to millions, these advancements represent the pinnacle of human achievement in the field of healthcare.



Shaping the future of healthcare

SIEMENS Healthineers

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January 2024

In 2021, researchers from Britain found that leptin, a hormone released by fat cells that limits hunger, acted on a part of the brain that also regulated sexual development. Mice and people with certain genetic mutations in this region experienced later sexual development.

And during the pandemic, pediatric endocrinologists from across the world noticed that referrals were increasing for earlier puberty in girls.

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Conversation

"Our relationship with the rest of the natural world is consumptive, intrusive, and disruptive. Those things shake loose viruses from their natural hosts. All these wild animals carry their own unique viruses."

Dr. Vanessa Kerry

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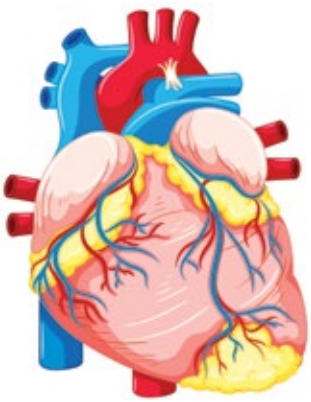

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GO GREEN

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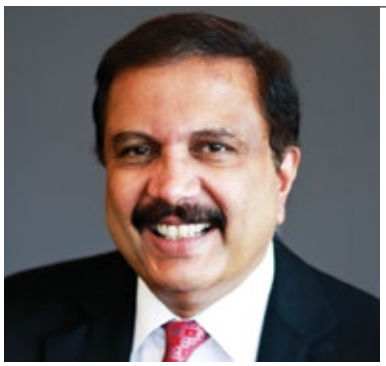
Prologue



UAE Declaration on Climate and Health: A Call to Action

In the dynamic landscape of modern medicine, breakthroughs have become the bedrock of progress, offering hope to millions grappling with debilitating conditions. From groundbreaking treatments for Alzheimer's to revolutionary gene therapies for sickle cell anemia and the application of Artificial Intelligence in pancreatic cancer treatment, 2023 witnessed remarkable strides in healthcare innovation.

However, as we celebrate these medical victories, it is imperative that we turn our attention to an equally pressing concern that demands our collective focus—the symbiotic relationship between healthcare and the climate crisis. In 2023, this relationship took center stage, emphasizing the vital intersection of medicine and the environment.

The importance of this intersection was underscored by the recently concluded COP28 summit in Dubai. The global community came together not only to discuss environmental policies and sustainable practices but also to recognize the profound impact of climate change on public health. It was heartening to witness healthcare garner the attention it deserves in the climate crisis discourse, acknowledging that a healthy planet is intrinsically linked to the well-being of its inhabitants.

The intersection of healthcare and the climate crisis took center stage during the first Health Day at the 28th UN Climate Change Conference (COP28). The historic moment, described as pivotal by top COP28 and World Health Organization (WHO) officials, saw 124 countries endorsing the Declaration of Climate and Health. The political declaration marks the first time that the health impacts of climate change have taken center stage in 28 years of UN climate talks.

The effects of climate change on health are diverse and far-reaching, from the rise in vector-borne diseases to the exacerbation of respiratory conditions due to air pollution. Looking ahead, the integration of healthcare and environmental stewardship is not just a trend but a necessity. As we celebrate medical breakthroughs, let us champion a holistic approach that considers the well-being of our planet and its people. The year 2023 marked a turning point where healthcare and the climate crisis converged, emphasizing the need for a united front in addressing the challenges that lie ahead.

Let us not only applaud the strides made in medicine but also commit ourselves to a future where the health of individuals and the health of our planet are intricately intertwined. Together, let us forge a path towards a healthier and more sustainable future.

Wishing you all a happy and healthy new year.

Dr Azad Moopen, MD, FRCP
Founder Chairman & Managing Director,
Aster DM Healthcare

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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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Case Reports

Editorial

Reflecting on Medical Marvels: A Year in Review

As we step into the promising dawn of 2024, it is with great pleasure that I present to you the first edition of *Aster Medical Journal* in 2024, featuring a comprehensive look back at the top 10 medical breakthroughs of 2023. In a year marked by unprecedented challenges, the medical community stood resilient, forging innovative paths towards advancements that promise to reshape the future of healthcare.

In the following pages, you will delve into a mosaic of discoveries, ranging from groundbreaking technologies to pioneering therapies, each contributing to the collective tapestry of medical progress.

At the forefront of our spotlight is the revolutionary gene-editing technique that emerged last year. This transformative technology holds the potential to cure genetic diseases at their roots, offering hope where previously there was none. As we traverse the intricate landscape of molecular medicine, the strides made in gene therapy stand as a beacon, illuminating a path towards a future where inherited conditions may become a relic of the past.

2023 also witnessed a renaissance in neuroscience, with breakthroughs in neurodegenerative diseases providing rays of optimism. Researchers have unveiled novel insights into the intricate workings of the brain, bringing us one step closer to unraveling the mysteries behind conditions such as Alzheimer's and Parkinson's. These discoveries not only deepen our understanding but pave the way for targeted interventions that may redefine the landscape of neurological healthcare.

In the field of infectious diseases, the development of mRNA-based vaccines has undoubtedly been a game-changer. With successful deployment against emerging threats, these vaccines exemplify the power of collaboration and innovation in times of crisis. As we navigate the ongoing challenges posed by infectious agents, the strides made in vaccine technology serve as a testament to our ability to adapt and overcome.

As you peruse the pages of this edition, you will also find an array of research articles and medical case studies, each contributing to the ever-expanding body of knowledge in the medical sciences. From the intricacies of personalized medicine to the nuances of patient-centered care, these studies underscore the holistic approach that defines modern healthcare.

In closing, this January edition encapsulates not just the achievements of the past year but also the enduring spirit of resilience and ingenuity that defines the medical community. As we embark on a new year, let us carry forward the lessons learned, the challenges overcome, and the victories achieved, standing united in our commitment to advancing the frontiers of medical knowledge and care.

Happy new year and happy reading.

Dr Geetha Philips, MD, FRCP

Gaza: WHO describes “sickening scenes” in hospital

The World Health Organization has described the harrowing scenes unfolding at Al Aqsa Hospital—the only functioning hospital in the governorate of Deir al Balah in central Gaza—as medical aid organisations say they were forced to pull out staff amid evacuation orders by the Israeli military. WHO visited the hospital on 7 January. Director general Tedros Ghebreyesus said, “Staff saw sickening scenes of people of all ages being treated on blood-streaked floors and in chaotic corridors. An unidentified child laid dead, partially covered by a sheet, on a bed. The bloodbath in Gaza must end."

UK Maternal Death Rates Surge to Levels Unseen in Two Decades

The MBRRACE-UK Collaboration's latest data reveals a concerning rise in maternal mortality rates in the UK, reaching levels not witnessed since 2003-05. Led by Oxford Population Health’s National Perinatal Epidemiology Unit, the investigation focused on women who died during or shortly after pregnancy between January 2020 and December 2022.

Key findings include:

- The maternal death rate from 2020-22 was 13.41 deaths per 100,000 maternities, a significant increase compared to 8.79 deaths per 100,000 maternities in the previous three-year period (2017-19).
- Excluding COVID-19-related deaths, the maternal death rate for 2020-22 (11.54 deaths per 100,000 maternities) still surpasses that of 2017-19.
- Thrombosis and thromboembolism emerged as the primary cause of maternal deaths, with COVID-19 ranking second, followed by heart disease and mental health-related issues.

Hidden Hazards: Bottled Water Contains 10x More Microplastics

In a new study conducted by scientists at Columbia University and Rutgers University, bottled water is revealed to contain significantly higher levels of microscopic plastic pollutants than previously believed. While marketed as pure and natural, the study challenges the perception of bottled water as a safer alternative to tap water.

The research, published in the Proceedings of the National Academy of Sciences on January 8, utilized innovative laser technology to detect even smaller plastic fragments, revealing a tenfold increase in the number of particles found in bottled water. On average, an alarming 240,000 plastic fragments per liter were identified, with approximately 90% classified as nanoplastics—particles smaller than 1 micrometer.

Nanoplastics, unlike their larger counterparts, can enter the bloodstream through the intestine and lungs, posing potential health risks. The study suggests that these tiny particles can travel to vital organs, including the heart and brain, and may even cross the placenta to affect unborn infants.

The brief

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The Brain–spine interface

In a groundbreaking development, neuroscientists in Switzerland have pioneered a wireless digital bridge that successfully restores the connection between the brain and the spinal cord. This medical breakthrough has enabled Gert-Jan Oskam, paralyzed in a bicycle accident over a decade ago, to regain the ability to stand, walk naturally, and even climb stairs.

The brain–spine interface, developed by researchers at the Ecole Polytechnique Federale de Lausanne (EPFL), acts as a "wireless digital bridge," allowing Oskam to reestablish control over his leg movements. This cutting-edge technology utilizes artificial intelligence to convert thoughts related to movement into actions, creating a direct link between the brain and specific spinal cord regions responsible for walking.

Mr. Oskam underwent two surgeries to implant electrodes in both the brain and spinal cord, forming the crucial components of the digital bridge.

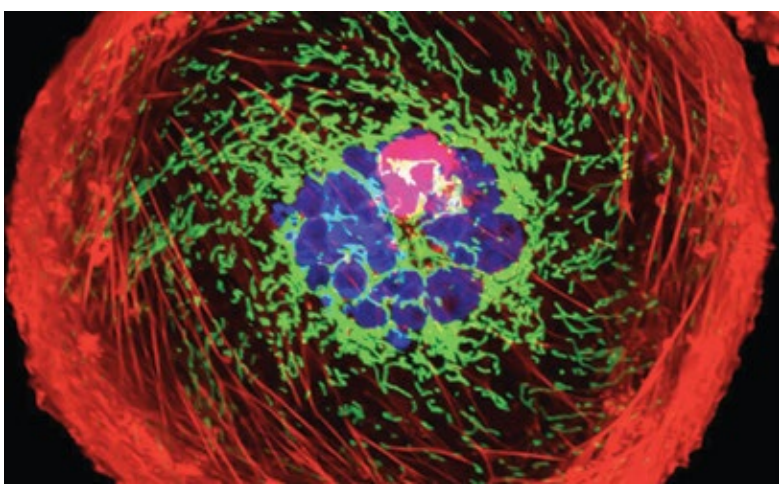
This pioneering achievement holds significant promise for individuals with spinal cord injuries, offering a transformative pathway to restoring mobility and enhancing overall quality of life.

India Ranks Second in Asia for Cancer Deaths, *Lancet* Study Reveals

Researchers found that India, along with China and Japan, are the three leading countries in Asia in terms of number of new cases and deaths.

A recent study published in The *Lancet* Regional Health Southeast Asia journal highlights India's significant contribution to the cancer burden in Asia. In 2019, India recorded approximately 12 lakh new cancer cases and 9.3 lakh deaths, securing the second-highest position in the region for that year. Alongside China and Japan, India emerged as one of the three leading countries in terms of both new cases and deaths, signifying the escalating threat of cancer as a public health concern.

The study, conducted by an international team of researchers, examined the temporal patterns of 29 cancers in 49 Asian countries from 1990 to 2019. While China led with 48 lakh new cases and 27 lakh deaths, Japan reported nine lakh new cases and 4.4 lakh deaths. Tracheal, bronchus, and lung (TBL) cancer emerged as the predominant type in Asia, accounting for an estimated 13 lakh cases and 12 lakh deaths.



Among women, cervical cancer ranked prominently in several Asian countries, with the human papillomavirus (HPV) vaccine proving effective in preventing the disease. Notably, factors such as smoking, alcohol consumption, and ambient air pollution remained dominant contributors to cancer risk. The rising cancer burden linked to increasing air pollution, especially in Asia, raised concerns among researchers.

The study emphasized the urgent need for addressing risk factors, including smoking and air pollution, to mitigate the cancer burden. It also underscored the importance of comprehensive cancer screening, treatment accessibility, and affordability, particularly in low- and medium-income countries where oncologic infrastructure is often scarce, leading to delayed diagnosis and treatment. The findings highlight the necessity of policy initiatives focusing on both prevention and affordable treatment to effectively combat the growing cancer epidemic in Asia.

They found that in Asia, the leading cancer was that of tracheal, bronchus, and lung (TBL), resulting in an estimated 13 lakh cases and 12 lakh deaths. It was also found to be most frequent in men and third most frequent in women.

"Specifically among women, cervical cancer is ranked second or among top-five cancers in several Asian countries. The human papillomavirus (HPV) vaccine, introduced in 2006, has proved to be effective in preventing the disease and reducing HPV-related deaths," the researchers said.

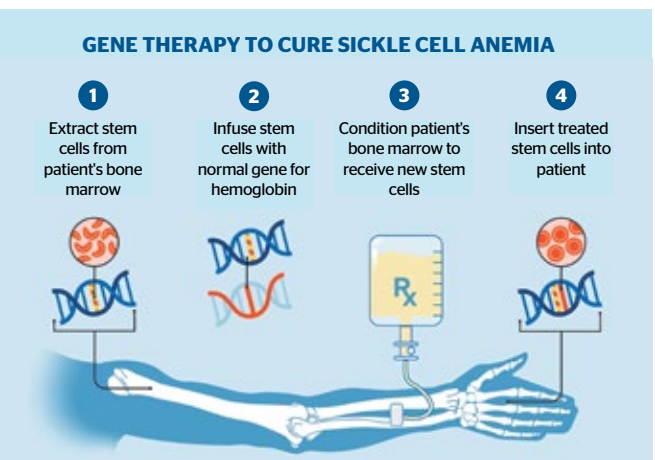
TOP 10 Medical Breakthroughs of 2023

JOIN US ON A JOURNEY THROUGH THE TOP 10 MEDICAL BREAKTHROUGHS OF 2023.

In the fast-paced world of medical science, 2023 was a year that witnessed unprecedented breakthroughs, pushing the boundaries of what we once deemed possible. From revolutionary gene therapies to innovative Alzheimer's treatments, these advancements promise to reshape the landscape of healthcare. Join us on a journey through the top 10 medical breakthroughs of 2023.

1 CASGEVY - World's First CRISPR-Based Gene Therapy

In a historic stride for medical science, CASGEVY, the groundbreaking CRISPR-based gene therapy, achieved regulatory approval in the United Kingdom on November 16 and in the United States on December 8. Conceived by Nobel laureates Emmanuelle Charpentier and Jennifer Doudna, CASGEVY emerges as a revolutionary therapeutic approach aimed at rectifying defective hemoglobin genes, offering a potential lifelong remedy for conditions such as sickle cell disease and beta thalassemia.



This pioneering technique involves a multi-step process: bone marrow stem cells are extracted from the patient, meticulously edited in a laboratory to rectify hemoglobin gene errors using CRISPR technology, and subsequently reintroduced into the patient's system through infusion. CASGEVY's approval signifies a significant leap in the quest for effective treatments for genetic diseases, cancer, and infertility, highlighting the transformative potential inherent in CRISPR technology.

As the inaugural success in a realm teeming with possibilities, CASGEVY not only holds promise for those grappling with hemoglobin-related disorders but also serves as a herald of an era wherein CRISPR-based therapies may unlock novel solutions for a myriad of medical challenges.

2 Leqembi: A Ray of Hope for Alzheimer's Patients

Taking a significant step in the battle against Alzheimer's disease, the FDA has granted full approval for Leqembi, a monoclonal antibody designed to target amyloid plaques in the brain—an integral characteristic of the disease. While not presenting a cure, Leqembi has demonstrated the ability to slow declines in memory

and cognitive function by approximately 30% over an 18-month period, exhibiting particular efficacy when administered in the early stages of the disease.

This milestone heralds a new era in Alzheimer's treatment, offering fresh possibilities and renewed hope for individuals grappling with this debilitating condition. Leqembi's approval signifies a crucial advancement, providing a tangible opportunity to enhance the quality of life for those affected by Alzheimer's and their families. As a promising intervention that addresses the progression of the disease, Leqembi stands as a beacon of optimism, underscoring the ongoing efforts to alleviate the burden of Alzheimer's on individuals and society as a whole.

3 Male-Only Reproduction in Mice Achieved by Japanese Researchers

In a groundbreaking scientific achievement, Japanese researchers have shattered traditional reproductive paradigms by successfully producing healthy and fertile mice without the involvement of a female. This extraordinary feat involved utilizing stem cells derived from the skin cells of a male mouse to generate eggs, which were subsequently fertilized with sperm from another male. The fertilized eggs were then transferred into a female mouse for gestation.

While the success rate indicated that only a small percentage of embryos developed into viable mice, the resulting pups exhibited normal growth and fertility as adults. This pioneering research challenges conventional notions of reproduction and opens avenues for further exploration into alternative methods. It is important to note that the

direct applicability of these findings to humans remains uncertain.

This breakthrough not only expands our understanding of reproductive biology but also paves the way for future investigations into unconventional methods of reproduction. By challenging established norms, this research lays a robust foundation for scientific inquiry that may redefine the boundaries of fertilization and reproduction, sparking discussions about the potential applications and ethical considerations surrounding such innovative technologies.

4 Scientists Unveil the First Complete Brain-Wiring Diagram of a Fruit Fly

In a remarkable scientific endeavor, researchers have achieved a significant milestone by producing the inaugural complete brain-wiring diagram of an insect, specifically focusing on a fruit fly larva. While previous mapping efforts had successfully navigated the brains of roundworms, sea squirts, and marine worms, the unique challenge posed by the complexity of a fruit fly larva's brain, which comprises over 3,000 neurons and half a million connections, required a dedicated five-year effort by an international team of scientists.

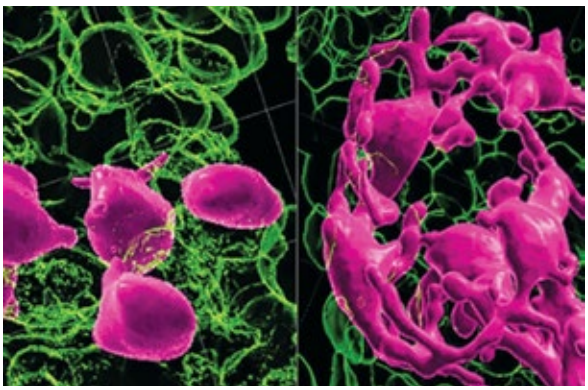
This comprehensive mapping initiative provides unprecedented insights into the neural circuits of the fruit fly larva, marking a crucial advancement in our understanding of insect brain functionality. Beyond its entomological significance, the research holds promise for broader applications, offering valuable insights into human brain function, neurological diseases, and the development of more efficient artificial intelligence systems.

The successful completion of this intricate brain-wiring diagram not only expands our knowledge of insect neurobiology but also serves as a stepping stone for future research endeavors. The potential applications of this breakthrough extend into the realms of neuroscience, as well as artificial intelligence, providing a foundation for further exploration and innovation in these critical fields.

5 Unraveling the Mystery of Gray Hair Formation: Insights from New York University Researchers

In a quest to demystify the intriguing process of gray hair formation, researchers at New York University have made significant strides, uncovering a key revelation: pigment-producing cells

This extraordinary feat involved utilizing stem cells derived from the skin cells of a male mouse to generate eggs, which were subsequently fertilized with sperm from another male.



known as melanocytes can become entrapped in an immature state. This stalling phenomenon hampers the normal development of hair color, ultimately resulting in the manifestation of graying strands.

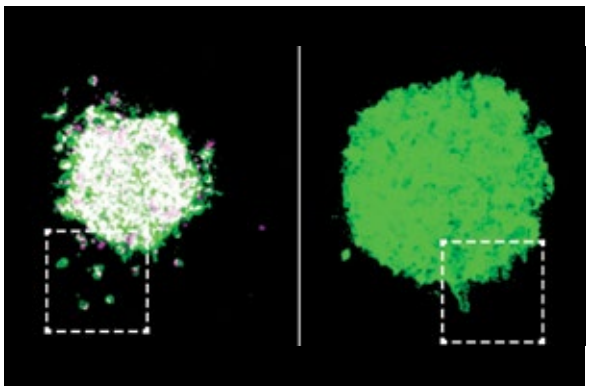
The study meticulously observed melanocyte stem cells navigating within individual hair follicles, dynamically transitioning between gray immature and mature colored states. This groundbreaking research not only deepens our comprehension of the intricate aging process but also unveils new avenues for potential interventions aimed at preventing or even reversing the phenomenon of graying hair.

By shedding light on the underlying mechanisms that contribute to the loss of hair color, this research contributes to a broader understanding of the aging-related changes in our bodies. Furthermore, the findings pave the way for future endeavors in developing innovative interventions that could have a transformative impact on how we perceive and address the natural aging of our hair.

6 Unveiling the Partnership: Bacteria's Contribution to Cancer Aggression

Bacteria found within tumors may enhance the aggressiveness of cancer, as indicated by recent research from the Fred Hutchinson Cancer Center. The oral bacterium Fusobacterium nucleatum, present in dental plaque and detected in oral and colorectal tumors, was the focus of two studies exploring the impact of microbes on tumors.

The research revealed that F. nucleatum and other bacteria inhabit areas of tumors associated with immune system suppression. Tumor cells infected with bacteria exhibited changes in molecules related to cell migration and metastasis.



In a petri dish, clusters of F. nucleatum-infected colorectal tumor cells attracted a specific type of cell that could mediate immunosuppression, and infected cells were more prone to migrate outside the cluster, resembling metastatic cells.

Published in Nature, the study proposes that bacteria may promote cancer progression by facilitating metastasis and creating an environment resistant to immune system destruction.

The data emphasizes "a crucial role for intratumoral bacteria," underscoring the need for further research in this area, according to a separate commentary in the journal. The findings also suggest that strategies to control bacteria might play a role in cancer treatment, according to a post by Fred Hutch discussing the research led by Assistant Professors Christopher Johnston and Susan Bullman.

In a second study published in Cell Reports, researchers sought compounds that specifically inhibit F. nucleatum. Surprisingly, among 1,846 tested compounds, certain chemotherapy agents, including the commonly used drug 5-fluorouracil, were found to inhibit F. nucleatum. Other bacteria in colorectal tumors were observed to break down 5-fluorouracil, potentially contributing to chemotherapy resistance.

Although 5-fluorouracil is known for inhibiting cancer by impeding cell division, it is more effective against colorectal cancer than other tumor types, possibly due to its ability to also eliminate Fusobacteria, according to the researchers.

These findings challenge the notion that intratumoral microbes are passive observers during disease progression, emphasizing the importance of considering the microbiota in designing optimal cancer treatments, as highlighted by Johnston in the post on the new studies. The results align with earlier studies linking F. nucleatum to tumor progression and worse patient outcomes in colorectal cancer and may have implications for various cancer types, challenging the previous belief that tumors are sterile environments.

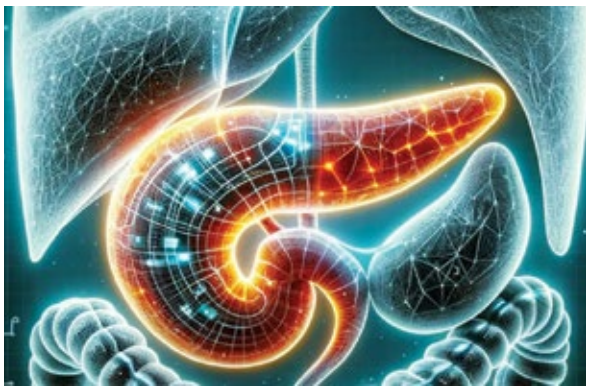
A groundbreaking discovery has unveiled a previously unrecognized alliance between certain bacteria residing in gastrointestinal tract tumors and cancer cells. This collaborative effort actively supports cancer progression while aiding in evading the body's immune response. Intriguingly, these bacteria have also been identified as contributors to drug resistance, diminishing the effectiveness of cancer treatments.

