First Edition

Faculty of Pharmacy
Zagazig University

Drug Information Centre Magazine 2020

Find your gift inside the issue

Guest of Honor
Professor Doctor
Tarek A. Okasha
Neuro-Psychiatric Complications of COVID-19

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Corona Virus Vaccines..All you need to know

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Neuro-psychiatric complications of COVID-19

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Magazine cover photo

Source*: NIH, National Cancer Institute (NCI),* Creator*: Daniel Sone (photographer)*

Opening Word

Dear Readers,

Since its early beginnings, the DIC has been working on establishing connection with its audience everywhere, alongside participating effectively to influence others.

Students, graduates, and everyone involved in the medical field is our top priority, even normal people in our community, starting from Zagazig University, Sharkia governorate, and hopefully Egypt as a whole. This publication is our way of doing so.

Thus, with our eyes targeted towards levering up awareness level and keeping you updated regarding everything novel in the medical field in general, and drugs specifically, we are pleased to issue the *first edition* of the DIC magazine.

Rich as it is in great topics, focusing on what interests you the most, we are all confident of meeting your expectations.

Hope it reaches you all well

DIC Team

Vision of the DIC

The Drug Information Center, affiliated to *Pharmacy Practice department*, Faculty of Pharmacy, Zagazig University will become one of the outstanding regional centers delivering scientific, evidence-based drug information.

Mission of the DIC

Through our work, we look up to becoming one of the most acknowledged drug information centers in whole Egypt, and to reach a wide variety of members in our community. To achieve these goals, we bear the following responsibilities:

1. Provide medication information to patients & health care professionals by effectively searching, retrieving, and evaluating literature and appropriately communicating and applying the information to the patient care situation.
2. Develop and participate in efforts to prevent therapeutic misadventures, including adverse medication events, medication error reporting, and analysis programs.
3. Develop methods of changing patient and provider behaviors to support optimal medication use.
4. Publish newsletters to educate patients, families, and health care professionals on medication use.
5. Educate providers about medication-related policies and procedures.
6. Coordinate investigational medication services.
7. Provide continuing-education services to the health care professional staff.
8. Educate pharmacy students and residents.

Guest of Honor

Professor Doctor

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Professor Doctor

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Our reputable guest of honor writes us on

"Neuro-Psychiatric Complications of COVID-19"

Neuro-Psychiatric Complications of COVID-19

***Source**: The Economic Times, English edition, E-Paper*
https://economictimes.indiatimes.com/magazines/panache/covid-19-may-cause-neurological-complications-like-stroke-psychiatric-problems-like-dementia-in-patients/articleshow/76643116.cms

“This pandemic Is not a race , but a marathon”

Introduction

In January 2020 the World Health Organization (WHO) declared the outbreak of a new coronavirus disease, COVID-19, to be a Public Health Emergency of International Concern. WHO stated that there is a high risk of COVID-19 spreading to other countries around the world.

In March 2020, WHO made the assessment that COVID-19 can be characterized as a pandemic.

The COVID-19 pandemic influences both physical and mental health, the economy, as well as social life on all continents. It is strongly recommended that during the time of pandemics not only to care for the ill, but also for the healthy, those in isolation and even the medical teams dealing with the ill.

It has previously been shown that during times of crises, suicide rates may momentarily decrease , but when the immediate crisis has passed suicide rates increase. Suicide occurs when an imbalance of risk and protective factors on individual, relationship, community and society levels takes place. Due to the likely increase of suicide during and after the COVID-19 pandemic, the evidence-based suicide preventive methods must be strengthened.

Mental Health Risks Due to Social Isolation

In response to the current coronavirus crisis, most state and local governments are requiring closures of non-essential businesses and schools, prohibiting large gatherings, and requiring quarantines for travelers, in addition to encouraging social distancing.

A majority of states have declared mandatory stay-at-home orders for all but non-essential workers.

A broad body of research links social isolation and loneliness to both poor mental and physical health. Attention to the widespread experience of loneliness as a public health concern in itself, pointing to its association with reduced lifespan and greater risk of both mental and physical illnesses.

Burnout and Strain among Frontline Health Care Workers

Many hospitals across the country are overwhelmed with the growing number of patients presenting with symptoms of COVID-19. This has rapidly increased the demands on frontline health care workers, some of whom are also overwhelmed by supply shortages.

Research indicates that burnout in hospitals is particularly high for young registered nurses and nurses in hospitals with lower nurse-to-patient densities. Physicians are also prone to experiencing burnout and can consequently suffer from mental health issues, including depression and substance use. The risk of suicide is also high among physicians.

The pandemic is likely to have both long- and short-term implications for mental health and substance use. Those with mental illness and substance use disorders pre-pandemic, and those newly affected, will likely require mental health and substance use services.

Limited access to mental health care and substance use treatment is in part due to a current shortage of mental health professionals, which will likely be exacerbated by the COVID-19 pandemic. While some mental health providers are increasing their use of telemedicine in light of social distancing, not all are able to do so.

Neuropsychiatric Complications of COVID 19 in the UK as an example

Broad clinical syndromes associated with COVID-19 were classified as a ***cerebrovascular event*** (defined as an acute ischaemic, haemorrhagic, or thrombotic vascular event involving the brain parenchyma or subarachnoid space).

Altered mental status (defined as an acute alteration in personality,

behavior, cognition, or consciousness), and ***peripheral neurology*** (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle), or others.

In a surveillance study carried out in the UK 77 (62%) of 125 patients presented with a cerebrovascular event, of whom 57 (74%) had an ischaemic stroke, nine (12%) an intracerebral haemorrhage, and one (1%) CNS vasculitis. (31%) of 125 patients presented with altered mental status, comprising nine (23%) patients with unspecified encephalopathy and seven (18%) patients with encephalitis. The remaining 23 (59%) patients with altered mental status fulfilled the clinical case definitions for psychiatric diagnoses as classified by the notifying psychiatrist or neuropsychiatrist, and 21 (92%) of these were new diagnoses. Ten (43%) of 23 patients with neuropsychiatric disorders had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and four (17%) had an affective disorder. 18 (49%) of 37 patients with altered mental status were younger than 60 years and 19 (51%) were older than 60 years. Whereas 13 (18%) of 74 patients with cerebrovascular events were younger than 60 years versus 61 (82%) patients older than 60 years.

In order to try to ameliorate the psychological sequel of the pandemic on the general population and special groups the WHO offered some advice.

a) Messages for the General Population

1) COVID-19 has and is likely to affect people from many countries, in many geographical locations. When referring to people with COVID-19, do not attach the disease to any particular ethnicity or nationality. Be empathetic to all those who are affected, in and from any country. People who are affected by COVID-19 have not done anything wrong, and they deserve our support, compassion and kindness.

2) Do not refer to people with the disease as “COVID-19 cases”,“victims”, “COVID-19 families” or “the diseased”. They are “people who have COVID-19”, “people who are being treated for COVID-19”, or

"people who are recovering from COVID-19", and after recovering from COVID-19 their life will go on with their jobs, families and loved ones. It is important to separate a person from having an identity defined by COVID-19, in order to reduce stigma.

3) Minimize watching, reading or listening to news about COVID-19 that causes you to feel anxious or distressed; seek information only from trusted sources and mainly so that you can take practical steps to prepare your plans and protect yourself and loved ones. Seek information updates at specific times during the day, once or twice. The sudden and near-constant stream of news reports about an outbreak can cause anyone to feel worried. Get the facts; not rumours and misinformation. Gather information at regular intervals from the WHO website and local health authority platforms in order to help you distinguish facts from rumors. Facts can help to minimize fears.

4) Protect yourself and be supportive to others. Assisting others in their time of need can benefit both the person receiving support and the helper. For example, check by telephone on neighbors or people in your community who may need some extra assistance. Working together as one community can help to create solidarity in addressing COVID-19 together.

5) Find opportunities to amplify positive and hopeful stories and positive images of local people who have experienced COVID-19. For example, stories of people who have recovered or who have supported a loved one and are willing to share their experience.

6) Honour carers and healthcare workers supporting people affected with COVID-19 in your community. Acknowledge the role they play in saving lives and keeping your loved ones safe.

b) Some advice for health care workers

7) Feeling under pressure is a likely experience for you and many of your colleagues. It is quite normal to be feeling this way in the current situation. Stress and the feelings associated with it are by no means a reflection that you cannot do

your job or that you are weak. Managing your mental health and psychosocial well-being during this time is as important as managing your physical health.

8) Take care of yourself at this time. Try to use helpful coping strategies such as ensuring sufficient rest and respite during work or between shifts, eat sufficient and healthy food, engage in physical activity, and stay in contact with family and friends. Avoid using unhelpful coping strategies such as use of tobacco, alcohol or other drugs. The COVID-19 outbreak is a unique and unprecedented scenario for many workers, particularly if they have not been involved in similar responses. Even so, using strategies that have worked for you in the past to manage times of stress can benefit you now. This is not a sprint; it is a marathon.

9) Some healthcare workers may unfortunately experience avoidance by their family or community owing to stigma or fear. This can make an already challenging situation far more difficult. If possible, staying connected with your loved ones, including through digital methods, is one way to maintain contact. Turn to your colleagues, your manager or other trusted persons for social support – your colleagues may be having similar experiences to you.

10) Use understandable ways to share messages with people with intellectual, cognitive and psychosocial disabilities. Where possible, include forms of communication that do not rely solely on written information.

11) Know how to provide support to people who are affected by COVID-19 and know how to link them with available resources. This is especially important for those who require mental health and psychosocial support. The stigma associated with mental health problems may cause reluctance to seek support for both COVID-19 and mental health conditions.

c) Some advice for Team Leaders or Managers in Health Facilities

12) Keeping all staff protected from chronic stress and poor mental health during this response means that they will

have a better capacity to fulfill their roles. Be sure to keep in mind that the current situation will not go away overnight and you should focus on longer-term occupational capacity rather than repeated short-term crisis responses.

13) Ensure that good quality communication and accurate information updates are provided to all staff. Rotate workers from higher-stress to lower-stress functions. Partner inexperienced workers with their more experienced colleagues. Ensure that outreach personnel enter the community in pairs. Initiate, encourage and monitor work breaks. Implement flexible schedules for workers who are directly impacted or have a family member affected by a stressful event.

14) Ensure that staff is aware of where and how they can access mental health and psychosocial support services and facilitate access to such services. It is important that the above provisions and strategies be in place for both workers and managers, and that managers can be role-models for self-care strategies to mitigate stress.

15) Orient all responders, including nurses, ambulance drivers, volunteers, case identifiers, teachers and community leaders and workers in quarantine sites.

16) Manage urgent mental health and neurological complaints (e.g. delirium, psychosis, severe anxiety or depression) within emergency or general healthcare facilities. Appropriate trained and qualified staff may need to be deployed to these locations.

17) Ensure availability of essential, generic psychotropic medications at all levels of health care. People living with long-term mental health conditions or epileptic seizures will need uninterrupted access to their medication, and sudden discontinuation should be avoided.

d) Some advice for Carers of Children

18) Help children find positive ways to express feelings such as fear and sadness. Every child has his or her own way of expressing emotions. Sometimes engaging

in a creative activity, such as playing or drawing can facilitate this process. Children feel relieved if they can express and communicate their feelings in a safe and supportive environment.

19) Keep children close to their parents and family, if considered safe, and avoid separating children and their careers as much as possible. Ensure that during periods of separation, regular contact with parents and carers is maintained, such as twice-daily scheduled telephone or video calls or other age-appropriate communication (e.g. social media).

20) Maintain familiar routines in daily life as much as possible, or create new routines, especially if children must stay at home. Provide engaging age-appropriate activities for children, including activities for their learning. Where possible, encourage children to continue to play and socialize with others, even if only within the family when advised to restrict social contact.

21) During times of stress and crisis, it is common for children to seek more attachment and be more demanding on parents. Discuss COVID-19 with your children in an honest and age-appropriate way.

e) Some advice for Older Adults, People with Underlying Health Conditions and their carers

22) Older adults, especially in isolation and those with cognitive decline/dementia, may become more anxious, angry, stressed, agitated and withdrawn during the outbreak or while in quarantine.

23) Share simple facts about what is going on and give clear information about how to reduce risk of infection in words older people with / without cognitive impairment can understand. It may also be helpful for information to be displayed in writing or pictures.

24) If you have an underlying health condition, make sure to have access to any medications that you are currently using.

25) Be prepared and know in advance where and how to get practical help if needed, like calling a taxi, having food

delivered and requesting medical care. Make sure you have up to two weeks of all your regular medicines that you may require.

26) Learn simple daily physical exercises to perform at home, in quarantine or isolation so you can maintain mobility and reduce boredom.

27) Keep regular routines and schedules as much as possible or help create new ones in a new environment, including regular exercising, cleaning, daily chores, singing, painting or other activities. Keep in regular contact with loved ones (e.g. via telephone, e-mail, social media or video conference). Messages for people in isolation.

28) Stay connected and maintain your social networks. Try as much as possible to keep your personal daily routines or create new routines if circumstances change. If health authorities have recommended limiting your physical social contact to contain the outbreak, you can stay connected via telephone, e-mail, social media or video conference.

