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THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.26 NO.1 January 2021

COVID-19

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

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Lecture 2: Mapping Nutrition to Child Cognitive Development and Learning

Prof. Sean DEONI (USA)

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The Cover Shot

Plum blossom has been depicted in the traditional Chinese artistic motif as a symbol of endurance, resilience, and diligence in the face of hardship for centuries. It is one of the few plants which bloom in the face of cold, harsh winter. Each petal symbolizes one of the five blessings: longevity, prosperity, health, honour, and good living.

May these flowers bloom miraculously against the barren winter landscape, and give people hope in the new year. May the pandemic due to COVID-19 viruses vanish speedily.

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Published by
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Editorial

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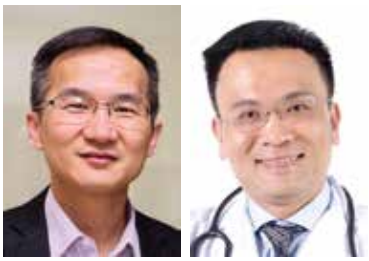

Dr Owen Tak-yin TSANG Dr Andrew Tin-yau WONG

Humankind is right now experiencing the worst pandemic in more than 100 years with over 1.5 million deaths as of early December 2020. While the global scientific community is earnestly looking for new treatments and effective vaccines, the vast amount of research on various aspects of COVID-19 in just 12 months has been phenomenal. Be that as it may, there remain lots of unknowns up till now in areas from immunology to genetics associated with the infection.

When we were invited by the Editorial Board of the Hong Kong Medical Diary to be guest editors for this commemorative anniversary issue on COVID-19, we agreed without hesitation and came up with a list of hot topics that have been frequently asked. We are indeed privileged to have a panel of experts from various disciplines to share their areas of expertise in this issue. Dr Kelvin To has written an excellent article on the various immunological aspects of the virus. These would carry important implications for herd immunity and, to a certain extent, vaccine development. Professor Ivan Hung compared the clinical presentations of two reinfected cases respectively reported in Hong Kong and the U.S.A. and discussed the clinical implications. As for diagnostics, Dr David Lung has provided an up-to-date review of the use of saliva in the diagnosis of COVID-19. Hong Kong has done exceptionally well in term of mortality figures when compared to other developed countries. Dr Kenny KC Chan has come up with a comprehensive review of the current management of COVID-19 patients in the intensive care units in public hospitals in Hong Kong. From the public health perspective, Dr Dennis Ip and Prof Benjamin Cowling have successfully used simple terms to explain a much heard-of term for the past year, the basic reproduction number, in relation to the current pandemic. Finally, for the much awaited vaccines, Dr Gilbert T Chua and Professor Yu-lung Lau have done an extensively researched review on vaccines on the horizon.

For the lifestyle section, Dr Peter Gruenewald, a doctor working in the U.K., has kindly shared, in his resourceful article, ways to enhance resilience during this time of high stress. Dr Gruenewald was initially was scheduled to contribute this article for the August 2020 issue. However, he came down with COVID-19, and fortunately, he recovered and agreed to contribute his article for this issue.

Both of us would like to express our sincere appreciation to all the contributing authors for their precious time and great effort. We would like to thank Prof Richard Yu, who has contributed a fabulous cover photo with a meaningful caption. Last but not least, we would like to thank the editorial team of FMSHK for assembling this memorable issue on COVID-19 in such a short time! We hope you will enjoy reading this issue and we much welcome your precious feedback. We wish your new year be filled with excellent health and great success.


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regimen
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Efficacy regardless of baseline viral load[2]
Significantly fewer neuropsychiatric adverse events vs. comparator in three pre-specified categories[2,#]
Convenient dosing[1]
Dizziness, Sleep disorders/disturbances and Altered sensorium
MSD

COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come

Prof Ivan Fan-ngai HUNG

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Prof Ivan Fan-ngai HUNG

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 January 2021.

INTRODUCTION

As of 1st December 2020, COVID-19 pandemic has affected over 66 million patients, with more than 1.5 million deaths in 191 countries[1]. Similar to other respiratory infections, COVID-19 reinfection should happen when neutralising antibodies decline one to two months after the acute infection[2,3]. In August 2020, we reported the world's first COVID-19 reinfection by a phylogenetic distinct SARS-coronavirus-2 (SARS-CoV-2) strain confirmed by whole genome sequencing[4]. Subsequently, another case of SARS-CoV-2 reinfection was reported in Nevada, U.S.A.[5]. Despite the involvement of a young healthy male patient in both cases, the outcome was very different. Here we compare the presentation of the two cases of COVID-19 reinfection and the implications.

THE PATIENT FROM HONG KONG

The patient was a 33-year-old Caucasian male residing in Hong Kong[4]. He enjoyed good past health. His first COVID-19 infection took place in March 2020 when he presented with cough and sputum, sore throat, fever and headache for three days. He was confirmed to have positive SARS-CoV-2 RT-PCR assay on his oropharyngeal saliva. He was hospitalised for 16 days, during which he remained asymptomatic. The patient was discharged following two negative SARS-CoV-2 RT-PCR assays on nasopharyngeal and throat swabs taken 24 hours apart.

During the second episode, the patient returned to Hong Kong from Spain via the United Kingdom and was tested positive by SARS-CoV-2 RT-PCR on the oropharyngeal saliva taken during screening at the Hong Kong airport in August 2020. Nevertheless, he remained asymptomatic all along. He was afebrile and his SpO_2 was 98% on room air. Physical examination was unremarkable. Cycle threshold (Ct) value of oropharyngeal saliva was 26.69 upon quarantine at the community hospital. Chest radiograph did not reveal any abnormalities. No antiviral treatment was given to the patient. The serum collected upon hospitalisation for the second episode was negative for IgG against SARS-CoV-2 nucleocapsid protein. Subsequent serum specimen collected was tested positive with high neutralising antibody and high avidity IgG within eight days after hospitalisation[6].

Whole genome sequencing was performed from oropharyngeal saliva specimens collected during the first episode in March and during the second episode in August[4]. Genomic analysis showed that the first viral genome belongs to a clade/lineage different from the second viral genome. The first viral genome belongs to GISAID clade V, Nextstrain clade 19A, and Pangolin lineage B.2 with a probability of 0.99. The second viral genome belongs to GISAID clade G, Nextstrain clade 20A, and Pangolin lineage B.1.79 with a probability of 0.70. The two genomes differ by 24 nucleotides, in which 14 were non-synonymous mutations resulting in amino acid changes. The difference in the amino acids between the two genomes are located in the spike protein (at the N-terminal domain, subdomain two and upstream helix), membrane protein, nucleocapsid protein, non-structural proteins (NSP3, NSP5, NSP6, NSP12), and accessory proteins (ORF3a, ORF8 and ORF10). Blast search revealed that the first viral genome was most closely related to strains from the U.S.A. or England collected in March and April 2020. The second viral genome was most closely related to strains from Switzerland and England collected in July and August 2020.

THE PATIENT FROM WASHOE COUNTY, NEVADA, USA

The patient was a 25-year-old Caucasian male residing in Washoe County, Nevada, U.S.A.[5]. He also enjoyed good past health. He was first diagnosed to have COVID-19 in late March 2020. He developed upper respiratory tract symptoms of sore throat, cough and headache, with gastrointestinal manifestations as well, including nausea and diarrhoea. The patient undertook isolation at home, and all symptoms resolved after one month in late April. However, in late May, his symptoms returned with fever, headache, dizziness, cough, nausea and diarrhoea. His condition further deteriorated and was found to be hypoxemic, requiring hospitalisation and oxygen support. Chest radiography confirmed viral pneumonia with patchy, bilateral, interstitial opacities. The patient's IgG and IgM against SARS-CoV-2 were tested positive.

Comparing the two nasopharyngeal specimens positive for SARS-CoV-2 taken 48 days apart[5], both specimens belonged to the clade 20C with the five hallmark single nucleotide variants (SNVs) (3037C-T, 14408C-T, 23403A-G, 1059C-T and 25563G-T). The first specimen had five

further SNVs compared with the reference genome. The second specimen had six additional SNVs and a mutation at position 14,407, adjacent to the SNV 14408C-T. Six SNVs were shared between the first and second specimens. The first specimen had four additional SNVs not seen in the second specimen, whereas the second specimen had seven SNVs not seen in the first specimen. These pieces of evidence suggested that the patient had a reinfection of COVID-19.

DISCUSSION

Despite both cases being proven COVID-19 reinfection, the presentation of the second episode in the two patients was very different. The first patient reported from Hong Kong showed a much milder presentation at the second time, and the patient remained asymptomatic during the second episode. During SARS-CoV-2 infection, neutralising antibody develops in most patients. In the Hong Kong patient, although anti-SARS-CoV-2 antibody was not detected initially during the second episode, the low residual titre of antibody might have partially controlled the virus. Since neutralising antibodies target the spike protein[2], variations in the spike protein may render the virus less susceptible to neutralising antibodies which had been induced during the first infection. Further serological studies are required to determine whether these amino acid differences in the spike protein of the SARS-CoV-2 strains between the first and second infection are responsible for the reinfection[7]. During the second episode, IgG against SARS-CoV-2 was not detected until 5 days after hospitalisation. One possibility is that he did not mount an antibody response after the first infection. Previous studies have shown that antibody response was not detected in some patients until 2-3 weeks after onset of symptoms. Another possibility is that he indeed mounted an antibody response after the first infection, but the antibody titre decreased below the detection limit of the assays. This waning of the antibody level has been well described. In one study, 33% of recovered COVID-19 patients were negative for neutralising antibodies during the convalescent phase (average 39 days after symptom onset)[3]. Another study showed that 40% of asymptomatic individuals are seronegative within eight weeks after the onset of symptoms[2]. Another implication of the rapid decline in antibody titers is that seroprevalence studies may underestimate the true prevalence of the infection.

In contrast, the second patient reported from the U.S. showed increased severity in his second infection, with radiographic evidence of pneumonia and requiring oxygen support. This phenomenon could be explained by a higher dose of virus or a more virulent virus acquired during the second time. A more likely explanation would be caused by the immune response of antibody-dependent enhancement[8], by which specific Fc-bearing immune cells become infected with virus binding to specific antibodies. The important difference between the first and the second patient was that the first patient acquired the second infection five months apart, by which time the patient's IgG and neutralising antibody against SARS-CoV-2 were undetectable. In contrast, the second patient acquired the second infection only two months later. Although the IgG titre was not measured during the first infection, it was likely that the patient still had a high level of positive IgG against SARS-CoV-2 developed during the first infection and hence resulting in the antibody-dependent enhancement which was manifested as pneumonia and worsened symptoms compared to the first episode.

Despite the difference in the clinical outcome of the two patients, the reinfection carries several important implications. First, it is unlikely that herd immunity can eliminate SARS-CoV-2[9]. IgG antibody will start to fall after a few months, and SARS-CoV-2 will continue to mutate. COVID-19 will likely continue to circulate in the human population similar to influenza virus and other human coronaviruses. Secondly, it is highly unlikely that COVID-19 vaccines will provide lifelong protection; repeated, possibly annual vaccination similar to influenza vaccination will be required to boost the immunity. The viral antigens of the COVID-19 might also be changing every year according to the 'antigenic drift' theory. Patients who have developed antibodies against COVID-19 via natural infection will also need to be vaccinated. Further studies on the immunological response after reinfection will be vital for the research and development of a more effective vaccine.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come" by Prof Ivan Fan-ngai HUNG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 January 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **As of 1st December 2020, COVID-19 pandemic has resulted in more than 1.5 million deaths.**
2. **Reinfection of COVID-19 has to be confirmed by whole genome sequencing of the comparing samples.**
3. **Reinfection of COVID-19 always results in mild symptoms in the second episodes.**
4. **The patient with reinfection from Hong Kong was symptomatic during the second episodes.**
5. **The patient from Hong Kong acquired the infection locally for both episodes.**
6. **There were 24 nucleotides differences between the first and second SARS-CoV-2 isolated from the oropharyngeal saliva samples.**
7. **The patient from US had more severe symptoms during the second episode of COVID-19 infection.**
8. **The patient from US failed to develop IgG antibody against SARS-CoV-2 during the second episode of COVID-19 infection.**
9. **The rapid decline in COVID-19 antibody for the first patient from Hong Kong might have led to reinfection.**
10. **The worsened symptoms during the second episode in the US patient could be related to the immune response of antibody-dependent enhancement.**

ANSWER SHEET FOR JANUARY 2021

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

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Answers to December 2020 Issue

LUTS Management in Primary Care – Alerts & Advice

1. T 2. F 3. T 4. T 5. F 6. T 7. F 8. T 9. T 10. T

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In Hong Kong, the product is conditionally approved with very limited safety, efficacy, and quality data for public health emergency to satisfy local unmet medical need and the registration status is subjected to be reviewed by the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee. The product can only be supplied to designated institutions.

