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COVID-19

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HEALTH NEWS

EDITORIAL

The current outbreak of SARS-CoV-2 and the resulting COVID-19 disease is a pandemic threat to the health of the public and a breaking news story that changes hour by hour. Actionable information and evidence are vital to combatting and controlling the pandemic.

The mission of this issue is to provide the physician with the highest quality research and information at the intersection of biomedical science and clinical practice to guide the care of patients. Our mission today remains of vital importance to the medical community.

Daily events show us how rapidly COVID-19 can spread. We can eventually take a long view of how to manage and prevent epidemics, but today practitioners need actionable information as soon as possible. As is our usual practice in public health crisis, in this issue we have focused on alarming topic "COVID-19".

We hope you will find this issue very informative. Your feedback will assist us to better meet your needs and to improve this service. Meanwhile, stay safe as we all fight against the novel corona virus.

Thanking you and warm regards,

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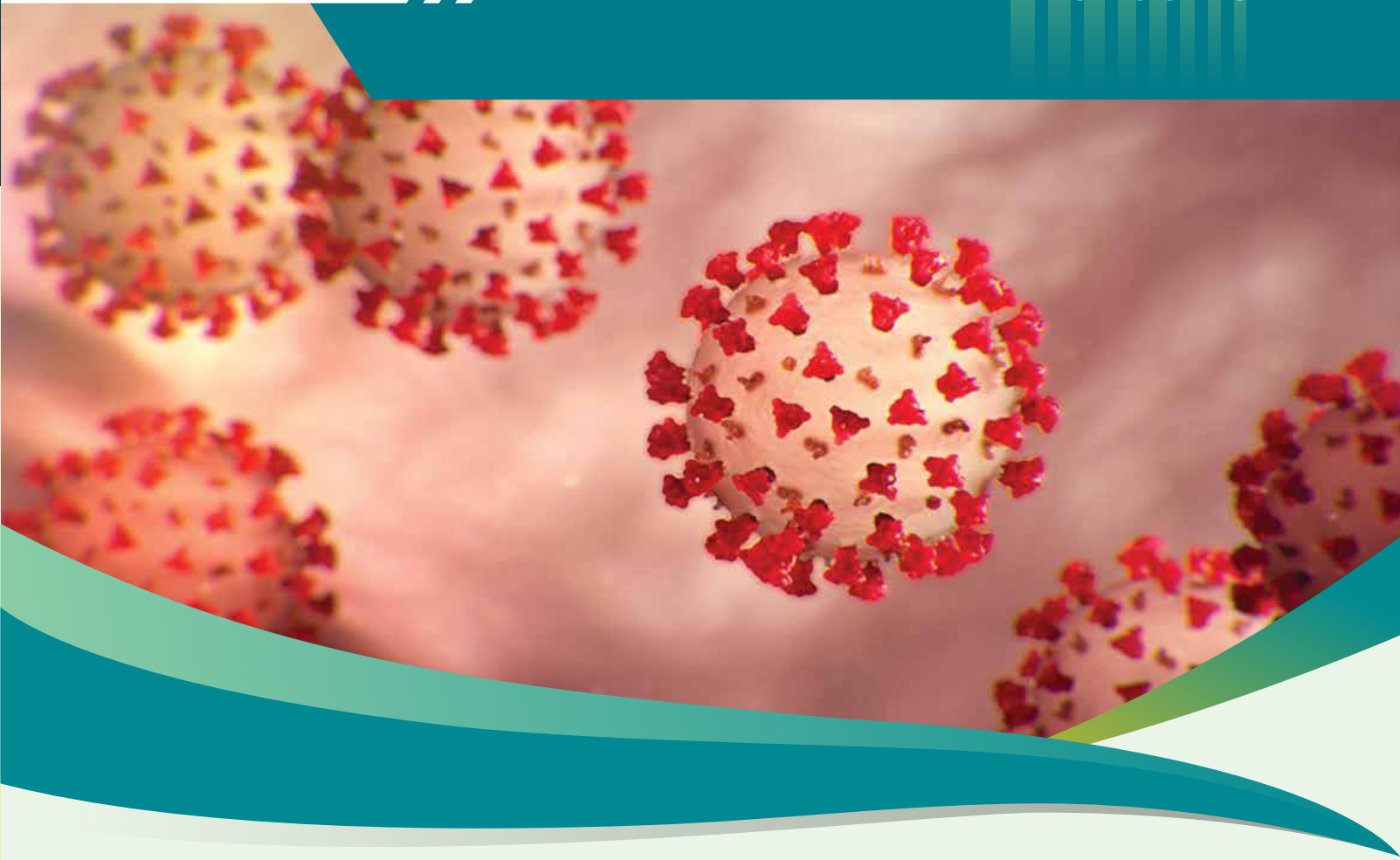
INTRODUCTION



COVID-19 is the pandemic disease declared by World Health Organization (WHO) on 11th March 2020 which is potentially severe acute respiratory infection caused by a novel evolving Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The virus was identified as the cause of an outbreak of pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019. The clinical presentation is that of a respiratory infection with a symptom severity ranging from a mild influenza like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. Globally 212 countries are reported to have the pandemic going on and the situation is evolving rapidly with global case counts and deaths increasing each day. The World Health Organization rates the global risk assessment as very high and community transmission is occurring in many countries, but it is uncertain how easily the virus spreads between people.

Bangladesh is also declared the COVID-19 infection reported from Directorate General of Health Service. Early recognition and rapid diagnosis are essential to prevent transmission and provide appropriate care in time frame. High index of clinical suspicion is needed for diagnosing COVID-19 patient and evaluation should be performed according to pneumonia severity indexes and sepsis guidelines (if sepsis is suspected) in all patients with severe illness. There is no specific treatments found to be effective for COVID-19 yet; therefore, the mainstay of management is early diagnosis and optimum supportive care to relieve symptoms and to support organ function in more severe illness. Patients should be managed in a hospital setting when possible; however, home care may be suitable for selected patients with mild illness unless there is concern about rapid deterioration or an inability to promptly return to hospital if necessary. If self-isolation at home is not possible because of lack of care giver, overcrowding at home or any other cause, patient should be brought to the hospital for institutional isolation in a designated area.

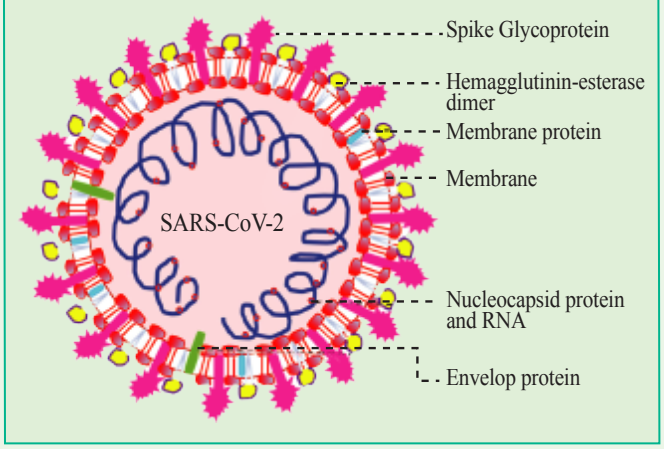
Rationing of medical resources may be required during the pandemic if healthcare infrastructures are overwhelmed. This raises many ethical questions on how to best triage patients to save the most lives. Recommendations have been suggested, but there is no international guidance on this issue as yet. A surveillance based case definition and approach to diagnose and management principles are highlighted in this guideline.

Reference: Nat. Guid. on Clin. Manag. of Coronav. Dis. 2019, 30 March 2020

Structure

The coronavirus genome is comprised of approximately 30000 nucleotides. It encodes four structural proteins, Nucleocapsid (N) protein, Membrane (M) protein, Spike (S) protein and Envelop (E) protein and several non-structural proteins (nsp) (Figure-1). The capsid is the protein shell, inside the capsid, there is nuclear capsid or N-protein which is bound to the virus single positive strand RNA that allows the virus to hijack human cells and turn them into virus factories. The N protein coats the viral RNA genome which plays a vital role in its replication and transcription. The M-protein is most abundant in the viral surface and it is believed to be the central organizer for the coronavirus assembly. The S-protein is integrated over the surface of the virus, it mediates attachment of the virus to the host cell surface receptors and fusion between the viral and host cell membranes to facilitate viral entry into the host cell. The E-protein is a small membrane protein composed approximately 76 to 109 amino-acid and minor component of the virus particle, it plays an important role in virus assembly, membrane permeability of the host cell and virus host cell interaction. Hemagglutinin-esterase dimer (HE) have been located on the surface of the viral. The HE protein may be involved in virus entry, is not required for replication, but appears to be important for infection of the natural host-cell.