Conclusion

During this unprecedented time of uncertainty and fear, it is likely that mental health issues and substance use disorders among people with these conditions will be exacerbated. In addition, epidemics have been shown to induce general stress across a population and may lead to new mental health and substance use issues. We should all work together in order to support each other and remember that this pandemic *"is not a race, but a marathon".*

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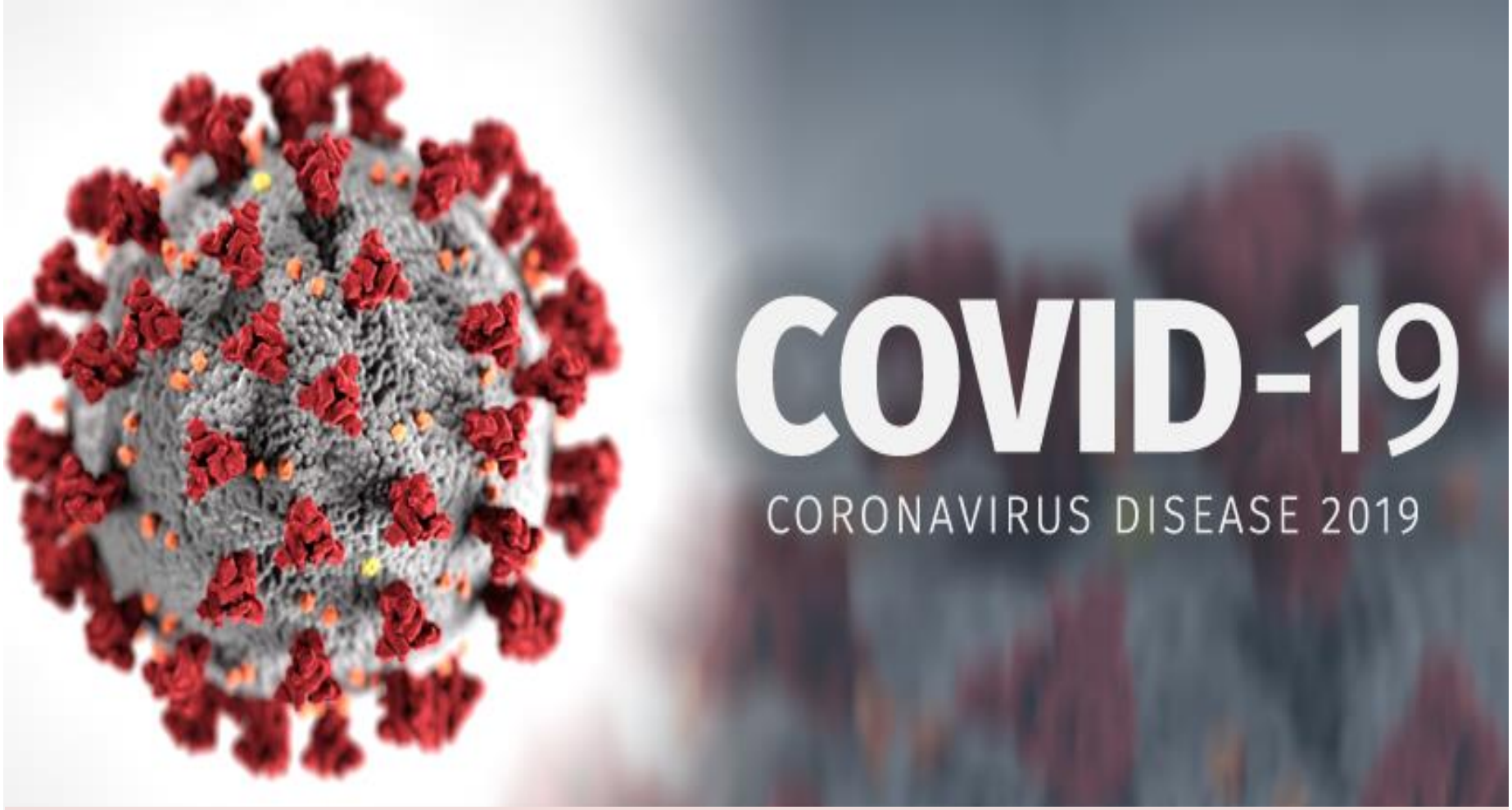


Interesting News

& Great Stories

On The World's Pandemic

Pain and Gain!

COVID-19 vaccines...

What we know so far

By: Nada Rady Badawy

Since the recognition of COVID-19 as a global pandemic in early 2020, it seems like the world has been revolving around finding a vaccine to that pandemic. Such a vaccine if proven safe and effective would be a "game changer" that leaves us at peace that at least the higher risk population would be safe from infection.

Now speaking about the predicted vaccine, there must be so many questions taking their way up to your head. It is nothing but normal since everyone is waiting for answers, especially since the image is still blurry regarding many aspects of candidate vaccines development.

Everyone is wondering when to expect to see a vaccine in the market. Others are concerned with whether we are late or going overspeed

As far as we know, many companies and collaborations between companies, universities, and scientific institutes are working so hard to develop such a vaccine, with speculations that one will be authorized and available by the end of this year or the early 2021, with the pace things are moving now.

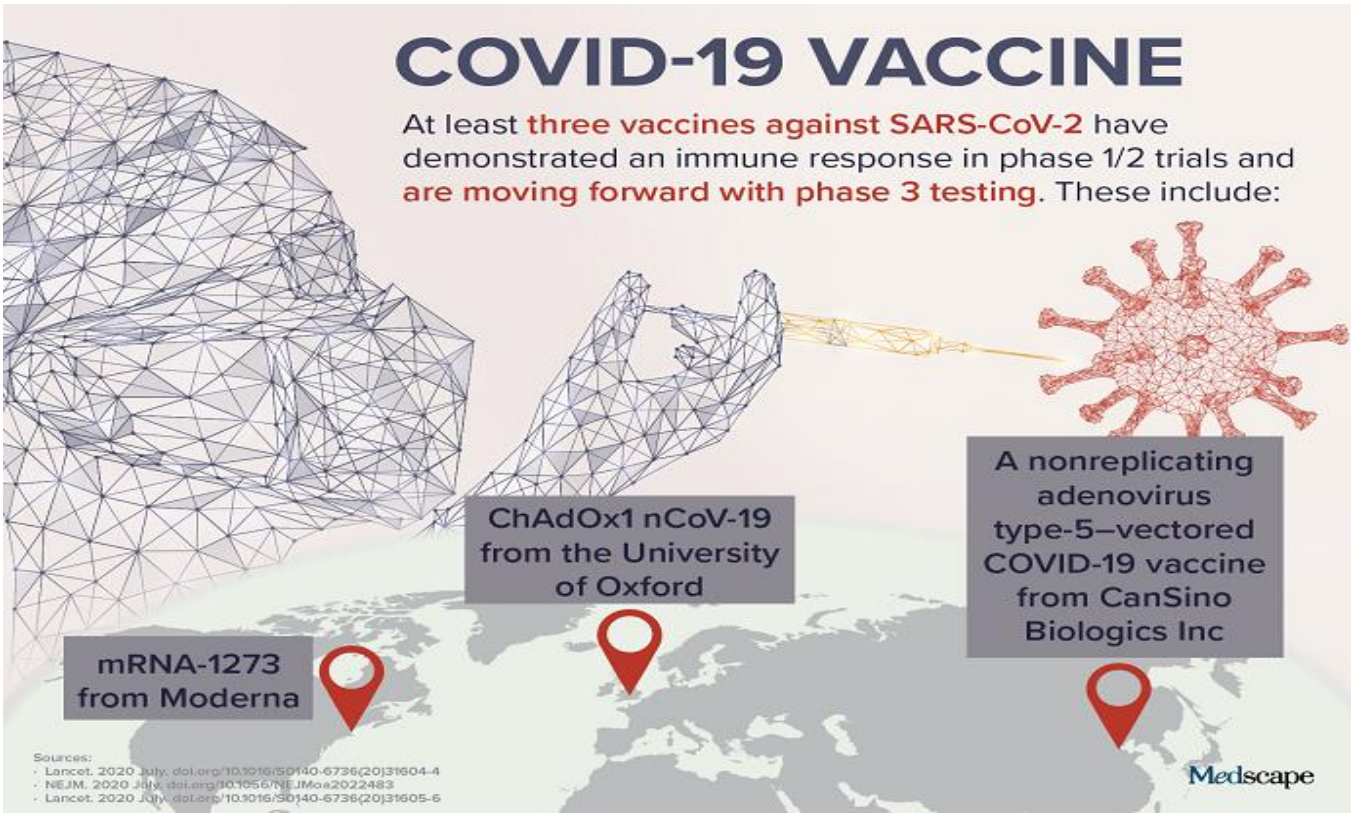
However, It is important to notice that normally vaccines take up to ***15-20 years*** to be developed, passing through various stages to ensure their

safety and effectiveness, starting from preclinical studies, then phase I, phase II, and phase III clinical trials. The candidate vaccine that passes through all these stages is then admitted to be approved by authorities. At this point, large-scale production starts.

The real challenge here resides in developing a vaccine as soon as possible that still possesses the characteristics of safety and effectiveness. Keep in mind that vaccines are different from drugs, in terms of preventing the occurrence of a disease, rather than treating or controlling symptoms of it.

As you can notice, that is why it consumes so many years to develop a single vaccine. Thus, it is clear that we are breaking the rules here working so fast.

Fortunately, it is in favor of us that scientists have been working already on developing vaccines against viruses of the same family, such as ***SARS***, which might have established the basis for developing a vaccine against the new corona virus disease.



Too many different candidate vaccines. Which one would be superior?

If you are curious, here is what you need to know..

As we said, various companies and institutes in different countries are currently developing candidate vaccines. Even more, studies for intranasal vaccines are being addressed by many companies, aiming at achieving better response, targeting the virus in the main site of infection.

This means so many different techniques and technologies being adopted. Many of these candidate vaccines are currently in phase III trials with promising results, that we could expect to see soon. However, the eyes are directed towards three specific vaccines developed by three major institutes.

The first is the one developed by the ***University of Oxford*** in collaboration with ***Astrazeneca***, a British-Swedish multinational pharmaceutical and bio-pharmaceutical company. With tens of thousands of participants from different countries, that vaccine is showing promising results with phase III trials.

The second is ***Moderna's*** vaccine, which is an American biotechnology company. This one is based on a relatively new and advanced technology based on *mRNA fragments* from the virus. This one too has shown promising results. Only two days ago, in November 16, the company declared higher than 94.5% efficacy rates in phase III trials and is aiming at Emergency Use Authorization (EUA).

The third candidate vaccine on the list is a result of collaboration between ***Pfizer***, the German company ***BioNTech***, and the Chinese company ***Fosun Pharma,*** which adopted similar mRNA-based technology. This one would most likely be the first to gain EUA, wherein November 9, the company declared efficacy of higher than 90% in the study population. Altogether, such results raise hope of a valid vaccine soon enough.


Pfizer

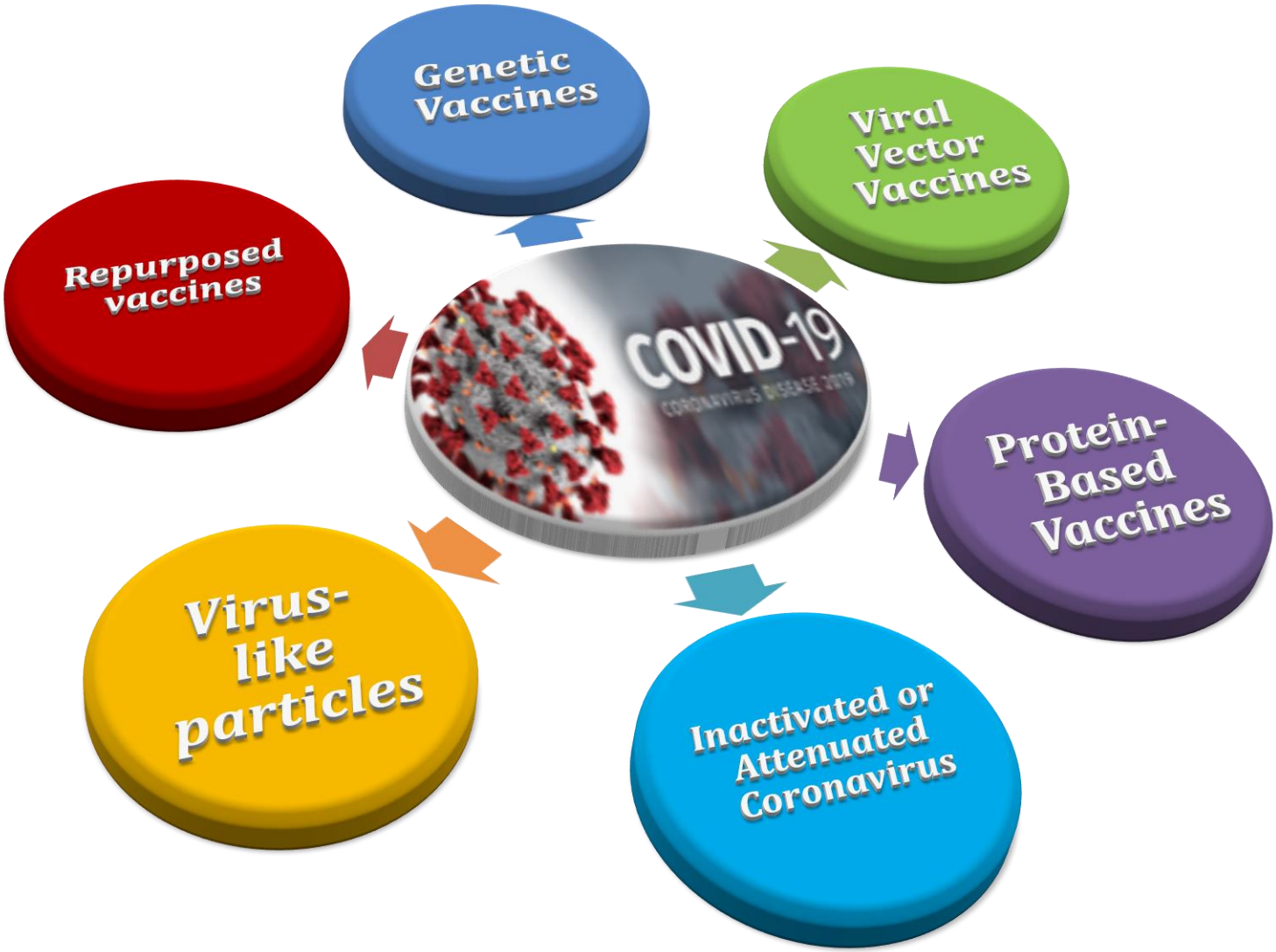

AstraZeneca


moderna
messenger therapeutics


BIONTECH


FOSUNPHARMA
复星医药

This figure illustrates varios vaccine development techniques



As Egypt, where are we from all of this?

