PREAMBLE

The Indian Society of Anaesthesiologists (ISA) issues the following advisory and position statement pertaining to the second wave of coronavirus disease-2019 (COVID-19) in India, the lessons learnt and future preparedness.

The months of April and May 2021 have been extremely challenging for all, especially the anaesthesiologists. In the second wave of COVID-19 pandemic, very large numbers of patients were infected in a very short span of time. The medical facilities were overburdened with patients leading to scarcity of oxygen, COVID beds, intensive care unit (ICU) facilities, essential drugs and other resources. Besides taking care of COVID and non-COVID clinical work, the anaesthesiology fraternity during this period was intensely focussed on arranging more and more beds and oxygen for the COVID patients and delivering oxygen from liquid medical oxygen (LMO) tanks, medical gas cylinders, oxygen concentrators or splitting the central oxygen supply (only as dire emergency measures). The clinical, administrative, psychological and social stresses were aptly handled by the anaesthesiologists.

As the understanding of COVID-19 is improving, the guidelines and recommendations are also being updated regularly; nevertheless, this ISA advisory and position statement is also subject to change and updation in the coming days.

INDIAN SOCIETY OF ANAESTHESIOLOGISTS POSITION STATEMENT

The sudden increased demand of medical oxygen led to its extreme shortage. To overcome this shortage, 93% ± 3% medical oxygen can be used for COVID-19 pandemic patients through the use of medical oxygen generation plants. These oxygen generation plants work on pressure swing adsorption (PSA) technology involving molecular sieve (Zeolite). Use of 93% ± 3% medical oxygen (oxygen 93) is approved by the Indian Pharmacopoeia (IP), United States Food and Drug administration and the European Union.

• Anaesthesiologists should ensure optimal utilisation of oxygen by guiding all hospital staff in implementing zero leaks at all oxygen ports
• When there is scarcity of oxygen, use regional anaesthesia techniques for the surgical procedure, wherever feasible. For surgery under general anaesthesia, use low-flow anaesthesia technique. Use oxygen judiciously in the post-operative period

- Different modes of oxygen delivery and ventilatory support for COVID-19 patients are nasal prongs, face masks, non-rebreathing bag masks, non-invasive ventilation, invasive ventilation, etc., to keep the target oxygen saturation to 94%. The high-flow nasal oxygenation should be used very selectively.

- Anaesthesiologists, being experts in critical care, successfully managed many critically ill COVID-19 patients in the ICUs. The expertise in critical care which the anaesthesiologists possess and the huge number of working hands of our anaesthesiology post-graduates and consultants helped tremendously in managing such a large number of COVID-19 patients and saving many lives.

- A large number of anaesthesiology residents and faculty/consultants were infected with COVID-19 in the second wave, thus decreasing the number of working hands; nevertheless, many of those infected returned to COVID-19 duties as soon as they tested negative and were asymptomatic. This is appreciable and they should continue to render their valuable and skilled services to the cause of this pandemic.

- Management of COVID-19 patients should be as per the standard guidelines, such as those laid down by the Ministry of Health and Family Welfare, Government of India and the respective state governments.

- The anaesthesiologists managing critically ill COVID-19 patients in the ICU should administer corticosteroids judiciously, when indicated.

- There are specific indications for the usage of drugs remdesivir and tocilizumab in COVID-19 patients. The shortage of these drugs in the intensive care management of COVID-19 patients should be managed by well-laid institutional mechanisms to make the availability of these drugs for the selective patients in the hospitals.

- The institutes and hospitals that have facilities for extracorporeal membrane oxygenation (ECMO) should utilise this technique judiciously in severely ill COVID-19 patients. ECMO ICUs should be set up in tertiary care institutes.

- There is a sudden surge in mucormycosis cases and anaesthesiologists are involved in the multidisciplinary management of mucormycosis in COVID-19 patients as these patients often require surgery under anaesthesia.

- The COVID-19 patients suffering from mucormycosis often have coexisting comorbidities such as diabetes mellitus (DM), oncopathologies and immunosuppression therapies. Meticulous attention must be paid to glycaemic control. Apart from these comorbidities, mucormycosis may make the airway management difficult. In addition, administration of injection amphotericin B (AmB) can have significant adverse effects which are of concern to the anaesthesiologists. Moreover, COVID-19 itself affects different organs of the body.

