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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Minutes of Virtual Meeting of CMAAO NMAs on "COVID-19 Update"

29th August, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Marthanda Pillai, Member-World Medical Council; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Prakash Budhathoky, Nepal

Invitees: Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr S Sharma, Editor-IJCP Group

Key points from the discussion

- Three acute phase reactants–C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and interleukin (IL)-6. In a resource-limited country, CRP is the best choice amongst the three. It is an indicator of intensity of inflammation. CRP cannot rise without increase in IL-6. When CRP is raised, presume that the D-dimer is high.
- We do not know how China with a higher population density than India has managed to control the disease. Mortality is 3 per million; new cases are 9.
- Antigens of various diseases such as typhoid, malaria, chikungunya and dengue are false-positive in coronavirus disease 2019 (COVID-19).
- "*All overseas players and support staff underwent two COVID-19 reverse transcription polymerase chain reaction (RT-PCR) tests before flying into the UAE and could fly only if the tests were negative. If not, then the same 14-day quarantine period and two negative tests was needed to be able to fly to the UAE. The players and support staff will be tested on Day 1, Day 3 and Day 6 of their quarantine in the UAE and after clearing that, they will be tested every fifth day during the 53-day event.*" Instead of three tests, pooled testing of the teams can be done daily.
- Oxygen administered without anticoagulation has no significance. Aspirin/anticoagulation must be given. For cases under home care, rivaroxaban (10 mg prophylaxis) can be given in place of low molecular weight heparin (LMWH); it is cheaper, can be taken by the patient, onset of action is 10 hours.
- According to a Times of India report, 87,000 healthcare workers (HCWs) in India are infected with COVID-19; there have been 573 deaths; 74% cases and over 86% deaths are from six states: Maharashtra, Tamil Nadu, Delhi, West Bengal, Gujarat and Karnataka. The numbers projected seem to be very high and need to be checked.
- Doctors have a high viral load so have higher chances of developing hypercoagulable state. Should prophylactic anticoagulation be initiated on Day 1 of the illness itself for doctors/HCWs?
- There are three phases of the illness: COVID (1-9 days, infectious phase), post-COVID (after 9 days, noninfectious, persistent inflammation) and non-COVID (after 3 months). After 3 months, the patient should be treated as non-COVID, instead of post-COVID. However, this comes laced with medicolegal aspects.
- In Hong Kong, the third wave is partly controlled. There have been less than 20 cases per day for the last week or more. One-third of confirmed cases have no known source of origin; so, the chain of spread of infection is not known. Universal community testing scheme will start from 1st September to find out silent carriers. The Hong Kong government has agreed to expand to high-risk group tracing and testing even with universal testing. With opening up of economy, better monitoring of industries is mandatory, to ensure there is no fourth wave. The third wave began with 9 cases with mutated virus strain (d614g). At that time, sailors coming to Hong Kong had been exempted from testing and quarantine; also restrictions of social distancing were relaxed. This created the third wave.
- Reinfection: A person from Spain tested positive in March then became negative reached Hong Kong and tested positive again in July. This raises a question whether this virus can re-infect. It was a mutated virus with 24 gene differences. It formed antibodies quickly, caused no symptoms and no

serious manifestations and disappeared early. We need to be vigilant about this. People in post-COVID phase getting recurrent corona-like illness may be getting reinfection with a different strain.

- Another case of reinfection reported in the US; a young person who had severe symptoms and required oxygen and assisted breathing in the second infection.
- A study from Mumbai has reconfirmed the US study that antibodies do not last for more than 3 months.

With input from Dr Monica Vasudev

Round Table Expert Zoom Meeting on "Role of Thymus in Enhancing Immunity Against COVID-19"

29th August, 2020 (Saturday, 11 am-12 noon)

Participants: Dr KK Aggarwal, Dr AK Agarwal, Dr Suneela Garg, Dr Jayakrishnan Alapet, Dr DR Rai, Dr Tripathi, Dr Angeli Misra, Dr Atul Pandya, Prof Bejon Misra, Dr Anil Kumar, Mrs Upasana Arora, Ms Ira Gupta, Dr S Sharma

Faculty: Dr Jagat Kaul, Director Prof and Former Head, Dept. of Anatomy, Maulana Azad Medical College, New Delhi; Consultant Academics and Advisor, Baba Saheb Ambedkar Medical College, Govt. of Delhi