ECMO=extracorporeal membrane oxygenation. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Reference: 1. VEKLURY Hong Kong Prescribing Information (version: RDV-MAY20 v1.0).

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Immunological Response of SARS-CoV-2 Infection

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Dr Kelvin Kai-wang TO

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) pandemic has devastated the world in 2020. The number of COVID-19 cases has surpassed 62 millions, with over 1.4 million deaths as of 30th November, 2020. COVID-19 has also led to severe disruption in the socioeconomic activity. The World Bank has forecasted a 5.2% reduction in global GDP in 2020[1].

COVID-19 is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified during a pneumonia outbreak in Wuhan in December 2019. Epidemiological studies showed that SARS-CoV-2 infection has a lower case-fatality rate than that of 2003 SARS-CoV, but can transmit much more efficiently between humans[2]. Seroprevalence studies showed that neutralising antibody against SARS-CoV-2 are not found in blood specimens collected before 2020 in Hong Kong[3].

Understanding the immune response for COVID-19 is important for clinical practice. First, the correct interpretation of serology results requires a good understanding of the antibody kinetics during infection. Second, although SARS-CoV-2 can infect different organs and can directly cause tissue damage, many complications of COVID-19 are related to the dysregulated inflammatory response or immune-mediated damage. Third, understanding the immune correlates of protection is critical for risk assessment and for determining the immunogenicity of vaccines.

CYTOKINE AND CHEMOKINE RESPONSE

Similar to other infections, SARS-CoV-2 infection is accompanied by elevated levels of cytokine and chemokines. Studies have shown that the cytokine/chemokine pattern in patients with critical illness is distinct from those with moderate disease severity [4]. Critically ill patients (those who died, required mechanical ventilation or ICU admission) had increased levels of all types of cytokines, including those from type 1 (against virus or intracellular bacteria, such as IFN-γ), type 2 (allergic or anti-helminth immunity, such as IL-5) and type 3 (against fungi or extracellular bacteria, such as IL-17) immunity. Critically ill patients also demonstrated persistently elevated levels of cytokines, while those with less severe disease demonstrated a progressive reduction in cytokine levels after day ten post-symptom onset.

Although the cytokine and chemokine levels are elevated among COVID-19 patients, the level is much lower than in other inflammatory conditions. A meta-analysis showed that the level of IL-6 is much lower among COVID-19 patients than patients with cytokine release syndrome, sepsis or acute respiratory syndrome unrelated to COVID-19[5]. This observation is important and suggests that the use of different cytokine inhibitors should be carefully evaluated.

ANTIBODY RESPONSE (HUMORAL IMMUNITY)

How Long Does it Take for Antibodies to Develop After Infection?

During the first week of symptom onset, only <50% of COVID-19 patients have detectable anti-SARS-CoV-2 antibody. The seropositive rate increases to over 95% two weeks after symptom onset[6,7]. Although some studies showed that IgM seroconversion is earlier than IgG, others showed similar timing in seroconversion[7,8]. Hence, antibody testing is not recommended for the diagnosis of COVID-19 during the acute phase of the illness, but it is useful to document infections in a retrospective manner during the convalescent phase of the illness.

What are the Different Types of Antibody Assays?

Antibodies against specific viral proteins can be measured using enzyme immunoassays, flow-cytometry based assays, or lateral flow assays. The advantage of these assays is that these can be performed in most clinical laboratories, or even at the point of care. But the disadvantage is that these methods cannot differentiate between antibodies that can protect cells from infection and those that merely bind to the viral proteins without neutralising effect.

On the other hand, neutralisation assays measure the antibodies that can protect cells from SARS-CoV-2 infection. Hence neutralisation assays are considered to be the gold standard for determining protective antibody response[9]. However, neutralisation assays are technically demanding, and neutralisation assays with live virus require biosafety level 3 facilities.

Studies have shown that serum collected before the COVID-19 pandemic contains antibodies against

different SARS-CoV-2 proteins due to the cross reaction with proteins from other human coronaviruses, including 229E, OC43, HKU1 and NL63[10]. However, antibodies against the surface spike protein and nucleocapsid protein are mainly found in COVID-19 patients[10]. Hence, current antibody assays usually target the spike protein (either the entire spike protein, or only the receptor binding domain [RBD]) or the nucleocapsid protein. Furthermore, antibodies against the ORF8 and ORF3b are also detected at higher levels among COVID-19 patients than controls[11,12], but their roles in antibody testing require further evaluation.

What is the Duration of Antibody Response?

There is conflicting data regarding the duration of antibody response among recovered COVID-19 patients. While some studies showed a rapid decline in antibody titers[13-16], others showed sustained antibody response for a few months[17,18]. IgA and IgM decrease more rapidly than IgG[19]. The rapid decline in antibody levels in some patients may be due to the defective T follicular cell differentiation and the lack of germinal centre formation in the lymph nodes[20].

Understanding the longevity of antibody response is important for several reasons. First, a rapid decline in antibody response may render recovered COVID-19 patients to be susceptible to reinfection. This was documented in our previous patient with reinfection, for whom neutralising antibody was not detected at the beginning of the second episode[21,22]. Second, if vaccine-induced antibody response is short-lasting, vaccination will need to be repeated. Third, seroprevalence studies are widely used to estimate the true burden of COVID-19 infection. If many recovered patients are seronegative due to antibody decay, the estimation of the burden of disease would be falsely low.

What are the Factors Associated with Antibody Response?

Several factors affect the antibody response. Patients with severe disease have a higher antibody response, while mildly symptomatic or asymptomatic patients have the poorest antibody response[16,23,24]. Disease severity is also a major factor associated with the duration of antibody detection. In one study, 40% of asymptomatic patients become seronegative during the early convalescent phase [25].

Age also plays an important role in the antibody response. Adults have been shown to have higher neutralising antibody titer than children[26]. One study showed that adult patients generate antibodies against both nucleocapsid protein and spike proteins, while pediatric patients generate much weaker antibody response against the nucleocapsid protein than the spike protein[27].

Symptom duration correlates with the sustainability of antibody titers. Those who recover more quickly are more likely to have sustainable titers of antibodies, while who takes longer to recover is more likely to have decline in antibody level[16].

Does Antibody Titre Correlate with Protection?

It is generally believed that a higher antibody titre correlates with protection. During an outbreak involving a fishing vessel, three members with pre-existing neutralising antibody were not infected, while 88% of people without pre-existing neutralising antibody were infected[28].

The S protein receptor binding domain (RBD) is responsible for binding to the host cell surface receptor. Hence, antibodies against the spike protein are considered to be most important for protection. Antibody against the spike protein RBD correlates well with neutralising antibody titre[29]. Although the N terminal domain (NTD) of the spike protein does not bind to the host cell receptor, monoclonal antibodies against NTD have also been found to have neutralising activity[30]. Monoclonal antibodies against either the RBD or NTD have been shown to be protective in animal studies[30].

Will Antibody-based Treatment Work?

Monoclonal antibody therapy is a promising treatment strategy. Several studies showed that monoclonal antibodies targeting the surface spike protein of SARS-CoV-2 reduce viral load and improve outcomes in animal models[30,31]. A phase 2 clinical trial showed that fewer out-patients treated with monoclonal antibody LY-CoV555 required hospitalisation or visited the emergency department than those treated with placebo[32].

One potential problem with monoclonal antibody therapy is the emergence of escape mutants. Mutations in the RBD and NTD of the spike protein have been shown to confer resistance to monoclonal antibodies[33]. Recently, in a patient with severe disease, we have identified the emergence of a mutation located at the epitope of the target of a monoclonal neutralising antibody[34]. Therefore, several groups have used a cocktail of antibodies for treatment[31].

Autoantibodies

In addition to antibodies against SARS-CoV-2, autoantibodies are also found in many COVID-19 patients, and some autoantibodies have been found to be associated with disease severity. Higher titres of antiphospholipid autoantibodies are associated with more severe respiratory disease[35]. Autoantibodies are also believed to play a role in pediatric multisystem inflammatory syndrome (PIMS) (also known as multisystem inflammatory syndrome in children [MIS-C])[36].

T CELL IMMUNITY

T cell immunity is identified among patients without prior SARS-CoV-2 infection. CD4+ T cells against SARS-CoV-2 epitopes can be identified in 20-60% of healthy blood donors[37-39]. After infection, T cell immunity is induced. However, by the end of the second week

after symptom onset, only about 50% and 25% of patients develop T cell response against nucleocapsid protein and RBD, respectively[40]. Furthermore, there is functional impairment of both CD4 and CD8 T cell subsets during the acute phase[40].

SARS-CoV-2-reactive CD4+ T cells can be found in almost all recovered COVID-19 patients, including those who were asymptomatic or mildly symptomatic[38,41]. The duration of T cell immunity appears to be long-lasting[42].

T cell response is associated with disease severity. A lower frequency of naïve CD8 or CD4 T cells are associated with more severe disease[4,43]. Patients with severe disease had robust CD4 T cell activation, while those with less severe disease had less CD4 T cell activation[44]. Mild disease is associated with a coordinated CD4 and CD8+ T cell response. However, the uncoordinated response was found in patients older than 65 years old[43].

OTHER IMMUNE CELLS AND COMPLEMENT ACTIVATION

During acute infection, the frequency of natural killer cells, monocytes, and dendritic cells are reduced[40]. The function of dendritic cell is impaired[40]. The complement pathways are triggered during infection, and are associated with lung injury. The triggering of the complement pathways has been associated with severe disease[45]. Patients with severe disease have higher levels of C5a. The anti-C5aR1 antibody has been shown to ameliorate lung damage in animal models.

DOES INTERFERON PLAY A ROLE IN IMMUNE RESPONSE AGAINST SARS-CoV-2?

Interferon is a key antiviral cytokine. Interferon β inhibits viral replication in airway cell lines[46]. SARS-CoV-2 suppresses interferon β response in order to replicate in host cells[46,47]. The importance of interferon during COVID-19 is well illustrated by patients having autoantibodies or genetic defects that affect the function of type I interferon. Autoantibodies against type I interferons are found in 10% of severe patients but not among asymptomatic or mildly symptomatic patients[48]. Genetic defects in the type I interferon-related pathways are also present at a higher frequency among severe cases than those with milder illness[49].

TREATMENT MODALITIES TARGETING THE IMMUNE SYSTEM

Several drugs targeting the host immune system have been evaluated in clinical trials. The most successful is steroid-based therapy. In a large randomised controlled trial in England, the incidence of death was significantly lower among severe patients receiving intravenous dexamethasone 6 mg once daily than those receiving usual care[50]. In a subsequent meta-analysis conducted by the World Health Organization, several corticosteroids have been shown to reduce mortality, including dexamethasone, hydrocortisone, and methylprednisolone[51].

Interferon β-1b, as part of a triple combination therapy with lopinavir-ritonavir and ribavirin, shortens the duration of symptoms in COVID-19 patients[52]. Inhaled nebulised interferon β-1a has also been shown to achieve faster recovery in a phase 2 randomised controlled trial[53]. However, intravenous interferon β-1a was not beneficial[54].

Tocilizumab is an anti-IL-6 receptor antibody. Early use of tocilizumab in the first two days of ICU admission was shown to reduce the risk of mortality[55]. However, no benefits were shown in two randomised controlled trials[56,57]. Anakinra, an IL-1 receptor antagonist, has been used in a case series of 8 patients with haemophagocytic lymphohistiocytosis and these patients showed improvement[58].

CONCLUSION

COVID-19 is a novel disease. Despite intensive research, there are still many unknowns on this disease. Further research on the immunology of COVID-19 will have a major impact on diagnostics, patient management and vaccine development.

