Imam Reza General Hospital Newsletter
Tabriz University of Medical Sciences

Masood Faghihdinevari

Founder and Director-In-Charge's Message

Dean of Imam Reza Generel Hospital

From the end of 2019 year, Corona virus disease (COVID-19) or SARS-CoV-2 has spread fast all over the world and has caused tensions and pressures on health, economic and political systems. Governments and related health organizations which has beem forced to support the production of drugs and vaccines. In order to obtain license for the production and commercialization of vaccines from the World Health Organization(WHO), it needs special steps to be taken at each stages to prove and approve the successful results (During this process, a large number of vaccines are eliminated and some with ideal results can be finalized). Fortunately, despite all the political and economic restrictions, we were able to vaccinate against the Corona virus in the country. Imam Reza General Hospital in the East Azerbaijan province is an educational, research and treatment center which has been done vaccination for the first time on February 11th, 2021. We hope that Iranian vaccines such as Barakat and Razi Vaccines and also common produced vaccines (Pasteur Vaccine) from cooperation with foreign companies, will successfully pass the scientific stages of registration state and reach large-scale manufacturing. It is important to note that the vaccine is for prevention and has no effect on the treatment. Vaccines stimulate the immune system response and keep it ready to fight against the probable disease. Everyone knows and agrees on this fact that keeping a social distance of at least 2 meters, using appropriate masks and regularly washing hands with soap, water and alcohol 70% are the best and effective hygiene protocols for prevention of Corona disease, ever. I am as the director of Imam Reza General Hospital, Tabriz, Iran, wishing a very happy New Year (1400 Shasmsi) in advance to all dear medical staff and hope that ahead New Year will full of health, peace and friendship for all nations and free from any disease, especially COVID-19 disease. God bless you all.

The first Russian COVID-19 vaccine was injected on February 11th ,2021 at the Imam Reza General Hospital, Tabriz, Iran.

According to the university's public relations, Prof. Ali Taghizadieh, a pulmonologist and vice chancellor in Education of Tabriz University of Medical Sciences, was the first volunteer who had received the first COVID-19 vaccine in Tabriz.

Wishing a Free-Corona life in New Year

Editorial

Evidence-Based Medicine and COVID-19 in Intensive Critical Unit

Hassan Soleimanpour

Editor-In-Chief

Dean of Education and Research Deputy

Professor of Intensive Care Medicine

The wisest person is the one who adds others' knowledge to his own knowledge (Muhammad Prophet)

Using of reliable and strong evidences has a key role in making the precise decisions in the area of medical sciences. Consequently, applying an identical approach can minimize the faults and guarantee the best decision which has made based on the best available evidences that has been primarily evaluated. For the first time, David Sacket and his colleagues have invented the term of Evidence-Based Medicine and defined the current definition of Evidence-Based Medicine as: Accurate, Clear, and Wise applying of the best available evidences for making decisions about patient care or combining the best research evidences with clinical skills and patient values. Evidence-Based Medicine consists of three main elements: published evidences, clinical judgment, and patients' values and preferences. The following contents are the relatively strong and credible evidence of the intensive care unit during the COVID-19 crisis.

Burden of COVID-19 in Intensive Care Medicine:

During the COVID-19 crisis, 1 in 5 hospitalized adult COVID-19 positive patients will require ICU admission. 70% of ICU patients will require any type of ventilatory support and more than 50% of them will need mechanical ventilation. The median age of ICU patients was 59.7 and 62% were male. Mean ICU and hospital length of stay is 7.3 and 12 days, respectively. ARDS was present in 38% of the patients. In other studies, the mean use of Non-invasive ventilation (NIV) and High-Flow Nasal Oxygen (HFNO) was 73% and 48.8%, respectively, and finally, 48.8% of patients with a mean stay of 7.8 days required mechanical ventilation. And 8% used extracorporeal membrane oxygenation (ECMO). Renal replacement therapy and vasopressors usage was 13.2% and 40.8%, respectively. Based upon UK data, up to 20% of COVID patients required renal replacement therapy. The mean ICU mortality rate was 34.9% and hospital mortality rate was 45%.

