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The essence of medical practice

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Update on COVID-19

CONTENTS

EDITORIAL

Dear Doctor

In the growing field of medical science our goal is to keep you informed about the current update management of diseases. This issue is enriched with a variety of topics those are very often encountered by the healthcare professionals. We have focused on the new burning issues of COVID-19.

In this issue the topics have been selected under three categories: Research, News and Clinical medicine. In the research section there are blend of interesting topics such as how prone position helps in spontaneous breathing in COVID-19 patients. You will be amazed to know how mouthwash can help us fight against COVID-19. Pregnant women are very vulnerable and so we have selected a topic about how a woman can be cared who is planning for a pregnancy or is pregnant or is in postpartum period.

In the news section there are five fascinating and useful topics such as how dexamethasone helps in the treatment of coronavirus and how ivermectin inhibits the replication of COVID-19. Many people are unaware of using masks properly, hence we have included a topic that will be helpful to explain many patients about the correct type of masks. Lastly we have introduced two very crucial topic in the Clinical medicine section that will help you in your daily practice during this pandemic.

Our efforts have been made to make this issue fascinating to you and we are quite sure you will appreciate this. We need your suggestions to make our efforts worthwhile.

Stay Safe!

With warm regards

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COVID-19 and post infection immunity

In the absence of effective treatment or biomedical prevention, efforts to control the coronavirus disease 2019 (COVID-19) pandemic have relied on non pharmaceutical interventions such as personal preventive actions (e.g., handwashing, face covers), environmental cleaning, physical distancing, stay at home orders, school and venue closures and workplace restrictions adopted at the national, state and local levels. In addition to these public health interventions, development of herd immunity could also provide a defense against COVID-19. However, whether immunity occurs among individuals after they have recovered from COVID-19 is uncertain. Many human infections with other viral pathogens such as influenza virus, do not produce a durable immune response. Understanding whether and how recovery from COVID-19 confers immunity to or decreased severity of reinfection is needed to inform current efforts to safely scale back population based interventions, such as physical distancing. Understanding potential postinfection immunity also has important implications for epidemiologic assessments (e.g., population susceptibility, transmission modeling), serologic therapies (e.g., convalescent plasma) and vaccines. In this viewpoint, it is described what is currently known about the immune response to COVID-19, highlight key gaps in knowledge and identify opportunities for future research. COVID-19 is caused by infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Following infection, detectable IgM and IgG antibodies develop within days to weeks of symptom onset in most infected individuals. Why some patients seem not to develop a humoral immune response, as reflected by detectable antibodies is uncertain. Adding to this uncertainty is the unclear relationship between antibody response and clinical improvement. The findings from a small study of 9 patients with COVID-19 found that greater clinical severity produced higher antibody titers.

However, antibody detection and higher titers have not always been found to correlate with clinical improvement in COVID-19. Moreover, mild COVID-19 symptoms can resolve prior to sero conversion (as reflected by detectable IgM and IgG), although detectable IgM and IgG antibodies have preceded declines in SARS-CoV-2 viral loads. What appears more certain is that viral burden typically peaks early in illness and then declines as antibodies develop and antibody titers rise over the subsequent 2 to 3 weeks. Success in culturing virus from nasopharyngeal specimen declines quickly during the first week of mild illness, but the absolute duration that a patient might shed infectious virus is

unknown. Persistent detection of viral RNA many days to weeks after recovery from COVID-19 at concentrations near the detection limit of available assays likely does not represent a meaningful clinical or public health risk especially in the absence of symptoms; however, definitive evidence does not yet exist.

The durability of neutralizing antibodies (NAbs, primarily IgG) against SARS-CoV-2 has yet to be defined; persistence up to 40 days from symptom onset has been described. Duration of antibody responses against other human coronaviruses may be relevant in this context. For example, following infection with SARS-CoV-1 (the virus that caused SARS), concentrations of IgG remained high for approximately 4 to 5 months before subsequently declining slowly during the next 2 to 3 years. Similarly, NAbs following infection with MERS-CoV (the virus that caused Middle East Respiratory Syndrome) have persisted up to 34 months in recovered patients.

Detection of IgG and NAbs is not synonymous with durable immunity. With regard to COVID-19, a small, nonpeer reviewed, preprint report provides the only data thus far on possible postinfection immunity in primates. In this study, 4 rhesus macaques were infected with SARS-CoV-2 and following recovery did not become reinfected when rechallenged with the same virus 28 days after the first inoculation. Whether persons can be reinfected with SARS-CoV-1 and MERS-CoV is unknown; SARS has not reemerged since 2004 and MERS cases remain sporadic. Reinfections can occur with at least 3 of the other 4 common human coronaviruses specifically, 229E NL63 and OC43, all of which generally cause milder respiratory illnesses. The reasons for this reinfection are not fully known, but evidence suggests that possibilities include both short lived protective immunity and reexposure to genetically distinct forms of the same viral strain.

To date, no human reinfections with SARS-CoV-2 have been confirmed. Evidence of reinfection typically requires culture based documentation of a new infection following clearance of the preceding infection or evidence of reinfection with a molecularly distinct form of the same virus. In one report, among 2 otherwise healthy individuals who had recovered from COVID-19 and had 2 or more sequentially Polymerase Chain Reaction (PCR) negative upper respiratory specimens at least 24 hours apart, SARS-CoV-2 RNA was detected again in throat swabs sporadically for upto 10 days. SARS-CoV-2 RNA has also been detected in throat or nasopharyngeal swabs more than 20 days after negative test results. In another report among 18 patients, viral burdens (as determined by PCR cycle threshold) were generally lower than and had declined substantially from, values during peak of illness. At the time of post recovery positive test results, the patients described in these reports had few, if any, symptoms and when radiographically examined, they demonstrated stable or improving pneumonia. There is also no evidence at present that such persons transmitted SARS-CoV-2 to others after they had clinically recovered. However, this possibility of transmission cannot be ruled out, especially for persons who may be predisposed to prolonged shedding of other pathogens such as due to immune compromised states.

It is also possible these cases represent persistent or recrudescent COVID-19 illness or even true reinfection. On the other hand, these cases may also represent prolonged sporadic viral RNA shedding at or near the limit of assay detection or variation in collection technique, specimen handling or storage conditions affecting test performance. Data to effectively differentiate these possibilities are lacking, highlighting an area of substantial uncertainty. Routine collection of such data, specifically viral burden (as measured by PCR assay cycle threshold) and viral culture and from a larger sample of patients under standard protocols is needed.

Serological assays to detect SARS-CoV-2 antibodies are rapidly becoming available and will be critical to estimate the prevalence of infections, including those that are asymptomatic. However, it is presently premature to use such assays to determine whether individuals are immune to reinfection. Performance standards, including sensitivity and specificity, for the burgeoning number of serologic assays and the potential for cross reactivity with other coronaviruses (yielding false positives) have yet to be determined. Widespread testing of persons who have not had COVID-19, a population with low SARS-CoV-2 prevalence can generate more false positives than true positives. This phenomenon may complicate clinical and epidemiologic interpretation of results, especially if the serologic tests do not have high specificity or some form of confirmatory testing is not used. More fundamentally, it remains to be determined whether a robust IgG response corresponds with immunity.

Well designed longitudinal cohort studies of persons who recovered from COVID-19 are needed to monitor for signs and symptoms of recurrent illness. Such longitudinal studies could also document possible reexposure events, all linked with clinical and laboratory investigations of other alternate etiologies, serologic testing, attempts to isolate virus by culture and viral genomic comparisons of isolated viral specimens. However, in the short term, possible recurrences of infection can be identified by monitoring surveillance data and by requesting clinicians and public health authorities to report and investigate cases of possible recurrence to determine whether recurrence can be confirmed.

Reference: JAMA, 11 May 2020

Favipiravir, an antiviral for COVID-19?

A novel coronavirus, SARS-CoV-2, emerged in December 2019 in Wuhan, China, which is spreading far more rapidly than its predecessors, having already infected millions of patients worldwide. As the scale of the ongoing COVID-19 outbreak has reached pandemic proportions, intensive worldwide public health efforts are underway to control the outbreak. However, as definitive therapies for established COVID-19 remain to be defined, significant interest exists in repurposing existing antiviral agents for use against COVID-19.

Favipiravir triphosphate is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA dependent RNA polymerase. It has activity against influenza A and B, including activity against oseltamivir and zanamivir resistant influenza viruses, several agents of viral haemorrhagic fever and SARS-CoV-2 *in vitro*. Favipiravir is approved for novel epidemic influenza strains that are unresponsive to standard antiviral therapies in Japan.

Favipiravir was identified to have activity *in vitro* against SARS-CoV-2, albeit requiring a high concentration compared with chloroquine or remdesivir (EC_{50} - 61.88 µM). Despite a similarly elevated EC_{50} identified for favipiravir and Ebola virus, it was identified in previous animal models to be highly effective as post exposure prophylaxis for mice exposed to Ebola virus challenges, with rapid virological response preventing mortality. Based on the dosing strategies and pharmacokinetic data from human influenza trials, an intensified dosing strategy of 6000 mg loading on day 1 followed by maintenance therapy of 1200 mg orally twice daily for 10 days was employed in a single arm clinical trial for Ebola virus disease in Guinea.