Figure-1: The viral surface proteins, spike, envelope and membrane, are embedded in a lipid bilayer. The single-stranded positive-sense viral RNA is associated with the nucleocapsid protein.



Typically, human cell ingests the virus in a process called endocytosis. Once entered the cytoplasm, it has been suggested most likely that COVID-19 employs a unique three step method for membrane fusion, involving receptor-binding and induced conformational changes in Spike (S) glycoprotein followed by cathepsin L proteolysis through intracellular proteases and further

activation of membrane fusion mechanism within endosomes. Then, the endosome opens to release virus to the cytoplasm, and uncoating of viral nucleocapsid (N) is started via proteasomes which typically can hydrolyse endogenous proteins, but they are also capable of degrading exogenous proteins such as the SARS nucleocapsid protein.

Transmission

Understanding of the transmission risk is incomplete. Epidemiologic investigation in Wuhan at the beginning of the outbreak identified an initial association with a seafood market that sold live animals, where most patients had worked or visited and which was subsequently closed for disinfection. However, as the outbreak progressed, person to person spread became the main mode of transmission.

Person to person (route of person to person transmission): It is thought to occur mainly via respiratory droplets, resembling the spread of influenza. With droplet transmission, virus released in the respiratory secretions when a person with infection coughs, sneezes or talks can infect another person if it makes direct contact with the mucous membranes; infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. Droplets typically do not travel more than six feet (about two meters) and do not linger in the air. Whether SARS-CoV-2 can be transmitted through the airborne route (through particles smaller than droplets that remain in the air over time and distance) under natural conditions has been a controversial issue. In a study, in which SARS-CoV-2 grown in tissue culture remained viable in experimentally generated aerosols for at least three hours.

References: 1. J. of Bio. Struc. and Dynamics
2. Nat. Guid. on Clin. Manag. of Coronav. Dis. 2019, 30 March 2020
3. www.uptodate.com

Syndromes associated with COVID-19 are:

- Mild illness (Influenza like illness-ILI)
- Pneumonia
- Severe pneumonia
- Acute respiratory distress syndrome
- Sepsis
- Septic shock

Mild illness (ILI): Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), sore throat, nasal congestion, anorexia, malaise, or headache. Rarely, patients may also present with diarrhea, nausea and vomiting. The elderly and immunosuppressed may present with atypical symptoms. Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events, such as dyspnea, fever, GI-symptoms or fatigue, may overlap with COVID-19 symptoms.

Pneumonia: Adult with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen. Child with non-severe pneumonia who has cough or difficulty breathing plus fast breathing: fast breathing (in breaths/min): < 2 months: ≥ 60; 2-11 months: ≥ 50; 1-5 years: ≥ 40 and no signs of severe pneumonia.

Severe pneumonia: For adolescent or adult, fever or suspected respiratory infection, plus one of the following clinical features will be present:

- Respiratory rate > 30 breaths/min
- Severe respiratory distress; or
- $SpO_2 \leq 93\%$ on room air

And for Children, cough or difficulty in breathing, plus at least one of the following clinical features will be present:

- Central cyanosis or SpO2 < 90%
- Severe respiratory distress (e.g., grunting, very severe chest indrawing)
- Signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
- Other signs of pneumonia may be present: chest indrawing, fast breathing (inbreaths/min): < 2 months: ≥ 60; 2-11 months: ≥ 50; 1-5 years: ≥ 40. While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications

Acute respiratory distress syndrome (ARDS): Onset occurs within 1 week of a known clinical insult or new or worsening respiratory symptoms. Chest imaging (radiograph, CT scan or lung ultrasound): bilateral or unilateral opacities, not fully explained by volume overload, lobar or lung collapse or nodules. Patient with pleural effusion unlikely to be COVID.

Pulmonary infiltrates or respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography or USG) to exclude hydrostatic cause of infiltrates or edema if no risk factor present.

Oxygenation impairment in adults:

- Mild ARDS: 200 mmHg < $PaO_2/FiO_2 \leq 300$ mmHg [with Positive End Expiratory Pressure (PEEP) or Continuous Positive Airway Pressure (CPAP) ≥ 5 cmH_2O or non-ventilated]
- Moderate ARDS: 100 mmHg < $PaO_2/FiO_2 \leq 200$ mmHg (with PEEP ≥ 5 cmH_2O or non-ventilated)
- Severe ARDS: $PaO_2/FiO_2 \leq 100$ mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated)
- When PaO_2 is not available, $SpO_2/FiO_2 \leq 315$ mmHg suggests ARDS (including in non-ventilated patients)

Sepsis: In adults, life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection.

Signs of organ dysfunction	Laboratory evidence of:
• Altered mental status • Difficult or fast breathing • Low oxygen saturation • Reduced urine output • Fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling	• Coagulopathy • Thrombocytopenia < 50,000/cmm • Raised lactate • Hyperbilirubiemia

Children: suspected or proven infection and ≥ 2 age based systemic inflammatory response syndrome criteria, of which one must be abnormal temperature or white blood cell count.

Septic shock: In adults, persisting hypotension despite volume resuscitation, requiring vasopressors to maintain Mean Arterial Pressure (MAP) ≥ 65 mmHg and serum lactate level > 2 mmol/L. In children, any hypotension Systolic Blood Pressure (SBP) < 5th centile or > 2 Standard Deviation (SD) below normal for age or two or three of the following: altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulse; tachypnoea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Reference: Nat. Guid. on Clin. Manag. of Coronav. Dis. 2019, 30 March 2020

TESTING FOR COVID-19

Detection of virus

- Specimen: Specimen type include-
  - Upper airway specimens: oropharyngeal swabs, nasal swabs, nasopharyngeal secretions
  - Lower airway specimens: sputum, bronchoalveolar lavage fluid, airway secretions

Sputum and other lower respiratory tract specimens have a high positive rate of nucleic acids and should be collected preferentially. SARS-CoV-2 preferentially proliferates in type II alveolar cells (AT2) and peak of viral shedding appears 3 to 5 days after the onset of disease. Therefore, if the nucleic acid test is negative at the beginning, samples should continue to be collected and tested on subsequent days.

- Detection of viral nucleic acid: Nucleic acid testing is the preferred method for diagnosing COVID-19. In our country viral nucleic acid is detected by RT-PCR (Real Time - Polymerase Chain Reaction).

Real time RT-PCR

Real time RT-PCR is a nuclear-derived method for detecting the presence of specific genetic material from any pathogen, including a virus. Originally, the method used radioactive isotope markers to detect targeted genetic materials, but subsequent refining has led to the replacement of the isotopic labelling with special markers, most frequently fluorescent dyes. With this technique, scientists can see the results almost immediately while the process is still ongoing; conventional RT-PCR only provides results at the end. While real time RT-PCR is now the most widely used method for detecting coronaviruses, many countries still need support in setting up and using the technique.

A sample is collected from parts of the body where the coronavirus gathers, such as a person's nose or throat. The sample is treated with several chemical solutions that remove substances, such as proteins and fats, and extracts only the RNA present in the sample. This extracted RNA is a mix of a person's own genetic material and, if present, the coronavirus' RNA.

The real time RT-PCR technique is highly sensitive and specific and can deliver a reliable diagnosis as fast as three hours, though usually laboratories take on average between 6 to 8 hours. Compared to other available virus isolation methods, real time RT-PCR is significantly faster and has a lower potential for contamination or errors as the entire process can be done within a closed tube. It continues to be the most accurate method available for detection of the coronavirus. To detect past infections, which is important for understanding the development and spread of the virus, real time RT-PCR cannot be used as viruses are only present in the body for a specific window of time. Other methods are necessary to detect, track and study past infections, particularly those that may have developed and spread without symptoms.

