# Aster Medical Journal

MARCH 2022
VOL. 3 / ISSUE 7&8

www.theamj.org

**Covid 19**
Negative Pressure Pulmonary Oedema

**Medical Apps**
Medical Apps Relevant To Paediatricians

**The Mind**
When Depression Sneaks Up On Menopause

# PANDEMIC *to* ENDEMIC

**Most scientists believe that COVID-19 will transition from pandemic to endemic. But what does this mean?**

**What will it be like when COVID-19 becomes endemic?**

# Shaping the future of healthcare

SIEMENS Healthineers

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March 2022


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**"Screens on our doors and windows helped keep out mosquitos that carried yellow fever and malaria. Sewer systems and access to clean water helped eliminate typhoid and cholera epidemics. Perhaps the lessons learned from COVID-19 in terms of disease prevention can yield similar longterm improvements in individual and global health."**

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# Prologue

# Pandemic Preparedness

As we enter the third year of the COVID-19, international medical community is deep into discussion on how to prevent future pandemics. The findings and recommendations of the Independent Panel for Pandemic Preparedness and Response has been reviewed by the Special Session of the World Health Assembly in November 2021.

The panel detected flaws at each phase of the COVID-19 response, from readiness to detection and vigilance, both in the initial and the continued response. The preparedness was suboptimal and the international warning systems including the International Health Regulations (IHR) mechanisms were not robust which led to fast spread of SARS-CoV-2. The worldwide and countrywide reactions failed to avert social and economic crisis. Inequities were intensified, as demonstrated by maldistribution of life saving equipment, oxygen and vaccines . The panel concluded that the potential of the pandemic to cause systemic collapse was not appreciated globally.

The panel has recommended pandemic preparedness and response be considered as the responsibility of the governments across the world . The pandemic threat is to be elevated to the highest leadership level with better coordination at national, regional, and international levels. It was also highlighted that a more focused and independent WHO has to be there to steer this from the front with pandemic treaties through a new global health threats council with package of reforms to ensure preventing another pandemic.

There is hope in the fact that many world leaders now recognize the devastation that health crises can create and the importance of preventing another such event . The experience of the pandemic must not be repeated, but the window of opportunity for securing the necessary change is small. Previous epidemics show the appetite for transformation declines fast once the emergency has passed.

Epidemics begin and end in communities as they are the first to notice the occurrence of an unusual health event, and the last to stop feeling its impacts. That's why our work needs to be brought to the ground, equipping communities and their first responders with the skills to recognize and respond to public health threats. We need to come together, engaging and training people worldwide, in epidemic preparedness and response to keep us safe. This will help to prevent, detect and quickly respond to outbreaks—saving countless lives and promoting healthier communities.

Sincerely

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

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**VOL. 3 | ISSUE 7&8 | March 2022**





**PLACE OF PUBLICATION**

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

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




**The paper issued by the Director of National Intelligence elaborates on findings released in August of a 90-day review ordered by President Joe Biden.**

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# Editorial

## Is COVID-19 Already Endemic?

This is my maiden editorial.

To be an editor of a scientific journal is itself a challenging task, and that too, amidst a busy clinical practice. I am fully conscious of the commitment delivered by my predecessors in this office, in curating each edition of the *Aster Medical Journal* – they have identified good science, and shared it with the scientific communities in a responsible way.

The outstanding job they have done over the years have set a standard of excellence that is difficult to improve upon. Their dedication has transformed an essentially in-house journal into a journal of the highest quality, with engaging articles, wide acceptance, and an appreciative readership. I put on record my gratitude for their entrusting me with this legacy.

As we cross two years and more of COVID-19, the discussions around the virus now look beyond the management of the pandemic. The possible endgame could be the pandemic turning endemic; in which COVID-19 will not be entirely eliminated, but its ability to overturn societies and livelihoods will be dramatically reduced. But is COVID-19 already endemic? Technically, as long as COVID is raging worldwide instead of only in certain places, we haven't reached endemicity. That's because infections in one place can complicate efforts to contain the virus – as it happened with Omicron.

I think the biggest misconception people have about endemicity is that it's kind of a safe level. Endemicity is not the end of COVID-19. It just means it's more predictable. A study conducted by Nature journal indicates many scientists expect SARS-CoV-2 is here to stay, but it could pose less danger over time. In a Nature poll, 89% of scientists opined SARS-CoV-2 was either very likely or likely to become an endemic virus.

This issue of Aster Medical Journal brings a different perspective to this pertinent topic. We also have an insightful conversation with Yonatan Grad, an Associate Professor of Immunology & Infectious Diseases at Harvard TH Chan School of Public Health, about immunity, patterns of social contact, and virus transmissibility.


The feature article in this issue sheds light on depression during menopause. This piece discusses how fluctuating levels of estrogen during perimenopause can wreak havoc on the mental health of women in midlife. The diagnosis and treatment of the condition has been elusive despite symptoms as serious as suicidal thoughts.

I look forward to your support and feedback to take AMJ to newer summits and standing.

Happy Reading.

**Dr Boby Varkey Maramattom**
Lead Consultant Neurology
Aster Medcity

## Dengue, chikungunya, malaria made notifiable diseases under Epidemic Diseases Act in India

Vector-borne diseases like dengue, chikungunya and malaria have been made notifiable diseases under the Epidemic Diseases Act, according to an official notification. The notification makes it compulsory for all hospitals to provide information to the government about any such case that they receive. On the basis of the data provided by the hospitals, areas where the vector-borne diseases are spreading will be identified and declared as 'infected' or 'threatened'.
The notification also said that legal action will be taken against individuals or institutions found not following adequate measures or not informing about the cases to the authorities. The national capital has seen a surge in dengue cases. Delhi has reported over 1,000 cases of dengue this year, with more than 280 cases logged in the last week, according to a civic report released on Monday. Of the total number of dengue cases this season, 665 were recorded in the first 23 days of this month alone. The city recorded its first death due to the vector-borne disease this season on October 18.

## Virtual autopsies to investigate causes of death at Abu Dhabi Central Morgue

Medical examiners will use virtual autopsy technology, also known as post-mortem imaging, for a number of purposes – most importantly to limit morgue staff's exposure to infectious diseases, said officials from Department of Health – Abu Dhabi.
"Virtual autopsy has modernised the medical investigation of bodies while ensuring the health and safety of medical staff and contacts of the deceased maintaining respect and privacy towards the bodies of deceased individuals," said Dr Nayef Hasan Aljanaahi, the first licensed consultant in forensic radiology for the DoH. The technique can specifically help identify damage to lung tissue and show signs of any previous respiratory distress that would indicated a Covid-19 infection. This would allow examiners to alert recent close contacts of the deceased that they may have contracted the virus. The UAE is among a group of countries that adopted the virtual autopsy technique, along with the U.S., the U.K., Canada, Germany, Australia and Japan. During a virtual autopsy, the body undergoes a CT scan while in a cadaver bag and no physical post mortem is carried out. The procedure takes up to 30 minutes. The technology was introduced in 2020 in Abu Dhabi and has assisted in the investigations of more than 700 legal cases. It can be used to detect evidence of physical violence.

## Bill Gates thanks Sheikh Mohamed bin Zayed for polio commitment

Billionaire philanthropist Bill Gates has thanked Sheikh Mohamed bin Zayed, Crown Prince of Abu Dhabi and Deputy Supreme Commander of the Armed Forces, for his commitment towards eradicating polio. The Microsoft founder said it was only with the "strong commitment of partners like Mohamed bin Zayed and the dedication on the front line" that polio will be eradicated. "We recognise progress and acknowledge that the fight continues," he said. Sheikh Mohamed and Mr Gates have pledged and raised millions of dollars to tackle diseases including polio and neglected tropical diseases. Such illnesses, which have long been cured in the developed world, kill and maim thousands of people in developing countries every year. Sheikh Mohamed reaffirmed his commitment to tackling such diseases. "Thanks to the dedication of many, including frontline health workers, remarkable progress has been made in the global effort to end polio," Sheikh Mohamed said.

# The brief

The winner of the Wellcome Photography Prize 2021 by **Sharwar Apo.**



## Health in a Heating World

Parents take their child to hospital in Rajshahi, Bangladesh, 10-15 miles across this drought-parched land, the mother holding a saline drip all the way. For much of the year, the land is dead like this, but for four months it's flooded. Either way, safe drinking water is scarce, crops can't grow, health problems abound – from dehydration to infection – and transport is limited. This family's journey succeeded, and the child was treated for her diarrhoea. But many of those who attempt this journey are not so lucky.

# Where Did the Coronavirus Come from? We May Never Know, Says U.S. Spy Agency

**The paper issued by the Director of National Intelligence elaborates on findings released in August of a 90-day review ordered by President Joe Biden.**

Barring an unforeseen breakthrough, intelligence agencies won't be able to conclude whether COVID-19 spread by animal-to-human transmission or leaked from a lab, officials said Friday in releasing a fuller version of their review into the origins of the pandemic.

The paper issued by the Director of National Intelligence elaborates on findings released in August of a 90-day review ordered by President Joe Biden. That review said that U.S. intelligence agencies were divided on the origins of the virus but that analysts do not believe the virus was developed as a bioweapon and that most agencies believe the virus was not genetically engineered.

China has resisted global pressure to cooperate fully with investigations into the pandemic or provide access to genetic sequences of coronaviruses kept at the Wuhan Institute of Virology, which remains a subject of speculation for its research and reported safety problems. Biden launched the review amid growing momentum for the theory — initially broadly dismissed by experts — that the virus leaked from the Wuhan lab. Former President Donald Trump and his supporters long argued that a lab leak was possible as they sought to deflect criticism of his handling of the pandemic.


AP Photo/Susan Walsh

**Director of National Intelligence Avril Haines issued a paper Friday, Oct. 29, that elaborates on findings released in August of a 90-day review ordered by Biden.**

China remains an exceedingly difficult place for intelligence operations and has fought back against allegations that it mishandled the emergence of the pandemic, which has killed 5 million people worldwide. Senior officials involved in the full report's drafting said they hoped it would better inform the public about the challenges of determining the virus's origins.

"We don't think we're one or two reports away from being able to understand it," said one official, who spoke on condition of anonymity to discuss intelligence matters.

The full report notes that the Wuhan Institute of Virology "previously created chimeras, or combinations, of SARS-like coronaviruses, but this information does not provide insight into whether SARS Cov-2 was genetically engineered by the WIV."

Information that lab researchers sought medical treatment for a respiratory illness in November 2019 "is not diagnostic of the pandemic's origins," the report said. And allegations that China launched the virus as a bioweapon were dismissed because their proponents "do not have direct access to the Wuhan Institute of Virology," are making scientifically invalid claims or are accused of spreading disinformation, the report said.

Four agencies within the intelligence community said with low confidence that the virus was initially transmitted from an animal to a human. A fifth intelligence agency believed with moderate confidence that the first human infection was linked to a lab.

Prior to writing the report, analysts conducted what the report describes as a "Team A/Team B" debate to try to strengthen or weaken each hypothesis. The report identifies types of data that investigators still want China to provide access to, including records and tissue samples from several markets in Wuhan, including the Huanan Seafood Wholesale Market, Qiyimen Live Animal Market, Dijiao Outdoor Pet Market and others. Scientists originally believed the virus emerged from animals sold at the Huanan market, which has since been ruled out by some as the origin site.

Confirming with 100% certainty the origin of a virus is often not fast, easy or always even possible. In the case of Severe Acute Respiratory Syndrome, or SARS — a disease caused by a beta coronavirus, like the current coronavirus — researchers first identified the virus in February 2003. Later that year, scientists discovered the likely intermediary hosts: Himalayan palm civets found at live-animal markets in Guangdong, China. But it wasn't until 2017 that researchers traced the likely original source of the virus to bat caves in China's Yunnan province.

# In focus


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**THE CORONAVIRUS WILL BECOME ENDEMIC**

A Nature survey shows many scientists expect SARS-CoV-2 is here to stay, but it could pose less danger over time.

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**HOW THE WORLD CAN LEARN TO LIVE WITH COVID-19**

With prospects of herd immunity fading, endemic COVID-19 is upon us, and new “whole of society” approaches are needed.


by **Nicky Phillips**

# THE CORONAVIRUS WILL BECOME ENDEMIC

**A *Nature* survey shows many scientists expect SARS-CoV-2 is here to stay, but it could pose less danger over time.**

© Rawpixel

**For much of the past year, life in Western Australia has been coronavirus-free. Friends gathered in pubs; people kissed and hugged their relatives; children went to school without temperature checks or wearing masks.**

The state maintained this enviable position only by placing heavy restrictions on travel and imposing lockdowns — some regions entered a snap lockdown at the beginning of the year after a security guard at a hotel where visitors were quarantined tested positive for the virus. But the experience in Western Australia has provided a glimpse into a life free from the SARS-CoV-2 coronavirus. If other regions, aided by vaccines, aimed for a similar zero-COVID strategy, then could the world hope to rid itself of the virus? It's a beautiful dream but most scientists think it's improbable. In January, Nature asked more than 100 immunologists, infectious-disease researchers and virologists working on the coronavirus whether it could be eradicated. Almost 90% of respondents think that the coronavirus will become endemic — meaning that it will continue to circulate in pockets of the global population for years to come.

"Eradicating this virus right now from the world is a lot like trying to plan the construction of a stepping-stone pathway to the Moon.

It's unrealistic," says Michael Osterholm, an epidemiologist at the University of Minnesota in Minneapolis.

But failure to eradicate the virus does not mean that death, illness or social isolation will continue on the scales seen so far. The future will depend heavily on the type of immunity people acquire through infection or vaccination and how the virus evolves. Influenza and the four human coronaviruses that cause common colds are also endemic: but a combination of annual vaccines and acquired immunity means that societies tolerate the seasonal deaths and illnesses they bring without requiring lockdowns, masks and social distancing.

More than one-third of the respondents to Nature's survey thought that it would be possible to eliminate SARS-CoV-2 from some regions while it continued to circulate in others. In zero-COVID regions there would be a continual risk of disease outbreaks, but they could be quenched quickly by herd immunity if most people had been vaccinated. "I guess COVID will be eliminated from some countries, but with a continuing (and maybe seasonal) risk of reintroduction from places where vaccine coverage and public-health measures have not been good enough," says Christopher Dye, an epidemiologist at the University of Oxford, UK.

"The virus becoming endemic is likely, but the pattern that it will take is hard to predict," says Angela Rasmussen, a virologist from Georgetown University, who is based in Seattle, Washington. This will determine the societal costs of SARS-CoV-2 for 5, 10 or even 50 years in the future.

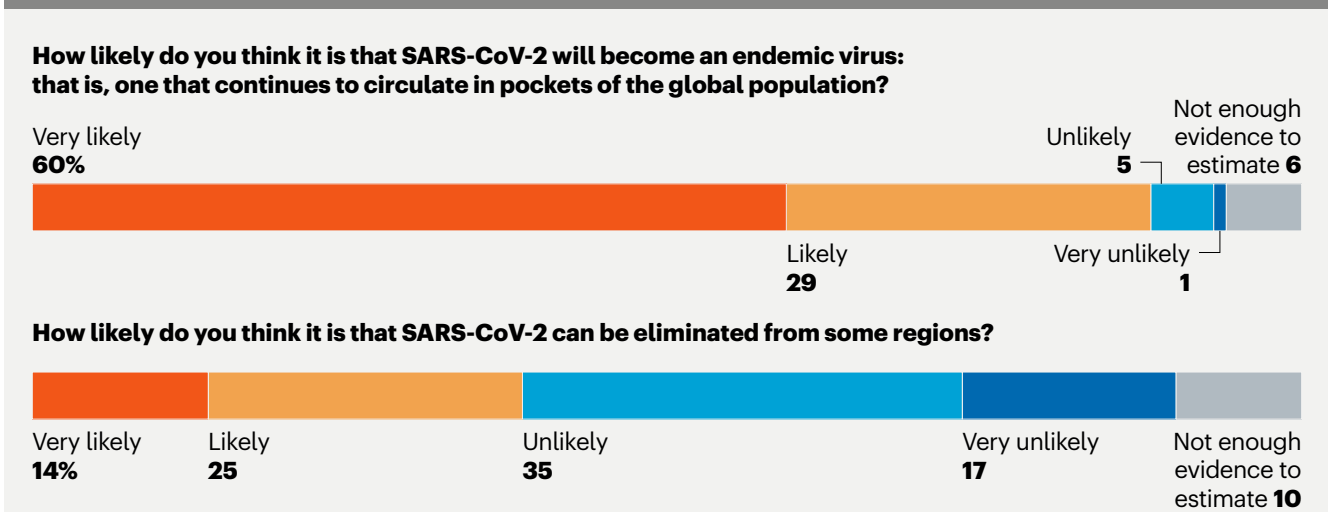
## Childhood virus

Five years from now, when childcare centres call parents to tell them that their child has a runny nose and a fever, the COVID-19 pandemic might seem a distant memory. But there's a chance the virus that killed more than 1.5 million people in 2020 alone will be the culprit.

This is one scenario that scientists foresee for SARS-CoV-2. The virus sticks around, but once people develop some immunity to it — either through natural infection or vaccination — they won't come down with severe symptoms. The virus would become a foe first encountered in early childhood, when it typically causes mild infection or none at all, says Jennie Lavine, an infectious-disease researcher at Emory University in Atlanta, Georgia.

Scientists consider this possible because that's how the four endemic coronaviruses, called OC43, 229E, NL63 and HKU1, behave. At least three of these viruses have probably been circulating in human populations for hundreds of years; two of them are responsible for roughly 15% of respiratory infections. Using data from previous studies, Lavine and her colleagues developed a model that

**ENDEMIC FUTURE** In a *Nature* poll, 89% of scientists felt that SARS-CoV-2 was either very likely or likely to become an endemic virus.




119 immunologists, infectious-disease researchers and virologists from 23 countries. Percentages do not add up to 100% because of rounding.

shows how most children first come down with these viruses before the age of 6 and develop immunity to them[1]. That defence wanes pretty quickly so it is not sufficient to block reinfection entirely, but it seems to protect adults from getting sick, says Lavine. Even in children, the first infection is relatively mild.

Whether immunity to SARS-CoV-2 will behave in the same way is so far unclear. A large study of people who have had COVID-19 suggests that their levels of neutralizing antibodies — which help to block reinfection — start to decline after around six to eight months[2]. But their bodies also make memory B cells, which can manufacture antibodies if a new infection arises, and T cells that can eliminate virus-infected cells, says Daniela Weiskopf, an immunologist at the La Jolla Institute for Immunology in California, who co-authored the study. It's yet to be established if this immune memory can block viral reinfection — although cases of reinfection have been recorded, and new viral variants might make them more likely, they are still considered rare.

Weiskopf and her colleagues are still tracking the immune memory of people infected with COVID-19 to see if it persists. If most people develop life-long immunity to the virus, either through natural infection or vaccination, then the virus is unlikely to become endemic, she says. But immunity might wane after a year or two — and already there are hints that the virus can evolve to escape it. More than half the scientists who responded to Nature's survey think waning immunity will be one of the main drivers of the virus becoming endemic.

Because the virus has spread around the world, it might seem that it could already be classed as endemic. But because infections continue to increase worldwide, and with so many people still susceptible, scientists still technically class it as in a pandemic phase. In the endemic phase, the number of infections becomes relatively constant across years, allowing for occasional flare-ups, says Lavine.

To reach this steady state could take a few years or decades, depending on how quickly populations develop immunity, says Lavine. Allowing the virus to spread unchecked would be the fastest way to get to that point — but that would result in many millions of deaths. "That path has some huge costs," she says. The most palatable path is through vaccination.

## Vaccines and herd immunity

Countries that have begun distributing COVID-19 vaccines soon expect to see a reduction in severe illness. But it will take longer to see how effectively vaccines can reduce transmission. Data from clinical trials suggest that vaccines that prevent symptomatic infection might also stop a person from passing on the virus.

If vaccines do block transmission — and if they remain effective against newer variants of the virus — it might be possible to eliminate the virus in regions where enough people are vaccinated so that they can protect those who are not, contributing to herd immunity. A vaccine that is 90% effective at

blocking transmission will need to reach at least 55% of the population to achieve temporary herd immunity as long as some social distancing measures — such as face masks and many people working from home — remain in place to keep transmission in check, according to a model[3] developed by Alexandra Hogan at Imperial College London and her colleagues. (A vaccine would need to reach almost 67% of people to provide herd immunity if all social distancing measures were lifted.) But if the rate of transmission increases because of a new variant, or if a vaccine is less effective than 90% at blocking transmission, vaccine coverage will need to be greater to blunt circulation.

Vaccinating even 55% of the population will be challenging in many countries. "The virus will stick around if parts of the world don't get vaccinated," says Jeffrey Shaman, an infectious-disease researcher at Columbia University in New York City.

Even if the virus remains endemic in many regions, global travel will probably resume when severe infections are reduced to levels that health services can cope with, and when a high proportion of people who are vulnerable to severe illness have been vaccinated, says Dye.

## Similar to flu?

The 1918 influenza pandemic, which killed more than 50 million people, is the yardstick by which all other pandemics are measured. It was sparked by a type of virus known as influenza A, which originated in birds. Almost all cases of influenza A since then, and all subsequent flu pandemics, have been caused by descendants of the 1918 virus. These descendants circulate the globe, infecting millions of people each year. Flu pandemics occur when populations are naive to a virus; by the time a pandemic virus becomes seasonal, much of the population has some immunity to it. Seasonal flu still has a significant toll globally, claiming roughly 650,000 lives per year.

Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle, thinks the coronavirus might follow a similar path. "I do think SARS-CoV-2 will become a less serious problem and something like flu," he says. Shaman and others say the virus could also settle into a seasonal pattern of annual winter outbreaks similar to flu.

Flu seems to evolve much faster than SARS-CoV-2, allowing it to sneak past the immune system's defences. This feature is why flu vaccines need to be reformulated each year; that might not be needed for SARS-CoV-2.

Still, the coronavirus might be able to dodge immunity acquired by infection, and possibly outsmart vaccines. Already, laboratory studies show that neutralizing antibodies in the blood of people who have had COVID-19 are less capable of recognizing a viral variant first identified in South Africa (called 501Y.V2), than variants that circulated earlier in the pandemic[4]. That is probably because of mutations in the virus's spike protein, which vaccines target. Trial results suggest that some vaccines might be less effective against 501Y.V2 than against other variants, and some vaccine makers are exploring redesigns of their products.

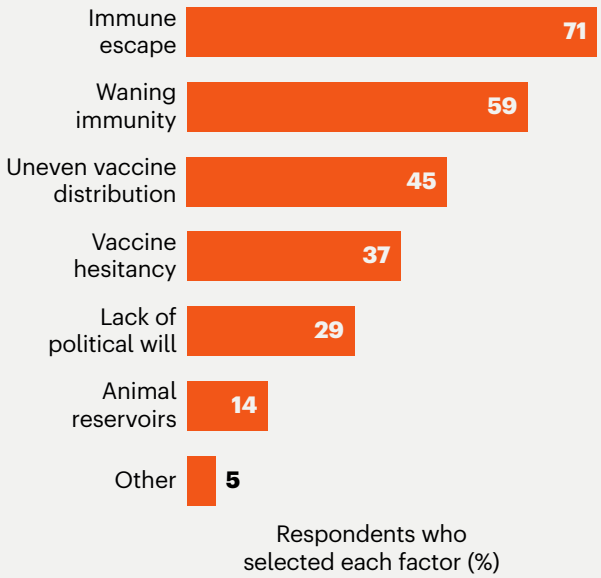
Still, the immune system has lots of tricks up its sleeve, and can respond to many features of the virus, not just spike, says Lavine. "The virus is probably going to have to go through lots of mutations to make a vaccine ineffective," she says. Preliminary trial results also suggest that vaccines can protect people with 501Y.V2 against severe disease, says Rasmussen.