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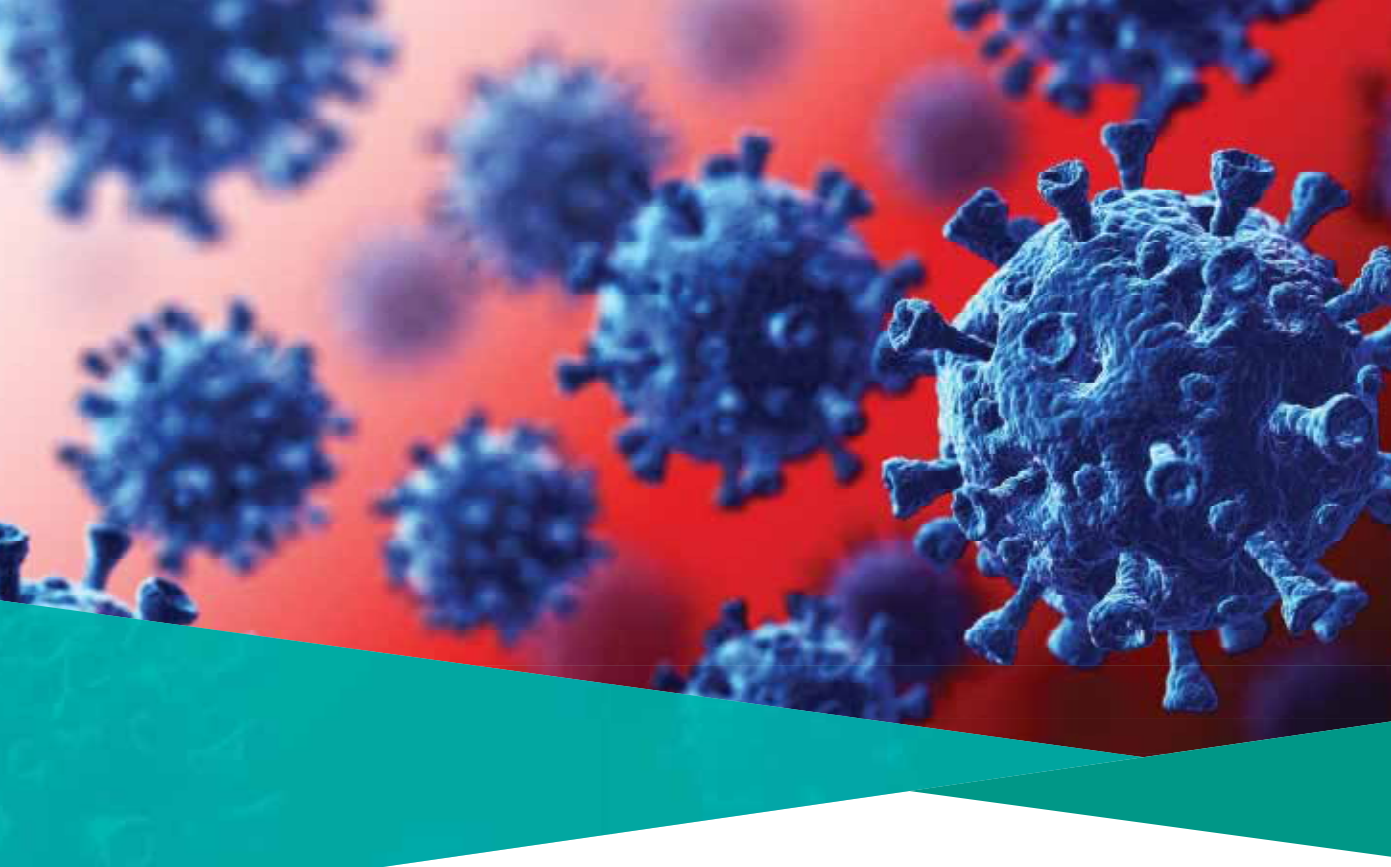


Simplify COVID-19 (SARS-CoV-2) testing

The BD Veritor™ Plus System
Rapid, reliable COVID-19 (SARS-CoV-2) testing at the point of care

The portable, easy-to-use BD Veritor™ Plus System provides reliable COVID-19 (SARS-CoV-2) results in 15 minutes

For use under Interim Order Authorization only

BD

Simplify COVID-19 Testing

The portable, easy-to-use BD Veritor™ Plus System provides reliable COVID-19 (SARS-CoV-2) results in 15 minutes.

Positive % Agreement (PPA)

BD Veritor System for Rapid Detection of SARS-CoV-2 with **84% PPA[1]**

Negative % Agreement (NPA)

BD Veritor System for Rapid Detection of SARS-CoV-2 with **100% NPA[1]**

Results in 15 minutes

*"How much **confidence** can I have in this result?"*

Negative Result −

98.2%[1] Probability that the negative result is **correct****

Positive Result +

>99%[1] Probability that the positive result is **correct*****

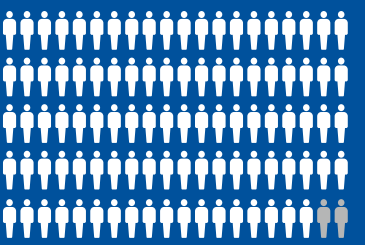
1.8% Probability that the negative result is incorrect

<1% Probability that the positive result is incorrect

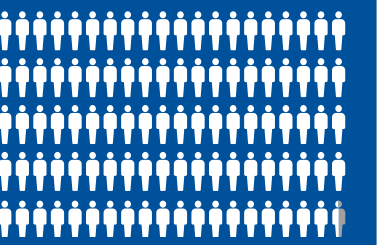
1,000 People tested (suspected of infection)†

100 People confirmed infected with SARS-CoV-2

10% Positivity rate*



Fewer than 2 of these people might receive a **false negative** result.



Fewer than 1 of these people might receive a **false positive** result.

† **The intended use of the BD Veritor System for Rapid Detection of SARS-CoV-2 assay only includes those who are suspected of COVID-19 by their health care provider within the first five days of the onset of symptoms.**

- This test has not been FDA cleared or approved;
- This test has been authorized by FDA under an EUA for use by authorized laboratories;
- This test has been authorized only for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens; and,
- This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

References: 1. BD Veritor System for Rapid Detection of SARS-CoV-2 package insert. Franklin Lakes, NJ: Becton, Dickinson and Company. * CDC, accessed July 21, 2020 @https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html. ** The negative predictive value is the probability that persons with a negative test result truly do not have the disease. *** The positive predictive value is the probability that persons with a positive test result truly have the disease.

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Current Status of COVID-19 Vaccine

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan, China in December 2019, rapidly spreading to 216 countries and territories and declared a pandemic by the World Health Organization (WHO) on March 11, 2020, with more than 60 million confirmed cases and 1.4 million deaths worldwide by the end of November 2020.[1] This SARS-CoV-2 is a perfect pandemic virus with higher reproduction number and case fatality rate than seasonal influenza virus, hence cannot be just treated as a "simple flu". Moreover, the incubation period is longer with infectivity begins days before symptoms onset and many cases are asymptomatic yet infectious resulting in difficulties in interrupting transmission.

There is currently no effective treatment, with only non-pharmacological strategies to control the spread of SARS-CoV-2 virus. However, measures such as social distancing, border restrictions, quarantine and isolation carry an enormous negative impact on health, economic, environmental and social changes.[2] The current hope to restore global norms is the development of an effective pandemic vaccine, compressing the usual development timeline from 10 – 15 years to 1 – 2 years by bypassing the conventional stepwise approach of vaccine development. Such compression of the timeline demands the development of multiple vaccine platforms and strategies simultaneously because there is so much uncertainty regarding vaccine efficacy and safety, demanding an approach as diverse as possible to increase the chance of success.

WHAT ARE THE CURRENT COVID-19 VACCINE CANDIDATES?

In less than 12 months since the identification of the SARS-CoV-2 virus, 44 vaccine candidates were undergoing clinical evaluation, and over 154 vaccine candidates in pre-clinical evaluation.[3] The speed of COVID-19 vaccine development is unprecedented, as compared to no suitable vaccine developed for MERS and SARS 6 years and 17 years after their first outbreaks, respectively. It usually takes more than a decade, and over USD 500 million investment in developing a vaccine, and up to 93% vaccine candidate tested in pre-clinical animal studies would not have been not able to be registered as a final product for clinical use.[4] Multiple vaccine production platforms for these COVID-19 vaccines are being pursued, and we have chosen one each from some of these platforms which provide leading vaccine candidates being tested in phase III. Table 1 summarises the different types of production platforms that were being applied in the development of COVID-19 vaccines.

1. Inactivated Vaccine – PiCoVacc

Developed by Sinovac (Beijing, China), it is an inactivated vaccine using the CN2 strain of SARS-CoV-2 virus, β-propiolactone to inactivate and alum as adjuvant. Pre-clinical studies have demonstrated that the vaccine could induce SARS-CoV-2-specific neutralising antibodies in mice, rats and non-human primates. Challenge study showed protection in vaccinated rhesus macaques in terms of a decline in viral load and in histopathological changes in the lungs, with no infection enhancement or immuno-pathological exacerbation observed.[5] This vaccine is currently undergoing phase III study involving 8,870 subjects and is estimated to be completed in October 2021.

2. Non-replicating Viral Vector Vaccine – University of Oxford/ AstraZeneca Vaccine (Cambridge, United Kingdom)

It is a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein. A phase I/II single-blind randomised controlled clinical trial conducted in the U.K. demonstrated that the vaccine induces both humoral and cellular immune responses, with homologous boosting which increased antibody responses. Local and systemic reactions were more common but were significantly reduced by prophylactic paracetamol.[6] A phase III clinical trial involving 30,000 subjects is ongoing, and is estimated to be completed in October 2022. Nevertheless, there was a six-day pause on trial for the investigation of an adverse reaction after a participant received the vaccine. Although there was no official release of information on the adverse reaction, some media outlet reported that the participant developed transverse myelitis after receiving the vaccine.[7] The trial was resumed after having been evaluated by an independent safety review committee. With regards to vaccine efficacy, 99% (208 out of 209) analysable participants had neutralising antibody responses 14 days after the booster dose, and T cell responses peaked at 14 days after a standard dose of the vaccine.[8] Latest update released by AstraZeneca on November 23, 2020 also

reported that vaccine efficacy of 90% could be achieved by giving half dose first followed by a full dose and was superior to the 62% efficacy of giving two full doses at least one month apart.[9] However, this preliminary result has been criticised, and another phase III clinical trial will be started to re-evaluate the efficacy.

3. Lipid Nano-particle Formulation with Nucleic Acid Vaccine – BNT162b1, BNT162b2 and mRNA-1273

Developed by BioNTech (Germany) and licensed to Fosun Pharma (Shanghai, China) with Pfizer (New York, USA), the two BNT vaccines are lipid nanoparticle–formulated, nucleoside-modified RNA vaccines encoding for either the trimerised SARS-CoV-2 receptor-binding domain (BNT162b1) or the membrane-anchored SARS-CoV-2 full-length spike protein (BNT162b2).[10,11] In principle, a lipid coat encases the nucleic acid segment coding for the viral antigen of interest so that it could enter the host cells. The viral nucleic acid, which will not be incorporated into the human genome, will then be translated to the viral protein and expressed on the host cells, which triggers the host's immune response. In a phase I/II clinical trial involving 195 healthy adults, both vaccines reported having mainly local injection site reactions, such as pain, redness and swelling, as well as mild systemic reactions such as fever. A lower incidence of adverse reactions was observed in older adults aged between 65 and 85. No severe systemic reactions have been reported. The two vaccine candidates were able to elicit dose-dependent SARS-CoV-2–neutralising antibody titres, peaked at 7 to 14 days after the second dose. Younger adults, aged between 18 and 55, generate higher antibody titres than older adults aged between 65 and 85. Nevertheless, all subjects had similar to or higher antibody titres than those of SARS-CoV-2 convalescent serum samples.[12] BNT162b1 and BNT162b2 are currently in Phase II and III studies, respectively involving approximately 30,000 subjects and are estimated to be completed in December 2022. Recent preliminary primary efficacy analysis report for BNT162b2 released from Pfizer and BioNTech demonstrated the vaccine is 95% effective against COVID-19 28 days after the first dose given to participants without prior COVID-19 infection across age, gender and ethnicity.[13]

mRNA-1273 is another RNA vaccine developed by Moderna (Massachusetts, USA) which also announced in November 2020 the first interim analysis of 95 participants in the phase III trial, the COVE study, co-conducted with the National Institute of Allergy and Infectious Diseases. Ninety and five of these participants who received placebo and the vaccine respectively contracted COVID-19, therefore a vaccine efficacy of 94.5%.[14]

4. Recombinant Protein Subunit (Trimeric) Vaccine with Adjuvant – NVX-CoV2373

Developed by Novavax (Maryland, USA), the NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine consisting of the trimeric full-length SARS-CoV-2 spike protein with a mutation at S1/S2 cleavage sites to stabilise the S2 subunit in a prefusion conformation, mixed with an adjuvant called Matrix-M1.[15] Animal study has demonstrated that NVX-CoV2373 with Matrix-M1 protected against SARS-CoV-2 challenge with no evidence of vaccine-associated enhanced respiratory disease.[16] In a phase I/II clinical trial, NVX-CoV2373 appeared to be safe, and was able to elicit immune responses that exceeded levels in convalescent serum from symptomatic COVID-19 patients.[15] Novavax has announced that a phase III clinical trial has been initiated in late September, targeting to recruit 10,000 healthy adults.