Strategies to overcome the shortage of ventilators:

We recommend the use of NIV and HFNO and hospitals increase the quantity of standard full-featured ventilators. In setting with shortage of standard full-featured ventilators, use emergency transport ventilators, anesthesia gas machines, **(Continue on next page)**

Radiologic Findings of COVID-19

Reza Javad Rashid

Professor of Radiology

When will covid-19's lung opacities disappear after the disease? (When does the patient get rid of the disease?)

Because covid-19 is a new disease with different aspects, the exact time cannot be said. But usually after two weeks opacities start to be disappeared.

What are covid-19 imaging findings?

Chest imaging is usually started with plain radiography, but the chest film is insensitive in early stage of this disease. Chest film can be used just for follow-up of the patients in the wards. The main method for diagnosis of covid-19 is CT-Scan, but CT-Scan is not a good method for screening of covid-19. The main imaging findings include: 1- Ground glass: Ground glass is the most common finding in covid-19 infection. This opacity is an area of increased attenuation in the lung on CT-scan with preserved bronchial and vascular markings. They are usually multifocal, bilateral and peripheral. Most commonly located in the inferior lobes of the lungs. 2- Crazy paving: Sometimes there are thickened interlobular and intralobular in combination with ground glass pattern, this is called crazy paving. 3- Vascular dilatation: A relatively late finding is vascular dilatation. A typical finding in the area of ground glass is widening of the vessels. 4- Reverse halo sign: The halo sign is a circular area of ground glass attenuation that is seen around pulmonary nodules at CT-Scan, but reversed halo sign is defined as Central ground glass opacity surrounded by denser consolidation. This lesion is seen in the middle and late phase of the disease. 5- Subpleural bands: There is architectural distorsion with the formation of subpleural bands in the peripheral and lower lobes of the lungs. The lesions are seen in hospitalized patients in the late stage. 6- Consolidation: This lesion contain an air-bronchoram inside of course, they are caused by superinfections and by other organisms. Attention to Clinical symptom in this case can be helpful. 7- Tractional bronchectasis: Another common finding in the area of ground glass is tractional bronchectasis. This symptom causes **(Continue on next page)**

Hamed Valizadeh

Assistant Professor of Internal Medicine-Pulmonology

Lung imaging is utilized as a part of patients with COVID-19 infection particularly when the PCR approach is not available. On the other hand, imaging could be considered as an additional evaluation beside lab testing and physical examinations for patients with critical conditions. Chest X-ray has low precision, especially in early phase and minimal symptoms. Therefore, by "imaging", it means lung CT- scan. Lung CT-scan has been indicated in patients with cough, chilling, sore throat with dyspnea and hypoxia (RR>24 & Spo2<93); Likewise in high risk patients with leukocytosis or leukopenia and fever, CT-scan should be carried out. Another important point is that lung imaging is not indicated for screening of COVID-19 .Generally, if severity of lung involvement is high in CT-imaging, hypoxemic intensity will be higher. However, necessarily this correlation is not linear. That is to say, maybe with moderately lung involvement, patients can be asymptomatic and without any lung involvement the saturation of O2 can decrease. This is a strong reason for not using CT-scan in patients with minimal symptoms and signs

CT-changes over time

Early stage	0-4 days	GGO, partial crazy paving, lower number of involved lobes
Progressive stage	5-8 days	Progressive (5-8 days): Extension of GGO, increased crazy paving pattern
Peak stage	10-13 days	Consolidation
Absorption stage	≥14 days	Gradual resolution

Image1

Hassan Soleimanpour

Evidence-Based Medicine and COVID-19 in Intensive Critical Unit

(Cont.)

and magnetic resonance imaging (MRI) compatible ventilators.

In the case of lack of mechanical ventilation, is it possible to use only one mechanical ventilation device as a practical solution for several patients?

We are strongly against of using one ventilator to ventilate multiple patients. Because the lungs of COVID patients have different resistances and compliance.

What are the available strategies of institutions to overcome the shortage?

