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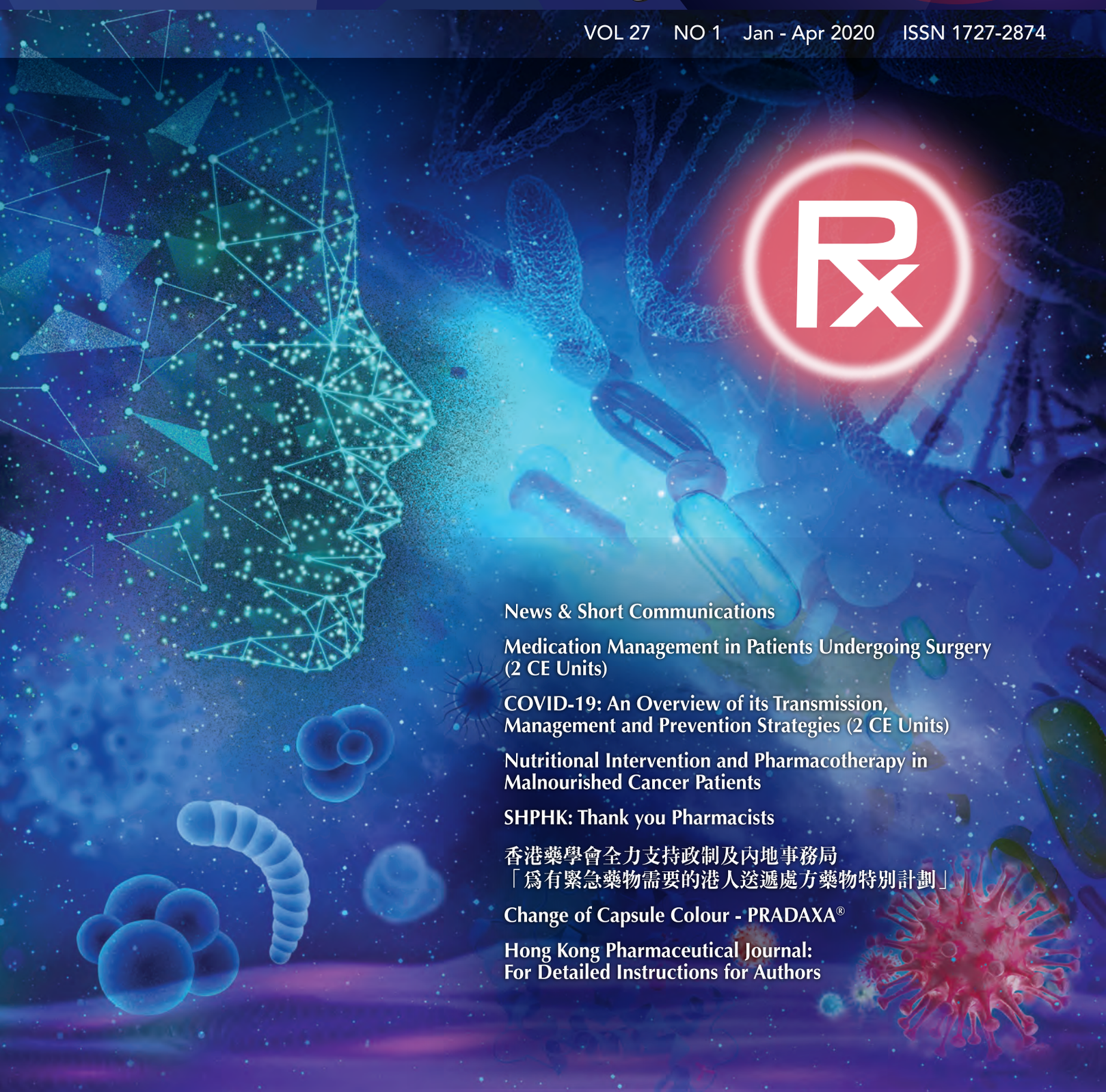

The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
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NEW