- Future preparedness for COVID-19 pandemic includes up-gradation of hospital oxygen supplies, alternative sources of oxygen generation, adequate number of good-quality working ICU ventilators and monitors, sufficient quantity of drugs used in the ICU management of COVID-19 patients, setting up ECMO ICUs and most importantly ensuring 100% vaccination for the anaesthesiologists.

- The ISA through its national/state/city units shall continue to train more doctors of other clinical specialities in teaching the basics of mechanical ventilation. The training has to be hands-on training on the ventilators actually available in different civil and general hospitals. The training can be conducted online, if physical training is not feasible.

- The two waves of COVID-19 have exposed the gross deficiencies in terms of availability of nursing staff and more so that of ICU trained nursing staff. The anaesthesiologists can take a lead in providing training to the nursing staff in critical care so that the care improves if and when a third wave occurs.

- The anaesthesiologists should be mentally relaxed and strong because, at times, they have to do duties on two fronts: managing patients in ICUs and also looking after their family members who are infected with COVID-19.

- The SARS-CoV-2 vaccination may cause mild symptoms in a very few individuals like fever, chills, myalgias, pain at injection site, headache, etc. These symptoms may mimic common post surgical conditions but resolve within 2-3 days. So, elective surgery / interventions can be done under anaesthesia upon resolution of these symptoms, if any (usually one week after vaccination) in consultation with a qualified anaesthesiologist.

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The post-graduate students have been busy in COVID-19 duties. They should be adequately taught and trained in the designated fields of the subject of anaesthesiology and supervised compassionately in completion of thesis and examinations that should be conducted in stress-free environment.

**INDIAN SOCIETY OF ANAESTHESIOLOGISTS ADVISORY**

**Mucormycosis in COVID pandemic and the anaesthesiologist**

Since the last few months, there are increasing case reports of rhino-orbito-cerebral mucormycosis in patients with COVID-19. Mucormycosis can also involve lung (pulmonary), gastrointestinal tract, skin, heart, kidney and mediastinum (invasive type). The symptoms appear during the recovery from COVID-19. An environment of low oxygen (hypoxia); high glucose (diabetes, new-onset hyperglycaemia, steroid-induced hyperglycaemia); acidic medium (metabolic acidosis, diabetic ketoacidosis); high-iron (ferritin) levels; lymphopenia, neutropenia; malnutrition; decreased phagocytic activity of white blood cells due to immunosuppression (SARS-CoV-2-mediated, steroid-mediated or background comorbidities) and contaminated oxygen therapy and delivery devices favours the growth of the fungus.

Management of mucormycosis aims at early diagnosis, a reversal of underlying predisposing factors, early administration of systemic antifungal therapy (intravenous liposomal AmB) and broad surgical debridement of infected tissue. The pathophysiologic profile of mucormycosis has numerous clinical and anaesthetic implications.

**Anaesthetic management of post-COVID mucormycosis**

These patients pose several challenges because it is usually a post-COVID illness population. The surgical procedures usually involve debridement, functional endoscopic sinus surgery, maxillecctomy, mandibulectomy, exenteration, enucleation, palatal debridement, craniotomy, etc., and for which general anaesthesia has to be administered. The timing of taking up for surgery is another debatable issue. Those with active COVID-19 infection are being taken up for debridement in some institutes, whereas others wait for a negative reverse transcription polymerase chain reaction (RT-PCR) report before taking up for surgery.

Endoscopic sinus surgery is an aerosol-generating procedure with high risk of transmission of the coronavirus. Use of personal protective equipment, barrier devices and instillation of pre-procedure povidone iodine drops in the nose are recommended in the patients with positive reports. However, majority of patients are RT-PCR negative at the time of hospital admission for mucormycosis.

Preoperatively, one has to carefully screen the patients for post-COVID pulmonary and cardiovascular residual dysfunction. The peripheral oxygen saturation should be checked, and the patient may be on some means of oxygenation (by nasal prongs/face mask/others). Complete biochemical work-up of renal functions, electrolytes and coagulation profile should be done in patients receiving AmB therapy. Optimisation and control of blood glucose including shifting over to insulin are important. Patients may be on heparin or on long-acting post-COVID oral anti-coagulants. Heparin is withheld before surgery and has to be restarted post-operatively. The decision to stop or continue oral anticoagulant has to be taken after multidisciplinary discussion, weighing the risk against benefit of stopping the drug. In cases with prosthetic cardiac valves or deep vein thrombosis, it may not be advisable to stop the anti-coagulants. A written informed consent should be taken depending upon patient’s clinical condition, present comorbidities and surgical procedure which can be disfiguring at times.