Intensive care personnel (doctors, nurses and other staff)?
1- Suspending all the elective medical and surgical procedures and activities once ongoing chains or community transmission of COVID-19 has been documented within a State/Province/Country.
2- Expediting the credentialing process to quickly approve both domestic and foreign healthcare workers to assist in critical areas of need.
3- Reclaiming critical care trained staff who are in other departments and also hiring retired critical care trained staff should be set as an immediate priority.
4- Temporarily redeploying healthcare workers and trainees to the ICU to work in a care-team model even if the ICU is normally outside the scope of their practice.
5- Providing just-in-time training and simulation sessions for non-ICU clinicians to work in ICU in order to better prepare them for their roles.
6- Creating and maintaining a safe working environment with the necessary supplies, personal protective equipment and education to protect staff and trainees.
7- Finally, employing telemedicine and other technology to increase the number of overseeing critical care providers.

What strategies can be used to reduce the exposure of healthcare workers to COVID-19?

1- Fundamental training should be given in the field of wearing and disposing of protective clothing.
2- It is recommended to use visual aids, checklists and trained supervisors to assist in safely dispose of protective equipment.
3- It is recommend minimizing the number of staff entering the rooms of patients with COVID-19, remote access to equipment controls and bundle care to minimize the number of exposures.
4- It is suggested minimizing the transport of COVID-19 patients out of patient care units (i.e. diagnostic radiology).
5- It is recommend that healthcare institutions and ICUs develop and implement response plans to clinical emergencies such as endotracheal intubation and cardiac arrest for patients with COVID-19.

Is the SOFA score recommended for triage of COVID-19 patients in the ICU?

We recommend against the use of the SOFA score for ICU triage of patients with COVID-19

What are the family support strategies in the ICU?
1- Using available communication technology including mobile phones, videoconferencing, and messaging to enable family members to communicate with patients and staff.
2- Using the hospital phone line 24/7 (this line is used outside Iran and it is recommended to set up such a line inside the country) to address questions, concerns, special requests of family members.
3- Involving family members in rounds and patient care discussions (virtually) and providing technological solutions by the hospital to enable this.
4- Involving chaplains/spiritual care, social workers, ethics consultants, patient advocates to provide support to patients and their families.

Latest new findings and recommendations about Remdesivir and Favipiravir

1- FDA has provided Emergency use of the drug Remdesivir and permits the emergency use of it for the treatment of COVID 19 cases in adult and children hospitalized with severe disease.
2- Remdesivir has named as a 'molecule of hope' to the world to stop the menace of COVID19
3- In a clinical trial study of Remdesivir, the 28 day mortality was similar between the remdesivir groups (14%) compared to placebo (13%). However, Remdesivir decreased the time to clinical improvement compared to placebo. And also, the study has reported no significant impact of remdesivir use on viral load measured on nasopharyngeal and oropharyngeal swabs.
4- In a clinical trial study, favipiravir had faster viral clearance and better chest imaging changes than those treated with lopinavir and ritonavir.

A living WHO guideline on drugs for COVID-19

1- The Solidarity Trial published results on 15 October 2020 about 4 treatments of (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had shown little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients. Only corticosteroids have been proven effective against severe and critical COVID-19 patients.
2- The incubation period of the disease was estimated to be 5.2 days which could be transmitted by respiratory droplets, bodily fluids, fecal-oral contact, direct contact, or through environmental surfaces.
3- It has not been reported vertical transmission of the virus during pregnancy.
4- Median time for recovery from the onset of symptoms was claimed to be approximately 2 weeks in mild cases and 3 to 6 weeks in severely or critically unwell individuals.
5- Increased age and chronic health care providers were advised not to be involved in direct contact with COVID patients
6- Mortality rate for the disease was reported 1 to 2%.
7- The adaptive strategy was introduced as an effective way to regulate the social distancing policies in the absence of a vaccine.
8- Management of critical COVID-19 patients included admission to intensive care unit (ICU), non-invasive ventilation (NIV), endotracheal intubation, invasive mechanical ventilation, extracorporeal membrane, oxygenation, and fluid resuscitation and vasopressors, continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) were specified with certain indications in order to attempting to avoid intubation and attempting to aid extubation.
9- Baricitinib, ruxolitinib, and fedratinib were introduced as three anti-inflammatory agents targeting JAK-STAT signalling pathway.
10- A double lung transplant surgery was reported as an example of operative management of COVID-19 which was conducted on 29 February 2020.