Key points from the discussion

- Thymus is the primary lymphoid organ besides bone marrow and provides T lymphocytes to the whole body. It provides specificity of T-cell responses and immune tolerance to self.
- It influences and is influenced by products of neuroendocrine axis of the body.
- Thymus varies at different stages of life under the influence of different physiological and pathological states.
- The shape of thymus is molded to the adjacent structures and weighs about 20 g in adults. It is reddish in color and becomes yellowish with advancing age due to adipose infiltration at the cost of active lymphoid tissue. The older thymus can be distinguished from surrounding mediastinal fat only by the presence of the capsule, which covers the gland.
- The thymic microstructure consists of cortex (thymocytes) and the medulla (epithelial cells, lymphocytes). The blast cells in the subcapsular cortex do not express any marker.
- Type 1 cells are subcapsular and attract blast cells from bone marrow by way of their negative surface charge. Type 6 cells are commonest and form thymic hormone.
- Hassall's corpuscles start to form in the intrauterine life and are very well-established by the 5th month of intrauterine life; they increase with age.
- The T lymphocytes carry out cell-mediated defense actions by their effector and controlling actions.
- Via the effector action, they directly kill by cytotoxic substances (which release toxic lysosomal proteins) and indirectly by cytotoxins. Through the controlling action, they induce or suppress immune responses in B and T lymphocytes or any other variety of cells derived from the bone marrow. It can also cause delayed hypersensitivity response causing release of cytokines, which stimulate phagocytosis and chemotaxis.
- The natural killer cells are devoid of T-cell receptors and are not restricted by MHC protein.
- Suppression cells are certain T cells, which when stimulated, suppress the activity of B cells and other T cells.
- There is a fine balance between positive and negative controls in the T-cell system, which is lost in COVID-19.
- The thymic hormones (thymulin, thymosin, thymopentin, thymic humoral factor) exert immunomodulatory effects on maturation of lymphocytes and induce markers of early differentiation on lymphoid cells and enhance function of T cells. Thymulin relies on zinc for its biological action.
- Thymocytes secrete IL-1, 2, 4, 6; thymic epithelium secretes IL-1, 3, 4, 6 and 7.
- Nonlymphocytic thymic cells are cells of mononuclear phagocytic system in the form of monocytes and interdigitating cells. They present antigens to T cells as they move from cortex to medulla.
- Hormones can affect thymic function and thymic factors often affect other endocrine organs.
- Thymocytes have receptors for corticosteroids, oxytocin and estrogens.
- High levels of corticosteroids kill cortical lymphocytes and low steroid levels have a thymopoietic effect.
- The thymus increases in weight up to the first year of life, then the weight remains fairly constant at around 20 g until the 6th decade of life, and then the weight starts reducing.

- Pathogens may be more infective and prevalent in the elderly, yet may affect the young also; these are gerophilic in nature.
- Infections including COVID-19 are gerolavic. It has been seen that older adults were at greater risk of serious illness due to COVID-19 compared to children.
- Emerging research has shown that there is a marked decrease in the number of T cells in some seriously ill patients.
- It seems that the entire process of COVID-19 (T cells, IL-6, CD4) is directly or indirectly linked to the thymus.
- The role of T and B lymphocytes has opened up vistas of knowledge. It has helped to understand memory, tolerance, autoimmunity, immunodeficiency as well as inflammatory and immunopathological phenomenon.
- Recent investigations have highlighted the role of increased proinflammatory cytokines, impaired type 1 interferon response and functional exhaustion of antiviral lymphocytes in the elderly.

With input from Dr Monica Vasudev

Nearly One Quarter of Children Hospitalized with COVID-19 Developed Eye Symptoms in China

Among Chinese children hospitalized for COVID-19, about a quarter of them developed ocular symptoms.

Most of them developed eye symptoms later in the disease; however, ocular manifestations were the first sign of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in 9 of them. Ocular symptoms resolved in all the children. The report is published in *JAMA Ophthalmology*.

Out of 216 children hospitalized with COVID-19 in Wuhan, China, 49, i.e., 22.7% had ocular manifestations, including conjunctival discharge, eye rubbing, and conjunctival congestion.

Children with systemic symptoms or cough had a higher likelihood of developing ocular symptoms, which were mild and recovered or improved by minimal eye-drops or self-healing.

Overall, 193 children had an exposure to a family member with confirmed (173) or suspected (20) COVID-19. Among the study children, 93 experienced no systemic or respiratory symptoms before being tested. The most common symptoms among symptomatic children included fever and cough. All the children with mild (101) or moderate (115) symptoms recovered.

The initial symptoms were predominantly fever and cough, while there were other symptoms including diarrhea, fatigue, nasal discharge, nasal congestion, conjunctival discharge and conjunctival congestion.

Forty-nine children had ocular manifestations. Conjunctival discharge was the most common manifestation, followed by eye rubbing and conjunctival congestion.

Children with systemic symptoms were more likely to develop ocular symptoms. It seems possible that cough can lead to ocular infection through hand-eye contact in children. It is also possible that the force of the cough could push nasopharyngeal secretions from the nasolacrimal duct into the conjunctival sac.

Most of the children had other symptoms before the ocular manifestations started.

The new findings are reassuring as all the children recovered from their eye symptoms.