ALUNBRIG®
BRIGATINIB
180mg | 90mg | 30mg
TABLETS

RAISING EXPECTATION IN ALK+ NSCLC TREATMENT

For patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib

Move ahead of progression with ALUNBRIG®

Unprecedented Survival[1#]

16.7-month median PFS[a,b]
(95% CI: 11.6-21.4; n=110)

34.1-month median OS[a,c]
(95% CI: 27.7-NR; n=110)

Durable CNS Efficacy[2#]

18.4-month median intracranial PFS[b,d]
(95% CI: 12.6-23.9; n=74)

16.6-month median intracranial DOR[b,e]
(95% CI: 3.7-NR; n=12)

67% intracranial ORR[b,e]
(95% CI: 41-87; n=18)

A Robust Response[1#]

56% ORR[b]
(95% CI: 47-66; n=110)

Manageable Safety Profile[3]

Convenient dosing: One tablet once daily taken with or without food[3]

ALK+ NSCLC = anaplastic lymphoma kinase positive non-small cell lung cancer; CI=confidence interval; CNS=central nervous system; NR = not reach; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
a=Kaplan-Meier estimate; b=Independent Review Committee; c=Investigator Assessed; d=in patients with any brain metastases at baseline; e=patients with measurable baseline brain metastases; #180mg once daily regimen with 7-day lead in at 90mg once daily

For further information, please consult full prescribing information

Reference: **1.**Huber RM et al., J Clin Oncol. DOI :10.1200/JCO.2018.36.15_suppl.9061 **2.**Huber RM et al., Poster presented at: the 54th Annual Meeting of the American Society of Clinical Oncology; June 1-5 2018; Chicago, IL. Poster 384 **3.**Alunbrig HK prescribing information (PLFT0156A1)

Abbreviated Prescribing Information: Alunbrig (brigatinib) tablets
Indication: Patients w/ anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. **Dosage:** Initially 90 mg orally once daily for the first 7 days; if 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily. **Special precaution:** Risk of interstitial lung disease (ILD)/ pneumonitis, hypertension (HTN), bradycardia, visual disturbances (eg, blurred vision, diplopia, & reduced visual acuity), creatine phosphokinase (CPK) & pancreatic enzyme elevation, hyperglycemia. Withhold treatment in patients w/ Grade 3 or 4 CPK elevation; Grade 3 or 4 pancreatic enzyme elevation; inadequate hyperglycemic control. Permanently discontinue in case of Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis; Grade 4 HTN or recurrence of Grade 3 HTN; life-threatening bradycardia; Grade 4 visual disturbances. Use w/ caution in combination w/ antihypertensive agents causing bradycardia. Females of reproductive potential should use effective non-hormonal contraception during treatment & for at least 4 mth following the final dose. Males w/ female partners of reproductive potential should use effective contraception during treatment & for at least 3 mth after last dose. **Adverse reactions:** Pneumonia, ILD/pneumonitis, increased CPK, nausea, diarrhea, vomiting, constipation, abdominal pain, fatigue, pyrexia, cough, dyspnea, hypoxia, headache, peripheral neuropathy, rash, hypertension, muscle spasms, back pain, myalgia, arthralgia, pain in extremity, decreased appetite, visual disturbance, insomnia, increased aspartate aminotransferase, hyperglycemia, increased CPK, increased lipase, increased alanine aminotransferase, increased amylase, increased alkaline phosphatase, decreased phosphorus, prolonged activated partial thromboplastin time, anemia, lymphopenia. **Drug interaction:** Increased plasma conc & adverse reactions w/ strong CYP3A inhibitors [eg, certain antivirals (boceprevir, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (clarithromycin), antifungals (itraconazole, ketoconazole, posaconazole, voriconazole), conivaptan]; grapefruit or grapefruit juice. Decreased plasma conc & efficacy w/ strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort). Decreased conc & loss of efficacy of CYP3A substrates (eg, hormonal contraceptives).