WHAT COULD WE EXPECT FROM THE CURRENT COVID-19 VACCINE CANDIDATES

The ideal COVID-19 vaccine should interrupt transmission so that we can resume life before the COVID-19 era. However, it will require a vaccine that could generate not only high titre of neutralising antibody in blood, but also long-lasting respiratory mucosal immunological memory. Studies in COVID-19 survivors have demonstrated that although all patients developed seroconversion,[17] their antibody titres can wane significantly as early as 1 – 2 months post-symptom onset.[18] Experience from SARS survivors in 2003 showed that there was a significant reduction in patients with detectable SARS-CoV IgG three years after infection,[19] and no memory B cell responses were detectable six years after infection,[20] suggesting that antibody responses to SARS-CoV wane significantly over time. On the contrary, memory T cell responses have been reported to have a significantly better longevity.[20] Therefore, the development of the ideal COVID-19 vaccine should not only be focused on the short-term development of neutralising IgG antibodies, but also whether long term effective T and B immunological memory could be generated. All the current vaccines do not offer data on the durability of the immune response beyond the immediate post-vaccination time points; hence the need for revaccination every year or so remains uncertain.

Alternatively, the vaccine given intranasally may generate adequate mucosal immunity to reduce transmission. Studies in animal coronaviruses, SARS-CoV and MERS-CoV have demonstrated that intranasal but not subcutaneous vaccination protected mice from human coronaviruses through airway memory CD4 T cell responses.[21] MERS vaccine animal studies have also shown that intranasally administered vaccines were superior over intramuscular ones in terms of neutralising efficacy.[22,23] Nevertheless, the current COVID-19 vaccines that have entered phase III clinical trials are all to be given parenterally. Currently, one intranasally administered vaccine candidate in the COVAX co-developed by the University of Hong Kong State Key Laboratory for Emerging Infectious Diseases, Xiamen University and Wantai Biopharmaceutical Company of Mainland China has been approved for non-phase III human clinical trial.[24]

The currently available phase III COVID-19 vaccine candidates, including those being mentioned above,

Table 1. Summary of different types of vaccine platforms (Excerpted from Jeyanathan M et al [26])

Vaccine Platforms	SARS-CoV-2 antigens	Neutralising Antibody	CD4 + T cells	CD8 + T cells	Phase III COVID-19 Vaccine Candidate
Inactivated virus	Multiple viral antigens	Strong induction	T_H1 or T_H2 response depending on adjuvant	Weak response	PiCoVacc
Non-replicating viral vector (ChAd)	S protein	Unimpeded as no pre-existing viral vector immunity	T_H1 response	Potent response	ChAdOx1 nCoV-19
m-RNA based vaccine	S protein or RBD (mRNA encapsulated in lipid nanoparticle)	Unimpeded as no pre-existing viral vector immunity	T_H1 or T_H2 response depending on adjuvant	Depends on the choice of adjuvant and formulation	BNT162b1 and BNT162b2 mRNA-1273
Protein subunit vaccine	S protein or RBD	Strong induction	T_H1 or T_H2 response depending on adjuvant	Weak response	NVX-CoV2373
Virus-like particle	Multiple viral antigens	Strong induction	T_H1 or T_H2 response depending on adjuvant	Weak response	Phase I in Canada

ChAd – chimpanzee adenovirus; RBD – receptor binding domain; S – spike

may only prevent the disease in individuals but not interrupting transmission, the latter requiring a high vaccine coverage rate of perhaps 70 – 80% of the global population. However, the next generation COVID-19 vaccines coming into phase III trials that could generate much higher neutralising antibodies titre and memory T cells at the mucosal level to stop viral replication in the nose within 1 – 2 days of infection may be able to reduce transmission more effectively.

OTHER VACCINATION STRATEGIES – CONCEPT OF THE TRAINED INNATE IMMUNE MEMORY

Innate immune memory is a recently recognised component of immunological memory induced by several live attenuated human vaccines, including the BCG vaccine. It mediates non-specific protective responses to heterologous infections in addition to pathogen-specific adaptive immune memory. Through transcriptional, epigenetic and metabolic reprogramming of myeloid progenitors in the bone marrow, the BCG vaccinated individuals demonstrated enhanced pro-inflammatory cytokines secretions from their monocytes when stimulated in-vitro by unrelated bacterial and fungal pathogens.[25] Studies have also explored whether BCG can offer a level of protection from COVID-19, in an attempt to explain why regions with universal BCG vaccination carry lower COVID-19 mortality.[26-28] More studies will be needed to confirm the hypothesis.

WHAT ARE THE POTENTIAL COMPLICATIONS OF VACCINATION AGAINST RESPIRATORY VIRUSES?

Safety of vaccination is of utmost importance. Apart from the extremely rare neurological adverse reactions such as Guillain Barre Syndrome with inactivated influenza vaccine, vaccine-associated enhancement of respiratory disease (VAERD) was observed in children during the development of whole-inactivated measles virus and respiratory syncytial virus (RSV) vaccines in the 1960's.[29,30] VAERD is an adverse immunological phenomenon observed in vaccinated subjects that leads to enhanced respiratory diseases after subsequent exposure to the virus. The pathophysiology could be either antibody-mediated, with the generation of non-neutralising antibodies leading to the immune-complex formation and complement deposition, or T_H2-biased (aka allergic inflammation) immune response resulting in an accentuated interleukin-4 (IL-4), IL-5 and IL-13 production.[30] Although VAERD has never been seen in any human and non-human coronavirus infections, in particular, SARS and Middle East Respiratory Syndrome (MERS),[31] animal models for SARS-CoV vaccine has shown the possibility of enhanced immunopathology.[32,33] The possibility of VAERD should, however, not delay efficacy trials as long as early trials demonstrated induction of neutralising antibodies and T_H1 response in human subjects, and the protection against virus replication as well as disease severity in non-human primates.

DISTRIBUTION OF THE VACCINE – THE ART OF THE SCIENCE

The three-staged goals of COVID-19 vaccination include (i) to maintain core community activities, (ii) to reduce disease severity, and (iii) to reduce transmission, all of which begin within each country and expand globally. Otherwise, safe international travel will not be possible. Apart from the development of a safe and effective COVID-19 vaccine, ensuring the vaccine being available to all people around the world is equally important in order to enable resumption of global travels and activities. Lower-income countries may not be able to afford these vaccines, and higher-income self-financing countries may not be able to secure adequate vaccine supplies through bilateral deals with manufacturers.

The United States Advisory Committee on Immunisation Practices (ACIP) endorsed five ethical principles targeting the development and phased implementation of recommendation for COVID-19 vaccine use. These ethical principles include maximising benefits and minimising harms, equity, justice, fairness and transparency.[34] The first phase entails the period of constrained supply, targeting to vaccinate healthcare personnel, including staff that work in the hospital, long-term-care facilities, pharmacies, etc. In the second phase, as the supply increases and a wider administration of vaccine becomes possible, coverage should include essential workers such as people working in borders, schools, law enforcement units, food industry, etc. In the third phase, as the vaccine supply further increases to meet the demand,

vaccination coverage would improve to cover high-risk individuals, including the elderly aged over 65 years old or those with co-morbidities. Children were not included in the initial phase for vaccination because of much milder diseases as well as the relative lack of paediatric subjects having been included in the current vaccine trials.[5] To interrupt transmission in the community, the whole population, including children, may need to be vaccinated ultimately.

A global collaboration, known as the Access to COVID-19 Tools (ACT) Accelerator, aimed to accelerate the development and production of, as well as to ensure equitable access to, COVID-19 tests, treatments, and vaccines. The COVAX was launched in April by the WHO, the European Commission and France in response to this pandemic, and is one of three pillars of the ACT Accelerator that focuses on vaccine development with the commitment to, upon successful vaccine development, provide innovative and equitable access to COVID-19 vaccines to every place across the globe regardless of their financial capabilities. The initial aim is to have 2 billion doses available by the end of 2021, which should be adequate to protect high risk and vulnerable people, as well as frontline healthcare workers.[35] Hong Kong has adopted a two-pronged approach to securing vaccines: buying directly from manufacturers and joining the global COVAX Facility. Furthermore, logistical challenges on the implementation and distribution of the vaccines shall be considered, since some vaccines discussed above demand -70°C storage and transport condition; the need to establish such ultra-low temperature cold chain will pose barriers for low-resource countries.

CONCLUSION

Thanks to the global efforts in combating the COVID-19 pandemic, an effective and safe COVID-19 vaccine might become available in 2021. Careful analysis of phase III clinical trial data will be needed to guide the government and our expert panel in choosing safe and effective vaccines for the people of Hong Kong. In addition to healthcare and essential workers, high-risk citizens should be prioritised for vaccination when the vaccine becomes available to the market as soon as a safe and efficacious vaccine is available. The uncertainty surrounding the availability and performance of these vaccines demands flexibility in the implementation of these policies.

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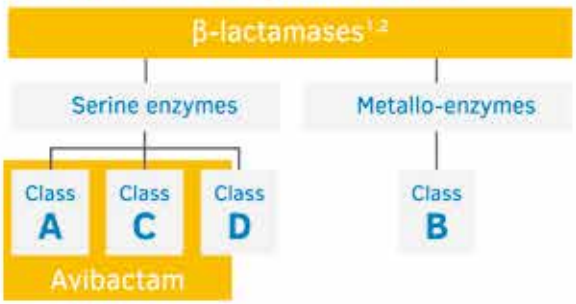

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References: 1. Zavicefta™ (Ceftazidime-avibactam) Prescribing Information. Pfizer Corporation Hong Kong Limited Version October 2018 **2.** Liscio JL, *et al. Int J Antimicrob Agents* 2015;46:266-71

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Intensive Care for COVID-19

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INTRODUCTION

The pandemic of COVID-19 begins at the end of December 2019. The first case was reported in Hong Kong on 22 January 2020, and by the end of October 2020, there were more than 5,300 confirmed cases. Although the majority of the COVID-19 patients had mild disease, a number of them developed a severe illness and required intensive care. Furthermore, the management of this novel disease has evolved rapidly along with ongoing research around the world. This article summarises the intensive care of COVID-19 patients in the context of Hong Kong, as at the time of this writing.

THE BURDEN ON HOSPITAL SERVICE AND INTENSIVE CARE

At the beginning of the pandemic, many western countries encountered an unprecedented ICU demand. For European countries, the average ICU occupancy was 11% of the total hospital occupancy.[1] So far, Hong Kong's epidemic curve of COVID-19 had peaked at the end of July 2020. We encountered the highest number of simultaneously hospitalised patients in early August, reaching more than 1,200 patients. The ICUs saw their peak patient load in the first week of August, amounting to 51 patients, comprising 4% of all the hospitalised COVID-19 patients.