This revelation not only illuminates the intricate relationship existing between tumors and the microbiome but also holds profound implications for the field of oncology. The identified collaboration between bacteria and cancer cells suggests a previously overlooked dimension in cancer aggression and therapeutic challenges. However, it also opens up new avenues for targeted cancer therapies. By disrupting this symbiotic relationship, there is potential to enhance treatment efficacy and overcome the hurdles posed by drug resistance.

This groundbreaking finding marks a crucial step forward in our understanding of the multifaceted interactions within the tumor microenvironment. Armed with this knowledge, researchers are now better positioned to explore innovative strategies that may reshape the landscape of cancer treatment, providing renewed hope for more effective and targeted therapeutic interventions.

7 AI for Early Detection of Pancreatic Cancer

Advancements in AI technology have significantly elevated the accuracy of pancreatic cancer detection, marking a substantial leap from a mere 10% to nearly 40% compared to conventional methods. This progress signifies a pivotal step forward in the ongoing battle against pancreatic cancer. The PRISM study, conducted by the Massachusetts Institute of



Technology's Computer Science & Artificial Intelligence Laboratory and Limor Appelbaum et al., demonstrated that AI achieved a detection rate of 35.9%, showcasing a considerable improvement over conventional methods.

AI's integration into healthcare represents a promising and impactful innovation, holding immense potential for the future of cancer detection and treatment. Beyond enhancing diagnostics, AI contributes to personalized treatments and operational efficiency, ultimately leading to improved patient outcomes.

This monumental breakthrough has the potential to reshape early detection strategies for pancreatic cancer—a disease often identified in advanced stages, leading to challenges in treatment and reduced patient outcomes.

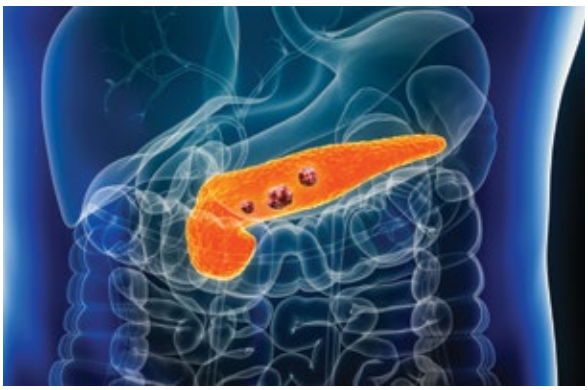
AI algorithms exhibit precision in analyzing medical images, aiding in early disease detection, and play a pivotal role in personalized medicine by scrutinizing patient data to tailor treatment plans. Nevertheless, it is imperative to address challenges such as data privacy, security, and ethical considerations associated with this transformative technology.

An outstanding AI-powered tool in the field is PANDA, developed by Alibaba Group's research institute, DAMO Academy. PANDA excels in screening for early signs of pancreatic cancer, one of the deadliest cancers globally. Demonstrating a sensitivity 34.1% higher than radiologists, with a false positive rate of only one in every 1,000 tests, PANDA has proven its efficacy. Validated in a clinical setting with over 20,000 patients, PANDA identified pathological changes in 31 patients that had been overlooked by doctors. This groundbreaking tool has the potential to integrate seamlessly into routine medical checkups or emergency department visits and may extend its capabilities to detect other types of cancer in the future.

AI technology is driving significant progress in pancreatic cancer detection, with tools like PANDA and the PRISM study showcasing heightened sensitivity and specificity compared to traditional methods. The application of AI extends beyond pancreatic cancer, with companies like Paige developing AI-enabled applications for detecting various cancers from diverse tissue types. This underscores the transformative potential of AI in revolutionizing the field of oncology.

8 Comprehensive RSV Vaccination Strategies Across Age Groups: A Milestone in 2023

The year 2023 witnessed a significant stride in Respiratory Syncytial Virus (RSV) prevention with the approval of vaccines tailored to cater to diverse age groups. Notably, for adults aged 60 and above, two FDA-approved vaccines have been introduced to provide robust protection against serious complications, acknowledging the increased vulnerability associated with aging immune systems.



In addition to vaccines for older adults, a pioneering maternal RSV vaccine has been approved for administration during the third trimester. This innovative approach aims to transfer protective antibodies to infants, offering defense during the critical first six months of life. Furthermore, monoclonal antibody shots have been made available for infants under 8 months, presenting an additional layer of preventive measures.

These multifaceted and age-specific vaccination strategies represent a substantial advancement in RSV management. By addressing the varying susceptibility across different age demographics, the approved vaccines in 2023 mark a pivotal step forward in fortifying our defenses against RSV and mitigating the potential impact of this respiratory virus on individuals at different stages of life.

9 Revolutionary Stride in Pancreatic Cancer Treatment: Personalized mRNA Vaccine Unveiled

Pancreatic ductal adenocarcinoma (PDAC), the most lethal form of pancreatic cancer, remains a formidable challenge with only a 12% survival rate five years post-treatment. Despite advancements in therapies, immunotherapies, which have revolutionized the treatment landscape for many cancers, have shown limited efficacy in PDAC due to uncertainties about the presence of neoantigens—proteins that can be targeted by the immune system.

Dr. Vinod Balachandran and his NIH-funded research team at Memorial Sloan Kettering Cancer Center (MSKCC) have embarked on a groundbreaking approach using personalized mRNA cancer-treatment vaccines. Their method aims to enable immune cells to recognize specific neoantigens on patients' pancreatic cancer cells. Results from a small clinical trial, published on May 10, 2023, in Nature, shed light on the potential of this experimental treatment.

Following PDAC surgery, tumor samples from 19 patients were sent to BioNTech, the company behind a COVID-19 mRNA vaccine, for gene sequencing. This process identified proteins capable of triggering an immune response, forming the basis for creating personalized mRNA vaccines. Each vaccine, targeting up to 20 neoantigens, was successfully tailored for 18 out of 19 participants within an average timeframe of about nine weeks from surgery to the first vaccine dose.

All patients received atezolizumab, an immune checkpoint inhibitor, before vaccination to prevent cancer cells from suppressing the immune system. The mRNA vaccine was administered in nine doses over several months, with standard chemotherapy for PDAC starting after the eighth dose, followed by a booster dose.

Sixteen participants were healthy enough to receive at least some vaccine doses. In half of these cases, the vaccines activated potent immune cells, known as T cells, capable of recognizing patient-specific pancreatic cancer. A novel computational strategy developed by Dr. Benjamin Greenbaum's lab at MSKCC tracked T cells produced post-vaccination, revealing that these immune cells were absent in the blood before vaccination. Among the eight patients with robust immune responses, half had T cells targeting more than one vaccine neoantigen.

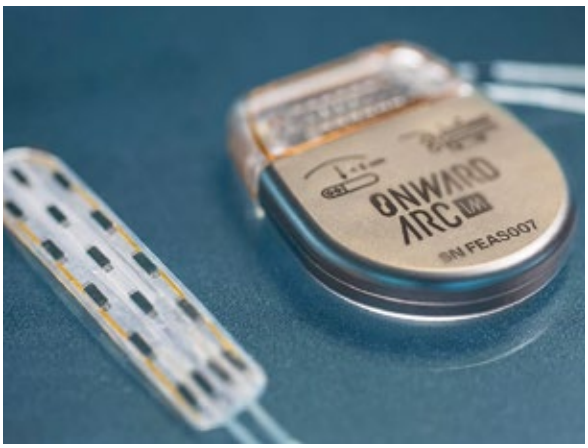
Remarkably, a year and a half post-treatment, none of the individuals with a strong T cell response experienced cancer recurrence. Conversely, those without a robust immune

response saw cancer recurrence within just over a year. In a noteworthy case, T cells produced by the vaccine seemingly eradicated a small liver tumor. These findings suggest that the activated T cells played a crucial role in restraining pancreatic cancers.

Dr. Balachandran expresses excitement about the potential of personalized vaccines in mobilizing the immune system against pancreatic cancer, emphasizing the urgent need for improved treatments. Plans are underway for a larger clinical trial to further investigate and refine this innovative approach. Additional research is essential to unravel the factors influencing varied immune responses and optimize the application of personalized vaccines for treating deadly cancers beyond pancreatic malignancies.

10 Brain-Computer Interface Enabling Paralyzed Man to Walk

A collaborative team led by Grégoire Courtine at Ecole Polytechnique Fédérale de Lausanne (EPFL), Jocelyne Bloch at Lausanne University Hospital and EPFL, and Guillaume Charvet at CEA-Leti achieved a remarkable breakthrough in neurotechnology by developing a digital bridge that restores communication between the brain and spinal cord. This innovative system has demonstrated the ability to enable a paralyzed man to stand and walk naturally, showcasing its tremendous promise for individuals with spinal cord injuries.



The development involves a brain–spine interface, utilizing two implantable systems to address the communication breakdown resulting from spinal cord injuries. The brain-monitoring system employs a 64-channel grid of electrodes implanted in the participant's brain, decoding real-time brain signals with an advanced artificial intelligence algorithm. These decoded signals predict motor intentions and convert them into stimulation commands, activating leg muscles. Simultaneously, a neurostimulator connected to an electrode array, implanted over the spinal cord region controlling leg movement, delivers electrical stimulation, creating a wireless digital bridge between the brain and spinal cord.

Successfully tested on a 38-year-old male with a decade-old spinal cord injury, the digital bridge allowed the participant to regain intuitive control over his leg movements. Achieving milestones such as standing, walking with crutches, climbing stairs, and navigating complex terrains, the brain–spine interface remained reliable and stable for over a year, including unsupervised home usage. This breakthrough not only brings hope to individuals with spinal cord injuries but also marks a significant stride in enhancing the quality of life for those affected by paralysis.

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Original Study

Epidemiological, Clinical and Microbiological Profile of Infective Endocarditis and its Outcome: Insights from a Tertiary Care Center in India

Dr. Sunil Roy T[1], Dr. Anup R Warrier[1], Dr. Arun Wilson[1], Dr. Thamizharasan V[1], Sulfia Jabbar P[1], Anithadevi T S[1], Dr. Anil Kumar R[1]

1. Aster Medcity, Kochi, Kerala—India

Corresponding Author:
Dr. Sunil Roy T N,
Consultant Interventional Cardiologist, Aster Medcity, Kochi —682027
Tel: +91 82818 69967
Email: drsunil.roy@asterhospital.com

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Infective endocarditis, Native valve, Prosthetic valve, Viridians Streptococci, Staphylococci

Abstract

Introduction: Infective Endocarditis (IE) is a serious condition with varied clinical presentations posing significant morbidity and mortality. This study aimed to describe the epidemiological, clinical, and microbiological profiles of IE.

Methodology: This retrospective cohort study was conducted at a quaternary care center in Kochi, India, for a period of six years. The study included 104 patients, and the pediatric population was excluded. Data were collected from electronic medical records and statistically analyzed.

Results: There were 104 patients with IE, of whom 71 were culture—positive. The mortality rate in this study was 16.3%. Native valves were affected in 80.8% of the cases. Gram—positive organisms were isolated in 52(73.24%), gram—negative in 12(16.9%), and fungi in 5 (7.04%) cases. Culture growth yielded two different organisms in two patients (2.82%). Streptococci were the most common organism isolated 21(29.57%), of which viridians streptococci accounted for 20.12%, followed by Staphylococci 20(28.16%), and Enterococci 11(10.6%). The study showed a significant association between complications like heart and renal failure, sepsis, septic and cardioembolic shock, embolism, and MODS with death.

Conclusion: Over a period of six years, a study was conducted to determine the epidemiological, clinical, and microbiological profiles of infective endocarditis. The findings showed streptococci, followed by staphylococci as the primary causative agent of IE, with the native valve being the most commonly affected.

INTRODUCTION

Infective endocarditis (IE) is a pathological condition characterized by a significant propensity for morbidity and mortality. The incidence varies between 1.7 to 6.2 cases in the Western population per 100000 patient—years (male—to—female ratio of 2:1) to 14.5 cases per 100000 patient—years in India.[1] The average age of individuals with IE was found to be greater than 65 years of age at present. Predisposing factors in this age group include prosthetic valves, indwelling cardiac devices, valvular diseases, hemodialysis, and diabetes mellitus (DM).[2] Rheumatic heart disease accounts for less than 5% of all IE cases, whereas recreational intravenous drug use is an emerging risk factor, contributing to approximately 10% of all cases of IE.[3]

The causative agents of IE include gram—positive cocci belonging to the Staphylococcus, Streptococcus, and Enterococcus species. In 80% to 90% of the cases, Staphylococcus aureus is the most frequently isolated pathogen that develops antibiotic resistance and methicillin—resistant strains.[4] Coagulase—negative staphylococci colonize indwelling catheters and devices, and are the most common isolates in early prosthetic valve endocarditis. Streptococcal infective endocarditis is common in low—income countries, and enterococci account for 10% of all cases. Other organisms causing IE include fastidious bacteria, zoonotic bacteria, and fungi. The clinical presentation ranges from general malaise to shock, depending on the virulence of the pathogen and host immune response. IE should be considered in cases of sepsis of unknown origin or fever with risk factors. The significance of echocardiography in patients presenting with Staphylococcus aureus bacteremia has been highlighted in the literature, given its association with IE in 20—30% of cases.[5,6] This study aimed to review the epidemiological, clinical, and microbiological profile of IE with outcomes in a quaternary care center.

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MATERIALS & METHODS

This retrospective cohort study was conducted at a quaternary care center in Kochi, Kerala, India. Patients with a definite diagnosis of IE according to the modified Duke Criteria between December 2015 and December 2021 were included in this study. Patients aged <18 years were excluded from the study. The study was reviewed and approved by the Institutional Ethics Committee. Data were collected from electronic medical records.

This retrospective cohort study was conducted at a quaternary care center in Kochi, Kerala, India. Patients with a definite diagnosis of IE according to the modified Duke Criteria between December 2015 and December 2021 were included in this study. Patients aged < 18 years were excluded from the study. The study was reviewed and approved by the Institutional Ethics Committee. Data were collected from electronic medical records.

Epidemiological, clinical, microbiological, echocardiographic, and laboratory data were collected. Epidemiological details included patient age, sex, length of hospital stay, coronary artery disease, atrial fibrillation, history of any surgeries (including valve replacement surgeries and cardiac surgeries), CKD on dialysis, diabetes mellitus, hypertension, and dyslipidemia. Clinical details included the presence of fever, angina, syncope, or dyspnea and the development of any complications such as heart failure, renal failure, cardioembolic stroke, septic shock, sepsis, embolism, and multiorgan dysfunction syndrome (MODS). Echocardiographic data collected included the presence of vegetation on any of the valves, the presence of a regurgitant or stenotic lesion on any of the valves, the presence of an intracardiac abscess, pseudoaneurysm, paravalvular leak, and pericardial/pleural effusion. The microbiological and laboratory data collected included the name of the infective organism grown in the blood culture/detected by PCR. The number of deaths in patients admitted with IE and the causes of death were examined. Data on the blood culture results and microorganism isolation were also collected. Microbiology laboratories use standardized methods to identify microorganisms and antimicrobial susceptibility. Additional tests, including fungal cultures, serology for Coxiella burnetti using enzyme immunoassay serology and Brucella melitensis, Brucella abortus and Bartonella hensale serologies byenzyme—linked immunoassay [7] were done for blood—culture negative endocarditis.

Table 1. Baseline characteristics of the study population

Parameters		Mortality		Total (n=104)	Sig.
		Yes (n=17)	No (n=87)		
Age, Median (IQR)		65 (57–71.5)	57 (45–65)	57 (47–66)	**0.034*a**
Length of hospital stay, Median (IQR)		7 (4.5–23.5)	11 (7–16)	10 (6–16.75)	0.706a
Gender	Male	11 (64.7%)	62 (71.3%)	73 (70.2%)	0.773b
	Female	6 (35.3%)	25 (28.7%)	31 (29.8%)	
Comorbidities	Diabetes mellitus	10 (58.8%)	33 (37.9%)	43 (41.3%)	0.177 b
	Atrial Fibrillation	4 (23.5%)	4 (4.6%)	8 (7.7%)	**0.023*c**
	History of Surgery	7 (41.2%)	3 1(35.6%)	38 (36.5%)	0.784 b
	Cardiac Devices	3 (17.6%)	17 (19.5%)	20 (19.2%)	0.856c
	CKD on Dialysis	5 (29.4%)	12 (13.8%)	17 (16.3%)	0.148 b
	CAD	5 (29.4%)	25 (28.7%)	30 (28.8%)	0.955 b
	Hypertension	11 (64.7%)	36 (41.4%)	47 (45.2%)	0.11 b
	Dyslipidemia	5 (29.4%)	11 (12.6%)	16 (15.4%)	0.133 b
Clinical Profile	Fever	11 (64.7%)	49 (56.3%)	60 (57.7%)	0.599 b
	Angina	0 (0%)	6 (6.9%)	6 (5.8%)	0.586c
	Syncope	4 (23.5%)	2 (2.3%)	6 (5.8%)	**0.006*c**
	Dyspnea	12 (70.6%)	34 (39.1%)	46 (44.2%)	**0.030*b**
Echocardiography findings	Native valve IE	14 (82.4%)	70 (80.5%)	84 (80.8%)	0.856c
	Prosthetic valve IE	3 (17.6%)	14 (16.1%)	17 (16.3%)	0.874c
	Device related IE	0 (0%)	3 (3.4%)	3 (2.9%)	0.437c
	Aortic valve vegetation	8 (47.1%)	24 (27.6%)	32 (30.8%)	0.151 b
	Mitral valve vegetation	6 (35.3%)	35 (40.2%)	41 (39.4%)	0.791 b
	Tricuspid valve vegetation	0 (0%)	5 (5.7%)	5 (4.8%)	0.589 c
	Pulmonary vegetation	0 (0%)	5 (5.7%)	5 (4.8%)	0.589c
	Septal vegetation /Atrial vegetation	1 (5.9%)	9 (10.3%)	10 (9.6%)	0.696c
	Prosthetic valve vegetation	2 (11.8%)	8 (9.2%)	10 (9.6%)	0.742c
	Aortic Regurgitation	10 (58.8%)	32 (36.8%)	42 (40.4%)	0.109 b
	Mitral Regurgitation	8 (47.1%)	39 (44.8%)	47 (45.2%)	0.866 b
	Tricuspid Regurgitation	2 (11.8%)	25 (28.7%)	27 (26%)	0.226c
	Cardiac Abscess	0 (0%)	2 (2.3%)	2 (1.9%)	0.528c
	Pseudo–aneurysm	0 (0%)	1 (1.1%)	1 (1%)	0.657c
	Paravalvular leak	0 (0%)	5 (5.7%)	5 (4.8%)	0.588c
	Pericardical/pleural efflusion	1 (5.9%)	6 (6.9%)	7 (6.7%)	0.870c

a: Mann–Whitney U Test, **b:** Chi–square Test, **c:** Fishers exact Test, *p<0.05 shows significance

Three sets of blood cultures were submitted to the microbiology laboratory within 24 hours of admission and were immediately loaded into the BACT/ALERT 3D system. Gram staining was carried out on bottles with positive results, and subsequent sub–culturing was performed by placing the Blood and Chrome agar plates in an incubator for 24 h at 37 °C. The Vitek 2 and Vitek 2 AST were used to identify Gram–negative and Gram–positive organisms respectively and Vitek 2 AST cards were used to test the antimicrobial susceptibility.

Table 2. Frequency of the isolated organisms

Organisms	Frequency (n%)
Gram positive	52(73.24%)
Gram negative	12(16.9%)
Fungi	5(7.04%)
Multiple organisms	2(2.82%)
No PET CT findings	1
Lost to follow up	0
TOTAL	**8**

STATISTICAL ANALYSIS

Descriptive statistics were used to present all outcomes; normally distributed data were presented as means and standard deviations, and binary and categorical variables were presented as counts and percentages. The chi—square test or Fisher's exact test was used to find the association of categorical variables, and the Mann—Whitney U test was used to compare quantitative parameters, as the data did not follow normality. The confidence interval was 95%; thus, the significance level was 5%. All data were entered into Microsoft Excel and analyzed using SPSS Version 28.00.

RESULTS

A total of 114 patients were admitted with the diagnosis of infective endocarditis, of which 107 fulfilled the modified Duke's criteria. A total of 104 patients aged >18 years were included in the analysis, and three patients aged <18 years were excluded from the study. The mortality rate was 16.34% (17/104). Seventy—three (70.2%) patients were male and 31 (29.8%) were female. The mean age of the study population ranged from 18 to 85 years, with an average of 57 years. The deceased patients had a mean age of 65 years and belonged to the older age group than the patients who were successfully discharged with a mean age of 57 years (p=0.034). The mean length of the hospital stay was 10 days. Atrial fibrillation was present in 23.5% of the patients and was significantly associated with mortality (p=0.023). Fever was the most common clinical presentation in 57.7%. Syncope was observed in 5.8% and dyspnea in 44.2% of patients, and both showed a significant association in the mortality group. No significant association with mortality was observed with either comorbidities or echocardiography findings in the study population. The most common comorbidity was hypertension (45.2%), followed by diabetes mellitus (41.3%), history of surgery (36.5%), and CAD (28.8%). The details of the baseline characteristics are presented in Table 1.

The culture reports were positive in 71 patients (68.26%) and negative in 33 patients (31.73%). Gram—positive organisms were isolated in 52 cases (73.24%), gram—negative in 12 cases (16.9%) and fungi were isolated in 5 cases (7.04%) cases. Culture growth yielded two different organisms in two patients (2.82%) (Table 2).

Streptococci were reported in 21 cases (29.57%), of which 15 were viridians streptococci (21.12%) and 6 were non—viridians streptococci (8.45%). Staphylococci were isolated in 20 patients (28.16%), of which 2 were MRSA, 8 were MSSA, 7 were coagulase—negative staphylococci, and 3 were Staphylococcus haemolyticus. Moreover, Staphylococci with other organisms were found in two cultures (2.82%). MSSA with Candida was observed in 1 patient, and MRSA with Burkholderia cepacia in 1 patient. Enterococci were isolated from 11 patients (10.6%). Gram—negative organisms were isolated in 12 cases (11.5%). Fungi were reported in 5 patients (7.04%), of which Candida spp. were grown in 4 cultures and Aspergillus niger in 1 patient. The distribution of organisms isolated from the cultures is presented in Table 3.

Native valve IE was reported in 84 cases (80.76%) of the study population. Gram—positive organism was the causative agent for native valve IE in 52.38% (44/84), Gram—negative organisms in 5.6% (5/84), and fungi in 5.8% (3/84). Viridian Streptococci was found to be approximately 29.54% (15/44) of the gram—positive organisms responsible for native valve IE.

Prosthetic valve IE was reported in 17 cases (16.34%). Gram—positive organisms as the causative organism for prosthetic valve IE were isolated in 52.94% (9/17), Gram—negative in 23.52% (4/17), and fungi in 5.88% (1/17). Viridian Streptococci were isolated in 22.22% (2/9) and CONS in 33.33% (3/9) of cases with gram—positive organisms. However, no significant association was found between the type of organism affecting each valve and mortality rate (Table 4).