In *September 2020*, the Egyptian ministry of health and population reached an agreement with the Chinese side, based on which, we are participating in phase III trials of 2 Chinese candidate vaccines supplied be the Chinese pharmaceutical group ***Sino-pharm***. One of the two vaccines gained emergency use authorization from the Chinese government, which is the one for which we are currently assembling volunteers. If proven effective in the Egyptian population, Egypt would be able to move to large-scale production of the vaccine, which is great news.

Also a few days ago, an agreement was made with the Russian side to supply us with 25 million doses of the Russian vaccine ***Sputnik V*** which has been approved in Russia.

In addition, Egypt reserved 30 million doses of the vaccine developed by ***Oxford / Astrazeneca***, in case the vaccine's safety and efficacy were proven.

If you are one of many wondering whether Egypt is participating in the race towards developing a vaccine…

The answer is yes!

There are about ***four Egyptian candidate vaccines*** in preclinical evaluation stage. With the aim that in the near future we will have a completely Egyptian vaccine distributed worldwide.

The following link provides you with insights into the Egyptian candidate vaccines enrolled in the tables of the ***WHO.***

file:///E:/Disc%20C/Downloads/novel-coronavirus-landscape-covid-194f70ec1fe74b48c783f07d79dc416386.pdf

But the real question here is.. "With that fast pace with which we are moving, would it be safe to administer such vaccination"?

Well, the answer will not be that simple, since surveys carried out in some countries found that the percentage of people willing to take the vaccine has decreased in the past few months.

This might be in part due to the fast pace with which things are moving, in addition to, lack of data and transparency about the trials carried out. Even worse, the suspension of major trials, where ***Oxford/Asrazeneca*** trial was halted in September for the *second time* due to detection of a case of ***"Transverse Myelitis"***, a serious disease affecting the spinal cord, most likely the reason why the trial was halted the first time.

Evaluation of the detected case was carried out by an independent committee to decide whether the cases were attributable to the administered vaccine, or just a coincidence, which is one possibility when giving a vaccine to a large population. From the point of view of the company, this reflects that the priority is always for safety of participants. However, data regarding the findings of these committees are still not known.

Despite the trial was resumed in Britain and Brazil a few days later, the United States has not resumed the trial yet, possibly waiting for more clarification after careful investigation of what really happened.

The same trial witnessed the death of one participant in his 20s last month, and though the trial was not suspended this time- possibly because that one participant was assigned to the placebo group- the reason behind his death is currently under investigation.

Again, this raises much doubt whether the approved vaccines will gain the required characteristics or not, since few months will not be enough to know for sure.

Most importantly, there is no way to ensure whether any candidate vaccine provides *long term immunity* against the virus or not which requires years of follow up, that even makes the effectiveness questionable.

Another thing is the worry that politics may have influence in some countries pushing towards authorizing a vaccine earlier than it should be, especially with the *Emergency Use Authorization (EUA)* that many regulatory authorities are considering under the current circumstances.

One more thing to consider is whether the effect would be the same in elderly, adults, and

children. A point yet to be answered in the upcoming days.

Another worrying issue is "Even if we have suitable approved vaccines, how will they be distributed to various countries of the globe ?!! "

Well, it is a quite edgy question, and more complicated than it seems. We still do not know exactly how this issue will be managed. Many ethicists are working on it and even studies have been released addressing this matter.

Moreover, the WHO is currently working on different initiatives to ensure equity and prioritization in distributing the vaccines once approved. Most likely, the vaccine will be supplied first to high-risk groups, particularly the elderly.

The upcoming days are to carry us the answers to all of this. All we can do for now is to work, hope and wait for what is coming.

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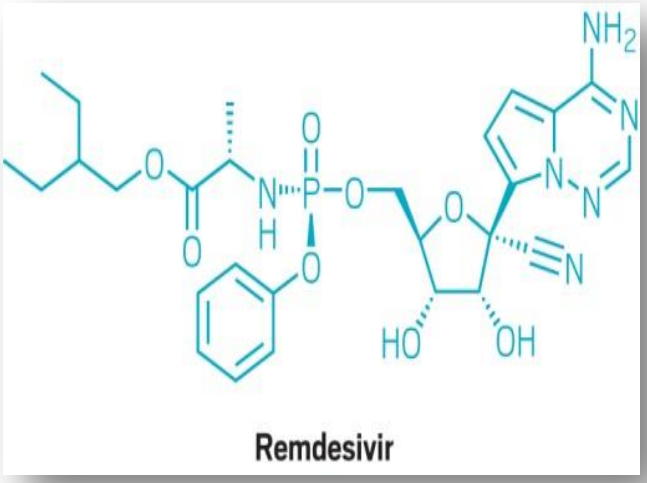
Remdesivir and COVID-19

By: Mohamed Wagdy Eldougdoug

On May 2020, remdesivir gained emergency use authorization from the FDA for confirmed or suspected severe COVID-19 in hospitalized adults & children. [1]



So, what is Remdesivir?

It is adenosine nucleoside analogue, given intravenously then rapidly enters target cells. Inside the target cells remdesivir is converted to an active nucleoside triphosphate metabolite. Remdesivir is a broad-spectrum antiviral pro-drug that is incorporated into nascent viral RNA chains leading to termination of viral RNA synthesis by inhibiting RNA dependent RNA polymerase. Remdesivir is given once daily to provide sustained intracellular levels of the active drug. [2]

Remdesivir and corona viruses

Remdesivir exhibits antiviral activity against corona viruses as

it has been found to inhibit its replication in human respiratory epithelial cell tissue culture without inhibition of host RNA or DNA polymerases, which has been also studied in macaque monkeys infected with these human corona viruses. [3, 4]

The efficacy of this antiviral against the new emerging coronavirus (SARS-CoV-2) in 2019 was studied in a small number of macaque monkeys after inoculation with SARS-CoV-2.

Following the inoculation a mild transient respiratory infection developed that lasted from 9 to 17 days in control monkeys. Remdesivir was started 12 hours after the inoculation of the virus (this time is considered to be close to the peak of the virus replication in the lungs), and the administration of the drug was continued as once daily dose for 6 days. From this study, administering remdesivir 12 hours after inoculation results in reduction of clinical symptoms, lung virus replication and lung lesions. However, high viral RNA loads and infectious virus titers were not reduced in the rectum, throat and nose in these treated animals meaning that they were still capable of transmitting infection to others. This is a result of inadequate tissue levels of the active drug metabolite at these sites. Known mutations in the RNA-dependent RNA polymerase that is responsible for remdesivir resistance in corona viruses were not found in any of samples from the treated animals. [5, 6]

It is important to know that these experimental animals may not mimic COVID-19 in humans; this is because humans wait many days to become sufficiently symptomatic to seek medical care in contrast to the experimental animals in which the drug started within 12 hours of infection. [7]

The interest to remdesivir in the clinical field came from the rapid improvement in symptoms in the first patient with COVID-19 in the US, January 2020.

Remdesivir was started on the 7th hospital day (11th day of onset) after chest radiograph became abnormal and the patient experienced hypoxia. [8] But since improvement in one patient does not mean that remdesivir is effective, large clinical trials that compare remdesivir to placebo are required.

In March 2020, FDA approved remdesivir for "compassionate use" allowing patients with serious or life-threatening cases of the virus to get the drug. The first published report on a group

of 53 patients who received the drug on compassionate use basis revealed clinical improvement in 36 patients (68%) with severe infection (including 17 of 30 patients (57%) receiving mechanical ventilation). A total of 25 patients (47%) was discharged, and 7 patients (13%) died. Mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation [9].

Summary

Studies in a non-human primate COVID-19 model have documented remdesivir can reduce viral replication in the lung and improve lung pathology, only if given early enough in the course of infection. This is a problem with COVID-19 in humans, when SARS-CoV-2 replication has already peaked before or at the onset of symptoms; if antiviral therapy is then not started until a week or more later when symptoms are maximal, the drug may not be able to prevent or limit damage to the lungs and other organs.

A better suggestion than intravenous administration of remdesivir may be an **orally administered** antiviral drug that could be given on an outpatient basis early in the course of the disease, before symptoms become severe enough to require hospitalization.

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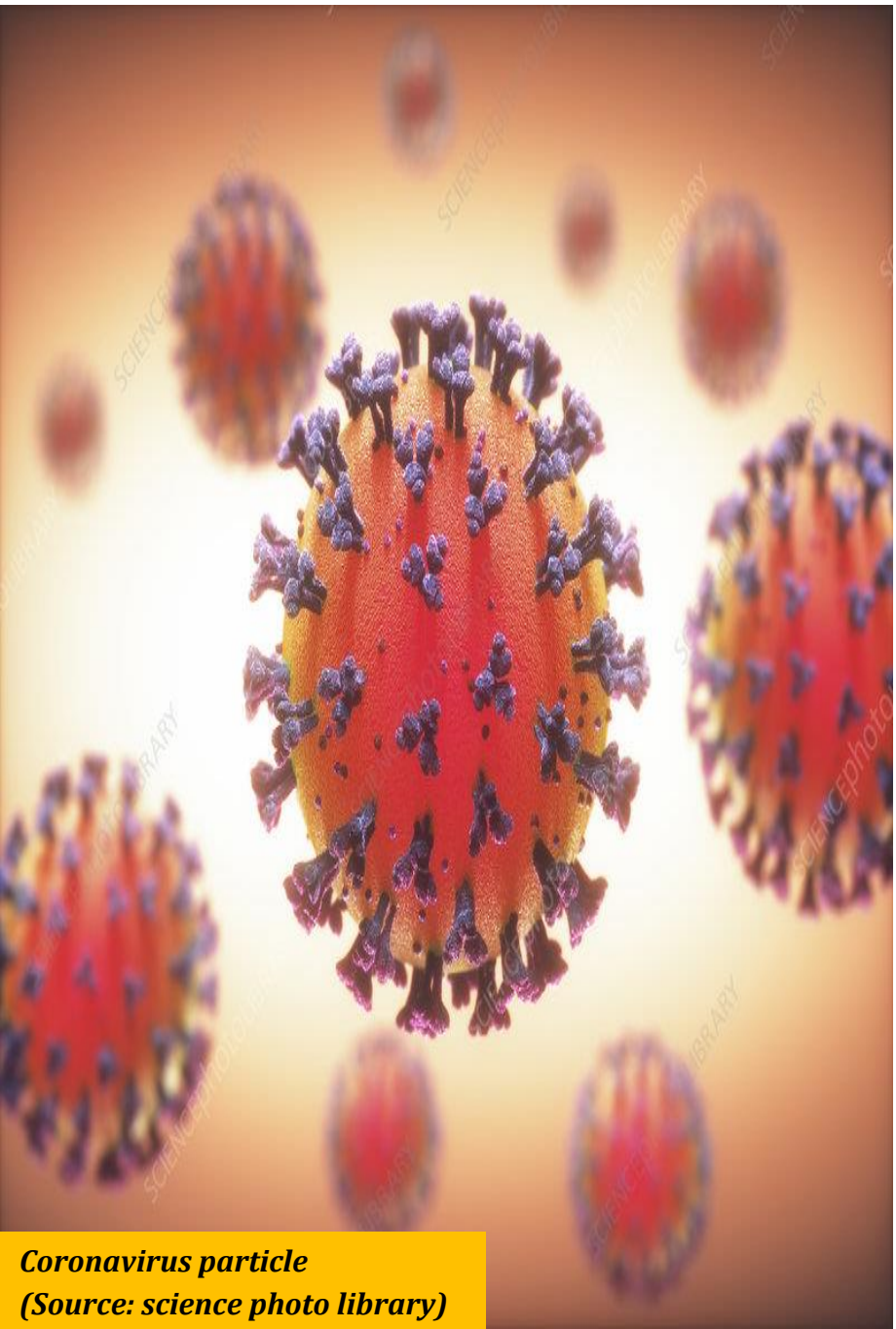
First case of COVID-19 reinfection reported by researchers in Hong Kong

By: Ahmed Mohamed Magdy



Coronavirus particle
(Source: science photo library)

The first case of someone being reinfected with coronavirus was reported by researchers in Hong Kong.

During his first episode of illness, the patient had cough, sore throat, fever and headache for three days, according to the study. He tested positive for Covid-19 on March 26.

Then during his second episode, the patient was returning to Hong Kong from travelling in Spain, via the United Kingdom, when he tested positive during his entry screening at Hong Kong airport on August 15, the researchers said. The man was hospitalized again, but remained asymptomatic.

The study was accepted by medical journal Clinical Infectious Diseases, but the full research is yet to be published.

The findings could have significant implications for the development of vaccines and what is known about natural immunity against Covid-19.

Researchers at the University of Hong Kong's (HKU) department of microbiology said that an "apparently young and healthy patient had a second episode of Covid-19 infection which was diagnosed 4.5 months after the first episode".

They added that the case illustrates reinfection can occur a few months after recovery from the first infection.

The man had no symptoms – was asymptomatic – during the second infection which was picked up by screening tests on returning passengers at Hong Kong airport.

Genetic sequencing of the virus showed he was infected twice by different strains of Covid-19, the researchers said.

Therefore, people with previous Covid-19 infection should comply with control measures like wearing face coverings and social distancing.

One of the researchers, Dr. Kelvin Kai-Wang To, clinical associate professor, Department of Microbiology, Li Ka Shing Faculty of Medicine, HKU said, "This case shows that patients recovered from Covid-19 can get reinfected. Therefore, the immunity against Covid-19 is not lifelong".

