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Pharmacy Newsletter

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Coagulopathy in Corona Disease (COVID-19)

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A novel coronavirus strain disease, Coronavirus Disease 2019 (COVID-19) has recently emerged in China, and rapidly spread through the world. Patients with COVID-19 usually present with fever, cough, and myalgia or fatigue. The complete spectrum of presentations and complications associated with COVID-19 is not fully elucidated. Clinical manifestations range from asymptomatic, mild illness to severe illness, and death. The majority of the severely ill patients initially present with single organ failure (i.e., respiratory insufficiency), others progress to more systemic disease and rapid multiple organ dysfunction syndromes and death. Proposed mechanisms for MODS in COVID-19 are multifactorial but include a hypercoagulable state with micro and macro-circulatory thrombosis. A strong predictor of mortality is disseminated intravascular coagulation. In an early COVID-19 cohort, it occurred in 71.4% and 0.6% of non-survivors and survivors, respectively [Tang N et al]. The coagulopathy seen in COVID-19 patients is quite different than what is seen in critically ill sepsis or trauma patients. The most common pattern of coagulopathy observed in COVID-19 patients is characterized by significant elevations in fibrinogen and D-dimer levels with a parallel rise in inflammatory markers (e.g. C-reactive protein). Therefore, based on the published evidence, the International Society of Thrombosis and Hemostasis (ISTH) recommended frequent monitoring of Prothrombin, D-dimer, platelet count and fibrinogen in all COVID-19 patients [Thachil J, et al]. Recently, Tang et al., assessed 183 patients with COVID-19, 21 of whom (11.5%) died. Among the notable differences between patients who died and those who survived were increased levels of D-dimer and fibrin degradation products. Further, 71% of COVID-19 patients who died fulfilled the ISTH criteria for DIC. Collectively, these hemostatic changes indicate some coagulopathy that may predispose to thrombotic events. It should be noted that, like all cases of DIC, patients may progress to a hypercoagulable phenotype when fibrinogen levels begin to decrease. At this point stopping anticoagulation should be considered. Elevated D-dimer levels with a hypercoagulable state and the presence of respiratory failure, have raised an important question regarding the incidence of venous-thromboembolism (VTE), specifically pulmonary embolism. However, respiratory failure could be a sequela of viral disease or profound inflammatory process, while in usual practice, the elevated D-dimer has low positive predictive value. Moreover, D-dimer is more frequently elevated in patients with cancer, hospitalized patients, severe infection or inflammatory diseases, and during pregnancy. On the other hand, a single-center study from China suggested that D-dimer levels >1,500 ng/mL have a sensitivity of 85 % and specificity of 88.5% for detecting VTE events. However, the study was limited by small sample size and lack of validation [Tang N, et al].

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Formulary & Therapeutics Committee Updates

The following are formulary changes by the Formulary & Therapeutics Committee (FTC) from April-June 2020 meetings. Please refer to the Online Hospital Formulary to check the status of the new medications and details on dosing and uses.

Approved New Formulary Addition

- **Human Hemin (Normosang®) 25mg/mL [10 mL Vial]**

  Management of patients with acute intermittent porphyria (AIP) who are ≥16 years old. Prescribing restricted to Medical Genetics Consultants.

- **Riociguat (Adempas®) 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg Tablet**

  Management of adult patients with pulmonary arterial hypertension (PAH) (Group 1) and adult patients with chronic thromboembolic pulmonary hypertension (CTEPH). Prescribing restricted to Adult Pulmonology Consultants.

- **Pirfenidone (Esbriet®) 267 mg and 801 mg Tablet**

  Management of adult patients with idiopathic pulmonary fibrosis. Prescribing restricted to Adult Pulmonology Consultants.

Approved Expansion of Indication and Waiver of Form B

- **Mitomycin-C Powder for injection: 20 mg vial**

  Use of higher dose of mitomycin-C after cytoreductive surgery for the treatment of peritoneal carcinomatosis as a part of hyperthermic intraperitoneal chemotherapy (HIPEC) management.

- **Cisplatin Injection: 1 mg/mL (50 mL)**

  Use of higher dose of cisplatin as a part of HIPEC management.

Approved New Dosage Form Addition

- **Brimonidine Tartate (Mirvaso®), 0.33% [30 g tube]**

  Management of persistent facial erythema of rosacea. Prescribing restricted to Dermatology Physicians.