This study showed a significant association between complications and mortality in IE. Patients with heart failure, renal failure, sepsis, septic shock, and multiorgan dysfunction syndrome (MODS) have higher mortality rates than

Table 3. Distribution of isolated organisms according to mortality

Organism	Mortality		Total (n=104)
	Yes (n=17)	No (n=87)	
Culture negative	5(29.4%)	28(32.2%)	33(31.7%)
Viridian Streptococci	1(5.9%)	14(16.1%)	15(14.4%)
Non Viridian Streptococci	2(11.8%)	4(4.6%)	6(5.8%)
MRSA	2(11.8%)	0(0%)	2(1.9%)
MSSA	1(5.9%)	7(8%)	8(7.7%)
Coagulase negative Staphylococci (CONS)	1(5.9%)	6(6.9%)	7(6.7%)
Staphylococcus haemolyticus	0(0%)	3(3.4%)	3(2.9%)
MSSA + Candida	1(5.9%)	0(0%)	1(1%)
MRSA + Burkholderia cepacia	1(5.9%)	0(0%)	1(1%)
Enterococci	0(0%)	11(12.6%)	11(10.6%)
Gram—negative organisms	1(5.9%)	11(12.6%)	12(11.5%)
Candida species	1(5.9%)	3(3.4%)	4(3.8%)
Aspergilus	1(5.9%)	0(0%)	1(1%)

those without these complications. Renal failure had a more profound impact, with a mortality rate of 64.71%. Sepsis, septic shock, heart failure, and MODS were also associated with elevated mortality rates of 52.94%, 52.94%, 47.06%, and 41.18% respectively ($p<0.05$) (Table 5).

DISCUSSION

After analyzing the data over a period of six years, the study showed a mortality rate of 16.3%. The mortality rate was 28% in the study conducted by Lakhdhar *et al.* and 9% by Mathew *et al.* (8,9). In the present study, 73 patients (70.2%) were male. The mean age of the study population was 57 (47—66) years. The results obtained were in accordance with the study by Barry *et al.*, in which 67% of their patients were males.[7] IE was reported more frequently in the elderly population in this study.

The clinical presentation of IE varied with studies; however, some common characteristics were observed among different studies which included fever, anemia, hematuria, splenomegaly, etc.[10] The clinical manifestation in this study was fever in 80.77%, angina in 57.69%, syncope in 45.19%, and dyspnea in 44.23%. Studies had reported association between dyspnea and infective endocarditis.[11,12] Infective endocarditis may affect the valve causing valve dysfunction affecting the normal blood flow and may also cause complications such as heart failure which may cause dyspnea. Native valves were the most affected in this study (80.8%) and prosthetic valve IE was reported only in 16.3%. Device—related IE was found only in 2.9% of cases. A study by Zhu *et al,* reported that IE primarily affected the left native valve in 65.3%, the left prosthetic valve in 6.6%, and the right valve in 24%.[10] A study by Mano *et al.* reported that the site of infection was most frequent in the aortic valve. In our study, mitral valve vegetation was most commonly found (39.4%). Mitral valve regurgitation was reported in 45.2% of the study population. Mitral valve regurgitation as a risk factor for IE was reported in several studies. Danchin *et al.* reported that the frequency of mitral valve prolapse was three times in patients with IE compared to the control group.[13] Another study reported that hypertrophic cardiomyopathy, can lead to mitral valve regurgitation increasing the risk of infective endocarditis.[14]

Treatment for IE can be associated with potential complications. The major complications developed in patients with IE were cardiogenic shock, septic shock, acute heart failure, systemic thromboembolism, heart block, in—hospital dialysis, and disseminated intravasucular coagulation (DIC).[15] A study conducted by Mir *et al.* found that septic shock, cardiogenic shock, thromboembolism, and DIC were the complications most strongly linked to mortality.[15] In our study, we identified a significant correlation between heart failure, renal failure, sepsis, septic shock, cardio embolic shock, embolism, and MODS with mortality.

Table 4. Distribution of organisms affecting cardiac valves and its association with mortality.

Valve		Mortality		Total	Sig.
		Yes	No		
Native	Gram Positive	6(85.7%)	38(84.4%)	44(84.6%)	0.722c
	Gram Negative	1(14.3%)	4(8.9%)	5(9.6%)	
	Fungi	0(0%)	3(6.7%)	3(5.8%)	
	Total	**7(100%)**	**45(100%)**	**52(100%)**	
Prosthetic	Gram Positive	2(66.7%)	7(63.6%%)	9(64.3%)	0.093c
	Gram Negative	0(0%)	4(36.4%)	4(28.6%)	
	Fungi	1(33.33%)	0(0%)	1(7.1%)	
	Total	**3(100%)**	**11(100%)**	**14(100%)**	

C: Fishers Exact Test. Cases with more than one organisms were excluded from this analysis.

We had 71 patients (68.26%) with positive blood cultures. Blood cultures were negative for 31.73%. Asopa *et al.* reported that 10% of their patients had no growth in the blood culture.[16] Literature showed that Staphylococcus aureus was the most common organism isolated, followed by Streptococci and Enterococci accounting for 80—90% of all cases of endocarditis.[17] Al—Tawfiq *et al.* documented Staphylococcus spp as the most prevalent microorganisms, with Staphylococcus aureus in almost 40%, MRSA in 4%, and CONS in 7.4% of the cases.[18] According to a study conducted by Mano *et al.* streptococci were found to be the most prevalent isolates (n=29), followed by staphylococci (n=23).[12] However, in our study, the most common organism isolated was Streptococci (29.57%), followed by Staphylococci (28.16%) and Enterococci (10.6%), together accounting for 68.33% of all cases of endocarditis.

Our study showed that Gram—positive organisms were responsible for 52.38% (44/84) of cases of native valve IE and 52.94% (9/17) of cases of prosthetic valve IE, with viridans Streptococci accounting for 29.54% and 22.22% respectively. However, considering the Staphylococci infection, there were 2 cases of MRSA, 8 cases of MSSA, 7 cases of CONS, and 3 cases of Staphylococcus haemolyticus. Habib *et al.* reported CONS as the main causative organism for prosthetic valve IE.[19] Our study showed CONS as a causative organism in 33.33% of the patients with prosthetic valve IE. Most studies reported Staphylococci as the most common organism causing IE. Barry *et al* reported that Staphylococci infection, especially MSSA as the most common cause of prosthetic valve IE and also reported that 31.5% of the native valve IE was caused by viridans group streptococci.[7] Studies had reported the mortality rate to be high, especially with S. aureus infection in prosthetic valve with one year mortality rate of 50%.[20,21] However, in our study the mortality rate in prosthetic valve endocarditis was 17% with MSSA, CONS, and Aspergillus niger as causative agent in 1 patient each.

Similarly, the incidence of viridan groups Streptococci infection was reported in one case involving prosthetic valve IE. Moreover, the study also identified Aspergillus niger as the causative agent for IE in one case resulting in the death of the patient. Fungal infection was reported only in native valves in our study. In two cases, the culture yielded the growth of other microorganisms together with gram—positive organisms.

The study was retrospective in nature and was a single—center study limiting the generalization of the findings with other healthcare settings. The sample size was small and a larger sample size could have given a better picture. This research contributes valuable insights into the profile and outcomes of IE in a quaternary care center setting. The findings emphasize the importance of attention to IE, especially in the elderly population. Multi—center studies with larger cohorts could further improve our understanding of this potentially life—threatening condition.

CONCLUSIONS

The study showed that the native valves were mostly affected. The most common causative organism in IE was Streptococci, especially viridians group streptococci, followed by Staphylococci and Enterococci. Culture—negative IE was found in 32.69% of the population. The overall mortality as per the study was 16.3%. The study showed a significant association between complications like

Table 5. Association between complications and mortality

Complications		Death	Alive	Test statistic (Sig.)
Heart failure	Yes	8(47.06%)	11(12.64%)	11.280b (.003*)
	No	9(52.94%)	76(87.36%)	
Renal failure	Yes	11(64.71%)	12(13.79%)	21.401a (<0.0001*)
	No	6(35.29%)	75(86.21%)	
Cardio embolic stroke	Yes	4(23.53%)	8(9.2%)	2.863a (.105)
	No	13(76.47%)	79(90.8%)	
Sepsis	Yes	9(52.94%)	20(22.99%)	6.345b (.018*)
	No	8(47.06%)	67(77.01%)	
Septic shock	Yes	9(52.94%)	2(2.3%)	38.561a (<0.0001*)
	No	8(47.06%)	85(97.7%)	
Embolism	Yes	4(23.53%)	14(16.09%)	.550a (.488)
	No	13(76.47%)	73(83.91%)	
MODS	Yes	7(41.18%)	5(5.75%)	17.489b (<0.0001*)
	No	10(58.82%)	82(94.25%)	

a: Fishers exact test, **b:** Chi square test, * significance

heart and renal failure, sepsis, septic and cardio-oembolic shock, embolism, and MODS with death.

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Hemodynamic Instability

Evidence—based Guideline for the Pharmacological Management of Low Blood Flow States in Babies of Less than 28 Weeks' Gestation

Dr. Issam Abdalbari[1]

1. Neonatal Department, Medcare Women and Children Hospital, United Arab Emirates

Email: Issam@medcarehospital.com

Introduction

Hemodynamic instability is common in high—risk infants admitted in NICU departments (Dilek Dilli, 2018); Normal hemodynamics necessities blood flow that provide adequate oxygen and nutrient delivery to the tissues. Diverse aspects may compromise hemodynamic status in preterm/term infants. The below paper highlights the management of low blood flow states in babies less than 28 weeks' gestation. Blood pressure is an important aspect in critical care of medicine, requires to be interpreted it better, examine systolic and diastolic, and not to only look on the mean blood pressure. Furthermore, its necessary to consider its association with organ blood flow. The application of Echocardiography in NICU, led to improved understanding of the underlying pathophysiologic mechanism in infant and directing proper management with less duration and exposure to medication(Elsayed and Fraser, 2016).

Summary

Low blood flow state is defined as the state when blood flow to an organ is insufficient to meet its oxygen demand (Kluckow., 2018). Hypotension is defined as a mean blood pressure in mmHg below the numerical gestational age of the infant in weeks, although this definition is considered with least supportive evidence (Kluckow., 2018). Evidence that blood pressure alone is not sufficient to accurately assess organ perfusion, ongoing frequent assessment with perfusion is required to detect any subsequent signs of poor perfusion.

Concerning pathophysiology of low blood flow state in ELGAN, maintenance of organ perfusion and tissue oxygenation requires maintenance of adequate systematic blood flow. The two main determines of oxygen delivery for maintenance of normal tissue and organ oxygenation are volume of blood flow and atrial oxygen content. These are defined by the equation:

Systemic oxygen delivery (mls O2/min) = Cardiac output (L/min) x Hb concentration (g/L) x 1.31 (mls O2 Hb) x % saturation.

Therefore, cellular oxygen requirements must be maintained for efficient energy production and its absence results in cellular death(Paradisis, 2013).

As shown in Figure 1, the aim is to improve Oxygen delivery, while trying to correct the low blood flow states, as cardiac output equals summation of stroke volume multiplied by heart rate [COP = SV x HR].

For management of low blood flow state in babies of less than 28 weeks' gestation,the current standard(one size fits all)pressure driven approach to manage circulatory insufficiency treat low blood pressure to achieve higher values .Nearly all NICU units use this approach as shown below, which was published in 2003, this guideline is basically considered if the child has cardiac compromised hypotension, treated with fluid bolus of normal saline 10—20 cc/kg and repeated if required. First line therapy is dopamine 5—20 mcg /kg /min, second line dobutamine 5—20 mcg / kg /min, then epinephrin should be added by 0.2 mcg / kg / min, if needed dexamethasone is added as rescue therapy. (S J Dasgupta, 2003a) (S J Dasgupta, 2003b).

This approach was used when neonatal echo is not being done routinely looking to hemodynamics in neonatal intensive care unit for sick babies. It is a blind approach which was more to increase blood pressure. there is no consideration of underlying cardiac function or physiology, compensatory mechanisms, or fluid loss. this kind of approach is neither evidenced base nor logical, this umbrella approach is not applicable to all scenarios in the clinical practice.

After introduction of neonatal echocardiography, our approach in management directed according to pathophysiology of the disease process. Now we individualized our approaches to individual circumstances looking to cardiac function, knowing the physiology, and end organ perfusion.

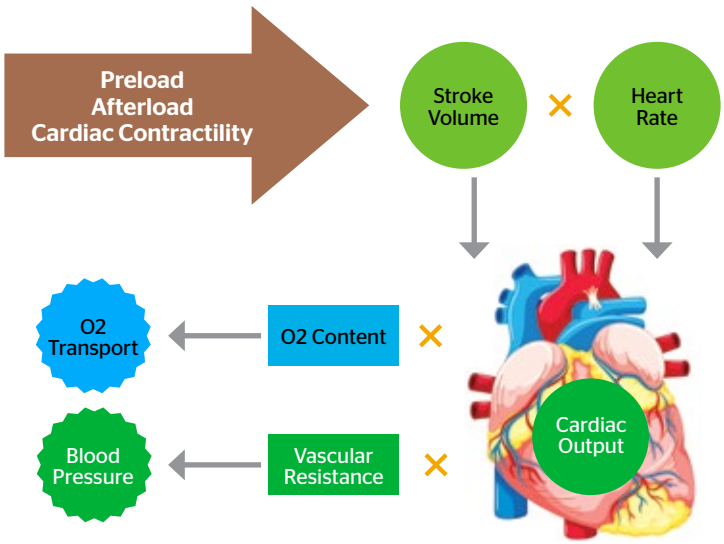
Our aim of treatment to improve end organ perfusion, tissue perfusion, increase oxygen delivery, and blood flow to the issue. The current dilemma is that there is not enough evidence to say Dobutamine is better than dopamine or milrinone, but there is evidence of the physiology and now after (POCUS) point of care ultrasound echo, we understand physiology better(Elsayed and Fraser, 2016b). It's not possible to recommend a drug over another just based on evidence, because there are no randomized control trials to support that. Physiology— based approach is deliberated to be better than pressurebased approach(Singh and Tissot, 2018), so perhaps focused individual approach is needed.

The management of low blood flow state in babies of less than 28 weeks' gestation infant in the first 48—72 hours of life,it depends upon the pathophysiology of the disease process. In these babies, there is diastolic myocardial dysfunction and poor compliance due to immature granular myocardium with increase left ventricular or biventricular mass. Increase sudden exposure to increase SVR after elimination of placenta, as well as persistence exposure to high pulmonary vascular resistance due to respiratory distress syndrome, wet lungs, and mechanical ventilation. Therefore, this will lead to impaired transitional circulation process with low cardiac output status, low systemic blood flow in superior vena cava and hypotension which may be due to low cardiac output and poor myocardial contractility, and persistent shunt in (PDA) patent ductus arteriosus / (PFO) patent foramen oval(Singh

Table 1. blood pressure values which are commonly used in practice as blood pressure below 3rd centile is hypotension

	Sys 3rd	Dias 3rd	Mn 3rd
24	32	15	26
25	34	16	26
26	36	17	27
27	38	17	27
28	40	18	28
29	42	19	28
30	43	20	29
31	45	20	30
32	46	21	30
33	47	22	30
34	48	23	31
35	49	24	32
36	50	25	32

Figure 1. Neonatal hemodynamics and management of hypotension in newborns



and Tissot, 2018).These infants also had decrease oxygen carrying capacity and oxygen extraction by tissues due to presence of high fetal hemoglobin in the first few weeks which gradually decreases, (S J Dasgupta, 2003a) (Singh and Tissot, 2018) .

Drugs used to treat circulatory compromised in babies of less than 28 weeks' gestation infants during first 48—72 hours after birth: —

According to the physiology mentioned, we should choose drugs which could improve contractility, and improve cardiac output.

1. Fluid boluses 10 cc/kg and repeat if needed in case of hypovolemia or blood loss, evidenced by echocardiography(Stranak *et al.*, 2014)
2. Dobutamine improve contractility and cardiac output (B1, B2) as compared to Dopamine (B) increase contractility at low doses 2.5mcg/kg/min, α at doses of (6mcg leading to increase SVR, PVR) (Dempsey *et al.*, 2014).
3. Low dose of Epinephrine < 0.3mq (B) can be used alternate to Dobutamine as it increases contractility and may increase SBF, but high doses more than 0.3mcg/kg/min, (α) will increase SVR, PVR with negative effect on which is not the case in this scenario.
4. Norepinephrine is predominant peripheral α effect, with more vasoconstrictor effect than epinephrine, not drug of choice in this scenario, its drug of choice in septic shock.
5. Milirinone phosphodiesterase III inhibitor, increases availability of cAMP, leads to improved contractility and fall in SVR, PVR, with net effect increased SBF, better to avoid in preterm infants because of its severe hypotensive effect and long half life. It can be used in post PDA ligation syndrome (Singh and Tissot, 2018).

Hence, drug of choice for this physiology is either dobutamine or low dose of epinephrin rather than dopamine or any other medication. The practitioner must beware of high dose of dopamine or vasopressor therapy in first 48—72 hours during transitional circulation, because it will increase the blood pressure and Systemic Vascular Resistance (SVR) where is not applicable in this scenario according to physiology described.

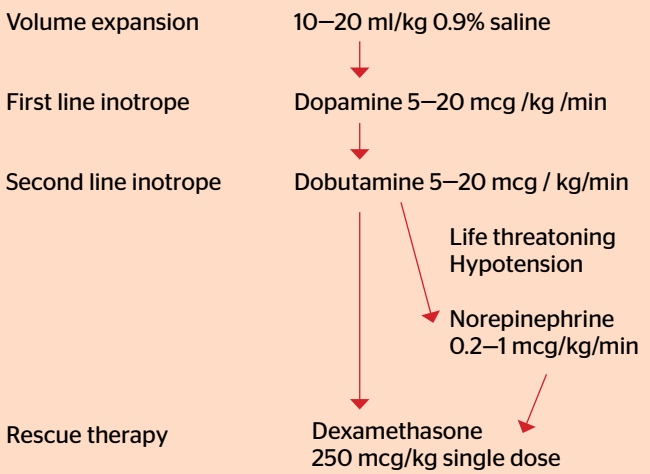
In Management of low blood flow states in septic shock, in quick and frequent monitoring, and not only blood pressure, should be with evidence of organ dysfunction (Schwarz and Dempsey, 2020).

1. Warm shock, which is due to over production of vasoactive substances cytokines which causes vasodilatation(Silveira, Giacomini and Procianoy, 2010). There will be low systemic vascular resistance, normal capillary refill time, bounding pulse, hypotension.(E.Schwarz and Dempsey, 2020).Management will include fluid boluses normal saline 30 —60cc/kg, norepinephrine at a dose of 0.05 mcg/kg/min, maximum 0.4 mcg/ kg/min., epinephrine improved blood pressure, urine output, and oxygen dependency in retrospective study of preterm infants (Rizk *et al*) (E.Schwarz and Dempsey, 2020).

2. Cold shock, which is a constrictive physiology state with high systemic vascular resistance, cold extremities, delayed capillary refill time, diminished peripheral pulses, low or normal blood pressure (Silveira, Giacomini and Procianoy, 2010) (E Schwarz and Dempsey, 2020).

In constrictive phenotype more likely to be dealing with cardiac dysfunction and low cardiac output. Treatment will start with normal saline boluses up to 30—60 cc/kg, if the blood pressure is low, then low dose of epinephrine at 0.02mcg/kg/min (Beau Batton, 2020).

Figure 2. Old Management of Hypotension (S J Dasgupta, 2003b)



If blood pressure is normal or high milrinone can be started with a dose 0.33 mcg /kg /min as negative inotrope, hydrocortisone in between if no response (E.Schwarz and Dempsey, 2020).

3. Cardiogenic shock, manifested by low systolic, diastolic, main blood pressure, and narrow pulse pressure. It occurs in hyperinflation of lungs compressing the heart in mechanical ventilation with high main airway pressure, poor filling, poor contractility of the heart, persistent pulmonary hypertension, and overdoses of inotropes affecting the myocardial performance. In cardiogenic shock, echocardiography showing poor myocardial performance.

In management, Bolus of normal saline in hypovolemia and drugs with dual effect like Dopamine or epinephrine and will not effect on the diastolic pressure. Dobutamine in low doses 5mcg/kg/min, dobutamine at doses more than 10 mcg/ kg/min will cause vasodilatation and decrease the diastolic pressure more treatment of the cause is crucial also in management (Beau Batton, 2020).

CONCLUSION

Understanding the pathophysiologic mechanism early before worsening of hemodynamics or progression to anerobic metabolism is helpful in targeting the management. Looking at the trend of systolic, diastolic and pulse pressure before and after any deterioration and intervention. Additionally, compare the values to the normalized centile curves for blood pressure values. Furthermore, integrate the impression of systolic and diastolic pressure of other parameters of delayed organ prefusion.

Finally, Echocardiography and other non—invasive measures is crucial in directing the management.

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Molecular Pathogenesis of Enteropathy Associated T—Cell Lymphoma (EATL)

Ali Alshareefy[1], Yasir Alshareefy[2]

1. Consultant Gastroenterologist, Medcare/ Saeed Alshaikh Centre, Dubai, United Arab Emirates
2. Medical student, Trinity College Dublin, Dublin, Ireland

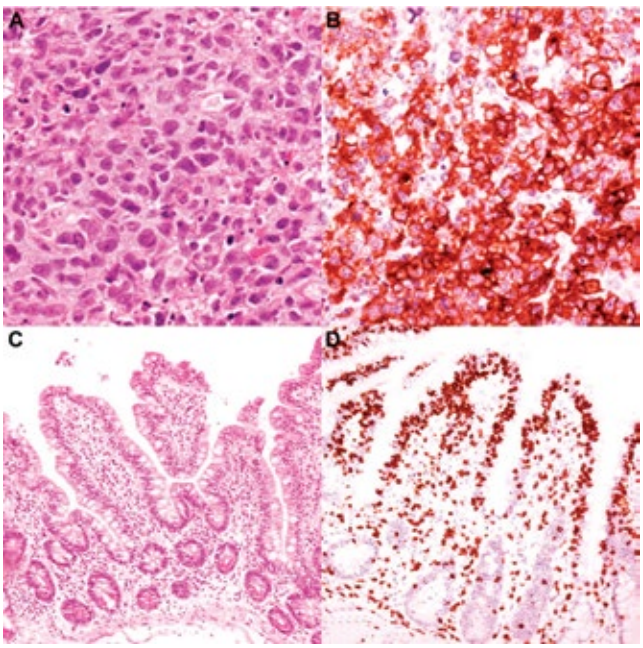
Introduction and Epidemiology

EATL is an aggressive non—Hodgkin lymphoma that arises from T cells present in the gut who express CD103 and CD8[1]. EATL is classified into two groups based on morphology, immunohistochemistry and genetic profile; type I which is most common (80—90%) associated with coeliac disease and is most common in those with Northern European ancestry and type II[2] which is most common in Asia. This type of lymphoma is preceded by enteropathy which is the reason patients with coeliac disease (CD) are at highest risk of this condition. EATL as well as coeliac disease are highly associated with HLA—DQ2 or HLA—DQ8 haplotypes[3]. Other risk factors in addition to HLA—DQ2/8 haplotypes are advanced age and male sex[4].EATL is a rare condition with an annual incidence of 0.5—1 million[5]. EATL has a poor prognosis with a 5—year survival between 8—20% due to the absence of a standard therapeutic regiment for patients for this condition[6] with the only means of prevention being to adhere to a strict no gluten diet[7].