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HK/BRI/2019/0-00055

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All communications and enquiries should be directed to:
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at the following email address: ***hkpjadv@gmail.com***

INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- Primary Care
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: ***editor@hkpj.org***
address: ***Room 1303, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong.***

For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

Editorial

News & Short Communications

Drugs & Therapeutics

Primary Care

Society Activities

New Product

Aims and Scope of the Journal

HKUSPACE
香港大學專業進修學院
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Pharmaceutical Studies

MSc Clinical Pharmacy*

This is a 2-year part-time programme in HK delivered through face-to-face and distance learning. Tutorials / workshops are run by visiting academics from the University of Sunderland, U.K. The degree is awarded by the University of Sunderland.

Programme Features:

- Updated specialist modules
- Realistic project workload for timely completion
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Entry Requirements:

A minimum of lower second class honours degree in pharmacy (or equivalent) and registration as a pharmacist in Hong Kong. BPharm graduates from countries that do not normally award honours may also apply, provided they are registered as a pharmacist in Hong Kong. The programme is open to both hospital and community pharmacists.

University of Sunderland

Application Code: 1850-HS073A
Programme Code: HS073A

Application Deadline: 30 June 2020

Enquiries
3762 0096
sheri.ip@hkuspace.hku.hk

BSc (Hons) Pharmaceutical Science*

This programme is a 2-year top-up degree offered in part-time mode of study in Hong Kong. The BSc (Hons) Pharmaceutical Science is to be awarded by the University of Wolverhampton, UK. The programme aims to produce high quality pharmaceutical science graduates with the generic, subject-specific and transferable knowledge and skills suited to a career in the pharmaceutical industry or other related laboratory based scientific discipline.

Programme Features:

- a 24-month part-time undergraduate programme
- it covers the area of pharmaceutical science including pharmacology, pharmaceutical design and manufacture, biopharmaceutical, methods of analysis, quality assurance and delivery of pharmaceutical substances

Entry Requirements:

Applicants should hold either:

- Associate of Health Science (Biomedical Sciences)/ Advanced Diploma in Pharmaceutical Science (HKU SPACE); or
- Higher Diploma in Medical and Health Products Management (HPSHCC); or
- Higher Diploma in Pharmaceutical Technology (Western Medicine)/ Dispensing Studies/ Pharmaceutical Science/ Hospital Dispensing Studies (HKIVE); or
- Higher Diploma in Pharmaceutical Dispensing (CBCC)

UNIVERSITY OF WOLVERHAMPTON

Application Code: 1850-HS072A
Programme Code: HS072A

Application Deadline: 30 June 2020

Enquiries
3762 0096
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Professional Diploma in Marketing for Pharmaceutical Industries

The objectives of the programme are to equip the practitioners of pharmaceutical industry or medical devices business or those who intend to develop their career in marketing in these two industries with solid knowledge and practical skills in marketing, selling, tender planning and pitching, market knowledge and the latest trends in product development. The graduates of this programme will be able to develop marketing strategies, prepare tender proposal and manage business pitching abiding by regulations and code of practice of the industry concerned.

Programme Features:

- Students can choose to focus on either the pharmaceutical market / the medical device business
- Emphasis on practicality and the curriculum responds to the business needs of the pharmaceutical and medical device industries
- Interactive learning with lots of case studies, discussion and sharing by guest speakers
- Experienced and well-qualified lecturers
- Strong connection with the industries

Entry Requirements:

Applicants shall hold:

- A Diploma/ Advanced Diploma awarded by a recognized institution; or
- A Professional Certificate in Marketing awarded within the HKU system through HKU SPACE or equivalent.

Applicants with a science background are preferred.
Applicants with other equivalent qualifications and relevant work experience will be considered on individual merit.

資歷架構 Qualifications Framework
Level 4
Registration Number:19/001296/L4
Valid From:01 Feb 2020 - on-going

Application Code: 1835-MK075A
Programme Code: MK075A

Application Deadline: 20 June 2020
Start date: 13 July 2020

Application fee: $150 (Non-refundable)
Course fee: $3,950 per module

Enquiries:
2867 8499 / 3762 0081
pharma.mkt@hkuspace.hku.hk

* These are exempted courses under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which these courses may lead.