Silent or 'Happy' Hypoxemia in COVID-19 patients

A condition where patients have low oxygen saturations (SpO_2 < 90%), but are not in significant respiratory distress and often look clinically well. Hypoxic pulmonary vasoconstriction (HPV) is the pulmonary circulation's homeostatic response to airway hypoxia and constricts pulmonary arteries serving hypoxic lung segments, diverts blood to better ventilated alveoli, and optimizes ventilation/perfusion (V/Q) matching. The mechanism of HAPPY HYPOXIA is that it causes mitochondrial-induced injury, which impairs carotid body function resulting in impaired respiratory drive and reduced dyspnea.

Baricitinib

In a clinical trial of Kalil AC et al, in 1033 patients to evaluate the therapeutic effect of baricitinib with remdesivir in comparison with remdesivir alone in patients with COVID-19 hospitalized, a reduction in the number of days required for oxygen or NIV, reduced mortality and reduced drug side effects were observed in the combination therapy group with baricitinib.

The best sedation in the ICU

Dexmedetomidine appears to have ideal results in the field of neuroprotection, cardioprotection, and renoprotection, which are the most commonly involved organ in COVID-19 patients. It has demonstrated that use of dexmedetomidine resulted in improved oxygenation and avoiding intubation by improving compliance with non-invasive ventilation.

Roleof artificialintelligenceinmanagingof COVID-19intheICU

Artificial Intelligence is transforming the Intensive Care Unit (ICU). The adoption of artificial intelligence in healthcare began with the development of expert systems in the early seventies. Such systems have been utilized for centralized monitoring (e.g., tele-ICU), automated surveillance (e.g., VAEs "ventilator-associated events",sepsis). And an effective, efficient and ethical clinical management of COVID-19 patients in ICUs urgently requires bringing artificial intelligence capabilities to the bedside.

COVID-19 and steroids

In the largest clinical trial called RECOVERY, taking 6 mg of dexamethasone daily for up to 10 days can reduce 28-day mortality by 2.7%. In another Brazilian clinical trial study called CODEX, also compared dexamethasone to placebo in patients with COVID-19 which has shown a much higher dose regimen than in RECOVERY (20 mg for 5 days than 10 mg for 5 days), which resulted in an increase in ventilator-free-days defined as days alive and free at day 28. NIH recently has recommended the use of dexamethasone at a daily dose of 6 mg (oral or intravenous) or hydrocortisone 160 mg/day, for up to 10 days, in hospitalized patients with COVID-19 who require delivery of oxygen through a high-flow device or non-invasive ventilation and in those who require invasive mechanical ventilation or extracorporeal membrane oxygenation. For hospitalized patients who require low-flow supplemental oxygen, the use of steroids is optional and should be associated with an antiviral (remdesivir) because of a theoretical risk of deceleration of viral clearance.

Tips on nutrition

Metoclopramide may be the preferable option compared to erythromycin considering the potential cardiac adverse effects. Systematic measurement of gastric residual volume is not advised as it constitutes a major risk of contamination. A safer alternative to diagnose delayed gastric emptying might be gastric ultrasound.

Reza Javad Rashid

Radiologic Findings of COVID-19

(Cont.)

CT-Scan to be repeated in Covid-19 patients (Image1).

How to report CT scan of patients with COVID-19?

Report of CT-scan is divided in 3 categories:
1-Typical appearance: (suggestive for covid-19) There are patients who have typical radiological finding of covid-19, of course these findings are not 100%, but if other clinical findings are in favor of covid-19, the patient can be considered covid-19.
2-Indeterminate for covid-19: The lesion cannot surely say that they are covid-19 or not.(Nonspecific features of covid-19) . In these cases, after explanation of image findings at the end of the report, we write indeterminate for covid-19.
3)Atypical: Atyical features are reported to be uncommon in covid-19, such as lobar consolidation or tree in bud opacities. But a small percentage of these patients also had a positive PCR, So in these cases, clinicians should be more careful about clinical findings.