More than 70% of the researchers surveyed by Nature think that immune escape will be another driver of the virus's continuing circulation (see 'Driving factors'). This would not be a first for a human coronavirus. In a study[5] yet to be peer reviewed, Bloom and his colleagues show that the endemic coronavirus 229E has evolved so that neutralizing antibodies in the blood of people infected with the viral variant circulating in the late 1980s and early 1990s are much less effective against more recent variants. People are reinfected with 229E over their lifetime, and Bloom suspects that it might be harder to stave off the variants that have evolved to escape previous immunity. But scientists don't know whether these reinfections are associated with worse symptoms. "I would expect that over many years, accumulated mutations to SARS-CoV-2 will more completely erode neutralizing antibody immunity as we saw for CoV-229E, although I can't say for sure how the rates will compare among the two coronaviruses," says Bloom.

Bloom thinks it's probable that SARS-CoV-2 vaccines will need to be updated, possibly every year. But even then, immunity from either past vaccination or infection will probably blunt serious disease, he says. And Lavine notes that even if people are reinfected, this might not be a big deal. With the endemic coronaviruses, frequent reinfections seem to boost immunity against related variants and typically

**DRIVING FACTORS**

*Nature* asked scientists to pick three of the biggest factors that would drive SARS-CoV-2 circulation in people if it became endemic.




people experience only mild symptoms, she says. But it is possible that vaccines won't stop some people developing severe symptoms, in which case the virus will continue to be a significant burden on society, says Shaman.

## Measles-like virus

If SARS-CoV-2 vaccines block infection and transmission for life, the virus might become something akin to measles. "It's probably less likely [than other scenarios] but it's still possible," says Shaman.

With a highly effective measles vaccine — two doses and a person is protected for life — the measles virus has been eliminated in many parts of the world. Before a vaccine was developed in 1963, major epidemics killed about 2.6 million people, mostly children, a year. Unlike flu vaccines, the immunization for measles has never needed to be updated because the virus has yet to evolve in ways that evade the immune system.

Measles is still endemic in parts of the world with insufficient immunization. In 2018, a global resurgence killed more than 140,000 people. A similar situation could emerge with SARS-CoV-2 if people decline vaccines. A survey of more than 1,600 US citizens found that more than one-quarter would definitely or probably decline a COVID-19 vaccine, even if it were free and deemed safe (see go.nature.com/3a9b44s). "How successful we are at addressing those concerns will determine how many people get the vaccine and how many remain susceptible," says Rasmussen.

## Animal reservoirs

The future of SARS-CoV-2 will also depend on whether it establishes itself in a wild animal population. Several diseases brought under control persist because animal reservoirs, such as insects, provide chances for pathogens to spill back into people. These include yellow fever, Ebola and chikungunya virus.

SARS-CoV-2 probably originated in bats, but it might have passed to people through an intermediate host. The virus can readily infect many animals, including cats, rabbits and hamsters. It is particularly infectious in mink, and mass outbreaks on mink farms in Denmark and the Netherlands have led to huge animal culls. The virus has also passed between minks and people. If it became established in a wild-animal population and could spill back into people, it would be very difficult to control, says Osterholm. "There is no disease in the history of humankind that has disappeared from the face of the Earth when zoonotic disease was such an important part of, or played a role in, the transmission," he says.

The path that SARS-CoV-2 might take to become an endemic virus is challenging to predict, but society does have some control over it. In the next year or two, countries can reduce transmission with control measures until enough people have been vaccinated either to achieve herd immunity or to drastically reduce the severity of infections. That would significantly reduce deaths and severe disease, says Osterholm. But if countries abandon strategies to reduce spread and let the virus reign unchecked then "the darkest days of the pandemic are still ahead of us", he says.

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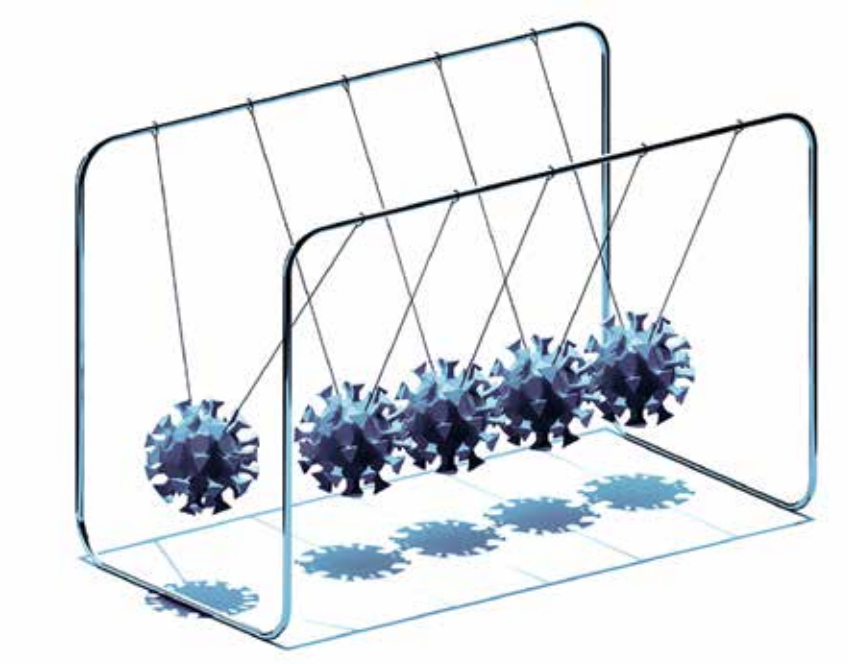
COVID-19

by **Sarun Charumilind, Matt Craven, Jessica Lamb, Shubham Singhal and Matthew Wilson**

# PANDEMIC *to* ENDEMIC

## HOW THE WORLD CAN LEARN TO LIVE WITH COVID-19





**With prospects of herd immunity fading, endemic COVID-19 is upon us, and new "whole of society" approaches are needed.**

A world that has been fervently hoping for a clean break with the COVID-19 pandemic may be disappointed. In many places, the pandemic continues unabated; some countries are currently suffering their highest rates of hospitalization and death. And even in areas where it has subsided, the end point continues to recede into the future. As we wrote in our most recent update to "When will the COVID-19 pandemic end?," few locations are likely to achieve herd immunity against SARS-CoV-2.

The highly transmissible nature of the Delta variant, ongoing vaccine hesitancy, and incomplete protection against transmission by current public-health measures mean that a goal of "zero COVID-19" is very likely unachievable without stringent public-health measures. Most societies, including the United Kingdom, the United States, and much of Europe, will need to learn to live with COVID-19, at least over the medium term.

What's happening now is not unusual. Epidemics end in one of two ways—either we close off all chains of transmission and drive cases to zero, as with all Ebola epidemics to date, or the disease becomes an ongoing part of the infectious-disease landscape, or endemic, as tuberculosis is today.[1] Occasionally, as with smallpox, a previously endemic disease is eradicated.[2] But, for the most part, endemic diseases are here to stay. The shift from pandemic to endemic entails a number of practical considerations, as we discuss in this article. But the shift is also psychological, as we will be deprived of the satisfaction that a clean pandemic end point would bring. Instead, societies will have to adapt to living alongside COVID-19 by making some deliberate choices about how to coexist.

Endemic disease does not mean unmanaged disease. Rather, what's needed is a shift from viewing COVID-19 as a one-time threat that defines society to seeing it as a part of everyday life that we must learn to endure. Around 38,000 Americans die every year in road-traffic accidents—far fewer than from COVID-19 over the past year but still a significant number.[3] As a society, we have developed tools to make road travel safer—seatbelts, airbags, impaired-driving laws, and so on. Each road death is a tragedy, and carmakers, public-safety agencies, and many others continually strive to reduce fatalities. But most of us don't spend much time thinking about road safety; we get in the car, buckle up, and go. Soon, the daily risks we run with COVID-19 may seem as much a part of normal daily life as the risks we run when we put the car in drive or navigate flu season each winter.

### A complete approach to managing endemic

COVID-19 requires the consideration of four interwoven elements. First, society will have to reach a consensus on what is an acceptable disease burden and use those targets to define an acceptable new normal. We will then need a comprehensive approach to track progress against this standard, define new disease-management protocols to limit deaths, and establish practices to slow transmission. Woven together, these four imperatives form a comprehensive approach to the management of endemic COVID-19 (exhibit). The work is vast and will require action across all segments of society, including government, healthcare providers, employers, the life-sciences sector, and the general public.

## Define the new normal

Societies need to set goals for what the new normal will look like and build consensus around them. Goals will vary across locations, but three guiding principles should apply. First, goals must recognize the "whole of society" impact of COVID-19. Targets for the health burden of the disease remain paramount, but countries can also introduce targets for economic and social disruption. Targets for the burden of death or severe disease (such as hospitalizations) and the related impact on healthcare-system capacity will continue to be as important as they have been during the pandemic. But beyond death or severe disease, COVID-19 has affected daily activities (learning and working, for example, and mental health). As such, measures of workdays lost, business closures, and school-absenteeism rates should also be considered.

Defining a new normal in a world where, for 18 months, societies focused on daily cases and test positivity is a material pivot that will need to be carefully communicated. The right metrics are likely to vary by geography: places where COVID-19 exposed the fragility of the health system may choose to focus primarily on not overwhelming their hospitals, while others may

embrace a more integrated mix of economic, social, and health factors. Local demographics, citizen sentiment, economic resilience, vaccination status, and other factors should inform these goals. Viewing the target for the total burden of COVID-19 relative to other diseases will be important context.

Second, goals must be realistic and balance the different needs of society. In many countries, zero cases will not be the appropriate target, since it requires ongoing public-health measures that place significant restrictions on society, particularly on businesses and schools. Some countries are, therefore, resetting their expectations: "For this outbreak, it's clear that long periods of heavy restrictions [have not gotten] us to zero cases," said New Zealand prime minister Jacinda Ardern. "But that is OK. Elimination was important because we didn't have vaccines. Now we do. So we can begin to change the way we do things."[4] Goals must also be realistic, or many sectors of society will quickly lose interest. And leaders must not set goals in a way that requires the most vulnerable in society to bear a disproportionate burden—for example, by requiring low-wage frontline workers to communicate or enforce policies.

Third, leaders must build the widest possible consensus around the goals through effective communication, emphasizing the whole-of-society nature of the targets. Much of the political discord created by COVID-19 over the past 18 months has arisen from differences of opinion about the relative importance of health, economic goals, and social goals. Not everyone will agree with every target, but part of managing endemic COVID-19 requires forging a social contract that recognizes the need to control the health impact of the disease while normalizing society to the greatest extent possible. While governments will lead in setting targets, all sectors of society will play a role in providing input and helping to build support for a shared definition of the new normal. Targets will evolve over time as we continue to learn more about what works and what doesn't, but clarity and consistency of communication will be critical.

## Track progress

Once realistic, multisector goals have been established, jurisdictions should track progress against them in easy-to-follow, transparent ways. This can include disease-surveillance metrics, such as hospitalizations and deaths, as well as measures of the wider societal impact of the milder cases of COVID-19, such as lost school days and missed workdays. Public-health measures, such as masking, physical distancing, and testing requirements, should also be deployed based on predefined thresholds of these metrics. In today's interrelated economies, metrics will have to be monitored globally to understand transmission dynamics and the emergence of new variants and to inform policy around travel restrictions.

As part of disease surveillance, ongoing genomic sequencing will be critical to monitor for the emergence of new variants that would necessitate changes in the approach to managing endemic disease. Many countries have made rapid progress this year in expanding their capacity to sequence SARS-CoV-2. Governments should take the next step and routinize that capability and integrate it with sequencing efforts for other pathogens.

As we better understand the virus and its transmission, monitoring systems should also include a real measurement of which interventions work and which do not. Over time, this information should let us better apply public-health measures in a way that is grounded in real evidence of how they work, with the aspiration of applying the minimum effective package for a given geographic area's disease status.

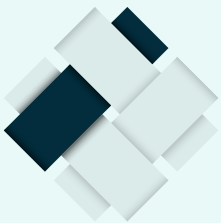
With this data and a dedicated focus, our ability to conduct meaningful predictive analysis will continue to improve. New efforts such as the WHO Hub for Pandemic and Epidemic Intelligence in Berlin, the United Kingdom's plan for a Global Pandemic Radar, and the US Centers for Disease Control and Prevention's new Center for Forecasting and Outbreak Analytics should help build on the progress in epidemic prediction made over the past 12 months. As our understanding of factors such as seasonality, heterogeneous mixing, and prior immunity improve, our ability to make meaningful forecasts for particular geographies will increase.

Lastly, communication of the monitoring data to the public must be simple and thorough. An analogy might be the fire-danger rating system in the United States, in which multiple factors are combined into a single rating—low, moderate, high, very high, extreme—that is communicated to the public, and which ties directly to policies used to mitigate the risks of fire.[5]

## Limit illness and death

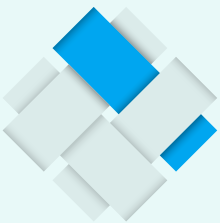
To achieve a new normal in which ongoing COVID-19 transmission is an accepted part of everyday life, societies need to effectively minimize immediate illness, the prevalence and persistence of long-term conditions ("long COVID"),[6] and COVID-19-related deaths. All are needed to limit the disruption to individuals' quality of life, societal well-being, and economic productivity.

**A comprehensive approach to management of endemic COVID-19 has four interwoven imperatives.**



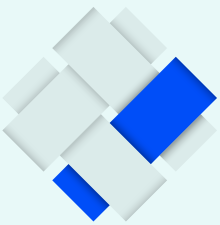
**Define the new normal**

- Set targets to define new normal in terms of burden of disease relative to other conditions, implications for the economy (eg, days of work lost), and other sectors of society (eg, school closures)
- Build widest possible public consensus around goals



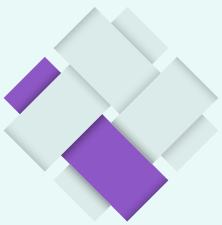
**Track progress**

- Monitor progress against targets through disease surveillance, tracking nonhealth burden across society, and response monitoring
- Use sequencing to track emerging SARS-CoV-2 variants
- Define framework and thresholds to activate or tighten public-health policies—eg, lockdowns, masking mandates, travel restrictions, taking seasonality into account
- Use predictive analysis to understand future scenarios



**Limit illness and death**

- Formalize and institutionalize vaccine infrastructure and integration with health system
- Develop tailored booster rollout plan based on emerging science
- Incentivize the development of new therapeutics and rapidly deploy new innovations to minimize case severity
- Develop surge plans and protocolize evidence-based COVID-19 management to ensure a consistently high standard of care
- Care for patients with "long COVID"



**Slow transmission**

- Define appropriate use for testing and ensure ubiquitous access
- Employ environmental and workplace modifications to enable safer interactions
- Coordinate across jurisdictions
- Respond rapidly to transmission hotspots

The challenge to come will take place on four fronts: the development and administration of vaccines, scaling effective treatments, the preparation of health systems, and the particular needs of vulnerable populations.

## Vaccines

The high efficacy of today's vaccines in preventing severe cases of COVID-19 is critical to normalizing society. Portugal illustrates the point: with 98 percent of those eligible fully vaccinated, severe COVID-19 cases are now rare and almost all public-health restrictions have been lifted.[7] In the months ahead, we will encounter old and new complexities in the push for vaccines: convincing vaccine-hesitant adults to get immunized; expanding immunization to younger ages as regulators evaluate filings from vaccine makers; and scaling boosters across the population. Reaching and sustaining high levels of vaccination, particularly as acute disease subsides, will require sustained and novel efforts to engage and educate consumers. Public-sector policies, private-sector practices, and shared cultural

values must create incentives for all of the above and make clear that immunization is a shared societal norm that is needed to effectively live with endemic COVID-19.

Moreover, as we transition from a heroic, one-time effort to stand up an infrastructure that put billions of doses in arms to a more routine program of booster vaccination, healthcare providers must integrate and institutionalize COVID-19 vaccinations into their broader ongoing operations.

To stay ahead of the virus, the vaccines themselves must continue to evolve.[8] Vaccine strategy, from development and manufacturing to selection, procurement, and distribution, must adapt to emerging science on the prevailing mix of variants of concern, appropriate intervals for boosters, and risk–benefit considerations for subpopulations (for example, the elderly or immunocompromised).

### Treatments

When people do get infected, effective treatments become critical. While monoclonal antibodies have proven very effective in a specific population, many COVID-19 patients are still being treated with a 50-year-old steroid (dexamethasone), fluids, and proning.[9] New data hold promise for the next generation of oral antivirals that could be widely scaled to help prevent disease progression to hospitalization and death, with several new treatments garnering excitement in late-stage development.[10] Improving the armamentarium of treatments would go a long way to limit COVID-19 deaths and remains a huge priority.

As they arrive, new and proven therapeutics and care practices must be incorporated into the standard of care, especially in communities at higher risk of COVID-19 infection and death and those with historical challenges in accessing high-quality care. New treatments are also needed for long COVID. To help navigate this as a society, healthcare providers will need to better characterize the range of symptoms associated with long COVID and develop tailored therapeutics and new innovations that improve recovery and limit disability after infection.[11]

### Health systems

Overwhelmed health systems and healthcare professionals faced with impossible decisions marked some of the darkest moments of the past 18 months. These moments have also been characterized by huge second-order health impacts, as excess deaths from other causes rapidly escalated.[12] To help manage future outbreaks, care-delivery systems must develop surge plans that can be quickly triggered to increase care capacity rapidly in response to local or widespread outbreaks and expected seasonal fluctuations, while still ensuring that non-COVID-19 care needs are met.[13] Effective management of endemic COVID-19 must also include catching up on preventive and elective care that was missed or delayed by the pandemic.[14]

### Vulnerable populations

The final critical element of limiting death from COVID-19 is outreach to those who are most at risk.[15] Some groups, whether because they live in crowded settings, suffer from socioeconomic disadvantage, or have limited access to healthcare, have been disproportionately affected by the pandemic to date. As the level of public attention focused on COVID-19 wanes, societies must be careful to avoid strategies that place a disproportionate burden on the most vulnerable. While some progress has been made, those with low-wage frontline jobs, those living in more crowded settings, and those with the least favorable access to healthcare have too often borne the greatest burden during the pandemic.

Equity should be woven into all of the interventions to limit illness and death. Any approach to living with endemic COVID-19 must have tailored strategies for outreach to these communities, and programs to ensure access to the vaccines, treatments, and care that can best keep them safe.

## Slow transmission

In a state of endemicity, slower transmission reduces the direct health burden of COVID-19, minimizes the likelihood that new variants arise, and mitigates the likelihood that epidemic outbreaks lead to societal disruption. In this new normal, we can expect four approaches to become a regular part of daily life: ubiquitous testing; safer interactions in workplaces, schools, and recreation and entertainment locales; and rapid response to transmission hotspots.

Widely available and rapid testing can help individuals and societies take the steps needed to limit further transmission. Current and future innovations in testing must be effectively deployed for specific uses such as screening, diagnosis confirmation, and surveillance. Ubiquitous, frictionless access to testing for all members of society, especially those at higher risk, has proven effective at blunting transmission. What, exactly, this should look like is up for debate but should be available through a wide range of channels—whether widely available, rapid-turnaround tests for asymptomatic patients such as those the United Kingdom has deployed,[16] regular employee testing like many employers have instituted, or simply the mass availability of rapid tests and institutionalized behavior of testing every runny nose. Who bears the cost of sustaining this infrastructure will likely be one of the next-order questions to arise.

Because transmission can occur wherever people congregate, most spaces—including workplaces, schools, events, and public areas—must consider how to enable safe interactions. The ways people work, learn, and socialize will return to normal or near normal, but must happen in safe ways that lessen the transmission of risk while being (and being accepted as) minimally disruptive (like wearing seat belts for road safety). The public and private sectors both have important roles to play: a range of policies and practices (like wearing masks in certain contexts or giving up handshakes[17])

and disincentives and incentives (such as the ability to join public gatherings) will likely hasten the arrival of a new set of social and cultural norms. Over time, infrastructure improvements can continue to reduce the risk of transmission in indoor spaces. For example, reconfiguring workspaces to enable physical distancing, scaling the use of HEPA filters, and improving air flow can all reduce risk of transmission.[18]

Lastly, when local outbreaks occur despite widespread safer interactions (and they will), societies must have rapid-response infrastructure in place to limit exponential transmission. While case-investigation and contact-tracing capacity have been overwhelmed at some points during the pandemic, they can play critical roles in responding to more localized outbreaks.[19] Rapidly deployable mobile testing units, staffed by officials with good local knowledge, can be just as important. Collaboration across the public sector, private sector, and care-delivery system—including the use of common communication platforms and data sharing where possible—will be critical for responding quickly and containing hotspots. While many jurisdictions deployed these approaches too late on the upslope of COVID-19 to have the desired impact, they have a critical role to play on the downslope.

Collectively, the four strands for managing endemic COVID-19 will require a momentous societal shift. Every stakeholder will have an important role to play:

- Governments can build consensus on goals, communicate superbly, and set the right incentives.
- Employers likely have an elevated role, setting policies for their workplace and helping their employees think through the changes.
- Health systems can strike the right balance among competing demands and plan for the inevitable outbreaks and surges.
- Individuals can challenge the convictions they've developed in the past 18 months and adopt new behaviors.

The costs will be meaningful, as these imperatives require sustained investment, but the return from enabling normal economic activity will be astronomical. It is critical that leaders align incentives such that sufficient investment is made across sectors to manage endemic COVID-19. Perhaps the hardest of all is the mindset shift, as we slowly accept that COVID-19 is not a temporary phenomenon that we can bury in our memories but rather a structural shift in how we live, requiring permanent changes in behavior. But if we are to truly reclaim our lives, now is the moment to start building.