COVID-19: Together, we fight the virus!

Coronavirus disease 2019 (COVID-19) was first detected in the city of Wuhan and is now infected millions globally. As there is no specific vaccine against the disease, the primary treatment is symptomatic and supportive therapy. To prevent and protect against the incidence or transmission of the disease, frequent hand washing, wearing face mask in public settings and maintaining distance from other people have been recommended.

In response to the outbreak of COVID-19 pandemic, various treatment approaches are being investigated. While scientists around the world are working on potential treatments and vaccines specific to COVID-19, the development process is a long and complex endeavor. On the other hand, the repurposing of the existing therapeutic agents provides a more rapid response to this emergent pandemic. The article by Mak et al provided an overview of the pharmacological management and preventing strategies of COVID-19 that are available for use in hospitals of Hospital Authority in Hong Kong.

Pharmacists globally are providing services amidst this COVID-19 pandemic and contribute greatly in the overall medical management. Pharmacists can act as health advisers, increase public awareness by providing accurate and reliable health information and advice. Moreover, pharmacists have the shared responsibility of ensuring adequate storage and supply of medications and other necessary preventative products. In addition, pharmacists are involved in recommending therapeutic management for minor ailments, reducing unnecessary hospital visits and minimizing COVID-19 exposure to patients. As lockdowns and travel restrictions are being observed and hours of non-urgent clinic services are being reduced, pharmacists offer flexible medication refill/renew services and home-delivery services for medications to safeguard patients' continuity of medication management. The section on Society Activities reported activities performed by pharmacists from Pharmacist of the Society of Hospital Pharmacists of Hong Kong and The Pharmaceutical Society of Hong Kong in response to this pandemic. Pharmacists in Hong Kong, like any other pharmacists globally, commit unselfishly to serve the best interests of public above everything.

Last but not the least, the articles by Ka-Yan-Karen HO and Marco Tsum LEE reviewed on medication management in patients undergoing surgery and nutritional intervention and pharmacotherapy in malnourished cancer patients. Both articles are highly informative and educational and provide in-depth knowledge on the related topics.

I hope that you enjoy this issue. As always, your suggestions on any part of the Journal is valuable and can send the comments to me or other members of the Editorial Committee.

May PS Lam
Editor-in-Chief
31 May 2020

Prepared by Howard Chan, Chiu TS Ching

Untied States: FDA Requires Boxed Warning About Risk of Neuropsychiatric Events Associated with Montelukast

Date: March 4, 2020

The U.S. Food and Drug Administration (FDA) announced that it is requiring a boxed warning – the agency's most prominent warning – for montelukast to strengthen an existing warning about the risk of neuropsychiatric events associated with the drug. The boxed warning advises healthcare providers to avoid prescribing montelukast for patients with mild symptoms, particularly those with allergic rhinitis.

The FDA continued to receive reports of neuropsychiatric side effects, including completed suicides, with montelukast use. Some occurred during montelukast treatment and resolved after drug discontinuation. Other reports indicated that neuropsychiatric side effects developed or continued after stopping montelukast. Although new data regarding the risk of neuropsychiatric side effects with montelukast are limited, the FDA recognized that many health care professionals and patient/caregivers are not aware of this risk and thus decided to strengthen the warning after conducting an extensive review of available information and convening a panel of outside experts.

Because of the risk of neuropsychiatric side effects, benefits of montelukast may not outweigh risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with other medicines. For allergic rhinitis, the FDA have determined that montelukast should be reserved for those who are not treated effectively with or cannot tolerate other allergy medicines. For patients with asthma, the authority recommended that healthcare professionals should consider the benefits and risks of neuropsychiatric side effects before prescribing montelukast.