He added, "Reinfection is likely occurring elsewhere. Our case was asymptomatic and was diagnosed because of screening at the airport."

In a statement, the university said, "Since the immunity can be short lasting after natural infection, vaccination should also be considered for those with one episode of infection."

However, experts in the UK say it is too early to say what the single case may mean on a global scale.

Brendan Wren, professor of microbial pathogenesis, London School of Hygiene and Tropical Medicine, said, "With over three million cases of Covid-19 worldwide, the first reported case of a potential reinfection with SARS-CoV-2 needs to be taken into context. It appears that the young and healthy adult has been reinfected with a slight SARS-CoV-2 variant from the initial infection three months previously".

"It is to be expected that the virus will naturally mutate over time. This is a very rare example of reinfection and it should not negate the global drive to develop Covid-19 vaccines".

Nevertheless, he added that it is "very hard" to make any strong

inference from a single observation, and that seeing one case of reinfection is not that surprising.

“This may be very rare, and it may be that second infections, when they do occur, are not serious”, said Dr. Barrett.

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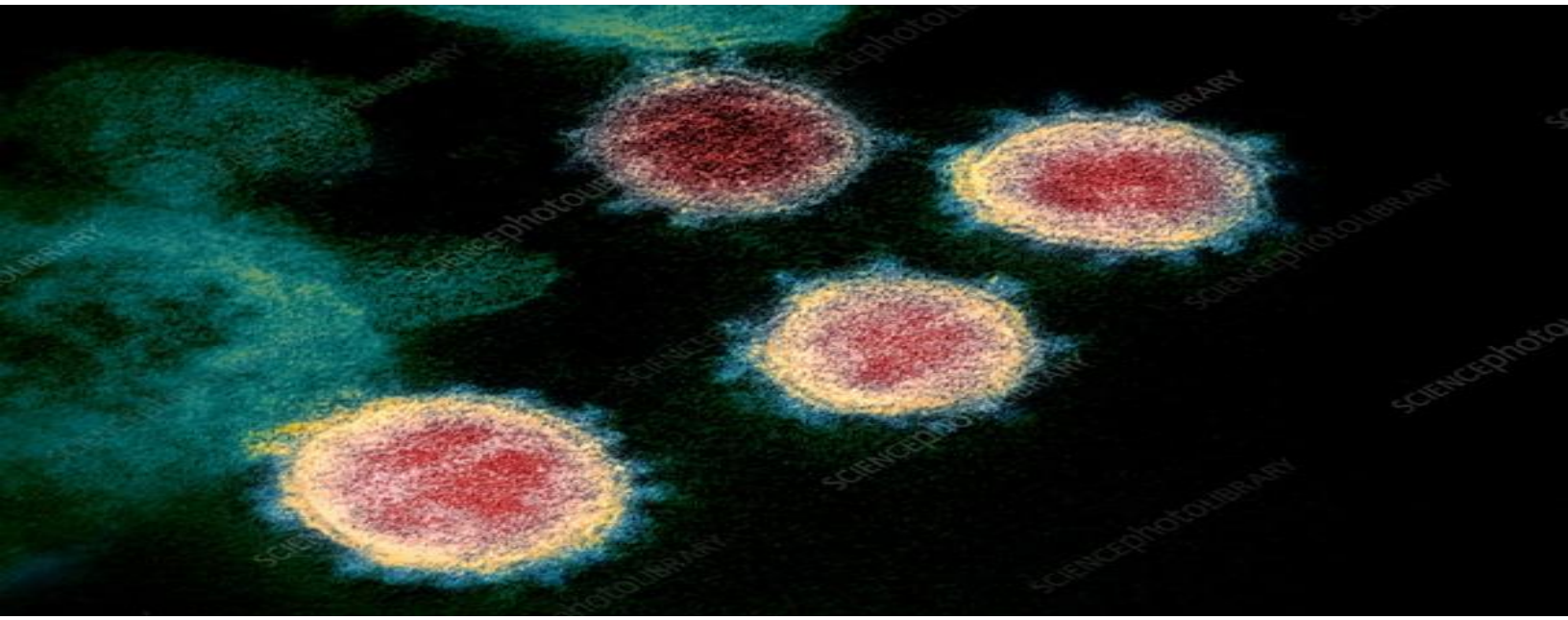
Ruxolitinib: FDA approved drug that may improve COVID-19 prognosis

By: Nada Khaled Shoura



Coronavirus particle, Source: science photo library

Coronavirus is a novel respiratory virus that appeared in December 2019 and rapidly spread globally, becoming one of the biggest areas of interest in the scientific field. The number of COVID-19 clinical trials has grown from 69 in the first week of January 2020 to 4271 by 10 July [1], in an attempt to understand the virus' nature and find a cure.

COVID-19 severity ranges from being an asymptomatic disease, in

most cases, to a severe lethal disease in 10-20% of cases who are older age population,those having comorbidities [2], and some other host factors including genetics [3].This variation in severity is still not well-understood.

One of the most severe complications is what is known as cytokine storm, where there is a significant increase in inflammatory cytokines such as IL-2, IL-7, IL-10, GSCF, IP10, MCP-1,

MIP1A and TNF-α, to a level that is harmful rather than beneficial, causing vigorous inflammatory response including severe interstitial pneumonia, acute respiratory distress syndrome (ARDS), thrombotic tendency and multi-organs inflammation that may progress to multi-organ failure and death. [2]

When the immune system recognizes the viral antigens, antigen-presenting cells (APC) process these antigens and present them to other immune cells to activate proper immune response, in order to combat the infection. Later after the antigenic activity is over, APCs are destroyed by natural killer cells (NK) and other cytolytic T lymphocytes to avoid unnecessary activation of the immunity. In case of severe COVID-19 cases, numbers of T lymphocytes–especially NK cells–are very low, leading to the inability of destroying infected and activated APCs, resulting in prolonged and exaggerated interaction between APCs and other immune cells, causing pro-inflammatory cytokines to be secreted in massive amounts. [2]

Another factor that contributes to cytokine storm is that pro-inflammatory cytokines were found significantly upregulated, while the anti-inflammatory cytokines such as IL-10 were found to be deficient. This imbalance in the inflammatory response promotes cytokine storm. [3]

In order to reduce mortality rate in critically ill patients suffering from cytokine storm, antiviral treatment must be combined with anti-inflammatory agents and immuno-modulators in an attempt to prevent further worsening of the patient's health status.

As long as this disease is still not well-understood, there is no certain agent that can be used specifically to manage cytokine storm, but there are many therapeutic options that can be used, including corticosteroids, IL-6R antagonists, IL-1 inhibitors, TNF inhibitors and IVIGs. [2]

A group of scientists who are interested in finding a cure to

COVID-19 found similar clinical features between COVID-19 cytokine storm and HLH (hemophagocytic lymphohistiocytosis) [4], which is an immune-mediated disorder resulting in hyper-activation of inflammatory cytokines. [5]

Ruxolitinib, the drug in discussion in this article, is an FDA approved drug, which has been recently successfully tested to treat secondary HLH patients who failed to respond to primary therapy. Based on promising results of Ruxolitinib in managing secondary HLH, scientists recommend it to be used in critically ill COVID-19 patients and conduct phase II clinical trial to test it for safety and efficacy. [4]

A bottle of Jakafi® (ruxolitinib) 10mg tablets, Source: Business Wire

Forty-three severely ill COVID-19 patients were enrolled in this study, 22 patients in the interventional group were to receive Ruxolitinib in addition to standard of care treatment, and 21 patients in the control group were to receive only standard of care treatment. The efficacy was evaluated based on the time of clinical improvement of CT scan and lymphocytopenia. [6]

The results showed no statistical significance between the two groups in terms of clinical improvement, but there was numerical shorter median time of clinical improvement. CT scan showed significant faster improvement at day 14 compared to control group.

In addition, lymphocytopenia recovery was faster in Ruxolitinib group, which is considered of clinical relevance, as lymphocytopenia was associated with bad disease prognosis.

Another important factor to consider is the mortality rate within the two groups[4].patients in the control group experienced clinical deterioration, which necessitated ICU admission and mechanical ventilation, three of them eventually died with respiratory failure. In the other group, no deaths nor clinical deterioration were recorded in the interventional Ruxolitinib group. [6]

Ruxolitinib inhibits two enzymes known as Janus Associated Kinases (JAKs) JAK1 and JAK2 which

mediate the signaling of a number of cytokines and growth factors. [7]

In order to evaluate whether Ruxolitinib will be effective in improving COVID-19 cytokine storm or not, 48 cytokines levels were measured. The level of seven cytokines were significantly decreased in Ruxolitinib group compared to the control group, one of them is IL-6, which is considered a critical cytokine in the process of cytokine-mediated tissue damage and inflammation.

These results bring a conclusion that Ruxolitinib targets multiple cytokines rather than a specific one , which could be used as surrogate biomarkers in future Ruxolitinib trials, as the study authors said. [6]

Ruxolitinb was generally well tolerated with low toxicity and no additional adverse events observed in its group compared to the control group. Also, no new safety issues – other than the well-known ruxolitinib side effects – have been observed during the use of Ruxolitinib with COVID-19 patients. [6]

All these promising results give us hope that Ruxolitinib may help in managing cytokine storm in critically ill COVID-19 patients and may save those patients' lives.

Now, a larger phase III clinical trial is proceeded to test Ruxolitinb on a larger sample (up to 400 severely ill patients) which will give us a wider range of data about safety and efficacy of using Ruxolitinb in COVID-19 patients. [4]

A counter perspective to the one discussed previously, is the appropriateness of describing COVID-19 associated elevation in plasma cytokines levels as cytokine storm. An article argues against terming COVID-19 acute respiratory syndrome a "cytokine storm", because it can be misleading during research around the most suitable protocol to manage these patients.

The article authors supported their point of view by comparing the IL-6 levels in more than 700 severally ill COVID-19 patients with IL-6 levels in patients with hyperinflammatory phenotype acute respiratory distress syndrome (ARDS).

The hyperinflammatory phenotype of ARDS is characterized by elevated proinflammatory cytokines, which could be considered the most consistent with the cytokine storm.

Median Interleukin-6 level in hyperinflammatory phenotype of ARDS was from 10 to 200 folds higher than IL-6 levels in severely ill COVID-19 patients. Before jumping to conclusions, there were some

limitations in these observations including that almost all of COVID-19 measurements are from clinical laboratory testing, which may lack calibration,leading to underestimating IL-6 levels. Also, lL-6 levels may not be reflective to the case severity. [8]

The article authors' main concern is that the use of the term "cytokine storm" encourged healthcare professionals to use potent immuno-modulators in managing severely ill patients, which may be inappropriate because of concerns about impaired and delayed virus clearance and elevated risk of secondary infection due to immunity suppression. [8]

In the previously discussed clinical trial; there was no significant difference neither in the viral load nor in the median time of virus clearance between the Ruxolitinb group and the control group. Furthermore, patients in the Ruxolitinb group had significantly higher IgM mean peak level specific to COVID-19 virus, but the results of this clinical trial still had some limitations such as small sample size and the exclusion of critically ill patients with invasive ventilator about the use of Ruxolitinib in pneumonia **[6]**

We can conclude that "current data are insufficient to ascertain the precise role and scope of dysregulated cytokine responses in COVID-19" as the article authors said. [8]

We still have a long way of researching until we reach to a well-understanding of this new pandemic virus pathogenesis and subsequently a cure, because most of the available data are from a very small fraction of cases relative to the whole number of cases worldwide, which are more than 15 million [9]. The scientific effort is magnificent and eventually we will reach to the long-awaited way out.

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The unexpected visitor…

PMIS

By: Nada Rady Badawy

Even now, we are still ignorant of the complete image of what exactly happens when one gets infected with SARS-CoV-2, also known as novel corona virus disease (COVID-19) or what symptoms could evolve.

However, COVID-19 symptoms are thought to be less severe in children compared to adults.

Since the beginning of that catastrophe that flooded the whole world and made those whom we hold dear leave our sides; since then, there has been some sort of consensus that children are less prone to the virus. Even when it happens, symptoms are mild in most cases and resolve with simple interventions, though few cases were reported of children admitted to hospitals or even to PICU following infection with COVID-19. That is why it did not gather much attention to the infection in children in the beginning.

It was not until May 2020, when reports from Italy, the United Kingdom, and various parts of Europe, and later on from the United states were pooled and announced, that we were forced to see the ugly truth. Our children are another group at risk from infection with COVID-19.

Those reports revealed sudden onset of cases for children with severe inflammatory syndrome,

requiring admission to hospital-or even worse-to PICU.

After these observations were reported in different areas of the world, enough to set alarm and to be recognized, that syndrome was given the name *"Pediatric Multisystem Inflammatory Syndrome"* ***(PMIS)*** in Europe and *"Multisystem Inflammatory Syndrome in children"* ***(MIS-C)*** in the United States.

The early observations of affected cases showed symptoms of PMIS to be similar to those of "Kawasaki syndrome"* or "Toxic shock syndrome"*, though there is no bacterial infection in our case.

***** Kawasaki disease (KD), also known as Kawasaki syndrome, is an acute febrile illness of unknown cause that primarily affects children younger than 5 years of age. The disease was first described in Japan by Tomisaku Kawasaki in 1967, and the first cases outside of Japan were reported in Hawaii in 1976 (Content source: Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) , Division of High-Consequence Pathogens and Pathology (DHCPP).

* Streptococcal toxic shock syndrome (STSS) is a rare, but serious bacterial infection. It can develop very quickly into low blood pressure, multiple organ failure, and even death (Content source: National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases, CDC).

Scientists are currently working on sorting out the relationship between these symptoms and SARS-CoV-2 infection, which raises lots and lots of questions…

1- Does PMIS result directly from infection with SARS-CoV-2 or is it attributable to other factors?