(*Source: Medscape; JAMA Ophthalmology, online August 26, 2020.*)

COVID-19 Often Undiagnosed in Frontline Hospital Workers

Reuters excerpts: A large number of COVID-19 infections among healthcare personnel in the US appear to go undetected, according to a report in the *Morbidity and Mortality Weekly Report* of the US Centers for Disease Control.

From April through June, among over 3,000 frontline workers across 12 states, approximately 1 in 20 had antibody evidence of a previous COVID-19 infection. Of note, 69% of those infections had never been diagnosed.

Among HCWs with antibodies to the novel coronavirus, nearly one-third did not recall having symptoms in the preceding months, about half of them did not suspect that they had been infected, and around two-thirds of them had never had a positive COVID-19 test.

Infections among frontline HCWs appear to be going undetected, as some infections may be minimally symptomatic or asymptomatic. Additionally, personnel with symptoms may not always have access to testing.

COVID-19 antibodies were less common among workers using a face covering for all patient encounters and more common among those who reporting a shortage of personal protective equipment.

With input from Dr Monica Vasudev

Minutes of Virtual Meeting of CMAAO NMAs on "One Year of CMAAO and COVID-19 Update"

5th August, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Marthanda Pillai, Member-World Medical Council; Dr Yeh Woei Chong, Singapore Chair, CMAAO; Dr Ravi Naidu, Malaysia, Immediate Past President-CMAAO; Dr N Gnanabaskaran, President-Malaysian Medical Association; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Marie Uzawa Urabe, Japan; Dr Prakash Budhathoky, Nepal; Dr Tashi Tenzin; Bhutan'Dr Md Jamaluddin Chowdhury, Bangladesh

Invitees: Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr S Sharma, Editor-IJCP Group

This meeting was dedicated to the memory of all those who lost their lives in the COVID-19 pandemic.

Key points from the discussion

- **Singapore Update:** The outbreak in the dormitories is reaching its tail end; 40-50 cases; while cases in the community range from 0 to 1-2 cases. The focus is now on the economic damage and how the economy will open up. Singapore has opened its borders to New Zealand and Brunei.
- **Bangladesh Update:** Around 2,000 cases per day; a concern is that people are not going for testing out of fear. A study in Bangladesh conducted by the Institute of Epidemiology, Disease Control and Research and the International Centre for Diarrhoeal Disease Research, Bangladesh in Dhaka has shown that 9% of population in slum areas and 6% in the non-slum areas have the infection. These are asymptomatic infections. The number of deaths is declining but hovering around 35-40 per day.
- **Nepal Update:** The infection rate is increasing, as are severity of infection and deaths. Random samples have tested positive. Russia/China/UK are conducting 3rd phase clinical trials in Nepal. Doctors are conducting awareness programs.
- **Hong Kong Update**: Universal community testing scheme is underway since the past week, although not too many people go for testing; less than 1 million people have joined testing in the last 5 days. Nasal (not nasopharyngeal) and oropharyngeal swabs are collected. Some silent cases have been detected. From 2 weeks of high incidence (140 per day) in end of July, cases have slowly decreased to now single digit in August. In some cases, no source could be traced. Schools have restarted; for now it is online learning; but planning to reopen schooling from end of September.
- **Bhutan Update:** The first case was detected on 5th March in an American tourist aged 76 years. Total 128 cases; 150 have recovered; no deaths have been reported. Some positive cases have been reported in the border town of Phuntsholing (red zone), but no severe cases. The King of Bhutan has actively participated in creating awareness. The quarantine period is 21 days. Cases are discussed with doctors from Singapore and India and other commonwealth countries. All schools have been closed countrywide.
- **Malaysia Update:** There are 9,385 active cases; 9,092 are recovering; less than 20 new cases and total deaths are 128. More than 2.5 million foreign/ migrant workers are a concern; there is no wide testing, like in Singapore. Malaysia has detected a mutated strain of SARS-CoV-2 virus in a cluster of cases, called the "Sivaganga cluster". The index case belongs to Sivaganga in Tamil Nadu. Because of clusters, recovery movement control order (RMCO) has been extended to 31st December. The number of children affected is very small. Young people recover quite well. The Ministry of Health and the Malaysia Medical Association are working close together. People from any country which has 1,50,000 cases are not allowed entry into Malaysia.
- **Japan Update:** About 70,000 have tested positive; 103 deaths; the mortality rate is less than 1%. Treatment of inpatient is being gradually consolidated. Flu will soon begin; preparing to how to deal with both.
- **India Update:** The numbers are rising; India now has the 3rd highest number of cases (at the time of virtual meeting). But, the mortality rate is less than 1.2%. Recovery rate is more than 70%. About 60% of infections are from southern states. Government has been proactive in controlling the disease as and when issues come up. Testing rate is going up. The pandemic in India should plateau within 2 weeks to a month.
- **Australia Update:** Victoria had a second wave due to failure of quarantine measures, but now the number has come down to around 70. Rest of the country has had no cases. The lockdown is going to continue for another week. August 6, the PM is going to give a pathway on how to relax the restrictions. Travel (airports, ships) has been stopped until December. Melbourne, Victoria is

completely closed down. Deaths are mostly in the aged care homes; deaths in Victoria are around 600.

