



NewsLetter 院訊

Current Pharmacological Treatment of **COVID-19**

HE CHIEF MEDICAL EXECUTIVE



Dr.William Ho Chief Medical Executive

Reflections on Covid-19

Hong Kong is undoubtedly among the very best performing healthcare systems in the world in the war against Covid-19. With a dense population of 7.45 million and adjacent to Mainland China where Covid-19 first broke out, we have a case rate of 140 per million population and a case fatality rate of 0.4% up to 12 May 2020, which compares with:

South Korea:	Cases 214 per million; CFR 2.3%
Singapore:	Cases 4,217 per million; CFR 0.01%
United States:	Cases 4,229 per million; CFR 5.9%
United Kingdom:	Cases 3,329 per million; CFR 14.5%"

The reason? We are much prepared after SARS in terms of infrastructure (isolation beds, ventilation system, PPE stocks), systems (CHP, contingency plans and drills), and culture (wearing masks, hand hygiene). There is widespread risk appreciation among the population, top-notch medical experts advising the government, dedicated staff with expertise and professionalism, and institutional execution machineries that work. Undoubtedly, the public hospitals bore the brunt. But the challenge is nowhere near what we experienced 17 years ago during SARS, when we had none of the knowledge and preparedness as we have now, with a much more deadly virus, and when hundreds of healthcare workers also came down with the disease. The challenge this time is more on timeliness of government decisions, sourcing of PPE, capacity to deal with the two waves of infections, and now - when and how to relax measures.

The private sector has taken a big hit. Patients are afraid to come to clinics or hospitals. Staff are afraid to deal with any patients with the slightest possibility of having Covid-19. Kids are not getting sick because they stay at home, likewise the drop in sports injuries as there can be no skiing, no golfing etc. Resources have to be spent in PPE and all kinds of protection measures, against a sharp drop in revenue. Mainland patients came to a halt. While the HA quickly launched a number of PPP projects to refer out non-Covid patients, the number actually referred out so far is disappointing, paling against the hundreds of people from all private hospitals and multiple divisions in the HA who have been involved in designing, negotiating and agreeing on those packages.

On the positive side though, all of these enhance our appreciation on vulnerability in the system. It is right to err on the side of precaution to ensure our hospital can provide a safe environment for private patients and our staff, even at the expense of short term loss of business. We clearly see that demand in the private sector can be very elastic, hence the need to prepare for rainy days and not be over-ambitious. Even the rather immaterial PPP programs could be seen as learning curve for both sides regarding future possibilities. These days everybody is talking about the New Normal, as Covid-19 is unlikely to go away completely like SARS. It is incumbent upon leaders to adapt continuously and effectively to the ever-changing environment and readjust strategies accordingly, that will lead to continued excellence and adding value to the healthcare system.





Dr. Lee Yin Yin, Candice Staff Consultant in Respiratory Medicine St. Paul's Hospital

A Roadmap to Success? Navigation Bronchoscopy

Lung cancer is the leading cause of cancer deaths worldwide. In 2016, it took the life of 3890 people and accounted for 27.1% of all cancer deaths in Hong Kong (1). The large majority of patients with lung cancer present with locally advanced or metastatic disease which explains the comparatively high mortality.

Precise, fast, and gentle diagnosis of lung lesions is important for patients but challenging for pulmonologists. Lung tumours may be central or peripheral. Central lung lesions are usually directly visible by the bronchoscope camera, and are sampled easily under direct visual guidance with a high success rate of almost 90%. Peripheral lung lesions (PLLs), defined as lesions located beyond the segmental bronchus, are outside the visible range of bronchoscope. They are much harder to reach and the success rates decrease sharply. The success rate in PLL of >2cm in diameter was reported to be 63%, and decreased to 34% for tumours <2cm. The yield is improved to around 70% by the concurrent use of fluoroscopy and/or radial-endobronchial ultrasound (R-EBUS) (2).

Navigation bronchoscopy uses a navigational system to guide the bronchoscope and tools though the airways to a target lesion for biopsy. Navigational systems can be electromagnetic or virtual, depending on the platform used. Both platforms involve 3 phases – planning, guidance, and biopsy.

Electromagnetic Navigation Bronchoscopy (ENB)

The Planning Phase

A CT protocol specialized for navigation is used to acquire images that are later transferred to a computer workstation where specific software is used to create a virtual bronchoscopic map. The pathway(s) to be used may be created by the pulmonologist or suggested by the ENB system.