Other tests which may help to diagnose COVID-19 are:

- CT Chest: a high resolution CT is highly preferable
- Chest X-ray
- USG of chest

References: 1. Nat. Guid. on Clin. Manag. of Coronav. Dis. 2019, 30 March 2020
2. Inter. Aton. Ener. Agen., 27 March 2020

MANAGEMENT GUIDELINES

For the practical purposes of patient management, the six syndromes of COVID-19 have been divided into mild, moderate, severe and critical cases (Table-1). Mild and moderate cases should be managed at home and severe and critical patients should be receive hospital care.

Table-1: Clinical criteria for case management

1.	Mild	Influenza like illness (ILI)
2.	Moderate	Pneumonia (CRB 65 score 0)
3.	Severe	Severe pneumonia, sepsis
4.	Critical	ARDS, septic shock

Mild

Patient with one or more features (fever, cough, sore throat, malaise, nasal congestion). To avoid diseases transmission and reduce the burden on hospitals, patients with Influenza Like Illness (ILI) should stay at home and consult physicians through different telephone or telemedicine services provided by various government and non-government organisations.

Advice for ILI patients

- Rest in home as self-isolation (If self-isolation at home is not possible because of lack of care giver, overcrowding at home or any other cause, patient should be brought to the hospital for institutional isolation in a designated area)
- Social distancing with family members (if possible, in a single room)
- No visitor
- Hand wash (20 seconds each time; repeated hand wash is beneficial)
- Cough etiquette (use tissue paper or elbow followed by hand wash)
  - Tab Paracetamol: 500 mg (1+1+1)
  - Tab antihistamine: Fexofenadin (0+0+1)
  - Steam inhalation or gurgle of lukewarm water
- Follow up
  - Self-home isolation for 14 days after clinical recovery
  - Ask about: dyspnoea, chest pain, persistent or worsen dry or productive cough, haemoptysis
- Patient should immediately seek hospital care if there is
  - Respiratory distress
  - Worsening cough and fever
  - Altered mental status
  - Extreme lethargy

Moderate

- Pneumonia
- No signs of severe pneumonia (CRB 65 score 0)
- No need for supplemental oxygen

Management of moderate group

The patient will be managed as like as mild illness (ILI). However, the patient should receive broad spectrum oral antibiotics as for uncomplicated Community Acquired Pneumonia (CAP).

Hospital care principles

- Severe and critical cases of suspected (or probable) or confirmed COVID-19 require hospital care
- Management of such patients warrant immediate implementation of appropriate infection prevention measures
- Patients with severe disease often need oxygenation support
- Aerosol generating procedures such as endotracheal intubation, bronchoscopy, nebulization, cardiopulmonary resuscitation, open suctioning respiratory tract, tracheostomy demand specific protection of physicians with appropriate personal protective equipment (PPE)
- The safety of high flow oxygen and non-invasive positive pressure ventilation in these measures is uncertain, and they should be considered aerosol generating procedures that warrant specific isolation precautions. Oxygen hood is suitable if patient needs oxygen in general ward
- Patient with sepsis with or without shock may require treatment in high dependency unit (HDU) or ICU depending on disease severity and clinical judgement of treating physicians
- If patients develop acute respiratory distress syndrome, intubation with mechanical ventilation will be needed
- Extracorporeal Membrane Oxygenation (ECMO) may be indicated in patients with refractory hypoxia in ICU setting

Severe

- Severe pneumonia
- Sepsis

These patients should be managed preferably in a High Dependency Unit (HDU) based on availability.

Management of severe group

- Give immediate supplemental oxygen for the following patients
  - If $SpO_2 < 93\%$
  - Respiratory rate ≥ 30 breaths/minute
  - Shock
- Initiate oxygen at 5 litres/min and titrate flow to reach target $SpO_2 \geq 93\ \%$
- Use face mask with reservoir bag (at 10-15 L/min) if patient in critical condition
- Once patient is stable, the target is $\geq 90\%$ SpO_2 in non-pregnant adults and $\geq$ 92-95% in pregnant patients
- Patients with severe pneumonia or sepsis should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation
- Give empiric antimicrobials to treat all likely pathogens causing severe pneumonia and sepsis as soon as possible, within 1 hour of initial assessment for patients with sepsis

  Closely monitor patients with COVID-19 for signs of clinical deterioration, such as rapidly progressive respiratory failure and septic shock and respond immediately with supportive care interventions
- Management of comorbid conditions

Critical

- ARDS
- Septic shock

Management of critical group

Critically ill patients should be managed in intensive care unit (ICU). They should be managed based on following recommendations: Recommendations of care of patient of COVID-19 in ICU. This recommendation is standard recommendation for survival sepsis campaign for COVID-19 in ICU setting. There is variable grade of recommendation from strong to weak and adjustment is advised through risk benefit in working team of ICU of COVID 19 hospitals in Bangladesh.

Hemodynamic

- In adults with COVID-19 and shock, use dynamic parameters skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness
- For the acute resuscitation of adults with COVID-19 and shock, use a conservative over a liberal fluid strategy
- For the acute resuscitation of adults with COVID-19 and shock, use crystalloids over colloids
- For the acute resuscitation of adults with COVID-19 and shock, avoid using hydroxyethyl starches, gelatins, dextrans and routine use of albumin for initial resuscitation
- For adults with COVID-19 and shock, use norepinephrine as the first-line vasoactive agent, over other agents
- If norepinephrine is not available, use either vasopressin or epinephrine as the first-line vasoactive agent, over other vasoactive agents, for adults with COVID-19 and shock
- For adults with COVID-19 and shock, avoid using dopamine if norepinephrine is available
- For adults with COVID-19 and shock, add vasopressin as a second line agent, over titrating norepinephrine dose, if target

- Mean Arterial Pressure (MAP) cannot be achieved by norepinephrine alone
- For adults with COVID-19 and shock, titrate vasoactive agents to target a MAP of 60-65 mmHg, rather than higher MAP targets
- For adults with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, add dobutamine, over increasing norepinephrine dose
- For adults with COVID-19 and refractory shock, use low dose corticosteroid therapy, over no corticosteroid. A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses

Ventilation

- In adults with COVID-19, start supplemental oxygen if the peripheral oxygen saturation (SpO_2) is < 92%, and recommend starting supplemental oxygen if SpO_2 is < 90%
- In adults with COVID-19 and acute hypoxemic respiratory failure on oxygen, SpO_2 be maintained no higher than 96%
- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, use High Flow Nasal Cannula (HFNC) over conventional oxygen therapy
- In adults with COVID-19 and acute hypoxemic respiratory failure, use HFNC over Nasal intermittent positive pressure ventilation (NIPPV)
- In adults with COVID-19 and acute hypoxemic respiratory failure, if HFNC is not available and there is no urgent indication for endotracheal intubation, a trial of NIPPV with close monitoring and short interval assessment for worsening of respiratory failure
- In mechanically ventilated adults with COVID-19 and ARDS, use low tidal volume (Vt) ventilation (Vt 4-8 mL/kg of predicted body weight), over higher tidal volumes (Vt >8 mL/kg)
- For mechanically ventilated adults with COVID-19 and ARDS, target plateau pressures (Pplat) of < 30 cm H_2O
- For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, a higher Positive End-Expiratory Pressure (PEEP) strategy is indicated, over a lower PEEP strategy
- For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, prone ventilation for 12 to 16 hours is suggested
- For mechanically ventilated adults with COVID-19 and moderate to severe ARDS use intermittent boluses of neuromuscular blocking agents (NMBA) to facilitate protective lung ventilation
- In the event of persistent ventilator desynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, use a continuous NMBA infusion for up to 48 hours
- In mechanically ventilated adults with COVID-19 and ARDS, avoid the routine use of inhaled nitric oxide
- In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, start a trial of inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off
- For mechanically ventilated adults with COVID-19 and hypoxemia despite optimizing ventilation, use recruitment manoeuvres
- In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning use venovenous ECMO if available, or referring the patient to an ECMO center

Therapy

- In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), avoid the routine use of systemic corticosteroids
- In mechanically ventilated adults with COVID-19 and ARDS, use systemic corticosteroids
- In mechanically ventilated patients with COVID-19 and respiratory failure, use empiric antimicrobials or antibacterial agents
- For critically ill adults with COVID-19 who develop fever, use acetaminophen or paracetamol for temperature control
- In critically ill adults with COVID-19, avoid the routine use of standard intravenous immunoglobulins, avoid the routine use of convalescent plasma and routine use of lopinavir or ritonavir

Pharmacotherapy

Pharmacological drug: This is indicated only for pulmonary syndrome without hypoxia.