How to determine the percentage of lung involvement?

The severity of CT-Scan can be estimated by visual assessment (qualitatively). Another method is by scoring the percentage of each the 5 lobes involvement. 3lobes in right lung and 2lobes in left lung
If involvement is less than 5%: score1
If involvement is between 5 to 25%:score2
If involvement is between 26 to 49%: score 3
If involvement is between 50 to 75%: score 4
If involvement is more than 75%: score 5
The total CT-Scan score is the sum of the individual lobar scores and can range from 0 (no involvement) to 25(maximum involvement), when all the five lobes show more than 75% involvement.

What are covid-19 differential diagnoses?

Ground glass mimickers: 1) inadequate insiration: Normally a CT-Scan should be taken in the adequate inspiration phase. But if it is taken in the expiration phase, the density of lungs especially in the lower parts will be increased. 2) Low dose CT scan: These days the protocol for CT scan is low dose .But in this type of CT-scan, density of Lungs is increased. 3)Mosaic attenuation: When there are vascular and airway disorders such as asthma, the density of the lungs is uneven.

There are some areas with increasing density and some areas with decreasing density.

Differential diagnosis: 1) Pulmonary cardiogenic edema: Ground glass opacities in this disease are typically more centrally distributed with sparing of the peripheral paranchyma. The patients have heart problems and they have enlarged heart with pelural effusion and other clinical presentation of the pulmonary edema. 2) Pulmonary infarctions: Patients present with shortness of breath as well as with radiological symptoms, especially reverse halo sign. Patient with covid-19, can also have this complication. 3) Alveolar hemorrhage: In this disease, opacities are ground glass and can be bilateral, but it is helpful to pay attention to clinical signs and history. For example, vasculitis disease like lupus. (Although more lesions are centrilobular and central). 4) Eosinophilic pneumonia: This condition is associated with asthma. There are ground glass lesions mainly in upper and peripheral lung zone distribution. Eosinophilia in blood samples is detected. In these patients, it is important to pay attention to the history. 5) Drug –induced pneumonitis: Drug associated with lung injury such as chemotherapy and transplant patients. On the other hand, these patients are at risk for covid-19. What will help whether opacitiesi improve with stopping the drugs or not? 6) Multifocal adenocarcinoma (especially adenocarcinoma insitu): Multifocal adenocarcinoma can be present as bilateral diffuse ground glass opacities, But it is important to pay attention to patient's symptoms at the time of these opacities begin. 7) organising pneumonia: Radiological imaging in this case is similar to covid-19 and clinical symptoms can be helpful. 8) Influenza: In the influenza, there is no clear differences in radiological imaging with covid-19. Differences in this case are in clinical manifestations. 9) PCP: This frequently occurs in a more central distribution than in covid-19 and only in immunocompromised patients. PCP is further more associated with pulmonary cysts (Pnematocele). In general, differential diagnosis can be differentiated according to the clinical symptoms.

Haleh Rezaee
Associate Professor of Clinical Pharmacy

Current Pharmacological treatments and recommendations for using in treatment of Covid-19

A novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China at the end of 2019; it has subsequently spread rapidly, resulting in a global pandemic. The optimal approach to treatment of COVID-19 is uncertain. Our approach is based on limited data and evolves rapidly as clinical data emerge. Many patients with suspected COVID-19 have mild disease that does not warrant hospital-level care. Having such patients recover at home is preferred, as it prevents additional potential exposures in the health care setting and reduces burden on the health care system. The evaluation of hospitalized patients with documented COVID-19 should assess for features associated with severe illness and identify organ dysfunction or other comorbidities that could complicate potential therapy. For patients with documented COVID-19, we do not routinely administer empiric therapy for bacterial pneumonia. Data are limited, but bacterial superinfection does not appear to be a prominent feature of COVID-19. Empiric treatment for bacterial pneumonia may also be reasonable in patients with documented COVID-19 if there is clinical suspicion for it. If empiric antibiotic therapy is initiated, we attempt to make a microbial diagnosis and reevaluate the need to continue antibiotic therapy daily. Patients hospitalized with COVID-19 should receive pharmacologic prophylaxis for venous thromboembolism. COVID-19 has been associated with thromboembolic complications. There are minimal data informing the risks of non-steroidal anti-inflammatory drugs (NSAIDs) in the setting of COVID-19. We suggest acetaminophen as the preferred antipyretic agent, if possible (Grade 2C). If NSAIDs are needed, we use the lowest effective dose. We do not discontinue NSAIDs in patients who are on them chronically for other conditions if there are no other reasons to stop them. People who are on an ACE inhibitor or ARB for another indication should not stop their medication. We make a point of continuing statins in hospitalized patients with COVID-19 who are already taking them. Our approach to COVID-19-specific therapy in hospitalized patients depends on the severity of disease. Severe disease is characterized by hypoxia (O2 saturation ≤94 percent on room air) or need for oxygenation or ventilatory support. For patients with non-severe disease, care is primarily supportive, with close monitoring for disease progression. When clinical trials for treatment of non-severe disease are available, we prioritize those who have laboratory features associated with disease progression. For hospitalized patients with severe disease (i.e., they have hypoxia) but who are not yet on oxygen, we suggest remdesivir, if available (Grade 2C). We suggest not using dexamethasone in such patients (Grade 2C). For hospitalized patients with severe disease who are receiving supplemental oxygen (including those who are on high-flow oxygen and noninvasive ventilation), we suggest low-dose dexamethasone (6 mg daily for 10 days or until discharge, whichever is shorter) and, if available, remdesivir (Grade 2C). For hospitalized patients with severe disease who require mechanical ventilation, we recommend low-dose dexamethasone (Grade 1B). We also suggest remdesivir for patients who have been intubated for a short period of time (e.g., 24 to 48 hours) (Grade 2C). If supplies of remdesivir are limited, we prioritize it for patients who are on low-flow oxygen supplementation at baseline. If dexamethasone is not available, other glucocorticoids at equivalent doses (e.g., total daily doses of hydrocortisone 150 mg, methylprednisolone 32 mg, or prednisone 40 mg) are reasonable alternatives. Patients receiving glucocorticoids should be monitored for adverse effects. The suggested adult dose for remdesivir is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation). If a patient is otherwise ready for discharge prior to completion of the course, remdesivir can be discontinued. Remdesivir is not recommended in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m2 unless the potential benefit outweighs the potential risk. Liver enzymes should be checked before and during