In a retrospective analysis of 124 patients with Ebola virus disease in Sierra Leone, those treated with favipiravir had a significantly higher survival rate compared with patients receiving supportive management (56.4% versus 35.3%; *P* - 0.027). Patients received favipiravir 800 mg orally twice daily on day 1 and 600 mg orally twice daily on days 3-11. Viral loads were quantified for 35 patients twice during their hospitalization and were significantly reduced amongst patients receiving favipiravir.

Favipiravir has also been used as pharmacological post exposure prophylaxis for Ebola virus disease. In a case series of four healthcare workers with higher risk Ebola virus exposures, including two hollow bore needlestick injuries, none of the patients who received 10 days of high dose favipiravir developed Ebola virus disease.

Early clinical experience with favipiravir for COVID-19 is promising. An open label non randomized trial of 80 patients with COVID-19 in China identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with lopinavir or ritonavir. Patients with mild or moderate COVID-19 were enrolled within 7 days from disease onset; those ≥ 75 years old, with severe or critical disease, chronic liver disease or end stage renal disease were excluded. Patients in the intervention arm received favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg orally twice daily on days 2-14. Both arms were co-treated with inhaled IFN-α1b 60 µg twice daily and therapy was continued until viral clearance, up to a maximum of 14 days. Thirty five patients were assigned to favipiravir and 45 patients to lopinavir or ritonavir, with a median age of 47 years (IQR = 35.8-61); 13.7% were ≥ 65 years old. There was a significant reduction in the median time to viral clearance with favipiravir (4 days; IQR = 2.5-9) compared with lopinavir/ritonavir (11 days; IQR = 8-13; $P < 0.001$). Further, by day 14, 91.4% of patients in the favipiravir arm had radiographic improvement versus 62.2% in the lopinavir or ritonavir arm. There was a significantly lower rate of adverse events in patients receiving favipiravir (11.4% versus 55.6%; $P < 0.01$).

Given the demonstrated *in vitro* of activity of favipiravir against SARS-CoV-2 and signals of benefit in early clinical experience for COVID-19, further studies are urgently needed. The results of several ongoing randomized controlled trials to assess the efficacy of favipiravir for COVID-19 will further elucidate the role of favipiravir in the management of the ongoing coronavirus pandemic.

Reference: Jour. of Anti. Chem., 17 May 2020

Emergency use authorization of remdesivir The need for a transparent distribution process

On February 4, 2020, the Secretary of the US Department of Health and Human Services (DHHS) determined that there was a public health emergency due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 27, 2020, the DHHS secretary declared that circumstances existed to justify the authorization of emergency use of drugs and biologics during the coronavirus disease 2019 (COVID-19) outbreak, pursuant to section 564 of the Federal Food, Drug and Cosmetic Act. To date, 3 medications chloroquine phosphate, hydroxychloroquine sulfate, and remdesivir have been granted Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) for COVID-19. Since chloroquine and hydroxychloroquine are FDA approved drugs, clinicians had options for prescribing them outside the EUA mechanisms and prescribing appears to have been robust.

Because remdesivir is not yet FDA approved, until now, the only way to access this drug was through clinical studies, expanded access programs and compassionate use programs. The issuance of a EUA on May 1, 2020 should expand access to remdesivir, yet details about how this drug will become available are opaque and distribution remains limited. A clear and transparent process for access to remdesivir through the EUA is needed and is in the best interest of patients. The authority of the FDA to issue a EUA was granted by congress through various statutes. An EUA can be issued only after the secretary of DHHS has declared a public health emergency. The FDA commissioner, in consultation with the DHHS Assistant Secretary for Preparedness and Response, US Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH), can then issue the EUA, if criteria under the statute are met. An EUA is not approval of a drug for sale and has a term of 1 year, which can be renewed, based on the circumstances of the emergency. Continued clinical studies are still needed to allow for permanent approval because the EUA is only a temporary means for making a product available.

Other agents have been made available under an EUA, the most relevant recent example was the EUA of intravenous peramivir in 2009-2010 for the influenza A(H1N1) pandemic. In that instance, the CDC was responsible for managing the drug distribution, which was done through an electronic system through which clinicians directly requested peramivir under the EUA. Only 1200 treatment courses were initially available for distribution through this process. From October 2009 to June 2010, the period that peramivir EUA was available to clinicians, 1371 requests for release of the drug were made, and at least 1274 patients received 1 or more doses. However, limited data were collected regarding the outcome and

adverse effects. Through revisions of the statutes authorizing EUA, more information is now allowed to be collected about individuals treated under the EUA to better understand safety of drugs issued through the EUA since then. Such data collection remains voluntary and will likely remain incomplete.

The May 1, 2020, EUA for the use of remdesivir for the treatment of COVID-19 was based on the following statement.

1. "SARS-CoV-2 can cause a serious or life threatening disease or condition, including severe respiratory illness, to humans infected by this virus
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that remdesivir may be effective in treating COVID-19 and that, when used under the conditions described in this authorization, the known and potential benefits of remdesivir when used to treat COVID-19 outweigh the known and potential risks of such products
3. There is no adequate, approved and available alternative to the emergency use of remdesivir for the treatment of COVID-19

The authorization is limited as follows:

- Distribution of the authorized remdesivir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply remdesivir to authorized distributors or directly to a US government agency, who will distribute to hospitals and other healthcare facilities as directed by the US Government, in collaboration with state and local government authorities, as needed
- The remdesivir covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as $SpO_2 \leq 94\%$ on room air, requiring supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- Remdesivir is administered in an in patient hospital setting via intravenous (IV) infusion by a health care provider
- The use of remdesivir covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized facts sheets

Two specific fact sheets, one for clinicians and one for patients and parents or caregivers, were made available to support this requirement. Since issuance of the EUA, Gilead initially announced donation of 1.5 million doses of remdesivir to the US government, but the total number of doses available for EUA use was clarified by DHHS when it announced that only 607000 vials of remdesivir will be made available over the next 6 weeks. This is enough drug to treat an estimated 78000 hospitalized patients with COVID-19. This number of doses is not likely to meet demand from the tens of thousands of patients per month who are projected to require hospitalization nationwide due to COVID-19 and meet FDA criteria for remdesivir treatment throughout the summer, but it at least represents a path forward.

On May 9, 2020, DHHS issued additional information about the distribution plan to be made publicly available. Before the plan was announced, a group of hospitals received allocations of remdesivir by the US government through a process that was unclear. Data about the distribution are only available from an ad hoc, grassroots effort to have hospitals self identify as having been informed that they will or will not be receiving one of the initial allocations of remdesivir. Since this is a self reported survey it is in no way complete, but provides the only available information about allocation decisions to date. Even with the announcement by DHHS confirming that 2 distributions one allocation of 35360 doses to Indiana, Massachusetts, New Jersey, New York, Rhode Island, Tennessee, and Virginia and a second allocation of 10800 doses to Connecticut, Illinois, Iowa, Maryland, Michigan, and New Jersey had been made, there remains no information on how these allocations were decided. Additionally, it is unclear how distributions were made to specific hospitals within those states.

A transparent plan for distributing remdesivir is imperative if a potentially life saving drug is to be given to the patients in most need. Allocation should be based on hospital, regional, and state COVID-19 infection data with equitable distribution within a region to states and within states to hospitals. The process should also include a mechanism for redistribution based on the constantly changing endemicity of the outbreak. The plan should ensure appropriate patient access and equitable distribution regardless of race, ethnicity, or socioeconomic status. The plan should be designed to prevent a surge in patients at institutions known or thought to have access to the drug or a large increase in requests to transfer patients to these centers from hospitals that may not have access to remdesivir.

Although the distribution of remdesivir via the EUA is an issue unique to the US, as worldwide demand for the drug increases, the imbalance between drug availability and need will be further exacerbated. Countries, working with the manufacturer, will need to develop a system of distribution. Not all patients in the world who are eligible may have access to remdesivir, but all patients deserve a fair and transparent allocation process that reflects the rapidly changing epidemiology of the emerging COVID-19 pandemic. However, more detailed and specific description of a transparent allocation process is needed to ensure that allocation is fair and understandable to patients and the clinicians caring for them.

Reference: JAMA, 14 May 2020

Is the prone position helpful during spontaneous breathing in patients with COVID-19?

A substantial proportion of patients with coronavirus disease 19 (COVID-19) develop severe respiratory failure and require mechanical ventilation, most often fulfilling criteria for Acute Respiratory Distress Syndrome (ARDS). The characteristics of these patients are heterogeneous, consistent with what is known about inflammatory edema leads to varying degrees of lung collapse resulting in Ventilation Perfusion Ratio (V/Q) mismatching, including a significant shunt fraction. Additionally, lung microthrombi are suspected and result in different levels of dead space and inefficient ventilation. In sedated patients, gravitational forces lead to lung atelectasis occurs in the dependent lung regions and the remaining aerated lung available for gas exchange becomes small. Insufficient hypoxic vasoconstriction, another feature of ARDS that contributes to V/Q mismatch, is suggested by the finding of hypoxemia with relatively preserved compliance in some patients.

Vigorous breathing efforts among patients with moderate and severe ARDS during spontaneous or assisted invasive or Noninvasive Ventilation (NIV) can worsen lung injury and result in Patient Self Inflicted Lung Injury (P-SILI). Strong respiratory efforts lead to large negative swings in pleural pressure generating excessive lung stress and strain and to increased lung edema due to negative transalveolar pressure. Because of atelectasis in the dependent regions, the force generated by diaphragmatic contractions remains predominantly localized in regions close to the muscular portion of the diaphragm and generates a pressure gradient inside the lung, with displacement of gas from nondependent to dependent areas. This phenomenon, called pendelluft, increases regional lung stress and strain even in the absence of large tidal volumes.