The multi-organ effects of COVID-19 and DM, a weakened post-COVID body state and the systemic effects of AmB administration including decrease in renal function can have serious perioperative implications. Perioperative hypotension and arrhythmias due to AmB, post-COVID adrenal suppression and myocardial dysfunction have been frequently reported. Maintenance of an adequate mean arterial pressure, cardiac output and normovolaemia while concomitantly avoiding further renal insults is of paramount importance. The tissue that is debrided is dead tissue and hence not much bleeding has been reported intra-operatively. However, intra-operative bleeding can be an issue in redo debridement. Electrolyte disturbances such as hypokalaemia and hypomagnesemia due to AmB can interfere with neuromuscular blocking drugs, leading to problems such as delayed recovery. When administering neuromuscular blockers such as succinylcholine, the possibility of hypokalaemia due to AmB and
hyperkalaemia due to critical illness-induced myopathy should be kept in mind. Serum potassium and blood glucose levels should therefore be closely monitored peri-operatively. The patients can have a difficult airway because of epiglottitis, sub- and supra-glottic oedema, restricted mouth opening due to jaw erosion and pain, palatal ulcers which bleed on touch, palatal perforations, crusts in the nose, oroantral fistulas and DM-induced joint stiffness. Facial swelling, proptosis and perioral wounds due to the use of tight fitting non-invasive ventilation masks during COVID treatment can hinder mask ventilation. An oral polyvinyl chloride/flexometallic endotracheal tube (of smaller size, if required) can take care of the airway; nonetheless, the difficult airway cart should be kept ready. Post-operative ICU care may be required due to the presence of comorbidities, post-COVID respiratory problems and airway-related issues. Wide excisions will warrant future flap reconstructive surgeries, which may pose as anticipated difficult airway.

Thus, a patient scheduled for mucormycosis surgery should be thoroughly screened for effects of mucormycosis on airway besides, multi-organ effects of COVID and DM, and systemic effects of AmB administration.

**Adequate oxygen supply and optimal utilisation**

**Oxygen supply to hospitals**

In India, The Central Drugs Standard Control Organisation (CDSCO) under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, monitors the manufacture and use of the medical gases. The medical oxygen should be of medical grade IP 2010 that is certified safe for human use. Medical oxygen is oxygen that is free from any contamination, generated by an oil-free compressor and is odourless. It has carbon monoxide less than 5 parts per million (PPM) and carbon dioxide not more than 300 PPM. It should be free from halogen, polymer and oxidising substance and moisture. It should not cause any damage to the materials of cylinders, gas pipeline, anaesthesia machines and ventilators and most importantly to the patients.

LMO, compressed gas cylinders, oxygen plants and oxygen concentrators are the sources of medical oxygen in health-care facilities. Any of these sources can be chosen depending upon the amount of oxygen needed at the health-care facility, the available infrastructure, cost, capacity and supply chain for local production (and delivery) of medicinal gases, reliability of electricity, access to maintenance services and spare parts, etc.

Up-gradation of central oxygen supply and medical gas pipeline system (MGPS) should be done based upon anticipated future requirements. There should be provision for monitoring oxygen delivery pressure with functional alarms and isolation of oxygen supply to different hospital areas. All big hospitals should have full-time dedicated biomedical engineer for planning, installation, monitoring and maintenance.

**Liquid medical oxygen**

Bulk liquid oxygen is generated off-site and stored in a large cryogenic tank: vacuum-insulated evaporator (VIE). The boiling point of oxygen is −183°C. In the VIE, it is kept at −160°C at 5–10 atmospheric pressure. This is much below its critical temperature of −118.4°C, the temperature above which no amount of pressure can hold oxygen in liquid state. At 15°C, 1 L liquid oxygen can lead to the production of 842 L of gas at one atmospheric pressure. A full 10 KL LMO tank is approximately equal to 1200 “D” type cylinders of 7000 L. Liquid oxygen is highly concentrated, so more oxygen can be stored in a smaller tank. The cryogenic storage tank is refilled periodically by a truck from a supplier.