Chloroquine: 500 mg BID for 7 days

Use of chloroquine is included in treatment guidelines in China's National Health Commission at Wuhan and was observed to be associated with reduced progression of disease and decreased duration of symptoms. However, there is no published data

Hydroxychloroquine: 400 mg BID (day 1) and then 200 mg TID (day 2 to day 10)

Hydroxychloroquine (200 mg tds for 10 days) was associated with a higher rate of undetectable viral RNA on nasopharyngeal specimens at day 6 compared with no specific treatment (70 vs 12.5%). In this study, the use of azithromycin in combination with hydroxychloroquine appeared to have additional benefit, but there are methodological concerns about the control groups for the study,

and the clinical basis for using azithromycin is not clear. Very recent analysis from big cohort of China patient showed no benefit of Hydroxychloroquine in COVID 19 patient (27th March report).

Azithromycin

One of the proposed drugs is the antibiotic azithromycin, which is widely used to treat chest, sinus, throat and skin infections, as well as sexually transmitted diseases. Azithromycin is known to stop the production of cytokines, a torrent of inflammatory mediators that trigger life threatening lung inflammation in corona virus patients. Azithromycin has also been shown to block the production of other viruses, such as the Zika and Ebola virus. In combination with hydroxychloroquine, azithromycin was recently shown to inhibit the replication of the COVID-19 corona virus, in a clinical trial in France. A dosage of 500 mg per day reversed small airway lesions, improved small airway stenosis, and decreased airway resistance. However, the effects of azithromycin alone were not assessed.

Remdesivir

Adult: Remdesivir is currently under investigation for use in the treatment of coronavirus disease 2019 (COVID-19). At this time, safety and efficacy have not been established. However, preliminary dosing information based on clinical trials in process. Whenever possible, treatment should be given as part of a clinical trial. Limited data available; dosing used in clinical trials (IV): 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days.

Pediatric: Remdesivir is currently under investigation for use in the treatment of COVID-19. Pediatric patients with severe disease are being considered for compassionate use access. At this time, safety and efficacy have not been established in adult or pediatric patients; as data and experience in pediatric patients continue to evolve, dosing will be updated as appropriate. Whenever possible, treatment should be given as part of a clinical trial.

Children and adolescents ≤ 17 years (IV): Dosing based on clinical experience and trials in pediatric patients treated for Ebola virus disease (WHO 2018); optimal dose has not been established for COVID-19. Optimal duration for treatment of COVID-19 not established; total duration of 5 to 10 days is being evaluated in clinical trials in adults with COVID-19. In pediatric Ebola virus experience, doses were infused over 30 minutes (WHO 2018).

- < 40 kg (IV): 5 mg/kg/dose as a single dose on day 1, followed by 2.5 mg/kg/dose once daily
- ≥ 40 kg (IV): 200 mg as a single dose on day 1, followed by 100 mg once daily

Adolescents ≥ 18 years (IV): 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days; dosing based on ongoing clinical trials for COVID-19 in adults.

Geriatric: Geriatric same as adult dose.

Favipiravir

The usual dosage of Favipiravir for adults is 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days. The total administration period should be 5 days.

Rivaroxaban

COVID-19 infection is associated with high morbidity and mortality in about 5%-10% patients. This is largely due to respiratory with the implication of microvascular pulmonary thrombosis and pulmonary embolism. It needs to address the suspected or diagnosed pulmonary thrombosis or embolism with anticoagulation.

Conditions of COVID-19 patients where empiric therapeutic anticoagulation, rivaroxaban may be considered-

- Intubated patients who are highly suspected of thrombosis
- Physical findings consistent with thrombosis, such as superficial thrombophlebitis, peripheral ischemia or cyanosis, thrombosis of dialysis filters, tubing or catheters, or retiform purpura
- Patients with respiratory failure, particular when D-dimer and/or fibrinogen levels are very high, in whom PE or microvascular thrombosis is highly suspected and other causes are not identified

Dosage

- Venous Thromboembolism (VTE) prophylaxis: Rivaroxaban 10 mg once daily
- Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) treatment: Rivaroxaban 15 mg BD for 21 days followed by Rivaroxaban 20 mg OD

Drug interaction with Rivaroxaban: Sarilumab, Atazanavir and lopinavir/ritonavir. All patients with COVID-19 are started on empiric therapeutic anticoagulation for a minimum course 3 months.

Corticosteroids

Initial routine methylprednisolone at a dose of 0.75-1.5 mg/kg intravenously once a day (nearly 40 mg once or twice a day). The WHO and CDC recommend corticosteroids are not to be used in patients with COVID-19 pneumonia unless there are other indications (e.g., exacerbation of COPD). Corticosteroids have been associated with an increased risk of mortality in patients with influenza and delayed viral clearance in patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection. Though widely used in management of Severe Acute Respiratory Syndrome (SARS), there was no good evidence for benefit, and there was persuasive evidence of adverse harm in the short and long term. Corticosteroid can be used in septic shock patient according to survival sepsis guideline hydrocortisone 200/day in divided doses.

Lopinavir and ritonavir combination

Investigators in China report the results of an open-label, randomised clinical trial of lopinavir and ritonavir combination for the treatment of COVID-19 in 199 infected adult patients. There was no difference in the primary end point, time to clinical improvement.

Important information of using pharmacological agents

- May consider for flu shot, zinc, melatonin, vit C, oseltamivir (75 mg twice daily for 5 days)
- Empirical antibiotics when procalcitonin is high, neutrophilic leukocytosis
- Use paracetamol as fever lowering agent
- WHO has started solidarity trial giving importance on 4 drugs (chlorquine, remdesavir, interleukin and lopinavir and ritonavir combination)
- As there is no high quality data regarding pharmacological agent, use of these agents (as repurpose drug) should be used judiciously by physician while working in COVID-19 hospital

Caring for infants and mothers with COVID-19: IPC and breastfeeding

- Infants born to mothers with suspected, probable or confirmed COVID-19 infection, should be fed according to standard infant feeding guidelines, while applying necessary precautions for IPC
- As with all confirmed or suspected COVID-19 cases, symptomatic mothers who are breastfeeding or practicing skin-to-skin contact or kangaroo mother care should practice respiratory hygiene, including during feeding (for example, use of a medical mask when near a child if with respiratory symptoms), perform hand hygiene before and after contact with the child, and routinely clean and disinfect surfaces which the symptomatic mother has been in contact with
- Breastfeeding counselling, basic psychosocial support and practical feeding support should be provided to all pregnant women and mothers with infants and young children, whether they or their infants and young children have suspected or confirmed COVID-19
- In situations when severe illness in a mother due to COVID-19 or other complications prevent her from caring for her infant or prevent her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk, and safely provide breastmilk to the infant, while applying appropriate IPC measures
- Mothers and infants should be enabled to remain together and practice skin to skin contact, kangaroo mother care and to remain together and to practice rooming-in throughout the day and night, especially immediately after birth during establishment of breastfeeding, whether they or their infants have suspected, probable or confirmed COVID-19 virus infection
- Parents and caregivers who may need to be separated from their children, and children who may need to be separated from their primary caregivers, should have access to appropriately trained health or non-health workers for mental health and psychosocial support

Caring for older persons with COVID-19

- For older people with probable or suspected COVID-19, provide person-centred assessment, including not only conventional history taking, but a thorough understanding of the person's life, values, priorities and preferences for health management
- Ensure multidisciplinary collaboration among physicians, nurses, pharmacists, other health care professionals in the decision making process to address multimorbidity and functional decline
- Early detection of inappropriate medication prescriptions is recommended to prevent adverse drug events and drug interactions for those being treated with COVID-19
- Older people are at greater risk of polypharmacy, due to newly prescribed medications, inadequate medication reconciliation and a lack of care coordination which increases the risk of negative health consequences

Discharge criteria

- Body temperature remains normal for at least 3 days (ear temperature is lower than 37.5 °C)
- Respiratory symptoms are significantly improved
- The nucleic acid is tested negative for respiratory tract pathogen twice consecutively (sampling interval more than 24 hours); the nucleic acid test of stool samples can be performed at the same time if possible
- Lung imaging shows obvious improvement in lesions
- There is no comorbidities or complications which require hospitalization
- SpO_2 > 93% without assisted oxygen inhalation

Medication after discharge

Generally, antiviral drugs are not necessary after discharge. Treatments for symptoms can be applied if patients have mild cough, poor appetite and thick tongue coating. Antiviral drugs can be used after discharge for patients with multiple lung lesions in the first 3 days after their nucleic acid are tested negative. Patients must continue two weeks of isolation after discharge. A specialized physician should be arranged for each discharged patient's follow-ups. The first follow-up call should be made within 48 hours after discharge.