Strong breathing efforts are controlled by the output of the respiratory centers, the respiratory drive, primarily regulated by the chemoreflex control system. The combination of a high metabolic rate (e.g,. sepsis, fever) and inefficient ventilation increases respiratory drive. Additionally, lung injury, through J receptors in the lung and systemic or brainstem inflammation stimulate the respiratory drive. A dissociation between what the brain expects and what the ventilatory system can achieve results in dyspnea that further stimulates the respiratory drive. Excessive drive can then overcome lung protective reflexes, such as Hering Breuer inflation reflex and worsen lung injury.

In the context of worsening oxygenation and increased work of breathing, invasive mechanical ventilation with sedation, paralysis

and positive end expiratory pressure to control breathing effort ensures lung protective ventilation (low tidal volume) minimizing P-SILI. However, potential adverse consequences are well known including immobilization, disuse diaphragmatic atrophy, associated infections, sleep disturbances and possibly neurocognitive dysfunction. Helmet NIV and high flow nasal cannula delivered oxygen were suggested to be clinically more effective than NIV delivered via facemask and regular oxygen in early hypoxemic respiratory failure. However, monitoring tidal volume and breathing effort in these patients is challenging with the potential risk of direct harm and delayed intubation, as shown during NIV. During the COVID-19 pandemic, high burden of intensive care unit workload and concern for possible ventilator shortage further prompted clinicians to pursue alternative strategies to avoid intubation.

Two small case series described the use of the prone position in awake patients with COVID-19 during spontaneous and assisted breathing outside the ICU. The studies have limitations but illustrate interesting points. A study that included 24 patients with acute hypoxemic respiratory failure and infiltrates on chest computed tomographic scans. Prone positioning was started without changing the system for oxygen supply or Fraction of Inspired Oxygen (FIO_2). Four patients did not tolerate the prone position for more than an hour (requiring later intubation); 6 of 15 patients who tolerated prone position showed a mean (SD) increase in PaO_2 of more than 20% from baseline (74 [16] to 95 [28] mm Hg; P = .006) but 3 patients returned to baseline PaO_2 after supination.

A 1 day cross sectional before after study was performed that included 15 awake patients with mild and moderate ARDS. The estimated mean (SD) PaO_2:FIO_2 was 157 (43). Patients received NIV with sessions of prone positioning after poor response to Continuous Positive Airway Pressure (CPAP) of 10 cm H_2O. On the day of the study, the patients had a median of 2 sessions (interquartile range [IQR], 1-3) of prone positioning for 3 hours (IQR, 1-6 hours). Compared with before receiving NIV, oxygenation and respiratory rate improved during NIV while prone (estimated PaO_2:FiO_2, 100 [IQR, 60-112] to 122 [IQR, 118-122] and respiratory rate 28 breaths/min [IQR, 27-30] to 24 [21-25] breaths/min) and remained improved 1 hour after NIV session in prone position in most patients (12 of 15). At 14 days, 1 patient was intubated and another died.

Several conclusions can be drawn cautiously from these case series, although the findings cannot be generalized without confirmation in larger trials. Many but not all patients with hypoxemic respiratory failure tolerate the prone position while awake, breathing spontaneously or while receiving NIV. Among patients who tolerated a session of prone positioning, improvement in oxygenation and decrease in respiratory rate occurred, suggesting a lower power of breathing (respiratory rate is poorly correlated with respiratory drive but in this context, it is potentially associated with lower power). The effects were transient and respiratory rates and oxygenation often returned to baseline after supination.

Limitations have been listed by the authors, including the small sample size and lack of control groups. Overall, prone sessions during the studies were short, partly because of limited patient tolerance. Important information for interpretation of the results was missing such as baseline severity of hypoxemia and which NIV interface and settings were used during the prone sessions. It is also unclear if the physiological changes while prone were due to the position, the use of NIV, or a synergistic effect of both. The inclusion of patients who initially worsened after a trial of CPAP may suggest that the prone position improved tolerance of NIV.

The prone position can improve oxygenation and can potentially result in less injurious ventilation. Because of a higher density of pulmonary vessels in the dorsal lung region (independently of gravity), the change of ventilation distribution while prone (ie, relative increase in ventilation in the dorsal nondependent areas) results in improved V/Q matching and oxygenation. While prone, the chest wall compliance decreases when the anterior, more flexible part of the chest is facing the bed, explaining in part a more homogeneous distribution of ventilation and regional lung stress and decreasing the risk of ventilation induced lung injury and possibly pendelluft. It is possible that the contraction of the muscular diaphragm, which faces the open dorsal lung during pronation exerts a more uniform distribution of stress, whereas the muscular diaphragm exerts a more localized stress when facing the collapsed lung during supination. These mechanisms and the effect of prone positioning on respiratory drive and effort need to be investigated in spontaneously breathing patients. In a crossover study involving 14 infants with bronchiolitis, the prone position with nasal CPAP reduced effort and improved neuromechanical coupling.

Prone position during invasive mechanical ventilation improved oxygenation in large randomized clinical trials (RCTs) of patients with ARDS. However, better oxygenation was not associated with improved survival in trials with short duration of prone positioning. In an RCT that included 466 patients with moderate and severe ARDS (PaO_2:FIO_2 <150), prone positioning for at least 16 hours per day with protective mechanical ventilation reduced 90 day mortality. However, clinicians should closely monitor patients for whom prone positioning is used for tolerance and response and aim to prevent delayed intubation and controlled mechanical ventilation when necessary.

Reference: JAMA, 15 May 2020

Venous thrombosis among critically ill patients with coronavirus disease 2019 (COVID-19)

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified as a new coronavirus causing pneumonia and acute respiratory distress syndrome. It has become a pandemic, spreading particularly quickly across Europe and the US. Most deaths are related to severe acute respiratory distress syndrome, but other organ failures, such as acute kidney failure and acute cardiac injury, seem also related to the disease. Inflammatory response is highly increased in coronavirus disease 2019 (COVID-19) infection and inflammation is known to favor thrombosis. High dimerized plasmin fragment D (D-dimer) levels and procoagulant changes in coagulation pathways were reported among patients with severe COVID-19. An elevated rate of venous and arterial thrombotic events associated with COVID-19 infection has also been reported. This case series reports a systematic assessment of deep vein thrombosis among patients in an intensive care unit (ICU) in France with severe COVID-19.

Methods

This case series was approved by the ethical committee of the Centre Cardiologique du Nord, which granted a waiver of consent because the research presented no risk of harm and required no procedures for which consent is normally required outside a research context. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Patients with severe COVID-19 pneumonia were admitted to the ICU located in the suburban Paris area from mid March 2020 to the beginning of April 2020. All patients had acute respiratory distress syndrome according to the Berlin definition and required mechanical ventilation.

A venous ultrasonogram was prospectively performed of the inferior limbs for all patients at admission to the ICU, considering previous data that showed increased levels of inflammatory markers, preliminary reports from the intensive care community signaling frequent events of deep vein thrombosis in ICU patients with COVID-19 at the time when first patients were received, and the high rate of deep vein thrombosis found among the first patients with COVID-19 admitted to the unit. Considering the high prevalence of venous thrombosis at admission, venous ultrasonography was systematically repeated after 48 hours if the first examination returned normal results. As recommended, all patients received anticoagulant prophylaxis at hospital admission.

Results

A total of 34 consecutive patients were included in this study. COVID-19 diagnosis was confirmed with polymerase chain reaction on nasopharyngeal swabs of 26 patients (76%); 8 patients (24%) had a negative result on polymerase chain reaction but had a typical pattern of COVID-19 pneumonia on chest computed tomography scan. Mean (SD) age was 62.2 (8.6) years, and 25 patients (78%) were men. Major comorbidities were diabetes (15 [44%]), hypertension (13 [38%]) and obesity (mean [SD] body mass index [calculated as weight in kilograms divided by height in meters squared], 31.4 [9.0]). Overall, 26 patients (76%) required norepinephrine at admission, 16 (47%) required prone positioning, and 4 (12%) required venovenous extracorporeal membrane oxygenation. Only 1 patient (3%) received anticoagulant therapy before hospitalization. Deep vein thrombosis was found in 22 patients (65%) at admission and in 27 patients (79%) when the venous ultrasonograms performed 48 hours after ICU admission were included. 18 patients (53%) had bilateral thrombosis and 9 patients (26%) had proximal thrombosis.

Discussion

Mortality of patients with COVID-19 admitted to ICUs has been reported to be high, at 50%. Frequent venous and arterial thrombotic events have been reported, with rates from 27% to 69% of peripheral venous thromboembolism and up to 23% of pulmonary embolism. In view of the high rate (79%) of deep vein thrombosis reported in this study, prognosis might be improved with early detection and a prompt start of anticoagulant therapy. Despite anticoagulant prophylaxis, 15% of the patients developed deep vein thrombosis only 2 days after ICU admission. Systematic anticoagulant therapy for all ICU patients with COVID-19 should be assessed.