**Oxygen generator plant**

The oxygen generator plant generates 93% oxygen (±3%) for medical use according to the IP, the remainder consisting mainly of argon and nitrogen. It generates oxygen by PSA with molecular sieve technology (Zeolite). It operates on the principle of adsorbing under pressure, gases other than oxygen in the atmosphere onto the surface of an adsorbent material, termed as Zeolite (aluminium silicate). After adsorption, those gases except oxygen are vented out. This process, also called as fractional distillation, ensures that only oxygen is the primary gas. The carbon dioxide and carbon monoxide in PSA-generated oxygen should not exceed 300 and 5 PPM, respectively. PSA oxygen generator comprises feed air package (include atmospheric air compressor, refrigerating driers and series of filters), absorber tower, storage tank, microprocessors and accessories. The oxygen generation capacity usually ranges from 100 to 3000 L per minute at around 65 PSI pressure. PSA oxygen generator should deliver stable oxygen concentration and at constant pressure. The oxygen
concentration delivered (93% ± 3%) is monitored by a paramagnetic oxygen analyser. The twin tower PSA module special grade adsorbent should last for at least 10 years. It is designed for 24/7 and 365 days continuous use and should have 100% safety as per the national and international standards.

It requires designing, engineering, civil work, electrical work, commissioning, training to plant personnel and connection to the existing MGPS. It is advisable to not only have a provision for automatic switch over from electricity mains to generator back up but also have LMO/oxygen cylinders as a backup supply in the healthcare centre.

The major advantage of oxygen generation plant is that it is self-sufficient in oxygen production with the requirement of electric supply only. The major limitation of oxygen generator plant is that its maximum flow output may be less than the oxygen requirements during the peak hours of its use in the hospital. In addition, the process generates lot of heat. Thus, ventilation and cooling for the product and the compressors are major considerations. Dusty environment poses increased load on the adsorbents. Provision of easy access, cooling and ventilation strategies are important issues when commissioning these plants. Moreover, the oxygen generation plant can be a source of significant noise pollution.

There is optional provision of bottling of oxygen cylinders. The filling of gases, quality of cylinders and premises where gas filling is done are regulated by the Chief Controller of Explosives (CCOE), Nagpur. CCOE-certified cylinders and -licensed premises and licenses to fill and store compressed gas in cylinders are required.

The National Medical Commission in its circular dated 26 April 2021 has instructed that all medical college hospitals are also required to have a dedicated PSA technology-produced oxygen supply in addition to supply from liquid oxygen tank, which is to be installed and made operational within 6 months.

Anaesthetists have used >99.5% medical oxygen since decades. The anaesthesia workstations and ICU ventilators are designed to work with the same. They will require recalibration when using 93% medical oxygen. Further, the oxygen generators may not singularly cater to the peak demand of oxygen in big hospitals and institutes. It is pertinent to have a separate MGPS attached to these oxygen generators, and this oxygen can be used for those areas of the hospital which have oxygen beds only, i.e., wards, triage, high-dependency units. The operation theatres and ICUs can keep on receiving oxygen supply (>99.5%) from LMO tanks.

The hospitals should not rely on a single medical gas pipeline from a particular location. This type of supply can be detrimental during disasters. A robust alarm system and a continuously manned gas supply room should be established to monitor oxygen supply and the alarm systems. Inspection of the pipelines and mock drills of pipeline failure, fire and explosion should be conducted routinely. A hospital should have primary supply oxygen to last for a minimum of 4 days and reserve oxygen supply to last for 3 days. The average daily use of oxygen and peak daily requirement in the hospital should be calculated. A logbook to this effect should be maintained and oxygen audit should be done regularly.

Oxygen concentrators
An oxygen concentrator is a self-contained, electrically powered medical device designed to concentrate oxygen from ambient air. Most concentrators currently available produce an oxygen concentration between 82% and 96% volume fraction when operated within manufacturer specifications.

Oxygen concentrators can range in size and portability, and accordingly, they can be moved between clinical areas or set up as stationary fixtures in patient areas. They should be positioned one foot away from the wall, in a well-ventilated area of the room. They deliver humidified oxygen regulated by flow-meter assembly. The flow rates vary from 0.5–15 L min⁻¹. For COVID-19 patients, oxygen concentrators that are able to deliver 5–10 L of 93% ± 3% oxygen flow per minute are useful. They are designed for continuous operation and can produce oxygen for 24 h a day for weeks together, but some models may require a break of 30 min. The prime requirement of oxygen concentrators is uninterrupted electric supply. A backup oxygen cylinder supply is preferable. The regular preventive maintenance includes daily cleaning of outer surface, changing water for humidification and cleaning oxygen delivery devices. The air and other filters are cleaned between two patients use and as per the manufacturer’s specifications. Some concentrators are available with oxygen purifiers also. Oxygen concentrators produce a low pressure output which is

not suitable for continuous positive airway pressure/ventilators.