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# Conversation

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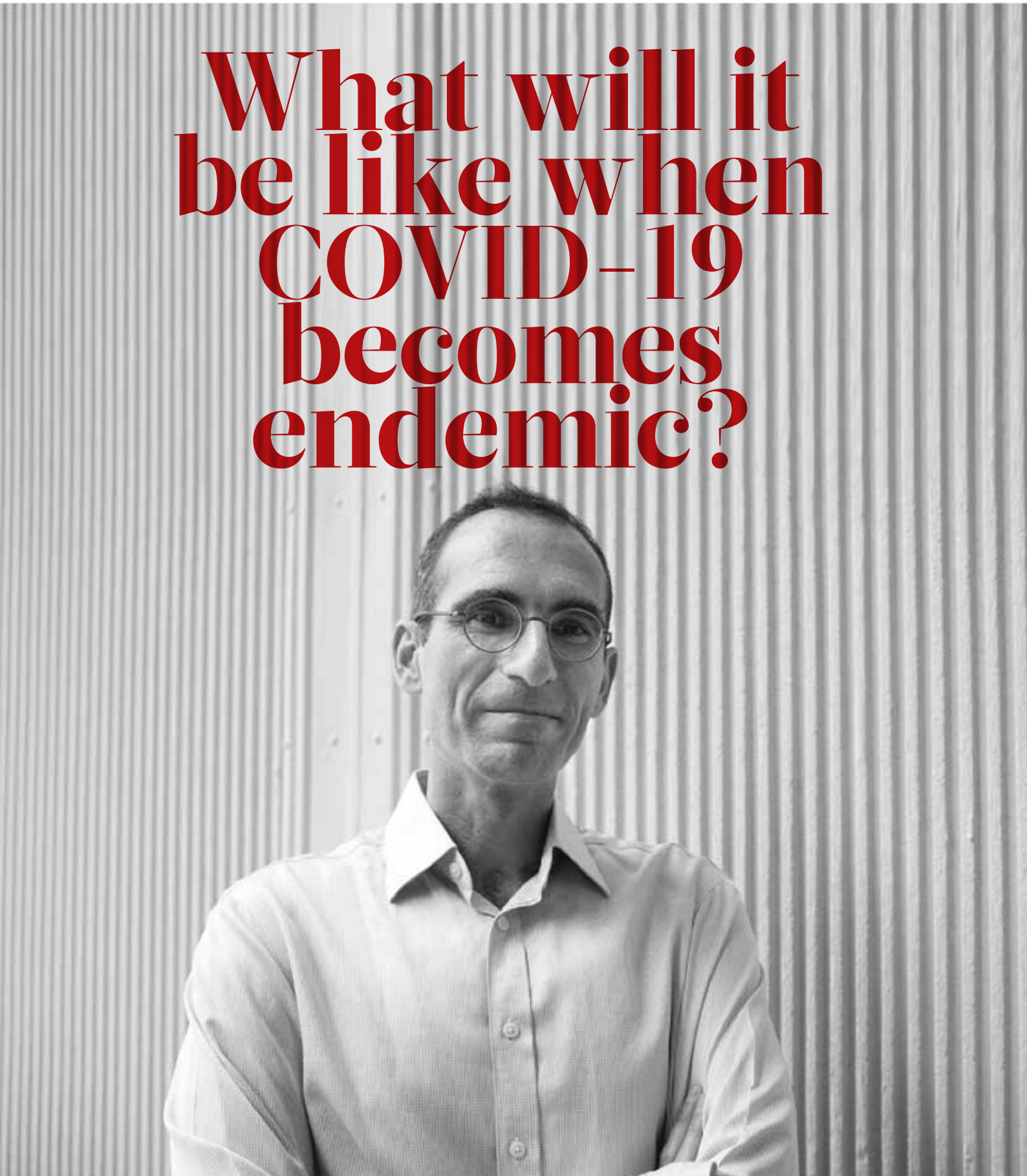
Conversation with *Yonatan Grad:*
**WHAT WILL IT BE LIKE WHEN COVID-19 BECOMES ENDEMIC?**

"The expectation that COVID-19 will become endemic essentially means that the pandemic will not end with the virus disappearing; instead, the optimistic view is that enough people will gain immune protection from vaccination and from natural infection such that there will be less transmission and much less COVID-19-related hospitalization and death, even as the virus continues to circulate."

– YONATAN GRAD

David Quammen

# What will it be like when COVID-19 becomes endemic?



Immunity conferred from natural infection and vaccines, patterns of social contact, and virus transmissibility will all play a role in what COVID-19 will look like as it continues to circulate in the months and years ahead, says Yonatan Grad, an Associate Professor of Immunology & Infectious Diseases at Harvard TH Chan School of Public Health.

**Q: Many experts have said they expect COVID-19 to become an endemic disease. How does a disease go from being acute to endemic? What factors shape the transition to endemicity? What's a likely timeline for COVID-19 to become endemic?**

A: The expectation that COVID-19 will become endemic essentially means that the pandemic will not end with the virus disappearing; instead, the optimistic view is that enough people will gain immune protection from vaccination and from natural infection such that there will be less transmission and much less COVID-19-related hospitalization and death, even as the virus continues to circulate.

The expected continued circulation of SARS-CoV-2 stands in contrast with the first round of SARS in 2003 and with the Ebola virus outbreak in West Africa in 2014, when public health measures ultimately stopped spread and brought both outbreaks to an end. While there are important differences among the viruses and the contexts, this comparison underscores the critical need to improve our global public health infrastructure and surveillance systems to monitor for and help respond to the inevitable next potential pandemic virus.

Since viruses spread where there are enough susceptible individuals and enough contact among them to sustain spread, it's hard to anticipate what the timeline will be for the expected shift of COVID-19 to endemicity. It's dependent on factors like the strength and duration of immune protection from vaccination and natural infection, our patterns of contact with one another that allow spread, and the transmissibility of the virus. So the patterns will likely differ considerably from what we saw with the other pandemics because of the heterogeneous responses to COVID-19 across the world—with some places engaging in "zero-COVID" policies, others with limited responses, and widely variable vaccine availability and uptake.

**Q: What does history tell us about how deadly viruses such as COVID-19 can, over time, become manageable threats?**

A: We know of a few respiratory viruses that were introduced into the human population, swept across the globe, and transitioned to endemic circulation, usually with annual wintertime peaks in incidence. The example most commonly invoked these days is the 1918 flu pandemic, caused by an A/H1N1 influenza virus. But there are other more recent examples from influenza: The 1957 flu pandemic caused by an A/H2N2 influenza virus, the 1968 flu pandemic from an A/H3N2 influenza virus, and the 2009 "swine flu" pandemic, from an A/H1N1 influenza virus.

The pandemics generally began with infection fatality rates higher than observed in the years following their introduction as the viruses continued to circulate. While declining fatality rates after pandemics may be due to a number of factors, one likely key contributor is that the first round of exposure to a pathogen confers some degree of protection against reinfection and severity of disease if reinfection does occur. Vaccines confer protection in much the same way, as the data from the COVID-19 vaccines has demonstrated.

**“ Screens on our doors and windows helped keep out mosquitos that carried yellow fever and malaria. Sewer systems and access to clean water helped eliminate typhoid and cholera epidemics. Perhaps the lessons learned from COVID-19 in terms of disease prevention can yield similar long-term improvements in individual and global health.”**

**Q: What is the likelihood that we will need booster shots every year?**

A: The need for annual boosters isn’t clear, and key biology and policy questions remain to be answered. On the biology side, how much antigenic evolution will we see in SARS-CoV-2—in other words, to what extent will it evolve to evade our immune system? We know of examples on both ends of the spectrum—some viruses, like influenza, require repeated vaccination because of its antigenic evolution, whereas others, like measles, are kept at bay for decades after childhood vaccination. How long does immune protection last, and what is the nature of that protection? How much does vaccine-conferred protection reduce the likelihood of infection, of severe disease if infected, or of the likelihood of transmission if infected? How quickly do each of these responses wane? On the policy side, what burden of disease are we willing to tolerate in a population?

These policy questions extend beyond COVID-19, of course, and should prompt us to reevaluate what we want to do about other preventable diseases. We’re in the midst of a wave of respiratory syncytial virus (RSV), another respiratory virus that for most of us causes cold and flu-like symptoms but that can be much more severe in infants, the elderly, and those with respiratory conditions. We don’t yet have an approved vaccine or highly effective treatment for RSV. And while we have modestly effective influenza vaccines and therapeutics, we usually see between 20,000 to 60,000 deaths a year in the U.S. from influenza. On a global scale, tuberculosis and malaria remain scourges that cause immense suffering. Investments in these areas and other measures that we’ve learned from COVID-19, such as the importance of ventilation and masking, can help reduce illness and death from a range of respiratory viruses and drive innovation in tools to tackle other infectious disease threats.

Past pandemics have led to massive changes in the way we live that we’ve come to accept as normal. Screens on our doors and windows helped keep out mosquitos that carried yellow fever and malaria. Sewer systems and access to clean water helped eliminate typhoid and cholera epidemics. Perhaps the lessons learned from COVID-19 in terms of disease prevention can yield similar long-term improvements in individual and global health.

# Research


**Functional Outcomes Following Fixation of Shaft of Humerus Fractures - Intramedullary Nailing Versus Plate Osteosynthesis: A Comparative Study**

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**Impact of COVID-19 Pandemic Lockdown on Children with Complex Care Needs: An Experience from One Centre in the United Arab Emirates**

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**Prevalence of Depressive and Anxiety Symptoms in Adults with Type 2 Diabetes, Peshawar, KPK, Pakistan**

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Analyses for preexisting antibodies showed high levels of class I and class II HLA antibodies, probably due to the previous administration of multiple blood products, including convalescent plasma.

# Functional Outcomes Following Fixation of Shaft of Humerus Fractures - Intramedullary Nailing Versus Plate Osteosynthesis: A Comparative Study

There is little data available describing the incidence of vestibular disorders in the Dubai population. This study therefore aims to report the etiological spectrum of vertigo and dizziness from a vertigo speciality clinic in Dubai.

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**Key words:**

Shaft humerus, Fracture, Plate fixation, Intramedullary nail, Operative management

## ABSTRACT

**Background:** The operative management of fractures of the shaft of humerus is most commonly accomplished with the help of open plate fixation, or closed intramedullary interlocking nails. Controversy exists so as to which modality is superior to the other, hence this study was conducted with an aim to compare the functional outcomes of humeral shaft fractures treated by two procedures - closed intramedullary interlocking nailing and open plate osteosynthesis. .

**Materials & methods:** This prospective observational study consisted of 32 participants, who were recruited to the study groups sequentially until the desired sample size was reached in each group. Participants were allocated to each of the surgical procedures based on their personal preferences. Patients were evaluated both clinically and radiologically at the end of 1 month, 3 months, 6 months and 1 year from the day of surgery. The study group (plating vs nail) was considered as an explanatory variable. Time to union, and functional outcome, as assessed by American shoulder and elbow society score, were considered primary outcome variables of interest. The need for bone grafting was considered as a secondary outcome variable.

**Table 1.** Comparison of patient characteristics between study groups

| Parameter | Plating (n=16) | Nailing (n=16) | P value |
|---|---|---|---|
| **Age (Mean years ± SD)** | 35.31 ± 15.45 | 37.13 ± 13.66 | *0.728* |
| **Gender** | | | |
| **Male** | 11 (68.8%) | 12 (75%) | *1.00* |
| **Female** | 5 (31.3%) | 4 (25%) | |
| **Limb dominance** | | | |
| **Dominant** | 11 (68.8%) | 8 (50%) | *0.280* |
| **Non-Dominant** | 5 (31.3%) | 8 (50%) | |

**Results:** Both study groups were comparable with respect to all baseline variables. The proportions of subjects showing signs of radiological union were 100% and 92.86% in the plating and nailing groups respectively. The proportion of subjects with radial nerve involvement was slightly higher in the plating group compared to the nailing group (12.5% vs 7.14%), but the difference was not statistically significant (P = 0.626). There was no statistically significant difference in the proportion of subjects needing bone grafting (18.75% in plating vs 14.29% in nailing group, P = 0.743). The mean time to union was slightly longer in the plating group compared to the nailing group (15.44 ± 2.39 vs 13.93 ± 1.85 weeks, P = 0.067), which was not statistically significant. Functional outcomes at the end of the follow up period, assessed by mean ASES score (26.44 ± 2.31 in plating vs 26.64 ± 1.65 in nailing group), was comparable between the two intervention groups.

**Conclusions:** Radiological and functional outcomes following humeral shaft fracture treatment with plate osteosynthesis and intramedullary nailing were comparable.

## INTRODUCTION

Fractures of the humeral shaft are common orthopaedic injuries, which result in a significant burden to society from lost productivity and wages.[1] Fractures of the humerus comprise approximately 5 to 8% of all extremity fractures.[2] Non-union rates for diaphyseal humerus fractures treated non-operatively range from 0 to 13%, with the incidence increasing to 15 to 30% for operatively treated fractures.[2,3] There is a bimodal distribution of humeral shaft fractures by age, with peaks primarily in young male patients aged 21–30 years, and a larger peak in older females from 60–80 years of age.[4]

Absolute indications for surgical intervention for humeral shaft fractures are specific circumstances including open fractures, associated neurovascular injury, proximal and distal articular extension, patients with multiple injuries or polytrauma, floating elbow, progressive radial nerve deficits, significant soft tissue injury (unable to brace), pathologic fractures and failed non-operative management.[5] Other relative indications include obese patients, patients with associated brachial plexus injuries due to the loss of muscle co-contraction and its ability to maintain bony alignment, and non-compliant patients.[6]

For patients with surgical indications, two different models are available: compression plate and intramedullary nailing (with open and closed approaches). Each has its advantages and disadvantages.[7,8] With plate and screw fixation, we may achieve more rigid fixation; however, in intramedullary nailing, fracture site soft tissue manipulation is possible. With plate and screw fixation, we may achieve more rigid fixation; however, in intramedullary nailing, fracture site soft tissue manipulation is much reduced.[7,8] Plating with rigid fixation, which is known to provide accurate anatomic reduction, can reduce the risk of mal-union, but requires wide intra-operative exposure, associated with soft-tissue stripping. Furthermore, the over-stripping of soft tissue at the fracture site also lowers the blood supply, which might raise the risk of non-union or infection.[9]

Closed nailing preserves the periosteal blood supply and promotes fracture union, by utilizing the osteogenic potential of the pluripotent cells in the fracture haematoma. Thus, closed intramedullary nailing supports the concept of biological fixation. Moreover, closed nailing procedures are associated with fewer complications, such as reductions in blood loss, infection rate and hospital stay. This treatment method has been the subject of controversy since its inception, because of concerns of damage to medullary circulation, possibilities of fat embolism, complications arising from application of incorrect technique, and lack of understanding of the biomechanical principles of intramedullary interlocking nail fixation (IINF). [10] Clinical series of fractures stabilized with humeral nails often report shoulder problems related to the insertion site, possible technical difficulties, more radiation exposure intra-operatively, and a higher rate of revision surgery.[11]

Choosing to plate or nail a humeral shaft fracture is becoming more a matter of patient preference or surgeon's choice, based on potential complications and surgeon fa-

miliarity. A meta-analysis that previously favoured plating over nailing was recently updated, and noted equivalent outcomes in rates of non-union, infection, nerve palsy, reoperation, and total complications between humeral plating and nailing.[9-12] However, few studies have definitively stated that IM nailing was a better surgical option for the management of humeral shaft fracture.[13] Hence, this study compared the functional outcomes of humeral shaft fractures treated by two procedures - closed intra-medullary interlocking nailing and open plate osteosynthesis.

## MATERIALS & METHODS

The study was a prospective observational study conducted in the Department of Orthopedic surgery, Aster Mims Hospital-Kottakkal, between July 2019 and July 2020. The study population consisted of patients with fractures of the shaft of humerus (Middle and Proximal 3rd), aged 18 years or above. The participants with open fractures, fracture distal third of humerus, pathological fractures polytrauma, fractures associated with neuro vascular injury, established non-union from previous fracture, and patients with multiple fractures, were excluded from the study.

The participants were divided into two groups: The intramedullary nailing group or the 2-plate osteosynthesis group. The ethics committee of the hospital approved the study, and each subject gave written informed consent.

**Sample Size:** Sample size was calculated assuming the expected mean ASES score (μ1 – μ0) in each of the treatment groups as 23.9 and 21.7, as per the study by Hashmi PM et al.[14] The other parameter considered for sample size (N) calculations was a common standard deviation (σ1, σ0) of 2, giving 5% alpha error and 80% power of study. Here, the constant value of u was 0.84 for 80% power and the value of v was 1.96 for a significance level of 5% .The sample size was calculated using the following formula.

$$N = \frac{(u+v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

The sample size as per the above mentioned calculation was 14 subjects in each group. To account for loss to follow up, it was decided to include an additional 10% of subjects. Hence, the final sample size decoded was 16 subjects in each group.

The study participants were recruited to each study groups sequentially until the sample size was reached in each group. Participants were allocated to either of the surgical procedures, as per patient preference. The relative advantages and disadvantages of each of the two treatment methods were explained to the participants, based on the best available evidence. The cost of treatment was also explained. Based on their choice, they were allocated to either of the two groups.

Patients were evaluated both clinically and radiologically at the end of 1 month, 3 months, 6 months and 1 year from the day of surgery. Clinical and radiological evaluation used the following measures:

- Subjective pain or tenderness at the fracture site (scored with visual analog scale)
- Functional activities at the shoulder and elbow joint.
- Documentation of radial nerve injury and Tinel's sign
- Presence of callus and bony trabeculae bridging the fracture site in follow up radiograph.
- American shoulder and elbow society score.

## STATISTICAL ANALYSIS

Functional outcome (age, ASES score, shoulder abduction ROM, elbow flexion ROM, time to union) were considered as primary outcome variables. Study group (plating vs nailing) was considered as an explanatory variable.

All quantitative variables (age, ASES score, shoulder abduction ROM, elbow flexion ROM, time to union) were checked for normal distribution within each category of explanatory variable, using visual inspection of histograms and normality Q-Q plots. A Shapiro- Wilk test was also conducted to assess normal distribution. A Shapiro-Wilk test p value of >0.05 was considered as normal distribution.

For normally distributed quantitative parameters, the mean values were compared between study groups using an independent sample t-test (2 groups). Categorical outcomes were compared between study groups using a Chi square test /Fisher's Exact test. (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.)

P values of <0.05 were considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[15]

## OBSERVATION & RESULTS

A total of 32 subjects were included in the final analysis. Among the study population, plating was conducted in 16 cases (53.33%), whereas nailing was chosen in 14 subjects (46.67%).

The mean age of subjects in the plating group was 35.31 ± 15.45 years, and in the nailing group, 37.13 ± 13.66 years (P Value = 0.728). In the plating group, 11 (68.8%) participants were male and 5 (31.3%) participants were female. In the nailing group, 12 (75%) participants were male and 4 (25%) participants were female. The difference in the proportion of gender between study groups was not statistically significant (P = 1.000). In the plating

**Table 2.** Comparison of outcome scores between study groups

| Parameter | Plating (n=16) | Nailing (n=16) | P value |
|---|---|---|---|
| ASES score (Mean ± SD) | 26.81 ± 2.54 | 26.88 ± 1.75 | *0.936* |
| **Radial nerve involvement** | | | |
| **Yes** | 3 (18.8%) | 1 (6.3%) | 0.600 |
| **No** | 13 (81.3%) | 15 (93.8%) | |
| **Need for bone grafting** | | | |
| **Yes** | 4 (25%) | 2 (12.5%) | *0.654* |
| **No** | 12 (75%) | 14 (87.5%) | |
| **Radiological signs of union** | | | |
| **Yes** | 16 (100%) | 15 (93.8%) | * |
| **No** | 0 (0%) | 1 (6.3%) | |
| Shoulder abduction ROM (Mean ±SD) | 155.63 ± 16.32 | 161.25 ± 8.85 | *0.235* |
| Elbow flexion ROM 0 -140 de (**Mean ± SD)** | 132.5 ± 7.75 | 136.25 ± 9.57 | *0.233* |
| Time to union (**Mean ± SD)** | 21.31 ± 3.59 | 19.31 ± 2.7 | *0.085* |

**** No statistical test was applied-due to 0 subjects in the cell***

group, 11 (68.8%) participants had a dominant upper limp. In the nailing group, 8 (50%) participants had a dominant upper limp. The difference in the proportion of dominant / non-dominant upper limb between study groups was not statistically significant (P = 0.280).

Among the plating subjects, 18.8% had radial nerve involvement. In the nailing group, this proportion was 6.3%. The difference in radial nerve involvement between the two groups was statistically not significant (P = 0.600). Among the plating subjects, 25% needed bone grafting, and in the nailing group this proportion was 12.5%. This was not statistically significant (P = 0.654). The mean ASES score of subjects in the plating group was 26.81 ± 2.54, and in the nailing group, 26.88 ± 1.75. The difference in the ASES scores between the two groups was not statistically significant (P = 0.936). In the plating group, all 16 (100%) participants had radiological signs of union. In the nailing group, 15 (93.8%) participants had radiological signs of union. The mean ROM of shoulder abduction in the plating group was 155.63 ± 16.32, and in nailing group, 161.25 ± 8.85. This was not statistically significant (P = 0.235). The mean elbow flexion ROM in plating group was 132.5 ± 7.75, and in the nailing group, 136.25 ± 9.57. This was not statistically significant (P = 0.233). The mean time to union of subjects in the plating group was 21.31 ± 3.59 weeks, and in the nailing group, 19.31 ± 2.7 weeks. This was not statistically significant (P Value=0.085).

## DISCUSSION

Humeral shaft fracture is unique amongst the long bone fractures in its tolerance of below-anatomical reduction. Shortening up to 3 cm, rotation of up to 300 and angulation of up to 200 are all considered acceptable. Due to this fact, most humerus fractures are still managed conservatively and have good functional results. The most common indication of operative intervention is an inability to achieve acceptable reduction, followed by associated vascular lesions, open fractures, radial nerve palsy, polytrauma patients, floating elbow and pathological fractures.16

Intramedullary nailing in humerus fractures is a less invasive procedure, which maintains the biology and gives a good, stable fixation. It is also assumed to result in quicker union, less blood loss and less chance of radial nerve injury. Even though many studies have reported on IMN fixation and plate fixation,[13, 17-21] controversy still exists over the best method of fixation. In this study, we aimed to compare the closed intra medullary interlocking nailing and open plate osteosynthesis in terms of the functional outcomes of Humeral shaft fractures treated by these two procedures. A total of 30 subjects were included in the analysis.

Among the study population, plating was conducted in 16 cases (53.33%), whereas nailing was chosen in 14 subjects (46.67%). The proportions of males were 68.75% among plating subjects, and 71.43% in the nailing group. There was no significant difference in age and gender between the two study groups (P > 0.05); The mean age of subjects

**Table 2.** Comparison of complications between study groups

| Parameter | Plating (n=16) | Nailing (n=16) | P value |
|---|---|---|---|
| Neuropraxia | 2 (12.5%) | 1 (6.25%) | *0.544* |
| Pre-operative neuropraxia | 1 (6.25%) | 0 (0%) | * |
| Rotator cuff impingement | 1 (6.25%) | 2 (12.5%) | *0.544* |
| Shoulder stiffness | 1 (6.25%) | 1 (6.25%) | *1.000* |

*No statistical test was applied- due to 0 subjects in the cells

in plating group was 35.63 ± 15.43 years and in the nailing group, 36.14 ± 11.8 years. Similar study settings have been reported in a few existing studies.[17-20] A study by Fan *et al.* (2015)[19] recruited a total 0f 60 participants with humeral shaft fractures, which were equally distributed to two study groups to receive IMN (N=30) and LCP (N=30), with similar mean ages of 39.3 ± 10.8 years in the IMN group and 39.2 ± 10.3 years in the LCP group. In the IMN group, the proportion of males were 60%, and in the plating group, 63.3%. In A 2014 study by Wali et al.,[17] 25 patients with humeral shaft fractures were selected for an ILN group and 25 to receive DCP. Similar to our study, the majority of participants in the two study groups were males (85% and 80%), with mean ages of 37.28 and 37.72 years respectively. In Yin et al. (2013)[18], again, no statistically significant difference was observed in age and gender between the two study groups.

In our findings, the proportion of subjects showing signs of radiological union was 100% among plating subjects and, in the nailing group, 92.86%. Union rates in our study were comparable with other studies.[13,17,19-20] In the study reported by Fan et al. (2015)[19], union rates were reported as 96.7% and 93.3% in the IMN and LCP groups respectively. Wali et al.'s study (2014)[17] was consistent with our findings, with 92 % union rates and only 8% non-union cases. The study findings of Putti et al. (2009)[20] reported union rates of 100% and 94% in their IMN and DCP groups respectively. Changulan, *et al.* (2007)13 reported a 85.7% union rate in an IMN group compared to 87.5% in a DCB group.

The mean ASES score was 26.44 ± 2.31 in our plating group and 326.64 ± 1.65 in our nailing group, which was not statistically significant (P = 0.784) in our study population, as has been reported by similar studies.[13,17,20] Results were similar in the study by Wali et al. (2014),[17] with a mean AECS score of 43.2 in the ILN group and 44.1 in the DCP group, which also was not significant. Mean AECS scores observed were 45.2 and 45.1 across IMN and DCP groups respectively in a study by Putti et al. (2009)[20], which was not significantly different. In Changulani *et al.* (2007)[13], mean AECS scores were observed as 44 min and 45 min in IMN and DCP groups respectively.