- **Bismuth Subcitrate Metronidazole Tetracycline (Pylera®) 140mg/125 mg/125 mg Capsule**

  Management of adult patients with H. pylori infection.

- **Subcutaneous Immune Globulin 20% (Cuvitru®) [1 g/5 mL; 2 g/10 mL; 4 g/20 mL Solution for Infusion]**

  Management of primary immunodeficiency disease. Prescribing restricted to Allergy/Immunology Consultants.

- **Subcutaneous Immune Globulin 10% with Recombinant Human Hyaluronidase (Hyqvia®) [2.5 g/25 mL; 5 g/50 mL; 10 g/100 mL Solution for Infusion]**

  Management of primary immunodeficiency disease. Prescribing restricted to Allergy/Immunology Consultants.

- **Fluticasone Furoate/ Vilanterol (Relvar Ellipta®) 100/25 mcg and 200/5 mcg Powder for oral inhalation**

  Maintenance treatment of adult patients with chronic obstructive pulmonary disease and patients (≥12 years) with asthma requiring a long acting beta-2 agonist and inhaled corticosteroids.

Approved Temporary Formulary Alternative

- **Sodium Polystyrene Sulfonate (Sodanor®) [454 g powder, Multi-Dose Container]**

  Approved as a temporary formulary alternative due to the shortage sodium polystyrene sulfonate (Kayexalate®) suspension

- **Azithromycin (Zithromax®) 500 mg [Vial]**

  Approved for patients with corona disease (COVID-19) who can not take orally or with absorption issues. Prescribing restricted to Critical Care and Infectious Diseases physicians for the approved indication.

- **Codeine Sulfate 30 mg Tablet**

  Approved as a temporary formulary alternative during the shortage of codeine phosphate.

Formulary & Therapeutics Committee

Updates *Continued …*

Approved Extension of Prescribing Privileges

- **Liraglutide (Victoza®) 18 mg/3 mL Prefilled Pen**
  Expanded to Adult Cardiologist
- **Tenofovir Alafenamide (Vemlidy®) 25 mg Tablet**
  Expanded to Liver Transplant Physicians
- **Bisoprolol (Concor®) 2.5 mg, 5mg ,10 mg Tablet**
  Expanded to Internal Medicine Physicians

Approved Expansion of Indication and Extension of Prescribing Privileges

- **Letrozole (Femara®) 2.5 mg Tablet**
  Prescribing privilege extended to include Obstetrics & Gynecology Consultants for ovulation induction in patients with polycystic ovarian syndrome.
- **Blinatumomab (Blicynto®) 35 mcg [Vial]**
  Prescribing privilege extended to include Adult Hematology/Bone Marrow Transplantation Consultants for treatment of adult patients with refractory ALL and patients with B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) ≥0.01%.

Approved Drug Sample Request

- **Ipilimumab (Yervoy®) 5mg/mL [10 mL Vial]**
  Advanced Renal Cell Carcinoma. Prescribing restricted to Dr. Mohammed Bazarbashi, Medical Oncology Consultant.

Approved Guidelines and Protocols

- Evolucomab (Repatha®) Guidelines for Homozygous Familial Hypercholesterolemia (HoFH) who are on Lipid Apheresis.
- Dupilumab (Dupixent®) Guidelines for the Treatment of Moderate to Severe Atopic Dermatitis. Prescribing is accompanied by indication form.
- Status Epilepticus Guidelines for adult and pediatric patients.

Approved Deletion

- **Fluticasone/Salmeterol (Seretide®Diskus) [100/50 mcg, 250/50 mcg, and 500/50 mcg powder for oral inhalation]**
  To be deleted when stock is zero.
- **Budesonide/Formoterol (Symbicort®) [80/4.5 mcg and 160/4.5 mcg powder for oral inhalation]**
  To be deleted when stock is zero.
- **Beclomethasone/Formeterol (Foster®) [100/6 mcg inhalation solution]**
  To be deleted when stock is zero.
- **Captopril (Kidcap®) Ready made formula 5 mg/mL [100 mL Oral solution]**
  Due to interruption of supply from the manufacturer of the commercially available product. Compounding oral preparation is available as alternative.
- **Subcutaneous Immune Globulin 16.5% (Gammanorm®) 1g/6mL, 1.65 g/10 mL, 3.3 g/20 mL [Solution for Infusion]**
  To be deleted when the stock is zero

For more information on the indication, age specifications, doses, and guidelines, please check the online hospital formulary

What is in the News

US-FDA Warns About Potential Interaction of Remdisvir with Hydroxychloroquine and Chloroquine

Based on laboratory studies, the U.S. FDA is warning health care providers about potential drug interaction related to remdesivir, which has received emergency use authorization for the treatment of hospitalized patients with corona disease (COVID-19) with severe disease. However, due to an antagonistic effect observed in vitro for chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir, concomitant use with chloroquine or hydroxychloroquine is not recommended. Of note, KFSHRC is a part of SOLIDARITY Trial.