Clinico—pathologic presentation of EATL

In a study[8] looking at the clinical presentation of 62 patients with EATL the following data was extracted; median age of presentation was 61 with 53% being male, 64% of patients presented with a tumor stage of IV, the small intestine was the most commonly involved location (90%) followed by the large intestine (16%). The mesenteric lymph nodes and para—aortic/iliac lymph nodes were involved in 35% and 11% of respectively. Common symptoms at presentation include abdominal pain (88%), fatigue (38%), anorexia (38%) and infection (23%). Less common symptoms include hepatomegaly (6%), splenomegaly (6%) and pruritis (3%). B symptoms (fever, night sweats and unexplained weight loss) was present in 63% of patients. 63% of tumors were greater than

Figure 1[12]. (EATL type I)



Immunophenotype of EATL type I[13]; CD3e (89%), CD2(43%), CD5(17%), CD4(11%), CD8(43%), CD30(37.5%), CD56(30%), TIA–1(81%).

or equal to 5cm. Bone metastases is an uncommon feature present in only 3% of these patients. Biochemical findings include elevated LDH (35%), elevated CRP (33%), hypercalcemia (9%), 52% of the patients had a history of coeliac sprue. One of the major complications associated with EATL is small bowel perforation; perforation of any part of the bowel can result in our gut flora which normally remain intra—luminally to escape and enter the peritoneum. This can lead to peritonitis and then abdominal sepsis which is extremely dangerous as abdominal sepsis has a mortality rate of 72%[9].

Genetic Analysis of EATL

In a 2017 study[10] conducted by Jan Delabie and colleagues the genomic and transcriptomic differences between EATL type I and EATL type II were examined. 41 patients with EATL I and 23 with EATL II were investigated and the following results were noted. It was found that the vast majority of genes studied (90%) such as TP53, BRAF, NRAS, GNAS etc. were mutated in both subtypes however there were a small number of genes that were found to be mutated frequently in one type compared to the other; DAPK3 and SOCS1 genes were found to be mutated in higher frequencies in EATL type I when compared to type II. Diagnostic guidelines derived from Arps and Smith 2013[11] have attributed chromosome 1q gain of function mutations to EATL type I however this study found the same gains in 20% of EATL type II cases. In regards to EATL type II, mutations that were observed in higher frequency when compared to type I include KRAS, STAT5B (>50%) in type II and SETD2 (>60%). In addition to this, gains at chromosome 8q which contains MYC gene were more frequent in type II.

Histology and Immunohistochemistry

In figure 1(A) we can see irregularly shaped/angulated cells with variable cytoplasm, the cells expressed CD30 as seen in 1(B), shortened villi in 1(C) and a "top heavy" intra—epithelial T cell in 1(D) via CD3 straining.

Type II lymphoma consists of monotonous—medium sized cells with round nuclei and have a stippled chromatin pattern as seen in 2(A). 2(B) shows cells expressing CD56. 2(C); mucosa adjacent to lymphoma shows villous atrophy and in 2(D) we can see intra—epithelial infiltration by lymphoma cells via CD56 staining.

As we can see according to histological and immunohistochemistry studies EATL type I and II are two distinct entities with EATL type I being characterized by irregularly shaped/angulated cells expressing CD30 and an intra—epithelial T cell infiltration seen via CD3 staining whereas in EATL type II we see monomorphic CD56+ lymphoma cells.

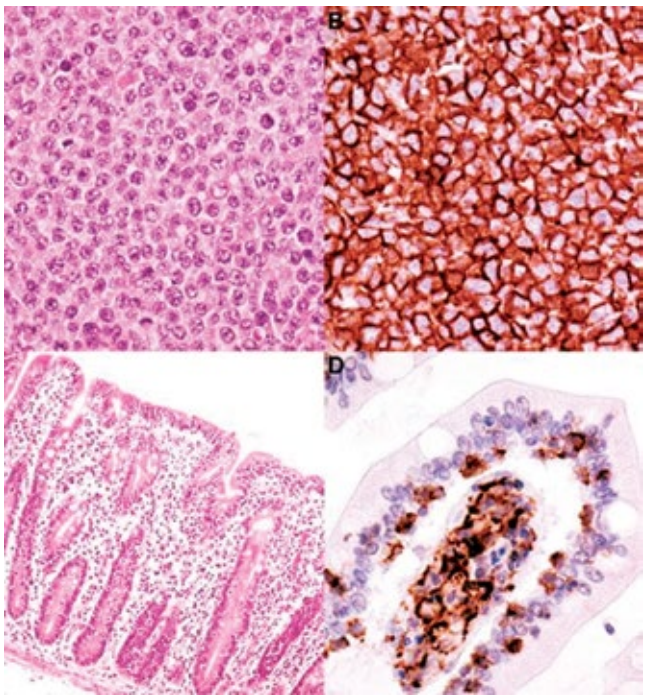
EATL Pathogenesis

Seeing as CD is the major risk factor for EATL it is vital we understand the pathogenesis underpinning CD to explain how EATL entails as a result. CD AKA gluten—sensitive enteropathy is an autoimmune condition that results in activation of a cell mediated (T cell) and humoral (B cell) immune response. Coeliac is characterized by the presence of a specific autoantibody called anti—tissue transglutaminase (anti—ttg). The

pathogenesis of CD occurs as a result of ingestion of gliadin, a peptide found in gluten which is a naturally occurring protein present in many common foods such as wheat, oats and rye. The gliadin peptide triggers an immune response which occurs as follows. Zonulin is a protein and modulator of tights junctions at the intestine which reversibly regulate intestinal permeability[16] and when exposed to gluten it is upregulated causing disruption to the integrity of these tight junctions present between epithelial cells and thus results in an increase in paracellular movement of protease resistant gluten fragments[17]. This results in the undigested gluten peptides (gliadin) to pass through epithelial cells and enter the lamina propria where it is deaminated by tissue transglutaminase which induces a negative charge on the gliadin peptide[18]. This step of deamination is the key pathogenic event contributing to the immunogenicity of gliadin in CD[19]. These negatively charged gliadin peptides bind to positively charged amino acids on HLA—DQ2 or HLA—DQ8 molecules[20]. This triggers an innate immune response and also an adaptive immune response which is initiated by the presentation of these negatively charged gliadin peptides on APCs to CD4+ T Lymphocytes which causes production of pro—inflammatory cytokines namely interferon gamma[21]. These cytokines can either proceed to activate Th1 cells which release IL—15 and IL—21 which results in the activation of CD8+ intra—epithelial lymphocytes (IELs) and also promote the activity of CD8+ T lymphocytes[22] which contributes to the intestinal lesions and damage seen in CD, or can activate Th2 cells which result in B cell antibody production such as anti—ttg and anti—endomysium which is thought of as characteristic of active CD[23]. IL—15 activated CD8+ IELs express NKG2D receptor which binds MIC—A on enterocyte surface causing release of granzymes and perforins resulting in enterocyte death by lysis resulting in the villous atrophy associated with CD[24].

Villous atrophy causes malabsorption resulting in a multitude of problems such as anemia from iron malabsorption, diarrhea, bloating, steatorrhea, vitamin B12 deficiency, abdominal pain, failure to thrive in infancy and other signs and symptoms that a patient with CD typically presents with. Strict adherence to a non—gluten diet can cause a reversal of symptoms however a small number of CD patients will develop refractory coeliac disease (RCD) which is defined as persistence or recurrence of malabsorptive signs and symptoms and villous atrophy despite strict adherence to a gluten free diet for > than 12 months[25]. RCD can be classified as follows; RCD I which is thought to represent proliferation of CD8—alpha—beta heterodimer expressing TCR—alpha—beta+ intraepithelial T cells[26] and RCD II IELs are believed to be derived from CD8+ TCR—alpha—beta+ T cells due to the expression of CD103, cytoplasmic CD3 and frequent detection of TCR gene rearrangements[27]. As mentioned previously EATL can be classified as type I (CD associated) and II (non—CD associated). Around half of RCD II patients develop EATL[28] and therefore RCD type II is considered a precursor lesion for EATL type I; partial trisomy of the one q region is highly associated with RCD type II and a gain of chromosome one q in 16% of EATLs implies a common

Figure 1[14]. (EATL type II)



Immunophenotype of EATL type II[15]; CD3e (95%), CD2(53%), CD5(6%), CD4(5%), CD8(63%), CD30(12.5%), CD56(30%), TIA—1(87.5%).

step in lymphomagenesis[29]. Another possible factor in the lymphomagenesis is the overexpression of IL—15 which maintains IEL activation and promotes T cell clonal proliferation which may lead to malignant transformation.[30] IL—15 has also been shown to upregulate anti—apoptotic protein BCL—xL via JAK3—STAT5 signaling pathway activation in RCD II IELs, prolonging their survival.[31] Further research is needed to truly establish the link between RCD II and EATL. EATL type II as mentioned before is not associated with CD and its pathogenesis is very poorly understood as it is an extremely rare cancer with not much research behind it. As eluded to previously recent studies have a shown an association between EATL type II and SETD2 mutations;[32] the tumor suppressor gene SETD2 encoding a non—redundant H3K36—specific trimethyltransferase was found to be altered (defective H3K36 trimethylation) in 14/15 cases, owing to loss of function mutations and/or loss of the associated locus 3q21.31, and according to the researchers of this paper this study describes that SETD2 inactivation is a molecular hallmark of EATL type II.

Diagnosis

EATL may be confused with IBD due to the similar clinical presentations in terms of symptomology. Radiographic imaging is also not highly specific; gastrointestinal lymphomas typically show bowel wall thickening on CT scan which is also seen in IBD. A history of coeliac disease or non—adherence to a gluten free diet which would be noted during history taking should point the physician to a possible diagnosis of EATL. At this point when EATL is suspected capsule endoscopy may be indicated where this small video capsule swallowed then passes through the whole length of the small intestine, before being excreted. The capsule during its course takes thousands of images that can be recorded and reviewed to detect any focal irregularities or mass lesions by a specialized gastroenterologist. Such abnormalities on capsule study will subsequently be followed by double—balloon enteroscopy which may be used to visualize the lesion in real time and to obtain a sample that can be sent for histological analysis which provides the definitive diagnosis of EATL via presence of histological/immunohistochemistry markers as discussed above.

Management & Prevention

There is not yet a standardized form of therapy for EATL with physicians using a mix of chemotherapy, surgical resection, radiotherapy and autologous stem cell transplantation.[33] Surgical resection of the tumor remains the mainstay of management however due to the tumors' location in the gastrointestinal tract surgical resection can often lead to other gastrointestinal related issues such loss of absorptive function of the small bowel where malabsorption is often encountered and in addition to surgical issues related to stoma formation such as high stoma output which can negatively impact a patients wellbeing and quality of life.[34] Strict adherence to a gluten free diet remains the only means of prevention.

Conclusion

EATL is a rare but serious complication of CD. It is subdivided into two distinct entities via genetic analysis where genes such SETD2 and KRAS are mutated in much higher frequency in type II when compared to type I, however in EATL type I we see genes such as DAPK3 and SOCS1 mutated in high frequency. In addition, histological analysis and immunophenotyping also show clear differences in the two subtypes; type I is characterized by irregularly shaped/angulated cells expressing CD30 and an intra—epithelial T cell infiltration seen via CD3 staining while type II EATL is characterized by CD56+ lymphoma cells. The 2 subtypes also differ in their pathogenesis with current research showing EATL type I follows a linear route of progression from RCD as a precursor lesion, in contrast to EATL type II which is non coeliac associated and has been associated with SETD2 loss of function mutations as a molecular hallmark. It is clear EATL has a complex pathogenesis with multiple factors involved, research thus far has highlighted a clear difference in the pathogenesis pathways of EATL subtypes however much more work is needed to be done. Currently there is no standard therapy used in the management of EATL as stated previously and there is lack of targeted therapies mostly due to a lack of understanding of the molecular basis underpinning this condition. Further research is required to identify novel molecular targets which can be used to develop targeted therapies that can treat this condition

with high specificity and efficacy, until then the prognosis of patients afflicted with this condition will remain poor. Equally as important, more emphasis is required on the awareness and early detection of EATL in the appropriate clinical context like RCD.

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Clinical Research Methodology Series Paper 1: An Approach to Evidence—Based Medicine

Dr Manoj Mohan[1]

1. Consultant and Head of the Department, Aster Hospital, Doha, Qatar.

Email: manojmohan@doctors.org.uk

Keywords

Evidence—based medicine, clinical research methodology, well—built questionnaire.

Abstract

This first paper in this clinical research methodology series focuses on understanding the need for evidence—based medicine, its applicability and how we should use it in our everyday clinical practice. The paper provides an overview of the evolution of evidence—based medicine and the five—step approach to simplify its use. Clinical research evolves through evidence—based medicine, and this paper assists a busy practitioner with the fundamentals of clinical research. Future papers in the clinical research methodology series will cover all relevant aspects of clinical research.

Introduction

Evidence—based medicine (EBM) is a systematic approach to clinical problem—solving that integrates the best available research evidence with clinical expertise and patient values. This paper explains the concepts of EBM and also introduces the five—step approach of EBM. Health practitioners must base their clinical decisions on the best available evidence. The clinical research methodology series aims at all health practitioners to understand the principles of research methodology to incorporate EBM in their practises. This first paper on the approach to evidence—based medicine provides the basic understanding and the reasoning for clinical research. The subsequent articles in the series will focus on principles and approaches for evidence—based practice, including methodology of systematic reviews, meta—analysis, randomised controlled trials, observational studies and all other clinical research methodologies required for healthcare practitioners.

What is evidence—based medicine?

EBM began as a movement in the 1990s[(1)] and is defined as the integration of the "best research evidence with clinical expertise and patient values"[(2)] (Fig i)[(3)]. The evidence—based working group showed a para-

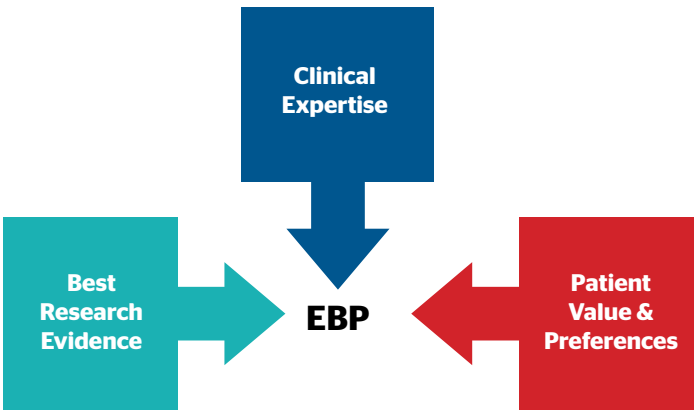
digm shift in teaching and training since the introduction of EBM[4], and the concept is embedded in the current clinical practice with clinical practice guidelines and guidance based on EBM. The Cochrane Collaboration was founded in 1993 by Ian Chalmers and a group of 70 other international colleagues based on EBM to establish a concrete approach for clinical trials.[5] Similarly, methodology setting and publication standards[6] have changed and evolved around the development of EBM. The need for EBM is growing as new research and evidence are coming out daily, and the need to stay current in clinical practice[7]. The task of reading every single paper out there and appraising it to use in clinical practice is highly impossible for clinicians.

Commonly, there are questions in clinical practice about diagnosis, prognosis, and treatment that often arise, and we need the answers to these questions. EBM allows the integration of good quality published evidence, clinical expertise, and the options and values of the patients and their families or carers. The alternative practices, including textbook description, basic scientific principles, clinical judgement, experiences, and clinical idiosyncrasies, continue as a challenge for EBM[8]. Therefore, incorporating an evidence—based approach should fulfil factors such as personal experience, judgement skills, and, more importantly, patient values and preferences can all be considered together in EBM.

Do we need evidence—based medicine?

The most important reason for practising EBM is for physicians to make decisions and patient outcomes[9] to improve the quality of care by identifying and promoting practices that work and eliminating ineffective or harmful ones. EBM provides a platform for critical thinking and reasoning to caregivers. It demands the effectiveness of clinical interventions, the accuracy and precision of diagnostic tests, and the power of prognostic markers that can be scrutinised for their usefulness in clinical practice. It requires clinicians to be open—minded and explore new methods and scientifically proven effective methods and, at the same time, to discard methods that are ineffective or harmful. EBM has a hierarchy of evidence, and getting the proper evidence to the question is challenging, especially when we need help understanding the context of the clinical entity. Grades and levels of evidence have been debated because of the complexity of their applicability in clinical practice[10]. Therefore, healthcare professionals must develop EBM skills, including effectively finding, critically appraising, and incorporating evidence—based knowledge and practice. Therefore, there is a need to use the five—step approach as a practical solution for every healthcare practitioner and provider.

Figure 1



EBM five—step approach

The EBM five—step approach involves converting information in clinical practice through a stepwise approach to ask the right question as the framework for EBM. The five—step approach (Figure 2)[11] allows the transformation of the answerable question to find the relevant evidence—based reasoning and the structure to provide an evidence—based answer to the question which can be applied in practice and allows a possibility of appraising our performance, which improves our clinical practice.

Step 1: Ask a clinical question.

The most critical and challenging task in practising EBM may be translating a clinical problem into an answerable question. When we come across a patient with a particular problem, various questions may arise for which we would

like the answers. These questions are frequently not structured, are usually complex and may need more clarity in one's mind. In the practice of EBM, we should begin with a well—formulated clinical question. We should develop the skill to convert the information we need into an answerable question. Good clinical questions should be straightforward, directly focused on the problem and answerable by searching the medical literature.

The PubMed PICO tool [12] assists in framing the correct clinical question as below:

I. The patient or problem in question
II. The intervention, test, or exposure of interest
III. Comparison intervention (if relevant)
IV. The outcome, or outcomes, of interest

Therefore, an answerable clinical question should be structured in the PICO (Patient or Problem, Intervention, Comparison, Outcome/s) or PIO (Patient or Problem, Intervention, Outcome/s) format.

For example,

I. Patients with Bell's Palsy (Patient / Problem)
II. Corticosteroids (Intervention)
III. Placebo or no treatment (Comparison)
IV. Facial function at three months (Outcome)

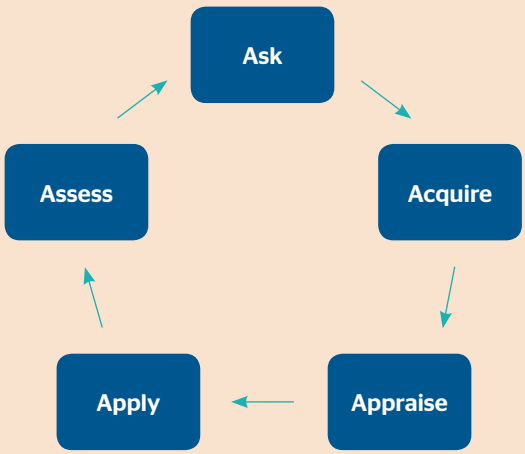
A four—part clinical question can be formulated: In patients with Bell's Palsy, do corticosteroids, compared to placebo or no treatment, improve facial function at three months?

Step 2: Acquire the best evidence.

Once we have formulated the clinical question, the next step is to seek the relevant evidence to help us find the answer. Many sources of information are available to answer this question; traditional sources suggest textbooks and journals are often outdated, and we may resort to asking a colleague or an expert, but again, the quality of information from these sources is variable. Other reliable sources are summarised evidence that can help, including UpToDate [13] and Best Practice from BMJ [14].

Other critical electronic bibliographic databases allow thousands of articles to be searched relatively quickly. The ability to search these databases effectively is an essential aspect of EBM. Effective searches help to maximise the potential of retrieving the relevant article within the shortest possible time. Studies[15,16] have shown that, even in countries where hospitals have facilities

Figure 2



for Internet access allowing healthcare professionals access to several electronic databases, many people are not familiar with the process of carrying out efficient searches and often conduct searches, which results in too few or too many articles. Therefore, healthcare providers need to undergo basic training and skills, either through their local library services or by attending formal courses.

Database search methodology

Basic search methods

A clinician must understand the basic search methods to derive the correct number of articles relevant to the clinical question.

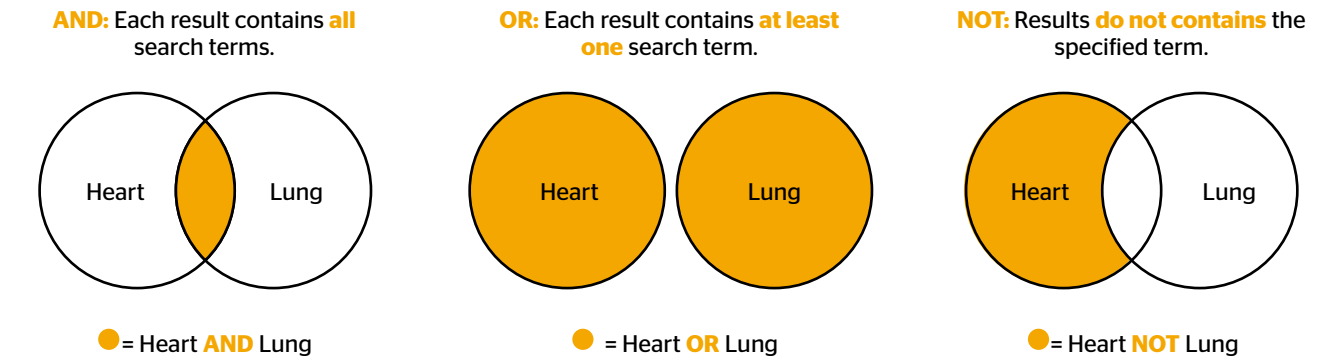
Keywords

Keywords can be generated based on the clinical question. For example, the following keywords could be used for the previous clinical question: Bell's palsy, Corticosteroids, Facial function. It is essential for the keywords as they form the base of the search strategy.

Databases

Numerous online databases are available; we must know which database to search for relevant articles. The databases which we should search include The Cochrane Library, MEDLINE(PubMed) [17], Embase [18] and CINAHL[19]. If one needs to gain the expertise or access to all the above databases, it is advisable to focus on PubMed initially.

Figure 3



Basic search principles

First, the keywords are formed, and then we can use PubMed to run the search. There are basic combining strategies of the keywords using specific combining words called "Boolean operators". There are three specific Boolean operators: "AND", "OR" and "NOT". When we do a search combining two words/ terms, we use AND, which allows articles containing both terms to be retrieved, while OR allows articles containing either term to be retrieved, and when we use NOT, then the articles with the first word but not the second word will be retrieved (Figure 3).[11]

When too many articles come up after the initial search, PubMed has a feature that allows you to limit your search results. You can modify your search by publication type (for example, randomised controlled trials or review articles) by publication date, language, study population, etc. PubMed Also has a feature called "clinical queries", which allows a straightforward approach to evidence—based search within the Medline database. "Clinical queries" is a preprogrammed research methodology filter that helps busy practitioners access the best available evidence by providing quick access to reliable clinical studies relating to therapy, diagnosis, aetiology, or prognosis.

You should build your initial search by forming and trying the keywords in PubMed. A Detailed approach to using PubMed, which includes all the search strategies, will be covered in the upcoming future series of clinical research methodologies.

Step 3: Appraise the evidence.

Research evidence is appraised in three main areas: the article's validity, its importance, and applicability to the patient or patients of interest. Critical appraisal provides a simple, structured method for assessing research evidence in all three areas. Developing critical appraisal skills involves learning how to ask a few key questions about the validity of the evidence and its relevance to a particular patient or group of patients. Such skills may be learned through small tutorials, workshops, interactive lectures and at the bedside.