Reference: JAMA, 29 May 2020

Potential role of oral rinses targeting the viral lipid envelope in SARS-CoV-2 infection

SARS-CoV-2 is an enveloped virus, characterized by an outer lipid membrane derived from the host cell from which it buds. Here, Mechanisms of viral lipid membrane disruption by widely available dental mouthwash components that include ethanol, chlorhexidine, cetylpyridinium chloride, hydrogen peroxide and povidone iodine have been reviewed. It is also reviewed that the impact of ethanol on mammalian cells in vitro. A study on corneal epithelial cells showed that a 30s incubation with 20% ethanol led to around 40% loss of viability, which increased to 70% loss at 40% ethanol. There was significant leakage of intracellular contents following 20% ethanol for 30s. In 2007, Roberts and Lloyd found that 20% ethanol completely inactivated three enveloped viruses: Sindbis, Herpes simplex-1, and Vaccinia, *in vitro,* while having no effect on the nonenveloped Poliovirus-1. In 2017, WHO recommended formulations against enveloped viruses, including coronavirus. Focusing on WHO formulation, which contains 85% (v/v) ethanol, 0.725% (v/v) glycerol, and 0.125% (v/v) hydrogen peroxide. A 30s exposure of a dilution containing 34% (v/v) ethanol (40% of neat) completely prevented subsequent viral replication. These studies indicate that relatively dilute ethanol will be highly effective against enveloped viruses.

Chlorhexidine is often formulated with ethanol at lower concentrations, which may in part explain its virucidal impact. A recent review of coronavirus literature identified that chlorhexidine exposure for 10 min only weakly inactivated coronavirus strains in suspension tests although the concentration used was low at 0.02%. Despite lower activity toward coronaviruses, a combination of chlorhexidine with alcohol may offer a useful strategy for reducing viral load over longer times. Povidone Iodine (PVP-I) mouthwash has been widely studied in relation to broad spectrum antimicrobial and virucidal actions. At 0.23%, rapidly inactivates SARS-CoV, MERS-CoV, influenza virus A (H1N1) and rotavirus *in vitro.* A study also showed that PVP-I (0.23%) is equivalent to 70% ethanol in inactivating SARS-CoV *in vitro.* Chlorinated water or hypertonic saline rinsing studies from Japan surprisingly found that gargling with chlorinated tap water reduced respiratory infections and was even better than PVP-I. Tap water reduced incidence of common cold by 36%, while PVP-I was not effective.

Recent study showed that gargling and nasal rinsing with hypertonic saline could reduce symptoms, duration of illness and viral shedding. Hydrogen Peroxide causes oxygen free radical induced disruption of lipid membranes and is widely used as an agent for tooth whitening. Coronavirus 229E and other enveloped viruses are inactivated at concentrations around 0.5%. While higher concentrations of hydrogen peroxide (> 5%) will induce damage to both soft and hard tissues, within the range of concentrations used in mouthwashes for whitening at 1-3% little damage is reported. Within the oral environment, hydrogen peroxide is rapidly inactivated due to the presence of host and bacteria derived catalase activity in saliva and other endogenous peroxidases.

Quaternary ammonium compounds are widely used as microbicidal agents that interfere with protein or lipid components on the cell surface. They have some virucidal activities against some enveloped viruses, relating to surface disinfection. Among this group of compounds, cetylpyridinium chloride (CPC) was recently shown to have activity against influenza both in vitro and *in vivo,* through direct attack on the viral envelope. Statistical epidemiological studies could establish on a population level whether mouth rinsing is associated with reduced rates of throat and respiratory infections including SARS-CoV-2.

Reference: Func., 2020, Vol.1(1)

Comparison of clinical characteristics of patients with asymptomatic versus symptomatic coronavirus disease 2019 in Wuhan, China

Introduction

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, in December 2019 and has spread globally with sustained human to human transmission outside China. To control the spread of COVID-19 and isolate patients as early as possible, the Chinese government requested that close contacts of individuals with COVID-19 must be screened for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. During the screening process, some patients whose test results were positive for SARS-CoV-2 were found but who had no symptoms or signs throughout the course of the disease. Considering that little is known about the differences of clinical features and prognosis between patients who were asymptomatic versus those who were symptomatic, this case series aimed to describe the clinical characteristics of patients with SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction (RT-PCR) from 26 transmission cluster series in Wuhan, China, from December 24, 2019 to February 24, 2020.

Methods

This case series was approved by the institutional ethics board of Zhongnan Hospital of Wuhan University. All consecutive patients with COVID-19 confirmed via RT-PCR admitted to Zhongnan Hospital of Wuhan University from December 24, 2019 to February 24, 2020 were enrolled. Oral informed consent was obtained from all patients. Epidemiological, symptoms, signs, laboratory values, and chest computed tomography (CT) scans, treatment measures, and outcomes data during the hospital stay were collected. Nasopharyngeal swab samples were collected for extracting SARS-CoV-2 RNA from patients suspected of having SARS-CoV-2 infection.

Results

The 78 close contacts confirmed with SARS-CoV-2 infection were hospitalized in same medical area and provided the same treatments administered by the same health care workers. A total of 33 patients (42.3%) were asymptomatic, while 45 patients (57.7%) were symptomatic. The symptoms and signs such as fever, fatigue and dry cough, were monitored every day. Detecting SARS-CoV-2 from nasopharyngeal swab was monitored every 24 to 48 hours. For patients with stable conditions, a second chest CT was conducted 4 to 6 days after the first time, then 6 to 7 days after the second time. Chest CT was also conducted at any time a patient's condition

became worse. $CD4^+$T lymphocyte count was tested every 5 to 6 days. Patients who were asymptomatic, compared with patients with symptomatic SARS-CoV-2 infection, were younger (median [IQR] age, 37 [26-45] years versus 56 [34-63] years; $P < .001$) and had a higher proportion of women (22 [66.7%] women versus 14 [31.%] women; $P = .002$), lower proportion of liver injuries (1 patients [3.0%] versus 9 patients [20.0%]; $P = .03$), less consumption of $CD4^+$T lymphocytes (median [IQR] CD4 lymphocyte count during recovery, 719 [538-963] per μL versus 474 [354-811] per μL $P = .009$), faster lung recovery in CT scans (median [IQR] duration, 9 [6-18] days versus 15 [11-18] days; $P = .001$), shorter duration of viral shedding from nasopharynx swabs (median [IQR] duration, 8 [3-12] days versus 19 [16-24] days; $P = .001$), and more stable results of SARS-CoV-2 testing (4 fluctuated results [12.1%] versus 15 fluctuated results [33.3%]).

Discussion

The less consumption of $CD4^+$T lymphocyte in asymptomatic infections suggests that damage to the immune system in asymptomatic infections was milder compared with symptomatic infections. Although patients who were asymptomatic experienced less harm to themselves, they may have been unaware of their disease and therefore not isolated themselves or sought treatment, or they may have been overlooked by health care workers and thus unknowingly transmitted the virus to others. Fortunately, patients with asymptomatic SARS-CoV-2 infection have a shorter duration of viral shedding from nasopharyngeal swabs and lower risk of a recurring positive test result of SARS-CoV-2 from nasopharyngeal swabs, which can provide a reference for improving the prevention and control strategies for patients who are asymptomatic.

Reference: JAMA, 27 May 2020

Neurologic features in severe SARS-CoV-2 infection

Neurologic features in an observational series of 58 of 64 consecutive patients admitted to the hospital because of acute respiratory distress syndrome (ARDS) due to COVID-19. The patients received similar evaluations by intensivists in two intensive care units (ICUs) in March 3 and April 3, 2020.

Six patients were excluded because of paralytic neuromuscular blockade when neurologic data were collected or because they had died without a neurologic examination having been performed.

In all 58 patients, Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assays of nasopharyngeal samples were positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2). The median age of the patients was 63 years and the median Simplified Acute Physiology Score II at the time of neurologic examination was 52 (interquartile range 37 to 65, on a scale ranging from 0 to 163, with higher scores indicating greater severity of illness). Seven patients had previous neurologic disorders, including transient ischemic attack, partial epilepsy and mild cognitive impairment.

The neurologic findings were recorded in 8 of the 58 patients (14%) on admission to the ICU (before treatment) and in 39 patients (67%) when sedation and a neuromuscular blocker were withheld. Agitation was present in 40 patients (69%) when neuromuscular blockade was discontinued. A total of 26 of 40 patients were noted to have confusion according to the Confusion Assessment Method for the ICU; those patients could be evaluated when they were responsive (e.g., they had a score of -1 to 1 on the Richmond Agitation and Sedation Scale, on a scale of -5 [unresponsive] to +4 [combative]). Diffuse corticospinal tract signs with enhanced tendon reflexes, ankle clonus and bilateral extensor plantar reflexes were present in 39 patients (67%). Of the patients who had been discharged at the time of this writing, 15 of 45 (33%) had a dysexecutive syndrome consisting of inattention, disorientation or poorly organized movements in response to command.

Magnetic Resonance Imaging (MRI) of the brain was performed in 13 patients. Although these patients did not have focal signs that suggested stroke, they underwent MRI because of unexplained encephalopathic features. Enhancement in leptomeningeal spaces was noted in 8 patients and bilateral frontotemporal hypoperfusion was noted in all 11 patients who underwent perfusion imaging. Two asymptomatic patients each had a small acute ischemic stroke with

focal hyperintensity on diffusion weighted imaging and an overlapping decreased apparent diffusion coefficient and 1 patient had a subacute ischemic stroke with superimposed increased diffusion weighted imaging and apparent diffusion coefficient signals.