References: 1. Nat. Guid. on Clin. Manag. of Coronav. Dis. 2019, 30 March 2020
2. www.uptodate.com/remdesivir
3. American Society of Hematology

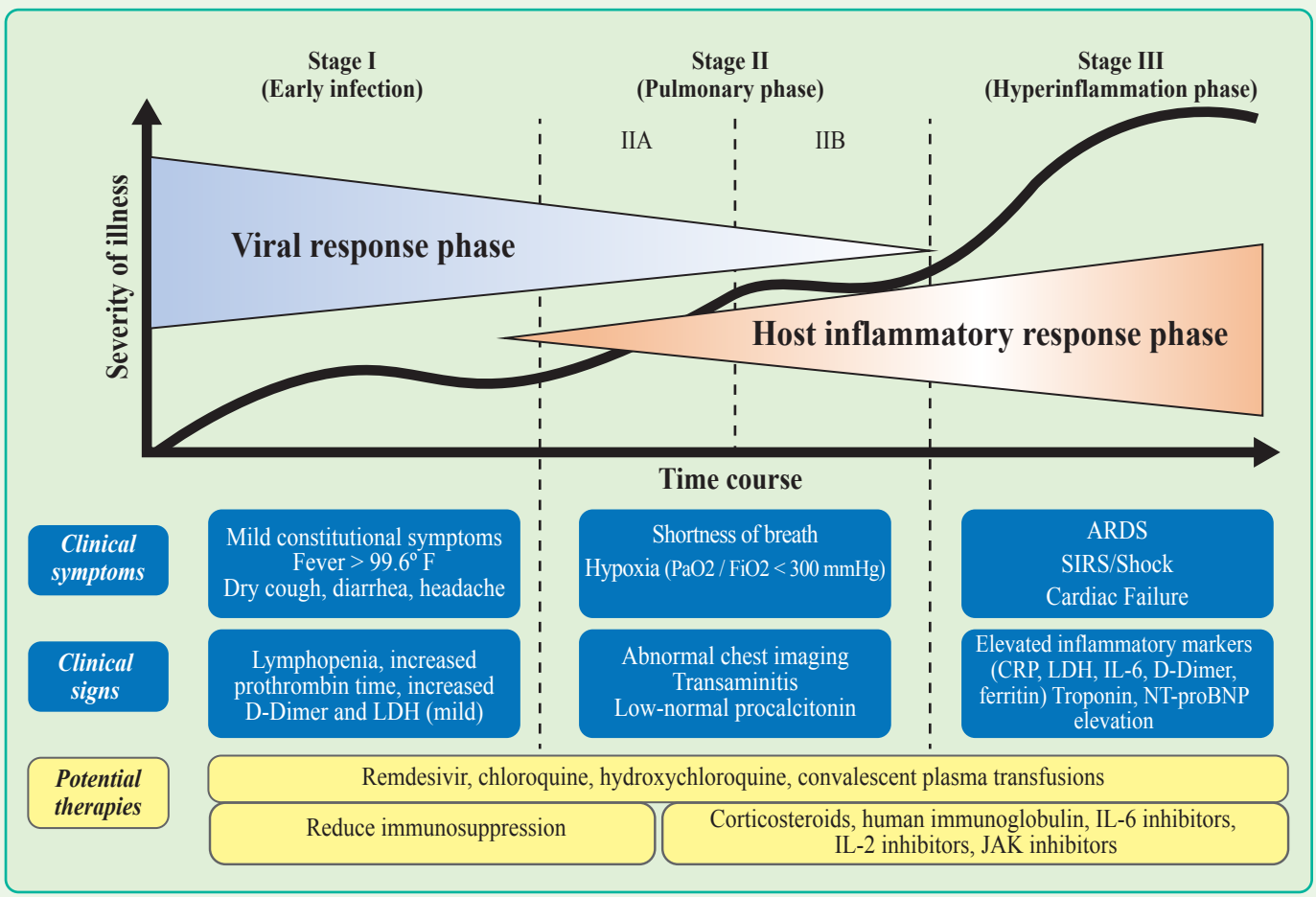
CLASSIFICATION OF COVID-19 DISEASE STATES AND POTENTIAL THERAPEUTIC TARGETS

The onslaught of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19) has gripped the world in a pandemic and challenged the culture, economy and healthcare infrastructure of its population. It has become increasingly important that health systems and their clinicians adopt a universal consolidated framework to recognize the staged progression of COVID-19 illness in order to deploy and investigate targeted therapy likely to save lives.

Stage I (mild): Early infection: The initial stage occurs at the time of inoculation and early establishment of disease. For most people, this involves an incubation period associated with mild and often non-specific symptoms such as malaise, fever and a dry cough. During this period, SARS-CoV-2 multiplies and establishes residence in the host, primarily focusing on the respiratory system.

Stage II (moderate): Pulmonary involvement (IIa) without and (IIb) with hypoxia: In the second stage of established pulmonary disease, viral multiplication and localized inflammation in the lung is the norm. During this stage, patients develop a viral pneumonia, with cough, fever and possibly hypoxia (defined as a PaO_2/FiO_2 of < 300 mmHg). Imaging with chest roentgenogram or computerized tomography reveals bilateral infiltrates or ground glass opacities. Blood tests reveal increasing lymphopenia, along with transaminitis. Markers of systemic inflammation may be elevated, but not remarkably so. It is at this stage that most patients with COVID-19 would need to be hospitalized for close observation and management.

Stage III (severe): Systemic hyperinflammation: A minority of COVID-19 patients will transition into the third and most severe stage of illness, which manifests as an extra-pulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation appear to be elevated. COVID-19 infection results in a decrease in helper, suppressor and regulatory T cell counts.



Reference: J. Hea. Lun. Trans., 20 March 2020

Considering BCG vaccination to reduce the impact of COVID-19

The BCG vaccine has beneficial nonspecific (off-target) effects on the immune system that protect against a wide range of other infections and are used routinely to treat bladder cancer, in addition to its specific effect against tuberculosis. This has led to the suggestion that vaccination with BCG might have a role in protecting health care workers and other vulnerable individuals against severe coronavirus disease 2019 (COVID-19). Randomized controlled trials have provided evidence that the BCG vaccine's immunomodulatory properties can protect against respiratory infections. In Guinea-Bissau, a high mortality setting, BCG-Danish reduced all cause neonatal mortality by 38% (95% CI 17–54), mainly because there were fewer deaths from pneumonia and sepsis. In South Africa, BCG-Danish reduced respiratory tract infections by 73% (95% CI 39–88) in adolescents.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single stranded positive sense RNA virus and the BCG vaccine has been shown to reduce the severity of infections by other viruses with that structure in controlled trials. For example, the BCG vaccine reduced yellow fever vaccine viraemia by 71% (95% CI 6–91) in volunteers in the Netherlands and it markedly reduced the severity of mengovirus (encephalomyocarditis virus) infection in two studies in mice.