Although more than half of the affected children had either active infection with SARS-CoV-2 or had antibodies against the virus, it is not clear whether it is a direct result to infection or not.

However, some speculations are that PMIS is a result of aggressive inflammatory or immune response to infection. Furthermore, the presence of *microangiopathy* in some of these children, which then led to multi- organ dysfunction, is similar to what happens in adults in response to infection.

On the other hand, reported cases of PMIS -surprisingly- showed only mild or no respiratory symptoms to begin with.

So, is it possible that we are misguided by something aside from SARS-CoV-2 infection ?! Who knows!

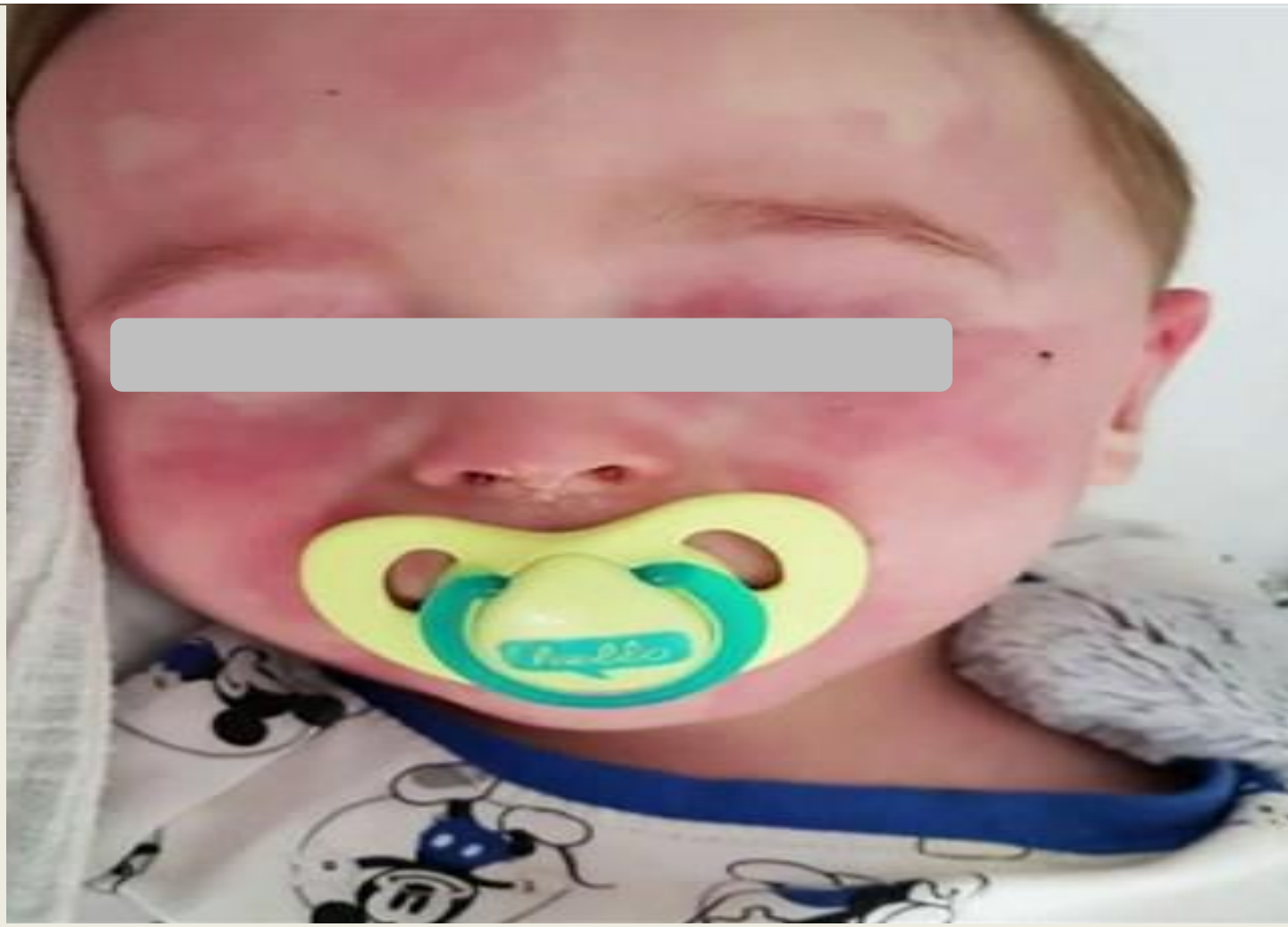
2- What symptoms could prompt a diagnosis with PMIS?

Though unique in some of its signs and symptoms-which granted it a separate nomenclature- PMIS is thought to be closely similar to "Kawasaki syndrome" or "Toxic shock syndrome".

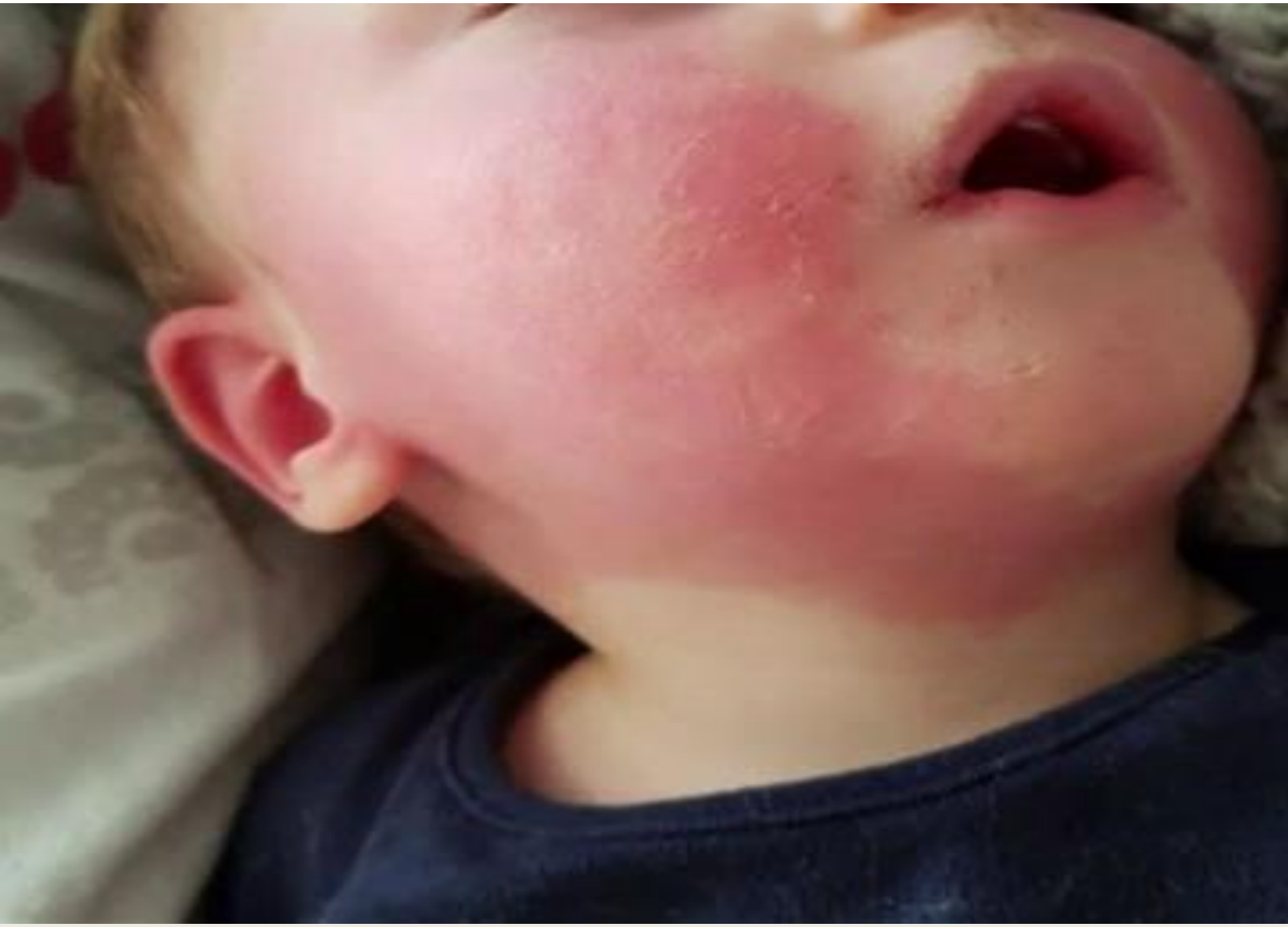
Where children are presented with variable symptoms including fever, abdominal rash, abdominal pain, gastrointestinal symptoms (most likely diarrhea).

Some cases that showed more severe presentation suffered from hypotension, and multi-organ dysfunction, possibly due to microvascular aneurysms, mostly affecting coronary artery, with rare occurrence of cardiogenic shock or kidney dysfunction.

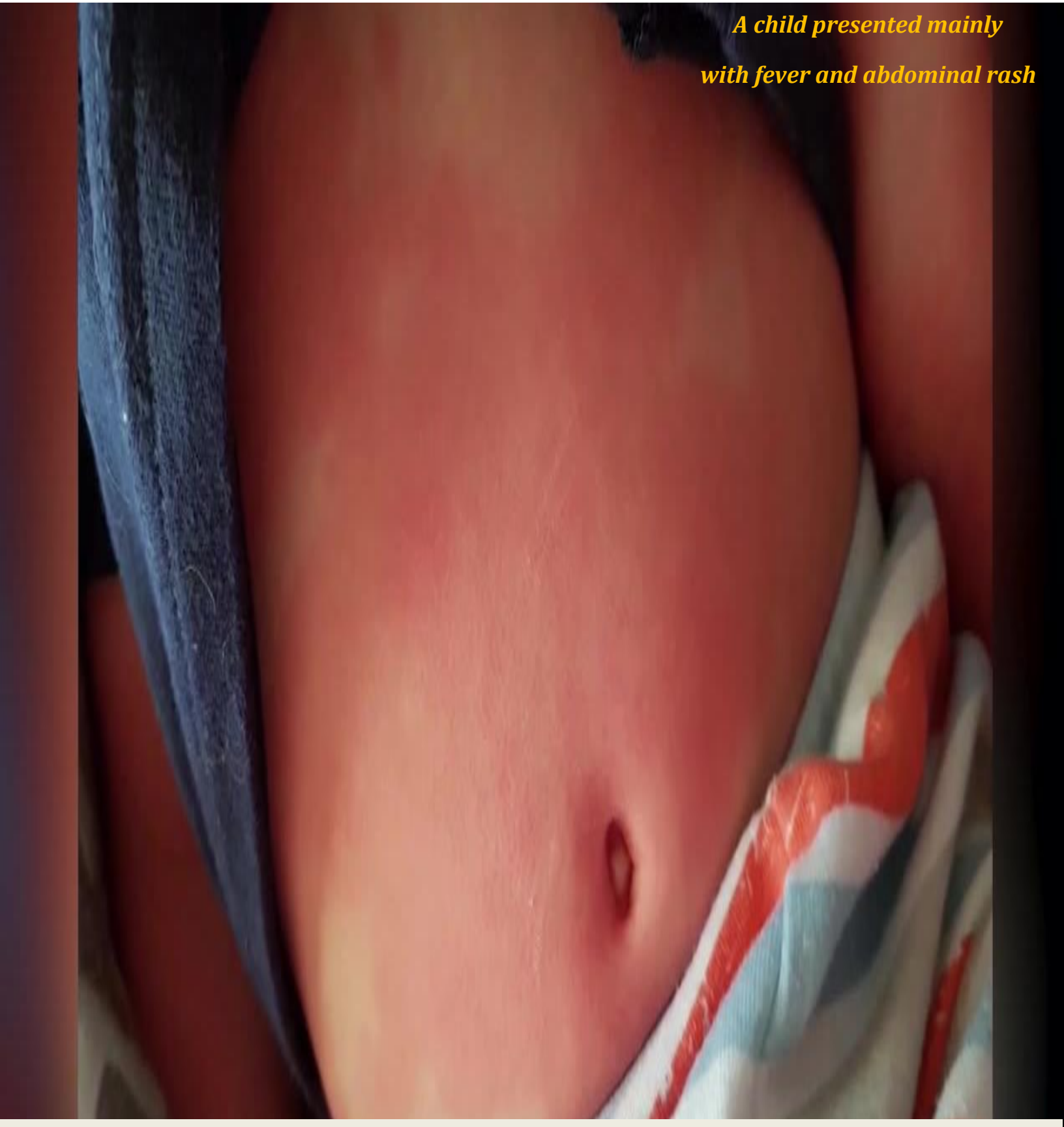
Source:https://www.nbcnews.com/health/health-news/least-85-kids-across-u-s-have-developed-rare-mysterious-n1202186



As we see, these photos show a child presented with facial and abdominal rash, in addition to fever



Source: https://www.nbcnews.com/health/health-news/least-85-kids-across-u-s-have-developed-rare-mysterious-n1202186



A child presented mainly with fever and abdominal rash

Source: https://www.wtnh.com/health-2/5-confirmed-cases-of-rare-pediatric-multi-system-inflammatory-syndrome-in-ct-possibly-covid-19-related/

Here is what the ***WHO*** has issued as a preliminary characterization of the disease, which is continuously updated:

a) Children with age ranging from 5 to 19 years with fever for ≥ 3 days.

b) Any two of the following signs/symptoms:

1- Skin rash, conjunctivitis, or inflammation of mucous membranes (in mouth, hands, or feet).

2- Hypotension or symptoms of shock.

3- Indicators of myocardial dysfunction, endocarditis, or any abnormality in coronary arteries (Usually identified through echocardiography and elevated troponin levels).

4- Laboratory investigations indicating coagulopathy (PT, and PTT).