remdesivir administration; alanine aminotransferase elevations >10 times the upper limit of normal should prompt consideration of remdesivir discontinuation. Remdesivir should not be used with hydroxychloroquine or chloroquine because of potential drug interactions. Convalescent plasma obtained from individuals who have recovered from COVID-19 is a potential option for therapy of SARS-CoV-2 infection in hospitalized patients. It is possible that convalescent plasma provides clinical benefit when it contains high neutralizing antibody titers and/or is given early in the course of disease (i.e., in patients who do not require mechanical intubation). However, clear data on efficacy from randomized trials are lacking. Several agents that target the IL-6 pathway have been evaluated in randomized trials for treatment of COVID-19; these include the IL-6 receptor blockers tocilizumab and sarilumab and the direct IL-6 inhibitor siltuximab. However, results from randomized trials do not indicate a mortality benefit or other clear clinical benefit of these agents. Additional trials of tocilizumab and other IL-6 pathway inhibitors, each in combination with other interventions, are ongoing. Use of IL-6 pathway inhibitors may be associated with an increased risk of secondary infections, although this was not observed in several randomized trials. We suggest not using hydroxychloroquine or chloroquine in hospitalized patients given the lack of clear benefit and potential for toxicity. Favipiravir may hasten SARS-CoV-2 RNA clearance, although data are limited. In a randomized, open-label trial from Russia that included hospitalized patients who were on room air or receiving supplemental oxygen through mask or nasal cannula, the rate of viral RNA clearance from upper respiratory tract specimens at day 5 was higher with favipiravir compared with standard of care, which included hydroxychloroquine or chloroquine. In a non-randomized study from China of patients with non-severe disease (including oxygen saturation >93 percent), use of favipiravir was associated with faster rates of viral clearance and more frequent radiographic improvement compared with lopinavir-ritonavir. However, since other therapies (e.g., immunomodulatory agents) were administered in these studies, the results should be interpreted with caution given potential confounders. Interferons modulate immune responses and may have antiviral effects. Interferon beta, specifically, has been reported to inhibit SARS-CoV-2 replication in vitro. Some trials have suggested a clinical benefit with interferon beta for patients with COVID-19, although methodologic limitations reduce confidence in the findings. Furthermore interim results of a large multinational trial of patients hospitalized with COVID-19 showed no difference in 28-day mortality with subcutaneous or intravenous interferon beta compared with standard of care. Inhaled interferon beta is also being evaluated in patients with COVID-19. We do not use azithromycin, either alone or in combination with hydroxychloroquine, for treating COVID-19. Studies have compared the combination of azithromycin and hydroxychloroquine with usual care or with hydroxychloroquine alone, and most have not suggested an associated clinical benefit. Furthermore, both azithromycin and hydroxychloroquine are associated with QTc prolongation, and combined use may potentiate this adverse effect. We suggest not using lopinavir-ritonavir for treatment of COVID-19 in hospitalized patients. Several clinical trials have failed to demonstrate efficacy. Whether lopinavir-ritonavir has a role in outpatients with nonsevere disease is uncertain; we suggest it only be used in outpatients in the context of a clinical trial. Although it has in vitro activity against SARS-CoV, lopinavir-ritonavir is highly protein-bound and does not appear to achieve plasma levels close to the EC50. Ivermectin has also been proposed as a potential therapy based on in vitro activity against SARS-CoV-2, but the drug levels used in vitro far exceed those achieved in vivo with safe drug doses; various clinical trials of ivermectin are underway.