The proportion of radial nerve involvement among the plating subjects was 12.5% and in the nailing group this proportion was 7.14%. There was no statistical significance in the difference in radial nerve involvement between the two groups (P value=0.626), which is similar to the findings of a few existing studies [13, 17-20]. In the study by Fan *et al.* (2015)[19], radial nerve palsy was reported in 3 (10%) patients from the LCP group, but no cases in the IMN group. Similarly, Wali *et al.* (2014)[17] reported radial nerve palsy in two cases from a DCP group and no cases in an IMN group. As per the findings of Yin *et al.* (2013)[18], radial nerve injury was reported in 4 cases from an LCP group, but no cases were found in an IMN group. In the study by Changulani *et al.* (2007)[13], only one case of radial nerve palsy was found in a DCP group and no cases in an IMN group. However, a contrary study by Putti *et al.* (2009)[20] reported two cases of transient radial nerve palsies but none in a DCP group.

In this study, the proportions of subjects needing bone grafting were 18.75% and 14.29% in the plating and nailing groups respectively, showing no significant difference (P = 0.743). Similar proportions have been observed in most prior studies.[13, 17, 20] Wali *et al.* (2014)[17] reported bone grafting completed as a secondary procedure in two patients in each study group (ILN and DCP). In the findings of Putti *et al.* (2009)[20], bone grafting was necessary in only one case in the DCP group and none in an IMN group. Changulani *et al.* (2007)'s study findings [13] show that bone grafting was required in 9.5% of cases in an IMN group, and 4.5% in a DCP group.

In our study, the mean elbow flexion ROM in plating group was 133.75 ± 7.19, and in the nailing group, this was 135.71 ± 10.89. The mean ROM of shoulder abduction in the plating group was 156.25 ± 16.68, and in the nailing group, was 161.43 ± 8.64. The differences between elbow flexion ROMs and shoulder abduction ROMs were not statistically

significant between groups. Similar to our study findings, the meta-analysis by Benegas *et al.* (2014)[22] reported that patients' shoulder movements after DCP treatment were superior to those after IMN fixation (RR = 9.27 95% CI: 2.22–38.72) Ma *et al.* (2013)[21] study also supported our study findings. There was no significant difference found with regard to shoulder function according to the University of California, Los Angeles, scale between the minimally invasive plate and locking intramedullary nail (31.4 points vs 31.2 points, P ¼ .98). There was also no difference in elbow function (94.8 points vs 94.1 points, P ¼ .96).

In the current study, our reported mean time to union in the plating group was 21.13 ± 3.74.19 days, and in the nailing group, was 19.07 ± 2.79 days (P Value=0.560). However, the study by Changulani *et al.* (2007)[13] reported a mean union time for an IMN group of 6.3 weeks, and 8.9 weeks for a DCP group, a statistically significant difference (P<0.001). The study findings of Wali *et al.* (2014)[17] reported that the mean duration of union in remaining patients in ILN group was 13.60 (SD 4.32) weeks, and in the DCP group was 15.2 (SD 5.65) weeks, which was also statistically significant (P=0.376). Fan *et al.* (2015)[19]'s study documented average union time as 6.7 weeks in an IMN group and 10.6 weeks in an LCP group, with a statistically significant difference (P <0.001). In the study by Yin *et al.* (2013)18, the average bone healing time was (11.77 +/- 0.75) weeks in an LCP group, and (11.38 +/- 0.82) weeks in an IMN group. The difference was not statistically significant. (t = 1.705, P = 0.095).

## CONCLUSIONS

There was no significant difference in radiological and long-term functional outcomes following humeral shaft fracture treatment with plate osteosynthesis and intramedullary nailing. No delay was observed in time to union.

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# Impact of COVID-19 Pandemic Lockdown on Children with Complex Care Needs: An Experience from One Centre in the United Arab Emirates

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**Keywords:**

COVID-19; Lockdown; Children; Neurodisability

**ABSTRACT**

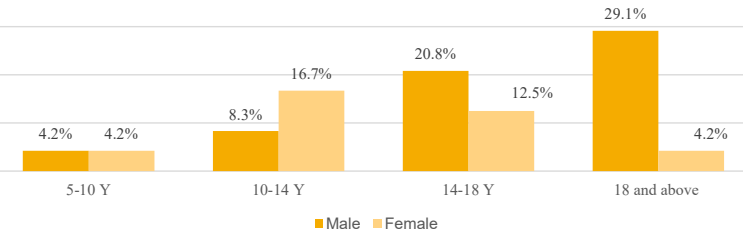
**Introduction:** The COVID-19 pandemic and the lockdown imposed have affected most of us, including children with complex care needs. Because of various reasons including changed routine and social isolation, the physical and psychological health of these children have been affected.

**Method:** This was an observational study with the objective of understanding and assessing the prevalence and spectrum of new-onset symptoms that children with complex care needs have been facing during lockdown, mainly due to their disrupted routine, including subsequent school closure. We selected a cohort of children who usually attend 'Al Noor Training Centre for Persons with Disabilities', which is a specialized center in Dubai, the United Arab Emirates, where they receive educational and therapeutic services from multidisciplinary team members. During the lockdown period, due to the COVID-19 pandemic, these children had to stay home and continue their sessions through a tele-rehabilitation program. All new symptoms presented and observed during these sessions were reported by the parents and interventionist to the research team.

**Result:** 14.6% of the participants presented with a new-onset symptom. Amongst the different symptoms which were mainly reported by the parents were sleep impairment, headache, behavioural issues, non-epileptic seizures, and motor and vocal tics. All of the children had some form of sleep impairment.

**Conclusion:** Children with special care needs were at a higher risk of having negative impacts on their well-being during the lockdown period induced by the COVID-19 pandemic. Identifying such symptoms in these children can be difficult, but is crucial to managing them effectively.

**Figure 1.** Distribution of the study participants according to their age groups




## BACKGROUND

The current COVID-19 pandemic has caused significant social, economic and health consequences across the world. Factors including social isolation and economic effects have also affected the mental and psychological health of many individuals. Children are one of the vulnerable groups to be affected.

Children's clinical services and social activities have been disrupted in many countries as the result of the temporary closures of medical centres, schools, and caregiving agencies in the lockdown period. Children with neurodisabilities have faced additional challenges as a result of their functional limitations and changes to their daily routine[1]. For example, a child with autism may find it difficult to cope up with the new environment and exhibit behavioural symptoms like agitation. There could be added negative impacts on skill development due to the suspension of speech therapy or occupational therapy type sessions. It is not uncommon for these children to present with somatic symptoms such as headaches or abdominal pain.

With this observational study, we wanted to understand the prevalence as well as the spectrum of new-onset symptoms that children with complex care needs have been facing during the COVID-19 pandemic; mainly due to their disrupted structured routine, including a lack of ongoing support from their respective therapists as the result of lockdown and closure of medical facilities as well as special need schools.

## METHODOLOGY

For this observational study, the cohort of children receiving tele-rehabilitation in 'Al Noor Training Centre for Persons with Disabilities' in Dubai, United Arab Emirates was chosen. This school caters to the complex care needs of children with developmental and intellectual disabilities, and children have access to various services including physiotherapy, occupational therapy, speech and language therapy and psychology. The study primarily aimed to understand and assess the prevalence and spectrum of new-onset symptoms that these children with complex care needs have been facing during the lockdown, mainly due to their disrupted routine including subsequent school closure.

Between March 2020 and September 2020, a total of 164 children who usually attended the school daily received tele-rehabilitation from various therapists, depending on their ongoing care needs. Participants who reported any new symptoms, which was the inclusion criteria, were studied further for the purpose of the study. Participants who did not show any new symptoms were excluded from the study. The newly reported symptoms were assessed by the respective specialists, or the child was referred to the relevant physician or specialist for formal assessment and management.

## RESULTS

Out of the total 164 participants, 24 (14.6%) were assessed for any new-onset symptoms as such symptoms were only reported in these 24 participants. These new symptoms were either reported by the parents of the respective participants or were observed by the therapists during the tele rehabilitation. All the participants who had such new symptoms during this period were seen by the relevant specialists for the formal assessment and diagnosis of these symptoms. Of these children,

8.4% were in the age group of 5-10 years, while 25% were aged 10-14 years. A third of these participants (33.3%) were between 14 and 18 years, and similarly, 33.3% were above 18 years. (Fig 1)

In terms of their background clinical diagnoses, 10 participants (41.7%) had Autism Spectrum Disorder with intellectual disability, 20.8% had Cerebral Palsy with intellectual disability, while 8.3% had diagnosis of Fragile X syndrome with intellectual disability. Predominantly, 91.6% of the new onset symptom episodes were observed in children who had intellectual disability. (Table 1)

All 24 participants (100%) had some form of sleep impairment, and were more vulnerable to disruption of sleep. Two-thirds of them had sleep-onset association type, and the rest had limit-setting type behavioural insomnia. All of the children were later referred to the clinical psychologist after the confirmed diagnosis by the sleep medicine specialist. The surge of behavioral

**Figure 2.** Distribution of the study participants based on their primary diagnosis

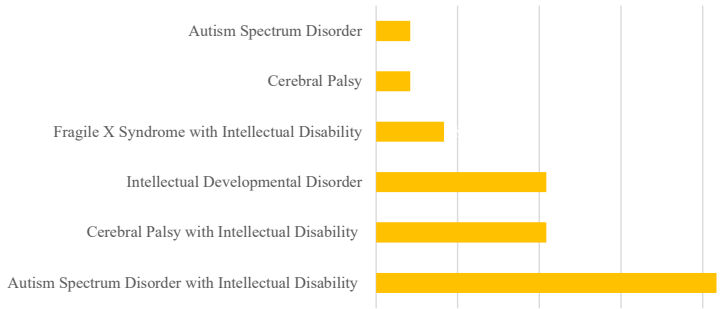
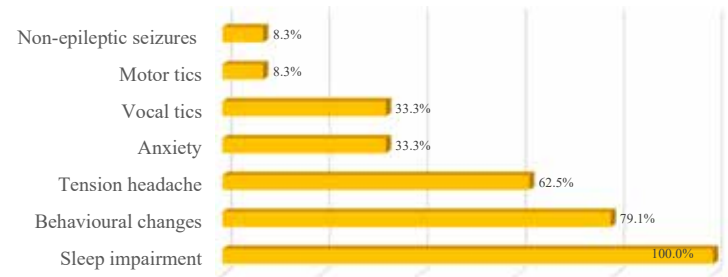



**Figure 3.** Comparative incidence of new-onset symptoms




problems was observed in 19/24 participants (79%). These included behavioural patterns such as increased aggression, agitation, being violent towards family members and headbanging episodes. 4/24 (16%) participants needed evaluation by a psychiatrist, while all of them were seen by the clinical psychologist. A third of these participants (33.3%) were diagnosed to have some form of anxiety and vocal tics respectively (Fig 2).

The next most common symptom was a headache. 62.5% of the participants included in the study had new onset symptom of headache. In all cases this was reported by their parents based on the observation. Following the assessment by the paediatric neurologist, all of these children were diagnosed to have tension-type headaches. None had any secondary type headache.

Two of the participants (8.3%) presented with new-onset seizure-like episodes which were assessed by the paediatric neurologist. These were diagnosed as non-epileptic seizures. Both of the cases had pre-existing epilepsy, but the new-onset seizures had a different semiology than their habitual seizures. Similarly, new-onset motor tics were observed in 2/24 male participants (8.3%), while vocal tics were seen in eight participants (33.3%), of which 5 (20.8%) were male. All of these children were subsequently assessed by a paediatric neurologist and neuropsychologist. (Fig 3)

## DISCUSSION

Widespread outbreaks of infectious diseases, such as COVID-19, are associated with psychological and mental health issues[2]. Children are not indifferent and are prone to the dramatic impact of the COVID-19 epidemic. Understanding their reactions and emotions is essential to address their needs properly. These could be challenging, especially in children with complex care needs. These children can have difficulty in understanding the complexity of the situation and are faced with missing ongoing learning and therapy support as the result of lockdown. Parents can find it difficult to cope during such times. The lockdown also appears to have affected the parents in the form of increased anxiety and stress. They may therefore struggle to identify any such new symptoms in their children[3].

There have been many published studies on the mental health consequences of children during the COVID-19 pandemic. Many children are presenting with various somatic symptoms such as tension-type headaches, tics, non-epileptic seizures, etc. Even children with complex care needs have been facing similar issues. The lockdown has been known to cause negative effects on morale, behaviour, and social interactions in these children. Although parents are performing therapies for such children at home, they could struggle to cope as they often lack the necessary professional expertise and usually rely on the support of their schools and therapists for any such issue[4].

With this study, we wanted to understand the physical issues that such children could be facing apart from their background physical and mental health needs. Such new symptoms could affect not only the children but their parents also. Moreover, these symptoms needed newer interventions which could be possible only after the appropriate identification and diagnosis of them.

Any new symptoms need to be carefully assessed as it can be very difficult to accurately diagnose them in children with complex care needs. Parents can play an important role in this process. For example, diagnosis of headaches according to the ICHD-3 classification for headaches can be challenging in such children[5]. Such diagnosis, however is important for appropriate management. The results of our study have also revealed that sleep is almost invariably affected in children

**Figure 2.** Distribution of the study participants based on their primary diagnosis

| Demographic details | | No of respondents (n = 24) | Respondents (%) |
|---|---|---|---|
| Age (yrs) | 5-10 | 2 | 8.4% |
| | 10-14 | 6 | 25.0% |
| | 14-18 | 8 | 33.3% |
| | 18 and above | 8 | 33.3% |
| Gender | Male | 15 | 62.5% |
| | Female | 9 | 37.5% |
| Diagnosis | Autism Spectrum Disorder with Intellectual Disability | 10 | 41.7% |
| | Cerebral Palsy with Intellectual Disability | 5 | 20.8% |
| | Intellectual Developmental Disorder | 5 | 20.8% |
| | Fragile X Syndrome with Intellectual Disability | 2 | 8.3% |
| | Cerebral Palsy | 1 | 4.2% |
| | Autism Spectrum Disorder | 1 | 4.2% |

with complex care needs. A changed routine during the lockdown may be the reason for their sleep impairment.

## CONCLUSION

It is important to understand and address any new symptom effectively as there may be an underlying psychological issue that needs attention. Children with neurodisabilities are prone to the long-term and negative effects of psychological stress, which is the result of environmental factors like the COVID-19 pandemic. They can eventually face high levels of stress, anxiety, and depression as a result[6]. If properly supported by healthcare professionals and the members of a multidisciplinary care team, children and their families can appropriately overcome any long-term distress. Such support can be provided through tele-health measures including tele-rehabilitation and tele-consultation. These could be appropriate and helpful ways to address the gap in the care of such children in situations such as lockdown[7].

**Acknowledgment:**

The authors would like to acknowledge all the class teachers and the parents of the children attending Al Noor Centre for Persons with Disabilities, Dubai, United Arab Emirates

**Statement of Ethics**

The study protocol was approved by the internal ethical committee of Al Noor Training Centre for Persons with Disabilities Committee on research on 26th February 2020 (Ref no 146/2020-2021/DD).

The parents of the children involved in this research have given their written informed consent to use their children's data for research.

**Data availability statement**

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Conflict of interest:

The authors have no conflicts of interest to declare

Funding:

No funding was needed for the study

**Author's contributions**

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by VM, TG, AP, SJ, and SB. The draft of the manuscript was written by VM. All the authors have read and approved the final manuscript.

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# Prevalence of Depressive and Anxiety Symptoms in Adults with Type 2 Diabetes, Peshawar, KPK, Pakistan

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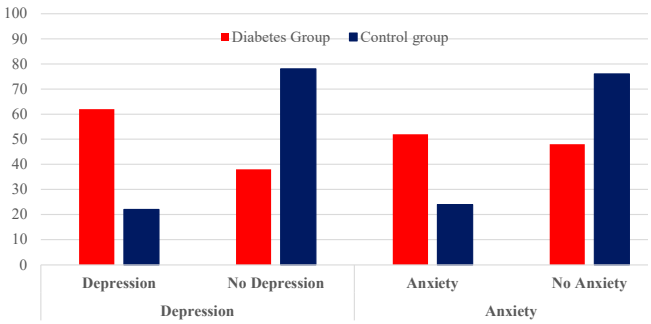
**Abstract**

Diabetes is a known cause of premature death, disability, morbidity and increased health-system costs. There is high prevalence of depression in patients with type 2 diabetes compared to that of people without diabetes. Objective: To determine the presence of depressive and anxiety symptoms in adults with type 2 diabetes and without diabetes. Methods: A questionnaire-based descriptive study was carried out at AIMS Sugar Hospital, Hayatabad, Peshawar, Pakistan. We used PHQ-9 and GAD-7 questionnaires for data collection. Results: A total of 1157 subjects were interviewed face to face, to complete PHQ-9 and GAD-7 questionnaires in Pashto (locally spoken language). Seventy seven percent (893) of the study population had type 2 diabetes and 23% (264) were healthy individuals. Of the 1157 subjects, 893 (55%) were male and 264 (45%) were female. The mean (S.D.) age of study participants was 46.2 ± 14.1 years (range 25–74 years). Both PHQ-9 and GAD-7 scores showed high prevalences of mild, moderate and moderately severe/severe depression symptoms, and mild, moderate and severe anxiety symptoms in the diabetes group compared to the control group. Females in the diabetes group were more likely to have depressive symptoms compared to males ($P < 0.01$, Pearson's Chi Squared). Increasing age (>50 years) was not associated with depressive and anxiety symptoms in either the control or diabetes group ($P= 0.3181$ and 0.431 respectively, Pearson's Chi Squared). We did not find any statistical association between duration of diabetes and severity of depressive and anxiety symptoms ($P = 0.561$, Pearson's Chi Squared). Conclusions: A high prevalence of depressive and anxiety symptoms was reported by patients with diabetes. Females were more affected than males. PHQ-9 and GAD-7 scales were found to be valid and reliable tools to screen, rate and monitor outcomes of depressive illness and anxiety disorder in primary healthcare settings in Pakistan.

**Figure 1.** Distribution of depression and anxiety symptoms




## INTRODUCTION

Diabetes is a known cause of premature death, disability, morbidity and increased health-system costs.[1,2] The prevalence of type 2 diabetes is rising, due to an ageing population, sedentary lifestyle and obesity. Around 400 million people worldwide have diabetes, and this number is expected to rise to 592 million by 2035.[3] Patients with chronic medical conditions such as diabetes are 2-4 times more likely to have depression compared to those without diabetes.[4-5] Research studies have shown that up to 40% of patients with diabetes have depression.[6-8]

Diabetes and depression represent the 8th and 4th causes of reduction in disability-adjusted life years worldwide, respectively.[9]

Depression is a leading cause of disability and a major contributor to the overall global burden of disease worldwide. Around 300 million people of all ages are affected with depression.[10] Depression can affect lives adversely, with poor functionality at work, school and within the family. At worst, it can lead to suicide. Around 800,000 people die due to suicide every year and this is the leading cause of death in the 15-29-year old age bracket. Depression is also a large burden on most economies[11] and leads to increased mortality.[12-13]

Depression is a recurrent disorder with many risk factors. Such risk factors include comorbidities with other chronic conditions,[14] other mental illnesses,[15] positive family history of depression and mental illness, childhood adverse events[16], past history of and treatment for depression,[17-18] lack of physical activity, female gender, younger age, smoking and unhealthy eating habits.[16]

Research studies have claimed that diabetes precedes the risk of developing depression, because of the psychological trauma of the diagnosis of diabetes and its associated burdens, for example hyperglycaemia/ hypoglycaemia and related complications and treatment, which cause significant challenges for clinical practice.[19-20] However, this notion has been challenged by longitudinal study results, that indicate depression can be a risk factor for diabetes,[19,21] and that diabetes may be modestly associated with depression.[20] The incidence of diabetes has also been reported in patients with depression in a number of systematic reviews and meta-analyses,[22-26] as opposed to considering diabetes as a risk factor for depression.[24,27-30] Recent studies have reported a bidirectional relationship of diabetes and depression as comorbidities existing simultaneously.[29,31-34] Depression is associated with hyperglycaemia (higher glycated haemoglobin, HbA1c,[35-36] increased morbidity & complications,[37-38] and increased mortality and healthcare costs.[4,39] Such associations may be linked to sub-optimal self-care,[40] noncompliance with medication,[41] and poor health-related quality of life.[42] Appropriate diagnosis and treatment of depression in diabetes can improve quality of life, improve glycaemic control and wellbeing, and improve social interaction of patients in general with their families, friends and carers.[43-44] AIMS Sugar Hospital recently presented our 'diabetes circle of care' complications data at the International Diabetes Federation (IDF) Congress,[45] which highlighted high reporting of depressive and anxiety symptoms in our out-patient population (77% of all patients, 88% of females compared to 22% of males). Therefore, the current study was designed to collect data specifically on depressive and anxiety symptoms in a diabetes cohort, compared with a control group with no diabetes and no other comorbidities.

## AIMS AND OBJECTIVES

To determine the presence/frequency of depressive and anxiety symptoms in adults with type 2 diabetes and without diabetes.

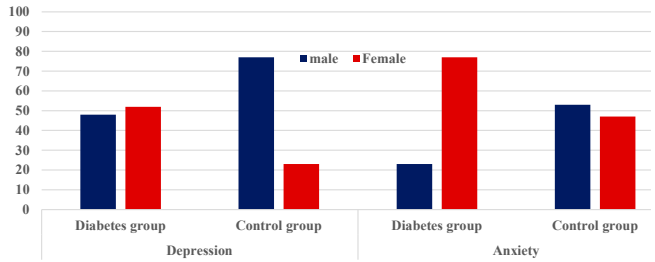
## METHODS

A questionnaire-based descriptive study was carried out at AIMS Sugar Hospital, Hayatabad, Peshawar, Pakistan, between 1st November 2018 and 31st January 2019. Study subjects were recruited to the diabetes group from our diabetes out-patient department. Their relatives were asked to participate in the study, and, if they consented, recruited to the control group. Ethical approval was given by our ethics committee. Written consent forms were signed by all participants.

We used PHQ-9 and GAD-7 for data collection through face-to-face interviews with study subjects during their visits to the hospital. Statistical analyses were carried out using SPSS-21.

The Patient Health Questionnaire-9 (PHQ-9) is a short self-report screening tool, used most commonly in primary healthcare settings to screen people with major depression, as well as to assess the severity of depressive symptoms.

**Figure 2.** Gender distribution of depression and anxiety




It has a high internal consistency (Chronbach's alpha 0.86 and 0.88) and high test-retest reliability (Chronbach's alpha 0.84 and 0.95).[46-47] A total score of 0-4 represents minimal to no depression, 5-9 represents mild symptoms of depression with minimal intervention and no medication required. Scores of 10-14 represent moderate depressive symptoms, which may benefit from psychological interventions such as brief counselling, cognitive behavioral therapy (CBT) or interpersonal psychotherapy. However, scores of 15-19 represent severe depression symptoms, which need treatment with or without psychological interventions. Scores above 20 show severe depression, requiring urgent referral to mental health services and treatment.

Major depression was diagnosed if any five or more responses were marked as "more than half of the days" (2), and either 1a or 1b was marked as "more than half of the days" (2) on the PHQ-9 questionnaire. Minor depression was calculated if 1b, 1c or 1d was marked as "more than half of the days" (2) plus either 1a or 1b was positive as "more than half of the days" (2).

The General Anxiety Disorder-7 (GAD-7) is a seven item based self-administered screening tool, used to measure the severity of generalized anxiety disorders. It is also a reliable screening tool for panic, social anxiety and post-traumatic stress disorder.[46] The GAD-7 has good internal consistency (Chronbach's alpha 0.89-0.92), good convergent validity[47] and a sensitivity of 83–89%.[48]

GAD-7 consists of seven questions, each of which ask the individual to rate his/her symptoms over the past two weeks. The subject's response can be one of the following: not at all (0), several days (1), more than half of the days (2) and nearly every day (3). Scores between 0-4 indicate minimal or no anxiety, 5-9 indicate mild anxiety, 10-14 indicate moderate anxiety (needing further evaluation), and scores 15 and above are indicative of severe anxiety, for which treatment needs to be initiated if the patient is not already taking anxiety medication.