- ***Dr KK Aggarwal introduced his initiatives:*** Health Patrol, International Journal of Pandemic Research and COVID Educator Course. The objective of Health Patrol is to filter out fake news; you can visit the website and ask to check its authenticity. He asked Singapore to join as Knowledge Partner and all NMAs as advisors. The International Journal of Pandemic Research will publish articles related to COVID-19 and any other pandemic, as they are, without any change. Anybody from anywhere can publish data. These would subsequently be peer reviewed. All participating member NMAs were invited to be peer reviewers. Similar COVID Educator Courses can be started in member countries to create COVID Educators in the community.
- There are still some unanswered questions: Why does it cause post-COVID illness after 9 days and causing recurrent inflammations; why children are not spreading infection; which vaccine will work.
- The number of deaths so far in healthcare professionals throughout the world is 8% and the number of infections in them is 10-15% (WMA).
- The vaccine may not be widespread till mid-2021.

IMA-CMAAO Webinar on "Understanding the Molecular Biology of Coronavirus Proteins"

5th September, 2020 (Saturday, 4-5 pm)

Participants: Dr KK Aggarwal, President-CMAAO; Dr RV Asokan, Hony Secretary General-IMA; Dr Ramesh K Datta, Hony Finance Secretary-IMA; Dr Jayakrishnan Alapet; Dr S Sharma

Faculty: Dr Pavithra Venkatagopalan, PhD Coronavirus Studies, Director-Care Health Diagnostic Center, Chennai

Key points from the discussion

- Life has three main domains: Bacteria and Archaea, which are single-celled; everything else - from yeast to humans - comes under Eukarya.
- Viruses have their own domain. A virus is neither living nor dead; it is an obligate intracellular parasite.
- All cells in the domain of life carry DNA (genetic information), which make mRNA (instructions for forming a protein from a gene) via transcription. This information is translated to form proteins.
- DNA viruses can be either double- or single-stranded; double-stranded can be enveloped or unenveloped.
- RNA viruses (coronaviruses) have no DNA in their entire life cycle.
- Coronaviruses are classified under order Nidovirales and family Coronaviridae. The viruses under this order typically infect humans and animals, so they are typically considered zoonotic viruses. Bats are a common reservoir (Nipah, rabies, etc.).
- They mainly cause respiratory and enteric infections. About 30% of all common colds are caused by coronaviruses.
- Coronaviruses are divided into three classes: Alpha, beta (COVID) and gamma. Genetic sequencing has been identified - COVID-19 virus as being very close to bat coronaviruses.
- The virus has four structural proteins (spike, membrane, envelope and nucleocapsid) and one RNA (viral genome).
- The S protein has two domains (N terminal and C terminal); the N terminal is the exposed part and binds to the ACE2 receptors. The C terminal causes change in the viral envelope structure so that it fuses with the cellular envelope, thereby releasing virus RNA into the cell.
- After infection occurs, the S protein downregulates the expression of ACE2 receptors and promotes lung injury, resulting in respiratory distress.
- The virus lifecycle is entirely in the cytoplasm. The viral genome resembles cell mRNA so the cell recognizes it as its own and starts making mRNA. RdRP (RNA-dependent RNA-polymerase) will make more copies of the genome. And, the cellular translation machinery will make all the viral proteins.
- RdRP is the target for antivirals (remdesivir).
- The coronavirus is a single-stranded, positive sense ~30 kb RNA genome virus.
- Functions of coronavirus proteins: The function of ORF 1ab-15 nonstructural protein is virus replication, proofreading and suppression of cellular immunity. The spike protein enables receptor binding and entry into the cell and initiates infection. ORF3 causes virus release, envelope protein is responsible for virus assembly and the membrane protein (most abundant of the viral protein) forms and stabilizes the viral envelope. ORF 6, 7a, 7b, 8a, 8b, 9b suppress

cellular immunity and help virus release. The Nsp 3 protein counteracts host innate immunity, while Nsp 4, 6 and Nsp 7-10 are involved in the replication of the genome. Nsp 16 is involved in proofreading. N proteins increase interferon resistance to cell.