Several tools for appraising technical research articles are available. The CEBM tool "Critical Appraisal Skills Programme (CASP), Oxford, UK, is a simple and practical tool that can be easily assessed and used by anyone[20]. These include specific CASP tools for appraising randomised control trials, systematic reviews, case—control studies, and cohort studies.

A detailed approach to how these tools are to be used will be discussed in the upcoming series on each of the different methodologies of clinical studies.

Step 4: Apply the evidence.

After critically appraising the evidence and understanding that it is valid and essential, we use it in our clinical practice. When we use this evidence, we consider the patient's values, circumstances, and the evidence we have appraised.

The evidence regarding efficiency and risk should be thoroughly discussed with the patient or patients to allow them to make an informed decision. This approach enables a therapeutic alliance to be formed with the patient, and the principles of EBM are integrated with the clinical expertise and patient values in EBM. Many international bodies that develop guidelines for clinical practice go through this step, which allows us to apply the pre—appraisal evidenced by expertise and complete Step 4 in EBM.

Step 5: Assess your performance.

As we routinely incorporate EBM into our practice, we also need to evaluate the applicable evidence in our practice and different methodologies are used for evaluating performances. One of the common methods is auditing the performance against benchmarked standards. It is essential to reflect on the performance evaluation and show that the response in one clinical practice is similar to the evidence obtained. By doing this, we understand that the evidence is factual. However, when there is a deviation, we realise that the evidence may not be appropriate to one's practice, which will be the reasoning for further research and changes in practice.

Conclusion

Evidence—based medicine forms the base of clinical research as the continuing process that allows unanswered questions for further research or when there is a deviation in practice or changes noted, allowing scope for further research and newer evidence. Each practitioner needs to understand EBM, which helps evolve clinical practice.

Useful Websites and links for EBM

1. PubMed EBM PICO and Well—Built questionnaire: https://pubmedhh.nlm.nih.gov/ebm/index.php
2. Centre for Evidence—Based Medicine EBM tools: https://www.cebm.ox.ac.uk/resources/ebm—tools

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20. CEBM. Available from: www.cebm.net

Feature

By **Claire Williams Bridgwater, Fatin Samara**

Desert dust storms carry human-made toxic pollutants, and the health risk extends indoors

Humans have contended with dust storms for thousands of years, ever since early civilizations appeared in the Middle East and North Africa. But modern desert dust storms are different from their preindustrial counterparts.

Around the world, deserts now increasingly border built structures, including urban dwellings, manufacturing, transportation hubs, sewage treatment and landfills.

As a result, desert dust lifts a growing load of airborne pollutants and transports these substances over long distances.

This is happening throughout the Global Dust Belt, an arid to semiarid region that stretches from western China through Central Asia, the Middle East and North Africa. Similar storms occur in the U.S. Southwest and central Australia.

To our thinking, modern desert dust storms have been overlooked as a public health crisis. Elevated exposure to these events is likely to contribute to rising respiratory and other diseases, including asthma and chronic obstructive pulmonary disease. We are environmental researchers whose work shows a need for better public health practices to protect people from dust storm pollutants.

Massive, fast-moving dust storms

To appreciate the scale of the threat, consider the Arabian Peninsula, where asthma rates have been the world's highest for the past two decades.

In spring 2011, one of the most severe desert dust storms in recent decades swept across the Middle East at the peak of the dust storm season. Its plumes spread from the west coast of the Persian Gulf to the eastern shores of the Caspian Sea, covering northern Saudi Arabia, southern Iraq, Kuwait and western Iran. One quadrant of this large storm alone covered most of the Arabian Peninsula.

This storm reached vertically as high as 5.5 miles (9 kilometers) above the ground. Its wind speeds exceeded 45 mph (72 kilometers per hour) – higher than average wind speeds in the region. Dust particle concentrations peaked at 530,000 micrograms per cubic foot (15,000 micrograms per cubic meter), blocking sunlight for days.

One study found that a large proportion of individuals exposed to sandstorms had symptoms that included increased cough, runny nose, wheezing, acute asthmatic attack, eye irritation and redness, headache, sleep disturbance and psychological disturbances. Another study reported that increased dust storm exposure in western Iran led to increases in hospital admissions for chronic obstructive pulmonary disease and more deaths from respiratory causes.

Needed: A climate + health framework

Researchers study desert dust storms in a dozen different fields, each with its own terminology, expertise and body of knowledge. This work includes analyzing satellite images, creating simulation models for predicting dust particle transport, and identifying each dust storm's particle content. So far, however, the health effects of desert dust storms and their changing particle content have gotten scant attention.

As we discussed in a recent review article, studies have found pollutants in dust storms that include bioreactive metals such as copper, chromium, nickel, lead and zinc, as well as pesticides, herbicides, radioactive particulates and aerosolized sewage. The extent to which desert dust storms transport a special class of pollution particles, those even smaller than one micron – or one millionth of a meter – is not yet clear.

This is the class of submicron pollutants, abbreviated as PM1.0, which includes degraded microplastics, metallic nanoparticles, diesel exhaust and fine particles from degraded tires. Of all particulate matter classes, submicron particles are the most harmful to human health because when once inhaled, they enter the bloodstream, affecting every organ in the body, and even crossing the blood-brain barrier.

Public health recommendations

We offer several practices here that we believe would help public health agencies successfully tackle the problem of polluted dust storms.

1: Identify particle content for each dust storm.

Existing technology now makes it possible to identify the types of particles being carried in any particular storm. Scientists can already conduct particle trajectory analysis to trace dust and pollutant particles back to their sources.

Knowing the particle content of dust storms can identify ways to make these storms less hazardous, whether capping sewage systems or securing waste at ports to prevent materials from being picked up by dust storms.

2: Archive samples from each desert dust storm.

One physical catalog for dust storm particles already exists at the 19th-century dust storm archive kept by the Natural History Museum at Humboldt University in Berlin. We see a need for a modern archive that collects digital data on particle types, particle trajectory analysis, spatial coordinates and meteorological data.

Keeping both physical samples and data from each dust storm would allow for a comparative understanding of how and why particle content is changing. This has been done to analyze particle content related to military activity in the Middle East.

Claire Williams Bridgwater
Research Professor in Environmental Science, American University

Fatin Samara
Professor of Environmental Science, American University of Sharjah

This is the class of submicron pollutants, abbreviated as PM1.0, which includes degraded microplastics, metallic nanoparticles, diesel exhaust and fine particles from degraded tires.

3: Protect indoor and closed spaces from the smaller dust storm particles.

During a major dust storm, high-speed winds blow fine particles around windows and doors for days. The particles most likely to penetrate indoors include the smallest, most harmful submicron class.

Typically, a gray, fluffy residue appears inside buildings after a dust storm, but data are not available on the identity and size of these particles. Our concern is that submicron pollutant particles are highly concentrated in this residue.

For a safe cleanup, we recommend that people should avoid dry vacuuming, which lofts particles back into the air. Instead, it is better to remove residues with water and a wet mop. We also recommend wearing face masks indoors before, during and after dust storms, since particulate concentrations start to rise ahead of the main storm. In our view, people should treat dust storm residue inside built structures as hazardous material until studies show otherwise.

4: Educate biomedical and meteorological experts together.

The rising human-made content of desert dust storms, particularly fine and ultrafine submicron particles, is a neglected public health concern that we believe calls for combined medical and meteorological expertise.

By educating biomedical and meteorological experts jointly about dust storms, public health agencies would have more complete strategies for how to best protect people. It would be valuable to have teams of health and weather experts carry out joint analyses of dust storm exposure data, and then apply the best statistical methods to both civilian and military health records.

Climate change is making already-dry areas around the world more arid. As deserts increasingly adjoin cities, industry and transportation corridors, desert dust storms will increasingly mirror human activity on land. These storms are becoming flying waste dumps, and we believe a public health perspective will help produce more effective responses.

Dr. Vanessa Kerry

Interview By **Aynsley O'Neill**

The climate crisis is a health crisis

Dr. Vanessa Kerry is the WHO special envoy for climate change and health, and helped organize Health Day. She also leads the nonprofit Seed Global Health, which works primarily to strengthen medical systems in Sub-Saharan Africa.

Dr. Vanessa Kerry, who has worked on global health issues for two decades, recently took a more prominent role as the World Health Organization's first Special Envoy for Climate Change and Health.

Dr. Vanessa Kerry also directs the Program in Global Public Policy and Social Change in the Department of Global Health and Social Medicine at Harvard Medical School, and she has a family tie to climate action. Her father, John Kerry, is President Joe Biden's Special Envoy for Climate. With the WHO appointment in June Vanessa Kerry is now a climate envoy as well, a position she said can bring broader awareness of the climate connection to health.

COP28 in Dubai became the first climate summit to observe Health Day. One hundred twenty-four countries endorsed the Declaration on Climate and Health, sounding the alarm on the severe public health and wellness implications of the climate crisis.

The World Health Organization (WHO) estimates that by the end of this decade the cost of the climate impact on health will be between $2 billion and $4 billion per year. But that may be an underestimate, because it doesn't include massive climate burdens on agriculture, water and sanitation, which all shape public health.

The health sector receives just one half of one percent of global climate financing, according to the WHO. In light of that shortfall, COP28 included an announcement of $1 billion toward climate and health, though some of that funding was already committed before the talks began.

Dr. Vanessa Kerry is the WHO special envoy for climate change and health, and helped organize Health Day. She also leads the nonprofit Seed Global Health, which works primarily to strengthen medical systems in Sub-Saharan Africa.

AINSLEY O'NEILL: According to the World Health Organization, between 2030 and 2050, climate change is expected to cause approximately 250,000 additional deaths per year from things such as undernutrition, malaria, cholera, diarrhea and heat stress alone. Can you walk us through the connection between the climate crisis and these particular diseases?

VANESSA KERRY: Absolutely. The climate crisis is a health crisis. The 250,000 deaths a year is probably an underestimate. The data has been changing rapidly. We're learning every day, we're playing catch-up on exactly how we're being impacted from climate change in terms of our survival, our human health and our well being. There are very direct impacts of climate change on human health in terms of extreme weather events, whether it is deaths from drowning, wildfires, air pollution; changes and increases in infectious diseases and non-communicable diseases.

To give a very concrete example, the floods in Pakistan in 2022 led to four times the rates of malaria, after the floods, including in provinces where malaria had been almost completely knocked out. We're also seeing this in non-communicable diseases. Data just came out just before COP that told us that over 5 million deaths a year are directly attributable to fossil fuel use and the air pollution from fossil fuels. We're seeing this in pregnancy.

But we're also seeing indirect impacts on human health from climate change. For example, we're seeing changes in dry seasons and drought, like in the Horn of Africa, and food insecurity; we're seeing changes in access to water. We're seeing this in terms of people's livelihoods and their abilities to go to work because of extreme heat.

We're also seeing it in terms of gender-based violence. We've heard reports of young girls who have to walk farther and farther now for water in Kenya, who then are at increased risk of gender-based violence and sexual assault

because of the distance, or traveling. So what we're dealing with is quite literally in every possible way, climate change is impacting our daily experience, here and now, and our ability to live healthy lives, and to have the opportunities that we want for ourselves and our families.

O'NEILL: There are all these overarching issues that tie together climate and health. But I want to think about some of the immediate impacts that we might be seeing. If we reduce fossil fuels, if we cut fossil fuel emissions, how immediately can we start to see health benefits from that?

KERRY: It is urgent that we absolutely commit to a phase out of fossil fuels. And it is urgent if we're going to keep to the Paris [Agreement goal of limiting warming to 1.5 degrees Celsius].

There are over 5 million deaths a year that are directly related to fossil fuel use. But what we know is there are scientific studies, for example, in inner cities and in communities and other places that show that when you get rid of gas or fuel-burning buses and pollutants, you can reduce asthma attacks and hospital and emergency room visits. You start to see direct benefits to health in the immediate moment of reducing fossil fuels.

"in inner cities and in communities and other places that show that when you get rid of gas or fuel-burning buses and pollutants, you can reduce asthma attacks and hospital and emergency room visits."

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Dr. Vanessa Kerry with World Health Organization Director-General Tedros Adhanom Ghebreyesus. Kerry is the first WHO Special Envoy on Climate and Health.

But as long as we are burning fossil fuels, and we are continuing to see an increase in greenhouse gas emissions, we are going to continue to drive the extreme weather that is leading to all the bad health outcomes.

So some of it is absolutely immediate, but some of it will drive a change that might take a little bit longer to see. But the important thing to remember is there is an urgency to reducing fossil fuel use today. We may not see all the direct outcomes for a year or two, until we start to really see the crest in terms of greenhouse gases. But we will be moving in completely the wrong direction and accelerating the number of deaths and accelerating the harm if we do not commit to a phase out of fossil fuels today.

O'NEILL: Your organization, Seed Global Health, works with nurses, midwives and physicians in Malawi, Sierra Leone, Uganda and Zambia. How have you seen the fallout from the climate crisis in the work that you do in that field?

KERRY: Seed Global Health got involved in the climate change discussions because we have felt very directly the impacts of climate change in the communities where we work and it's made our job harder. We have trained over 34,000 healthcare workers over the last decade who are in service to catchment areas of about 73 million people.

Extreme storms in Malawi are more severe, happening more frequently, lasting longer and are making it harder for the healthcare workers to be trained to do their job. There's more malaria at the height of the malaria season. There's more malaria when it's not malaria season. We're seeing bridges washed out. A colleague of ours, Chauncey Banda, who's a

midwife in the Sonjay district in Malawi, ended up having to advocate for the government to set up new birthing centers that Seed helped stand up, because the bridges washed out to the existing birthing centers. And it turns out that when you're in a climate crisis, or when you have storms, women go into preterm birth more frequently. There's a very real impact if you can't have continuity of services. Together, we opened these facilities so that C-sections could be provided, and so that women could have that continuity of care. And not a woman or child died in the wake of some of these storms after they lost their original facility.

But that makes our job harder, when we could be delivering primary care services or ensuring services elsewhere. We're seeing more and worse health outcomes because of climate change. It's the same in Uganda, it is the same in Sierra Leone, it is the same in Zambia, it's across the continent, and it's across the world. It's here in the United States. We're going to need more workforce to meet the challenges from climate change, we're going to need health systems that can be resilient to the climate changes to keep delivering services. And we need to adapt to these changes here and now or we're going to lose more lives.

O'NEILL: What inspired you to get into this world of strengthening global health care?

KERRY: I grew up in a house with both my parents very, very committed to being global citizens, and to being advocates for those who maybe couldn't advocate for themselves. I was always interested in going into medicine, and I very much brought some of those experiences forward with me into my medical career.

When I was 14, I had the opportunity to travel to Vietnam back before we normalized relations with the country and saw a level of poverty that was just shocking at the scope, the scale and the degree of poverty. And I didn't know what to do with it at age 14.

But I held on to it, and when I went to medical school it became very clear to me that my medical career needed to integrate some of that experience that I had had in Vietnam. It put me on a path to realize that it is unacceptable that there are two such different standards of medical care in the world.

We have the technology, we have the wherewithal, we have the resources—we're just not making the choice to provide the services to people. And that is just fundamentally unacceptable. My colleagues and I are all committed to that same mission, to really close that gap with every capability that we can to make sure that there's a strong and robust healthcare workforce to deliver services. To make sure that we're diagnosing patients appropriately, managing them appropriately and that the medicines are available to treat them.

For us, climate change is just exacerbating that gap, which is what has brought me to this place of getting engaged in the climate. The work that we spent a decade doing is all at risk if we don't step up to this moment with a new and accelerated commitment and to bring others on board to meet this moment.

"We're going to need more workforce to meet the challenges from climate change, we're going to need health systems that can be resilient to the climate changes to keep delivering services. And we need to adapt to these changes here and now or we're going to lose more lives."

PUBERTY

by **Azeen Ghorayshi**

Puberty Starts Earlier Than It Used To. No One Knows Why?

Some girls are starting to develop breasts as early as age 6 or 7. Researchers are studying the role of obesity, chemicals and stress.

Marcia Herman-Giddens first realized something was changing in young girls in the late 1980s, while she was serving as the director for the child abuse team at Duke University Medical Center in Durham, N.C. During evaluations of girls who had been abused, Dr. Herman-Giddens noticed that many of them had started developing breasts at ages as young as 6 or 7.

"That did not seem right," said Dr. Herman-Giddens, who is now an adjunct professor at the University of North Carolina Gillings School of Global Public Health. She wondered whether girls with early breast development were more likely to be sexually abused, but she could not find any data keeping track of puberty onset in girls in the United States. So she decided to collect it herself.

A decade later, she published a study of more than 17,000 girls who underwent physical examinations at pediatricians' offices across the country. The numbers revealed that, on average, girls in the mid-1990s had started to develop breasts — typically the first sign of puberty — around age 10, more than a year earlier than previously recorded. The decline was even more striking in Black girls, who had begun developing breasts, on average, at age 9.

The medical community was shocked by the findings, and many were doubtful about a dramatic new trend spotted by an unknown physician assistant, Dr. Herman-Giddens recalled. "They were blindsided," she said.

But the study turned out to be a watershed in the medical understanding of puberty. Studies in the decades since have confirmed, in dozens of countries, that the age of puberty in girls has dropped by about three months per decade since the 1970s. A similar pattern, though less extreme, has been observed in boys.

Although it is difficult to tease apart cause and effect, earlier puberty may have harmful impacts, especially for girls. Girls who go through puberty early are at a higher risk of depression, anxiety, substance abuse and other psychological problems, compared with peers who hit puberty later. Girls who get their periods earlier may also be at a higher risk of developing breast or uterine cancer in adulthood.

No one knows what risk factor — or more likely, what combination of factors — is driving the age decline or why there are stark race- and sex-based differences. Obesity seems to be playing a role, but it cannot fully explain the change. Researchers are also investigating other potential influences, including chemicals found in certain plastics and stress. And for unclear reasons, doctors across the world have reported a rise in early puberty cases during the pandemic.

"We are seeing these marked changes in all our children, and we don't know how to prevent it if we wanted to," said Dr. Anders Juul, a pediatric endocrinologist at the University of Copenhagen who has published two recent studies on the phenomenon. "We don't know what is the cause."

Obesity

Around the time that Dr. Herman-Giddens published her landmark study, Dr. Juul's research group examined breast development in a cohort of 1,100 girls in Copenhagen. Unlike the American children, the Danish group matched the pattern long described in medical textbooks: Girls began developing breasts at an average age of 11 years old.

"I was interviewed quite a lot about the U.S. puberty boom, as we called it," said Dr. Juul. "And I said, 'it's not happening in Denmark.'"

At the time, Dr. Juul suggested that the earlier onset of puberty in the United States was probably tied to a rise in childhood obesity, which had not occurred in Denmark.

Obesity has been linked to earlier periods in girls since the 1970s. Numerous studies since have established that girls who are overweight or obese tend to start their periods earlier than girls of average weights do.

In one decades-long study of nearly 1,200 girls in Louisiana published in 2003, childhood obesity was linked to earlier periods: Each standard deviation above the average childhood weight was associated with a doubled chance of having a period before age 12.

And in 2021, researchers from Britain found that leptin, a hormone released by fat cells that

limits hunger, acted on a part of the brain that also regulated sexual development. Mice and people with certain genetic mutations in this region experienced later sexual development.

"I don't think there's much controversy that obesity is a major contributor to early puberty these days," said Dr. Natalie Shaw, a pediatric endocrinologist at the National Institute of Environmental Health Sciences who has studied the effects of obesity on puberty.

Still, she added, many girls who develop early are not overweight.

"Obesity can't explain all of this," Dr. Shaw said. "It's just happened too quickly."

Chemicals

In the decade after the Herman-Giddens study, Dr. Juul began noticing an increase in the number of referrals for early puberty in Copenhagen, mostly of girls who were developing breasts at 7 or 8 years old.

"And then we thought, 'Is this a real phenomenon?'" Dr. Juul said. Or, he wondered, had parents and doctors become "hysterical" because of the news coverage of Dr. Herman-Giddens's study?

In a 2009 study of nearly 1,000 school-aged girls in Copenhagen, his team found that the average age of breast development had dropped by a year since his earlier study, to a little under 10, with most girls ranging from 7 to 12 years old. Girls were also getting their periods earlier, around age 13, about four months earlier than what he had reported before.

"That's a very marked change in a very short period of time," Dr. Juul said.

"I don't think there's much controversy that obesity is a major contributor to early puberty these days."

— Dr. Natalie Shaw, Pediatric endocrinologist at the National Institute of Environmental Health Sciences.

But, unlike doctors in the United States, he did not think obesity was to blame: The body mass index of the Danish children in the 2009 cohort was no different than it had been in the 1990s.

Dr. Juul has become one of the most vocal proponents of an alternate theory: that chemical exposures are to blame. The girls with the earliest breast development in his 2009 study, he said, had the highest urine levels of phthalates, substances used to make plastics more durable that are found in everything from vinyl flooring to food packaging.

Phthalates belong to a broader class of chemicals called "endocrine disrupters," which can affect the behavior of hormones and have become ubiquitous in the environment over the past several decades. But the evidence that they are driving earlier puberty is murky.

In a review article published last month, Dr. Juul and a team of researchers analyzed hundreds of studies looking at endocrine disrupters and their effects on puberty. The methods of the studies varied widely; some were done in boys, others in girls, and they tested for many different chemicals at different ages of exposure. In the end, the analysis included 23 studies that were similar enough to compare, but it was unable to show a clear association between any individual chemical and the age of puberty.

"The big takeaway is that there's few publications and a paucity of data to explore this question," said Dr. Russ Hauser, an environmental epidemiologist at the Harvard T.H. Chan School of Public Health and a co-author of the analysis.

That lack of data has led many scientists to be skeptical of the theory, said Dr. Hauser, who recently reported on how endocrine disrupters affect puberty in boys. "We don't have enough data to build a strong case for a specific class of chemicals."

Stress and lifestyle

Other factors may also be involved in earlier puberty, at least in girls. Sexual abuse in early childhood has been linked to earlier puberty onset. Causal arrows are difficult to draw, however. Stress and trauma could prompt earlier development, or, as Dr. Herman-Giddens hypothesized decades ago, girls who physically develop earlier could be more vulnerable to abuse.

Girls whose mothers have a history of mood disorders also seem more likely to reach puberty early, as are girls who do not live with their biological fathers. Lifestyle factors like a lack of physical activity have also been linked to changes in pubertal timing.

And during the pandemic, pediatric endocrinologists from across the world noticed that referrals were increasing for earlier puberty in girls. A study published in Italy in February showed that 328 girls were referred to five clinics across the country during a seven month period in 2020, compared with 140 during the same period in 2019. (No difference was found in boys.) Anecdotally, the same thing might be happening in India, Turkey and the United States.

"I've asked my colleagues around the country and a number of them are saying, yes, we're seeing a similar trend," said Dr. Paul Kaplowitz, a professor emeritus of pediatrics at Children's National Hospital in Washington. It's unclear whether the trend was caused by increased stress, a more sedentary lifestyle or parents being in close enough quarters with their children to notice early changes.

If puberty begins younger than those cutoffs, doctors are supposed to screen the child for a rare hormonal disorder called central precocious puberty, which can spur puberty as early as infancy.

Several factors are most likely contributing at once. And many of these issues disproportionately impact lower-income families, which may partly explain the racial differences in puberty onset in the United States, the researchers said.

A new normal?