Many of the mechanisms underlying the beneficial off-target effects of the BCG vaccine are now understood. The BCG vaccine and some other live vaccines induce metabolic and epigenetic changes that enhance the innate immune response to subsequent infections, a process termed trained immunity. The BCG vaccine might therefore reduce viraemia after SARS-COV-2 exposure, with consequent less severe COVID-19 and more rapid recovery. Randomized controlled trials are underway in the Netherlands and Australia to assess whether BCG-Danish reduces the incidence and severity of COVID-19 in health care workers and the effect this has on time away from work. It is possible that BCG-Tokyo would be preferable to BCG-Danish.

Until these trials are complete, there are four main reasons why it is very important to adhere to WHO's recommendation that the BCG vaccine is used for COVID-19 only in randomized controlled trials.

First, the BCG vaccine is already in short supply, and indiscriminate use could jeopardize the supply needed to protect

children against tuberculosis in high risk areas. Second, whether BCG will be effective remains unknown: findings from the ecological studies suggesting less COVID-19 in countries with routine BCG immunization are weak evidence because they are based on population rather than individual data and are prone to confounding.

Also, it is unlikely that a BCG vaccine given decades ago in childhood will ameliorate COVID-19 now. One reason for this is that the beneficial off-target effects of the BCG vaccine might be altered by subsequent administration of a different vaccine.

Third, if the BCG vaccine is not effective against COVID-19, BCG vaccination could engender a false sense of security. Fourth, careful safety monitoring in randomized trials is needed to guard against the remote possibility that up-regulation of immunity by BCG will exacerbate COVID-19 in a minority of patients with severe disease. If the BCG vaccine or another inducer of trained immunity provides non-specific protection to bridge the gap before a disease specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics.

Reference: The Lancet, 30 April 2020

Coronavirus: Plasma treatment to be trialled

The UK is gearing up to use the blood of coronavirus survivors to treat hospital patient's ill with the disease. The US has already started a major project to study this, involving more than 1,500 hospitals. National Health Service Blood and Transplant (NHSBT) is asking some people who recovered from Covid-19 to donate blood so they can potentially assess the therapy in trials. The hope is that the antibodies they have built up will help to clear the virus in others. When a person has Covid-19, their immune system responds by creating antibodies, which attack the virus. Over time these build up and can be found in the plasma. NHSBT is now approaching patients who have recovered from Covid-19 to see if plasma from them can be given to people who are currently ill with the virus. A statement from the organization said: "We envisage that this will be initially used in trials as a possible treatment for Covid-19. If fully approved, the trials will investigate whether convalescent plasma transfusions could improve a Covid-19 patient's speed of recovery and chances of survival."

In Bangladesh, a group of doctors have started working on the method under the Directorate General of Health Services. A technical committee was making a protocol for the trials expected to start in the first week of May, DGHS Director Aminul Hasan told bdnews24.com on Wednesday. On Apr 19, the DGHS formed a committee headed by Prof Khan to study the therapy and make the protocol within five days. The other members are Prof Ahmedul Kabir of DMC's medicine department, Prof Mazharul Haque Tapan, head of transfusion medicine department, and Saifullah Munshi, head of virology department at the Bangabandhu Sheikh Mujib Medical University. Professor MA Khan of the Dhaka Medical College's haematology department said the disease control wing of the DGHS discussed the issue on Apr 12 after he had submitted a report on whether to use the therapy in Bangladesh.

For the first time ever, plasma therapy has been used for treating a Covid-19 patient admitted at the Ever Care Hospital in Dhaka. The patient who received the convalescent plasma therapy at the hospital, has responded well to the treatment, Dr Abu Jafar Mohammad Saleh, senior consultant and coordinator at Hematology and Stem Cell Transplant Department in Ever Care Hospital Dhaka, said on 06 May 2020.

References: 1. www.bbc.com/health
2. www.bdnews24.com

SARS-CoV-2 and influenza virus co-infection

Since December 2019, coronavirus disease 2019 (COVID-19) has been an international public health emergency. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) mimics the influenza virus regarding clinical presentation, transmission mechanism and seasonal coincidence. Thus, co-infection by both viruses is feasible. Here, four cases of SARS-CoV-2 and influenza co-infection are presented. Patients 1-3 were men aged 53, 78 and 56 years, respectively and patient 4 was a woman aged 81 years. All four patients had a medical history of hypertension. Patients 1 and 4 had a history of end stage kidney disease on haemodialysis and patients 2 and 4 had type 2 diabetes. All four patients attended the emergency department because of non-productive cough, fever, and dyspnea for 3 days. Physical examination revealed tachypnea and bronchospasm with low oxygen saturation for all patients except for patient 3 whose values were normal. Chest radiography at admission was pathological in two patients: patient 2 had bilateral infiltrates and patient 4 had a right bilobar pneumonia.

Rapid nucleic acid amplification test for influenza A was positive in patients 1 and 2. Patient 3 tested positive for both influenza A and B, and patient 4 tested positive for influenza B. Following the local diagnosis protocol for SARS-CoV-2, simultaneous RT-PCR was done and was positive for all four patients. Treatment with lopinavir and ritonavir combination 400/100 mg twice a day, oral hydroxychloroquine 200 mg twice a day (in haemodialysis patients, 100 mg twice a day) and oral oseltamivir 150 mg twice a day (in haemodialysis patients, 30 mg every 48 hour). Subcutaneous interferon β-1b 8MU was added every 48 hour in patients 2 and 4. Patient 1 showed clinical improvement and 72 hour after admission he remained stable with minimal oxygen requirements. Patients 1 and 4 remained under mechanical ventilation 72 hour after admission. The clinical and analytical courses in these patients did not differ from those previously reported for COVID-19. However, more studies are needed to assess the effect of the SARS-CoV-2 and influenza co-infection in clinical outcomes.

Reference: The Lancet, 05 May 2020

Coronavirus: first patients injected in UK vaccine trial

The first human trial in Europe of a coronavirus vaccine has begun in Oxford. Two volunteers were injected, the first of more than 800 people recruited for the study. Half will receive the Covid-19 vaccine, and half a control vaccine which protects against meningitis but not coronavirus. The design of the trial means volunteers will not know which vaccine they are getting, though doctors will. Elisa Granato, one of the two who received the jab, told the BBC: "I'm a scientist, so I wanted to try to support the scientific process wherever I can." The vaccine was developed in under three months by a team at Oxford University. Sarah Gilbert, professor of vaccinology at the Jenner Institute, led the pre-clinical research. "Personally I have a high degree of confidence in this vaccine," she said. "Of course, we have to test it and get data from humans. We have to demonstrate it actually works and stops people getting infected with coronavirus before using the vaccine in the wider population." Prof Gilbert previously said she was "80% confident" the vaccine would work, but now prefers not to put a figure on it, saying simply she is "very optimistic" about its chances. The only way the team will know if the Covid-19 vaccine works is by comparing the number of people who get infected with coronavirus in the months ahead from the two arms of the trial. That could be a problem if cases fall rapidly in the UK, because there may not be enough data.

More than 70 COVID-19 vaccines are currently in development worldwide, according to the World Health Organization. The University of Oxford vaccine is one of four currently in human trials, according to the statement. Even with an accelerated timeline, it could take up to 12 to 18 months to develop, test and approve a vaccine for public use, Live Science previously reported.

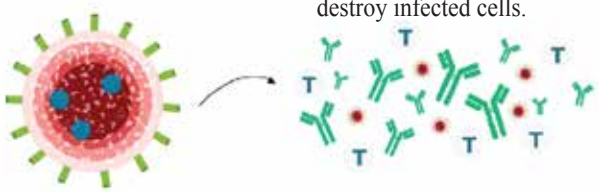
How coronavirus vaccine will work

Scientists have taken genes for the spike protein in the surface of coronavirus and put them into a harmless virus to make a vaccine

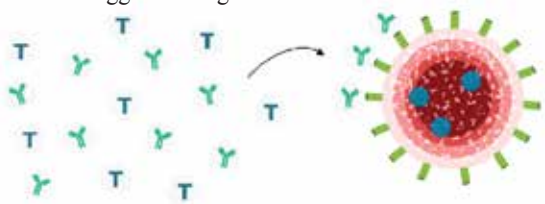
This is injected into the patient

The vaccine enters cells, which then start to produce the coronavirus spike protein

This prompts the immune system to produce antibodies and activate killer T-cells to destroy infected cells.