In the 8 patients who underwent electroencephalography, only nonspecific changes were detected; 1 of the 8 patients had diffuse bi-frontal slowing consistent with encephalopathy. Examination of cerebrospinal fluid (CSF) samples obtained from 7 patients showed no cells; in 2 patients, oligoclonal bands were present with an identical electrophoretic pattern in serum and protein and IgG levels were elevated in 1 patient. RT-PCR assays of the CSF samples were negative for SARS-CoV-2 in all 7 patients.

In this consecutive series of patients, ARDS due to SARS-CoV-2 infection was associated with encephalopathy, prominent agitation and confusion, and corticospinal tract signs. Two of 13 patients who underwent brain MRI had single acute ischemic strokes. Data are lacking to determine which of these features were due to critical illness related encephalopathy, cytokines, or the effect or withdrawal of medication and which features were specific to SARS-CoV-2 infection.

Reference: N. Eng. J. Med., 15 April 2020

Caring for women who are planning a pregnancy, pregnant or postpartum during the COVID-19 pandemic

Since its recognition in China in December 2019, coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has rapidly spread throughout the world and become a pandemic. Although considerable data on COVID-19 are available, much remains to be learned about its effects on pregnant women and newborns.

No data are currently available to assess whether pregnant women are more susceptible to COVID-19. Pregnant women are at risk for severe disease associated with other respiratory illnesses (e.g., 2009 H1N1 influenza), but thus far, pregnant women with COVID-19 do not appear to be at increased risk for severe disease compared with the general population. Data from China showed that among 147 pregnant women, 8% had severe disease and 1% had critical illness which are lower rates than observed in the nonpregnant population (14% with severe disease and 6% with critical illness). Case series from China consisting primarily of women with third trimester infection have shown that clinical findings in pregnant women are similar to those seen in the general population. Conversely, a small Swedish study reported that pregnant and postpartum women with COVID-19 were 5 times more likely to be admitted to an intensive care unit compared with nonpregnant women of similar age.

Data on pregnant women with COVID-19 in the US are beginning to accumulate. For example, a recent report included 43 pregnant women with COVID-19 who presented for care at 2 hospitals in New York City. Although this case series did not include a nonpregnant control group, the proportion of pregnant women with severe disease was similar to that described in nonpregnant adults with COVID-19. More information is needed about the effect of pregnancy and comorbidities to understand how they affect clinical outcomes of COVID-19. The US experience might differ from other countries because of the high frequency of comorbidities among pregnant women in the US.

The effects of COVID-19 during pregnancy on the neonate are not well understood. Nearly all infections reported from China were during the third or late second trimester, so whether first trimester SARS-CoV-2 infection might cause birth defects or pregnancy loss is unknown. Some newborns born to mothers with COVID-19 during pregnancy were born preterm or of low birth weight, but whether these outcomes were COVID-19 related is unclear. SARS-CoV-2 transmission from a mother to her newborn could occur prenatally, perinatally or postnatally. In most newborns tested after birth, results have been negative for SARS-CoV-2. However,

symptomatic newborns born to mothers with COVID-19 have been reported to have SARS-CoV-2 infection at a few days of life; whether this was due to prenatal, perinatal or postnatal transmission is unknown. Recently, a probable case of congenital infection was reported in a newborn born to a woman with familial neutropenia who was diagnosed with COVID-19 before delivery. A neonatal nasopharyngeal swab collected on the day of birth prior to skin-to-skin maternal contact was positive. The presence of IgM and IgG antibodies in 3 infants born to mothers with COVID-19 during pregnancy was recently reported. IgG antibodies freely cross the placenta; however, IgM antibodies do not typically cross the placenta, suggesting the possibility of prenatal transmission of SARS-CoV-2. However, these studies do not provide definitive evidence for intrauterine transmission because cross reactivity and false positive IgM test results can occur. Whether transmission can occur through breastfeeding is unknown. SARS-CoV-2 RNA has been detected in breast milk samples from a single woman with COVID-19 and her infant tested positive for SARS-CoV-2, but whether the infant was infected through breastfeeding is unclear. Given the benefits of breast milk, when feasible, breast milk should be fed to infants regardless of maternal COVID-19 status.

Based on experiences with other infections (e.g., influenza), adverse effects on the fetus or newborn related to prenatal infection might occur even without intrauterine transmission. For example, severe maternal illness with influenza requiring intensive care unit admission was associated with increased risks for preterm birth, low birth weight, and low APGAR scores. Whether an increased risk for adverse outcomes among newborns born to women with COVID-19 will be seen is unknown.

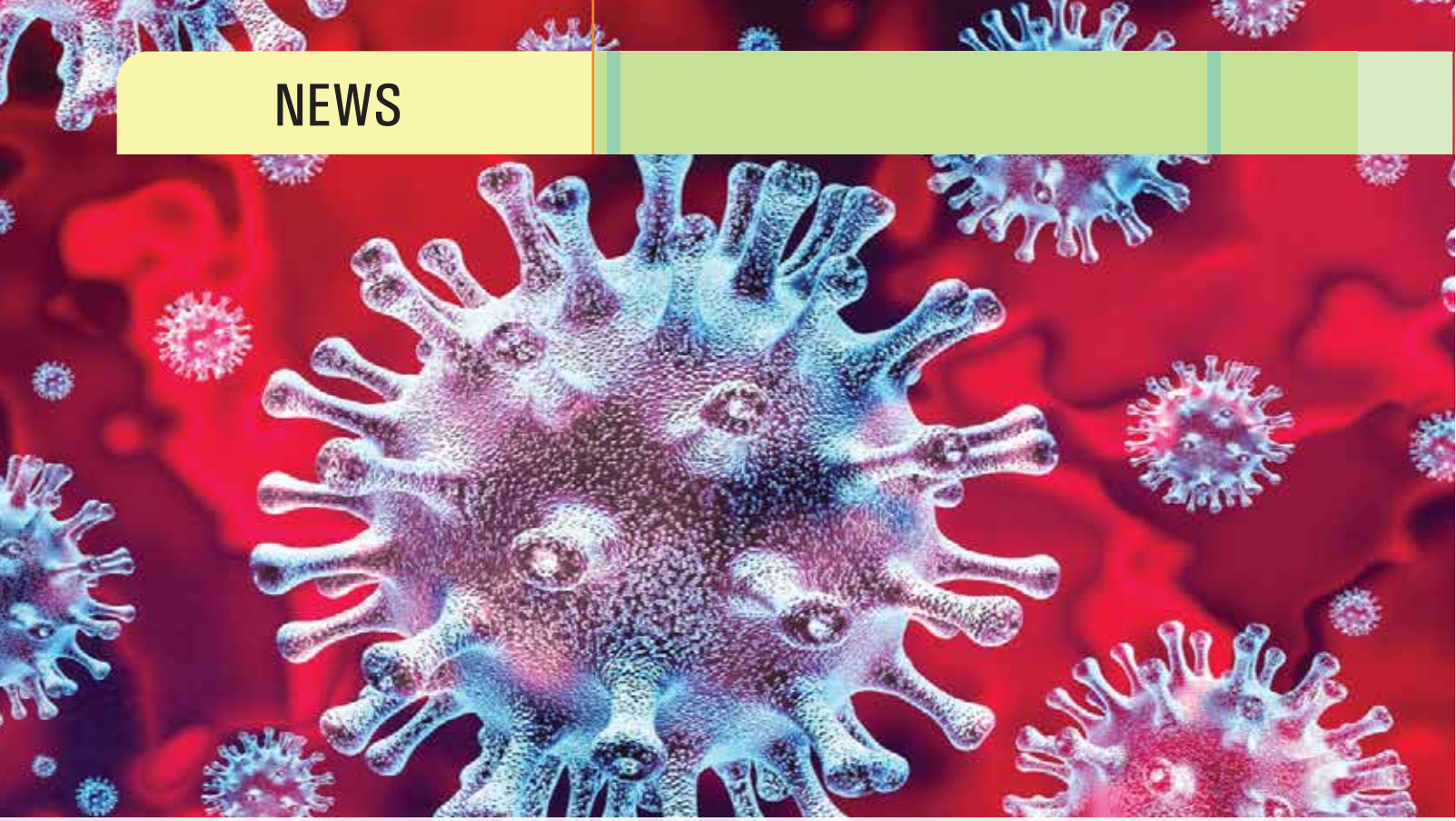
Given the limited data, recommendations for caring for women who are planning a pregnancy, pregnant or have given birth during the COVID-19 pandemic are based on expert opinion. Women planning a pregnancy in the time of COVID-19 might ask whether they should delay pregnancy until after the pandemic. Based on limited data, there does not seem to be a compelling reason to recommend delaying pregnancy. For women who are pregnant, the primary recommendation is to avoid becoming infected with SARS-CoV-2 through hygiene and social distancing measures. Early recognition of COVID-19 in a pregnant patient admitted to a labor and delivery unit is necessary so appropriate infection control practices can be instituted. Given that some women with COVID-19 might be asymptomatic or presymptomatic, health care facilities may consider polymerase chain reaction testing for SARS-CoV-2 at the time of admission.