Up till the end of October 2020, 214 adult patients in Hong Kong had received ICU service for their COVID-19. Two-thirds were male. Their median ICU length of stay was nine days, and the crude hospital mortality was 17%. One-third of them were younger than 60 years, and one-third of them were older than 70 years. The hospital mortality for those ICU-treated and younger than 60 years, 60 to 70 years and more aged than 70 years were 1.3%, 18%, and 36% respectively. In a meta-analysis of reported overseas data before June 2020, the in-ICU mortality of COVID-19 was 41.6%, which was higher than the usual mortality from other forms of viral pneumonia.[2] The mortality rates as reported in the study have fallen as the epidemic progresses, possibly as a result of the adaptation of the healthcare system to the epidemic, in the form of resource provision and of mounting experience among ICU staff.[3]

TRIAGE OF COVID PATIENTS

As ICU care provides a reasonable chance of survival, its availability becomes a critical issue in the battle against COVID-19. ICU beds were doubled in many overseas hospitals to cope with the surge of patients.[4] Currently, there are around 18,000 acute hospital beds in Hong Kong, of which about 300 are ICU beds, and approximately 200 are intermediate care beds. The number of critical care beds is 7.1 per 100,000 population and is the lowest among the well-developed regions in Asia.[5]

There were suggestions to plan and allocate resources using the assumption that 1 in 5 hospitalised adult COVID-19 patients would require ICU admission.[6] Such target is unrealistic in the short term, and some form of triage has to be exercised during an uncontrolled outbreak. The triage policy has to be fair for patients with or without COVID-19. Careful weighing of the benefits and risks involved in ICU admission is required while striving to guarantee a fair distribution of available resources. A recommendation was published recently, outlining the crucial factors to consider during a triage. They included the patient's usual functional state, the severity of any pre-existing disease, the number of organ failure and the predicted probability of survival with ICU care.[4]

MEDICAL MANAGEMENT

Respiratory Support

Oxygen supplement is the mainstay of respiratory support for COVID-19 patients. In the RECOVERY trial, 24% of the patients did not require oxygen upon their randomisation, while 60% received oxygen, with or without non-invasive ventilation, and 16% required invasive mechanical ventilation.[7] In the Oxygen-ICU study, it was found that targeting oxygen therapy at a SpO2 level of 94-98% was associated with lower ICU mortality than a level of 97-100%.[8] As such, the author would recommend oxygen to be started only when SpO2 is less than 94% and targeting a SpO2 of 94-98%.

High flow nasal cannula (HFNC) is an emerging form of respiratory support where heated, humidified and oxygen-enriched air, typically at an oxygen concentration of 30-100%, is delivered to patient's nostrils at a flow rate of 30-60 litre per minute. With its simplicity, HFNC can be done in settings where nursing care is less intensive, or there is a shortage of ventilators. In a prospective multicentre observational study, 47% of COVID-19 patients could be weaned from HFNC.[9] The main concern on the use of HFNC is the possibility of aerosol generation, which might spread the disease

within the hospital. However, a systematic review found no direct study using COVID-19 patients or virus particles to study the risk of aerosolisation. As such, the risk of SARS-CoV-2 aerosolisation with HFNC remained undetermined.[10] The author only had experience with HFNC in recovering COVID-19 patients who were extubated and had developed neutralising antibodies.

Non-invasive ventilation (NIV) has also been used for COVID-19 patients and could provide more respiratory support than HFNC. However, in a post-hoc analysis of the LUNG SAFE study, NIV use was independently associated with increased ICU mortality.[11] Also, the guideline of the European Respiratory Society and American Thoracic Society does not make any recommendation on the use of NIV for de novo acute respiratory failure (ARF).[12] To the author's knowledge, no COVID-19 patient in Hong Kong received NIV in ICU for ARF in their early phase of the disease. As our mechanical ventilators and other ICU resources had never been exhausted by COVID-19, our mortality of the severe COVID-19 cases was not higher than that of the acute respiratory distress syndrome in general.[13] The therapeutic role of NIV is probably limited in the COVID-19 unless there is a shortage of mechanical ventilators. Another concern about NIV is the risk of aerosolisation. Negative pressure room with adequate air change is required if NIV is to be used.[14]

Invasive mechanical ventilation using a lung-protective strategy remained the mainstay of support for patients with severe ARF. Components of lung protection include: using a tidal volume of 4-6 ml per kg ideal body weight, keeping a plateau pressure of less than 30 cm H2O, minimising the driving pressure, and tolerating a higher than normal PaCO2 if the arterial pH is greater than 7.15. The setting of PEEP had been a subject of debate at the beginning of the epidemic, as two different types of lung mechanics, namely "L-type" and "H-type", were described.[15] However, subsequent studies showed no apparent evidence for different types of ARF in COVID-19[16] and most ICU specialists would set a PEEP level to minimise the driving pressure and to achieve adequate oxygenation (SpO2 88-95%) with a safe level of inspired oxygen concentration.

After the PROSEVA trial, mechanical ventilation in the prone position has been used as an adjunct for severe ARF patients, especially during the early period of ARF.[17] In particular, prone positioning had been shown to improve the PaO2/FIO2 (P/F) ratio in COVID-19 patients.[18] Therefore, it should be considered for mechanically ventilated patients with inspired oxygen concentration greater than 60% and a P/F ratio less than 20 kPa.

Having seen the improvement of oxygenation from prone positioning in mechanically ventilated patients, people started to ask awake non-ventilated COVID-19 patient to turn prone and see if their oxygenation improves. A systematic review of reported case series confirmed the improvement in oxygenation with awake prone positioning.[19] However, in a randomised control trial of awake prone positioning for patients receiving HFNC, such treatment only resulted in a one-day delay in intubation, but could not reduce the need for intubation.[20]

For the sickest COVID-19 patients, extracorporeal membrane oxygenation (ECMO) is the ultimate life support that we could offer. The hospital mortality was 39% according to an international ECMO registry.[21] To the author's knowledge, Hong Kong provided ECMO to nine COVID-19 patients, and the hospital mortality was greater than 70%. This poor outcome could be due to case selection, as the median age of the patients in the registry was only 49, while all of the Hong Kong ECMO patients were 60 or above.

Other Organ Support

COVID-19 patients are prone to thrombosis, and a meta-analysis consisting of mostly western population and a small number of Chinese patients found that the pooled incidence of pulmonary embolism was 23.4%.[22] Patients in ICU should receive routine low molecular weight heparin (LMWH) as pharmacological thrombosis prophylaxis, and the author routinely provides mechanical prophylaxis in addition to the LMWH.

Acute kidney injury is also common in severe COVID-19 patients. For those treated in the ICU, around 20% received renal replacement therapy (RRT).[23] In the Hong Kong cohort, 19% of the ICU COVID-19 patients received RRT, and the crude mortality for those having received RRT was 56%.

Moreover, restrictive fluid intake should be attempted to improve oxygenation. Full nutritional support should be provided according to international recommendations.[24] Use of omega-3 lipid may be considered, and physical activity should be promoted to preserve muscle mass and function.

Anti-Viral Therapy

The most widely used anti-viral therapy for COVID-19 in local ICUs was the combination of Interferon, Lopinavir-Ritonavir (Kaletra), and Ribavirin.[25] However, reports were finding no therapeutic effect with Kaletra[26] and Ribavirin[27], while the role of interferon required further study.[28]

The most promising anti-viral therapy is Remdesivir[29], and it has been used in a few ICU patients in Hong Kong. However, the clinical effect was difficult to appreciate with too few patients.

Virus neutralisation may also be achieved by infusion of convalescent plasma harvested from patients having recovered from COVID-19. Again, a small number of ICU patients in Hong Kong were treated with convalescent plasma, and no remarkable clinical effect could be seen in this small cohort. A recent phase II trial showed no benefit in moderately ill COVID-19 patients.[30] It was not a surprise as most of the patients were antibody positive at the peak of their acute respiratory failure. It could be the immune response, rather than the viral replication, causing the profound disease.

Immunomodulation

After the RECOVERY trial, Dexamethasone 6 mg daily for up to 10 days is the most accepted treatment for

COVID-19 patients requiring oxygen supplement.[7] The 28-day mortality was dropped by 12% for mechanically ventilated patients. In a meta-analysis, corticosteroids were associated with lower 28-day mortality in the critically ill.[31] This finding agreed with the hypothesis that the host's immune response plays a significant role in the deranged physiology.

It was observed that COVID-19 patients might deteriorate rapidly, with a clinical picture similar to the cytokine release syndrome.[32] As such, Tocilizumab, an interleukin-6 receptor antibody, was used in several sick COVID-19 patients in Hong Kong. Retrospective observation studies had found lower mortality in patients receiving Tocilizumab.[33] However, such benefit was not seen in prospective trials.[34,35]

Extracorporeal blood purification may have a role in controlling the cytokine release syndrome. Some ICU patients had received haemo-adsorptive therapy, where blood was exposed to medical devices which could absorb cytokines. Cytosorb (CytoSorbents, Germany) and oXirus (Baxter, US) are two such devices that are available in Hong Kong. From the author's experience, there was an association between improvement in oxygenation and the use of such therapy. However, it is uncertain if such transient physiological improvements could be translated into a survival benefit. The main advantage of blood purification over pharmacological immunosuppression is a lower risk of nosocomial or opportunistic infection.

INFECTION CONTROL MEASURES

Last but not least, infection control is of utmost importance for COVID-19. After the SARS epidemic in 2003, Hong Kong's hospitals and ICUs have developed an excellent infection control practice for highly infectious disease. So far, no hospital personnel contracted COVID-19 during their work. Mask, cap, eye protection, full-length gown and gloves are the standard personal protective equipment when managing COVID-19 patients who are still infectious. When an aerosol-generating procedure is contemplated, an N95 mask and full-face shield will be used to avoid inhalation of aerosols and minimise deposition of aerosols onto one's face. Intubation and cardiopulmonary resuscitation are standard ICU procedures that carry the highest risk. The Adult ICU of Queen Mary Hospital has produced videos demonstrating the practice of CPR.[36] and intubation[37] of COVID-19 patients. You may also find the CPR and intubation protocol of the Prince of Wales Hospital ICU online[38].

CONCLUSION

There are very few specific therapies for COVID-19 disease, but with proper ICU care, the mortality is not more than other forms of ARDS. It is believed that the high mortality rate seen at the beginning of the pandemic is due to inadequate healthcare resources to cover the vast number of patients. Having a low number of beds and a continuously high occupancy rate, Hong Kong's ICUs are at risk of collapse if a major outbreak occurs. Thanks to the excellent public health measures, an overwhelming surge of patients has not happened. Before the availability of an effective vaccine, everyone must continue with the highest vigilance for COVID-19.

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Dermatology Quiz

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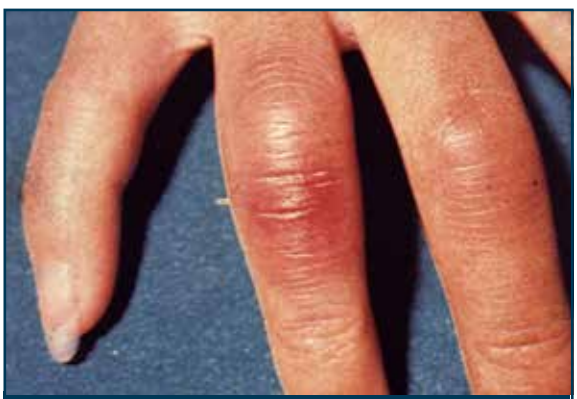

Fig.1: Painful erythematous swollen fingers.

This 20-year-old woman developed painful erythematous-to-violaceous swollen fingers (Fig. 1) and toes during a trip to a cold area. The period when she stayed had a temperature of few centigrade but never below zero. The lesions persisted even though she had returned to a warm area.

Questions

1. What is your diagnosis and differential diagnoses?
2. What are the possible underlying causes?
3. What is your treatment for these lesions?
4. Currently, what important disease should be watched out?

(See P.36 for answers)

Use of Deep Throat Saliva for the Diagnosis of Coronavirus Disease 2019 in Adults and Children in Hong Kong

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INTRODUCTION

Hong Kong has been adopting precision measures to control the Coronavirus disease 2019 (COVID-19) pandemic, which mainly consist of universal masking, social distancing, border control, liberal laboratory testing, mandatory isolation, contact tracing and quarantine of contacts. The mainstay of laboratory diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is by reverse-transcriptase polymerase chain reaction (RT-PCR), where nasopharyngeal swab (NPS) or nasopharyngeal aspirate (NPA), with or without a throat swab was initially used as a standard specimen type in Hong Kong. However, the collection of nasopharyngeal specimens (NPsp) results in patient discomfort and is considered an aerosol generating procedure (AGP), which poses risks to healthcare workers. Moreover, the supply of personal protective equipment (PPE) was very limited during the earlier phase of the pandemic. These constraints limit large-scale testing. Hence there was a need to explore alternative and more convenient specimen types.

Deep throat saliva (DTS) has been demonstrated to be a reliable specimen type for influenza and different respiratory viral infections[1,2]. DTS is easy to collect, does not cause any patient discomfort and allows conservation of PPE. Hong Kong is the first place in the world to use DTS as a convenient specimen for extensive screening of COVID-19. In February 2020, the World Dream Cruise sat dock at the Kai Tak cruise terminal, and self-collected DTS was used to screen more than 1,800 crew members and passengers. This outbreak created the first ever opportunity in the world for DTS to be used for mass screening of COVID-19.