Afshin Gharekhani
Assistant Professor of Clinical Pharmacy

COVID-19 in Solid Organ Transplant Patients: Imunosuppressive medications management

COVID-19 has shown widespread community spread across most countries. The exact prevalence of infection in the general population is unknown since the pandemic is ongoing; however, a case fatality rate of 2%–4% has been described. Solid organ transplant recipients are perceived to be at increased risk of severe COVID-19, because of their chronic immunosuppressed status because of the using of immunosuppressive drugs (ISD). At present, there is limited experience with the treatment of affected transplant recipients. The continuation and proper dose or target of ISD is still matter of debate. Moreover, There is no proven effective therapeutic intervention than other supportive care which is now available. The scale of the outbreak and the considerable severity of the disease in many cases, have prompted several pharmacologic interventions. Laboratory research has identified more than 30 agents that may have potential efficacy against SARS-CoV-2. Drugs that have been and are being tested in humans include (hydroxy)chloroquine, darunavir/cobicistat (DRV/COB) or DRV/ritonavir (DRV/r), favipiravir, interferon (IFN), lopinavir/r (LPV/r), ribavirin, remdesivir, and tocilizumab. The last 2 being are available for compassionate usage or for clinical trials. There is no consensus on which pharmacotherapeutic strategy to follow. Several professional societies have developed recommendations and guidelines to help clinicians with these investigational and off-label medicinal products. Transplant patients are treated with ISD whose pharmacodynamics (PD) and pharmacokinetics (PK) can be affected by these antivirals. Furthermore, COVID-19 patients may exhibit features of systemic hyperinflammation (designated as "cytokine storm"), which can be associated with so called "phenoconversion," a phenomenon whereby extensive metabolizers transiently exhibit drug metabolizing enzyme activity at a comparable level as poor metabolizers. Commonly, ISDs are characterized by a narrow therapeutic index and wide PK variability, requiring close monitoring of the blood concentrations. Also, the metabolic pathways involved in clearance of ISDs make these drugs extremely susceptible for drug–drug interactions (DDIs). Calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORi) are primarily metabolized by cytochrome P450(CYP). Their oral bioavailability is poor, erratic and also limited by the fact that they are substrate for P-glycoprotein (P-gp or ABCB1). Mycophenolate mofetil is a prodrug that is converted into mycophenolic acid. The metabolism of MPA mainly involves glucuronidation by the uridine 50-diphosphate-glucuronosyltransferase (UGT) enzyme superfamily. Mycophenolic acid is subjected to entero-hepatic recirculation, which extends its terminal half-life. Hepatic excretion of MPA glucuronide (MPAG) is driven by uptake from the portal vein through OATP1B3 and, to a lesser extent, OATP1B1. The purpose of this summery is to inform the clinician about the potential interaction of drugs against coronavirus with IS drug, therapy used in transplantation. (Hydroxy)chloroquine, CNIs [both cyclosporin and tacrolimus], and mTORis can all cause prolongation of the QT interval (PD interaction). Even if unpredictable in theory, the concurrent use of 2 drugs cause QT interval prolongation may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and, although rare, sudden death. So, When coadministration of (hydroxy)chloroquine together with CNI and/or mTORi is considered, the following recommendations should be implemented. QT interval monitoring is strongly recommended. These drugs should only be administered when cardiac monitoring is available. Ciclosporin A, Tacrolimus, Everolimus, and Sirolimus blood concentrations should be closely monitored. By increasing in exposure, the dose may need to be decreased. **Protease inhibitors (Lopinavir/Ritonavir (Kaletra).**Co-treatment with boosted protease inhibitor regimens is inherently challenging, because of their complex spectrum of drug-drug interactions (PK interactions). Lopinavi/ritonavir inhibits various cytochromes and transporters, thereby affecting other therapies like ISD. When considering boosted protease inhibitor therapy, it is recommended that ISD dose be significantly reduced and also dosing intervals be increased to once a week or twice a week. For Tacrolimus and Ciclosporin A, data suggest that dosing regimens of 0.5–1 mg once weekly for Tac and 25 mg, every 1–2 days for Ciclosporin A are appropriate when coadministered with boosted protease inhibitor regimens. In addition to drastic dose reduction, therapeutic drug monitoring should be conducted from day 1 of the coadministration, on a daily basis until stable concentrations are reached. With boosted protease inhibitor coadministration, it has been suggested to decrease the Sirolimus maintenance dose to 0.2mg/wk. No data are currently available to support an important PK interaction between boosted protease inhibitor regimens and Mycophenolic acid. In cardiothoracic transplant recipients, it is recommended to consider stopping mycophenolate mofetil while the patient is admitted with severe/critical illness (with close monitoring for rejection). Similar decisions should be considered in critically ill COVID-19–positive patients than cardiac transplant recipients. Glucocorticoid clearance has been reported to be significantly reduced in patients on ritonavir-boosted protease inhibitor resulting in higher serum concentrations and side effects. So it is recommended for patients who regularly use low-dose glucocorticoids for chronic diseases, a conservative but cautious attitude should be adopted with preservation or slight reduction of the usual dose. **Remdesivir:** No clinical interaction is expected beween any of the above-mentioned ISD and remdesivir. Nevertheless, it is recommend caution and suggest close monitoring of ISD concentrations during co-administration with remdesivir because of the lack of knowledge and studies evaluating the safety of co-administration. Therefore, a strict therapeutic drug monitoring of ISD is proposed especially since these drugs may be used in severe and rapidly evolving situations. **Tocilizumab**:To date, no data on DDI with ISD are available. However, drastic reduction of IL levels can influence CYP3A activity by reverting the phenoconversion. We recommend caution and careful ISD therapeutic drug monitoring need when tocilizumab is administered. Because of the long half-life of tocilizumab, it has been suggested that monitoring of this interaction may be necessary for months after tocilizumab is discontinued. **Favipiravir:** There is no information available on drug-drug interaction. **Interferone:α/β**:The treatment with interferon-α after transplantation should be avoided because of an increased risk of rejection. Additionally, there is no proven benefit (and potential harm) of interferon- β in solid organ transplant patients and their routine use is not recommended.

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