## RESULTS

A total of 1157 subjects were interviewed face to face to fill out PHQ-9 and GAD-7 questionnaires. Seventy seven percent (n=893) of the study population were patients with type 2 diabetes (diabetes group), while 23% (n=264) were healthy individuals (control group). Of the 1157 subjects, 523 (45%) were females and 634 (55%) were males. The average age (S.D.) for the study population was 46.2 yrs (±14.1). Age ranged from 25-74 years. Patients with diabetes were comparatively older (50.1± 11.7 yrs) than healthy individuals in the control group (31.7 ± 11.3 yrs, Table 1.).

Depression was reported by 52.6% (n=609) of the total study population (point prevalence), while 47.4% (n=548) of study subjects reported no symptoms of depression on the PHQ-9 scale. Major depression was noted in 274 (23.7%) study subjects, and minor depression in 335 (28.9%) subjects.

A statistically higher number of patients (551/893, 61.7%) in the diabetes group reported symptoms of depression compared to the control group (58/264, 21.9%, P = 0.001, Pearson's Chi Squared, Figure 1.).

Similarly, according to the GAD-7 scale, 46.5% of our study population (539/1157) reported anxiety, compared to 53.5% (618/1157) with no anxiety. Among the subjects reporting anxiety, the majority indicated mild anxiety symptoms (257/539, 48%). Severe anxiety symptoms were reported by 17% (89/539) and 35% (193/539) had shown moderate anxiety symptoms.

Between-group comparisons showed that anxiety was reported significantly more frequently among the diabetes group (475/893, 52%) compared to the control group (64/264, 24%, P = 0.001, Pearson's Chi Squared, Figure 1).

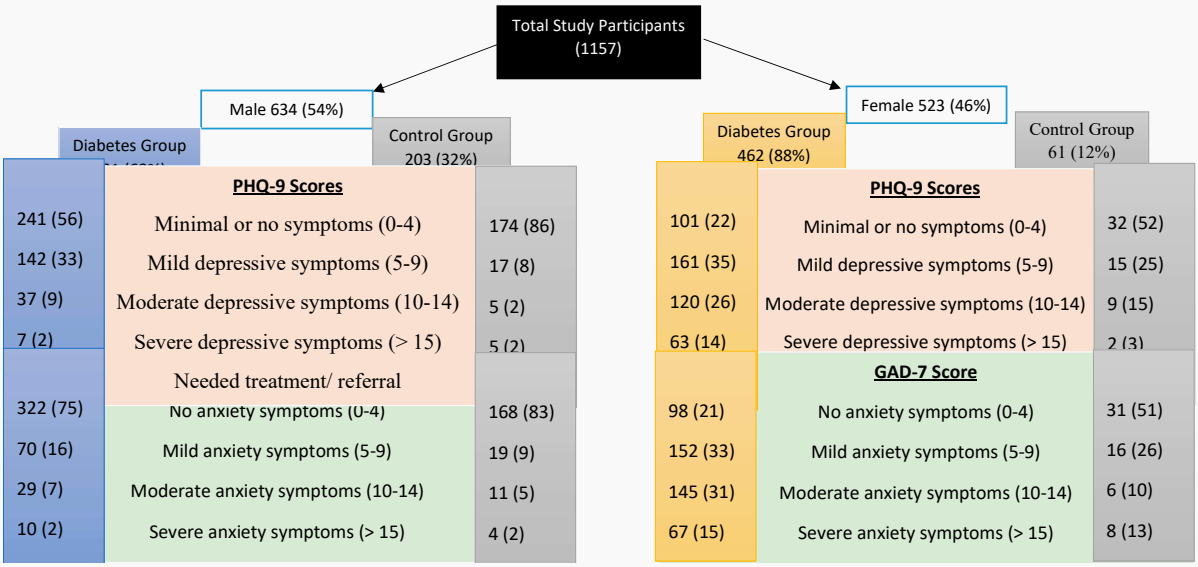
Female gender (361/551, 65.5%) was significantly associated with depression, with a higher frequency compared to males (190/551, 34.5%) within the diabetes group (P < 0.01, Pearson's Chi Squared). However, female gender was not associated with depression in our control group (29/58, 50% vs 29/58, 50%; Figure 2).

Within-group analysis of the diabetes group demonstrated that a significantly higher number of female patients with diabetes reported symptoms of anxiety (364/475, 77%) than male patients in the same group (109/475, 22.8%, P = 0.001, Pearson's Chi Squared). On the other hand, in the control group, anxiety symptoms were reported equally frequently by male and female subjects (30/64, 47% and 34/64, 52%, respectively).

Figure 3 illustrates the distribution of depressive and anxiety symptoms between the two groups, according to gender.

Within-group analysis showed that increasing age (>50 years of age) was not statistically associated with increased depressive or anxiety symptoms within the diabetes group (P = 0.3181 and 0.431 respectively, Pearson's Chi Square test).

**Figure 3.** Flow chart illustrating the distribution of male and female study subjects and their PHQ=9 and GAD-7 scores (n (%)).




Similarly, there was no statistical association between the duration of diabetes and the presence of depressive or anxiety symptoms (P = 0.561, 0.514 respectively, Pearson's Chi Squared).

## DISCUSSION

Our study shows that adult patients with type 2 diabetes are more susceptible to psychological symptoms (depression and anxiety). Female gender is also a risk factor. Therefore, psychological symptom screening should be considered in the treatment of patients with diabetes, as this may affect the treatment pathway and outcome as well as the quality of life.

Previous research by Zahid *et al.* (2007) has shown similar results, that patients with diabetes have a high prevalence of depression (14.7%, CI 6.6-22.8) compared to patients without diabetes (4.9%, CI 3.7-6.1).[49] A higher prevalence of depression has also been reported in females (5.4%, CI: 4.2-6.6) compared to male patients.[49] Similarly, Khan *et al.* (2014)[50] have shown high prevalence of depression (60%, 84 out of 140 patients with type 2 diabetes). In comparison to Zahid *et al.*'s findings,[49] our diabetes group has shown a higher prevalence of depressive symptoms, more than 60%, compared to 23% in the control group. This is consistent with Khan *et al.*'s findings,[50] irrespective of the different screening tools that were used for depression screening.

Furthermore, females were found to be more vulnerable to psychological symptoms when compared to males across different studies.[50,51] Our study findings are in agreement with Khan *et al.* (2014);[50] more than 65% of our female patients with diabetes reported depressive symptoms, compared to 34.5% of male patients with diabetes. Khan *et al.* (2014) found that 68% of females, compared to 31% male patients with diabetes, had depression. Such a high occurrence of depression in females could be associated with social traits such as passivity and dependence, and comparatively high emotional expression in women compared to men.[50,51] Irrespective of the etiology of depression in women, depression adversely affects women's lives physically, emotionally and socially.

Our results have shown no statistically significant association between the duration of diabetes and depressive/anxiety symptoms in our adult diabetic population. However, research has shown that, generally, immediately after a new diagnosis of diabetes, there is an increase in depressive symptoms. These gradually reduce over a period of a few years, however, reoccurrence of psychological symptoms are associated with a longer duration of disease, characterised by a J-shape curve.[52] Almeida *et al.* (2016) found that the odds of depression were highest in patients with diabetes with a duration of less than 10 years or more than 30 years.[53] Similarly, Arshad *et al.* (2016) have shown, using the PHQ-9 questionnaire, that 40% of their study population, with a short duration of diabetes, was depressed, which is indicative of increased depression in early diabetes.[54]

Chen *et al.* (2017) studied relationships between various chronic medical conditions and symptoms of depression.[55] They found no significant increase in depressive symptoms after an initial diagnosis, however their research has shown a gradual increase in psychological symptoms over a period of time, in accordance with Darwish *et al.*'s J-shaped curve model.[52] In addition to the above, Hood et al. (2011),[56] report a peak in depressive symptoms at baseline

**Table 1.** Characteristics of study population and distribution of depression and anxiety symptoms.

| | | Depression (PHQ-9) | Anxiety (GAD-8) |
|---|---|---|---|
| Group | Diabetes group | 551/893 (61.7%) | 475/983 (52%) |
| | Control group | 58/264 (21.9%) | 61/264 (24%) |
| Gender | Male | 190/551 (35.5%) | 110/475 (23%) |
| | Female | 361/551 (65.5%) | 365/475 (77%) |
| Age (years) | <=50 | 303/551 (55%) | 271/475 (57%) |
| | >50 | 248/551 (45%) | 204/475 (43%) |
| Duration of diabetes (years) | <1 | 215/551 (39%) | 171/475 (36%) |
| | 1-10 | 176/551 (32%) | 162/475 (34%) |
| | >10 | 160/551 (29%) | 142/475 (30%) |

(initial diagnosis), with a gradual decline over the next few years, and an increase in psychological symptoms with a longer duration of diabetes, suggestive of a J shape-curve model of depressive symptoms in diabetes. Although an increase of depressive symptoms with initial diabetes diagnosis has not been fully investigated, such psychological symptoms might be related to distress caused by a new diagnosis and lifelong treatment routine, including blood testing and diet and exercise regimens.[57] Incidence of depressive symptoms have been reported with initiation of anti-diabetes oral medication during the first year, although after adjustment to medication routines with no diabetes-related complications in the following few years, there appear to be improvements in symptoms.[55,58,59]

Our within-group analysis showed that increasing age (>50 years) in the diabetes group was not significantly associated with depressive/anxiety symptoms. Previous studies have shown that increasing age in patients with diabetes is associated with reduced psychological symptoms, however the relationship between age and risk of depression in diabetes is multifactorial.[60-62] Berge *et al.* (2015)[61] conducted a population-based cross-sectional survey, and found that patients with diabetes in their forties are twice as likely to be depressed relative to patients with no diabetes in the same age group. They also found that patients with diabetes on oral anti-diabetic medication were three to five times more likely to be depressed, and using antidepressants, respectively.

The association between diabetes and depression with respect to age is complex, and other factors such as physical inactivity, diabetes complications, HbA1c and glucose control, body mass index (BMI), low educational level and socioeconomic class all contribute to disease risk. A relatively low risk of psychological symptoms in older patients with diabetes as compared to younger patients could be related to better coping mechanisms, and patients' experience of managing the disease gained over time (with extended duration of diabetes).

Screening for psychological symptoms in diabetes is recommended by many clinical guidelines,[63,64] and a range of questionnaires is available to assess depressive symptoms. Research has shown that the Beck Depression Inventory (BDI), the Patient Health Questionnaire-9 (PHQ-9), the Center of Epidemiological Studies' Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale-Depression (HADS-D) are frequently used tools for depression identification in patients with diabetes at the primary care level.[65,66]A questionnaire's effectiveness for depressive symptom identification is usually assessed by reliability, validity, and responsiveness.[66] A reliable questionnaire will have minimum measurement error, while being valid in its ability to measure the intended construct. A good responsive questionnaire shows sensitivity to any changes in the construct.[67] In addition to the above, it is crucial that a questionnaire gives clinically meaningful outcomes and has interpretability.[67] The PHQ-9 and GAD-7 scales were found to be valid and reliable tools to screen, rate and monitor outcomes of depressive illness and anxiety disorder in primary healthcare settings in Pakistan.

Our study limitations include possible selection bias, as we included every consecutive patient who consented to participate in the study, with or without their relative (as a control) from our outpatients department. Therefore, our groups (diabetes and control) were not equally distributed, due to a lower participation rate among relatives (22.8%).

Previous studies have demonstrated that patients with severe psychological symptoms are less likely to participate in surveys,[67] and a high prevalence of depression was noted in non-participants relative to participating patients.[68] However, the implication is that we are more likely to underestimate the prevalence of depressive/anxiety symptoms rather than that the validity of measures between the diseases (diabetes and psychological symptoms) will be impacted.

We excluded all those participants who were on antidepressants currently or have used treatment for psychological symptoms in the past, as this could have reduced the specificity of our measures of psychological symptoms (depression and anxiety). However, we did not collect data for other existing medical conditions including asthma, heart disease or gastrointestinal disorders, either in the diabetes group or the control group.

Finally, we did not assess some confounding factors for psychological symptoms which can affect patients with diabetes negatively, such as their treatment history (oral treatment vs insulin injections), HbA1c levels, presence of diabetes related complications, socioeconomic history and educational level.

## CONCLUSION

The bidirectional relationship between diabetes and depression is complex. These two chronic conditions occurring together can create difficulty in managing both the conditions and their associated long-term effects, such as stroke, dementia and mortality. Identification of psychological symptoms in patients with diabetes in primary care settings is important. Appropriate treatment with established pathways for referral by primary care physicians is necessary to avoid the progression of both conditions. From a public health perspective, it is important to initiate preventive strategies, at the primary care level, to reduce the prevalence and impact of depression comorbid to diabetes.

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# Views & Reviews

## Medical Apps Relevant to Paediatricians

*Page 46*

There are a plenty of good apps which a paediatrician needs to have on their mobile.

## Medical Apps

By **Dr Jeeson C Unni**


# Medical Apps Relevant to Paediatricians

There are a plenty of good apps which a paediatrician needs to have on their mobile.

**Dr Jeeson C Unni** is Editor-in-chief, IAP Drug Formulary and ASSC Consultant, Dept of Child and Adolescent Medicine, Aster Medcity, Kochi

Over the past 10 years, our smartphones and tablets have transformed the way in which we practice medicine. It has been some time since I reviewed medical applications for mobile devices, and many paediatricians have requested an update. I have therefore put together my recommendations for the *best* applications for paediatric providers - apps that I have been using for years (applications that are associated with "connected" devices, such as pulse oximeters, blood pressure cuffs, otoscopes and so on, are not detailed in this article).

I would classify the various mobile apps as follows:

- Almost everything in one app
- Medscape
- IAP Drug formulary
- Pediatrics On Call
- Calculators and convertors
- Ped(z) – Pediatric calculator
- IAP
- Indian Pediatrics app
- Immunisation app
- IAP Growth Charts app
- E-vote IAP
- Differential Diagnosis
- Isabel
- Pediatrics On Call
- Medline search
- PubMed
- Other useful apps
- Diagnostic tool for Autism Spectrum Disorders
- PedNeuroAiims Diagnostics
- Bone Age Anthropometric Calculator
- Pedi Crisis 2.0
- Totsguide
- Track And Act
- ADR PvPI
- GCS app
- Surakshith
- Bal Suraksha
- Journals
- Read by QxMD
- Podcasts
- Podcast Republic

## Almost everything in one app

There are a plenty of good apps which a paediatrician needs to have on their mobile.

**Medscape** from **WebMD** is one of the leading medical resources used by physicians, medical students, nurses, and other healthcare professionals for clinical information. Since 2009, Medscape has released an annual update of its Medscape Mobile app. The mobile app is used by over 3 million health care professionals, and was the #1 most downloaded free app in the medical category of iTunes for 2010.

The app, as with previous versions, offers evidence-based disease reference and updated medical news and education resources. An independent team of 7700 physicians and pharmacists author and review the content, so current information is ensured. Medscape has recently released its 4.0 version, that includes several new features.

**The IAP Drug Formulary (IAP DF)**, first published in 2004-2005, has completed 13 yrs of service to the paediatric specialists in India and abroad, being the only exclusively paediatric formulary in the world other than the British National Formulary for Children (BNFc). The IAP DF 2019 now contains recommendations for drug therapy for >500 paediatric ailments and detailed, well researched information for more than 630 medications licensed for use in neonates, children and adolescents.

The user interface of the IAP DF mobile apps has been improved to make it more user friendly. It is available for the iOS (iPhone, iPad), Android, Symbian and Blackberry platforms. The quarterly Web Updates get automatically updated on the mobile app.

**The Pediatric Oncall** apps contains calculators (growth calculators, renal calculators, pregnancy calculator, blood group calculator, drug dose calculator, critical care calculators,

diarrhoea calculator and biochemical test calculators), drug dosing, MCQs, video podcasts, poison information, an image gallery and more. One can take part in Grand rounds (Teaching Files), get a differential diagnosis in the Diagnostic Aid section, ask an expert panel of doctors a medical query in the Post Query section, or watch videos on the latest topics.

## Calculators and convertors

Ped(z) – Pediatric calculator as an app for Android and iPhone/iPad is available for free. The features of the app are the same as on the website (except for the plotter, which is missing in the app). Calculates percentiles, z-scores and many more things a paediatrician needs.

***IAP* - Indian Pediatrics mobile app -** the official publication of the Indian Academy of Paediatrics (IAP) – the app allows the user to browse the contents of the current issue of IP, search articles by author or keyword, and search contents of past issues up to 2002.

**IAP Immunization app** of the IAP Advisory Committee on Vaccines & Immunization Practices (ACVIP) – contains recommended vaccines. An immunization schedule and vaccine reminders are also available on this app.

**IAP Growth Charts app -** This smart *app* can plot entered data efficiently on reference graphs and analyse the data, to give an instant diagnostic interpretation. This *app* aims to give a completely new outlook to *growth* monitoring practice in India by digitalizing *growth charts*.

**The App turns your smartphone into a discreet personal safety device for use during an emergency.**

## Differential Diagnosis

**Isabel app** is a differential diagnosis generator designed to ensure no diagnosis is overlooked. It is a web-based program designed for clinicians making a diagnosis, as well as medical students and residents honing their skills. It can assist in thinking through all possibilities in any case with diagnostic uncertainty.

The differential diagnosis process begins by entering patient data (age, gender, travel history) into the "clinical features" box on the homepage. Next, the user enters any abnormal clinical features, including the chief complaint, labs, vitals and comorbidities. Clicking the "Get Checklist" button generates a ranked diagnoses list organized by a color bar or "Likelihood Indicator": dark orange designating "most likely", through to light yellow representing "less likely." The list can be sorted by specialty or by red flags (conditions requiring immediate attention). Another tab lists drugs whose side effects may cause the symptoms.

Clicking on a possible diagnosis brings up a separate window – the "knowledge window" – containing evidence-based information on that particular condition.

Isabel Pro, which boasts a 96 percent accuracy rate, applies artificial intelligence pattern recognition software onto a database of more than 10,000 diagnosis presentations for all ages and specialties.

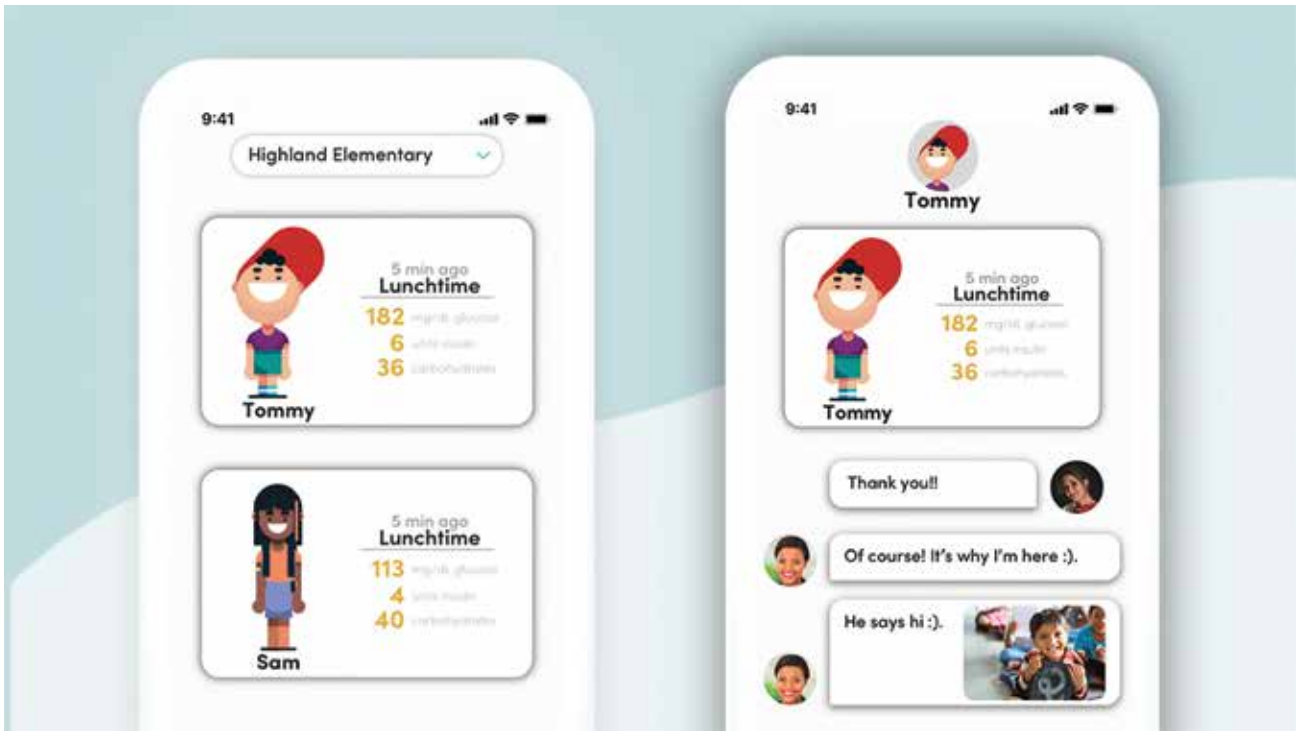
## Medline search

**PubMed app -** The free "PubMed Mobile" option provides access to a mobile friendly, simplified PubMed version which connects to the most up-to-date journal citations and abstracts from the complete PubMed database.

## Other useful apps

**Diagnostic tool for Autism Spectrum Disorders –** AIIMS, a modification of the INDT-ASD tool, was developed and validated by the Child Neurology Division of the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi. The app can diagnose autism in children between the ages of 1 and 14 yrs, with the help of questions such as whether the child talks about his/ her achievements and emotions without being asked, whether they like to play alone or in a group, or whether they make eye contact whilst talking.

PedNeuroAiims Diagnostics app - Diagnostic Tools for Epilepsy, Autism, Attention-deficit/




hyperactivity disorder (ADHD) and Neuromotor impairment (NMI). The free PedNeuroAiims Diagnostics app guides doctors through a set of questions and observations to diagnose whether a child has one of the above conditions. Each child that the paediatrician assesses using this tool can be archived in the app.

**Totsguide** - Totsguide is an online self-education portal for parents, doctors and guardians to take complete care of their child's development. One has to pay for features such as Track and Act and SCoPE.

**Pedi Crisis 2.0** - The Society for Pediatric Anesthesia (SPA) presents Pedi Crisis 2.0! As an interactive version of the SPA critical event checklists, crucial details for these 26 paediatric critical events are now just a 'tap' away on your pocket device! Quick reference drug dosage summaries are available for each emergency. Enter the patient's weight to automatically calculate patient-specific dosages.

**Surakshith**: App on personal safety for 6-18 years olds. Children learn Body Safety Rules, Safe - Unsafe Touch, how to identify Safe Adults. Stories help children learn No - Go - Tell mantra & understand that the perpetrators of abusive actions are solely responsible for them. Blame & shame are discussed. The Internet Safety & Digital Citizenship features are for older children.

Suraksha App by Bengaluru City Police SOS is a fully integrated personal safety *app* with Policing. The *App* turns your smartphone into a discreet personal safety device for use during an emergency. A call to the police service can be triggered by simply activating the SOS button, featured as an icon on your cell phone.

**ADR PvPI** - PvPI adverse drug reaction reporting android application. Using PvPI adverse reporting android application, healthcare professionals or consumers can instantly report any suspected Adverse Drug Reaction to PvPI from any part of India.