- RT-PCR detects ORF 1ab and E proteins to see if full genome replication is taking place.
- Proteins are synthesized in the endoplasmic reticulum and the assembly takes place in ERGIC (ER-Golgi Intermediate Compartment) and then the virus is released from the cell.
- Testing is relevant as we want to see active virus replication. It checks the entire genome. Whatever gene you test, they should be spaced apart.
- Most labs have cut off value of 40 cycles; New York Public health system says this has to be higher as otherwise asymptomatic cases can be missed.
- Worsening infection does not mean lower cycle threshold (Ct) value.

With input from Dr Monica Vasudev

Anticoagulation or Not

Direct oral anticoagulants widely used among patients requiring both short- and long-term anticoagulation

Direct oral anticoagulants (DOACs) are preferred agents owing to their ease of use, favorable pharmacokinetic profile with fixed dosing, decreased drug-drug interactions and the lack of monitoring requirements. With the increasing use of DOACs, physicians must be able to manage patients on these medications in the perioperative period, while balancing the risk of bleeding with that of thromboembolic events.

COVID-19: Hypercoagulability

Outpatient thromboprophylaxis

Patients discharged from the hospital—Those with documented venous thromboembolism (VTE) need at least 3 months of anticoagulation.

Some individuals who have not had a VTE may also require extended thromboprophylaxis following hospital discharge.

- In individuals with other risk factors for VTE like immobilization, recent surgery or trauma.
- Older age.
- Bleeding risk must be incorporated into decision-making.
- Options for post-discharge prophylaxis include those used in clinical trials, such as rivaroxaban 10 mg daily for 31-39 days.

Patients not admitted to the hospital—Outpatient thromboprophylaxis may be appropriate for some individuals with COVID-19 who are not admitted to the hospital, particularly those with other thrombotic risk factors such as prior VTE or recent surgery, trauma or immobilization. This is based on clinical judgment. If thromboprophylaxis is used in an outpatient, rivaroxaban 10 mg daily for 31-39 days may be given. (*UpToDate*)

Clinical indications for therapeutic anticoagulation

For inpatients, particularly those who are critically ill, LMWH or UFH (unfractionated heparin) for any indication is preferred in place of a DOAC, on account of their shorter half-lives and ability for parenteral administration.

COVID-19 patients tend to have elevated levels of fibrinogen.

The issue of using therapeutic-dose anticoagulation for presumed pulmonary embolism has been encountered in many ICUs across the world owing to the difficulty in moving mechanically ventilated patients to computed tomography (CT) scanners and the desire or the need to limit staff exposure to COVID-19 positive patients. D-dimer is often not helpful, on account of the significant baseline elevations in these patients. Sudden respiratory decompensation, evidence of right-heart strain on echocardiography, or DVT evident on lower-extremity ultrasound performed for these reasons have been used to increase to therapeutic-dose anticoagulation. (*Connors JM, et al. Blood. 2020;135(23):2033-40.*)

Blood thinners may improve survival in hospitalized COVID-19 patients

A study published May 6 in the *Journal of the American College of Cardiology* found that hospitalized COVID-19 patients treated with anticoagulants had improved outcomes both in and out of the ICU setting.

The study revealed that anticoagulants taken orally, subcutaneously or intravenously may play a pivotal role in COVID-19 patients, and may prevent possible fatal events associated with COVID-19, including heart attack, stroke and pulmonary embolism.

Using anticoagulants should be considered when patients get admitted to the ER and have tested positive for COVID-19 in order to improve outcomes. However, each case should be evaluated on an individualized basis to account for potential bleeding risk.

This study follows recent research from the Icahn School of Medicine at Mount Sinai, which showed that a large number of patients hospitalized with COVID-19 developed high levels of life-threatening blood clots, leading to potentially deadly thromboembolic events. (*Source: https://www.eurekalert.org/pub_releases/2020-05/tmsh-btm050420.php*)

The current crisis thus offers several arguments in favor of anticoagulation with DOACs in patients without contraindications.

- For patients in whom oral anticoagulation must be started, it seems appropriate to favor the use of DOACs.
- For patients on long-term vitamin K antagonist (VKA), the current crisis seems to be an opportunity to switch them to a DOAC.
- For patients who should remain on VKAs (mechanical cardiac valve, antiphospholipid syndrome, renal impairment depending on it severity…), the use of point-of-care (POC) devices for measuring INR should be promoted.

(*Impact of the COVID-19 pandemic on therapeutic choices in Thrombosis-Hemostasis. Journal of Thrombosis and Haemostasis. Available at: http://www.sah.org.ar/pdf/covid-19/bibliografia_14845.pdf, First published: 15 April 2020***)**

Dabigatran offers potential advantages over currently available anticoagulants. It excludes the need for parenteral or subcutaneous administration, increasing compliance especially when outpatient antithrombotic treatment is needed following early hospital discharge. (*Wurnig C, et al. Thromb J. 2015;13:37.*)

Rivaroxaban

Rivaroxaban is usually given at a fixed dose without monitoring.