For decades, medical textbooks have defined the stages of puberty using the so-called Tanner Scale, which was based on close observations between 1949 and 1971 of about 700 girls and boys who had lived in an orphanage in England.

The scale defines normal puberty as starting at age 8 or above for girls and age 9 or above for boys. If puberty begins younger than those cutoffs, doctors are supposed to screen the child for a rare hormonal disorder called central precocious puberty, which can spur puberty as early as infancy. Children with this disorder often undergo brain scans and take prescribed puberty-blocking drugs to delay sexual development until an appropriate age.

But some experts argue that the age threshold for alarm should be lowered. Otherwise, they said, healthy children could be referred to specialists and undergo unnecessary medical procedures, which can be physically taxing and expensive.

"There's plenty more data that age 8 is not the optimal cutoff for separating normal from abnormal," Dr. Kaplowitz said. In 1999, he argued that the age cutoff for normal puberty should be lowered to age 7 in white girls and 6 in Black girls. "That did not go over too well," he recalled.

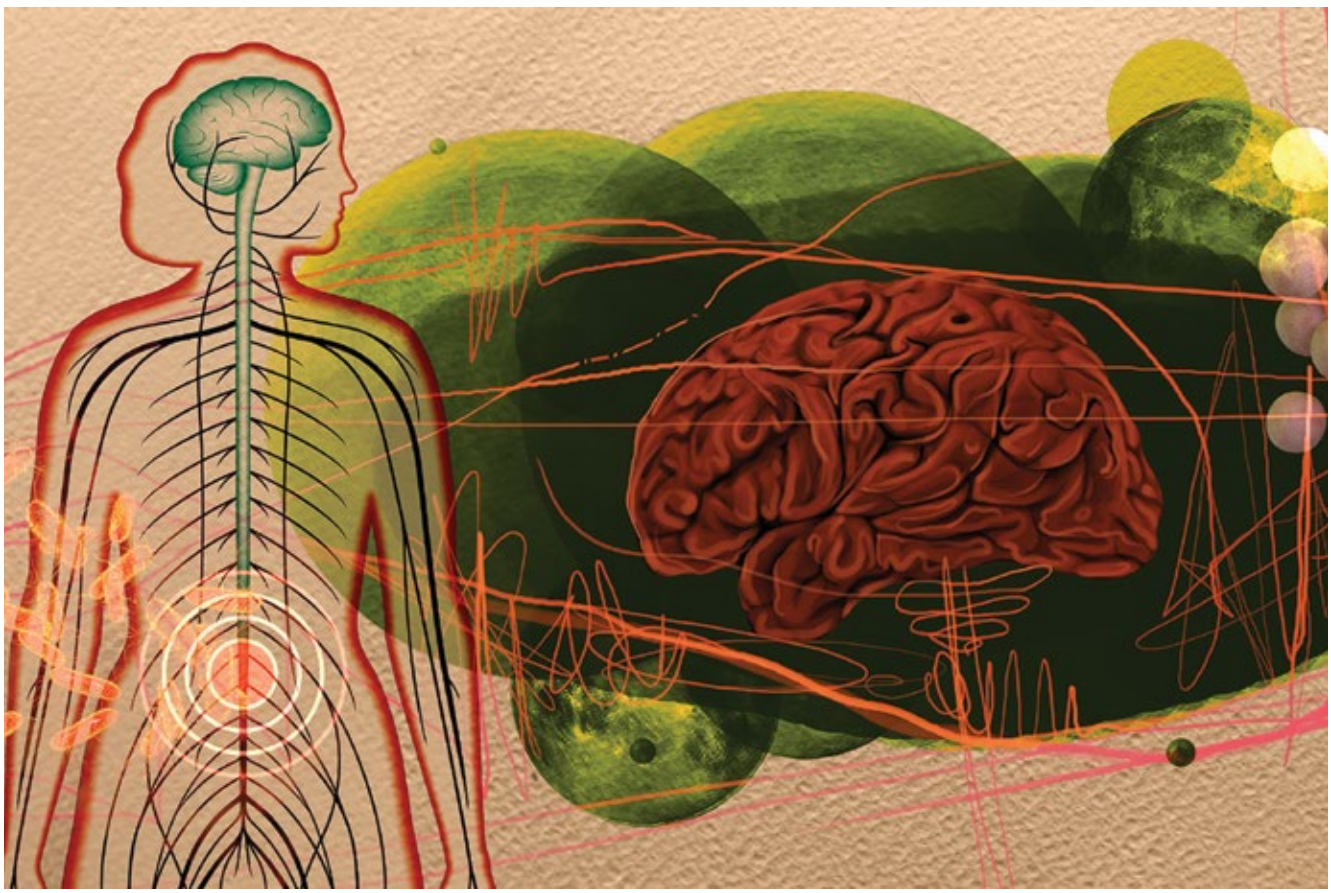
That stance, though, was bolstered by a recent study from Dr. Juul's group showing that, of 205 pubertal children younger than 8 who underwent brain scans, just 1.8 percent of girls and 12.5 percent of boys had brain abnormalities indicating central precocious puberty.

But lowering the age cutoff remains controversial, with many pediatricians arguing that the risk of a disorder is still large enough to justify extra precautions. Others, like Dr. Herman-Giddens, say that the changes are a sign of a legitimate public health problem and should not be accepted as normal.

"It might be normal in the sense of what the data are showing," Dr. Herman-Giddens said, "but I don't think it's normal, for lack of a better word, for what nature intended."

by **David Levin**

HOW GUT BACTERIA CONNECT TO PARKINSON'S DISEASE



Growing evidence suggests a link between the debilitating neurological illness and the microbes that live in our intestines. The vagus nerve may be a pathway.

It can start small: a peculiar numbness; a subtle facial tic; an inexplicably stiff muscle. But then time goes by — and eventually, the tremors set in. Roughly a million people in the United States (and roughly 10 million people worldwide) live with Parkinson's disease, a potent neurological disorder that progressively kills neurons in the brain. As it does so, it can trigger a host of crippling symptoms, from violent tremors to excruciating muscle cramps, terrifying nightmares and constant brain fog.

Roughly a million people in the United States (and roughly 10 million people worldwide) live with Parkinson's disease, a potent neurological disorder that progressively kills neurons in the brain. As it does so, it can trigger a host of crippling symptoms, from violent tremors to excruciating muscle cramps, terrifying nightmares and constant brain fog. While medical treatments can alleviate some of these effects, researchers still don't know exactly what causes the disease to occur in the first place.

A growing number of studies, however, are suggesting that it may be tied to an unlikely culprit: bacteria living inside our guts.

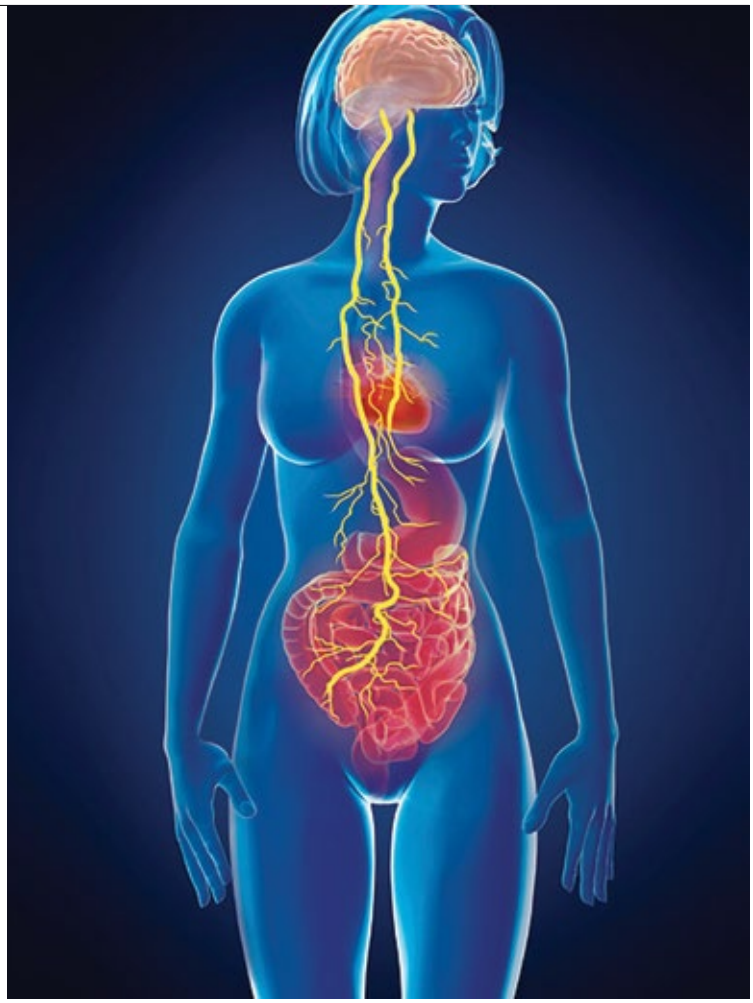
Every one of us has hundreds or thousands of microbial species in our stomach, small intestine and colon. These bacteria, collectively called our gut microbiome, are usually considerate guests: Although they survive largely on food that passes through our insides, they also give back, cranking out essential nutrients like niacin (which helps our body convert food into energy) and breaking down otherwise indigestible plant fiber into substances our bodies can use.

As Parkinson's advances in the brain, researchers have reported that the species of bacteria present in the gut also shift dramatically, hinting at a possible cause for the disease. A 2022 paper published in the journal Nature Communications recorded those differences in detail. After sequencing the mixed-together genomes of fecal bacteria from 724 people — a group with Parkinson's and another without — the authors saw a number of distinct changes in the guts of people who suffered from the disease.

The Parkinson's group had dramatically lower amounts of certain species of *Prevotella*, a type of bacterium that helps the body break down plant-based fiber (changes like this in gut flora could explain why people with Parkinson's disease often experience constipation). At the same time, the study found, two harmful species of Enterobacteriaceae, a family of microbes that includes *Salmonella, E. coli* and other bugs, proliferated. Those bacteria may be involved in a chain of biochemical events that eventually kill brain cells in Parkinson's patients, says Tim Sampson, a biologist at Emory University School of Medicine and coauthor of the study.

At first glance, the relationship between bacteria and brain disease isn't exactly obvious. How can a change in gut microbes kick off a devastating neurodegenerative disorder? The relationship between the two may seem counterintuitive — but Sampson says it comes down to the subtle ways that the brain and the gut are connected.

In the walls of the intestines, a network of neurons called the enteric nervous system lets the body sense what's going on in the gut and respond accordingly. This circuitry controls muscle movement, local blood flow, secretion of mucus and other essential digestive functions.



The vagus nerve (shown in yellow) is a physical conduit between the gut and brain that might traffic misfolded proteins that trigger Parkinson's disease, scientists suggest.

Since the cells of the enteric nervous system are embedded in the gut wall, many of them come into close contact with the lumen — the cavity of the gut that contains the microbiome — where they can interact directly with biochemicals created by bacteria. Some of these are sticky proteins called curli (pronounced CURL-eye) that may be implicated in Parkinson's.

Under normal circumstances, curli proteins let Enterobacteria build biofilms, the gooey mats that protect the microbes and help them stay put in the gut. Yet if a curli molecule touches a common protein created by nerve cells — called alpha-synuclein — that protein begins to misfold and form a dangerous mass called an aggregate. Once created, these aggregates can spread widely though the nervous system, leapfrog from cell to cell and eventually enter the brain through the vagus nerve, the main pathway that carries signals between the brain and the gut. It's thought that in some cases of Parkinson's in humans, changes in the gut microbiome may activate that process, says Emeran Mayer, a gastroenterologist and neuroscientist at UCLA and coauthor of a recent overview of the gut-brain connection in the *Annual Review of Medicine*.

Suspicion that the vagus plays a key role in neurodegenerative disease has been growing in recent years. A 2017 study in the journal *Neurology*, Mayer notes, showed that "If you cut the vagus nerve, it decreases the risk for Parkinson's disease. That's a pretty strong indication that ... this degenerative material is transported, apparently, through the vagus nerve."

Over the past few decades, a number of animal studies have shown that the vagus provides a physical conduit that molecules can use to move between the gut and brain — but although this neurological superhighway could play an important role in Parkinson's, it's still not clear if the nerve is a lynchpin in causing the disease itself.

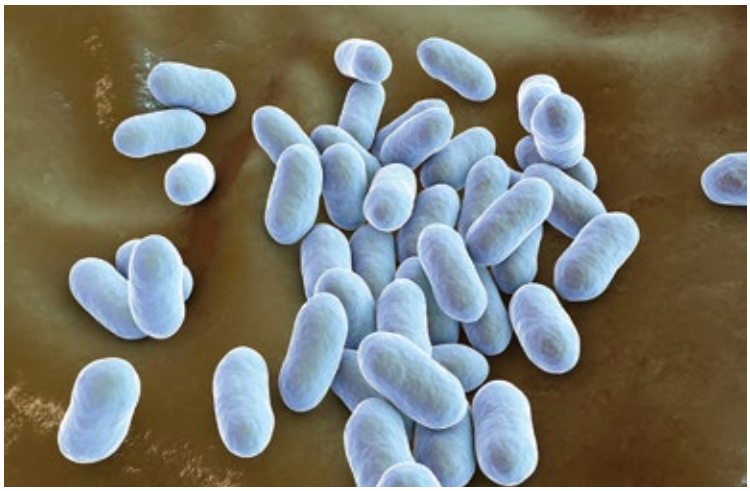
In addition to aggregates moving through the vagus, different triggers — like the lipids, vitamins and other organic compounds that gut bacteria produce — could travel through blood vessels to the brain, where they may cause inflammation and damage tissue. Likewise, says David Hafler, a neuroimmunologist at Yale University, immune cells that are activated in the gut may contribute to the neurological damage and dysfunction that occurs in Parkinson's.

These immune cells, called T cells, can migrate out of the gut, enter the bloodstream and cross the blood-brain barrier, where they ultimately may kill off neurons. This sort of autoimmune response is the driver for other

neurological diseases like multiple sclerosis, Hafler reasons, so it's feasible that it plays a role in Parkinson's as well. In both diseases, changes in the gut microbiome could be the potential trigger.

There's already strong evidence for this idea. In 2016, Sampson found a direct connection between gut microbes and Parkinson's disease: Using fecal samples from Parkinson's patients, Sampson inoculated the guts of germ-free mice (animals with no naturally occurring microbiome), and the animals quickly developed Parkinson's symptoms. Today, using the new genetic survey of gut microbes he and his colleagues published in Nature Communications, he's narrowing in on a few microbe families and using similar methods to reveal which precise species are the culprits.

Sampson's approach comes with some caveats: Parkinson's disease, after all, might be linked to multiple bacteria interacting in complex ways — so there likely won't be a single smoking gun. It's also not totally clear if changes in the microbiome are the root cause or if they just accelerate damage already taking place in the brain. The complexity of the microbiome is mind-boggling: There are hundreds of different types of bacteria involved, and each creates myriad molecules that affect digestion, the immune system and other important bodily functions. Sorting through all those components and identifying how they change in the face of disease will be an important next step.



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Species of bacteria from a group known as Prevotella (shown here in a 3-D illustration) are dramatically lower in the fecal matter of Parkinson's patients, research has found.

Under normal circumstances, curli proteins let Enterobacteria build biofilms, the gooey mats that protect the microbes and help them stay put in the gut.

And so, as tantalizing as the links between the microbiome and Parkinson's may be, it could be decades before people who suffer from the disorder can reap any tangible benefits. Many of the researchers examining those links, like Mayer, also warn patients to be of wary of sweeping claims about drugs, supplements or even fecal transplants — seeding the gut with microbes from another, healthy person — that "treat" Parkinson's by altering the microbiome.

"A lot of people make a lot of money selling individuals supplements, telling you that they're going to slow your cognitive decline or prevent Parkinson's disease," says Mayer. But, he adds, "we don't know the causal roles of the microbiome for sure. We know it from animal studies, so we have indirect evidence for it — but it's been difficult to show in humans without a doubt that the microbes, and some of their signal molecules, play the main causal role."

Until definitive answers are found, researchers like Mayer will continue to chip away at the problem, microbe by microbe.

Case Report

A Case of Infectious Mononucleosis Induced Jaundice Complicated by Possible Drug Induced Liver Injury

Infectious mononucleosis is not a common cause for jaundice and normally does not require specific treatment when it does occur. Drug induced liver injury (DILI) is, on the other hand, a common occurrence. It is usually a diagnosis of exclusion and other possible causes of liver injury must be explored.

Dr. Jyoti Upadhyay[1] , Dr. Amal Upadhyay[2], Dr. Yusra Mashkoor[3], Dr. Hamdan Iftikhar[3]

1. Internal Medicine Specialist, Aster Hospital, Dubai
2. Consultant gastroenterologist, Aster Hospital, Dubai
3. Medical Intern — Dubai Health Authority, Aster Hospitals, Dubai

Corresponding author:
Dr. Jyoti Upadhyay,
MBBS, M.D (Internal Medicine)
Email: jomaldhi@yahoo.com

Keywords:
Infectious mononucleosis, jaundice, drug induced liver injury, lymphadenopathy

Abbreviations:
DILI — Drug induced liver injury, CBC — Complete Blood Count, CRP — C Reactive protein, LFT — Liver Function Tests, MRCP — Magnetic Resonance Cholangiopancreatography, SGOT — Serum Glutamic Oxaloacetic Transaminase, SGPT — Serum Glutamic Pyruvic Transaminase, ALP — Alkaline Phosphatase, PCOD — Polycystic Ovarian Disease, F/U — Follow up, HAV — Hepatitis A virus, HBV — Hepatitis B virus, HCV — Hepatitis C virus, HEV — Hepatitis E virus

ABSTRACT

In this case, a young female presented with non—specific features such as fever, sore throat, headache and fatigue. She went on to develop epigastric pain, darkening of urine and jaundice, with no resolution of prior symptoms. Physical and Laboratory tests confirmed the primary diagnosis of infectious mononucleosis, however, recent exposure to multiple drugs required consideration of DILI as a probable contributor the the patient's jaundice. Appropriate treatment with steroids as well as discontinuation of all potential hepatotoxic agents proved curative.

INTRODUCTION

Infectious mononucleosis is caused by Epstein Barr Virus (EBV) and presents with the classic triad of fever, tonsillitis, and lymphadenopathy. Additional findings include tonsillar exudates, palatal petechiae, hepatosplenomegaly, and hepatitis. Elevations in liver transaminases are commonly seen, but are usually transient and rarely progress to fulminant hepatitis. Most infections are self—limiting with good prognosis. However, there is a <5% risk of developing significant cholestasis and jaundice, which are rare complications.[(1)]

The liver is the main point of metabolism of most drugs, making it susceptible to drug—induced injury. DILI can mimic all forms of acute and chronic liver diseases, which poses a significant challenge[(2)]. Symptoms of drug—induced liver injury (DILI) include: jaundice, weakness, abdominal pain, dark stools or urine, nausea, and pruritus. It can also present as acute or chronic liver failure, which complicates the diagnosis[(3)]. Although liver parameters are sensitive in detecting DILI, they cannot be used to predict the patient's subsequent clinical course. DILI is also a leading cause of drug withdrawals, restrictions and project terminations[(4)].

Here we present an original case

of infectious mononucleosis induced jaundice complicated by possible superimposed drug induced liver injury.

CASE REPORT

A 29—year—old female presented to the outpatient department with complaints of continuous fever for 1 week associated with sore throat, headache and fatigue. Prior to this visit, she consulted another physician for her complaints. Investigations such as CBC, CRP, COVID PCR, Influenza, and chest X—ray were done which were within normal limits. She was given inj. Ceftriaxone 1g, inj. vitamin B complex (Medivitan) and I.V. Paracetamol, and discharged on amoxicillin—clavulanic acid (amoxiclav) and anti—congestant (fludrex).

However, she felt that her symptoms did not improve and now developed epigastric pain and noticed darkening of her urine.

Repeat laboratory tests revealed a C—Reactive protein of 59 (normal <5) and deranged Liver Function Tests (Bilirubin—4.1, SGOT—250, SGPT250, ALP). She was then referred to our hospital for further management.

Her past medical history is significant for PCOD and insulin resistance, controlled on Glucophage and GLP—1 receptor antagonist. She also disclosed that she had recently completed a 1 week course of doxycycline 100mg for PCOD—related acne. Her drug history was insignificant for any other short or long term drug use. No other known comorbidities viz. diabetes mellitus, hypertension, dyslipidemia, asthma, or liver/biliary diseases. There is no past surgical history and family history is insignificant for any comorbidities or liver diseases.

On general physical examination, she was conscious, alert, and oriented, however she appeared febrile and pale. Inspection of the sclera revealed mild icterus. Capillary refill time was normal (<2s) and no asterixis present. There were enlarged and painful cervical lymph nodes. No stigmata of chronic liver disease were found. The abdominal exam on inspection showed normal abdominal contour and symmetry. No masses, skin changes, dilated veins, change in hair distribution, or surgical scars were noted. No hepatosplenomegaly, hepatic or splenic bruit noted. No peripheral edema was observed.

A hepatitis panel was done covering HAV, HBV, HCV, HEV which were all negative. Antibody serology screen which included Liver Kidney Microsomal (LKM) antibody, anti—nuclear antibody (ANA), anti—smooth muscle antibody (ASMA), serum immunoglobulin IgG, anti—soluble liver antigen, were all negative.

Table 1: Laboratory investigations sought in this

PARAMETER	NORMAL RANGE	VALUE	INFERENCE
Hemoglobin	12—15	11.8	low
Hematocrit	36—46	34.1	low
WBC	4—10	10.24	normal
Platelet	150—410	304	normal
Total protein	6.4—8.3	6.6	normal
Globulin	2.3—3.5	3.13	normal
A/G ratio	1.0	1.0	normal

On abdominal ultrasound, hepatosplenomegaly was detected along with slightly elevated echogenicity of the liver and mild pericholecystic edema. Monospot test yielded a positive result. Ultrasound examination of the neck revealed several bilaterally enlarged cervical lymph nodes (level 1A, 1B, 2, 3 and 5), with the largest one measuring 13.6 x 5.4 mm in size on the right side and 23 x 10.8 mm in size on the left (Fig 1). These lymph nodes showed increased vascularity, according to a Doppler examination (Fig 2). MRCP done to rule out any hepatobiliary disorders revealed hepatosplenomegaly with edema of the gallbladder wall; however, no choledocholithiasis was noted (Fig 3). Clinically a probable diagnosis of IM was made. In view of recent exposure to multiple medications, it was not possible to rule out probability of DILI. Liver biopsy was advised but however the patient refused.

Table 2: LFTs and CRP values. Note the change in liver parameters and CRP over the course of treatment in the hospital.