If the patient encounters coronavirus again, the antibodies and T cells are triggered to fight the virus



Microbiologist Elisa Granato and cancer researcher Edward O'Neil volunteered themselves to be the first two participants for the coronavirus vaccine trial.

References: 1. www.bbc.com
2. www.livescience.com

Second trimester miscarriage in a pregnant woman with SARS-CoV-2 infection

No data exist regarding the effect on fetuses of maternal severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) infection during the first or second trimester of pregnancy, and data are limited regarding infections that occur during the third trimester. However, reports of newborns with fetal distress or requiring admission to the intensive care unit and a stillbirth after maternal coronavirus disease 2019 (COVID-19) in the third trimester suggest the possibility of COVID-19 induced placental pathology. A case of miscarriage during the second trimester in a pregnant woman with COVID-19 has been presented.

A pregnant woman in her second trimester who had a miscarriage was evaluated at Lausanne University Hospital on March 20, 2020. Institutional review board approval and written informed consent were obtained. Information was obtained from medical records. Reverse transcriptase–polymerase chain reaction (RT-PCR) to detect SARS-CoV-2 and cultures to detect bacterial pathogens and PCR for *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis,* and *Ureaplasma urealyticum* were performed on samples from the mother, fetus, and placenta. Placental histological examination and fetal autopsy were performed by 2 experienced perinatal pathologists.

A 28 year old obese, primigravida woman presented at 19 weeks' gestation with fever (102.5 °F [39.2 °C]), myalgia, fatigue, mild pain with swallowing, diarrhea, and dry cough for 2 days. A nasopharyngeal swab was positive for SARS-CoV-2. She was given oral acetaminophen and discharged home. Two days later, she presented with severe uterine contractions, fever, and no improvement of her symptoms. Physical examination did not reveal any signs of pneumonia. Vaginal examination demonstrated bulging membranes through a 5 cm dilated cervix. Active fetal movements; fetal tachycardia (180/min); and normal fetal morphology, growth, and amniotic fluid were detected on ultrasound. Prophylactic amoxicillin–clavulanic acid and regional anesthesia were started. The patient wore a mask throughout her labor, as did 2 health care professionals who both tested negative for SARS-CoV-2. Amniotic fluid and vaginal swabs sampled during labor tested negative for SARS-CoV-2 and bacterial infection.

A stillborn infant was delivered vaginally after 10 hours of labor. Swabs from the axillae, mouth, meconium, and fetal blood obtained within minutes of birth tested negative for SARS-CoV-2 and bacterial infection. Fetal autopsy showed no malformations, and fetal lung, liver, and thymus biopsies were negative for SARS-CoV-2. Within minutes of placental expulsion, the fetal surface of the placenta was disinfected and incised with a sterile scalpel, and 2 swabs and biopsies (close to

the umbilical cord and peripheral margin) were obtained. All were negative for bacterial infection but were positive for SARS-CoV-2. At 24 hours, the placenta remained positive for SARS-CoV-2. At 48 hours, maternal blood, urine, and vaginal swab were all negative for SARS-CoV-2, whereas a nasopharyngeal swab remained positive.

This case of miscarriage during the second trimester of pregnancy in a woman with COVID-19 appears related to placental infection with SARS-CoV-2, supported by virological findings in the placenta. Contamination at the time of delivery, sampling, or laboratory evaluation is unlikely, as all other swabs were negative for SARS-CoV-2. No other cause of fetal demise was identified. There was no evidence of vertical transmission, but absence of the virus is not surprising given the stage of fetal development and short time of maternal infection. Whether SARS-CoV-2 crosses the placental barrier warrants further investigation. Limitations include the single case and that other causes of miscarriage, such as spontaneous preterm birth, cervical insufficiency, or undetected systemic or local bacterial infection, cannot be ruled out.

Infection of the maternal side of the placenta inducing acute or chronic placental insufficiency resulting in subsequent miscarriage or fetal growth restriction was observed in 40% of maternal infections with Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus. Additional study of pregnant women with COVID-19 is warranted to determine if SARS-CoV-2 can cause similar adverse outcomes.

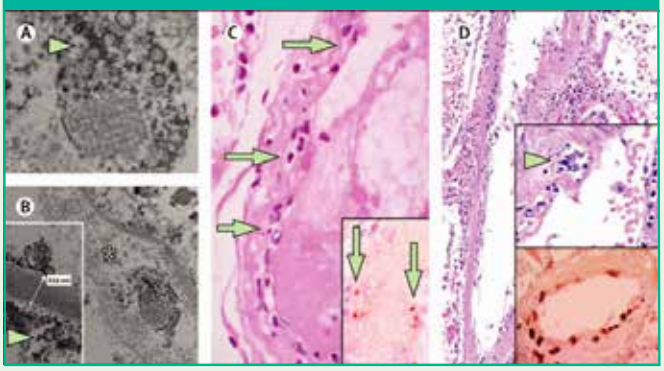
Reference: JAMA, 30 April 2020

Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood. SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney and intestine. ACE2 receptors are also expressed by endothelial cells. Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro. Here demonstration of endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19.

Patient 1 was a male renal transplant recipient, aged 71 years, with coronary artery disease and arterial hypertension. The patient's condition deteriorated following COVID-19 diagnosis, and he required mechanical ventilation. Multisystem organ failure occurred, and the patient died on day 8. Post-mortem analysis of the transplanted kidney by electron microscopy revealed viral inclusion structures in endothelial cells (figure A, B). In histological analyses, founded an accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies, in the heart, the small bowel (figure C) and lung (figure D). An accumulation of mononuclear cells was found in the lung, and most small lung vessels appeared congested.

Figure: Pathology of endothelial cell dysfunction in COVID-19



Patient 2 was a woman, aged 58 years, with diabetes, arterial hypertension, and obesity. She developed progressive respiratory failure due to COVID-19 and subsequently developed multi-organ failure and needed renal replacement therapy. On day 16, mesenteric ischaemia prompted removal of necrotic small intestine. Circulatory failure occurred in the setting of right heart failure consequent to an ST-segment elevation myocardial infarction, and cardiac arrest resulted in death. Post-mortem histology revealed lymphocytic endotheliitis in lung, heart, kidney, and liver as well as liver cell necrosis. Histological evidence of myocardial infarction but no sign of lymphocytic myocarditis. Histology of the small intestine showed endotheliitis (endothelialitis) of the submucosal vessels.

Patient 3 was a man, aged 69 years, with hypertension who developed respiratory failure as a result of COVID-19 and required mechanical ventilation. Echocardiography showed reduced left ventricular ejection fraction. Circulatory collapse ensued with mesenteric ischaemia, and small intestine resection was performed, but the patient survived. Histology of the small intestine resection revealed prominent endotheliitis of the submucosal vessels and apoptotic bodies.

Recruitment of immune cells, either by direct viral infection of the endothelium or immune mediated, can result in widespread endothelial dysfunction associated with apoptosis. The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homoeostasis. Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema and a pro-coagulant state.

The presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilize the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins. This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19.

Reference: The Lancet, 02 May 2020, Vol. 395

Chloroquine and hydroxychloroquine: Old drugs in a new covid-19 world

The COVID-19 pandemic is challenging the slow and highly regulated drug approval process in the United States. On March 28, 2020, the U.S. FDA authorized use of the antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) to treat COVID-19 patients for whom a clinical trial is not available, despite inconclusive clinical evidence of effectiveness.

Most COVID-19 patients probably are in an antiviral susceptible stage before clinical presentation. Following a primary phase marked by the usual respiratory symptoms, fevers and malaise, patients most affected by COVID-19 develop a severe inflammatory respiratory illness, driven largely by the host immune response. Laboratory data show evidence of massive inflammation, including elevated C-reactive protein, ferritin and interleukin-6. CQ and HCQ have demonstrated activity in vitro against SARS-CoV, SARS-CoV-2, and other viruses. The mechanism is not entirely understood but involves (1) raising the pH of cellular endosomes, rendering less efficient the process of viral entry, replication, and infection and (2) interference with glycosylation of cellular receptors for the virus. In addition, these drugs also appear to reduce host cell autophagy. Given these apparent antiviral and immunomodulatory effects, CQ or HCQ seemed promising.