- VTE prophylaxis in surgical patients: 10 mg daily; duration (12 days vs. extended to 35 days) depends on the type of surgery.
- Treatment and secondary prevention of VTE: 15 mg twice a day (with food) for 21 days, followed by 20 mg once a day (with food). If treatment is continued after 6 months, the dose can be reduced to 10 mg once daily for selected individuals. For those with an increased risk for VTE beyond 6 months of anticoagulation (e.g., two or more episodes of VTE), the 20 mg once daily dose should be used.
- Stroke prevention in atrial fibrillation (AF): 20 mg once a day with the evening meal (CrCl >50 mL/min); or 15 mg once a day with the evening meal (CrCl ≤50 mL/min).

Rivaroxaban is not recommended for VTE prophylaxis, treatment or secondary prevention in individuals with a creatinine clearance of <30 mL/min.

Apixaban

Overview (apixaban)—

- VTE prophylaxis in surgical patients: 2.5 mg twice daily; duration (12 days vs. extended to 35 days) depends on the type of surgery.
- Treatment and secondary prevention of VTE: 10 mg twice daily for 7 days, followed by 5 mg twice daily. If therapy continues beyond 6 months, the dose is reduced to 2.5 mg twice daily.Stroke prevention in AF: 5 mg twice daily (CrCl >50 mL/min); or 2.5 mg twice daily for those with any two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL.

Dabigatran

- VTE primary prophylaxis in surgical patients: 110 mg 1-4 hours after surgery, followed by 220 mg once daily for 28-35 days (hip replacement) or 10 days (knee replacement).
- Treatment and secondary prevention of VTE: 150 mg orally twice daily after 5-10 days of parenteral anticoagulation (CrCl >30 mL/min).
- Stroke prevention in atrial fibrillation (AF): 110 mg orally twice a day or 150 mg orally twice a day (CrCl >30 mL/min). European labeling suggests dose reduction in patients >75 years of age (for instance, 150 mg orally once a day or 110 mg orally twice a day).

(*UpToDate*)

Should seriously ill COVID-19 patients be given therapeutic-intensity anticoagulation empirically (in the absence of confirmed or suspected VTE)?

Microvascular thrombosis is believed to be involved in hypoxemic respiratory failure in some patients with COVID-19. Autopsy studies have been limited but they demonstrate large vessel and microvascular thrombosis, pulmonary hemorrhage and high prevalence of VTE.

Should COVID-19 patients receive post-discharge thromboprophylaxis?

Patients hospitalized for acute medical illness have an increased risk for VTE for up to 90 days following discharge. Whether this risk is sufficiently high in patients with COVID-19 to warrant post-discharge

thromboprophylaxis is not clearly known. Non-COVID clinical trials which pointed to a benefit for post-discharge thromboprophylaxis given for up to 42 days enrolled patients with combinations of risk factors, including age, comorbidities such as active cancer, and elevated D-dimer >2 times the upper normal limit.

The decision to use post-discharge thromboprophylaxis should consider the individual patient's VTE risk factors at the time of discharge, which should include reduced mobility and bleeding risk, as well as feasibility.

Aspirin has been evaluated for VTE prophylaxis in low-risk patients following hip or knee arthroplasty but has not been assessed for COVID-19 post-discharge thromboprophylaxis. Patients should be educated on the signs and symptoms of VTE at hospital discharge and advised to seek urgent medical attention if any of these develop.

If a patient with COVID-19 requires therapeutic anticoagulation for VTE or AFIB stroke prevention, do we have any special considerations?

Dexamethasone is an inducer of CYP3A4 and the extent of the drug interaction with DOACs is not well understood. Sarilumab and tocilizumab can heighten CYP450 enzyme activity and should not be used in association with apixaban or rivaroxaban and may also increase the doses of warfarin required.

Atazanavir and lopinavir/ritonavir can increase drug concentrations of apixaban and rivaroxaban and reduce the active metabolite of clopidogrel and prasugrel. The University of Liverpool has assembled a list of drug interactions, which can be accessed at covid19-druginteractions.org. LMWH or UFH in hospitalized critically ill patients is preferred because of the shorter half-life and fewer drug-drug interactions compared with DOACs. Regular warfarin users who cannot get INR monitoring during isolation may be candidates for DOAC therapy; however, patients with mechanical heart valves, ventricular assist devices, valvular AF, antiphospholipid antibody syndrome, or lactation should continue treatment with warfarin therapy. LMWH or UFH are the anticoagulants of choice in pregnancy. *(https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation)*