Source: www.fda.gov

Low-dose Aspirin Associated with Lower Risk of Hepatocellular Carcinoma and Liver-Related Mortality in Patients with Chronic Viral Hepatitis

Date: March 12, 2020

Experimental and clinical data suggest that aspirin may prevent liver disease progression and hepatocarcinogenesis through diverse mechanisms. However, epidemiological data remain limited and previous observational studies lacked detail data regarding key determinants of hepatic outcomes. A nationwide study was therefore conducted in Sweden to characterize the long-term effects of low-dose aspirin (≤160 mg) on incident hepatocellular carcinoma, liver-related mortality, and gastrointestinal bleeding in persons with chronic hepatitis B or hepatitis C virus infection.

Using nationwide Swedish registries, 50,275 adults who received a diagnosis of chronic hepatitis B or C from 2005 through 2015 without history of aspirin use were identified. 14,205 patients who were starting to take low-dose aspirin were identified by their first-filled prescriptions for ≥90 consecutive days of aspirin. A propensity score was constructed and inverse probability of treatment weighting to balance baseline characteristics between groups was applied. Risk of hepatocellular carcinoma and liver-related mortality were estimated using Cox proportional-hazards regression modeling, accounting for competing events.

With a median of 7.9 years of follow-up, the estimated cumulative incidence of hepatocellular carcinoma was 4.0% among aspirin users and 8.3% among non-aspirin users (difference, −4.3%; 95% CI, −5.0% to −3.6%; adjusted HR, 0.69; 95% CI, 0.62 to 0.76). This inverse association appeared to be duration-dependent; as compared with short-term use (3 months to <1 year), the adjusted HRs were 0.90 (95% CI, 0.76 to 1.06) for 1 to less than 3 years of use, 0.66 (95% CI, 0.56 to 0.78) for 3 to less than 5 years of age, and 0.57 (95% CI, 0.42 to 0.70) for 5 or more years of use. Ten-year liver-related mortality was 11.0% among aspirin users and 17.9% among non-users (difference, −6.9% [95% CI, −8.1% to −5.7%]; adjusted HR, 0.73 [95% CI, 0.67 to 0.81]). However, the 10-year gastrointestinal bleeding risk did not differ significantly between users and non-users of aspirin (7.8% and 6.9%, respectively; difference, 0.9%; 95% CI, −0.6% to 2.4%).

Study results showed that use of low-dose aspirin was associated with a significantly lower risk of hepatocellular carcinoma and lower liver-related mortality, without a significantly higher risk of gastrointestinal bleeding.

Source: www.nejm.org

Medication Management in Patients Undergoing Surgery

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ABSTRACT

All surgical procedures may result in complications. Proper perioperative and postoperative management is crucial in minimizing unnecessary risk and in promoting early recovery from surgical procedures. Some medications should be continued throughout the peri-operative period to prevent disease relapse, while some medications have to be withheld or switched to alternatives before surgery. Perioperative antibiotic prophylaxis is recommended in many types of surgery in order to prevent postoperative wound infections, and cefazolin is the drug of choice for most procedures. Screening and decolonization of Methicillin-resistant Staphylococcus aureus (MRSA) before surgery is also important in preventing postoperative infection. Apart from perioperative preparation, proper pain assessment and use of multimodal analgesics in the immediate postoperative period are essential for acute pain management associated with surgery. For patients undergoing knee surgery, intra-articular injection of tranexamic acid and prophylaxis of venous thromboembolism should also be considered.

Keywords: *Surgery; Peri-operative; post-operative; surgical procedures*

INTRODUCTION

"Surgery" is defined as a procedure performed for the purpose of structurally altering the human body by incision or destruction of tissues for the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transportation of live human tissue.(1) Peri-operative management is essential in order to minimize unnecessary risks and complications to patients. Proper post-operative management is also crucial in promoting early recovery from surgical procedures.