SCIENTIFIC BASIS OF THE USE OF DTS FOR THE DIAGNOSIS OF SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) receptors are known to be the functional receptor of SARS-CoV and SARS-CoV-2, and a recent study showed high expression of ACE2 receptors in the mucosa of the oral cavity[3]. A Chinese rhesus macaque model demonstrated that epithelial cells of the salivary gland ducts are early targets for SARS-CoV soon after infection and infected epithelial cells act as a significant source of virus in saliva[4]. SARS-CoV-2 was first demonstrated to be present in saliva in a local study[5], in which the virus was found in saliva in 11/12 (91.7%) COVID-19 confirmed cases and the live virus was also recovered from the viral culture. Another study conducted by the same group demonstrated that posterior oropharyngeal saliva (POPS) sample had the highest viral load near the presentation of infection and declined steadily afterwards[6].

Since there is limited data on the performance of saliva in the initial phase of the epidemic, early morning DTS was collected to enhance the yield. While POPS is a more precise description of the anatomical origin of DTS, the two terms are interchangeable. The posterior oropharynx is the meeting point of secretions from the following anatomical sites[6]:

- posterior nasopharynx
- salivary glands
- upper and lower respiratory tracts

A recent study of the viral shedding pattern of POPS showed that there is a diurnal variation of viral shedding, with the viral load being the highest in the early morning but POPS could still be taken at any time throughout the day[7]. To facilitate all-day collection of POPS, patients are instructed to refrain from eating, drinking and teeth-brushing for at least 2 hours before obtaining POPS regardless of the actual collection time[8].

PERFORMANCE OF POPS

Evaluation of the performance of POPS may be challenging since there is the absence of a "gold standard" specimen type[8] and the viral shedding can be intermittent. Therefore, assessment of the performance of POPS is ideally done by head-to-head comparison of paired POPS and NPsp collected simultaneously, expressed by percent agreement or concordance rate. Pooled evaluation of the positive rate of POPS compared with NPsp or comparing non-same day specimens may not be able to truly reflect the performance of POPS. Studies with head-to-head comparison of paired saliva and NPsp are listed in table 1. The PPA can range from 78.9-100%[8-12], where the agreement would be higher during the early stage of the disease[8] and discordance usually occur when the viral load starts to drop after seven days of onset of illness. There are also studies demonstrating that the performance of saliva may be inferior to NPsp[13]. The variation in performance could be due to different practices in collecting saliva and analysing pooled saliva data from different stages of the disease. POPS has been evaluated on different platforms and showed promising results[14,15].

Table 1: Studies comparing the performance of Saliva (Summarised by author)

Reference	Method	Number of subjects	Result
Wyllie et al.[18]	Saliva Paired sample collected at the same time point	70 patients with COVID-19	Day 1-5: 81% saliva vs 71% NPS positive Higher viral RNA generally detected in saliva
Wong et al. [8]	Deep throat saliva Same day paired specimen	299 matched pairs 161 pairs from 44 symptomatic COVID-19 patients	PPA (overall): 85.2% PPA (<7 days): 96.6%
Leung et al. [9]	Deep throat saliva Same day matched pairs	95 matched pairs from 62 patients, including 29 confirmed patients	PPA (overall): 78.9% Discordant pairs favour DTS
Yee et al. [11]	Saliva Saliva followed by NP for parallel testing	300 patients recruited 97 confirmed COVID-19	PPA: 82.4% PPA (Adult): 83.3% PPA (Paed): 93.8%
Rao et al.[19]	Early morning saliva Day 8-10 isolation during sampling	217 COVID-19 positive in quarantine centre 160 individuals tested positive for either DTS, NPS or both	Concordance: 45.6% Detection rate of saliva was higher than NPS
Pasomsub et al.[12]	Saliva collected before NPS	200 patients 19 COVID patients	Agreement: 97.5%
Procop et al.[10]	Enhanced saliva specimen collected prior to NPS collection	224 patients 38 COVID-19 positive	PPA: 100%

*PPA: Positive percentage agreement

USE OF SALIVA FOR DIAGNOSIS OF COVID-19 IN PAEDIATRIC PATIENTS

The use of saliva for the diagnosis of COVID-19 has also been explored in the paediatric age group. One Singaporean study involving 18 children concluded that saliva was not useful in diagnosing COVID-19 in children[16]. The sensitivity of saliva was calculated based on positive NP results, and no percentage of agreement was stated in the study. The study also stated that in around 12% of children had delayed saliva collection.

Another study reviewed both adult and paediatric data, and the performance of saliva remained good in both young and older children. The saliva PPA reached 83.3% in children aged 4-10 years and 81.8% in older patients between 11-18 years[11]. A study conducted in Hong Kong, including seven paediatric patients demonstrated fair categorical concordance in children[8], but the sample size was relatively small. Before having more comprehensive data, POPS should only be used in children who are able to obey the command.

CONCLUSION

Saliva is currently recognised as an acceptable specimen for the diagnosis of SARS-CoV-2 PCR in Hong Kong and other regions[17]. It is a convenient tool for mass screening, especially in community outbreak settings, outpatient settings, surveillance of high-risk groups, elderly homes or schools. Collection of POPS is simple and non-invasive, allows self-collection and return, ease to distribute specimen bottles as plain bottles are sufficient and viral transport medium is not required unless there is delay in specimen processing[8,18], allowing POPS collection kits to be distributed by automatic vending machines.

To ensure the diagnostic yield of POPS, the following measures should be ensured:

1. Standard and clear instruction sheets, including video demonstration, should be provided to patients.
2. Abstain from eating, drinking and rinsing of mouth at least 2 hours prior to specimen collection.
3. Avoid collection of POPS before bedtime.
4. Collect sufficient volume and remind patient to spit at least 3-5 mouthful of POPS into the sputum bottle.
5. Direct supervision may be necessary, especially for young children, whose compliance to instructions cannot be ensured.

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ZERBAXA®
ceftolozane and tazobactam
for injection

ZERBAXA® is now indicated for
Hospital-acquired Pneumonia (HAP) / Ventilator-associated Pneumonia (VAP)[1]

FIGHT IT NOW
CHOOSE ZERBAXA®

Consider ZERBAXA® for ventilated patients

ZERBAXA® was studied in critically ill patients with vHAP/VAP, including[2]

- Patients in the ICU **(92%)**
- Mechanically ventilated **(100%)**
- Failing current antibiotic therapy **(13%)**

ZERBAXA® in vHAP/VAP[2]

PRIMARY ENDPOINT

Non-inferior to meropenem in 28-day all-cause mortality in ITT population

FAVOURABLE SUBGROUPS

Favourable 28-day all-cause mortality for the subgroups of vHAP and previous failure of antibiotics for current nosocomial pneumonia episode

MICROBIOLOGICAL RESPONSE RATE

Higher microbiologic eradication rates in ME population with *P. aeruginosa*

Study Design: A randomized, controlled, double-blind, non-inferiority trial conducted between Jan 16, 2015 and April 27, 2018 at 263 hospitals in 34 countries. Patients were randomly assigned (1:1), and stratified by type of nosocomial pneumonia (either VAP or vHAP) and age (<65 years vs ≥65 years), to receive either 3 g ZERBAXA® or 1 g meropenem intravenously every 8 h for 8-14 days. The primary endpoint was 28-Day all-cause mortality (at a 10% non-inferiority margin). ME population: patients with key gram-negative lower respiratory tract pathogens at baseline

Reference: 1. ZERBAXA® Hong Kong Product Circular. 2. Kollef M *et al.* Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *The Lancet, Infectious Diseases.* 2019;19(12):1299-1311.

ICU = Intensive Care Unit, ITT = Intent-to-treat, vHAP = ventilated Hospital-acquired Pneumonia, HAP = Hospital-acquired pneumonia, ME population = Microbiologically evaluable, VAP = ventilator-associated Pneumonia

Zerbaxa® Selected Safety Information

Indications:
Zerbaxa® is indicated for the treatment of the following infections in adults:
- Complicated intra-abdominal infections;
- Complicated urinary tract infections, including pyelonephritis;
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Contraindications:
ZERBAXA® is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA® (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class.

Precautions:
- Decreased Efficacy in Patients with Baseline Creatinine Clearance of 30 to 50 mL/min

  In a subgroup analysis of a Phase 3 cIAI trial, clinical cure rates were lower in patients with baseline CrCl of 30 to 50 mL/min compared to those with CrCl greater than 50 mL/min (below Table). The reduction in clinical cure rates was more marked in the ZERBAXA® plus metronidazole arm compared to the meropenem arm. A similar trend was also seen in the cUTI trial. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage of ZERBAXA® accordingly [see Dosage].

Clinical Cure Rates in a Phase 3 Trial of cIAI by Baseline Renal Function (MITT Population)

Baseline Renal Function	ZERBAXA® plus Metronidazole n/N (%)	Meropenem n/N (%)
CrCl greater than 50 mL/min	312/366 (85.2)	355/404 (87.9)
CrCl 30 to 50 mL/min	11/23 (47.8)	9/13 (69.2)

- Hypersensitivity reactions

  Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.
  Before initiating therapy with ZERBAXA®, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. If this product is to be given to a patient with a cephalosporin, penicillin, or other beta-lactam allergy, exercise caution because cross sensitivity has been established. If an anaphylactic reaction to ZERBAXA® occurs, discontinue the drug and institute appropriate therapy.
- *Clostridium difficile*-associated diarrhea

  Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZERBAXA®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.
  If CDAD is confirmed, discontinue antibacterials not directed against *C. difficile*, if possible. Manage fluid and electrolyte levels as appropriate, supplement protein intake monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.
- Development of Drug-Resistant Bacteria

  Prescribing ZERBAXA® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Adverse Events:
- Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis

  The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA® were nausea, diarrhea, headache, and pyrexia.
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

  The most common adverse reactions (2% or greater) occurring in patients receiving ZERBAXA® were hepatic transaminase increased[1], renal impairment/renal failure[2], diarrhea, intracranial hemorrhage[3], vomiting, clostridium difficile colitis[4].

[1] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasaemia, liver function test abnormal.
[2] Includes acute renal failure, anuria, azotemia, oliguria, prerenal failure, renal failure, renal impairment.
[3] Includes cerebellar hemorrhage, cerebral hematoma, cerebral hemorrhage, hemorrhage intracranial, hemorrhagic stroke, hemorrhagic transformation stroke, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma.
[4] Includes Clostridium difficile colitis, Clostridium difficile infection, Clostridium test positive.

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  In clinical trials, there was no evidence of hemolysis in patients who developed a positive direct Coombs test in any treatment group.

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HK-ZER-40005 Dec'2020

Using R_0 to Inform Public Health Policy for the 2019 Novel Coronavirus (COVID-19) Pandemic

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BACKGROUND

A wide variety of human respiratory viruses cause acute respiratory infections in all ages. Most infections are mild and self-limiting, and typically referred to as "common colds". Some infections can cause more serious disease requiring hospitalisation. From time to time, viruses jump from non-human animals to humans, causing zoonotic infections. If these infections are able to spread efficiently from one human to another, a global pandemic may result. Considerable effort has been made to plan for the risk of influenza pandemics, three of which occurred in the 20th century and one so far in the 21st century. Rather less attention has been given to the potential for respiratory virus pandemics other than influenza, although it is possible that common cold viruses were originally animal infections that spread to humans decades or centuries ago. For example, Vijgen et al. proposed that the seasonal coronavirus OC43 might have jumped to humans in 1890, causing a global pandemic[1].

In January 2020, it was reported that a novel coronavirus had been detected in patients with severe respiratory disease in Wuhan, China[2]. Infections began to be detected outside of mainland China in the second half of January, and it soon became clear that infections had spread globally, with major epidemics occurring in other locations in Asia, as well as in Europe and North America within the next few months. One of the greatest challenges faced by governments across the world has been determining the most appropriate public health responses to infections, with a variety of measures being employed. Public health measures have typically aimed to increase "social distancing" which could more appropriately be termed "physical distancing". This approach aims to reduce the number and duration of interactions between persons in a population in order to reduce the opportunities for transmission to occur. The most extreme has been termed "lockdown" where people are encouraged or even forced to remain in their homes for days, weeks, or even months, as a way to limit community transmission.

Here, we discuss how transmission can be quantified, and then used to assess the impact of control measures and allow fine-tuning of public health strategies to suppress transmission effectively.