Health Canada Warns About Hydroxyure Association with Interstitial Lung Disease

Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and allergic alveolitis; including fatal cases have been reported in patients treated with hydroxyurea for myeloproliferative neoplasm. Hydroxyurea should be discontinued in patients with interstitial lung disease. Corticosteroid therapy should be initiated to manage respiratory symptoms. Canadian label has been updated to include the new safety concern

Regulatory Bodies warns About Use of Hydroxychloroquine and Chloroquine in Patients with Corona Disease (COVID-19)

Regulatory bodies including; SFDA reviewed the data for hydroxychloroquine and chloroquine use in the treatment of COVID-19. It is not recommended to use either one outside clinical trial setting. Both drugs are contraindicated in patients with hypersensitivity to 4 aminoquinoline compounds or in the presence of retinal or visual field changes. Patients should be monitored for presence of retinopathy, QT interval prolongation, cardiomyopathy, severe hypoglycemia, renal or hepatic impairment, worsening of psoriasis and porphyria, and neuropsychiatric adverse effects. In KFHSRC guidelines, its use as treatment for COVID-19 is under clinical trial setting or compassionate use and patients should be consented.

Health Canada Warns About Amlodipine Association with Pulmonary Edema

In a long term placebo controlled study, patients with severe heart failure (New York Heart Association Calss III and IV) in amlodipine group had higher incidence of pulmonary edema. Amlodipine is considered contraindicated in patients with outflow tract obstruction of the left ventricle and hemodynamically unstable heart failure patients after acute myocardial infarction.

Health Canada Warns About Nivolumab Association with Myocarditis

Myocarditis has been reported with the use of nivolumab. Severity ranges from asymptomatic to death. If suspected, myocarditis should be treated with prednisone or methylprednisolone. If myocarditis diagnosed, nivolumab should be withheld or permanently discontinued in patients with grade 3 myocarditis. Nivolumab Canadian label has been updated to include the new safety concerns

Health Canada Warns About Hypofibrinogenema and Bleeding Events with Tigecycline

In post-marketing surveillance, Health Canada associated the use of tigecycline with hypofibrinogenemia. Identified cases reported bleeding events; some were serious. The risk of bleeding increased with thrombocytopenia, other comorbidities the patient might have, and drug-drug interactions. The monitoring of blood coagulation parameters has been recommended , and the drug label was updated.

All drug safety alerts are communicated to the end-users of concern, as per the Dissemination and Action Related to Drug Safety Alerts at KFSH&RC Policy.

Tip of the Issue

Autophagy, Malnutrition and Nutrition Triangle in Critically ill Patients

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Malnutrition is common in critical-care setting. The combination of stress and undernutrition can cause negative energy balances and loss of lean body mass, which associated with decrease organ function, abnormal laboratory values, longer hospital stay, increased falls, increased incidence of pressure ulcers, and significantly increased mortality.

Malnutrition causes secondary immune deficiency by reducing cell-mediated immunity, phagocytosis function, secretory antibody response, and antibody affinity, and influencing the complement system and cytokine production. Also, impaired respiratory muscle strength which leads to decrease ventilation capacity, prolong mechanical ventilation time, delay wound healing, prolong ICU stay, morbidity, and mortality. Current A.S.P.E.N. guidelines suggest using screening tools (e.g. nutritional risk screening [NRS 2002] and NUTRIC score) for assessing nutritional status and determination of nutrition risk for all patients admitted to the ICU.

Apoptosis is a programmable cell death (Type I), in which cells destroy themselves without inflammation, and is controlled by genes, needs protein synthesis and energy, and promotes homeostasis in an organism.

In sepsis, apoptosis of lymphocytes from immune cells increased accompanied by decreased apoptosis gastrointestinal and pulmonary epithelial cells undergo intense apoptosis.