The FDA's authorization of CQ or HCQ for COVID-19 occurred after there had been extensive publicity related to a small nonrandomized study, now published, of 36 patients with confirmed COVID-19; 22 had upper respiratory tract infections, 8 had lower respiratory tract infections and 6 had no symptoms. Of these patients, 20 received HCQ (600 mg daily) and 16 did not (control patients). Among the HCQ patients, 6 also received azithromycin (AZM; 500 mg on day 1, 250 mg on days 2–5) as a bacterial super infection prophylactic. Within 6 days, virologic clearance was seen in 70% of HCQ recipients and in 12.5% of controls. All patients treated with HCQ plus AZM cleared virus compared with 57.1% who received HCQ alone only. These findings were not compelling: the effect was purely microbiological and not clinical, in a study that was not optimally designed and potentially subject to bias.

Notably, in previous epidemics of chikungunya, dengue, and influenza, the apparent in vitro antiviral effects of CQ or HCQ did not translate into clinical benefits. The first randomized study of HCQ in COVID-19 from China had only 30 patients from a single center and did not show any clinical benefit. A second report published February 15, 2020, indicated that there were better outcomes associated with CQ therapy than in controls in a review

of 100 patients, but the full results have yet to be published in a peer-reviewed journal.

Beyond these concerns about efficacy, CQ and HCQ are not without toxicity. Photosensitivity, gastrointestinal side effects, and other toxicities, while rare may be augmented in severely ill COVID-19 patients. Of particular concern is QT prolongation due to these agents, as myocarditis and cardiomyopathy appear to be relatively common complications in patients with severe COVID-19. Highlighting these concerns, in a double blind, randomized trial in Brazil of two doses of CQ (600 mg twice daily for 10 days or 450 mg twice daily for 5 days) for hospitalized patients with COVID-19 recently, the higher dose arm was discontinued per a data safety monitoring board for increased mortality. An additional retrospective review of 368 male patients hospitalized with COVID-19 in U.S. veterans medical centers, released as non–peer reviewed preprint on April 21, 2020, raises a similar concern. Although HCQ recipients and non-recipients differed in several baseline characteristics that could have influenced the findings, the risk for death was higher in the HCQ group than in the non-HCQ group.

Placebo controlled studies evaluating the role of CQ or HCQ as post-exposure prophylaxis, in outpatient clinics (mild disease), and in hospitalized patients have now been started. Given the currently available limited efficacy data and the concerns regarding toxicity, we believe that CQ/HCQ should not be used for COVID-19 until controlled clinical trials demonstrate that benefits outweigh potential harms.

Reference: N. Eng. J. Med., 24 April 2020

Renin angiotensin aldosterone system inhibitors and risk of Covid-19

Background: There is concern about the potential of an increased risk related to medications that act on the renin angiotensin aldosterone system in patients exposed to coronavirus disease 2019 (Covid-19), because the viral receptor is angiotensin converting enzyme 2 (ACE2).

Methods: Assessment the relation between previous treatment with ACE inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers or thiazide diuretics and the likelihood of a positive or negative result on Covid-19 testing as well as the likelihood of severe illness (defined as intensive care, mechanical ventilation or death) among patients who tested positive. Using Bayesian methods, compared the outcomes in patients who had been treated with these medications and in untreated patients, overall and in those with hypertension, after propensity score matching for receipt of each medication class. A difference of at least 10 percentage points was pre-specified as a substantial difference.

Results: Among 12,594 patients who were tested for Covid-19, a total of 5894 (46.8%) were positive; 1002 of these patients (17.0%) had severe illness. A history of hypertension was present in 4357 patients (34.6%), among whom 2573 (59.1%) had a positive test; 634 of these patients (24.6%) had severe illness. There was no

association between any single medication class and an increased likelihood of a positive test. None of the medications examined was associated with a substantial increase in the risk of severe illness among patients who tested positive.

Conclusions: No substantial increase in the likelihood of a positive test for Covid-19 or in the risk of severe Covid-19 among patients who tested positive in association with five common classes of antihypertensive medications.

Renin angiotensin aldosterone system blockers and the risk of Covid-19

Background: A potential association between the use of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (Covid-19) has not been well studied.

Methods: A study was carried out by a population based case control study in the Lombardy region of Italy. A total of 6272 case patients in whom infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed between February 21 and March 11, 2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age and municipality of residence. Information about the use of selected drugs and patients' clinical profiles was obtained from regional databases of health care use. Odds ratios and 95% confidence intervals for associations between drugs and infection, with adjustment for confounders, were estimated by means of logistic regression.

Results: Among both case patients and controls, the mean (±SD) age was 68±13 years and 37% were women. The use of ACE inhibitors and ARBs was more common among case patients than among controls, as was the use of other antihypertensive and non-antihypertensive drugs and case patients had a worse clinical profile. Use of ARBs or ACE inhibitors did not show any association with Covid-19 among case patients overall (adjusted odds ratio, 0.95 [95% confidence interval {CI}, 0.86 to 1.05] for ARBs and 0.96 [95% CI, 0.87 to 1.07] for ACE inhibitors) or among patients who had a severe or fatal course of the disease (adjusted odds ratio, 0.83 [95% CI, 0.63 to 1.10] for ARBs and 0.91 [95% CI, 0.69 to 1.21] for ACE inhibitors), and no association between these variables was found according to sex.

Conclusions: In this large, population based study, the use of ACE inhibitors and ARBs was more frequent among patients with Covid-19 than among controls because of their higher prevalence of cardiovascular disease. However, there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.

Reference: N. Eng. J. Med., 01 May 2020

“Immunity passports” in the context of COVID-19

Scientific brief
24 April 2020

World Health Organization

WHO has published guidance on adjusting public health and social measures for the next phase of the COVID-19 response. Some governments have suggested that the detection of antibodies to the SARS-CoV-2, the virus that causes COVID-19, could serve as the basis for an “immunity passport” or “risk-free certificate” that would enable individuals to travel or to return to work assuming that they are protected against re-infection. There is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.

The measurement of antibodies specific to COVID-19

The development of immunity to a pathogen through natural infection is a multistep process that typically takes place over 1-2 weeks. The body responds to a viral infection immediately with a non-specific innate response in which macrophages, neutrophils and dendritic cells slow the progress of virus and may even prevent it from causing symptoms. This non-specific response is followed by an adaptive response where the body makes antibodies that specifically bind to the virus. These antibodies are proteins called immunoglobulins. The body also makes T-cells that recognize and eliminate other cells infected with the virus. This is called cellular immunity. This combined adaptive response may clear the virus from the body, and if the response is strong enough, may prevent progression to severe illness or re-infection by the same virus. This process is often measured by the presence of antibodies in blood.

WHO continues to review the evidence on antibody responses to SARS-CoV-2 infection. Most of these studies show that people who have recovered from infection have antibodies to the virus. However, some of these people have very low levels of neutralizing antibodies in their blood, suggesting that cellular immunity may also be critical for recovery.

Laboratory tests that detect antibodies to SARS-CoV-2 in people, including rapid immunodiagnostic tests, need further validation to determine their accuracy and reliability. These tests also need to accurately distinguish between past infections from SARS-CoV-2 and those caused by the known set of six human coronaviruses. Four of these viruses cause the common cold and circulate widely. The remaining two are the viruses that cause Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome. People infected by any one of these viruses may produce antibodies that cross react with antibodies produced in response to infection with SARS-CoV-2. Many countries are now testing for SARS-CoV-2 antibodies at the population level or in specific groups, such as health workers, close contacts of known cases or within households. WHO supports these studies, as they are critical for understanding the extent of and risk factors associated with infection.

Other considerations

At this point in the pandemic, there is not enough evidence about the effectiveness of antibody mediated immunity to guarantee the accuracy of an “immunity passport” or “risk-free certificate.” People who assume that they are immune to a second infection because they have received a positive test result may ignore public health advice. The use of such certificates may therefore increase the risks of continued transmission. As new evidence becomes available, WHO will update this scientific brief.

Reference: The Lancet, 04 May 2020

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