PARAMETER	NORMAL RANGE	DAY 0	DAY 2	DAY 5
Total bilirubin	0.1—1.2 mg/dL	5.01	6.54	5.36
Direct bilirubin	<0.3 mg/dL	3.33	6.21	5.06
Indirect bilirubin	0.1—1.0 mg/dL	1.68	0.33	0.30
SGOT (AST)	<35 U/L	178	220	285
SGPT (ALT)	<33 U/L	199	165	187
ALP	35—104 U/L	398	548	559
GGT (U/L)	<42 U/L	144	—	—
CRP	<5 mg/L	43.7	20.70	11.12

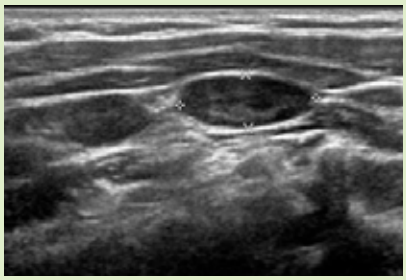


Figure 1: Lymphadenopathy seen on USG of the cervical lymph nodes

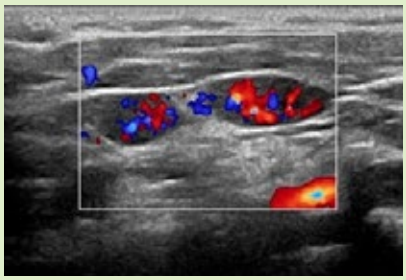


Figure 2: Doppler scan of cervical lymph nodes showing increased vascularity

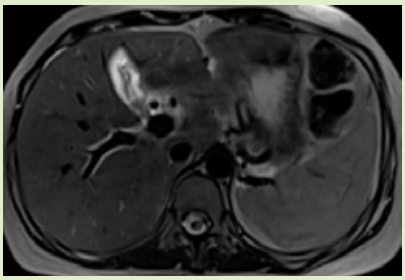


Figure 3: MRI of the abdomen revealing hepatomegaly with edema of gall bladder wall

All potentially hepatotoxic medications were withdrawn in view of suspected DILI. Broad spectrum IV antibiotics were started initially due to longstanding fever and jaundice which were discontinued later. Ursofalk and N—acetylcysteine were started for liver protection.

Steroids are commonly used for treating complications in IM. Steroids are also used in treating severe DILI. This patient had neither severe complications of IM nor did she suffer from severe hepatitis due to DILI. However, she had a prolonged course of jaundice that seemed to be worsening in spite of supportive measures. She also remained symptomatic with unresolved pharyngitis and fever in spite of anti—inflammatory and anti—pyretic agents— some of which may also prove hepatotoxic in higher doses. At this point, it was decided to initiate steroids (Prednisolone 30 mg daily). Patient became afebrile rapidly and pharyngitis seemed to respond as well. LFT was monitored closely and was noted to improve progressively. Patient was discharged and after 2 weeks, showed complete recovery with normalization of liver function (Table 3) (Fig 4, Fig 5). Steroids were then withdrawn gradually. Patient has remained well at the time of her final follow up 8 weeks later.

Table 3: LFT values on subsequent follow up

PARAMETER	NORMAL RANGE	F/U 4 DAYS	F/U 2 WEEKS	F/U 8 WEEKS
Total bilirubin	0.1—1.2 mg/dL	1.78	0.92	0.60
Direct bilirubin	<0.3 mg/dL	1.43	0.71	—
Indirect bilirubin	0.1—1.0 mg/dL	0.35	0.21	—
SGOT (AST)	<35 U/L	230	27	21
SGPT (ALT)	<33 U/L	245	21	13
ALP	35—104 U/L	441	157	50

DISCUSSION AND CONCLUSION

Infectious mononucleosis may present with the following symptoms: fever, sore throat, headache, body ache, swollen lymph nodes in neck and armpit with enlarged liver and spleen. However, jaundice is a rare presentation [1]. Normally no specific treatment is required and most immunocompetent patients make uneventful recovery. Steroids are required in some patients for significant complications like impending upper airway obstruction, massive splenomegaly or myocarditis. Interestingly, steroids also help in treating severe drug induced liver injury which cannot be ruled out in this patient. Liver biopsy may help in determining the underlying etiology of jaundice/hepatitis. It also helps in ruling out other possible causes of acute/subacute liver injury. We do not have this information since patient refused liver biopsy due to its invasive nature.

Liver is the main point of metabolism of most drugs, making it susceptible to drug—induced injury (DILI). DILI can mimic all forms of acute and chronic liver diseases, which poses a significant challenge, as seen in this case. Investigating acute liver injury can sometimes be complicated. Multiple factors may affect the liver apart from the traditionally accepted "hepatotrophic viruses". To confound the matter, jaundice may at times be of multifactorial etiology wherein DILI plays an important role.

The mainstay of management of DILI is early identification and removal of the offending agent. Failure to identify and removal of the offending agent may lead to severe liver injury.

Acetaminophen and amoxicillin/clavulanic acid have been common causes of DILI in developed countries. However, many other commonly used drugs are now being reported as well. DILI is the most common cause of acute liver failure in the United States. Incidence of this disease is not well established as it is usually under reported, however, recent studies have shown that the numbers may be approximately 20 in 100,000. [3] Our patient was exposed to the following drugs—acetaminophen, amoxicillin/clavulanic acid, doxycycline, ibuprofen.

Figure 4: Progression of SGOT, SGPT & ALP over the course of 8 weeks

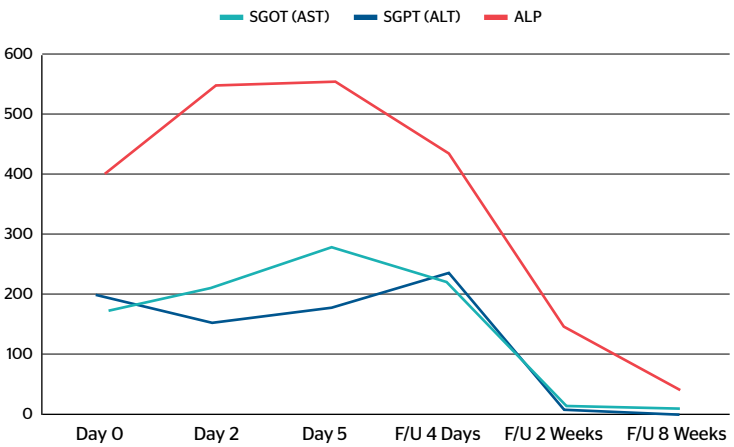
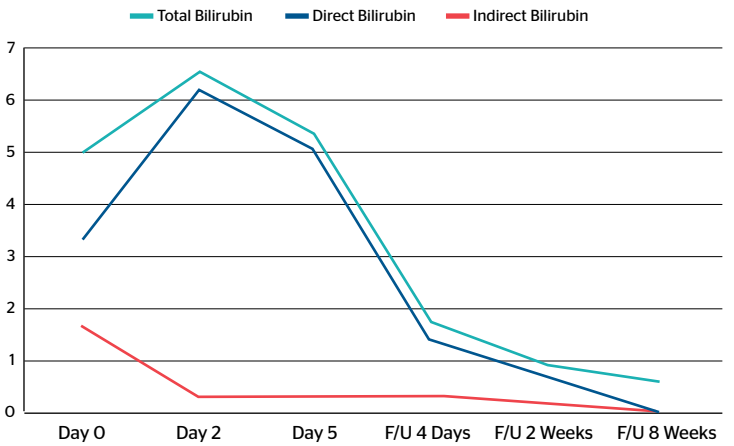


Figure 5: Progression of total, direct and indirect bilirubin over the course of 8 weeks



Acetaminophen: A small portion of acetaminophen is metabolized by the liver enzyme CYP 2E1 into a hepatotoxic metabolite known as NAPQI which binds to a number of cellular proteins, especially mitochondrial proteins leading to ineffective mitochondrial function. Other mechanisms of hepatotoxicity include the formation of toxic free radicals in the mitochondria, which leads to damage of the mitochondrial DNA and termination of ATP production. All of this eventually leads to hepatocellular necrosis. [5]

Doxycycline: It causes a mixed pattern of liver injury; from hepatocellular to cholestatic and arises 7—14 days after starting the drug. The exact mechanism of liver injury is unknown but owing to the fact that it has a short latency period and reoccurs with re—exposure, an immuno—allergic etiology is likely. [6]

Amoxicillin—clavulanic acid: Hepatotoxicity from amoxicillin and clavulanate is most likely immuno—allergic in nature. Re—exposure to amoxicillin alone has not been linked to recurrence, but re—exposure to the combination is generally followed by a rapid onset of severe hepatic injury. However, studies suggest that the liver injury appears to be caused by the clavulanate rather than the amoxicillin. [7]

Ibuprofen: Although the exact mechanism of ibuprofen—induced liver damage is unknown, it may be multi—factorial. The quick onset points to a toxic metabolite, yet the hypersensitive symptoms that come along with liver damage suggest an immuno—allergic response. [8]

This case highlights the importance of thorough history taking, especially when patients present with such vague symptoms. A high index of suspicion is crucial in such cases and all differentials should be explored and ruled out. Even though this case seemed fairly straightforward in the beginning, several factors complicated the symptoms which prompted a thorough evaluation.

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Case Report

Dialysis Related Amyloidosis

Dialysis related amyloidosis (DRA) is a very rarely reported disabling condition caused by deposition of beta2—microglobulin in the bone, periarticular structures, and viscera of patients with chronic kidney disease on long term dialysis. Histologically documented cases are not common today. We describe a patient with DRA who was on maintenance hemodialysis for a total period of 12 years.

Abhinav Menon[1], V N Unni[1], Nanda Kachare[2], Vinod Kumar[1], Bipi Prasannan[1]

1. Department of Nephrology, Aster Medcity, Kochi, Kerala, India — 682027
2. Department of Pathology, Aster Medcity, Kochi, Kerala, India - 682027

Corresponding author:
Dr.V.N.Unni, Lead senior consultant, Dept. of Nephrology, Aster Medcity, Kochi
Email: unnivn1@gmail.com
Tel: + 91 9847049857

Keywords:
Amyloidosis
Dialysis related arthropathy
Hemodialysis

INTRODUCTION

Amyloidosis is a disorder of abnormal deposition of a protein referred to as amyloid. These fibrils are insoluble, disrupt tissue structure and cause disease. In systemic amyloidosis, the deposits may be present in the parenchyma of the viscera , causing progressive organ dysfunction, often leading to death of patients. [(1)] Dialysis related amyloidosis (DRA) is a rare, but serious complication of both long term hemodialysis (HD) and peritoneal dialysis (PD). DRA is characterized by accumulation and tissue deposition of amyloid fibrils consisting of beta2—microglobulin (β2M) in the bone, joints and surrounding soft tissues as well as viscera of patients on long term maintenance dialysis, usually over ten years. Four decades ago, histological features of DRA was almost a universal finding in patients on long term hemodialysis.[(2)] However, there has been a decline in symptomatic presentation of DRA, especially in the first decade of patients on hemodialysis.[(3)] According to a study by Schwalbe *et al,* clinical and radiological prevalence of DRA has decreased from 1988 to 1996 by 80%; DRA was hence considered to be a vanishing entity.[(4)]

We report a case of dialysis—related amyloid arthropathy in a patient on long term hemodialysis.

CASE REPORT

A 71—year—old female was diagnosed to have end stage renal disease (ESRD) due to diabetic nephropathy and was on thrice weekly maintenance hemodialysis since 2006. She underwent renal transplantation in 2009 at another center. Within six months, she had graft loss and was restarted on hemodialysis through a left radiocephalic arteriovenous fistula; a low flux polysulfone dialysis membrane was used for dialysis. She was anuric, was on hemodialysis thrice weekly (three hours every session) for a total duration of 12 years. She developed painful restriction of movements and swelling of right shoulder joint one year back, which was treated with

analgesics and physiotherapy. However, her symptoms persisted and she was referred to our center for further management.

On examination, her right shoulder joint was swollen with local rise of temperature, joint movements were restricted. Left shoulder joint movements were also restricted, there was no swelling or local rise of temperature. X—Ray of shoulder joints showed erosions of humeral head and distal clavicle and deeper soft tissue margin, depicting effusion in the right shoulder joint; there was subchondral lucency along humeral head adjacent to greater tuberosity, erosions at distal end of clavicle and periarticular osteopenia in the left shoulder joint. (Figure 1a,1b). MRI of both shoulder joints showed features consistent with florid synovitis — T1/T2 low signal intensity deposits, erosion and synovitis (figure 1c,1d). She had no features of carpal tunnel syndrome. Radiographs of wrists were normal. Serum Beta micro globulin levels were elevated — 38,508 ng/ml [Normal: 700—1800 ng/ml]. Serum Calcium 7.2mg/dl; Serum phosphorus:8.2mg/dl. (Table 1).

Table 1

Investigation	Results
Hemoglobin	8.2g/dl
Serum creatinine	15.6mg/dl
Blood urea	280mg/dl
Serum Calcium	7.2mg/dl
Serum phosphorus	8.2mg/dl
Serum albumin	3.2g/dl
Serum globulins	3.6g/dl
Serum beta 2 Microglobulin	38,508ng/ml

(Normal: 700 —1800ng/ml)

She underwent arthroscopic synovectomy of right shoulder joint and arthroscopic synovial biopsy of left shoulder joint under regional anesthesia. Tissues from bilateral synovial tissue and bone were subjected to histopathological examination. Light microscopy revealed cortical bone trabeculae and synovial fibrocollagenous tissue with diffuse deposits of extracellular pale eosinophilic material on Hematoxylin and eosin—stained sections (figure 2a), which were weakly positive on Periodic acid Schiff stain. Thioflavin T stain showed bright green deposits on immunofluorescence (IF) (figure 2b). Congo red stained sections showed apple green birefringence on polarized light examination (figure 2c). Electron Microscopy of the sample showed aggregates of randomly oriented non—branching fibrillary structures measuring about 9—12 nm in diameter with mean fibril diameter of 10.6 nm and focal “streaming” arrangement (figure 2d). A diagnosis of dialysis related amyloid arthropathy was confirmed based on light microscopy with special stains and ultrastructural studies. Liver function tests, serum protein electrophoresis and bone marrow examination were normal. She underwent radio—frequency ablation of axillary and supra scapular nerves of both shoulder joints for reduction of pain and obtained good symptomatic pain relief.

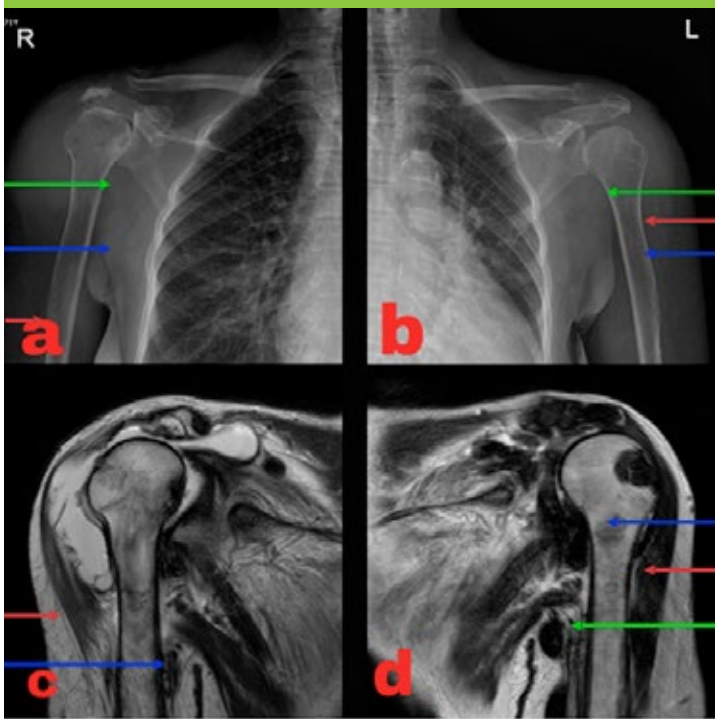
She was advised hemodiafiltration using high flux Polysulfone dialyzers four times a week (four hours each time) for better middle molecular weight clearance. She tolerated the procedure well and her symptoms improved by eight weeks; pain subsided totally. She was sent back with an advice to continue hemodiafiltration thrice weekly at her hometown.

DISCUSSION

The term ‘amyloid’ was coined initially by Schleiden and later by Virchow in the mid 19th century; they described deposits stained by iodine, found in the liver at an autopsy. These are fibrous, proteinaceous and insoluble deposits found in organs and tissues, dominated by β pleated sheet structure. [1] Amyloid can be identified with congo red stain as an "apple—green birefringence" under polarized light, with hematoxylin & eosin (H&E) stain as waxy, homogenous, pale eosinophilic material. Other stains may also be used to identify amyloid such as crystal violet or thioflavin T. DRA is a complication of both long—term HD and PD. In 1975, Warren and Otieno reported a 63.8% incidence of Carpal tunnel Syndrome (CTS) in patients on intermittent hemodialysis.[5] In 1980, amyloid deposition was found in CTS and later, Beta 2 Micro globulin (β2M) was recognised as the predominant protein.[6]

In DRA, amyloid fibrils consist of β2M in the osteoarticular structures and viscera.[7] In ESRD, plasma levels of β2M are elevated and tissue deposition occurs over time. DRA mainly involves the osteoarticular system (bone, synovium, muscle, tendon, ligaments);

Figure 1



a) Early erosions of humeral head (blue arrow) and distal clavicle (green arrow), deeper soft tissue margin depicting effusion (red arrow).
b) Subchondral lucency along humeral head adjacent to greater tuberosity (blue arrow), erosions at distal end of clavicle (green arrow) and periarticular osteopenia (red arrow).
c) T2 weighted image of right shoulder joint showing gross effusion with loculations (red arrow) and hypointensity in the axillary recess (blue arrow).
d) T2 weighted image of left shoulder joint showing hypointensity at bony erosions in the humeral head (red arrow), hypointensity in the axillary recess (green arrow) and acromioclavicular joint. (Blue arrow).

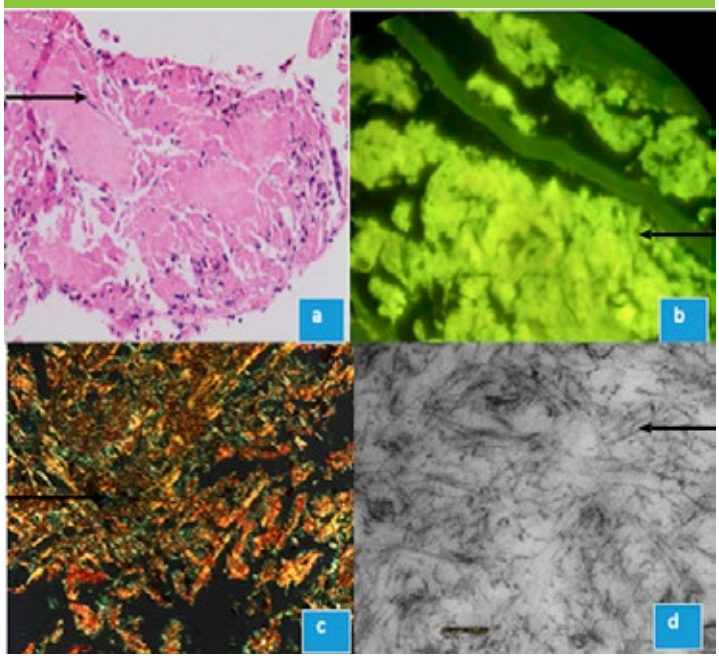
usually presenting as CTS, bone cysts, scapulohumeral periarthritis, joint arthropathy, and destructive spondyloarthropathy. [7]

Beta—2 microglobulin was first discovered in 1964 in the urine of subjects with Wilson's disease and cadmium poisoning [8], From the plasma, β2M is freely filtered by the glomerulus.[9]; it is reabsorbed and catabolised by the proximal renal tubule. Normal serum β2M levels range from 700—1800 ng/ml. As renal function falls, serum level of β2M increases. According to Kidney Disease Outcomes Quality Initiative guidelines, tissue biopsy is the "gold standard" test to detect β2M for diagnosing DRA. β2M is positive on Congo red staining and exhibits apple—green birefringence under polarized light. Standard immunofluorescence cannot detect the type of amyloid protein, but can be recognised by specific immunohistochemistry for β2M and/or laser micro dissection mass spectrometry.[7] Under the electron microscope, amyloid deposits are seen as filamentous fibrils, both intracellularly and extracellularly, in ultra—thin sections of synovial membrane. Extra cellular deposits are visualised as loose filaments (3—10 nanometer thick) or fibrillar structured (10—40 nanometer thick). [10]

Amyloid deposits cause inflammation which leads to destructive lesions of bones and joints. Dialysis is an inflammatory stimulus that induces cytokine production and complement activation. Cytokines are thought to stimulate synthesis and release of β2M by macrophages. Common risk factors for DRA are long term hemodialysis, late initiation of hemodialysis, elderly patients, absence of residual renal function (RRF), use of low—flux and bio—incompatible dialysis membranes (like Cuprophane) with small pores which cannot clear substances of molecular weights higher than 200 Da and use of improperly treated water for hemodialysis.[7] Patients having DRA suffer from symptoms associated with infiltration of β2M in soft tissues and visceral organs. Shoulder and scapulohumeral joints, carpal bones and cervical spine are most commonly involved.[11] β2M amyloid deposition can occur in rectal mucosa, liver, spleen, blood vessels and the heart as well.

Progression of DRA is greater in hemodialysis patients because patients on peritoneal dialysis show better maintenance of residual renal function; however, some studies suggested that the incidence of DRA is similar in hemodialysis and peritoneal dialysis.[12] The 2003 KDOQI guidelines suggest highly biocompatible high—flux membranes should be used for hemodialysis patients with DRA.[13] It is possible to prevent or slow progression of DRA by using a biocompatible high flux dialysis membrane, hemodiafiltration, use of ultrapure dialysate and using a beta2—M adsorbent column. Patients with CTS and pathological

Figure 2



a) Synovial biopsy with extracellular pale eosinophilic deposits (H&E,x 20).
b) Positive immunofluorescence staining (immunofluorescence, Thioflavin T stain, x 400).
c) Apple green birefringence of deposits on polarised light examination,(Congo red stain, x 400). d)Electron microscopy showing aggregates of randomly oriented fibrillary structures measuring about 9–12 nm in diameter (x 25000).

fractures can be given treatment with analgesics, non–steroidal anti–inflammatory drugs and steroids. [7] Renal transplantation reduces serum β2M levels; amyloid deposits are found to regress in patients with renal grafts that function well. [5]

In our case, amyloidosis was suspected as the patient was on long term hemodialysis. Imaging studies showed joint effusion and bone erosions. A confirmatory diagnosis of amyloidosis was made by biopsy and ultrastructural study. She had significant symptomatic improvement with appropriate analgesia and use of biocompatible high flux filters for hemofiltration and ultrapure dialysate.

CONCLUSION

Amyloidosis must be suspected in patients on long term hemodialysis, who present with bone pains or joint symptoms. Disease progression can be halted by modification of dialysis prescription and use of hemodiafiltration with high flux dialyzers.

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Case Report

Hypertensive Encephalopathy in a Patient with Unconsciousness

Hypertensive encephalopathy (HE) is characterized by acute onset severe arterial hypertension associated with confusion, headache, seizure and even unconsciousness. It is usually reversible but any delay in recognition and treatment can be life threatening.

Dr. Mouhammad Ekbal Al Kalaf[1], Dr. Tapendu Sarkar[2]

1. Specialist Emergency Medicine, Head of Department, Medcare Hospital, Al Safa
2. Specialist Emergency Medicine, Medcare Hospital, Al Safa

Keywords:
Hypertensive encephalopathy, seizure, unconsciousness

INTRODUCTION

A hypertensive emergency is a life—threatening condition where ongoing target—organ damage occurs due to markedly elevated blood pressure. Pulmonary edema, cardiac ischemic events, acute renal failure, aortic dissection, eclampsia, retinopathy, and encephalopathy may present as a result of organ injury due to hypertension.