The Pharmacovigilance Program of India (PvPI) was launched with a broad objective to safeguard the health of the 1.27 billion people of India. Adverse drug Reactions (ADRs) are reported from all over the country to PvPI, which also work in collaboration with the global ADR monitoring centre (WHO-UMC), Sweden, to contribute in the global ADR data base. PvPI monitors ADRs among the Indian population and helps the regulatory authority of India (CDSCO) in taking decisions for the safe use of medicines. PvPI invites all health

care professionals and patients/consumers to join in their mission to promote patient safety.

**ABG Calculator: Blood Gas App** - With an intuitive design and easy-to-read display, ABG Calculator makes it a breeze to answer even the most complex blood gas problems in seconds. Features:
- Fast, accurate input using the dial
- Expected Lab values
- Easy Reset

This ABG app has been "stress tested" against 100+ triple acid-base ABG problems.

**Bone age assessment app** - This application allows one to evaluate, by visual comparison of a radiograph, what is the age of a paediatric patient, based on the maturity status of his/her bones.

**The Glasgow Coma Scale Android App** is an must-have app. An intuitive interface leads a great list of features. The Glasgow Coma Scale Android app is routinely used in the ER and during ICU rotations, for assessing brain injury. The scale checks for a patient's motor response, verbal response, and eye opening, and objectively creates a score. This app includes options to select grade or severity of symptoms based on eye, verbal, or motor response. The app has an intuitive user interface with instructions in a Q&A format. The app is free and performs quick calculations. It lacks medical information correlating GCS scores with disease conditions, but is perfect for ER and neurology rotations.

**The Glasgow Coma Scale Android app is routinely used in the ER and during ICU rotations, for assessing brain injury. The scale checks for a patient's motor response, verbal response, and eye opening, and objectively creates a score.**

## Journals

**'Read by QxMD'** provides a single place to keep up with new medical & scientific research, read outstanding topic reviews and search PubMed. Read's simple interface drives discovery and seamless access to medical literature by reformatting it into a personalized digital journal.

**Features**:
- Get full text PDFs with one tap on payment
- Keep up with the latest new research that will impact your practice
- Browse through 1000s of outstanding topic reviews
- Search millions of articles from PubMed and its database of outstanding topic reviews
- Read ones favorite journals or browse article collections.
- Share articles with colleagues over email, Twitter and Facebook
- Organize and review your personal collection of articles

## Podcasts

Podcasts are ready for download multimedia audio or video files. The audio files usually take the MP3 format.

The term 'podcasts' is an amalgam of 'iPod' and 'broadcasts'. These files or collection of files are accessed via syndication feeds through RSS readers, and so, unlike broadcasts, they are not necessarily streamed at a certain time but rather can be subscribed to and accessed at any time using a device. NEJM, for example, offers some headlines and news in the form of podcasts and RSS feeds

# Features

**WHEN DEPRESSION SNEAKS UP ON MENOPAUSE**

*Page 52*

"THE RECOGNITION OF THE IMPACT OF SOCIAL ISOLATION ON THE REST OF MENTAL HEALTH IS GOING TO HIT EVERYONE REALLY SOON."

By **Natasha Gilbert**

# WHEN DEPRESSION SNEAKS UP ON MENOPAUSE

# Fluctuating levels of estrogen during a period known as perimenopause can wreak havoc on the mental health of women in midlife. Diagnosis and treatment have been elusive despite symptoms as serious as suicidal thoughts.

In May of 2018, Tabitha Bird spent a memorable day with her eldest son at a comic book convention in London. Later that evening, after she made sure that her two younger kids were safely tucked up in bed, Bird gathered every sleeping tablet, antidepressant, anti-anxiety med and ibuprofen pill she could find and walked out of the house. She drove to a nearby store where she bought a big bottle of water and some acetaminophen. Then she stopped in an empty industrial park and began to take the lot.

Bird woke up from a coma four days later. The 47-year-old, from a town in West Sussex in the UK, now attributes her suicide attempt and the depression leading up to it to perimenopause — the time in most women's lives when menstrual cycles become irregular and fertility wanes.

During this transition, many women experience a suite of changes, including hot flashes, disrupted sleep and mood swings. Some breeze through perimenopause with little difficulty, but many — about 45 percent to 68 percent — experience depression, symptoms of which can include low mood, a loss of interest in things and even thoughts of suicide. Women with a history of depression, like Bird — who also suffered with it while pregnant — are the most vulnerable. During perimenopause, they are twice as likely to experience debilitating full-blown depressive disorder than women who haven't had past episodes.

As researchers probe for reasons why some women fall prey to depression at this time and others don't, a leading candidate has emerged: widely fluctuating levels of the sex hormone estrogen. Estrogen directs fertility, but mounting research shows that it also holds sway on parts of the brain involved in regulating emotion and stress.

"There is quite strong evidence that there is a special kind of depression linked to the hormonal changes," says Pauline Maki, a researcher in the neuropsychiatry of women's health at the University of Illinois at Chicago.

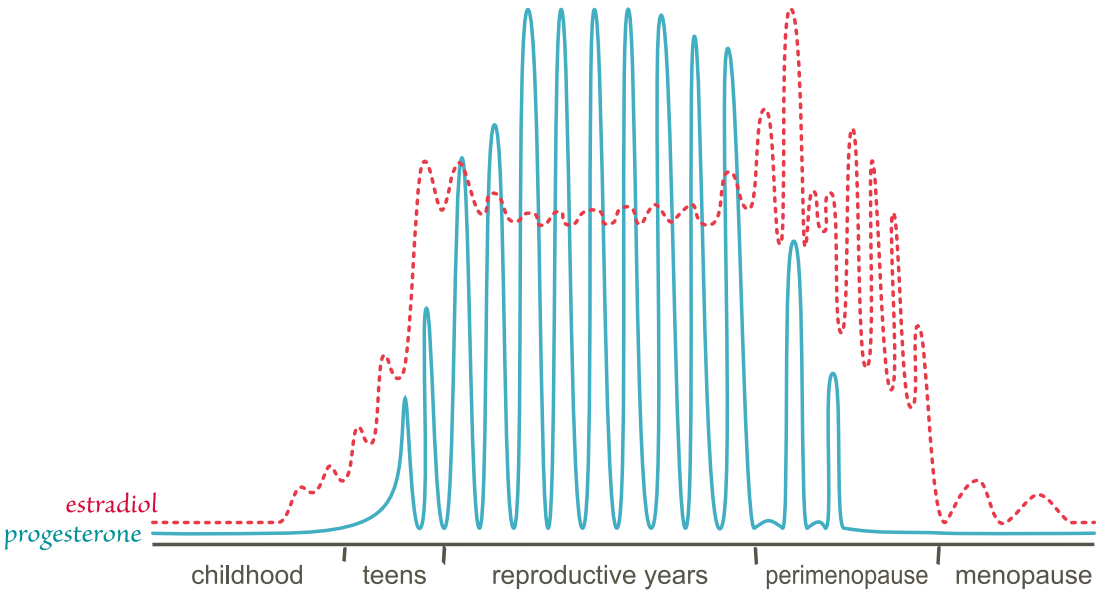
The good news is that women don't have to just grin and bear it. Over the past decade, several large studies have shown that perimenopausal depression can be effectively treated. Antidepressants and psychotherapy work for many women. And a body of research finds that hormone therapy — in which patients take a low dose of estrogen or other hormones to supplement what the body makes — can treat or even prevent depression symptoms.

But many doctors are reluctant to prescribe hormone therapy amid concerns that it could raise the risk of heart attacks and breast cancer, a finding from a decades-old study that focused on post-menopausal women. Science has since clarified instances in which the treatment's benefits outweigh the risks, yet these lingering fears have stymied both research and women's use of hormone therapy in treating depression, says Maki.

And medical education often skips over menopause, producing doctors who don't know how to recognize the menopause transition, let alone connect it to episodes of depression, researchers say. Consequently, many people suffer because their mental health symptoms are missed, dismissed or ineffectively treated.

Bird was one such patient. She had experienced a plethora of symptoms that included hot flashes, disturbed sleep and changes in mood and menstrual flow in

Estrogen levels fluctuate wildly during perimenopause, a period preceding menopause.




L. BRIDEN / HORMONE REPAIR MANUAL 2021

(Estradiol, shown in the chart, is the strongest of the three naturally occurring estrogens. Also shown are levels of progesterone, another reproductive hormone.)

the lead-up to her suicide attempt. "Looking back now, I can see this was the beginning of my perimenopause," she says. But her doctor, she adds, doubted that it was linked to her depression.

Maki says it is all too common for health-care workers to overlook symptoms of the menopause transition. "The major problem in women's midlife health right now is that providers just aren't trained. It's quite appalling."

## Estrogen and the brain

Many women are accustomed to the emotional ups and downs that can accompany the run-up to menstruation. These monthly mood swings coincide with fluxes of a suite of hormones. These include progesterone, which is made in the ovaries and encourages the uterus lining to thicken, and other hormones regulating ovulation that are secreted from the brain's pituitary gland and hypothalamus.

But of all the reproductive hormones, estrogen is the most formidable. It's produced in the ovaries, and its levels rise and fall over the typical 28-day menstrual cycle to direct local tasks such as helping to spark ovulation and preparing the lining of the uterus for fertilization. Estrogen also orchestrates an array of activities in the brain.

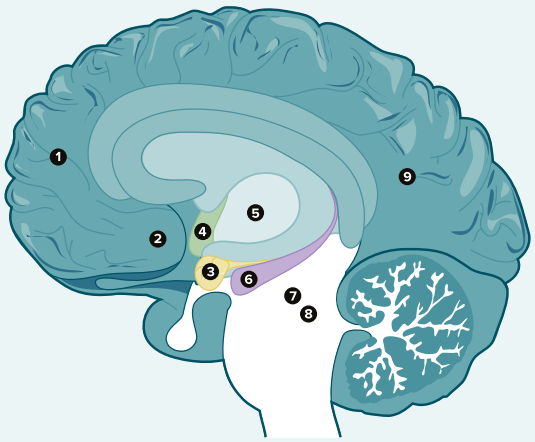
As women transition toward menopause, these hormonal fluxes become extreme. Estrogen, in particular, can ebb and flow wildly — soaring to levels three times that of younger women or dipping to post-menopausal lows. The brain feels the impact of these fluctuations as much as five years before the rest of the body does, says Jayashri Kulkarni, a psychiatrist specializing in women's mental health at Monash University in Australia.

"The brain is the first organ that starts to register the menopausal process. It's happening before the hot flashes, before the menstrual cycle starts to change," Kulkarni says.

In the past decade, a clearer picture has emerged of estrogen's role in the brain. Estrogen receptors are present in the hippocampus, amygdala and hypothalamus, regions that are important to cognition, emotional processing and stress responses. Before perimenopause hits, the hormone, in the form of circulating estradiol, helps keep these systems running smoothly, says Paul Newhouse, who investigates cognitive and neuropsychiatric disorders at Vanderbilt University in Nashville, Tennessee.

Estrogen's buffering effect plays out in a number of ways. The hormone can influence mood by way of its positive effect on serotonin, the mood-regulating neurotransmitter, for example. Animal studies show that

## Estrogen receptors in the brain




1. **Prefrontal cortex** Executive function and working memory
2. **Basal forebrain** Learning and memory
3. **Amygdala** Emotion and motivation
4. **Hypothalamus** Regulation of temperature, sleep, energy, balance and food intake
5. **Thalamus** Sensory integration
6. **Hippocampus** Information processing and short term memory
7. **Raphe nucleus** Serotonergic system: affect and mood
8. **Locus coeruleus** Adrenergic system: attention, arousal and anxiety
9. **Posterior cingulate** Default mode network, working memory, task preparation

Estrogen receptors are present in many parts of the brain, as shown in this picture, suggesting that the hormone has broad influences.

estrogen increases the density of serotonin receptors in rats' brains, potentially helping buoy mood. It also seems to enhance the antidepressant effects of selective serotonin-reuptake inhibitors (SSRIs) in women.

Estrogen also helps to balance activity between areas of the brain that traffic in emotions: The hippocampus and the amygdala are both involved in recognizing, assessing and responding to emotional information. Neuroimaging studies show that when estrogen levels dip, the amygdala becomes more active. This may make negative information seem more important and can prolong the body's response to stress. When estrogen levels are higher, images show that the hippocampus is more active, helping to regulate the amygdala and creating a more balanced emotional and cognitive response. Overall, estrogen appears to temper women's response to negative and stressful information, helping them react with a more positive outlook.

"High estrogen levels essentially 'protect' the activity of these regulatory structures" in the brain, says Newhouse, coauthor of an overview on estrogen's role in depression in the 2019 Annual Review of Clinical Psychology.

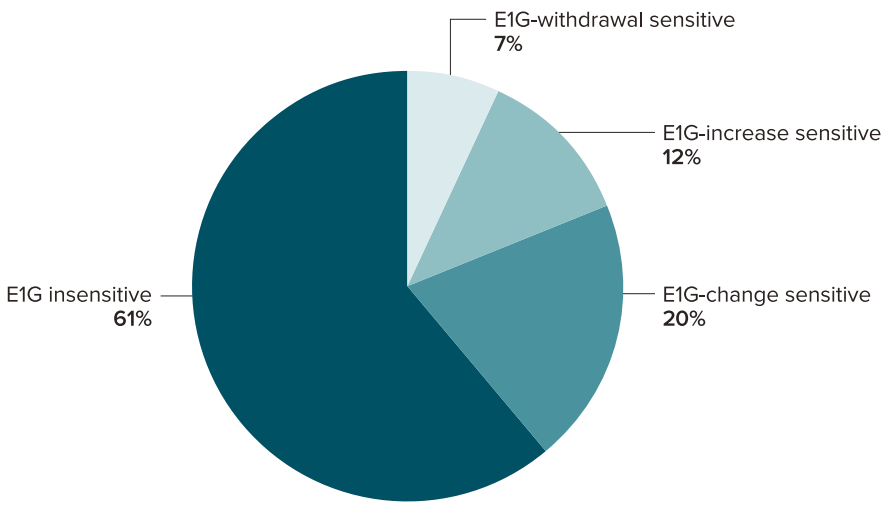
But during the transition to menopause, that changes, he says. Women who are already vulnerable to depression may plunge back into it when they lose the buffering effects of estrogen. This includes women who experience severe depression and anxiety during their menstrual cycle, who may also be more likely to experience depression due to the sudden hormonal shifts of pregnancy and childbirth. Similarly, it is these women who are more likely to be struck by perimenopausal depression.

Bird falls into this group. She suffered sudden crippling bouts of depression and anger while pregnant with her two youngest children. Usually she is very easygoing, she says. But one day, while carrying her daughter, she stepped out in front of a bus with the intension of ending her own life. And while pregnant with her youngest son, she felt so angry that she threw a cup of coffee at her husband.

"I'm not that type of person," she says. "It does completely change your personality."

A landmark study published in JAMA Psychiatry in 2015 demonstrated that women with a history of depression are more sensitive to changing levels of estrogen and that those fluctuations can trigger severe depression. Healthy postmenopausal women, some with a history of depression and some without, were given estradiol through a skin patch. After three weeks, some women from each group got a placebo instead of the estradiol. Roughly 80 percent of the women who had suffered with severe depression in the past experienced a recurrence when estrogen was withdrawn and they were switched to the placebo, the National Institutes of Health study found. But those with no history of

## As estrogen levels change, women's responses vary




Some women appear to be more sensitive than others to changes in estrogen levels. In this study, researchers gauged changes in estradiol over a 12-week period by measuring levels of estrone-3-glucuronide (E1G), a urinary metabolite of estradiol. At the same time, the researchers assessed the participants' depression symptoms. Most women felt no mood shift as E1G fluctuated (E1G insensitive). But one-fifth of the women reported depression when E1G rose or fell (E1G change sensitive). A small number were sensitive to either an E1G rise (E1G increase sensitive) or drop (E1G withdrawal sensitive).

depression were fine when the estrogen was taken away.

Maki says that this "very important study" clearly suggested a link between loss of estrogen and depression and that there is a category of women who are sensitive to estrogen withdrawal.

More recent studies support the link between depression and estrogen during perimenopause. Researchers from Brigham and Women's Hospital and Harvard Medical School in Boston, and colleagues, measured estrogen levels in blood serum of 50 women, ages 35 to 56, over a period of eight weeks. The most variable estrogen levels were linked to greater depressive symptoms, the team reported in the Journal of Clinical Endocrinology & Metabolism in 2020. A follow-up study found that feelings of irritability are common among mildly depressed perimenopausal women.

Researchers are also learning more about the group of women whose mood is susceptible to estrogen fluctuations. A recent study suggests that estrogen-sensitive women fall into three groups: those whose mood slumps when estrogen declines, those who feel low when estrogen rises high and those who are sensitive to large shifts in either direction. The study could help explain other conflicting results concerning whether sensitivity to high versus low estrogen levels plays a role in perimenopausal depression.

The reasons for the differences between women's response to estrogen aren't clear, says Newhouse. But some researchers suggest it may be down to variations in the way enzymes biosynthesize estradiol or the hormone's role in protein production.

Of course, estrogen isn't the only factor tipping people over the edge to a depression in midlife. For some, the perimenopausal years can feel like life is piling on. Hot flashes and poor sleep can worsen mood. Careers near their peak, and children fly the nest, or parents grow older, requiring more care. These challenges can drag people down, says Maki. Women who don't have a partner or are in unhappy relationships are also more likely to feel low during the menopause transition. Some evidence suggests that women of color are more at risk, as are those with less formal education or who are financially hard-up, research shows.

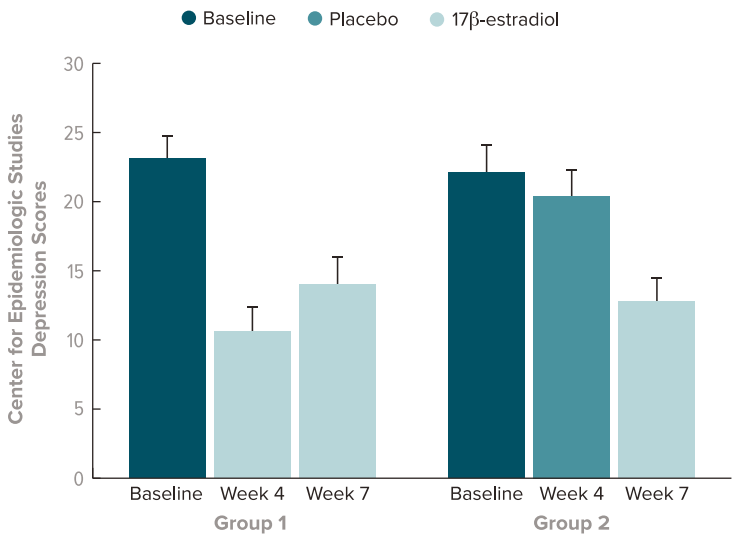
While estrogen clearly can play a critical role in whether someone sinks into perimenopausal depression, for others a mix of shifting hormones, changes in social circumstances and physiological issues like hot flashes, may tip the scales, says Kulkarni. Doctors need to be aware of these interacting factors to recognize and treat depression during the menopause transition, she says.

## Beating the blues

As scientists learn more about who is susceptible to perimenopausal blues, they are also coming to grips with how best to help people beat it.

For those who are affected by estrogen withdrawal, topping up estrogen can help. Several small but strong

## Estrogen improves mood in depressed women




In a study, 16 women (left) received three weeks of estradiol therapy, which helped to alleviate perimenopausal depression. Their mood remained lifted for a further three weeks of estradiol treatment. Fifteen additional women (right) were given a placebo for three weeks and showed no improvement in their frame of mind. Their mood began to rise when given estradiol after week four.

studies demonstrate that replenishing the body's estrogen — alone and in combination with progestin, a synthetic hormone with properties similar to progesterone — is effective at treating depressive symptoms experienced during the transition to menopause. For example, a trial of 50 perimenopausal women with depression found that 68 percent felt their symptoms improve with estradiol, a team reported in JAMA Psychiatry in 2001.

Other research shows estrogen can boost or speed up the mood-enhancing effects of antidepressants. A small study of 17 women between the ages of 40 and 60 years who were taking antidepressants for major depression found that estrogen significantly improved their mood compared with a placebo. A larger study of 293 depressed post-menopausal women found that mood improved in nearly 84 percent of those who used an antidepressant and hormone therapy compared with 63 percent of those who just used antidepressants.

Hormone therapy may even help prevent the onset of depression. Research has found that a regimen of estrogen administered as a skin patch, along with a pill containing a synthetic hormone with an identical structure to progesterone, is better than a placebo at preventing depression in 172 women in their perimenopausal and early postmenopausal years. Just 17 percent of women on the hormone therapy developed depression compared with 32 percent taking the placebo.

Estrogen therapy also boosts low mood following a hysterectomy that removes both ovaries, known as surgical menopause. It is even in helpful in treating post-traumatic stress, research suggests. A study found that women who had been sexually assaulted were less likely to experience intrusive flashbacks of the trauma if they took emergency contraceptive containing estrogen and progestin compared to progestin only or none at all.

"This is a genius study," says Newhouse. "It suggests that estradiol levels can impact how the brain responds to, organizes and maybe even remembers extremely stressful events."

Despite estrogen's clear mood-enhancing effects, its use in treating depression is still controversial, partly because a large, highly publicized study from nearly 20 years ago found that hormone therapy raised the risk of breast cancer, heart attacks and stroke. Since then, research has clarified that the increased cardiovascular risks are mainly in cases of older women who re-started combined estrogen and progestin therapy after menopause.

Research is also working to clarify the connection between hormone therapy and breast cancer. Most menopause specialists' interpretation of the data is that hormone therapy is linked to a small increase in breast cancer risk, raising the risk to a level slightly above that attributed to drinking one glass of wine per day (annually, one additional case of breast cancer for every 1,000 users).

But the type of hormone therapy can affect the risk. Studies have found that estrogen taken alone can protect against breast cancer. But estrogen is typically prescribed only to women who have undergone a hysterectomy as too much of the hormone can cause uterine cancer; women with an intact uterus take a combined therapy of estrogen and progestin or synthetic bioidentical progesterone. A recent large study of women with an average age of 63 years found that out of 8,506 women taking combined estrogen and progestin, some 584 developed breast cancer, compared to 447 cases among 8,102 women taking a placebo. But the study did not find that significantly more women died from breast cancer as a result of taking combined hormone therapy.

These findings are backed up by another recent study that shows an increase in rates of breast cancer in women taking estrogen and progestin. Both studies contradict earlier findings of a higher risk of breast cancer among all types of hormone therapy.

The stigma attached to hormone therapy has stuck around, Kulkarni says.

And there are still questions about how best to use estrogen to treat depression, says Jennifer Gordon, a clinical psychologist at the University of Regina in Saskatchewan, Canada, who studies how female reproductive hormones affect mood. For example, it's not clear if estrogen works better when administered as a skin patch or orally, she says. The US Food and Drug Administration has not approved estrogen to treat low mood and depression. The North American Menopause Society suggests that estrogen can augment antidepressants but urges caution in the hormone's use, advising doctors to limit prescription to people who have additional symptoms such as hot flashes.

Doctors reach for antidepressants first because most people who suffer with major depression during midlife have a history of the disease, says Maki, who helped write the society's menopause guidelines.

This is Bird's experience. She is now taking very strong antidepressants that worked for a while, though they made her feel numb. But recently, she adds, feelings of anger and irritability started to sometimes break through. Bird had come to accept that she will take antidepressants for the rest of her life but began to wonder whether hormone therapy could help too.

Kulkarni is concerned that a failure in care for women in midlife is contributing to high suicide rates in this age group. In Australia, the highest female suicide rate is among women aged 45–49. A similar trend is seen in the US and the UK. Kulkarni wants to see hormone therapy play a more prominent role for people like Bird and others with a similar psychological history. "If you recognize there's a hormone factor that's leading to depression, common sense says it needs to be a hormone solution," she says.