5- Acute GIT symptoms, such as diarrhea,vomiting, or stomachache.

c) Presence of inflammatory biomarkers (CRP, ESR, Procalcitonin).

d) Absence of any known cause of inflammation, such as toxic shock syndrome.

e) Confirmation of current or previous infection with SARS-CoV-2 (+ve RT-PCR test, +ve antibody testing, or even history of contact with SARS-Cov-2 confirmed cases).

3- Are children the only group at risk? Or does PMIS unrecognizably affect adults?

We still do not know.

Our belief in the beginning was that SARS-CoV-2 does not affect children or only yields mild to moderate symptoms. Thus, when these severe cases were reported along with few reports of deaths among those children, it was enough to draw our attention that something was going on.

It is worth noting that children ≤ 19 years are the most at risk of PMIS. In some cases, more specifically in New York City, it was also observed that children five years old or younger represented most of cases admitted to hospital.

However, we cannot say the same about adults. Assuming that multisystem inflammatory syndrome could take place in them, it is possible that symptoms are being diagnosed in the context of COVID-19 infection. We all know by now that severe inflammatory response takes place in those with severe SARS-CoV-2 infection who are admitted to hospitals or even require mechanical ventilation as a last resort.

4- What are the chances of children getting PMIS? And what is the exact percentage expected?

We still have a lot to sort out before answering this question.

It is only normal that children showing these inflammatory symptoms in the time of COVID-19 would be thought of as COVID-19 patients and would be our highest priority, but does it mean that all PMIS cases have been diagnosed?!

Well; it raises much doubt, since one cannot think of PMIS when he does not expect it in the first place! Is not it true?! Thus, our calculations might not be that accurate after all.

5- Are there any risk factors that make some children more prone to PMIS than others?

Researches are carried out while you dear reader wander your eyes through these lines to figure out whether SARS-CoV-2 infection, genetic, environmental or any other factors could contribute to PMIS.

6- Does the presence of most of PMIS cases in the United States and Europe make it a pattern?

Honestly, I have no answer to the question so far.

However, numbers are not that big to reflect a pattern. Besides, it could be a result of ignorance of the novel condition (i.e. PMIS) in other parts of the world, and hence resides unrecognized.

7- Last, but not least, how to deal with cases of PMIS?

It is a very important aspect, knowing what to do and how to treat such a case when facing it; though we hope we do not.

Currently, there is no specific intervention, but it is a case-by-case scenario. We still do not know which is best. However, as with inflammatory conditions, intravascular immunoglobulin (IVIG) is one line. In addition, inflammatory modulators, steroids, tocilizumab, as well as supplementary and fluid replacement therapy can be used.

By now you might be wondering, could it be that our children are at higher risk than we expected?!

Despite all that being said; and the concern with which the scientific research community addresses the topic, despite all that, doctors tend to have more hope than fear, mostly because only few of those affected by the disease died after hospitalization. Sad as it is, the rates are not that to worry us up till now.

Besides, doing the back of the envelope calculations, based on the current numbers, PMIS could be called “rare”.

Hopefully, we pray to keep our children safe. We pray that the problem would be resolved soon enough without further losses and that the rates of infection in general would subside as soon as possible, so that we can return to what was once called “our daily life”.

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Pregnancy & Lactation

Highlights in Preeclampsia

By: Mohamed Wagdy Eldougdoug

What is preeclampsia?

First, we should know the difference between **gestational hypertension**, **preeclampsia**& **eclampsia**. In brief, **gestational HTN** is high blood pressure (> **140/90 mmHg**, old definition of HTN) occurring after 20 weeks gestation without proteinuria or pathologic edema. **Preeclampsia** is high blood pressure during pregnancy plus proteinuria (300 mg or more every 24 hr.) while **eclampsia** occurs as tonic-clonic seizures. [1]

Figure 1 Source : Medscape , Dreamstime

New definition of HTN!

According to The American College of Cardiology and American Heart Association (ACC/AHA) guidelines at 2017, people with elevated BP(systolic BP 120-129 mm Hg and diastolic BP >80 mm Hg) are classified as prehypertension, those with systolic 130-139 mm Hg or diastolic 80-89 mmHg are classified as stage1 hypertension. Previously hypertension was defined as BP at / above systolic 140 mmHg or at / above diastolic 90 mmHg, now called stage 2 hypertension. It has been long

associated with adverse maternal and fetal effects. However, it was unclear whether lesser elevation in BP is also associated with the same adverse effects or not. [2]

New risks!

According to research (cohort study) published in Obstetrics & Gynecology by Elizabeth F. Sutton(PhD, of the University of Pittsburgh) and colleagues, they found that pregnant women with **even modest elevation in BP** are **at increased risk for preeclampsia**. Three quarters of women involved in this study had normal BP, 14% had elevated BP and 5% had stage 1 hypertension before 20 weeks' gestation. Finally, 6% have stage 2 hypertension. [3]

The authors found that as BP elevation increases, preeclampsia risk also increases. ***Table 1*** shows the results. It is important to know that the pattern of increasing risk with higher BP category was similar in both white and black women.[3] Researchers also investigate about gestational diabetes (which can lead to sever maternal and neonatal morbidity and placental abruption,) and they found that the risk of gestational diabetes increased gradually as BP increased compared with normotensive women. Higher risk was seen only in women with stage 2 hypertension. [3]

Table 1

Group	% had preeclampsia
Women with normal blood pressure before 20 weeks' gestation	**5**
Women with elevated blood pressure	**7**
Women with stage 1 hypertension	**12**
Women with stage 2 hypertension	**30**

What should we do?!

The previous findings show the importance of screening for early pregnancy BP elevation so that we can reduce risk for preeclampsia. Some clinicians tend to use low dose aspirin, which has shown to safely reduce preeclampsia risk among women with elevated BP, stage 1 or stage 2 hypertension.

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Brexanolone

A new achievement in treatment of postpartum depression

Source: Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC

By: Nada Rady Badawy

It is the dream of every mother to see her baby born healthy and to be able to love and care for him or her. But when this special bond between mother and baby is severed and she is no longer able to feel it, it is then that something abnormal gets in the way of maternal love; something so devastating.

Today's advances in medicine, as well as prioritization of human well-being in modern communities have shed more light on maternal health. For all of that we chose to discuss a critical, yet ignored topic of ***"Postpartum depression" (PPD)***, especially with the approval of a novel drug for treatment of the condition.

Though we do not have accurate estimates of prevalence rates of PPD, it is possibly more common than expected, and it should be differentiated from "Baby blues" in terms of severity and duration of the condition.

Baby blues includes feeling tired, sad, or worried for a few days following pregnancy, while PPD yields more severe presentation that may last longer.[1]

Generally speaking, PPD is a mood disorder that can affect women after childbirth with

[1] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion

symptoms ranging from mild, moderate or even severe. The cause of which is still one of our body's mysteries, but it is thought to be a combination of genetic and environmental factors.[2]

A wide range of signs and symptoms based on the severity of the condition could evolve. Where PPD could result in trouble forming bond and emotional attachment with the new baby and even doubts about the ability of taking care of the baby, up to suicidal thoughts and harming oneself or the baby.[1]

A range of interventions has been used to control and treat the condition case-based.

Regarding pharmacological therapy; since it is depression after all, antidepressants are considered the main line of treatment of such conditions.

In this article, we are discussing a novel drug for treatment of PPD. ***Brexanolone (BRX)***; a drug that was described by one expert as "a revolution" in the care of PPD. The first drug to gain approval by the ***FDA*** on March 19, 2019 to be used specifically in cases of PPD.

BRX is administered as an intravenous infusion over 60 hours with the advantage of ultra-rapid action.

[2] National Institute of Mental Health, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health NIH Publication No. 20-MH-8116

Brexanolone

Source: Drug Topics (www.drugtopics.com)

By now, most of our readers are curious enough to ask about *how this drug works*…

Well, BRX is an intravenous formulation of allopregnanolone, an endogenous progesterone metabolite, thought to modulate gamma-aminobutyric acid (GABA) receptors.

This is important because one of the mechanisms potentially suggested for PPD is possibly attributed to altered GABA receptor regulation, hence the inability of the GABA system to regulate neural network activity.

It was not until results of three randomized-controlled double blind trials were in favor of the new drug, that it got approved.

As introduced by these trials, BRX yields rapid remission in those treated patients, a state of remission, which was even

sustained over 30 days following therapy.

In the trials carried out using BRX, 140 women diagnosed with PPD were treated with either one of two doses of the drug, BRX60 µg/kg/hr or BRX90 µg/kg/hr.

The results of these 140 patients were compared to those of more than 100 patients given placebo.

The severity of the condition in women recruited in these trials was identified based on the score of the ***Hamilton Rating Scale for Depression (HAM-D)***. Patients with severe or moderate to severe disease were recruited.

The results of these studies were introduced at the European Psychiatric Association (EPA) Congress in 2019.

Based on the findings of these studies, 75% of patients achieved a response. Furthermore, 50% were in remission by the end of the 60-hour infusion.

Not only was the response sustained during the 30 days follow-up period, but also 56% were still responding and 36% were in remission.

What is even more is that when it comes to reducing depressive symptoms, brexanolone injection showed to be significantly better than placebo, where the mean reduction from baseline till the end of infusion (hour 60) was significantly greater with BRX90 than placebo.

Compared to oral medications, BRX proved to be even better; according to *Robert Lasser*[3].

However, speaking of a drug that is used in such a critical group of patients (nursing mothers), during such a sensitive period in their lives (postpartum), would get

[3] Robert Lasser, MD, a psychiatrist at Sage Therapeutics, Cambridge, Massachusetts

many of us worried about safety of both mothers and their babies.

But here we get you what you need to know…

Based on the safety analysis of the previously mentioned RCTs, the most noticeable adverse events were gastrointestinal disorders, such as dry mouth, dyspepsia and diarrhea; cardiovascular disorders, including tachycardia, and flushing, which typically took place in 2% to 3% of patients who received BRX.

However, aside from the previously mentioned adverse events, ***excessive sedation*** was the one of great interest, being the one singled out by the FDA in its approval announcement for the drug, which granted it a ***Black Box Warning*** on the product label.

Where the ***FDA*** stated that, " Because of the risk of serious harm due to the sudden loss of consciousness, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring."

The safety analysis also showed that sedation or somnolence occurred in 13% of patients given BRX90 and 21% of those who received BRX60. In addition, loss of consciousness was reported in 3% and 5% of those receiving BRX90 and BRX60, respectively. On the other hand, 12% and 13% respectively experienced dizziness, vertigo, or presyncope.

What make us rest assured are the very similar overall rates of sedation of BRX compared to available antidepressants, as Lasser said. Even in those cases, simple dose interruption was enough to resolve the adverse effect.

Furthermore, BRX is only available through a restricted program called *"REMS"* which means that patients are receiving it under direct medical supervision.

Regarding the safety of BRX during breast feeding, currently the available data from a previous lactation study can set us at ease; with only about 1% excreted in breast milk, out of that only 5% is available to the baby.

To finalize our talk, it is worth noting that patients recruited in the discussed studies were hospital inpatients, which means that the placebo group was subject to more potential for bias.

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Rational Drug Use

Antibiotic Resistance

By: Ahmed Mohamed Magdy

Key facts

- Antibiotic resistance is one of the biggest threats to global health, food security, and development nowadays.

- Antibiotic resistance can affect anyone, of any age, in any country.

- Antibiotic resistance occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process.

- A growing number of infections - such as pneumonia, tuberculosis, gonorrhea, and salmonellosis- are becoming harder to treat as the antibiotics used to treat them become less effective.

- Antibiotic resistance leads to longer hospital stays, higher medical costs, and increased mortality.

Scope of the problem

Where antibiotics can be bought for human or animal use without a prescription, the emergence and spread of resistance is made worse. Similarly, in countries without standard treatment guidelines, antibiotics are often over-prescribed by health care workers and veterinarians and over-used by the public.

Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.

Impact

When infections can no longer be treated by first-line antibiotics, more expensive medicines must be used. A longer duration of illness and treatment, often in hospitals, increases health care costs as well as the economic burden on families and societies.

Prevention and control

Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance.

Here is how each member in our community can help control or even prevent the spread of antibiotic resistance.

1- Individuals

To prevent and control the spread of antibiotic resistance, individuals can:

- Only use antibiotics when prescribed by a certified health professional.
- Never demand antibiotics as long as your care giver says you don't need them.
- Always follow your care giver's advice when using antibiotics.
- Never share or use leftover antibiotics.
- Prevent infections by regularly washing hands and avoiding close contact with sick people.
- keep vaccination up to date.
- Prepare food hygienically, following the *WHO Five Keys to Safer Food* (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals.

2- Health professionals

To prevent and control the spread of antibiotic resistance, health professionals can:

- Prevent infections by ensuring their hands, environment, and instruments are clean.

- Only prescribe and dispense antibiotics when they are needed, according to current guidelines.

- Report antibiotic-resistant infections to surveillance teams.

- Talk to their patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.

- Talk to their patients about preventing infections (for example, vaccination, hand washing and covering nose and mouth when sneezing).

3- Agricultural sector

To prevent and control the spread of antibiotic resistance, the agricultural sector can:

- Only give antibiotics to animals under veterinary supervision.

- Avoid using antibiotics for growth promotion or preventing diseases in healthy animals.

- Vaccinate animals to reduce the need for antibiotics, and use alternatives to antibiotics when available.

- Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.

- Improve biosecurity on farms and prevent infections through improved hygiene and animal welfare.

Antibiotic resistance is putting the achievements of modern medicine at risk. Organ transplantation, chemotherapy and surgeries such as caesarean section would become much more dangerous without effective antibiotics for the prevention and treatment of infections.

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Off-Label Use of Drugs

Unusual uses of aspirin

By: Ahmed Mohamed Goda

A salicylate drug, often used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication.