Hypertensive encephalopathy is a less commonly encountered type of hypertensive emergency. It is characterized by signs of cerebral edema that occur after a severe episode of hypertension. This condition is usually diagnosed retrospectively after symptoms dramatically resolve by lowering the patient's blood pressure, and other causes of the neurologic disease have been ruled out. Symptoms of hypertensive encephalopathy include the gradual onset of headache, nausea, and vomiting, followed by neurologic symptoms such as restlessness, confusion, seizures, unconsciousness and potentially coma. If hypertension is treated promptly, the symptoms of encephalopathy are usually reversible.[1]

Elevated blood pressure is considered as a potential predisposing factor as well as a precipitating factor for acute changes in mental status. The pathogenesis of the link between chronic hypertension and altered mental status (AMS) is uncertain, but proposed mechanisms include: 1) associated brain atrophy leading to cognitive impairment and 2) atherosclerosis resulting in brain hypoperfusion and cellular hypoxia.[1] AMS is also a possible complication of hypertensive crisis (i.e. sudden elevation of blood pressure above 180/120) secondary to cerebral edema, which occurs when the autoregulation of cerebral blood flow is overwhelmed and cerebral vasodilation ensues. Hypertensive encephalopathy is the general term for the presence of altered consciousness and other neurologic findings in the context of a hypertensive crisis.[2]

CASE PRESENTATION

A 60 year old Chinese lady was brought by ambulance in unconscious state. No past history was available as she was a tourist. Her GCS on arrival was 4/15; Pupils bilat-

erally reacting with normal in size .There was left beating nystagmus which precluded proper fundoscopic examination. Her BP was 210/120 mm of Hg (no discrepancy in any arm with normal peripheral pulses). There was no sign of lateralization in any limbs. Inj. Labetalol was given for reduction in BP with target of 15% reduction initially. She had two episodes of generalized tonic clonic seizure upon arrival which were controlled with Diazepam IV. Airway protection measures were taken.

Blood tests were normal. ECG showed only sinus tachycardia. ABG showed mild respiratory acidosis. CT scan brain showed no abnormality. CT angio brain revealed normal arteries in all cerebral territories. MRI brain was normal as well. IV Levetericetam was started subsequently. EEG studies revealed no significant abnormality. Urine toxicology was normal. CSF analysis did not reveal any infective etiology or any albumino—cytological dissociation. Patients' sensorium improved dramatically with control of blood pressure and she was alert, conscious, and cooperative within 48 hours of presentation without any neurological deficit.

DISCUSSION

The initiation of the patient's altered mental status after persistent hypertension in the critical range, resolution following successful management of hypertensive emergency with CT scan brain which showed no abnormality. MRI brain was normal as well. Labetalol was given for reduction in BP with target of 15% reduction initially. IV Levetericetam was started subsequently. Patients' sensorium improved dramatically with control of blood pressure and she was alert, conscious, and cooperative within 48 hours of presentation without any neurological deficit. This suggests that his AMS was most likely secondary to hypertensive encephalopathy. Posterior reversible encephalopathy syndrome is another presentation of HE which could not be found in our case as MRI did not reveal any cerebral edema.

Normally, the brain sustains blood flow within a narrow perfusion pressure range without being affected by fluctuations in systemic arterial pressure. For healthy individuals, the pressure ranges are 50—150 mm Hg cerebral perfusion pressure (CPP) or 60 to 160 mm Hg mean arterial pressure (MAP). The CPP = MAP – intracranial pressure (ICP) (Armstead, 2016). With increased MAP, cerebral arteriolar vasoconstriction occurs, and conversely, with decreased MAP, arteriolar dilation occurs to keep the CPP constant. This adaptive process maintains brain perfusion at a constant level despite systemic blood pressure changes. However, a sudden and severe increase in arterial pressure can exceed this autoregulatory mechanism because the arterioles are limited in their ability to constrict. The then intracerebral elevated blood pressure causes a breach in the blood—brain barrier, and vascular fluid diffuses across the capillary membranes into the brain parenchyma. This leads to the development of cerebral edema, increased intracranial pressure, and neurologic deficits such as altered mentation, visual deficits, seizures and even unconsciousness [(1)].

A thorough physical exam and history are primarily used to diagnose hypertensive encephalopathy in patients presenting with elevated blood pressure in addition to altered mental status, visual abnormalities, headache, or seizures. Eliciting a thorough drug history is essential for identifying any previously used antihypertensive drugs. Typically, patients who develop hypertensive encephalopathy have chronic uncontrolled hypertension and may have recently discontinued their antihypertensive medication. Individuals that have rapidly developing and/or intermittent episodes of hypertension are also more at risk for developing hypertensive encephalopathy [(1)].

The majority of patients with this diagnosis have blood pressures in excess of 220/120 mm Hg.[(4)] These patients should be evaluated for signs of organ damage that can be found during a hypertensive emergency. In particular, thoracic auscultation may reveal signs reflective of cardiac dysfunction, such as extra heart sounds or pulmonary edema, with rales heard on lung auscultation. Fundoscopy may show retinal hemorrhages and papilledema, which is a sign of severe hypertensive retinopathy. A complete neurologic exam can identify whether focal or non—focal deficits are present and may warrant other differential diagnoses for conditions that cause similar symptoms to be considered [(5)].

This case highlights that state of the patients unconsciousness associated with severely elevated BP without any abnormality detected and that the most probable cause of these is cerebral edema secondary to sudden rise of BP as complete resolution after BP control occurred and no abnormality in imaging and other studies, establishes Hypertensive encephalopathy (HE) as the cause of patients unconsciousness and convulsions.

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Case Report

A Curious Case of Right Shoulder Pain

Shoulder pain (right or left) are common emergency department presentations and patients usually present to ED after an episode of trauma. Diagnosis in such cases can often be made by observation, palpation, and plain radiographs.

Dr Mouhammad Al Kalaf[1], Dr Nazish Ijaz[2]

1. Specialist Emergency Medicine, Head of Department, Medcare Hospital, Al Safa
2. Specialist Internal Medicine, Emergency Department, Medcare Hospital, Al Safa

ABSTRACT

Shoulder pain (right or left) are common emergency department presentations and patients usually present to ED after an episode of trauma. Diagnosis in such cases can often be made by observation, palpation, and plain radiographs.

Other non—traumatic causes of shoulder pain are many and most of them are documented in text books but "a referred shoulder pain and it's causes are something that need to be highlighted and clinicians need to be vigilant, as extrinsic causes of shoulder pain are hidden high risk presentations which are only and simply associated with a common chief compliant such as shoulder pain."

BACKGROUND

Patients experiencing a problem intrinsic to the shoulder may present with complaints of pain provoked by specific movement(s), stiffness or lack of flexibility, weakness or loss of function, instability, or a combination of these symptoms.

A standard pain history (i.e, onset, duration, palliation/provocation, quality, location, and radiation) aids diagnosis. The clinician should inquire about activities that exacerbate symptoms either at work (eg, lifting overhead, painting) or leisure (e.g, racquet sports, swimming). In addition, questions about previous injuries and treatment, including past surgery, and about comorbidities such as diabetes (which increases the risk of adhesive capsulitis) are important.

A distinguishing characteristic of referred pain, in contrast to intrinsic shoulder problems, is that shoulder movement is normal and does not alter the character of the pain. A careful history can often distinguish among the causes of referred shoulder pain.

We are all well aware of the common / typical symptoms of pulmonary embolism but it is uncommon symptoms (shoulder pain) or the "asymptomatic PE" that always gives the clinician a challenging puzzle to solve.

CASE PRESENTATION:

A 38—year—old Lebanese lady presented to ED with right shoulder pain for last two days. She was being treated in other facility as shoulder sprain and subsequently as a case of LRTI.

She was on oral contraceptive pill regularly. No prior history of DVT or PE, no history of prolonged bed rest or recent surgery. She was hemodynamically stable at presentation without any tachypnoea with normal oxygen saturation. Clinical exam was normal, right shoulder exam was normal. Blood tests revealed normal total count, mild rise in CRP 8 mg/L (normal up to 6), normal Creatinine and Raised D dimer 0.71ug/ml.

ECG showed sinus rhythm, no tachycardia (92/min). CXR showed bilateral increased bronchovascular markings.

CTPA revealed Pulmonary thromboembolism involving the anterior basal segmental branch of the right lower lobe with resultant developing pulmonary infarct in anterior basal segment of the right lower lobe.

Mild right pleural effusion, associated with passive basal subsegmental atelectasis. (As shown below in the CT pulmonary angiogram images)

Subsequent Duplex ultrasound of lower extremity did not reveal any venous thrombosis. Echocardiography was normal including normal right heart function.

She was treated with subcutaneous Clexane followed by Rivaroxaban oral therapy which resulted in improvement of her symptoms.

Referred pain to the shoulder may be seen in a variety of clinical settings:

Neurologic	**Abdominal**
Cervical nerve root compression (C5, C6)	Hepatobiliary disease
Suprascapular nerve compression	Diaphragmatic irritation (eg, splenic injury, ruptured ectopic pregnancy, perforated viscus)
Brachial plexus lesions	**Thoracic**
Herpes zoster	Upper lobe pneumonia
Spinal cord lesion	Apical lung tumor
Cervical spine disease	Pulmonary embolus
Cardiovascular	
Myocardial ischemia	
Axillary vein thrombosis	
Thoracic outlet syndrome	

DISCUSSION

In our case, the cause of shoulder pain was referred pain from the infarcted lung due to underlying PE. Physicians must be vigilant as this uncommon symptom may be a forgotten sign of underlying PE which can be life threatening.

ABOUT PULMONARY EMBOLISM

Acute pulmonary embolism (PE) is a form of venous thromboembolism (VTE) that is common and sometimes fatal. Pulmonary embolism (PE) has a wide variety of presenting features, ranging from no symptoms to shock or sudden death. The most common presenting symptom is dyspnea followed by chest pain (classically pleuritic) which can present as refered shoulder pain or scapular pain, cough, and symptoms of deep venous thrombosis.

A meta—analysis of 19 studies (25, 343 patients) found that clinical impression alone had a sensitivity and specificity of 85 and 51 percent, respectively, for the diagnosis of PE. Thus, it is critical that a high level of suspicion be maintained such that clinically relevant cases are not missed.

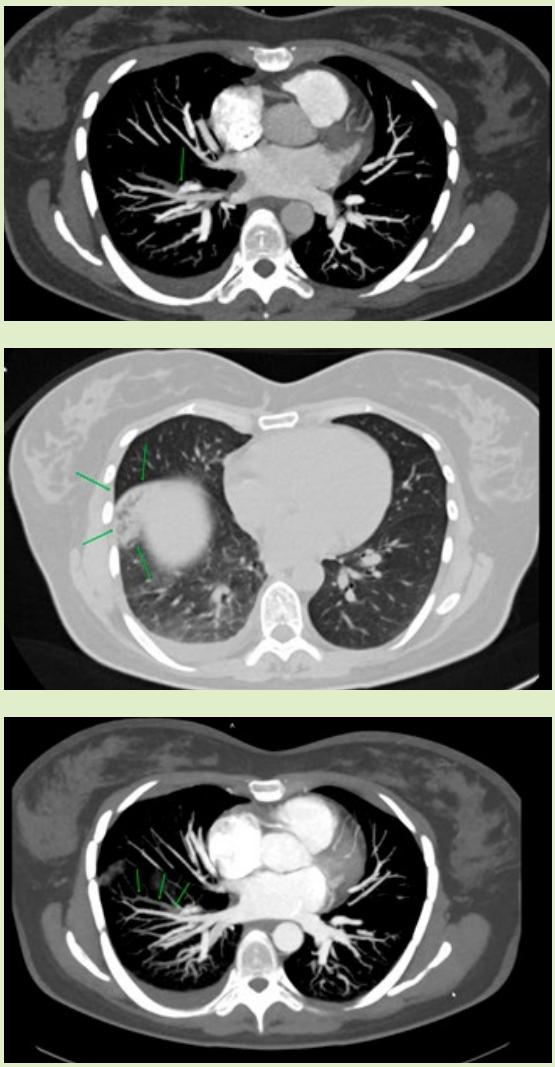
Less common presentations include transient or persistent arrhythmias (eg, atrial fibrillation), presyncope, syncope, and hemodynamic collapse (<10 percent each).

Pathophysiologic response to PE — Pulmonary emboli are typically multiple, with the lower lobes being involved in the majority of cases. Once thrombus lodges in the lung, a series of pathophysiologic responses can occur which include abnormal gas exchange, cardiovascular compromise and pulmonary infarction.

Pulmonary Infarction – In about 10 percent of patients, small thrombi lodge distally in to the segmental and subsegmental vessels resulting in pulmonary infarction. These patients are more likely to have shoulder pain, pleuritic chest pain and hemoptysis, presumed to be due to an intense inflammatory response in the lung and adjacent visceral and parietal pleura.

CONCLUSION AND CLINICAL TIPS

1. A detailed history and directed physical examination are always essential.



As shown in the CT pulmonary angiogram images CTPA revealed Pulmonary thromboembolism involving the anterior basal segmental branch of the right lower lobe with resultant developing pulmonary infarct in anterior basal segment of the right lower lobe. Mild right pleural effusion, associated with passive basal subsegmental atelectasis.

The most common symptoms in patients with PE were identified in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) group. They include the following:
Dyspnea at rest or with exertion (73 percent)
Pleuritic pain (66 percent)
Cough (37 percent)
Orthopnea (28 percent)
Calf or thigh pain and/or swelling (44 percent)
Wheezing (21 percent)
Hemoptysis (13 percent)
Myocardial ischemia
Axillary vein thrombosis
Thoracic outlet syndrome

2. Always remember that patients with myocardial infarction, pulmonary embolus and other life—threatening disorders may initially present with atypical symptoms (e.g., isolated shoulder pain).
3. Be cautious of making a musculoskeletal diagnosis in patients with shoulder pain if you are unable to reproduce the pain.
4. Always consider a cardiac etiology in patients with shoulder pain and evaluate those patients appropriately. While younger patients may be less likely to have coronary disease, they are not immune.
5. Patients with repeat visits to the emergency department and/or other health care providers may require more extensive evaluation and testing.
6. Broaden your differential diagnosis when patients return.
7. Always try to evaluate return visits with an open mind.
8. Close follow up is always necessary in patients with unusual symptoms or unclear diagnoses. Contact with the primary care physician will help to ensure follow up and continuity of care.

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Tuberculosis of the Cervix Uteri in a Renal Transplant Patient: A Therapeutic Conundrum

Tubercular infection of the cervix is a rare occurrence. But in organ transplant patients who are immunosuppressed, it is a growing problem, especially in countries like India where TB is endemic. Cervical TB often mimics Ca cervix in its presentation.

Dr. Ayona Barthakur[1]

1. Specialist ObGyn, Medcare Medical Center, JBR

Keywords:
Cervical Tuberculosis
Renal Transplant
Genital TB
Mimicking Ca Cervix

ABSTRACT

Tubercular infection of the cervix is a rare occurrence. But in organ transplant patients who are immunosuppressed, it is a growing problem, especially in countries like India where TB is endemic. Cervical TB often mimics Ca cervix in its presentation. It also presents therapeutic problems as some drugs are nephrotoxic and others have drug interactions with the commonly used immunosuppressants. Here we discuss a thirty—five—year—old kidney transplant patient who presented with a bleeding proliferative lesion on the cervix.

INTRODUCTION

TB is an important opportunistic infection in post renal transplant patients as they are on lifelong immunosuppressants. Worldwide, incidence of Mycobacterium TB in organ transplant patients range from 0.35% to 15%. In countries like India where TB is endemic, incidence in renal allogenic recipients is 12.3%.(1) The common sites in such patients are pulmonary (70—80%) and extra pulmonary sites like skin, joints, testis, urinary tract, lymphnodes. Tuberculous cervicitis is very very rare as the stratified columnar epithelium is generally very resistant to tubercular infection. In nonimmunosuppressed patients, cervical TB accounts for 0.1—0.65% of all cases of TB and 5—24% of genital tract TB. Tuberculosis more commonly affects the upper genital tract like the fallopian tube and endometrium.

CASE REPORT

A 35yr old divorced woman presented with complaints of irregular vaginal bleeding of 1—month duration. She gave significant medical history of being on immunosuppressive medications—Tacrolimus, Mycophenolate and Prednisolone for a kidney transplant done 11 months back. She was also on the antihypertensive medication Cilnidipine. Chronic renal failure was the indication for the transplant. She had no history of Diabetes Mellitus, Hypothyroidism or previous exposure to or treatment for Tuberculosis. She had no significant family or genetic history. Her menstrual history post—transplant was of delayed cycles (3—4

months) followed by scanty flow. Lifestyle— She had a sedentary lifestyle, eats non veg food and is not a smoker. She was nulliparous.

On physical examination, her vitals were stable. On examination of her abdomen, the transplanted kidney could be easily felt in the right lumbar region. On speculum examination, an irregular, proliferative lesion could be seen on both lips of the cervix, which bleeds on touch (Fig 1). Bimanual examination revealed a mobile, non tender, normal sized uterus with no induration felt through the fornices. After making a provisional clinical diagnosis of early stage invasive Ca Cervix, the lady was sent for Colposcopy and USG pelvis. Pap smear report was HSIL. Her biochemical reports were normal except a minimally raised serum creatinine. HIV test was negative.USG report showed a bulky cervix with a 3—4mm endometrium. On Colposcopy, an irregular, raised aceto white lesion (Fig 2,)was seen on both lips of cervix. With green filter, there was no sign of abnormal vascularity. With iodine application, iodine nonuptake seen (Fig 3) and punch biopsy was taken. Biopsy showed a chronic inflammatory reaction, few epitheloid cell granulomas and occasional Giant cells (Fig 4). No signs of dysplasia or malignancy was detected. So final report was Granulomatous inflammation suggestive of Tuberculosis. Endometrial biopsy showed a chronic inflammatory reaction. CXR was normal. Sputum, urine and cervical secretions were negative for AFB. Culture of biopsy specimen failed to grow AFB and fungi. Other common causes of granulomatous cervicitis were also ruled out :urine samples were negative for schistosoma ova, schistosomal, amoebic and brucella antibodies were negative and a serum level of ACE was normal. So a presumptive diagnosis of Cervical Tuberculosis was made.

Therapeutic Focus was to give a trial of ATT. She was treated with dose adjusted and rifampicin sparing regimen of ATT (INH, Moxifloxacin, Ethambutol) for a total of 9 months after consultation with her nephrologist.

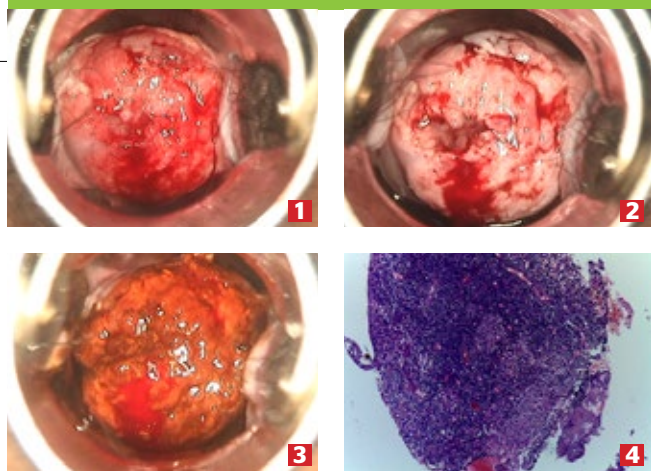
FOLLOW UP

She was followed up at 2 monthly intervals clinically as well as with biochemical investigations like CBC, LFT, RFT. Visualisation of the cervix after 2 months of ATT showed a definite regression of the lesion. At the end of 9 months, her symptoms had disappeared and her cervix looked normal, both clinically and colposcopically. She is disease free for the last one year.

DISCUSSION

Tuberculosis in renal transplant recipients is usually acquired as reactivation in those with past history of TB or can be a freshly acquired air borne infection [2]. The engrafted organ has also been shown to be the carrier in some cases. In rare cases, cervical TB can be sexually acquired from an infected partner with TB of genital tract or by infected saliva used as lubricant[3]. Diagnosis can be challenging because of atypical presentation and atypical extra pulmonary sites. In TB of cervix, radiological and biochemical investigations are frequently normal. Although isolation of mycobacterium is the gold standard, one—third of cases are culture negative, and therefore, the presence of typical granulomata is sufficient for diagnosis if other causes of granulomatous cervicitis are excluded[3]. Screening by Tuberculin skin testing (Mantoux) also has limitations in immunosuppressed patients and it has been suggested that 5mm rather than the standard 10mm should be taken as the cut—off. This case is important because it highlights 2 issues: one, that tuberculosis can have an atypical presentation in organ transplant patients, so a high index of suspicion is needed for diagnosis when there is a suspected cervical malignancy and two, Rifampicin has to be avoided in allograft recipients as it activates cytochrome—P450 enzymes and thereby decreases the therapeutic levels of cyclosporine, tacrolimus and prednisolone [4].

Figures



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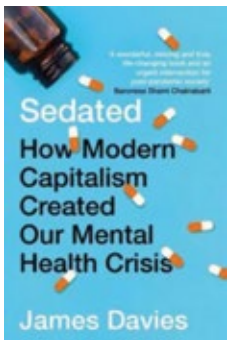
Sedated: How Modern Capitalism Created Our Mental Health Crisis

This book is written clearly and concisely, without being patronising or watering anything down. Such a welcome departure from what I've come to expect from the genre means that *Sedated* will be able to reach and be read by those who need it most.



Sedated: How Modern Capitalism Created Our Mental Health Crisis

Author:
James Davies

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ISBN:
9781786499875

James Davies is a reader of medical anthropology and mental health at the University of Roehampton. He is also a qualified psychotherapist and had a stint volunteering for the NHS. Sedated can be considered as a sort of sequel to Cracked, with Davies turning his attention to psychiatrists' treatment of choice: medications, specifically antidepressants. In Sedated, Davies shows that the so-called mental health crisis stems from the assumption that mental illnesses arise within the 'broken brain' of an individual sufferer. This is the 'biochemical model' of mental illness. In contrast to what many of us assume, the idea that mental illnesses are caused by an imbalance of neurochemicals and can only be treated by using psychotropics like antidepressants, or mood stabilisers or antipsychotics, is a theory that has never been proven. Neither depression nor schizophrenia, neither anxiety nor bipolar disorder, have ever been observed in vivo. No one has ever been able to point to an MRI or CT scan and say, 'Look! There is it!'

According to Davies, this is because the biochemical model of mental illness is wrong. He argues that many diagnosed conditions (though in his book he sticks to the example of depression), are not down to malfunctioning grey matter, but are, instead, an understandable reaction to wider societal problems. In Sedated, Davies painstakingly debunks the individual, brain-based view of mental illness and explains why its apparently unquestioned acceptance by the general public as the only means of conceiving human distress should concern us. Not only does our taking this model for granted encourage the administration of potent drugs to those who don't necessarily need them, it also results in the obfuscation of other plausible sources of hardship such as poverty, discrimination, loneliness, and environmental factors such as pollution. These are undoubtedly complex and more challenging to tackle than the comparably simple option of taking a pill every day. Pharmaceutical companies created the narrative of the broken brain to profit from them, and most governments of industrialised countries went along with it.

Sedated, read either before or after Cracked, serves as an excellent entry point into the area of research known as critical psychiatry. Davies' overarching argument isn't new exactly, there are countless other books that question psychiatry, the biochemical model, and our reliance on medications, but they are often sadly inaccessible (either through their writing style or because they are literally housed in specialist libraries) to the average reader. This book is written clearly and concisely, without beingpatronising or watering anything down. Such a welcome departure from what I've come to expect from the genre means that Sedated will be able to reach and be read by those who need it most: all of us.

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