The Guidance Phase

Real-time tracking of instruments is made possible by placing an electromagnetic field board under the patient's thorax. A locator guide catheter, together with the steerable sheath, is placed through the working channel of the flexible bronchoscope. The locator can be tracked in the electromagnetic field by the system and therefore can guide the operator towards the target lesion according to the "map" created in the planning phase. Consistent bronchoscopy suite set-up with pre-procedure calibration is imperative as metal objects and/or mobile communications devices within one metre of the electromagnetic field will reduce system accuracy.

The Biopsy Phase

PPL biopsies are often done with the aid of both fluoroscopy and R-EBUS, in order to maximize the diagnostic yield.

Virtual Bronchoscopic Navigation (VBN)

The Planning Phase

Similar to ENB, a virtual bronchoscopic pathway to the target lesion is created by computer software with CT scan images. Up to 3 pathways are calculated based on target location.

The Guidance Phase

The position of the bronchoscope tip is found by comparing and matching the real-time images from the bronchoscope with the acquired virtual images of the airway pathway. This allows the bronchoscope to be advanced branch-by-branch through the airway to the target lesion. However if the view from the bronchoscopy is obscured by blood or mucus, which is not uncommon, the tracking between the real-time images and virtual images may be disrupted.

The Biopsy Phase

Same as ENB.



Diagnostic yield and complication rates of navigation bronchoscopy

A large international prospective cohort study using ENB (NAVIGATE) enrolled 1000 patients and found the diagnostic yield to be up to 73% (3). A local study also found a similar accuracy of 71.7% (4). A large review of 1033 ENB procedures reported pneumothoraces in 3.1 % with only 1.6 % requiring a chest tube. Significant bleeding occurred in 0.9 %. (5)

Comparison with CT-guided fine needle aspiration (CT-FNA)

CT-FNA of PLLs performed by interventional radiologists has sensitivity rates close to 90%. However the complication rates, including haemorrhage and pneumothorax, occur in as much as 25% of patients (6,7). CT-FNA is preferred for PPL located close to the chest wall, in the absence of surrounding emphysema (which increases the risk of pneumothorax), and when the needle does not have to traverse a fissure. There is no study directly comparing the 2 techniques. The modality to be chosen must be individualized according to patient factors and lesion characteristics.





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Current Pharmacological Treatment of COVID-19

PHARMACEUTICAL

SPH Pharmacy Department

The rapidly evolving pandemic of COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first found in December 2019 in Wuhan, China. By April 2020, COVID-19 has spread globally and almost every country has confirmed cases. Up until now, there is limited evidence from randomized controlled trials to recommend any specific pharmacological treatment for COVID-19. World Health Organization (WHO) has issued an interim guidance and updated it in March 2020. It covers the clinical management of COVID-19, including issues on symptomatic treatment, supportive care, treatment of co-infections and management of septic shock¹. This article discusses the pharmacological agents that are currently used for the treatment of COVID-19 worldwide (as of 22 April 2020).

Use of Investigational Pharmacological Therapy

In Hong Kong, the Hospital Authority (HA) has issued an interim recommendation on the clinical management of COVID-19 in adult patients in February 2020². For confirmed cases, the following therapy can be considered:

Oral lopinavir/ ritonavir 400mg/100mg twice daily for 14 days

+/- Oral ribavirin 400mg twice daily for 14 days

+/- Subcutaneous interferon beta-1b 0.25mg every alternate day for 3 doses

The above regimen is determined based on evidence extrapolated from research performed for other coronaviruses, expert opinion, and the availability of therapeutic options in Hong Kong.

Lopinavir/ Ritonavir

Lopinavir/ ritonavir inhibits coronavirus replication as protease inhibitor. Although it is considered as the "backbone" of the therapy in the HA guideline, a recent clinical trial in China has shown the use of such combination of antiviral drugs has little to no role in the treatment of COVID-19³. In the randomized, controlled, open-labeled trial involving 199 hospitalized adults with severe COVID-19, 99 patients were given oral lopinavir/ ritonavir 400mg/100mg twice daily in addition to standard care with 100 patients received standard care alone. There was no difference in the time to clinical improvement in the two groups (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.9 to 1.72), and mortality at 28 days (19.2% in lopinavir/ ritonavir group vs 25% in standard care group; 95% CI, –17.3 to 5.7). It was also found that the lopinavir/ ritonavir group experienced more gastrointestinal side effects, but serious adverse events were more common in the standard care group. However, the trial was considered as underpowered by Centers for Disease Control and Prevention (CDC), and lopinavir/ ritonavir is currently undergoing investigation in various studies^{4,5}.