Aspirin also has an antiplatelet effect by inhibiting the production of thromboxane, which under normal circumstances binds platelet molecules together to create a patch over damaged walls of blood vessels, because the platelet patch can become too large and block blood flow, locally and downstream.

1-Aspirin used in reducing risk of preeclampsia

Pregnant women at high risk for preeclampsia should take low-dose aspirin (75mg - 81mg) every day after their first trimester.

Mechanism

High or normal doses (>325 mg) block production of prostacyclin and thromboxane, and low-dose aspirin (60–83 mg) results in selective block of thromboxane production, and favors the prostacyclin (vasodilation) pathway.

This provides the basis for the use of low-dose aspirin to forestall or prevent pregnancy-induced hypertension. Importantly, low-dose aspirin does not completely inhibit thromboxane and does not completely 'spare' prostacyclin. One group of investigators found that 81 mg of aspirin inhibited thromboxane by 75 percent, but also inhibited prostacyclin by approximately 20 %.

2-Topical Aspirin for Relief of Pain due to Herpes Zoster and Postherpeic Neuralgia

In this case, topical aspirin dissolved in chloroform is an effective means of reducing pain due to herpes zoster and post herpetic neuralgia in most patients.

The locus of pain origin and analgesia induced by topical aspirin is most likely at cutaneous free-nerve ending pain receptors.

The mechanism responsible for the analgesic properties of aspirin is probably not the same as that responsible for its anti-inflammatory properties.

3-Aspirin and Alzheimer's

The Baltimore Longitudinal Study appearing in the journal of Neurology reported that the incidence of Alzheimer's was 45% lower for people who took aspirin for more than two years than those who did not.

Mechanism

There are numerous theories about why it seems to work. For example, one theory is that Alzheimer's is caused by an inflammatory process in the brain. Taking an anti-inflammatory medication might then reduce the risk. Another theory is that with Alzheimer's, enzymes in the brain cause a breakdown of proteins. When this occurs, amyloid plaque is formed and disrupts brain activity. Perhaps aspirin and other anti-inflammatory medications prevent this from occurring.

4- Aspirin for the prevention of colorectal cancer

Aspirin has been studied as adjuvant therapy for colorectal cancer, with promising results. Earlier prevention studies demonstrated the efficacy of aspirin against the development of colorectal tumors prompting investigation into its potential treatment efficacy.

Mechanism

The proposed mechanism draws on the fact that certain colorectal tumors overexpress prostaglandin endoperoxide synthase 2, better known as cyclooxygenase-2 (COX-2). Mutations of the sort seen in colorectal cancer are known to sustain tumor cell growth by preventing apoptosis. By blocking COX-2, aspirin therapy is hypothesized to suppress tumor growth.

Taking aspirin in doses as low as 325 mg per day reduces CRC risk also

there is also strong evidence from secondary analyses of cardiovascular trials that daily doses as low as 75 mg per day may be effective.

5-Aspirin helps in sore or ulcerated mouth

Aspirin can be used as a gargle or mouthwash, where 300 mg of aspirin are dissolved in half glass of water, rinsed around mouth and spitted out. This should be used up to 8 times in 24 hours, half an hour before meals.

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New Drug Application (NDA)

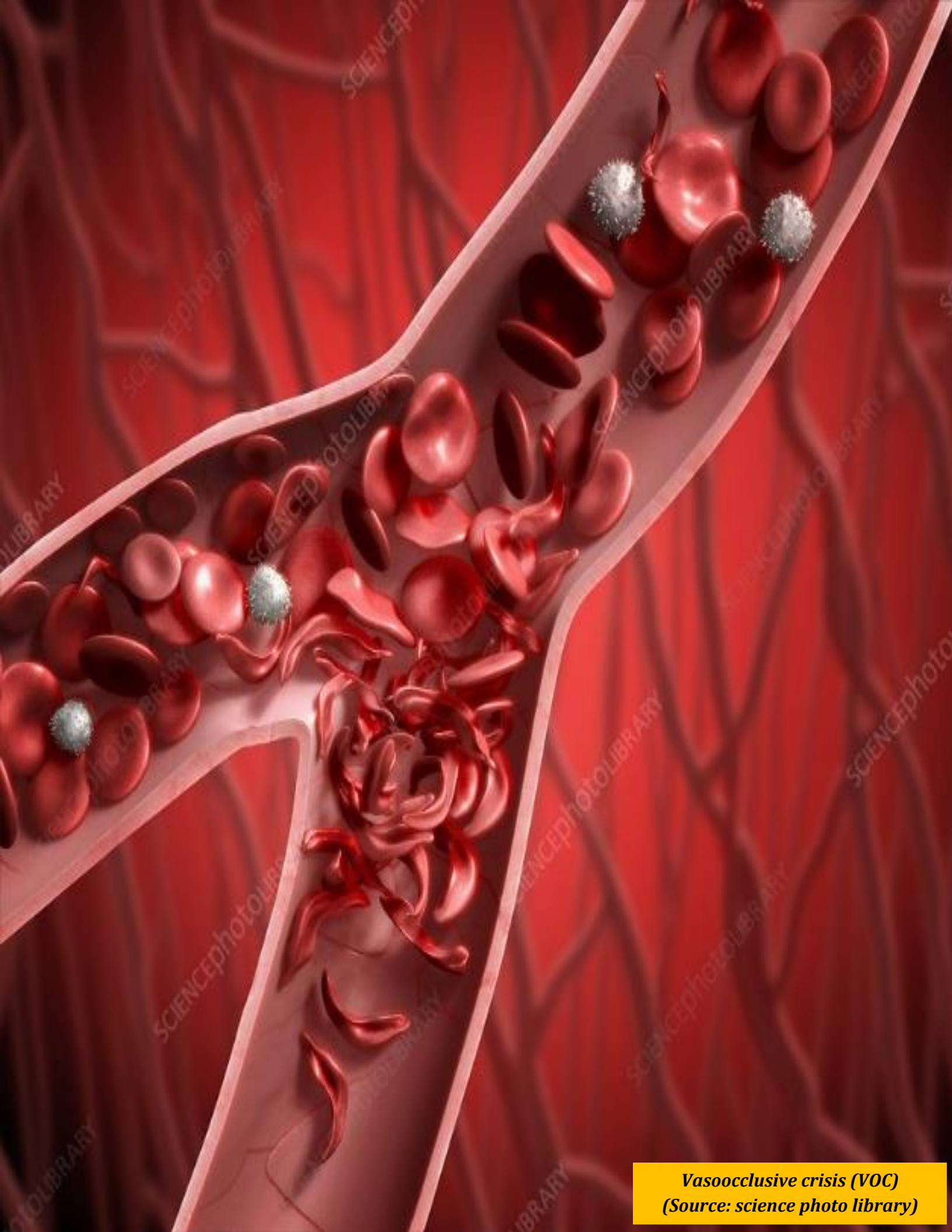
Voxelotor: The first hemoglobin oxygen-affinity modulator for the treatment of Sickle Cell Disease

By: Nada Khaled Shoura

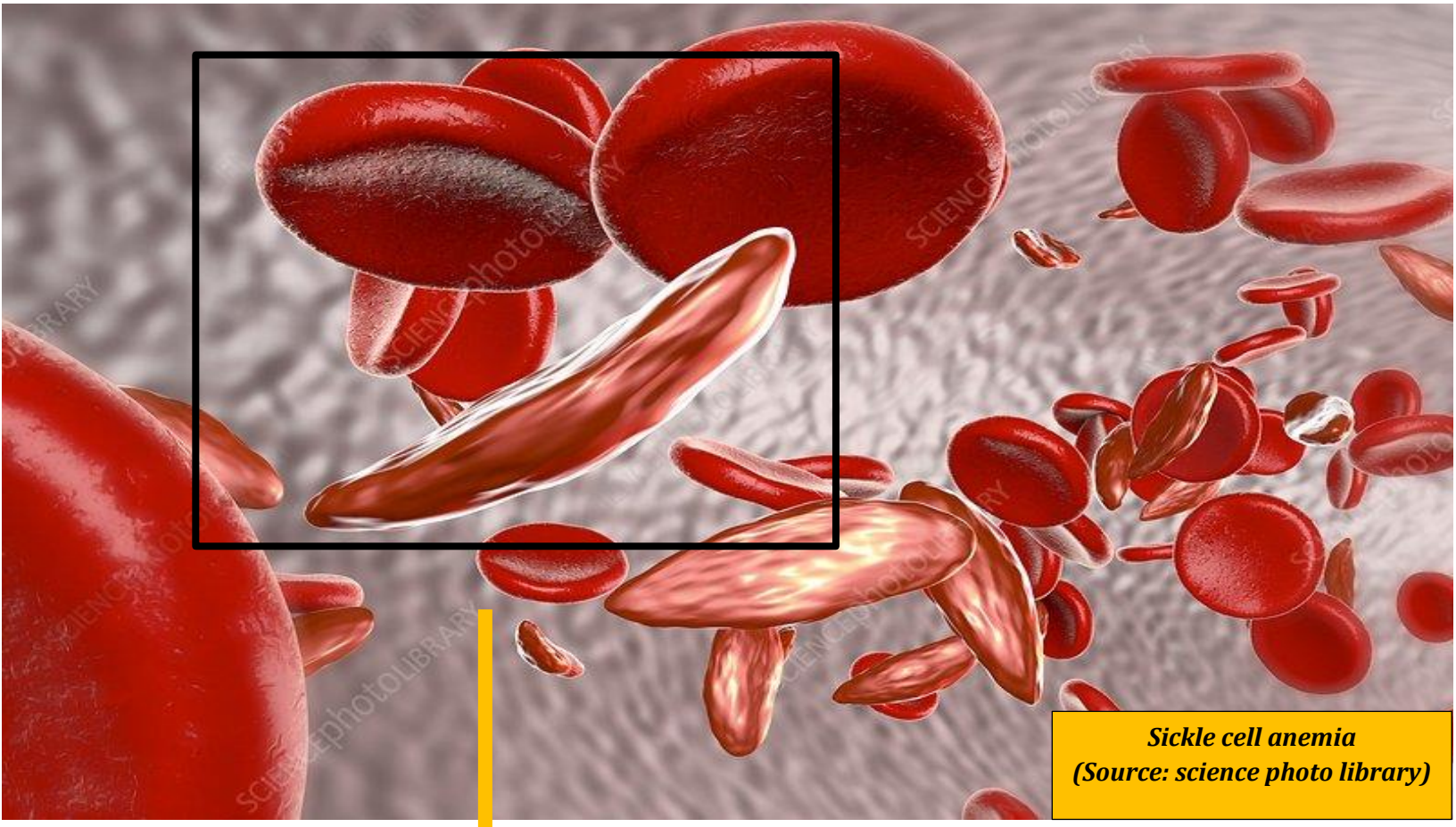
Sickle Cell disease is an inherited disorder resulting from substitution of glutaminic acid by valine at position 6 in beta globulin chain in diseased erythrocytes. This mutation causes mutant hemoglobin (HbS) to polymerize when erythrocytes are deoxygenated, resulting in change of erythrocytes' shape from a bi-concave shape to a sickle shape, and when erythrocyte are re-oxygenated HbS is de-polymerized and return to its normal bi-concave shape. This process is repeated each time erythrocytes are oxygenated and deoxygenated resulting in fragility of erythrocyte membrane, thus decrease the erythrocytes' lifespan due to high susceptibility to hemolysis. [1]

Treatment guidelines of sickle cell disease mainly depend on the management of symptoms, reducing pain crisis incidence, and prevention of complications. These treatments include blood transfusions to increase hemoglobin concentration, hydroxyurea to decrease both the incidence of pain crisis and the need for blood transfusions, and painkillers to relieve pain during the pain crisis. The only cure for sickle cell disease is bone marrow and stem cell transplantation, which is only allowed to children and teenagers with severe complications, due to possible life-threatening complications of the transplantation procedure. [2]

There was no disease-modifying drug for treatment of Sickle Cell Disease. That was until November 2019 when FDA granted accelerated approval to Voxelotor [3], which is the first in its class as a disease-modifying drug targeting the main pathophysiology of sickle cell disease. [4]



Vasoocclusive crisis (VOC)
(Source: science photo library)



Sickle cell anemia
(Source: science photo library)

Sickle cell anemia
(Source: science photo library)

Voxelotor acts on inhibiting the polymerization of mutated beta globulin chains in HbS by modulating hemoglobin oxygen binding affinity. Voxelotor binds to alpha globulin chain of HbS causing an increase in oxygen binding affinity, typically acting as an allosteric effector, keeping HbS in the oxygenated state, thus preventing it from changing to sickle shape [4]−which exists in HbS deoxygenated form as mentioned before−bringing a net result of decreasing the process of sickling and unsickling. In other words, Voxelotor stabilizes HbS. [1]

The main effect of Voxelotor is the reduction in blood hemolysis [1], which is indicated clinically by improvement in hemolysis indicators such as indirect bilirubin, percent reticulocyte count and Hemoglobin concentration. [3]

Further notes are that sickled RBC counts on peripheral blood smears decreased [5], there was an improvement in erythrocyte deformability, reduction in blood viscosity, and reversal of sickled HbS under in vitro deoxygenated conditions.

It also prevents sickling of HbS under in vitro hypoxic conditions and in sickle cell diseased mouse model; Voxelotor prolonged the lifespan of erythrocytes. [1]

Voxelotor is generally well tolerated with only mild side effects such as rash, nausea, abdominal pain and headache [6], but like any other drug, there are many points healthcare professionals should take into consideration before and during

Voxelotor therapy

A bottle of Oxbryta® (voxelotor) 500mg tablets (Source: international thalassaemia international federation)

Monitoring

Monitoring signs and symptoms of hypersensitivity is necessary, as serious hypersensitivity reactions after administration of Voxelotor have occurred in <1% of patient treated,

which necessitate discontinuing Voxelotor and it was sever enough to contraindicate voxelotor use again. Clinical manifestations of hypersensitivity include generalized rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia. [6]

Also, it is recommended to monitor oxygen saturation when therapy is initiated, due to concerns about tissue hypoxia associated with Voxelotor therapy [1], which will be discussed in detail later.