But medication and hormones are not the only option, says Gordon. Her research shows that yoga and meditation can help to prevent depressive symptoms as the menstrual cycle wanes, even for people with a history of severe depression.

## A push for more awareness

Despite a range of treatments available, many people in need are not reached. Stephanie Faubion, a clinical researcher specializing in menopause at the Mayo Clinic in Jacksonville, Florida and medical director of the North American Menopause Society, says that a major hurdle is that doctors of a broad array of specialties are not taught about menopause. Those specialties include psychiatry and gynecology. Consequently, a number of related midlife health issues are often overlooked, she says. "Depression is one of many symptoms that goes undiagnosed and untreated at this time."

Some medical societies are now working together to increase awareness of changes common around menopause and to improve diagnosis and treatment of related problems, says Faubion. For example, the American Medical Women's Association, which aims to support women working in medicine and women's health issues, is advocating for clinicians to hold regular health visits for people as they approach menopause. The North American Menopause Society contributes to this initiative, and it also provides training for healthcare practitioners. Faubion says the society has pushed for more menopause education in medical school curriculums and doctors' residency programs but it has been a hard sell.

In the meantime, people may at least help themselves by seeking care when they are struggling with their mood, says Faubion. There are even technologies and apps that track reproductive changes that can help individuals understand their symptoms and make a case to their healthcare provider.

But if doctors dismiss concerns that low mood could be linked to perimenopause, people must not give up, says Bird. She says she was discouraged that her doctor didn't do more for her — still, she persisted and has since seen a menopause specialist who prescribed hormone replacement therapy.

"You need to go back to the doctor," she says. "Don't let them fob you off."

# Case Reports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As the patient had diffuse proliferative glomerulonephritis, with massive proteinuria and renal failure, he was started on Prednisolone 60mg/day (1.5 mg/kg/day). Renal functions improved gradually after initiation of steroids.

# *Scedosporium Apiospermum* as a Rare Cause of Allergic Fungal Rhinosinusitis (AFRS)

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**Abstract**: Over the past few decades, allergic fungal rhinosinusitis (AFRS) has become increasingly defined. Rhinosinusitis cases caused by *Scedosporium spp*. are not very common. So far, very few such cases have been reported worldwide1-5. We report a case of AFRS by *Scedosporium spp*. in an immunocompetent female. The patient underwent functional endoscopic sinus surgery (FESS) and remains on regular follow-up, showing positive signs of recovery.

**Keywords:** Allergic fungal rhinosinusitis, *Scedosporium apiospermum*, functional endoscopic sinus surgery

## INTRODUCTION

*Scedosporium apiospermum* is a ubiquitous fungus. The clinical importance of this fungus is mostly seen with immunocompromised hosts and rarely in immunocompetent patients. It can present with a broad clinical spectrum. Hereby, we report a case of *Scedosporium apiospermum* infection-causing rhinosinusitis, a rare clinical entity in an immunocompetent female.

## CASE REPORT

A 63 yr old female presented with a complaint of left side facial pain (maxillary region) which had been present for 1yr. There was no history of nasal blockage, nasal discharge, fever or headache. The patient was also given an opinion from a dentist but experienced no improvement. On examination, the nasal cavity was found to be clear, with no significant nasal secretions or discharge. There was significant maxillary sinus tenderness on the left side on palpation.

An X-Ray-PNS showed complete haziness in the left maxillary sinus. A CT-PNS scan (plain) showed that the nasal septum was deviated towards the right side, with a bony spur towards the right side. Bilateral inferior turbinate hypertrophy was evident. Mucosal thickening was seen in the left maxillary sinus, with occlusion of the ostium, and sinus wall thickening and sclerosis suggestive of chronic left maxillary sinusitis. Possible erosion of the floor of the maxillary sinus was seen at the site of an absent molar tooth. Mucosal thickening was seen in the right sphenoid sinus. The patient underwent left side functional endoscopic sinus surgery (FESS) only. The left maxillary sinus was opened and found to be full of a fungal element, which was sent for fungal culture. The sinus was cleaned completely.

On biopsy, direct KOH mounts revealed the presence of hyaline thin septate hyphae. The fungal culture from the sinus tissue biopsy was identified as *Scedosporium apiospermum*. The patient is kept on regular follow-up and continues with a daily alkaline nasal douche. As per follow-up visits, the left maxillary sinus is healing well.

## DISCUSSION

Allergic fungal rhinosinusitis (AFRS) is a distinct type of chronic rhinosinusitis (CRS), accounting for between 5 and 10 percent of all CRS cases. AFRS

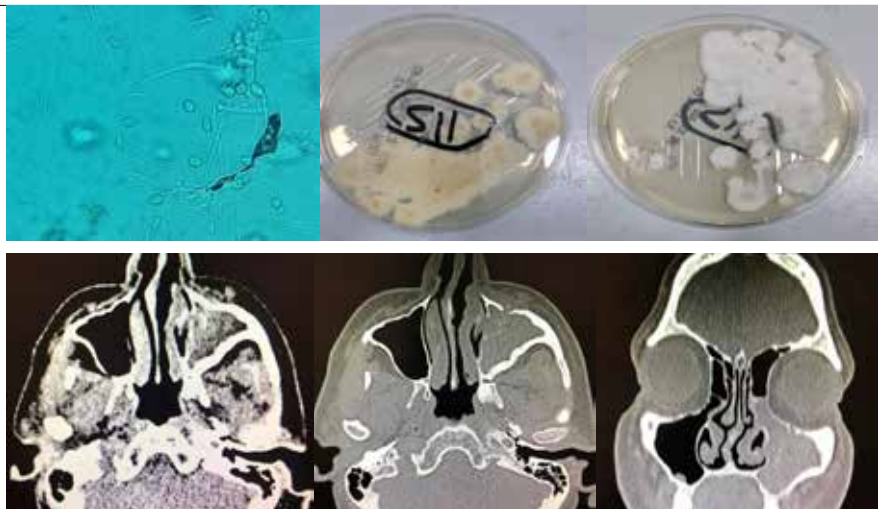
is believed to result from chronic, intense allergic inflammation directed against colonizing fungi. Patients with AFRS are immunocompetent and show evidence of allergy to one or more fungi. Definitive diagnosis is usually confirmed after sinus surgery.

The diagnostic criteria for AFRS vary among authors, but most widely accepted are the 5 criteria described by Bent and Kuhn[6]: (1) type 1 hypersensitivity to fungi; (2) nasal polyposis; (3) characteristic radiographic finding of serpiginous areas of high attenuation; (4) eosinophilic mucin; and (5) a positive fungal stain.

*Scedosporium spp.* are found in soil and polluted or stagnant waters. Although these organisms are commonly considered agents of phaeohyphomycosis, the hyphae are hyaline. Infection occurs most often in the upper and lower extremities, but may occur on any exposed parts of the body.

*Scedosporium spp.* can infect subcutaneous tissues, muscle, tendon and bones, as well as lungs, sinuses, eyes, the central nervous system and other body sites. *Scedosporium spp*. are the most common cause of fatal lung and central nervous system infections complicating near-drowning accidents in immunocompetent victims. Disseminated infection is most commonly seen in immunocompromised patients. Invasive Scedosporium lung disease in immunocompromised patients may clinically resemble invasive pulmonary aspergillosis. Patients with cystic fibrosis have a high frequency of colonization by *Scedosporium spp*. or chronic infection in the form of fungus balls in the lower respiratory tract, but seldom with progression to locally invasive disease or dissemination.

Diagnosis of infections caused by *Scedosporium spp*. is made using radiological and microbiological tests. In microscopy, the appearance of this fungus is similar to common hyaline hyphomycetes, therefore the final diagnosis of scedoporiosis is based on isolation of the fungus in culture[7]. In the present case, the final diagnosis of this infection was made on the basis of tissue biopsy culture isolation of *Scedosporium apiospermum*.



Accurate and prompt diagnosis of *S. apiospermum* is essential, as this organism can be often misidentified as other moulds such as *Aspergillus spp*. and *Fusarium spp.* These three genera are angioinvasive, and have non-pigmented, slender, septate hyphae 2–4 µm in width. *Scedosporium spp*. can be differentiated by their more irregular branching pattern, compared to the orderly dichotomous 45° angle branching observed in Aspergillus, and also by their production of ovoid conidia with truncated bases, which can be confused with yeast.

Identification of the fungus by culture is crucial because of the variable susceptibility of *S. apiospermum* to amphotericin B and other antifungal agents. *Scedosporium spp.* are inherently resistant to amphotericin B and frequently, though unpredictably, resistant to azoles[8]. The broad-spectrum azole voriconazole is the drug of choice for *S. apiospermum* infections.

Prompt clinical suspicion in patients of chronic sinusitis with suspicious signs and symptoms and timely sampling of the adequate patient specimens and processing of samples by microscopy and culture examination will help early diagnosis and management of these patients. Successful treatment involves a combination of surgical and medical management.

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# Cerebellar stroke presenting with positive head impulse test and centripetal nystagmus

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Cerebellar strokes are one of the sinister causes of 'acute vestibular syndrome'(AVS)[1]. In an emergency setting, it is crucial to differentiate between central and peripheral causes of AVS. The head impulse, nystagmus, and test of skew (HINTS) protocol helps in differentiating between the two[2]. Stroke at some specific locations can present with a positive head impulse test (HIT)[3], and signs such as gaze-evoked nystagmus (with fixation) or skew deviation can be absent. In such a scenario, other central signs can help to differentiate a central from a peripheral cause.

We are presenting a case wherein the HINTS score favoured a peripheral lesion, but other central signs, including centripetal nystagmus without fixation and severe postural instability, helped in diagnosing the stroke. A 66-year-old hypertensive and diabetic man presented with a history of sudden onset rotatory vertigo, associated with nausea and vomiting, which had lasted for three days. The vertigo was spontaneous, and was associated with an imbalance of gait. He complained of swaying to either side on standing. The ocular alignment was normal during an alternate cover test. He showed no spontaneous nystagmus with visual fixation in light. The bedside HIT was positive to the left, with catch-up saccades. The patient also showed significant postural instability, with a tendency to fall to the right while standing. The findings of the HINTS testing are shown in Table 1.

Video-oculography (Cyclops, Medtech. Bengaluru, India) showed normal saccades (Fig 1A, 1B). Smooth pursuit movement was saccadic in both the horizontal and vertical planes (Fig 2A,2B). The patient additionally showed centripetal nystagmus during lateral gazes in darkness, i.e. right-beating nystagmus during leftward gaze, and left-beating nystagmus during rightward gaze.

An urgent CT of the brain (Fig-3) showed a hypodense lesion in the territory of the right medial posterior inferior cerebellar artery (m-PICA). MRIs confirmed the diagnosis (Fig-4).

The patient was managed on an antiplatelet and a statin. He showed a significant recovery in 10 days. Positive HIT implies a deficit in the vestibulo-ocular reflex (VOR)[4]. Thus, a positive HIT in our case suggested the possibility of a peripheral lesion. However, positive HITs were also reported in patients with central lesions e.g. in patient with unilateral cerebellar lesion[5]. Indeed, in a cross-sectional study, three of eleven patients with acute vestibular syndrome had a stroke and positive HIT[3]. The authors proposed three different mechanisms defining the positive HIT in these particular cases. For vestibulo-cerebellar stroke, a positive HIT was considered to be the result of mass effect on the vestibular nucleus or eighth nerve root-entry zone in the pons. In a pontocerebellar stroke, a positive HIT was speculated to be due to labyrinthine infarction. In extensive case of Ponto-cerebello-labyrinthine stroke, a positive HIT was thought to be due to the infarction of the vestibular nucleus or eighth nerve root-entry-zone in the lateral pons[2]. However, positive HITs have also been

**Fig-1A.** Horizontal saccades

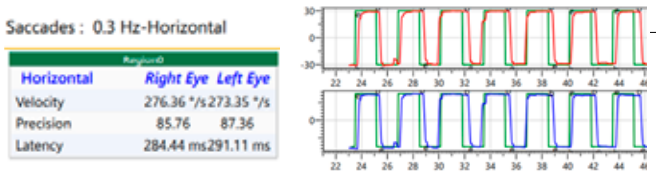


**Fig-1B.** Vertical saccades

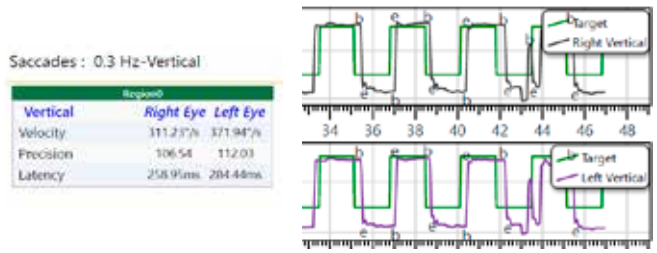


**Fig-2A.** Horizontal smooth pursuit

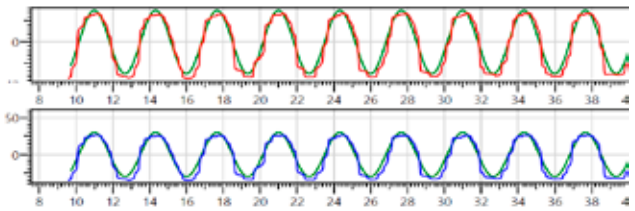

**Fig-2B.** Vertical smooth pursuit

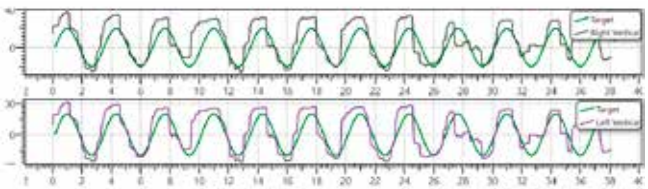

**Table 1.** HINTS (Head-Impulse-Nystagmus-Test-of-skew) testing

| | HINTS positive in the central cause | HINTS positive in the peripheral cause | HINTS positive in the index case |
|---|---|---|---|
| Head impulse test | Negative | Positive | Positive |
| Nystagmus | Fast-phase alternating | Unidirectional nystagmus | Centripetal nystagmus without fixation |
| Cover-uncover test | Refixation Skew deviation | No refixation No skew deviation | No skew deviation |
| Hearing test | Hearing loss | Normal | Normal |

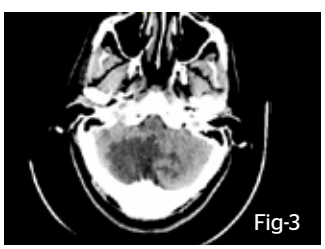
Fig-3

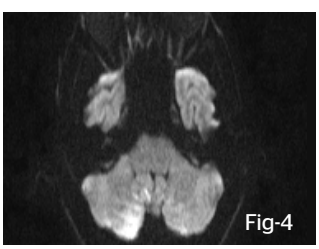
Fig-4

**Fig-3. The axial CT scan images demonstrate a large region of hypoattenuation involving the right cerebellar hemisphere as well as patchy areas of infarction in the left cerebellar hemisphere.**
**Fig-4. The diffusion-weighted images through the posterior fossa demonstrated restricted diffusion in right cerebellar hemisphere involving the right cerebellar tonsil (Ventral paraflocculus), biventral lobule (Dorsal paraflocculus), gracile lobule and inferior semilunar lobule. There were patchy areas of diffusion hyperintensities within the left biventral lobule (Dorsal paraflocculus), gracile lobule and inferior semilunar lobule – consistent with an acute infarct in the territory of the bi-hemispheric right posterior inferior cerebellar artery.**

observed in lesions restricted to the cerebellar nodulus or flocculus.[6,7] A lesion involving the nodulus could have been the cause of the positive HIT in our patient. Thus, contrary to conventional perception, the presence of a positive HIT cannot be exclusively relied upon, and additional clinical features must be considered.

The cerebellum plays a significant role in maintaining optimal ocular motor performance. Centripetal nystagmus during eccentric gaze may reflect instability in the gaze-holding networks, similar to the velocity-increasing waveforms of downbeat nystagmus seen in some patients with cerebellar disease. Impairment of postural control is a common finding in posterior circulation strokes. Thus, significant postural instability, the presence of vascular risk factors and centripetal nystagmus hinted towards a central cause of AVS. This case highlights that clinical evaluation suggesting a peripheral lesion should never be taken in isolation, and needs to be correlated with other associated central signs.

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# A rare case of incidentally diagnosed Compound Hb S/beta-thalassemia at 40 years of age

Sickle cell disease has a high clinical importance because of its worldwide distribution, prevalence and variety of manifestations.

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**Key Words**

Compound sickle cell β thalassemia, chronic anaemia, sickle cell disease, haemoglobin electrophoresis, Hb S, Hb F, delayed diagnosis, Oman.

**Abbreviations**

Hb S- sickle haemoglobin; Hb A- normal adult haemoglobin; Hb F- foetal haemoglobin; SCD- sickle cell disease; MCV- mean corpuscular volume; MCH- mean corpuscular haemoglobin; MCHC- mean corpuscular haemoglobin concentration; RDW- red cell distribution width; RBC- red blood cell.

## ABSTRACT

Sickle cell diseases are generally diagnosed in infancy or early childhood, with very few cases being undiagnosed until early adult life. Moreover, with a high percentage of Hb S in the blood, the patients present with variety of manifestations related to the disease. We present a rare case of a woman with minimal symptoms and no diagnosis of compound sickle cell β thalassemia up to the age of 40. The only complaint was of intermittent dull pain in the right upper abdominal quadrant. Haemoglobin electrophoresis revealed 92.5% Hb S

## INTRODUCTION

Sickle cell disease has a high clinical importance because of its worldwide distribution, prevalence and variety of manifestations.[1] It is a genetic haematologic disorder presenting clinically at different years of childhood or early adulthood,[2-4] depending on the genotype[5,11] and the percentage of Hb S and Hb F in the peripheral blood.[5] The genetic status of sickle cell disease includes a homozygous form, a heterozygous form and a double heterozygous form.[1] Homozygous sickle cell anaemia cases have a higher percentage of Hb S, and totally lack normal adult haemoglobin (Hb A).[1] These cases are typically diagnosed in the first year of life.[1] The heterozygous forms have smaller percentages of Hb S and Hb A and rarely have phenotypic expression of the trait.[1] The double heterozygous forms have varied amounts of Hb S and the other haemoglobin variant.[1] These cases can vary clinically from being asymptomatic to having severe complications.[1] Cases with high Hb S typically are diagnosed early in life.[2-4]

**Case Presentation**: A 40-year-old nulliparous woman presented to the hospital with the complaint of right upper quadrant abdominal pain of three-day duration. The pain was dull in nature and she had experienced similar episodes in the past. It was not related to food intake, nausea or vomiting. Her vitals were normal, with no tenderness or organomegaly on abdomen examination. The patient's haemoglobin was 6.7 gm/dl, with low mean corpuscular parameters as shown in **Table 1**. The WBC and platelet counts were within normal limits. The serum iron was low (4.3 µmol/L), with normal ferritin (103.9 ng/ml). The total iron binding capacity and serum LDH were within normal limits. The peripheral blood smear showed a microcytic hypochromic blood picture with a few sickle-shaped cells and target cells with mild polychromasia (**Figure 1**). The corrected reticulocyte count was 6%. A screening test using sodium metabisulphite was positive for sickling. The conjugated bilirubin was slightly raised (5.1 µmol/L), while the total bilirubin was within normal limits. The other liver function tests, renal function tests and urine examination were normal. There were no abnormalities identified on CT abdomen and pelvis. Haemoglobin electrophoresis revealed 92.5% Hb S (shown in **Table 2**). High performance liquid

**Table 1.** Haemogram with RBC parameters

| Sr. No. | Parameter | Patient value | Reference range |
|---|---|---|---|
| 1 | Haemoglobin | 6.5 gm/dl | 12-14.5 gm/dl |
| 2 | Haematocrit | 24.5% | 36-51% |
| 3 | MCV | 56 fl | 80-100 fl |
| 4 | MCH | 14.8 pg | 26.5-33.5 pg |
| 5 | MCHC | 26.5 gm/dl | 31.5-35 gm/dl |
| 6 | RDW | 26.4% | 11-15% |

**Table 2.** Haemoglobin electrophoresis

| Sr. No. | Haemoglobin composition | Patient's value (%) | Reference range (%) |
|---|---|---|---|
| 1 | Hb A | 1.2 | 96.5-98.5 |
| 2 | Hb $A_2$ | 3 | 1.5-3.5 |
| 3 | Hb F | 3.3 | <2.0 |
| 4 | Hb S | 92.5 | 0 |

**Table 3.** High Performance Liquid Chromatography

| Sr. No. | Haemoglobin composition | Patient's value (%) | Reference range (%) |
|---|---|---|---|
| 1 | Hb $A_0$ | 9 | 96.5-98.5 |
| 2 | Hb $A_2$ | 4.4 | 1.5-3.5 |
| 3 | Hb F | 2.6 | <2.0 |
| 4 | Hb S | 84 | 0 |

chromatography (HPLC) showed 84% Hb S (shown in **Table 3**). With these findings, it was concluded that the case is one of compound sickle cell/ $\beta^+$ thalassemia (Hb S/$\beta^+$-Thal). It was found later that the patient's haemoglobin had been in the range of 6-7 gm/dl for many years.

## DISCUSSION

The Sultanate of Oman has a high prevalence of hereditary haemoglobinopathies.[6] Of these, SCD has a prevalence of 0.46%.[7] In 40% of the cases of SCD, the diagnosis is made in the first year of life.[8] This is based on the clinical manifestations and severity of the disease.[1,8] The

clinical manifestations result from polymerization of the deoxygenated haemoglobin, which forms the molecular basis of sickling. This, in turn, is dependent upon the concentrations of Hb S and other haemoglobin variants. Thus, the severity of the disease is determined primarily by the genotype.[1,11]

In Hb S/$\beta^+$-Thal, variable amounts of Hb A dilute Hb S and prevent polymerization of Hb S.[11] Hb F has an inhibitory effect on sickling,[1,13] however, the Hb A and Hb F in our case were 1.2% and 3.3%, respectively, which are minimal in comparison with the 92.5% Hb S. This fails to explain the mild, intermittent symptoms in our case. There have been a few case reports of incidentally diagnosed doubly heterozygous Hb S/ $\beta^+$-Thal patients in the prior literature, but all have

**Table 1.** Haemogram with RBC parameters

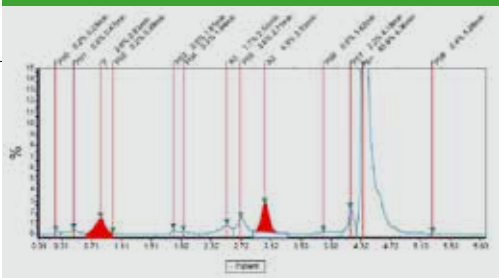

**Figure 2:** High Performance Liquid Chromatography.

been diagnosed at a younger age than our patient.[12,13,14]

Haemoglobin electrophoresis for the patient's parents, and genetic analysis for the patient, are mandatory to determine the genotype of the disease. Hence, the patient was referred to a government hospital for further evaluation and treatment. The patient has ten siblings, none of which have any symptoms of any haemoglobinopathy.

## CONCLUSION

High Hb S% is generally related to severe clinical manifestations and early diagnosis. However, there can be mild clinical presentation with high Hb S%, which can lead to delayed diagnosis, as in our case. Hence, premarital, prenatal and new-born screening should be carrid out to rule out haemoglobinopathies. Newborns with the disease should be offered genetic tests and appropriate treatment.

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# Negative Pressure Pulmonary Oedema/Haemorrhage

An interesting case of negative pressure pulmonary oedema/ haemorrhage in a 17-year-old who underwent emergency laparoscopic appendicectomy using LMA Supreme.