PERI-OPERATIVE MANAGEMENT

Medications to be discontinued prior to surgery

Many patients admitted to hospital for an operation will be taking medicines which might affect, or be affected by the drugs used during surgery or by the surgical procedure itself.(2) It is important to obtain an accurate and complete medication history, including over-the-counter and herbal medications, as well as prescription medications before the surgical procedure. Allergy history of the patient should also be reviewed while planning surgical procedures.(3) Some medications should be continued throughout the peri-operative period to prevent disease relapse or drug withdrawal effect.(2) Omission of certain medications may increase the risk of surgical complications and impede recovery.(3) Continuation may require an alternative route of administration or alternative product with a similar action.(2) On the other hand, medications thought to increase the risk of anesthetic or surgical complications and are not essential for the short-term should be withheld during the peri-operative period.(4)

Aspirin and other antiplatelets (e.g. clopidogrel, prasugrel, ticagrelor)(5-9)

Aspirin is the mainstay of antiplatelet for secondary prevention of cardiovascular diseases or ischemic stroke in patients with atherosclerotic disease. $P2Y_{12}$ inhibitors, including clopidogrel, prasugrel and ticagrelor, are usually added to aspirin in patients with acute coronary syndrome (ACS) with or without percutaneous coronary interventions (PCI).

Aspirin induces an irreversible inactivation of platelet cyclo-oxygenase (COX), which leads to inhibition of thromboxane A_2 (TXA_2) and prostaglandin I_2, thus resulting in platelet aggregation inhibition. This effect lasts for the platelet's lifespan, which is about 7–10 days. Hence, if it is deemed necessary, aspirin should be stopped 7–10 days before surgery to allow sufficient replacement of normal circulating platelets **(Figure 1)**. Similarly, clopidogrel is usually discontinued one week before elective surgery. These drugs should be restarted as soon as adequate haemostasis has been achieved,

Agent	Elimination Half-life	Duration of Platelet Inhibition	Recommended Time for Discontinuation before Surgery
Aspirin	15–20 min[a]	Permanent	7–10 days
Clopidogrel	7–8 hr[b]	Permanent	7–10 days
Ticlopidine	12 hr	Permanent	7–10 days
Ibuprofen	2–4 hr	6–12 hr	10–12 hr
Naproxen	10–20 hr	36–75 hr	72 hr
Ketorolac	4–6 hr	24–48 hr	24 hr
Fenoprofen	2.5–3 hr	6–15 hr	12 hr
Rofecoxib	17 hr	Minimal	2–3 days
Celecoxib	11 hr	Minimal	2–3 days

Figure 1. *Pharmacokinetics of Selected Antiplatelet Agents*(6)

which is usually 24 hours post-operation or in the next morning after surgery.

The management of antiplatelet therapy during peri-operative period requires consideration of the risks of precipitating thromboembolic complications or cardiovascular events with premature cessation and any risk of increased bleeding or development of epidural hematoma in spinal or epidural anesthetic procedure with continuation of therapy. The use of antiplatelets should be made on a case-by-case basis. Prior to surgery, the patient, primary care physician, cardiologist, anaesthesiologist, and surgeon should be involved in decision making. For patients receiving dual antiplatelet therapy (DAPT), any planned non-emergent noncardiac surgery should be delayed until after the recommended duration of DAPT.

Other nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors may also inhibit platelet COX and platelet aggregation to various extents. These medications should therefore be stopped in time to allow recovery of adequate platelet function, which is usually about 1 day for short-acting NSAIDs and 3 days for long-acting NSAIDs.[2] Withholding NSAIDs for longer period is unnecessary and may result in poor pain control.

Warfarin and Direct Oral Anticoagulants (DOAC)[6-7, 10-11]

Similar to anti-platelet therapy, peri-operative management of patients receiving warfarin or DOAC should be based on the assessment of thromboembolism and peri-operative bleeding risk. In most elective surgeries, warfarin is stopped temporarily for 5 days before the surgery to achieve an INR of 1.5 or less. For patients with a high risk of thromboembolism, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) may be considered as bridging therapy during the interim period to maintain activated partial thromboplastin time (aPTT) 1.5-2.5 times of upper limit of normal range. Due to the longer half-life of LMWH and delayed subcutaneous absorption, LMWH should be withheld for 24 hours before surgery. UFH can be given till approximately 4-6 hours before surgery. Both UFH and LMWH can be resumed about 12-24 hours after surgery.