Ribavirin and Interferon

Ribavirin targets viral RNA synthesis, inhibits viral RNA polymerase activities and guanosine triphosphate synthesis; it is also suggested ribavirin exerts an indirect immunomodulatory effect rather than its antiviral activity in the role against coronavirus as seen in mice. Interferons bind to cellular surface receptors and initiate the JAK-STAT signaling cascades and exert immunomodulatory effects. A synergistic effect is observed when interferon is given in combination with ribavirin. Addition of

ribavirin and/or interferon to lopinavir/ ritonavir has been used in Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), however, both ribavirin and interferon have no published clinical efficacy data in the role of COVID-19 and are currently included in the phase 2, randomized, open-labeled clinical trial with lopinavir/ ritonavir for the treatment of COVID-19 initiated by the University of Hong Kong⁵.

Remdesivir

Remdesivir is an investigational intravenous nucleotide analog with a broad spectrum of antiviral activity. Through the premature termination of RNA transcription, it inhibits viral replication and has in-vitro activity against SARS-CoV-2 and in-vivo activity against related betacoronaviruses found in MERS and SARS⁴. Remdesivir has not been approved to be used anywhere globally and there is no established safety or efficacy data for the treatment of any condition. A recent interventional study with patients enrolled worldwide was carried out via compassionate-use basis in hospitalized COVID-19 patients who had an oxygen saturation of 94% or less. Data from 53 patients who received at least one dose of remdesivir was analyzed. Clinical improvement in oxygen support status was observed in 36 of 53 patients (68%)⁶. Currently other clinical trials are being conducted worldwide to evaluate the safety and efficacy of remdesivir in COVID-19⁷. In Hong Kong, two clinical trials are being initiated by Gilead, the manufacturer of remdesivir, to evaluate the efficacy of remdesivir in moderate and severe patients of COVID-19⁵.

Hydroxychloroquine/ Chloroquine

Both hydroxychloroquine and chloroquine, drugs that are used for malaria or some other rheumatology conditions, are considered as one of the options in the treatment and/or prevention of COVID-19, which was highlighted by US president Donald Trump in March 2020. He touted hydroxychloroquine as a "game-changer" in the fight of COVID-19. The exact mechanism of hydroxychloroquine or chloroquine as an antiviral is unclear, but it is known to reduce acidity in endosomes, which might then prevent the endosomes from releasing the virus into the cytoplasm. Hydroxychloroquine or chloroquine can also inhibit glycosylation, inhibit angiotensin-converting enzyme 2 (ACE2) receptor and prevent SARS-CoV-2 from binding to the target cells. It is also shown to inhibit replication and spread of virus in vitro. To date, there is insufficient clinical data to support the safety and efficacy of using hydroxychloroquine or chloroquine in the treatment and/or prophylaxis of COVID-19. Four anecdotal trials were conducted in China and France, which seemed to have suggested positive results. However, all the trials involved very limited number of patients in open-labeled studies; unclear baseline severity of disease in each arm; and recruitment of patients with only mild to moderate symptoms or even asymptomatic carriers. Large clinical trials are underway in various countries to generate robust data for establishing the dosing, efficacy and safety of hydroxychloroquine/ chloroquine for COVID-19⁵. Some clinicians believe it is reasonable to give hydroxychloroguine/ chloroguine in patients who cannot tolerate other treatment options. However, it has to be reminded of the possibility of drug toxicity (e.g. QT prolongation and retinal toxicity). With the limited supply of hydroxychloroquine/ chloroquine globally, their use should be restricted to licensed indications unless it is given in a controlled environment for the treatment of severely ill patients in a hospital setting or when more evidence is established for use in COVID-19^{4, 8-13}. In Hong Kong, there is currently no on-going clinical trial which involves hydroxychloroquine/ chloroquine for the treatment or prophylaxis of COVID-19.

Use of Other Supportive Pharmacological Treatments

Apart from the investigational drugs mentioned above, there has been much debate on the role of corticosteroids, tocilizumab and azithromycin as supportive drug treatments of COVID-19.

Corticosteroids have been widely used during the outbreaks of SARS and MERS due to its anti-inflammatory properties. However, it is also suggested that the use of corticosteroids can inhibit immune responses and delay viral clearance. The use of long term and high-dose corticosteroids is associated with adverse effects such as osteoporosis, psychosis and diabetes. WHO and various international guidelines do not recommend the routine use of corticosteroid in COVID-19, unless the benefits outweigh the risks of treatment, for instance, the short term use of corticosteroids in septic shock⁵.

Tocilizumab is a recombinant humanized monoclonal antibody specific to interleukin-6 (IL-6), a cytokine which has been observed to be elevated in severely ill COVID-19 patients. The release of a large amount of IL-6 can trigger the cytokine storm and result in acute respiratory distress and even fatality. Tocilizumab is therefore hypothesized to have a beneficial role in the

COVID-19 treatment although the role of IL-6 in mediating of cytokine storm associated with COVID-19 has not been established yet. Currently there is no recommendation on the use of tocilizumab in COVID-19 by WHO or other national health authorities. Nonetheless, it is being used in China for patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in a laboratory setting⁵.