REPRODUCTION NUMBERS IN EPIDEMICS

Originally developed in the field of demographics for describing the potential of population growth, the basic reproduction number (R_0) is now a key concept in infectious disease epidemiology to represent the transmission potential of a contagious disease. The basic reproductive number is defined as the average number of secondary infections produced by a typical case of the infection when being introduced into a population where everybody is susceptible[3].

When R_0 is > 1, each infected individual would, on average, infect more than one new person, and the disease would be expected to spread through the susceptible population as an epidemic, with the number of cases increasing exponentially. Conversely, when R_0 is < 1, each case can only transmit the disease to less than one individual on average, and the infection would be expected to die out from the population. Because of chance events, it might still be possible to have small outbreaks even when R_0 is < 1, but a sustained epidemic would not occur. This threshold concept of R_0 provides an assessment of inherent transmissibility of an infection, and the potential difficulty in controlling its spread. An infection with R_0 just above one could be easier to control than an infection with a much higher R_0.

A related concept is the effective reproductive number, R_t at time t. Similar to the basic reproductive number, the R_t represents the average number of secondary infections produced by a typical case of the infection, but R_t can vary over time because of the implementation of public health measures or because of the accumulation of immunity in the population either as a consequence of natural infections or because of the use of effective vaccines. The objective of public health measures is to reduce R_t below 1. For example, suppose R_0 were estimated to be 2, meaning that each individual infects on average two other persons. In that case, the objective of public health measures could be to reduce transmission by at least 50% so that Rt is brought below 1, and the epidemic will then gradually fade out. If R_0 were greater, we might determine that more stringent public health measures are needed to control an epidemic[4].

During the course of an evolving epidemic, the effective reproduction number can be estimated by the product of the basic reproductive number and the fraction of the host population that is remaining susceptible (x), as in the following formula:

$$R_t = R_0 x$$

For example, for an infection with a R_0 of 6 in a population where one-third of the population has become immune, the effective reproductive number would be reduced to 4. This leads to the important concept that transmissibility of an infection can

effectively be reduced by rendering a significant proportion of the population immune. With a larger number of people being immune in a population, the likelihood of contact between an infectious case and a susceptible person will be lower, thus effectively breaking the chain of transmission and reducing the potential of a sustaining epidemic. This concept has been referred to as "herd immunity", where a substantial proportion of immune individuals in a population is also protecting the whole population against an epidemic. A simple calculation of the threshold required to achieve herd immunity is provided by the formula

$$(R_0 - 1)/ R_0 \quad or \quad 1 - 1/ R_0.$$

THE PRINCIPLES BEHIND THE CALCULATION OF R_0 and R_t

A detailed exploration of the technical aspect of how the calculation of R_0 is beyond the scope of the present article, as although the concept of R_0 is very intuitive, its calculation is much less straightforward. The two broad approaches for estimating R_0 included individual level modelling (ILM) and population level model (PLM). For ILM, detailed individual-level contact tracing data obtained at the very start of an epidemic is used. Such contact tracing included the tracing and laboratory testing for the ascertainment of infection status of all the contacts once an individual is diagnosed, so as to identify all secondary and tertiary cases as the infection is spreading in the population. The R_0 is then calculated by averaging over the number of secondary cases caused by many diagnosed individuals.

Population level models, which are being more commonly employed, use population-level data of cumulative incidence in the community without actual tracking of individuals. Basing on a number of individual-level assumptions, such as the mass-action principle of infectious spread and time independent infection rates, mathematical models are constructed using Ordinary Differential Equations to describe the dynamics of the expected population size in different disease stages of the infection (susceptible, infectious, and recovered, etc.)[4]. Population level parameters in terms of disease transmissibility and progression rates are obtained by fitting the model to population-level data, with a threshold parameter obtainable from bifurcation analysis of the mathematical model[5].

It is important to be aware that R_0 values obtained from different ILMs using contact tracing data do not necessarily agree with those obtained from PLM based on mathematical models, as the former calculates the value of R_0, whilst the latter calculates the value of a threshold parameter; how parameters generated from population-level data are related to the individual-level processes is generally unknown. The accuracy of ILMs, in particular, depends on the extensiveness and efficiency of contact tracing, the accuracy of laboratory test employed for diagnosis, and the ease of recognition of the infection as dictated by its clinical profiles.

On the other hand, it is important to remember that R_0 is not an intrinsic variable of the infectious agent but being affected by a large number of factors, including the rate of contacts of individuals in the population, the probability of the infection being successfully transmitted during a contact, and the average duration of infectiousness, including periods of asymptomatic infectiousness, the population size, and the rate of recovery or death. These factors may explain the wide variability of estimates reported for the same infection by different researchers, as they can be very different in different localities, and continuously changing over the course of an epidemic. Moreover, the use of different models for the estimation of R_0 may also play a role in the discrepancies observed among different studies, thus making their direct comparison being less straightforward.

For instance, in the case of COVID-19, the World Health Organization (WHO) had initially estimated the R_0 to range between 1.4 and 2.5. Other early studies have estimated the R_0 to range from 2 to 3.5[6-8]. Two reviews of early studies in China have reported mean estimates of R_0 of 3.28 (ranging between 1.4 to 6.49)[9] and 3.38 (ranging between 1.90 to 6.49)[10]. Another work argued that there is global convergence of R_0 reported across many nations to a value 4.5[11]. In fact, there is no single true value of R_0, and we would expect the R_0 in Hong Kong to be relatively higher than many other locations because of the high population density and population mixing in Hong Kong.

UNDERSTANDING R_0 AND R_t IN RELATION TO COMMUNITY EPIDEMICS

In previous epidemics of different emerging infectious diseases, the basic reproductive number has been estimated and employed for various different purposes. One such use of R_0, as in the case for the 1918 pandemic influenza, was for quantifying and understanding the relative infectious risk and transmissibility associated with a novel pathogen, in comparison with some known and better understood pathogens[12]. Such comparison, though potentially useful in enhancing our understanding of an emerging pathogen, is necessarily retrospective until the epidemic has run at least part of its course for sufficient incidence data to be accumulated. On the other hand, the evaluation and comparison of the changing R_0 before and after the application of some putative control measures would help to assess the potential impact, and the required magnitudes of different control measures or their combinations, for bringing the R_0 to less than the threshold of unity. Such comparison may inform policy decision and practical guidelines in a more objective manner[13].

POTENTIAL CONTRIBUTION OF R_0 and R_t IN THE SETTING OF THE EVOLVING COVID-19 PANDEMIC

Estimation of R_0 and R_t has been critical in guiding public health responses to the COVID-19 pandemic. The School of Public Health at the University of Hong Kong has been providing daily updates on the local R_t values on a dashboard at https://covid19.sph.hku.hk. Fig.1 shows the estimated R_t for the period from late January through to early November 2020, covering Hong Kong's first three waves. Our earliest estimate of R_t was approximately 2.5 on 24 January 2020; this may already be lower than R_0 because people had

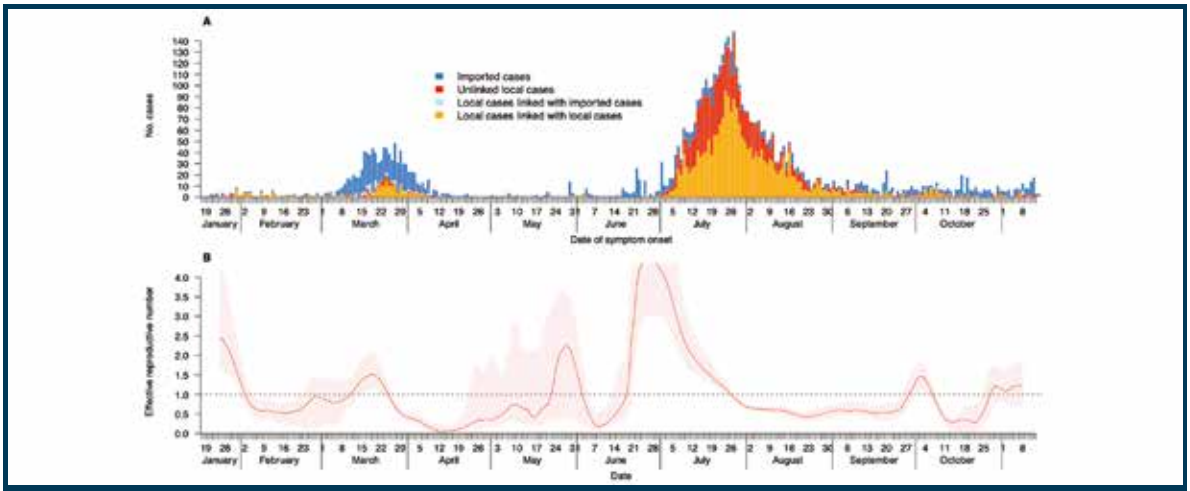

Fig. 1. Incidence of confirmed local cases of COVID-19 in Hong Kong as of 16 November (dark blue bars) and imported infections (light blue bars). Panel B: Estimates of the daily effective reproductive number R_t over time for local cases (red) and imported cases (black), with red and grey shaded areas indicating the uncertainty range. The dotted line indicates the critical threshold of R_t=1. If the reproductive number exceeds that for a prolonged period, we would expect an epidemic to occur. 'Possibly local cases' were re-classified as imported cases if they had a travel history to affected regions. Daily updates of the R_t have been provided at https://covid19.sph.hku.hk (Excerpted from https://covid19.sph.hku.hk)

begun wearing face masks and taking other preventive measures. The preventive measures in place from early February onwards were effective at limiting the spread, and our local first wave was mainly comprised of sporadic outbreaks. R_t rose back above 1 in mid-March, corresponding to Hong Kong's second wave, but was effectively controlled by the re-implementation of work-from-home policies and physical distancing measures in restaurants and bars in the second half of March. Hong Kong's large third wave began in early July, but this was preceded by a considerable rise in R_t in late June, at a time when physical distancing measures had been mostly relaxed. Re-introduction of these measures in the second half of July was effective in bringing R_t back down below one by the start of August. R_t rose above 1 in early November, corresponding to the start of the fourth local wave.

SOME LIMITATIONS OF R_0 and R_t

Although being an intuitive measure of the potential impact of control measures on the transmissibility of an infection, R_0 does have a number of important limitations. First, as mentioned earlier, R_0 does not have a single true value but will vary from one location to another because of population density, social mixing patterns, and perhaps other factors. In addition, R_0 and R_t represent average values, but there can be considerable variability in transmission at the individual level. For example, if R_0 is 2, it means on average, one case will infect two others, but some cases might not spread infection while others might transmit infection to more than two others. In extreme cases, super-spreading events can occur where one case infects a large number of others[14]. Variability in transmissibility has been reported for COVID-19[15]. More broadly, transmissibility is only one aspect of an epidemic, and the severity profile of infections and the availability of effective treatments would also affect the public health impact of an epidemic.

CONCLUSIONS

In conclusion, ongoing estimation of R_0 and R_t can help to inform public health policy in an evolving epidemic by the objective guiding and impact assessment of changing implementation and magnitude of different public health measures. Caution needs to be exercised; however, when comparing R_0 or R_t across different settings as they may vary from one location to another due to different population and local factors.

Acknowledgments

The authors thank Tim Tsang, Eric HY Lau, Peng Wu, Tiffany WY Ng, Jessica Y Wong, Dillon C Adam, Faith Ho, Huizhi Gao, Zoe Xiao and Caitriona Murphy.

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Techniques to Enhance Well-being in the COVID-19 Era

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It is easy to feel daunted by the COVID-19 pandemic: constant reporting of the number of infections and fatalities; fear of infection, illness and death; shielding in the case of increased risk, if suffering from obesity, heart disease, hypertension or being immune compromised. Social distancing and lockdown can have an enormous impact on our relationships, bringing about potentially tense relationships at home, increase in domestic violence, and experiences of profound isolation, with a sense of detachment from other human beings, community and nature. Alcohol consumption increases, diets may be less balanced, screen time may be increased, exercising reduced. Jobs are being lost; the financial livelihood of individuals and families are art risk.

Being affected by increasing levels of stress, anxiety, and depression can, in turn, affect the functioning of our immune system, making us potentially more vulnerable to infections.