ChAdOx1 nCoV-19 and Transverse Myelitis

- AstraZeneca had voluntarily halted a randomized clinical trial of its coronavirus vaccine after a volunteer developed transverse myelitis (*NY Times*).
- Phase 1/2, single-blind, randomized controlled trial at five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control.
- We presume that the team has confirmed that the case was not in the control arm.
- ChAdOx1 nCoV-19 given at a dose of 5×10^{10} viral particles.
- The booster vaccine administered 28 days after the first dose.
- ChAdOx1 nCoV-19 is made from a virus (ChAdOx1), which is a weakened form of a common cold virus (adenovirus) known to cause infections in chimpanzees; it has been genetically changed thus rendering it impossible to grow in humans. Genetic material has been added to the ChAdOx1 construct that is used to make proteins from the COVID-19 virus (SARS-CoV-2) called Spike glycoprotein (S). This protein is usually found on the surface of SARS-CoV-2 and plays a pivotal role in the infection pathway of the SARS-CoV-2 virus. The SARS-CoV-2 virus uses its spike protein to bind to ACE2 receptors on human cells and enters the cells and causes an infection. (*https://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials*)
- The patented Vaccitech adenovirus vectors are chimpanzee adenovirus Oxford 1 and 2 (ChAdOx1 and ChAdOx2), and belong to the group E simian adenovirus family, similar to the chimpanzee adenovirus 63. These viruses have been engineered to make them replication deficient and can be manufactured in well-established HEK293 cell lines containing the adenoviral E1 gene. The viruses have high carrying capacity for the genes encoding cancer or pathogen antigens of interest. (*https://www.vaccitech.co.uk/technology*)
- Chimps can have transverse myelitis (*Miyabe-Nishiwaki T, et al. J Med Primatol. 2010;39(5):336-46.)*
- **Adenoviruses and transverse myelitis:** Species B adenoviruses can be linked with more severe disease, including severe pneumonia, aseptic meningitis, encephalitis and transverse myelitis. Amongst species B adenovirus, type 21 (Ad21) may have caused paralysis. (*Clin Infect Dis. 2003;36(5)550-9.)*
- Acute transverse myelitis is seen in COVID-19 infection. (*https://casereports.bmj.com/content/13/8/e236720*)

Investigators did not detect SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) and postulated that this presentation was likely a result of an immune-mediated inflammatory process rather than direct invasion of SARS-CoV-2 into the central nervous system (CNS).

The incidence of acute myelitis associated with COVID-19 infection is not clearly understood. Three case reports of similar cases have been noted to link COVID-19 to acute myelitis as a neurological complication. The first one is in Wuhan, China by Kang Zhao et al where COVID-19 was first reported. The second is in Boston where the patient presented with symptoms of upper respiratory tract infection and then developed acute myelitis 7 days later by Sarma et al. Whether the myelitis occurs directly from the viral infection or as an autoimmune sequelae is still not known. (*https://www.sciencedirect.com/science/article/pii/S1930043320302478*)

Acute transverse myelitis

It is a neuro-inflammatory spinal cord disorder presenting with rapid onset of weakness, sensory alterations and/or bowel and bladder dysfunction.

Types: Idiopathic transverse myelitis (TM) occurs without a definite etiology. Secondary (disease-associated) TM is related to a systemic inflammatory autoimmune condition. Idiopathic TM is often a post-infectious complication and presumably results from an autoimmune process.

TM can be associated with infectious, systemic inflammatory or multifocal CNS disease. Acquired CNS demyelinating disorders known to cause TM include multiple sclerosis, neuromyelitis optica and acute disseminated encephalomyelitis.

Incidence: 1-8 new cases per million.

Onset: Acute or subacute development of neurologic signs and symptoms consisting of motor, sensory and/or autonomic dysfunction. Motor symptoms include rapidly progressing paraparesis that may involve the upper extremities; initial flaccidity followed by spasticity. In most patients, a sensory level can be identified. Sensory symptoms include pain, dysesthesia and paresthesia. Autonomic symptoms involve heightened urinary urgency, bladder and bowel incontinence, difficulty or inability to void, incomplete evacuation and bowel constipation, and sexual dysfunction.

Diagnosis: No evidence of a compressive cord lesion; exclusion of a compressive cord lesion by magnetic resonance imaging (MRI) and confirmation of inflammation by either gadolinium-enhanced MRI or lumbar puncture.

When inflammation is evident in the absence of cord compression, one must evaluate for the presence of infection, systemic inflammation and the extent and sites CNS inflammation.

Acute idiopathic TM: High-dose intravenous glucocorticoid treatment.

Most patients with idiopathic TM have at least a partial recovery, which usually starts within 1-3 months and continues with exercise and rehabilitation therapy. Some degree of persistent disability is common, and is seen in nearly 40% of the individuals. A very rapid onset with complete paraplegia and spinal shock has been associated with poorer outcomes. Recovery can proceed over years.

Majority of patients with TM have monophasic disease. Recurrence can occur in approximately 25-33% of patients with idiopathic TM. With secondary TM, the recurrence rate may be nearly 70%.