Industrial oxygen
The industrial oxygen contains impurities from the containers of industrial oxygen and contaminants of cylinders, and most importantly, it is not sterilised like medical oxygen. Industrial oxygen can be generated by oil-lubricated, oil-less or oil-free compressors. Only oil-free compressors are suitable for generating oxygen that can be diverted to the health-care system. There can be the presence of water in industrial-grade oxygen cylinders which can cause rusting of cylinders. Thus, industrial oxygen should never be used for medical purposes unless stringent parameters of decontamination and sterilisation are followed strictly.

Emerging treatment modalities for COVID-19 patients
The anaesthesiologists managing critically ill COVID-19 patients in the ICU should use corticosteroids judiciously. There are very specific indications of the drugs remdesivir and tocilizumab in COVID-19 patients. These drugs are approved under the emergency use authorisation only. The shortage of these drugs in the intensive care management of COVID-19 patients should be managed by well-laid institutional mechanisms to make the availability of these drugs for the selective patients in the hospitals. The institutes and hospitals that have facilities for ECMO should utilise this technique judiciously in severely ill COVID-19 patients. ECMO ICUs should be set up in tertiary care institutes.

Apart from the recommended therapies for COVID-19 patients, few more modalities are also emerging.

Monoclonal antibody therapy
Monoclonal antibody cocktail therapy comprising a combination of casirivimab and imdevimab has been approved by the CDSCO and the Drugs Controller General of India for emergency use authorisation for the treatment of symptomatic mild-to-moderate COVID-19 and in those at high risk of severe COVID-19. Casirivimab and imdevimab are monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2, designed to block the virus attachment and entry into human cells. Using two antibodies protects against emergence of resistance. Preferably, a multidisciplinary team or a three-member team consisting of the treating intensivist involved in COVID-19 patient care should recommend the use of monoclonal antibody therapy. The therapy is most suited for high-risk COVID-19 patients who meet the criteria such as body mass index (BMI) ≥35, chronic renal disease, DM, immunosuppressive disease, currently receiving immunosuppressive treatment, age ≥65 years, age ≥55 years of age with cardiovascular disease or hypertension or chronic obstructive pulmonary disease/other chronic respiratory disease; age 12–17 years with BMI ≥85th percentile for their age and gender, or sickle cell disease, or congenital or acquired heart disease, or neurodevelopmental disorders (cerebral palsy), or a medical-related technological dependence (tracheostomy, gastrostomy), or positive pressure ventilation (not related to COVID-19), or asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

It should not be given in patients with more than 10 days from symptom onset; if the date of symptom onset is known; patient is hospitalised due to COVID-19; patient has oxygen requirement due to COVID-19; or those who require an increase in baseline oxygen flow rate due to COVID-19 and in those on chronic oxygen therapy due to underlying non-COVID-19–related comorbidity.

Evidence is still accumulating on the use of this drug. The authorised dosage currently in India is a combined dose of 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) administered together as a single intravenous infusion in normal saline over 20–30 min/as subcutaneous injections simultaneously at four different sites as soon as possible after positive viral test for SARS-CoV-2. Each packaged vial is to be used for two patients. After opening, the vial is to be stored at 2°C–8°C and can be used within 48 h.

2-Deoxy-D-glucose therapy
A glucose analogue 2-deoxy-D-glucose (2-DG) has recently received emergency use authorisation in India for use as an adjunct to standard of care in the treatment of hospitalised moderate-to-severe COVID-19 cases. It exerts antiviral effect by inhibiting both the entry and the replication of the SARS-CoV-2 inside the host cells and anti-inflammatory effects by inhibiting the release of cytokines from inflammatory cells. It is available in powdered form in sachets and given orally dissolved in water in the dose of 45 mg/kg twice daily, up to 10 days or until discharge, whichever is earlier. The drug has gone through phase 2 and 3 clinical studies and patients have shown early clinical improvement by day 3 with independence from supplemental oxygen. The results of many of the trials are yet to be
published. The methodological robustness of the trials is not clear. India is the pioneer in using 2-DG for the treatment of COVID-19. Commercial supplies of the drug have started, and it is now available in some major hospitals. The drug is yet to be widely studied in COVID-19 treatment.

The above document is an advisory and position statement based on the current literature, resources and expert opinion. It is pertinent to state that new evidence is continuously emerging and guidelines are being issued regularly.

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RESOURCES