Guidelines for the care of pregnant women known or suspected to have COVID-19 admitted for delivery have been developed by the Centers for Disease Control and Prevention (CDC) and several professional organizations. On presentation, a mask should be placed on the woman and she should be isolated in a single patient room with the door closed, with an airborne isolation room used for aerosol generating procedures. Clinical care of a pregnant woman with COVID-19 should be based on illness severity; diagnostic measures and treatments should not be withheld based on pregnancy status. Given the risks of maternal respiratory depression, consideration should be given to limiting the use of magnesium sulfate for seizure prophylaxis and fetal neuroprotection. Given concerns about potential harm from corticosteroid use in patients with COVID-19, antenatal corticosteroid use for fetal maturation should be carefully considered and should depend on the gestational age. Early epidural analgesia should be considered to mitigate the risks associated with general anesthesia in the setting of an urgent cesarean delivery. Decisions regarding timing and mode of delivery should be based on standard fetal and maternal indications.

Issues related to hospital placement of the newborn born to a mother with known or suspected COVID-19 are challenging. Measures to reduce the risk of transmission from an infected mother to her newborn include placing them in separate rooms or using other controls (e.g., physical barriers, the mother wearing a face mask during contact with the newborn); shared decision making between the mother and the care team regarding this issue is recommended. For those who select temporary separation, expression of breast milk with careful hand and breast hygiene should be encouraged, with feeding of the breast milk done by a healthy caregiver. A mother who chooses to room with her newborn should use a face mask and careful hand and breast hygiene before breastfeeding. Newborns born to mothers with COVID-19 at delivery should be considered to have suspected COVID-19 and isolated from healthy newborns.

Information on COVID-19 is changing rapidly. As additional data become available recommendations might change, so clinicians should follow the CDC website and those of professional organizations for updates.

Reference: JAMA, 05 June 2020



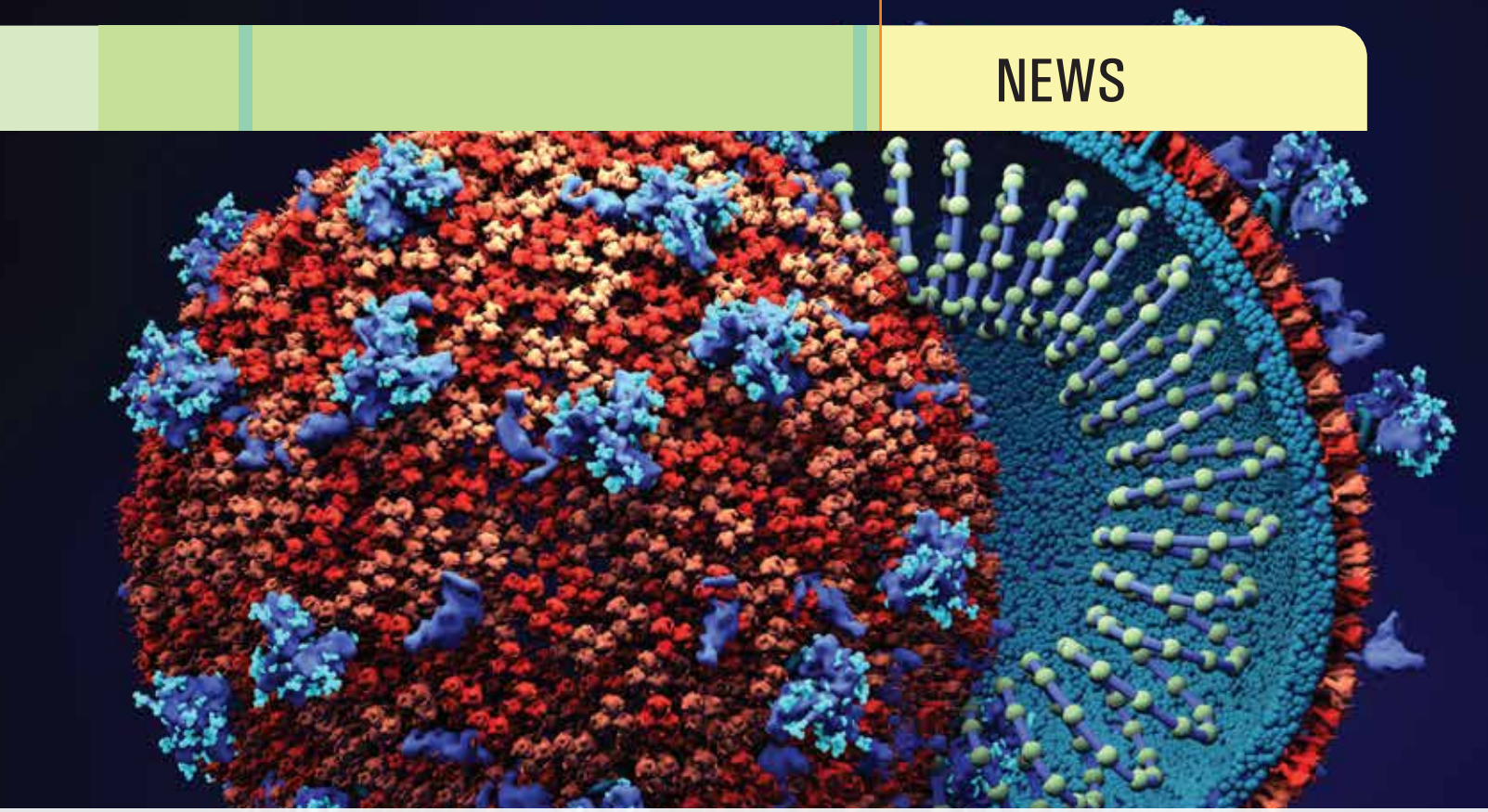
WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients

The World Health Organization (WHO) welcomes the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO. The benefit was only seen in patients seriously ill with COVID-19 and was not observed in patients with milder disease.

Dr. Tedros Adhanom Ghebreyesus, WHO Director General said that this is the first treatment to be shown to reduce mortality in patients with COVID-19 requiring oxygen or ventilator support. He also said that this is a great news and he congratulates the Government of the UK, the University of Oxford and the many hospitals and patients in the UK who have contributed to this lifesaving scientific breakthrough. Dexamethasone is a steroid that has been used since the 1960s to reduce inflammation in a range of conditions, including inflammatory disorders and certain cancers. It has been listed on the WHO Model List of Essential Medicines since 1977 in multiple formulations and is currently off patent and affordably available in most countries. The researchers shared initial insights about the results of the trial with WHO and they are looking forward to the full data analysis in the coming days.

WHO will coordinate a meta analysis to increase their overall understanding of this intervention. WHO clinical guidance will be updated to reflect how and when the drug should be used in COVID-19. Today's news builds off the WHO Research and Development Blueprint meeting, which took place in Geneva in mid February to accelerate health technologies for COVID-19, where further research into the use of steroids was highlighted as a priority. WHO will continue to work together with all partners to further develop lifesaving therapeutics and vaccines to tackle COVID-19 including under the umbrella of the access to COVID-19 tools accelerator.

Reference: World Health Organization, 16 June 2020



Covid-19: Low dose steroid cuts death in ventilated patients by one third, trial finds

Low dose dexamethasone reduces deaths in patients hospitalized with COVID-19 who need ventilation, according to preliminary results from the recovery trial. The drug was also found to reduce deaths by one fifth in other hospitalized patients receiving oxygen only, but no benefit was seen among COVID-19 patients who did not need respiratory support.

For the randomized controlled trial, the team recruited 2104 patients for the dexamethasone arm (6 mg once daily, taken orally or by injection for 10 days) and compared them with 4321 patients receiving standard care. Among the patients who received usual care alone, 28 day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%) and lowest among those who did not require any respiratory intervention (13%). Based on these results, one death in eight would be prevented by treatment in ventilated patients or around one in 25 patients requiring oxygen alone, the team said. The findings suggest that taking dexamethasone reduces mortality from around 41% to 27% for ventilated patients and from 25% to 20% among those needing oxygen.

The chief investigators from the University of Oxford trial said that the findings represent a "major breakthrough" which is "globally applicable" as the drug is cheap and readily available. Martin Landray, professor of medicine and epidemiology at the University of Oxford and one of the chief investigators on the trial, said, "The search has been on for a treatment that can actually reduce the risk of dying and there hasn't been one until today. The results are significantly clear, so people can be treated tonight or tomorrow. That is a major step forward. This is globally applicable. This is not an expensive drug or one where there are supply or manufacturing problems. This is a drug that is locally available."

Peter Horby, professor of emerging infectious diseases at University of Oxford and another chief investigator on the trial, added, "This is the only drug that has so far been shown to reduce mortality and it reduces it significantly. It is a major breakthrough." Siu Ping Lam, director of licensing at the Medicines and Healthcare Products Regulatory Agency, said that the results were "very encouraging."