All of these have been reported to contribute to the development of impaired immune response during sepsis and sepsis-induced organ dysfunction. It has been reported that malnutrition in critically ill patients causes increased apoptosis, changes defense mechanisms, leads to dysfunction of lympho-hematopoietic organs, and changes immune response, and is an important risk factor for the development of sepsis.

Previous published studies reported that parenteral nutrition causes significant physical changes in the intestinal mucosa and significant changes in the intestinal mucosal immunity. It has been reported that parenteral nutrition increases intestinal permeability, induces apoptosis of intestinal epithelial cells, reduces intraepithelial lymphocyte and lamina propria lymphocyte counts, and causes mucosal imbalance of intestinal cytokines. However, it has been shown that administration of parenteral nutrition instead of enteral nutrition leads to changes in the expression of intestinal Toll-like receptors and cytokine by inducing apoptosis in interferon-g mediated intestinal cells, resulting in the development of bacterial translocation and sepsis.

It is as an immunological process can be summarized in four principals: direct elimination of microbes, control of inflammation, antigen presentation and lymphocyte homeostasis , and secretion of immune mediators. Also, it plays important role for repair organ dysfunction.

Fasting stimulates autophagy and autophagy stimulation has also been shown to be protective against organ dysfunction and mortality. Early initiation of enteral nutrition has been shown to help promote intestinal mucosal integrity, motility, and intestinal blood flow.

In addition, enteral nutrition has been shown to provide significant improvement in organ dysfunction score, reduce the incidence of infection, shorten the length of hospital stay, and accelerate wound healing. Early parenteral nutritional support inhibits autophagy in critically ill patients, leading to suppression of natural immunity, infection development, and increased organ dysfunction.

[References available on request]

Pharmacy Newsletter

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Coagulopathy in Corona Disease (COVID-19), *Continued ...*

The available data on thrombotic risk in COVID-19 patients is quite limited and based largely on case series from China, Netherlands, and France. In China, routine VTE prophylaxis was not given to hospitalized patients, which may, at least partly, explain the high VTE rate in that population. In a report from the Netherlands, where routine VTE prophylaxis was given, high rates of VTE were only noted among ICU patients. More than one-third of those patients, however, had a PE limited to sub-segmental arteries. Regardless, it is important to remember that critical illness is associated with a substantial risk of VTE (8-10%) despite the use of prophylactic anticoagulants as shown in the PROTECT study. There may be a higher risk among COVID-19 patients in the ICU, as suggested by a French cohort study, but high-quality data are lacking [Bikdeli B, et al]. Furthermore, evidence regarding Acute Coronary Syndrome (ACS) with concurrent COVID-19 infection is limited to anecdotal reports. A single center retrospective study reported 11 cases of acute ischemic stroke among 221 patients with COVID-19. The risk has garnered huge interest in the potential uses of anticoagulation in COVID-19 patients; specifically, the use of Low Molecular Weight Heparin (LMWH) and Unfractionated Heparin (UFH). Both have a potential benefit over other anticoagulants due to their anticoagulant, anti-inflammatory (decreased lung inflammation and decrease cytokines release) and potentially anti-viral properties.

The use of an anticoagulant appears to be associated with decreased mortality in all hospitalized patients and particularly in patients with sepsis-induced coagulopathy [Thachil J, et al]. The existing data are limited, primarily based on a subgroup analysis from a single retrospective study with limited control for potential confounders. Moreover, a study published by Ning Tang et al. included 449 patients with severe COVID-19; of which 99 received heparin (mainly LMWH) at prophylactic doses. In patient with a sepsis-induced coagulopathy (SIC) score ≥ 4, anticoagulant therapy with LMWH appears to be associated with better prognosis and decreased mortality as compared to those who did not take LMWH 40.0% vs 64.2%, P = 0.029. A similar benefit was noted in those patients with D-dimer more than six-fold of the upper limit of normal (32.8% vs 52.4%, P = 0.017). Based on the currently available evidence that markedly increased D-dimer is associated with high mortality in COVID-19 patients, the ISTH and Journal of the America College of Cardiology (JACC), released a report recommending the use of prophylactic dose of LMWH in all patients, including non-critically ill patients, who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25 x 10^9/L) (1, 10). On June 25th, Adult Guidelines for the Management of Coronavirus Disease 2019 (COVID-19) was updated to reflect suggested dosing regimens for treatment and prophylaxis of VTE.

[References available on request]