Monitor hepatic function, as Voxelotor is mainly metabolized by the liver and in case of severe hepatic impairment (child pugh class C), dose adjustment is necessary. [1]

Voxelotor interferes with measurement of hemoglobin subtypes (HbA, HbF, HbS) using HPLC, leading to inaccurate hemoglobin monitoring. Testing facilities must be informed with treatment regimen in order to avoid misdiagnosis and unnecessary additional testing. [7]

Pregnancy and lactation

There are no available human data about the use of Voxelotor in pregnant women, but animal studies on pregnant rats and rabbits showed no adverse developmental effect at maximum recommended dose. Pregnant sickle cell diseased women have greater potential of adverse pregnancy outcomes including greater risk for vaso-occlusive crises, pre-eclampsia, eclampsia, and maternal mortality.

As for the fetus, there is an increased risk for intra-uterine growth restriction, preterm delivery, low birth weight, and perinatal mortality. Due to all these harmful effects of sickle cell disease, Voxelotor should only be used during pregnancy if benefits of the drug outweigh potential risks. [6]

Just like pregnancy, there are no available human data about the existence of Voxelotor in breast milk, but since Voxelotor exists in animal milk in a concentration lower than plasma concentration, it is predictable that it exists in human milk. It is not recommended to prescribe Voxelotor for lactating women because of possible risk of serious adverse effects in infants including changes in the hematopoietic system. [6]

Drug interactions

Voxelotor is mainly metabolized through phase II hepatic oxidation

mediated by CYP3A4, so it is recommended to avoid concomitant administration with moderate or strong inhibitors and inducers of CYP3A4.

If concomitant administration is unavoidable, Voxelotor dose should be adjusted. Also, avoid concomitant administration with sensitive CYP3A4 substrates with narrow therapeutic index such as Midazolam. Lowering of CYP3A4 substrate dose is a must if co-administration is unavoidable. [6]

Efficacy of Voxelotor

Based on the improvement of surrogate endpoint such as Hb concentration and hemolytic markers in phase III clinical trial [8] , FDA granted accelerated approval for adults and pediatric patients 12 years of age and older with sickle cell disease. The recommended dose is 1500 mg orally once daily with or without food. [3]

In phase III clinical trial, 274 patients were enrolled in order to evaluate Voxelotor efficacy. The primary efficacy outcome measure was Hb response rate defined as an Hb increase of >1 g/dL from baseline to week 24. The response rate for Voxelotor was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group. Additional efficacy evaluations included percent change in indirect bilirubin and percent reticulocyte count during 24 weeks. All of them showed improvement compared to placebo group. [8]

In one case report, a patient gained compassionate access (access to investigational drug outside clinical trials for patients with serious condition and no other alternative options available [9]), Voxelotor failed to show increase in Hb level. The patient had history of severe anemia, which was refractory to blood transfusion due to auto-antibody mediated hemolysis.

Authors hypothesized that failure may be attributed to already existing auto-antibody mediated hemolysis, that further shortened the erythrocytes lifespan. Authors concluded that patient with severe anemia may need higher doses of Voxelotor to show efficacy. [10]

Clinical benefits of Voxelotor

The primary clinical benefits of Voxelotor are the improvement in hemoglobin level and hemolysis, but there was no statistically significant

difference in the vaso-occlusive crisis rate. [1]

Products of hemolysis such as heme and free hemoglobin bind to nitric oxide causing nitric oxide deficiency and depletion, which in turn will cause vasoconstriction and inflammation [11], contributing to chronic organ dysfunction on the long term run. Patients with sickle cell anemia on Voxelotor therapy may benefit from reduced hemolysis in preventing chronic organ damage [1], which is one of the leading causes of mortality in those patients. [12]

Also, many patients come with chronic severe anemia who almost depend on chronic blood transfusions, leading to development of blood transfusion complications such as auto-immunity and iron overload. As Voxelotor raise Hb levels, it may provide an effective therapeutic alternative to those patients leading to reduction in blood transfusion rate and improvement in quality of life. [1]

Despite how promising Voxelotor looks, there are theoretical concerns about possible peripheral tissue hypoxia due to increased oxygen affinity to HbS, that may impair its oxygen delivering function, especially that patients have already an existing risk of hypoxia due to impaired blood flow. The theory suggests that hemoglobin level improvement may not be sufficient to compensate Voxelotor-HbS complex impaired function. [1]

The other perspective suggests that if tissue hypoxia occurred, erythropoietin serum level rises followed by reticulocytosis and an increased cardiac output under conditions of exercise stress, which has not happened in practice.

In one study, evaluated this concern, a number of evaluations were performed to a number of healthy volunteers who received multiple doses of Voxelotor and achieved 40% oxygen modification. Results show no evidence of elevation in neither erythropoietin plasma level nor reticulocyte count and no increase in heart rate in both resting and exercise stress conditions. [13]

In addition, in one case series, 7 patients had severe anemia for which they received Voxelotor. 4 out of 7 had a baseline oxygen saturation of <95%, which improved to 98%-99% with Voxelotor treatment, allowing 2

patients of them to discontinue long-term supplemental oxygen. [14]

In one conference paper, Voxelotor has been tested in improving hypoxemia and resultant tissue hypoxia in a patient suffering from idiopathic pulmonary fibrosis. Results show improvement in oxygen saturation and reduction in oxygen desaturation after a 6 minutes walk test with no evidence of Voxelotor related tissue hypoxia. [15]

Despite these clinical evidences, controversy is still standing and only post marketing phase IV clinical trials will settle this argument and give us clear and satisfying answers to all the concerns and question marks about long term clinical effects, safety, and use in wider population, hoping for answers that open wider horizons in treatment of sickle cell disease.

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Guidelines

Recent guidelines for hypertensive patients with diabetes

By: Omar Yasser El Azzazy

Introduction

Several guidelines are released to aid clinicians in managing hypertension in patients with diabetes. Although there is an absolute desire to treat hypertension in diabetes, professional organizations and experts have contradicted assumptions towards the best blood pressure targets and treatments to minimize vascular risks in diabetic patients. Therefore, the purpose of this article is to abstract the most up to date hypertension management guidelines in diabetic patients.

Screening and Diagnosis

According to **Grundy et al.** (2019), **DeFilippis et al.** (2017), *and* **Bohula et al.** (2017):

- Blood pressure should be evaluated at each clinical visit. Subsequently, if blood pressure is more than or equal 140/90 mmHg, patient's blood pressure should be ascertained by several readings, including measurements on a separate day.
- Every patient with diabetes and hypertension should monitor his blood pressure at home.

HYPERTENSION CONTROL

According to **De Boer et al.** (2017), **Bobrie et al.** (2001), *and* **Omboni et al.** (2013):

- For patients with diabetes and hypertension, blood pressure targets should be determined through a shared compromise that collects adverse effects of antihypertensive and antidiabetic medications and patient preferences (Association 2020).
- For patients with existing atherosclerotic cardiovascular disease (ASCVD) or 10-year ASCVD risk >15% that have diabetes and hypertension, a blood pressure goal of <130/80 mmHg may be appropriate, if it can be safely achieved.
- For pregnant women with diabetes and preexisting hypertension, a blood pressure goal of ≤135/85 mmHg is *targeted in* order to reduce the risk for maternal hypertension and minimize impaired fetal growth.

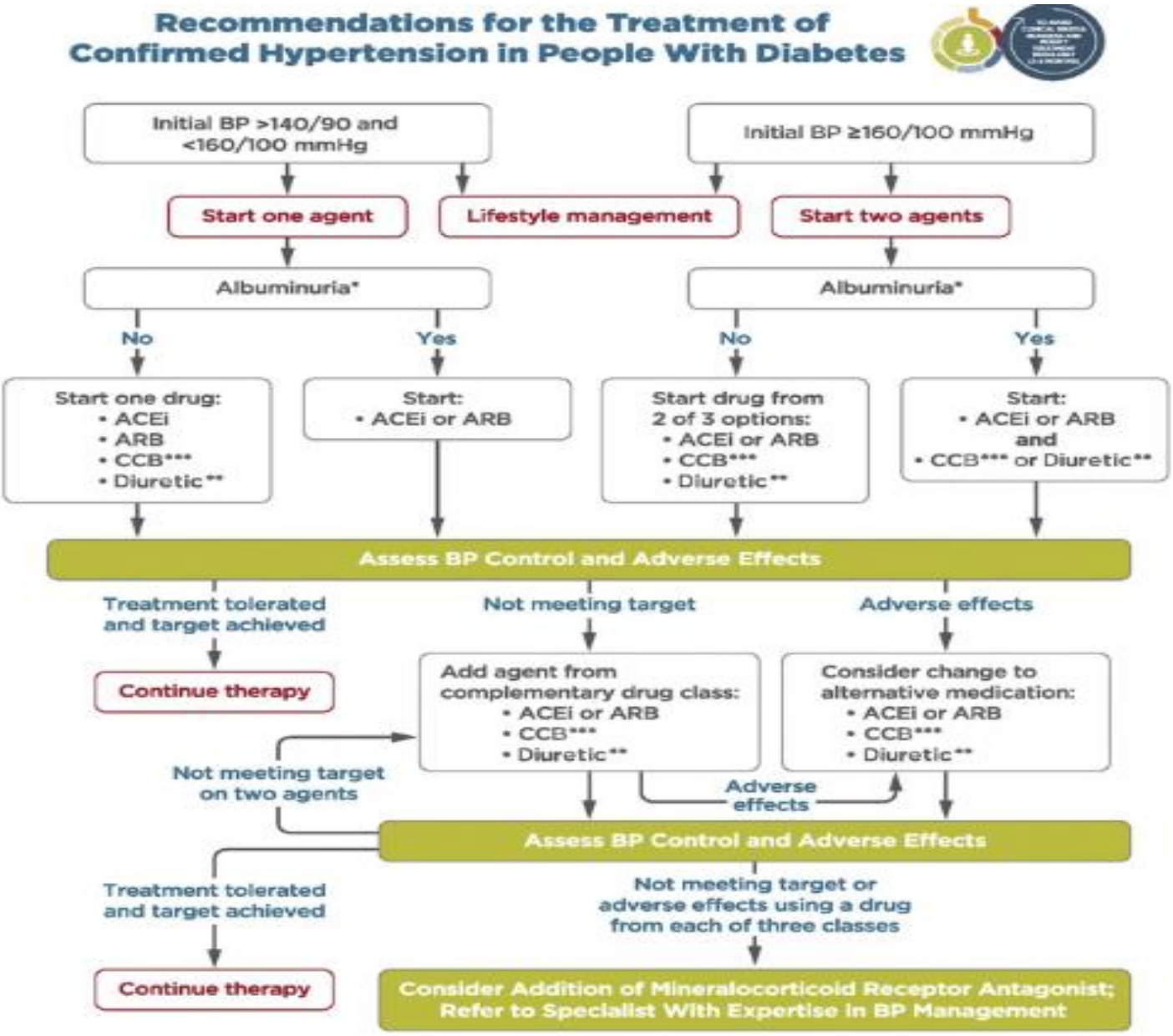
Recommendations

(Emdin et al. 2015), (Ettehad et al. 2016), (Brunström and Carlberg 2016), (Thomopoulos, Parati, and Zanchetti 2017), *and* (Bakris 2016)

- Patients with blood pressure ≥140/ 90 mmHg should have immediate initiation and gradual titration of pharmacologic therapy to achieve blood pressure goal besides lifestyle modifications.
- Patients having blood pressure ≥160/ 100 mmHg should have immediate initiation and gradual titration of two drugs, since combination of drugs demonstrated to minimize cardiovascular events in patients with diabetes besides lifestyle modifications.
- Hypertension pharmacological treatment includes ACE

inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers to reduce cardiovascular events in patients with diabetes.

- Multiple-drug therapy is typically prescribed to achieve blood pressure targets. On the other hand, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should be prevented.
- An ACE inhibitor or angiotensin receptor blocker is the first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g.
- For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic; serum creatinine/estimated glomerular filtration rate, and serum potassium levels should be checked at least every year.



Recommendations for the treatment of confirmed hypertension in people with diabetes (De Boer et al. 2017)

ACE inhibitor (ACEi), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), blood pressure (BP)

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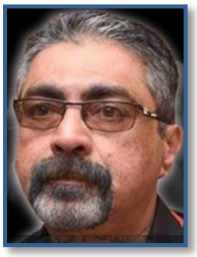
Gone, but not forgotten

We dedicate this part *in memoriam of* our colleagues in the "*white army*", for the sake of their sacrifices, being in the front lines fighting the pandemic. For them we say, "Thank you, we owe you our lives".

Mohammad Abdelbasett Eljabri, age unknown, Infectious Disease Specialist, Imbaba Fevers Hospital, Egypt

Amro Abed, age unknown, Professor of Internal Medicine and Nephrology, Alexandria University Hospital, Alexandria, Egypt



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Mohamed Fathi Khalil, 33, Pharmacy, Minya Al-Qamh, Egypt

Medhat Reesha, age unknown, Pharmacist, Kafr Elzayyat, Egypt

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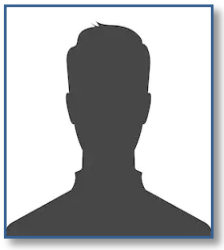

Michael Wageeh, age unknown, Orthopedics, Egypt

Walid Yahya Abdelhaleem, 32, OB-GYN, Almuneerah General Hospital, Cairo, Egypt

These data are based on *Medscape memorial list.*

And you dear reader can help us honorify those who save lives, by sending us names and photos of members of medical teams who are "gone, but not forgotten", through the following link:

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