Azithromycin is a macrolide antibiotic which has a broad spectrum of antibacterial activity and is used in various types of infection. Currently there is no published information regarding the use of azithromycin in COVID-19, but it has been shown that azithromycin has immunomodulatory and anti-inflammatory properties as it is reported to reduce neutrophilic inflammation, interleukin-1beta and interleuklin-8. It is also noticed that the combination of hydroxychloroquine and azithromycin might have a synergistic effect in vitro on SARS-CoV-2. However, clinical trials on using such combination of drugs in the treatment of COVID-19 have conflicting results. There is insufficient data to support the clinical benefits on using azithromycin and hydroxychloroquine unless confirmation is obtained from randomized controlled trials with larger sample size⁵.



Figure 1. SARS-CoV-2 Viral Lifecycle and Potential Targets for Drug Therapies¹⁴

Myth and Fact of Pharmacological Treatment of COVID-19

Myth: Use of ibuprofen (or other Non-Steroidal Anti-Inflammatory Drugs, NSAIDs) can worsen COVID-19 infection.

Background: A statement from Olivier Véran, French Health Minister, was issued on Twitter which warned COVID-19 patients to avoid taking anti-inflammatory drugs such as ibuprofen as it could aggravate the COVID-19 infection¹⁵. His concern was based on a letter published in the Lancet on 11 March 2020, which hypothesized that SARS-CoV-2 binds to ACE2 receptor expressed by epithelial cells of the lung, intestine, kidney and blood vessels to infect cells. ACE2 level is induced by ibuprofen thus could make the virus spread faster¹⁶.

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Fact: Currently there is no scientific evidence to support the association of the use of ibuprofen (or other NSAIDs) and more severe infection with COVID-19. More studies are being conducted worldwide to further elucidate such a link. Meanwhile, if symptomatic treatment of COVID-19 infection is needed, healthcare professionals should consider the risks and benefits of the available treatment options on a case-by-case basis. Paracetamol can be considered as the first-line treatment for pain or fever. Patients who are already on NSAIDs (such as ibuprofen and aspirin) for the management of chronic conditions should NOT self-discontinue the treatment unless advised by the doctors¹⁵⁻²³.

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Hello, I'm Anthony. It is my great pleasure to join the St. Paul's family. My major milestones of my career coincidentally occurred in the difficult times in Hong Kong - I graduated from the Chinese University of Hong Kong and worked as an intern during the SARS outbreak, while I begin my new career at the St. Paul's Hospital during the COVID-19 outbreak. But, as Albert Einstein once said: "in the middle of difficulty, lies opportunity." I completed my pathology training at Prince of Wales Hospital and underwent my subspecialty training in the Newcastle University. I worked at Prince of Wales Hospital all along and joined the Chinese University of Hong Kong as a clinical academic in 2015. I subspecialize in gastrointestinal and liver pathologies, and collaborate closely with physicians, surgeons, and oncologists in both clinical services and research activities. Through various collaborations, I fully understand that communication is the key to success in providing good diagnostic services and fruitful research outputs. Although you usually "communicate" with me through my written pathology reports, you are more than welcome to give me a call to discuss challenging and difficult situations. I look forward to working with everyone in the St. Paul's family!



Dr. CHAN Wing Hung, Anthony Staff Consultant Pathologist



HAND HYGIENE AWARENESS DAY 2020

Awards to staff for their excellence in hand hygiene

Highest Compliance



Greatest Improvement





An angiographic photo showing the new device alongside the patient's own old device in the heart



Successful TAVI operation on a high risk patient

Mailing Option & Personal Contact Details Update

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選民須知 Notes to electors

- 臨時選民登記冊及取消登記名單已於6月1日發表。 The Provisional Registers of Electors and Omissions Lists were released on June 1.
- 選民可登入選民資料網上查閱系統 (www.voterinfo.gov.hk),查閱自己的登記資料是否正確。如有疑問,請於6月25日或 之前通知選舉事務處。 Electors can log in to the Online Voter Information Enquiry System (www.voterinfo.gov.hk) to check if their
 - registered particulars are correct. For enquiries, please contact the Registration and Electoral Office by June 25.
- 被納入取消登記名單的選民會收到提示信, 謹記於6月25日或之前按信上的指示, 確認或更新登記住址, 以保留 其選民登記。
 - Electors on the Omissions Lists will receive a reminding letter requesting them to confirm or update their registered addresses. They should respond by June 25 according to the letter's instructions so that they can maintain their registration status.









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