Research into the field of stress and resilience has shown that the psycho-physiological impact of stress and anxiety on the autonomic nervous system balance, inflammation and the hypothalamic-pituitary-adrenal axis has a profound immune-modulating impact and may influence the outcome of viral infections (cytokine response and appropriate levels of corticosteroids).[1]

Emotion regulation and the ability to shift from negative (anxiety, fear, sadness, frustration etc.) to positive emotions (courage, engagement, passion, compassion, care, appreciation etc.) promotes flexibility, adaptability rhythm, and dynamic balance of the autonomic nervous system, with an increasingly positive impact on developing physical and emotional, mental and spiritual resilience whilst facing pressure, through for example enforced change and/or adversity.[2] This may in turn have a positive impact on acute and chronic inflammation parameters, such as immunoglobulin levels, T-cell activity and cytokine response.[3]

Predisposition to the negative impact of stress and extreme emotions is not just genetically predisposed, but also determined by a preverbal and precognitive exposure to toxic stress or trauma, defined as adverse childhood events during pregnancy and also during the time of early attachment.[4] The earlier the adverse experience during the development of the child, the more physiological is the response to stressful events later on in life.

An effective, evidence-based and practical approach to developing adaptive resilience and reducing the negative effect of so-called negative emotions, such as stress and anxiety, should therefore not be purely based on psychological interventions, such as cognitive behaviour therapy based exercises, but should include body awareness (mindfulness, breathing and relaxation techniques) to effectively create optimal and flexible adaptation of levels of arousal to inner and environmental challenges.[5]

One of the particularly helpful technique in this context is the resonant frequency training or coherence training, a breathing technique with simultaneous focus on positive emotional states.[6]

This audio-guided breathing technique deploys slow diaphragmatic breathing at a pace of approximately 5.5 breathing cycles per minute, whilst simultaneously focusing on a positive feeling, such as appreciation. During this exercise, the breathing rhythm is, with the help of an audio-breath pacer, being rhythmically aligned with blood pressure rhythm and heart rate variability (HRV), creating a resonance phenomenon that leads to a significant increase in the amplitude of heart rate variability during the exercise and beyond. HRV is a measure for the rhythm, flexibility, dynamic and balance of the autonomic nervous system and has been a predictor for ill health and all-cause mortality in middle-aged and older people. Optimising heart rate variability through paced breathing and/or HRV biofeedback has also been shown to improve mental and emotional health, through reducing negative stress, improving mood, reducing anxiety.[7,8,9,10]

It is important to note that the resonant frequency training creates a physiological state of autonomic balance between stimulation (sympathetic) and relaxation (parasympathetic), comparable with the physiological state underpinning flow and engagement, when we are simultaneously alert and mobile (sympathetic) and relaxed and laid back (parasympathetic). Training body and mind repeatedly (1x to 2x daily for 10 to 15 minutes) into this state of autonomic balance will allow to access this resourceful state on demand in challenging circumstances, i.e. when exposed to pressure. This will allow to prevent being fixed in a physiological fight or flight response or conversely in a freeze and flow response, allowing for optimal adaptation and health promotion, even when exposed to short- or long-term pressure.

This psycho-physiological approach to stress management and developing of physical and emotional resilience should be supplemented by techniques that enhance the capacity to shift from negative to positive emotional states.

Mindfulness-based exercises, such as nature observation[11] and active listening[12,13,14] can be very helpful here, as are exercises that lift subconscious negative emotions into our consciousness, in order to neutralise them.[15] Gratitude journaling has also shown to be highly effective in regard of accessing positive emotional states as resources for physical and emotional resilience and health.[16,17,18,19]

Finally, using positive self-talk[20,21] and mental rehearsing[22] can help create clear goals, vision and purpose in order to build resilience and protect health[23].

The guided breathing technique (resonant frequency training – coherence training) and the breath pacers are made available on www.bestfutureself.org.

All other evidence-based techniques being referred in this can be found in my 'Manifesting Your Best Future Self. Building Adaptive Resilience.' available on Kindle and Amazon.

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3	4	5	6	7	8	9
10	11	12	13 * The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed	14	15	16 * Facebook Live Symposium on End of Life Care (3-session) Session 1 - Palliative Home Care in the Eye of Family Physicians Session 2 - Hospital at Home and End of Life Care: Focus on Pain Control Session 3 - Legal Aspect of End of Life Care
17	18	19	20	21 * HKFMS Foundation Meeting * FMSHK Executive Committee Meeting	22	23 * Facebook Live Certificate Course on Lower Urinary Tract Symptoms (LUTS) management 7. LUTS and heart disease (CHF) 8. LUTS and Mortality (Falls And Fractures) 9. LUTS and incontinence
24	25	26	27	28	29	30
31						

Date / Time	Function	Enquiry / Remarks
13 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker(s): Dr Michael Ka-wing SEE Chairman: Dr YAM Kwong-yui Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	CME Accreditation College: 1.5 points College of Surgeons of Hong Kong Enquiry: Name: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
16 SAT 2:00 PM	**Facebook Live** **Symposium on End of Life Care (3-session)** **Session 1 - Palliative Home Care in the Eye of Family Physicians** **Session 2 - Hospital at Home and End of Life Care: Focus on Pain Control** **Session 3 - Legal Aspect of End of Life Care** Organiser: HKMA-Hong Kong East Community Network; Speaker: Session 1: Dr Patrick Hung-wai CHAN; Dr Luke Chiu-yee TSANG; Dr Henry Wing-ming KONG Session 2: Dr Charles CHAN Fei Session 3: Ms Olivia LEUNG	Ms. Candice Tong 2861 1979 1 CME Point
21 THU 7:00 PM	**HKFMS Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
23 SAT 2:00 PM	**Facebook Live** **Certificate Course on Lower Urinary Tract Symptoms (LUTS) management** **7. LUTS and heart disease (CHF)** **8. LUTS and Mortality (Falls And Fractures)** **9. LUTS and incontinence** Organiser: Hong Kong Medical Association Hong Kong Elderly Welfare Foundation; Speaker: Dr CHU Wing-hong Dr John Tai-hung WONG Dr CHU Wing-hong Dr Cecilia Willy CHEON / Dr Toby CHAN	HKMA CME Dept. 2527 8452 2 CME Points

醫護誠信同行
Medical Conscience

Medical Conscience
醫護誠信同行

The Medical Conscience is formed by a group of medical professionals with common beliefs in the virtues as professionals and values as citizens of Hong Kong. We uphold the values of peace, liberty, and justice.

A group of us met on 20 December 2019 and resolved to establish an organisation. We named ourselves 醫護誠信同行Medical Conscience the very same day and formed our first Council. We received our Certification of Registration on 8 January 2020. As of today, we have over 300 Members.

As doctors and medical professionals, we strongly insist that beliefs and convictions, whether religious, political or otherwise shall in no way come between our patients and us in harm's way. We must treat every single patient equally and wholeheartedly to the furthest of our capabilities.

We take it upon ourselves as our moral duties to advise society on medical and health care issues, including crisis and policies. We shall provide volunteer services if we consider it necessary.

We shall do all we can to provide mentoring to students of our professions in order to nurture virtuous generations of our peers.

In November, we successfully became a Member of the Federation of the Medical Societies of Hong Kong. This, to me, is a landmark of our acceptance into the wider Medical community.

Dr David Lam
Chairman, Medical Conscience

Answers to Dermatology Quiz

Answers:

1. Chilblains (Pernio), also known as "蘿蔔仔" in Cantonese. The differential diagnoses should include frostbite (凍瘡), erythromelalgia, Raynaud's phenomenon, acrocyanosis and thrombo-ischaemic diseases.

2. Majority of chilblains are idiopathic due to an abnormal vascular response to cold exposure (non-freezing temperature), especially in humid conditions, causing itching or painful erythematous, swelling and blistering on hands and feet. Most frequently it occurs in young and middle-aged women and children. In chronic chilblains, it may be secondary to systemic diseases such as myeloproliferative diseases, paraproteinaemia, antiphospholipid syndrome, Raynaud's disease, lupus erythematosus, etc.

3. Chilblains usually resolve spontaneously within one to three weeks when the weather returns warmer. Preventive measures for recurrence include limiting exposure to cold and dressing warmly.

4. Chilblains-like lesions are now known as one of the cutaneous signs of SARS-CoV-2 infection (also known as "COVID toes"). One should therefore have a high index of suspicion of this disease if the patients also have anosmia /ageusia, fever or flu-like symptoms and signs.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

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References :
1. L. Pradelli et al. /Clinical Nutrition 33 (2014) 785-7 92
2. Singer et al. (2009) ESPEN Guidelines on parenteral nutrition: Intensive Care. Clinical Nutrition 28: 387-400
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http://www.espen.org/espenguidelines.html

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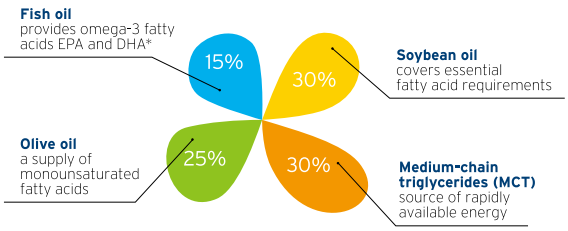

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§ When added to SOC, which included oral antidiabetic treatment, insulin, antihypertensives, diuretics and lipid-lowering therapies.[3]

Other diabetes treatments refer to sitagliptin, dulaglutide, exenatide ER, liraglutide, canagliflozin and glargine U100. Target refers to American Diabetes Association target of HbA_{1c} <7%.

† In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal myocardial infarction [MI] or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

* Results apply to Ozempic® across SUSTAIN trials, which included placebo, DPP-4I, SGLT-2I, GLP-1 RA and basal insulin.[1,2]

For adults with type 2 diabetes with established ASCVD or indicators of high ASCVD risk
2019 ADA/EASD consensus report recommends a GLP-1 RA therapy with proven CV benefit[6]

CV=cardiovascular, CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Abbreviated prescribing information Ozempic® (semaglutide). Ozempic 0.25 mg solution for injection in pre-filled pen; Ozempic 0.5 mg solution for injection in pre-filled pen; Ozempic 1 mg solution for injection in pre-filled pen. **Consult Summary of Product Characteristics before prescribing. Presentation:** Ozempic 0.25 mg & 0.5 mg solution for injection: Each pre-filled pen contains 2 mg semaglutide in 1.5 ml solution. Ozempic 1 mg solution for injection: One pre-filled pen contains 4 mg semaglutide in 3.0 ml solution. **Uses:** Ozempic® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as Monotherapy: when metformin is considered inappropriate due to intolerance or contraindications, Combination therapy: in addition to other medicinal products for the treatment of diabetes, For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see the full Summary of Product Characteristics, **Dosage and administration:** The starting dose is 0.25 mg Ozempic® once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Ozempic® should not be administered intravenously or intramuscularly. When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged. When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. **Elderly:** No dose adjustment is required based on age. Therapeutic experience in patients aged ≥75 years of age is limited. **Renal impairment:** No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience in patients with severe renal impairment is limited. Not recommended for use in patients with end-stage renal disease. **Hepatic impairment:** No dose adjustment is required for patients with hepatic impairment. Experience in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Ozempic®. **Paediatric population:** The safety and efficacy of Ozempic® in children and adolescents below 18 years have not yet been established, No data are available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Ozempic® is not a substitute for insulin. There is no experience in patients with congestive heart failure NYHA class IV and Ozempic® is therefore not recommended in these patients. The possibility of gastrointestinal adverse reactions should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration, which could cause a deterioration of renal function. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Patients treated with Ozempic® in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. Consider reducing the dose of sulfonylurea or insulin when initiating treatment with Ozempic®. In patients with diabetic retinopathy treated with insulin and Ozempic®, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using Ozempic® in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. **Interactions:** Ozempic® delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products, Ozempic® should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, No dose adjustment of paracetamol, oral contraceptives (ethinylestradiol and levonorgestrel), atorvastatin, warfarin, digoxin or metformin is necessary when administered with Ozempic®. For further details of these interaction studies, please see the Summary of Product Characteristics. **Pregnancy and lactation:** Ozempic® should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs during treatment, Ozempic® should be discontinued. Ozempic® should not be used during breast-feeding, Effect of Ozempic® on fertility in humans is unknown. **Driving or using machines:** When Ozempic® is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, **Undesirable effects:** The most frequently reported adverse reactions with Ozempic® in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. Adverse reactions by system organ class and absolute frequencies identified in all phase 3a trials listed here as Very common (≥1/10): Hypoglycaemia when used with insulin or sulfonylurea; nausea, diarrhoea; Common (≥1/100 to <1/10): Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro-oesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased; Uncommon (≥1/1,000 to <1/100): Dysgeusia, increased heart rate, injection site reactions; Rare (≥1/10,000 to <1/1,000): Anaphylactic reaction.

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Further information is available from
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