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## BACKGROUND

Negative pressure pulmonary oedema (NPPE) is no doubt a rare and life-threatening complication following general anaesthesia in mostly otherwise healthy individuals. It has an incidence of 0.05-0.1% of general anaesthesia cases with tracheal intubation[1]. An undiagnosed NPPE carries a risk of around 40% mortality[2]. Typically it is witnessed immediately after extubation (76%) or during the initial airway management (26%) in patients with head and neck tumours, Ludwig angina or laryngospasm. It can follow elective general anaesthesia after intubation while the patient is on a ventilator. However, rarely, as in our case, the onset is delayed. Our patient developed cough and haemoptysis with expectoration in the recovery room 3 hours after an uneventful removal of the patient's LMA at emergence and following monitoring in the Post-Anaesthesia care unit (PACU). The patient woke from sleep with bouts of cough and haemoptysis with expectoration of about 6 tablespoons of frank blood causing respiratory distress with desaturation.

Negative pressure pulmonary haemorrhage (NPPH) is a rarer phenomenon, which is due to increased pulmonary capillary transmural pressure, leading to stress failure of the blood-gas barrier at the level of the capillaries, resulting in alveolar haemorrhage[3]. Based on the patient's clinical findings, lab works, X-rays, CT scans and history, we suspect the diagnosis of negative pressure pulmonary oedema leading to alveolar haemorrhage.

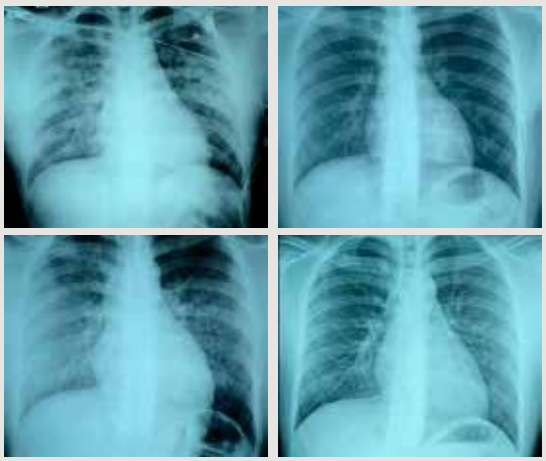
## CASE REPORT

A 17-yr-old young man weighing 71 kg was referred to our hospital for emergency laparoscopic appendicectomy, having been diagnosed and referred from outside of the hospital after he developed abdominal pain. He had no comorbid conditions. He had never had any previous surgery and his baseline peripheral oxygen saturation was 100% on ambient air. The patient was preoxygenated with 100% oxygen through a face mask for 3 minutes. The patient was pre medicated with glycopyrrolate 0.2mg. Anaesthesia was induced with Propofol 200mg and rocuronium 40mg was given for muscle relaxation. An atraumatically Supra glottic airway device (LMA Supreme™ no:4) was inserted. Anaesthesia was maintained with oxygen, air, and sevoflurane. Paracetamol 1g intravenous was given for analgesia.

The intra-operative course was unremarkable. The patient was haemodynamically stable with minimal blood loss and was easily ventilated and oxygenated. A total of 750 ml lactated Ringer's solution was administered during the 120-min surgical procedure. At the end of surgery (90 minutes), the patient was reversed with neostigmine 2.5mg and glycopyrrolate 0.4 mg. The LMA was removed after eye-opening, when spontaneous breathing with a good tidal volume was established. The patient was comfortable in the PACU for an hour. He was later moved to the recovery room.

After exactly 2 hours in the recovery room, the patient woke from sleep and started coughing vigorously. It was 3 hours after the LMA

Xray Images on Day 1, Day 2, Day 4 & Day 12 respectively- showing radiological resolution of bilateral diffuse pulmonary infiltrate over time.



was removed at emergence. The patient started coughing, had haemoptysis and later started to expectorate frank blood for the next 45 mins to a total of about 6 tablespoons.

Physical examination revealed crepitations bilaterally covering more than 70% of the lung fields. The bedside monitor revealed a heart rate of 144/min, RR of 42/min, SpO2 of 85% and BP of 130/84. He was started on Oxygen 10 litres via anon-rebreather mask and IV fluids were stopped. He was given IV furosemide 40mg in divided doses monitoring the blood pressure over the next 45 mins along with IV hydrocortisone 200mg, suspecting NPPE/ NPPH clinically.

With a non-rebreather mask delivering 10 litres initially and later up-titrating to 15 litres and the IV therapy, the patient's cough and haemoptysis reduced and the SpO2 gradually increased to 94%. The patient was conscious, alert and obeying commands well. His heart rate reduced to 120/min and his respiratory rate to 30/min. The cough with expectoration and haemoptysis stopped and he was shifted for higher imaging with oxygen support after explaining the plan to the patient who felt better and agreed.

A CT-PA was done with the following report: "In view of clinical settings, the revealed alveolar opacities are likely to represent diffuse alveolar haemorrhage versus pulmonary oedema without sizeable emboli in the main pulmonary arteries". Thus, the findings correlated with the clinical suspicion of NPPE/NPPH.

The patient was shifted to the Intensive Care Unit and continued on oxygen 15 litres via non-rebreather mask. A 2D ECHO done bedside revealed a normal study. His oxygen requirement reduced over the next 8 hrs and he was tapered to 6 litre oxygen via Hudson mask. Clinically his condition was much better. The chest X-ray taken the next day showed fluffy bilateral opacities. The lungs were but clear on auscultation. After 24 hrs, the patient was off oxygen and a saturation of 99% was maintained on room air. A chest X-ray repeated after 24 hours showed better radiological clearance.

Routine labs showed elevated WBC and CRP which was addressed with piperacillin, tazobactam and metronidazole. Hydrocortisone and furosemide IV was continued for a day. A SARS-CoV-2 RNA PCR test was reported negative and so was the antibody test. The baseline haemoglobin was 15gms. There was a drop in Hb to 12gms the next morning. The patient's LFT, RFT, platelet count, peripheral smear, LDH and uric acid levels were normal. Routine urine tests showed he did not have haematuria or proteinuria. His coagulation profile, including fibrinogen levels, was all within normal limits. As part of the work up for granulomatosis with polyangiitis, both C-ANCA and P-ANCA were sent, which came back as negative. The ANA profile was also normal. HIV antibody (ELISA) was non-reactive, hepatitis B and C serologies were also negative. A bronchoscopy was deferred, as the cough with expectoration of blood stopped and he clinically improved. Additional work up for alveolar haemorrhage was unrevealing.

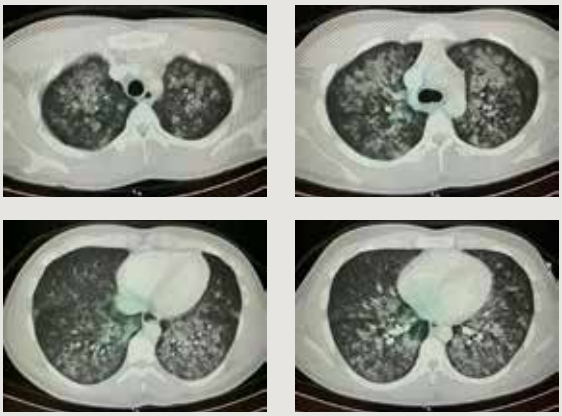
The patient was continued on nebulisation for 2 days and IV antibiotics for 4 days. The labs started showing downward trends and the WBC counts normalised. USG Abdomen & Pelvis repeated the next day showed normal post-operative findings only. He was discharged from the ward on post-operative day 4, to follow up with the internal medicine team on an OP basis. A chest X-ray taken prior to discharge was normal.

## DISCUSSION

NPPE was first described by Oswalt *et al.* in 1977[1]. It is non-cardiogenic in origin. There are two types. Type 1 NPPE is due to an upper airway obstruction, and is rapid in onset. Type 2 NPPE occurs mostly after the surgical intervention of a long-standing airway obstruction[4-5]. Type 1 NPPE, which we faced here, has two variants. It classically occurs within one hour[6] of a precipitating event or, as in our case, it can manifest within 6 hours[7]. Both manifest with restlessness, cough, expectoration, tachycardia, tachypnoea, progressive desaturation and, on auscultation, as crepitations. These start at the lung base and extend up to the lung apex like a florid pulmonary oedema picture, with pink frothy secretion/ haemoptysis, even to the expectoration of multiple spoons of blood due to alveolar haemorrhage, as in our case.

NPPE results from the generation of high negative intrathoracic pressure following spontaneous breathing against any upper airway obstruction. The most common aetiology reported is laryngospasm during intubation or during recovery after anaesthesia[8]. Individuals with obesity and difficult intubation, from a young age group with athletic build, or a paediatric group, or receiving oral,

**CT Images showing alveolar opacities which are likely to represent diffuse alveolar haemorrhage**



nasal or pharyngeal growth surgeries, are more at risk for NPPE. The factors which cause NPPH include negative pulmonary pressure, inhaled anaesthetic, smoking and positive airway pressure from coughing[9].

Our patient was young, and developed cough and haemoptysis with expectoration of about 6 tablespoons of frank blood, possibly due to alveolar haemorrhage. Laryngospasm as the result of post-obstructive pulmonary oedema was the probable cause in our patient, and this accounts for approximately 50 % of cases of NPPE during intubation or after anaesthesia during the post-operative phase[1,8,10]. Clinical examination, signs and symptoms, auscultation and bed side monitor parameters remain the best mode of diagnosis of NPPE with a history of surgery using general anaesthesia. Chest X-ray can confirm the clinical judgement with findings of pulmonary oedema or Alveolar haemorrhage. In the current times of COVID-19, due to the desaturation faced, higher imaging methods like CT or CTPA can clear doubts and allay fears if available. In our case, these confirmed diffuse bilateral alveolar airspace opacities.

Common differential diagnoses of NPPE include fluid overload, multiple other causes of airway obstruction, acute non-cardiogenic pulmonary oedema, aspiration pneumonitis, COVID-19 phenotypes, anaphylaxis, lung manifestation of vasculitis and pulmonary embolism.

NPPE is managed with supplemental oxygen therapy, preferably using a non-rebreather mask, after propping up the patient. Certain cases may need high flow nasal oxygen, non-invasive ventilation, or even possible reintubation. This is relevant to patients with persisting distress and deterioration in sensorium owing to hypoxia, in cases which are picked up, diagnosed and managed late.

Treatment is mostly supportive. In our case, we used furosemide IV in divided doses, though its effectiveness is uncertain[11], along with IV hydrocortisone and oxygen via a nonrebreather mask, with which the patient clinically improved. The patient was continued on hydrocortisone and furosemide for a day with a nebulised bronchodilator and steroids.

## CONCLUSION

NPPE should be the one of the first differential diagnosis entertained in mind whenever a patient post-general anaesthesia, who is using laryngeal mask ventilation[12] or an endotracheal tube post-extubation, develops acute respiratory distress suddenly, or within 6 hrs of extubation[7]. The diagnosis can be made at the bedside of the patient in respiratory distress clinically, by auscultation and from monitor parameters. This enables us to initiate immediate treatment, which will relieve the patient and reduce morbidity and mortality. When picked up immediately and managed aggressively, this benign condition results in a full recovery over 12-24 hrs. NPPE, though mostly seen as bilateral, has also been reported as being infrequently unilateral[13].In this case, the biggest support was the young patient's parents who were calm and trusted us with our counselling and management which enabled us to work up the case, stabilise and discharge him fast.

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Case Report

# COVID-19 Positive Term Neonate—Acute Fulminant Presentation

SARS-CoV-2 belongs to the beta coronavirus genus, and causes the acute infection labelled COVID-19. Reports of neonatal cases are still sparse, though we are seeing more case reports describing the clinical course in infected neonates.

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## CASE PRESENTATION

Our case presented at 2 days of life to the emergency department, with one episode of fever, poor oral intake, reduced activity and vomiting. The infant was born by ventouse-assisted vaginal delivery at 38 weeks gestation, with birth weight 2.77 kg, without any complications. The mother had an uneventful antenatal course, and both of the parents were asymptomatic. The baby was discharged home within 24 hours of life, and was active and feeding well at home according to the parents. The following day, the baby presented with the above symptoms.

The physical examination showed that the baby was febrile and lethargic. There was reduced responsiveness, with decreased tone and sluggish reflexes, suggestive of encephalopathy. The anterior fontanelle was normal, with no evidence of abnormal movements or focal neurological deficit. The baby was tachycardic but, at that stage, had normal perfusion and cardiac rhythm. The baby was also tachypneic, with increased labour in breathing. The rest of the examination findings were normal. There was no obvious dysmorphism and the head circumference was 32 cm.

The baby was admitted to the Neonatal intensive care unit (NICU), kept in a negative pressure isolation room, and started on a humidified high flow nasal cannula. Baseline investigations, a sepsis screen and SARS-Cov2 PCR were sent for analysis. The baby was started on IV antibiotics in view of suspected early onset sepsis with meningitis. One episode of a right focal seizure was noted, following which the baby was started on phenobarbitone.

The fever persisted, along with the ongoing seizure and worsening neurological status. The baby was electively intubated and ventilated. Acyclovir (intravenous) was administered in view of the worsening clinical and neurological status.

During the ICU stay, the baby was noted to have cardiac arrhythmia, with the rhythm suggestive of ventricular tachycardia. A 2D Echo conducted by a paediatric cardiologist was suggestive of severe cardiac dysfunction, with mitral & aortic regurgitation, an ejection fraction of 30%, and normal structure & normal coronaries. The arrhythmia was managed with antiarrhythmic treatment (adenosine & amiodarone). Subsequently, the baby developed hypotension with worsening perfusion, for which inotropic support was initiated and escalated in view of persistent hypotension.

The SARS-CoV-2 testing, based on a polymerase chain reaction assay processed at an authorised laboratory in Dubai, UAE, returned positive after the day of admission. In view of the above history and clinical presentation, a presumptive diagnosis of viral myocarditis with severe cardiac dysfunction secondary to COVID-19 was considered.

Troponin I, D-dimer, CPK and ferritin levels were all markedly elevated, with severe lactic acidosis. The baby had refractory coagulopathy,

in spite of multiple fresh frozen plasma transfusions. Blood and urine cultures showed no growth. A chest X-ray showed bilateral haziness of the lung fields. CT-chest could not be performed in view of the poor clinical condition.

There was an unexplained neonatal death of the father's previous baby, born of a different partner (first wife), possibly due to asphyxia and sepsis. This baby's mother had lost two male siblings of hers during their neonatal period. This marriage was not consanguineous. In view of the previous deaths in both the mother's family and the father's first baby, the possibility of an inborn error of metabolism as the underlying condition, with COVID-19 infection precipitating the clinical worsening, was considered as a likely possibility. The newborn screening was normal except for an elevated alanine level (the lab confirmed that urea cycle disorders could not be fully excluded). The baby had elevated serum ammonia levels with very low urea levels.

In view of the worsening cardiac function & arrhythmia, the baby was shifted to another centre for intensive paediatric cardiac support and monitoring. The baby continued to have deteriorating cardiac function with hypotension, requiring maximum inotropic support. The baby was empirically started on intravenous immunoglobulin (IVIG) & methylprednisolone, which did not generate any positive response. There was severe metabolic acidosis which was intractable to treatment, and though ammonia levels reduced during this period without specific treatment, they remained high. Serum amino acids showed high levels of multiple amino acids (unclear implication) and the organic acids in the urine and serum were normal. Cranial ultrasound findings revealed a grade I germinal matrix haemorrhage on the left side.

The baby expired on day 7 of life with severe cardiac dysfunction & refractory hypotension. The repeat COVID-19 test performed using ET suction (possibly an inadequate sample) on the day prior to demise was reported as negative.

## DISCUSSION

COVID-19 infections are rapidly increasing all over the world. The UAE government has been very active in trying to limit the spread, and, though the number of cases has been rising (to close to 50000 cases by the end of June), the mortality rate has not been very high here. We are reporting this case as a neonatal COVID-19 patient presenting with acute cardiac dysfunction and a fulminant course. There are very few reports of deaths in the newborn period related to COVID-19 infection, and though this case could be complicated by a possible inborn error of metabolism, since we lack clear results to confirm the same, the possibility of a significant role of the infection has to be considered, given the very high procalcitonin levels and ferritin/D dimer levels and reducing ammonia levels, despite no specific treatment targeting the same.

The possibility of vertical transmission was considered as the baby became symptomatic with in first 48 hours of life, although the mother was asymptomatic. The prevalence of COVID-19 in the community was high during this time period. As per the literature available to date, most babies with COVID-19 infections are asymptomatic or mildly symptomatic. To date there is only one reported case of a neonatal COVID-19 infection with cardiac involvement, published, by Amiraskari *et al.*[1] This case was considered to be vertically transmitted, with the mother having tested positive for COVID-19. This baby was symptomatic from birth with respiratory distress, and later developed cardiac dysfunction. This case was reported as congenital myocarditis and was treated with inotropes, IVIG and diuretics. The baby gradually improved and was discharged home after 10 days of life[1].

In our case, we noticed abnormal lab parameters including markedly elevated ferritin, troponin I, D-dimer and CPK. All of these lab parameters are very much supportive of COVID-19 infection. Refractory coagulopathy was also noted in our case. The baby continued to have a fever throughout the hospital stay, which was managed symptomatically. All of the blood and urine cultures were sterile. Though the repeat COVID-19 test on day 6 of life (just prior to demise) from an ET suction sample was negative, there is a high possibility of this being a false negative. A third sample could not be sent due to the baby's demise.

Munoz et al. reported a 3-week-old neonate presenting with fever and lower respiratory symptoms, with significant chest radiographic changes2. The baby required ventilatory support and intercostal drain insertion for pneumothorax. The baby was treated with IV antibiotics and given a 5 day course of hydroxychloroquine and azithromycin[2].

Conclusion: There is limited information available on COVID-19 infection in neonates, and our case report could help to alert colleagues that a sick presentation is possible, especially as a trigger to a fulminant presentation with any predisposing condition (as in this case, where the possibility of inborn errors of metabolism contributing to the clinical condition could not be ruled out). Unfortunately, our case did not respond to all of the supportive measures we provided. We need to await further information from specific guidance on how best to successfully manage myocardial dysfunction in this condition.

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# Regulars

**Making Sense of Senses**
Medicine Nobel for Duo Who Discovered Biology of Senses.
*Page 72*

**Book Review**
*Page 74*

That first discovery led to identification of several other receptors. Just like there are receptors sensitive to heat, there are others that can sense coldness. And yet others, that can sense pressure. We now know several of these.

by **Amitabh Sinha**

# Making sense of senses

## David Julius and Ardem Patapoutian identified the mechanism through which touch detectors communicate with the nervous system. What are the implications of their research for medicine?

The five senses through which human beings perceive and experience the world around them are well known. The internal mechanisms inside the human body through which we become aware of, and respond to, light, sound, smell and taste have been fairly well-understood for several decades. The understanding of how we sense through touch – the perception of hot or cold, squeeze or strain or the feeling of physical pain – eluded scientists for long.

Until David Julius and Ardem Patapoutian, working independently in the United States, made a series of discoveries in the late 1990s and early 2000s to figure out the touch detectors in our body and the mechanism through which they communicate with the nervous system to identify and respond to a particular touch. For their ground-breaking research, which is still continuing, 66-year-old Julius and 54-year-old Patapoutian were declared joint winners of the 2021 Nobel Prize in Physiology on Monday.

Julius and Patapoutian have been awarded the prize "for their discoveries of receptors for temperature and touch". Simply put, they discovered the molecular sensors in the human body that are sensitive to heat, and to mechanical pressure, and make us "feel" hot or cold, or the touch of a sharp object on our skin.

**Medicine Nobel for duo who discovered Biology of senses.**

Artificial sensors are familiar in today's world. A thermometer is a very common temperature sensor. In a room, a table or bed would not be able to perceive changes in temperature even when they are exposed to heat, but a thermometer would. Similarly, in the human body, all the molecules do not sense heat when they are exposed to it. Only very specific proteins do, and it is their job to relay this signal to the nervous system, which then triggers an appropriate response. Scientists knew that such sensors must exist, but were not able to identify them until Julius discovered the first heat receptor.

"It was a very fundamental discovery. The identification of heat receptor by Julius in the late 1990s came through a very tedious scrutiny of hundreds of genes for their sensitivity to temperature. Today, we have very efficient computers

and models that can reduce the work, and fast-track the process, but in those days a lot of painstaking research was required. That first discovery led to identification of several other receptors. Just like there are receptors sensitive to heat, there are others that can sense coldness. And yet others, that can sense pressure. We now know several of these," said Dipanjan Roy, a neuroscientist at National Brain Research Centre in Manesar.

## The mechanism

The human ability to sense heat, or cold, and pressure is not very different from the working of the many detectors that we are familiar with. A smoke detector, for example, sends off an alarm when it senses smoke beyond a certain threshold. Similarly, when something hot, or cold, touches the body, the heat receptors enable the passage of some specific chemicals, like calcium ions, through the membrane of nerve cells. It's like a gate that opens up on a very specific request. The entry of the chemical inside the cell causes a small change in electrical voltage, which is picked up by the nervous system.

"There is a whole spectrum of receptors that are sensitive to different ranges of temperature. When there is more heat, more channels open up to allow the flow of ions, and the brain is able to perceive higher temperature. Similar things happen when we touch something extremely cold," said Aurnab Ghose, a neuroscientist at the Indian Institute of Science Education and Research in Pune.

Ghose said that these receptors were sensitive not just to external touch, but could detect temperature or pressure changes inside the body as well.

"When our body temperature deviates from the optimum level, for example, there is a reaction. The body makes an effort to revert to the optimum, or core, temperature. That happens only because the heat receptors are able to sense a change in temperature, and the nervous system tries to restore that," he said.

"But that is not all. When our urinary bladder is full, for example, the pressure in the bladder increases. This change in pressure is sensed by the pressure receptors and relayed to the nervous system which creates this urge to relieve oneself. Changes in blood pressure is sensed in a similar fashion, and remedial actions initiated... That is why the discoveries of these receptors are so fundamental to our understanding of how our body functions," Ghose said.

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## Therapeutic implications

Breakthroughs in physiology have often resulted in an improvement in the ability to fight diseases and disorders. This one is no different. As Sneha Shashidhara, a PhD in cognitive neuroscience, pointed out, the identification of these receptors opens up the possibility of regulating their functioning. For examples, there are receptors that make us feel pain. If these receptors can suppressed, or made less effective, the person had feel less pain.

"Chronic pain is present is a number of illnesses and disorders. Earlier, the experience of pain was a mystery. But as we understand these receptors more and more, it is possible that we gain the ability to regulate them in such a way that the pain is minimised," she said.

Ghose said, in fact, research in this field was already underway. "It is possible that the next generation of pain-killers would work in this fashion," he said, adding that there were several other therapeutic implications as well, including interventions that might be useful in treatment of diseases like cancer or diabetes

# Life Lessons From A Brain Surgeon

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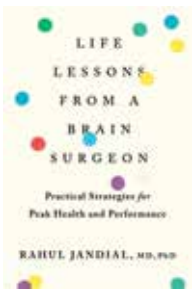


**Life Lessons From A Brain Surgeon: Practical Strategies for Peak Health and Performance**

Written By:
**Rahul JandialHarvest**

Publisher:
**Harvest Publications**

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Printed and published by Dr Gopakumaran Kartha on behalf of Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O, Cheranelloor, Kochi, Kerala- 682 027, India and printed at Anaswara Offset Pvt Ltd, Perandoor Junction, Elamakkara, Kochi - 682 026 and published at Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O, Cheranelloor, Kochi, Kerala- 682 027. Editor: Dr Boby Varkey Maramattom. RNI No: **KERENG/2019/77520**


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