Patients presenting with acute complete TM have a risk of multiple sclerosis of only 5-10%. However, for patients with partial myelitis as the initial presentation and cranial MRI abnormalities showing lesions typical for multiple sclerosis, the transition rate to multiple sclerosis over three to 5 years is 60-90%. Patients with acute partial myelitis with normal brain MRI develop multiple sclerosis at a rate of only 10-30% over a similar time period.

Round Table Expert Zoom Meeting on "Considerations for Wearing Face Masks in Pandemic Era in Different Situations"

12th September, 2020 (Saturday, 11 am-12 pm)

Participants: Dr KK Aggarwal, Dr AK Agarwal, Dr Suneela Garg, Dr Jayakrishnan Alapet, Dr JA Jayalal, Dr KK Kalra, Dr AM Kochhar, Dr Atul Pandya, Dr Anoop Mohta, Dr DR Rai, Dr Anil Kumar, Mrs Upasana Arora, Dr Pragati Sawhney, Ms Ira Gupta, Dr S Sharma

Key points from the discussion

- When virus enters the cell (nasooropharyngeal), different scenarios can result.
- One, it is taken up and is killed by the macrophages. No antibodies are formed, the patient remains asymptomatic.
- In some persons, the virus enters the blood → dendritic cells in thymus → T cells and then to B cells and produces IgG and IgM. The patient is asymptomatic, but antibodies are formed.

- In a third scenario, the cells produce IFN-1 on Day 1, which initiates neutrophils, NK cells and monocytes. The NK cells and monocytes produce IFN-γ, which kills the virus as do the neutrophils. The patient is asymptomatic because of adequate immunity.
- Another scenario, the IFN-γ will produce TNF-α, which causes inflammation. The person will be symptomatic on Day 1 (fever, diarrhea, headache, rash, loss of smell/taste).
- If the immunity is inadequate, the virus is not killed. The cells do not form IFN-1 in such a situation, alternate pathway opens up on Day 3. Macrophages produce NLRP3, which produces IL-1β and IL-18. IL-1β increases ferritin levels, glucuronidase causing tissue damage. IL-18 adds to the inflammation. Cells, through the cellular dendritic cells, produce Th1 cells, which produce IL-6 (formed on Day 3), TNF-α and IL-8. IL-6 causes clot formation, TNF-α (formed on Day 1), IL-8 and IL-1β (formed on Day 3), cause inflammation.
- Masks can be medical masks or fabric masks. Medical masks (surgical and N95) are part of personal protective equipment (PPE) kit, while fabric masks are not.
- Respirators are rated "N," if they are not resistant to oil, "R" if somewhat Resistant to oil, and "P" if they are oil proof, i.e., strongly resistant to oil.
- The number 95 means that these masks have 95% filtration efficiency.
- In areas with known or suspected community transmission, medical masks and not fabric masks in patient care must be used, irrespective of whether patient is confirmed positive or not.
- Medical masks must meet three criteria: High filtration, adequate breathability and fluid penetration resistance.
- Medical masks must filter droplets (3 μm) and particles (0.1 μm).
- The World Health Organization (WHO) recommends that persons with any symptoms suggestive of COVID-19 should wear a medical mask.
- The selection of material is important; higher the filtration efficiency, the more of a barrier provided.
- Breathability is measured in millibars (mbar) or Pascals (Pa). Acceptable breathability of a medical mask should be below 49 Pa/cm^2. For non-medical masks, it should be below 100 Pa.
- Non-medical masks should have a minimum of 3 layers. Nylon or polyester fabric masks may be 2-layered or 4-layered. Cotton handkerchiefs used as masks have only 17% filtration efficiency. Gauze has only 3% filtration efficiency, even if multiple layers are used.
- Users are confused about which mask to use for themselves.
- Guidelines need to be redefined based on whether there is suspected community transmission or not.
- If there is a suspected case in a house, everyone should wear a medical mask.
- All patients coming to a healthcare setting, especially in clinics/OPDs or those who have corona-like illness, should wear a medical mask.
- Even fabric masks should be regulated. It should not be left upon the user to decide the quality of the mask in the event of a pandemic.
- Heart Care Foundation of India (HCFI) may file a question to the ministry or even file a public interest litigation (PIL).
- Masks have to be combined with other prevention measures such as physical distancing, hand washing.
- Correct and consistent use of masks is important if physical distancing is not possible.
- There is a greater need for education of public about masks.
- Fit of the mask is also important.
- Electrostatic charge of the mask is lost by ultraviolet, washing, etc.
- As per the Central Pollution Control Board (CPCB) guidelines, the mask should be stored for 72 hours in a paper bag after use before disposing or kept in sodium hypochlorite solution for 15 minutes.
- Hand hygiene before and after wearing a mask is very important.
- Awareness needs to be created about the correct method of wearing and removing a mask and its disposal.

With input from Dr Monica Vasudev

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