Reference: BMJ, 16 June 2020, Vol. 369

Medical masks

Medical masks are a tool that can be used to prevent the spread of respiratory infection. These masks cover the mouth and nose of the wearer and if worn properly may be effective at helping prevent transmission of respiratory viruses and bacteria. There are 2 main types of masks used to prevent respiratory infection: surgical masks, sometimes referred to as face masks and respirators. These masks differ by the type and size of infectious particles they are able to filter. Face masks are used more commonly for respiratory viruses that spread via droplets, which travel short distances and are transmitted by cough or sneeze. Face masks often fit loosely and prevent the wearer from spreading large sprays and droplets, as well as preventing hand to face contact. N95 respirators block 95% of airborne particles. They are tight fitting and prevent inhalation of smaller infectious particles that can spread through the air over long distances after an infected person coughs or sneezes. Diseases that require use of N95 respirator include tuberculosis, chickenpox and measles. N95 respirators cannot be used by individuals with facial hair or by children because it is difficult to achieve a proper fit. In those cases, a special respirator called a powered air purifying respirator may be used instead.

Best time to use a mask

Face masks should be used by individuals who have symptoms of respiratory infection such as coughing, sneezing or in some cases fever. Face masks should also be worn by health care workers by individuals who are taking care of or are in close contact with people who have respiratory infections. Face masks should be reserved for those who need them because masks can be in short supply during periods of widespread respiratory infection. Because N95 respirators require special fit testing, they are not recommended for use by the general public.

Procedure of wearing a mask

If wearing a face mask is indicated, it is important to wash the hands with soap and water for at least 20 seconds prior to putting on the face mask. An alcohol based sanitizer that contains at least 60% alcohol can also be used if soap and water are unavailable. After cleaning the hands, place the face mask over the nose and mouth. Make sure there are no gaps between the face mask and the face and ensure a tight seal. Try to avoid touching the face mask when wearing it. If touching the face mask, wash the hands or use hand sanitizer again. After using the face mask, remove it without touching the front of the face mask and discard it into a closed bin. Wash the hands again after discarding the face mask.

Medical masks

Face mask

There are 2 main types of medical masks: **face masks** and **N95 respirators**.

Face masks fit more loosely and prevent the wearer from spreading large sprays and droplets when coughing or sneezing.

N95 respirator

N95 respirators fit more tightly and prevent the wearer from inhaling smaller, airborne infectious particles.

N95 respirators are not recommended for use by the general public.

Face masks should only be used by

- Individuals with symptoms of respiratory infection such as coughing, sneezing and sometimes fever
- Health care workers
- Persons taking care of or in close contact with someone with a respiratory infection

How do I use a face mask?

1. Wash hands for at least 20 seconds prior to putting on a face mask
2. Place face mask over nose and mouth. Ensure a tight seal with no gaps and secure elastics or straps
3. Avoid touching the front of the face mask. If anyone do, wash hands for at least 20 seconds
4. Remove the face mask without touching the front. Discard in a closed bin
5. Wash hands again for at least 20 seconds

Reference: JAMA, 21 April 2020; Vol. 323, N. 15

New onset diabetes in COVID-19

There is a bidirectional relationship between COVID-19 and diabetes. On the one hand, diabetes is associated with an increased risk of severe COVID-19. On the other hand, new onset diabetes and severe metabolic complications of preexisting diabetes, including diabetic ketoacidosis and hyperosmolarity for which exceptionally high doses of insulin are warranted, have been observed in patients with COVID-19. These manifestations of diabetes pose challenges in clinical management and suggest a complex pathophysiology of COVID-19 related diabetes.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, binds to Angiotensin Converting Enzyme 2 (ACE2) receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine and the kidneys. Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of disease. There are also several precedents for a viral cause of ketosis prone diabetes, including other coronaviruses that bind to ACE2 receptors. Greater incidences of fasting glycemia and acute onset diabetes have been reported among patients with SARS coronavirus 1 pneumonia than among those with non-SARS pneumonia.

In the aggregate, these observations provide support for the hypothesis of a potential diabetogenic effect of COVID-19, beyond the well recognized stress response associated with severe illness. Answering a few issues like how frequent is the phenomenon of new onset diabete and is it classic type 1 or type 2 diabetes or a new type of diabetes, whether the patients remain at higher risk for diabetes or diabetic ketoacidosis and whether COVID-19 change the underlying pathophysiology and the natural history of the disease is a priority. To address these issues, an international group of leading diabetes researchers participating in the CoviDIAB Project have established a global registry of patients with COVID-19 related diabetes. The goal of the registry is to establish the extent and phenotype of new onset diabetes that is defined by hyperglycemia, confirmed COVID-19, a negative history of diabetes, and a history of a normal glycated hemoglobin level. The registry, which will be expanded to include patients with preexisting diabetes who present with severe acute metabolic disturbance, may also be used to investigate the epidemiologic features and pathogenesis of COVID-19 related diabetes and to gain clues regarding appropriate care for patients during and after the course of COVID-19. The study of COVID-19 related diabetes may also uncover novel mechanisms of disease.

Reference: N. Eng. J. Med., 12 June 2020

Ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

The causative agent of the current COVID-19 pandemic, SARS-CoV-2, is a single stranded positive sense RNA virus that is closely related to severe acute respiratory syndrome coronavirus (SARS-CoV). Studies on SARS-CoV proteins have revealed a potential role for IMPα/β1 during infection in signal dependent nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein, that may impact host cell division. In addition, the SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the $STAT_1$ transcription factor by sequestering IMPα/β1 on the rough endoplasmic reticulum or golgi membrane. Taken together, these reports suggested that ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2.

Physicians from Bangladesh Medical College Hospital (BMCH), led by Prof. Tareq Alam, Head of the Medicine Department at Bangladesh Medical College and Hospital (BMCH), claimed that a combination of the anti-parasitic drug 'Ivermectin' with antibiotic 'Doxycycline' yielded amazing results against COVID-19. The Bangladesh Medical Research Council (BMRC) has recently permitted International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) to run a clinical trial of the drug combination. Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring or containment.

It is reported here that ivermectin, an FDA approved anti parasitic previously shown to have broad spectrum anti-viral activity *in vitro*, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 hours post infection with SARS-CoV-2 able to effect approximately 5000 fold reduction in viral RNA at 48 hours. Altogether the current report, combined with a known-safety profile, demonstrates that ivermectin is worthy of further consideration as a possible SARS-CoV-2 antiviral.

References: 1. The Lancet, June 2020, Vol. 178
2. www.thedailystar.net

Convalescent plasma and COVID-19

What is convalescent plasma?

Most people who recover from COVID-19 develop antibodies (proteins that the immune system produces in response to infection) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Antibodies are found in plasma, the yellow liquid portion of blood. Plasma is collected from donors who have recovered from COVID-19 through a process called apheresis, which uses a special machine to separate the blood into different components. The plasma is removed, while the rest of the blood components are returned into the donor's body.

Potential benefits of convalescent plasma

Convalescent plasma has been used to treat other infections and may be beneficial for COVID-19. Researchers hope that convalescent plasma can be given to patients with severe COVID-19 to boost their ability to fight the virus. Studies are underway to evaluate use of convalescent plasma as treatment for patients with severe COVID-19 and to prevent infection (prophylaxis) in certain high risk patients exposed to COVID-19. Convalescent plasma might provide immunity by giving patients neutralizing antibodies for SARS-CoV-2. Although there is a lot that is unknown, convalescent plasma may work best for patients earlier in the disease course. Currently, convalescent plasma is being given to small numbers of hospitalized patients with severe or life threatening COVID-19 illness. Several case reports suggest treatment is helpful, but larger studies are still needed.

Potential risks of convalescent plasma

Plasma transfusions are safe and well tolerated by most patients. Side effects of convalescent plasma are similar to those of regular plasma transfusions. The most common side effect is a mild allergic reaction. Rare but serious side effects include problems with the heart or lungs, or infection. As with all blood products, convalescent plasma is thoroughly tested before use. All donated blood is screened for blood type compatibility as well as infections like hepatitis B and C, HIV and many other less common infections. SARS-CoV-2 is not spread by blood and there is no risk of transmission from recovered donors.

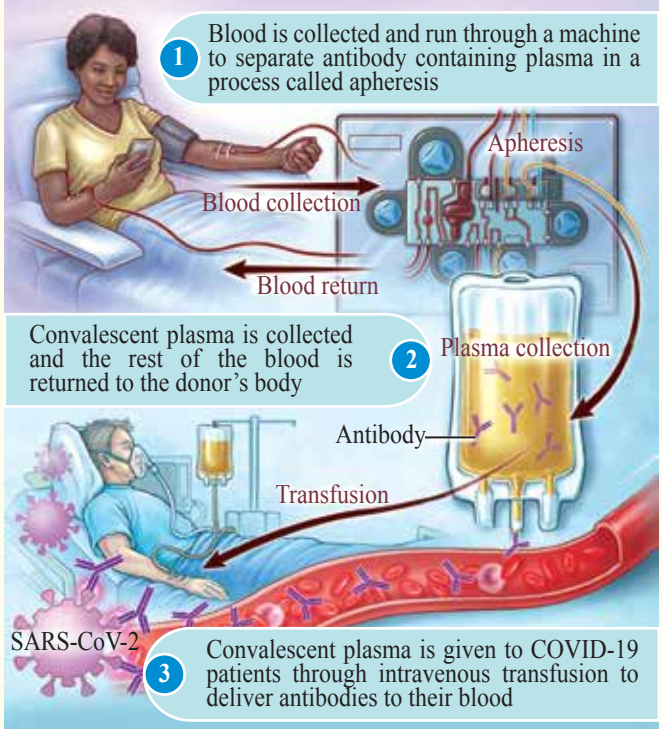
How to donate plasma

Currently, people who have recovered from COVID-19 who had a confirmed positive test result can donate plasma after they have been symptom free for at least 14 days. People who have recovered from suspected COVID-19 but never had a confirmed positive test result can also become donors if tests show they have SARS-CoV-2 antibodies. All donors must meet other blood donation criteria.

Convalescent plasma and COVID-19

The blood of recovered COVID-19 patients contains proteins called antibodies developed by the immune system to fight the SARS-CoV-2 virus. Antibodies are found in the blood plasma, which can be collected and used to treat other COVID-19 patients with a convalescent plasma transfusion that is safe and has few side effects.

How does convalescent plasma therapy work?

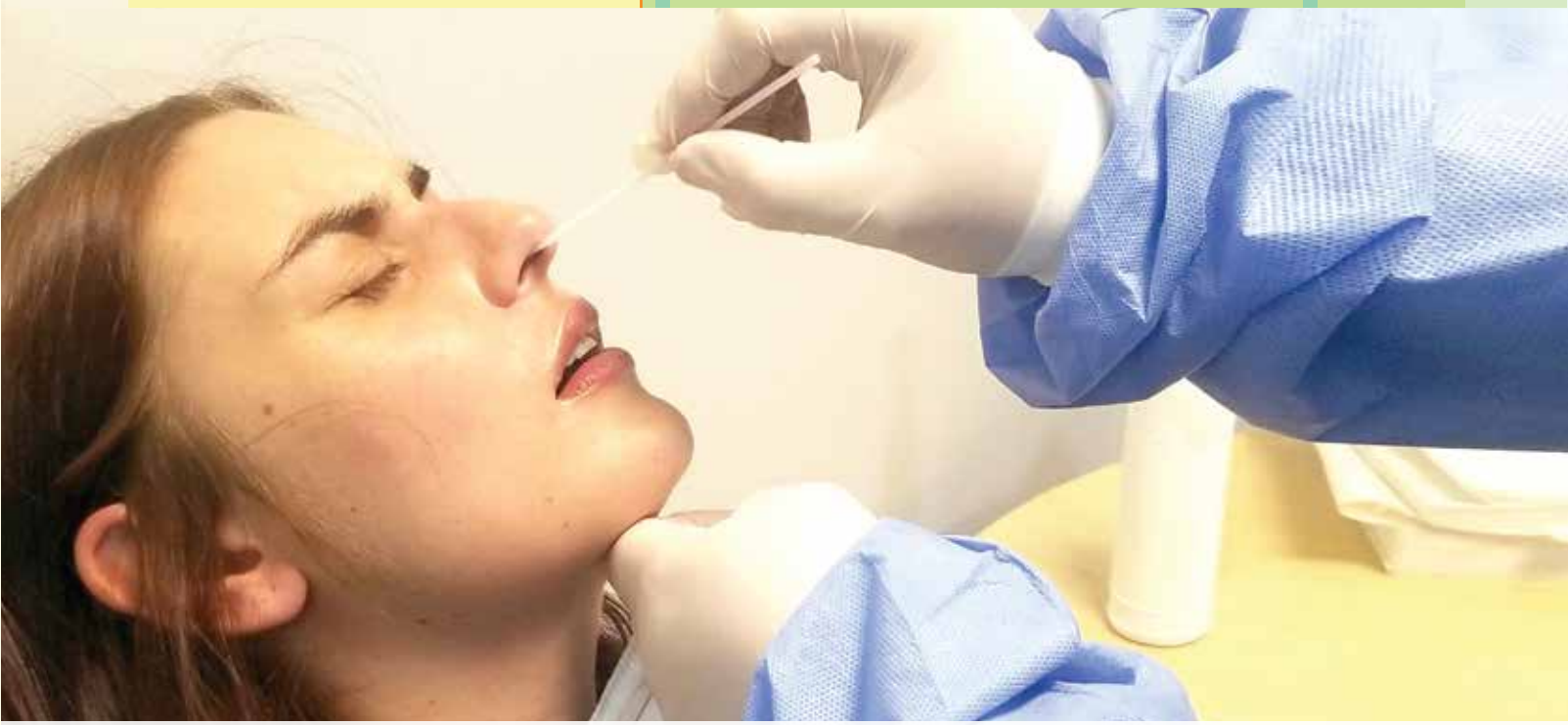


Who can become a convalescent plasma donor?

People who tested positive for COVID-19 and have been symptom free for 14 days. People never confirmed to have had COVID-19 but who have recovered from COVID-19 symptoms and also tested positive for SARS-CoV-2 antibodies.

All donors must meet all other standard blood donation criteria.

Reference: JAMA, 12 June 2020



Procedure of obtaining a nasopharyngeal swab specimen

Overview

Collection of specimens from the surface of the respiratory mucosa with nasopharyngeal swabs is a procedure used for the diagnosis of COVID-19 in adults and children. The procedure is also commonly used to evaluate patients with suspected respiratory infection caused by other viruses and some bacteria. This article describes the collection of nasopharyngeal specimens for detection of COVID-19, the illness caused by infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). There are no specific contraindications for collecting specimens with nasopharyngeal swabs. However, clinicians should be cautious if the patient has had recent nasal trauma or surgery, has a markedly deviated nasal septum or has a history of chronically blocked nasal passages or severe coagulopathy.

Preparation and equipment

Nasopharyngeal swabs are specifically manufactured to have long, flexible shafts made of plastic or metal and tips made of polyester, rayon or flocked nylon. In addition to nasopharyngeal swabs, personal protective equipment (PPE) is needed which include:

- A gown
- Non-sterile gloves
- A protective mask
- A face shield

Make sure that all sample tubes have been labeled and that the appropriate requisition forms have been filled out before starting the procedure. It is essential to follow the pertinent respiratory and contact precautions specified by the Centers for Disease Control and Prevention (CDC) that put the PPE correctly (Figure-1). If possible, should put on and take off the PPE in the presence of an observer to make sure there are no breaks in technique that may pose a risk of contamination. First, put on a protective gown, wash the hands with soap and water or use an alcohol based solution and put on a pair of non-sterile gloves. Then put on a protective mask with a rating of N95 or higher, as recommended by the CDC. Finally, put on a face shield for face and eye protection.

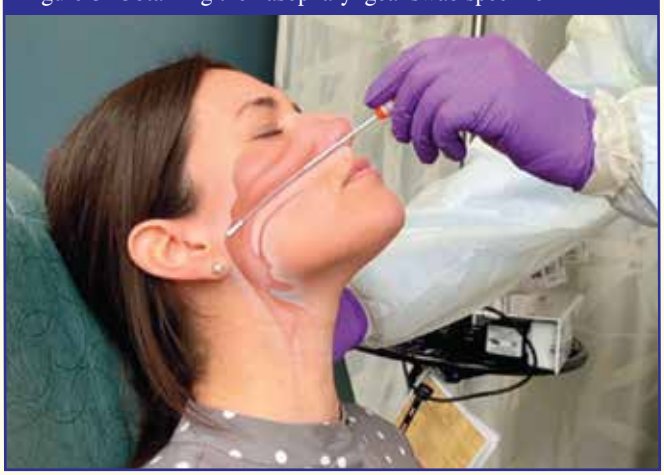
Figure-1: Personal protective equipment

Procedure

Masks are recommended for all patients suspected of having COVID-19 (Figure -2). Ask the patient to take off her mask and blow her nose into a tissue to clear excess secretions from the nasal passages. Remove the swab from the packaging. Tilt the patient's head back slightly, so that the nasal passages become more accessible. Ask the patient to close her eyes to lessen the mild discomfort of the procedure. Gently insert the swab along the nasal septum, just above the floor of the nasal passage, to the nasopharynx, until resistance is felt (Figure-3).

Figure-2: Patient wearing a mask

Figure-3: Obtaining the nasopharyngeal swab specimen



Insert the swab into the nostril, parallel to the palate. If resistance is detected to the passage of the swab, back off and try reinserting it at a different angle, closer to the floor of the nasal canal. The swab should reach a depth equal to the distance from the nostrils to the outer opening of the ear. The CDC recommends leaving the swab in place for several seconds to absorb secretions and then slowly removing the swab while rotating it. It is also recommend to rotating the swab in place several times before removing it. Ask the patient to reapply the mask.

Handling of the specimen

Open the collection tube and insert the swab into the tube. Break the swab at the groove and discard what remains of the swab. Close the labeled collection tube, wipe the tube with a surface disinfectant wipe and insert the tube into an open biohazard bag held by an assistant (Figure-4). Depending on institutional practices, instead returning the sample to its original packaging for transport. Follow the CDC directions for direct processing of the swab specimen or placement of the swab in media with or without refrigeration.

Figure-4: Handling the nasopharyngeal swab specimen

Removing personal protective equipment

Remove the PPE in accordance with the standards instruction. First, remove the gown and gloves. Clean the hands with an alcohol based solution or soap and water. Put on a new pair of gloves and then remove the face shield and either dispose of it or clean and store it in accordance with the guidelines. Remove the gloves, rewash the hands, and put on another pair of gloves; then remove the mask and follow the guidelines for disposal or reuse. Finally, remove the last pair of gloves and wash the hands.

Summary

For the collection of specimens from the surface of the respiratory mucosa with nasopharyngeal swabs for the diagnosis of COVID-19 in adults and in children, it is important to use approved PPE and the appropriate technique to minimize the possibility of spreading the virus.

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