Direct oral anticoagulants (DOAC), including dabigatran, rivaroxaban, apixaban and edoxaban, should also be stopped before surgery if patient has a high bleeding risk. Depending on the patient's renal function and bleeding risk, DOAC should be discontinued 2-5 days before the procedure **(Figure 2)**. DOACs may be resumed 24 hours after surgery for patients with low bleeding risk and 48-72 hours after surgery for patients with high bleeding risk when haemostasis has been achieved.

For emergency operations when there is insufficient time to withhold anti-coagulants before surgery, fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs) may be used to rapidly reverse the anticoagulation effect. Vitamin K_1 may also be given to reverse the anticoagulant effect of warfarin.[9] Idarucizumab, a specific reversal agent for dabigatran, may also be initiated to neutralize the anticoagulant effect of dabigatran.

Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB)[6-7, 14]

Most cardiovascular drugs, including drugs for hypertension, coronary heart disease and arrhythmia should be continued before surgery to prevent the development of cardiovascular complications, as surgery may increase blood pressure and provoke tachycardia.[6] ACEI and ARB have been shown to intensify the hypotensive effects of anesthesia due to the suppression

Creatinine clearance	Interval between last dose and procedure	
	High bleeding risk	Low bleeding risk
Dabigatran		
>50 mL/min Dose 150 mg BD	Last dose: 3 days before surgery (skip 4 doses)	Last dose: 2 days before surgery (skip 2 doses)
30-50 mL/min Dose 150mg BD	Last dose: 5 days before surgery (skip 8 doses)	Last dose: 3 days before surgery (skip 4 doses)
Rivaroxaban		
>30 mL/min Dose 20 mg daily	Last dose: 3 days before surgery (skip 2 doses)	Last dose: 2 days before surgery (skip 1 dose)
≤30 mL/min Dose 15 mg daily	Last dose: 4 days before surgery (skip 3 doses)	Last dose: 3 days before surgery (skip 2 doses)
Apixaban		
>50 mL/min Dose 5 mg BD	Last dose: 3 days before surgery (skip 4 doses)	Last dose: 2 days before surgery (skip 2 doses)
30-50 mL/min Dose 2.5 mg BD	Last dose: 4 days before surgery (skip 6 doses)	Last dose: 3 days before surgery (skip 4 doses)
Edoxaban		
51-95 mL/min Dose 60 mg daily	Last dose: 3 days before surgery (skip 2 doses)	Last dose: 2 days before surgery (skip 1 dose)
15-50 mL/min Dose 30 mg daily	Last dose: 3 days before surgery (skip 2 doses)	Last dose: 2 days before surgery (skip 1 dose)

Figure 2. *Timing of Interruption of DOAC before Surgery or Invasive Procedures[12-13]*

of the renin-angiotensin-aldosterone system (RAAS) in several case reports. Therefore, depending on the comorbidities of the patients, ACEI or ARB may be withheld 24 hours before induction of anesthesia and should be resumed as soon as possible.[14]

Corticosteroid replacement for patients on long-term steroid therapy[15-16]

Though surgery generally triggers a stress response and result in an increase in plasma adrenocorticotrophic hormone (ACTH) and cortisol concentrations, patients who take regular oral corticosteroids may have their hypothalamic pituitary adrenocortical axis (HPA) suppressed, a process known as secondary adrenal insufficiency. Therefore, they cannot produce sufficient cortisol to mount the stress response during surgery and will then be at risk of adrenal crisis, leading to circulatory collapse and shock. Hence, patients who are on long-term steroid therapy due to conditions like inflammatory bowel disease, rheumatologic disease, adrenal insufficiency, reactive airway disease or immunosuppression for transplant recipients should be given corticosteroid replacement before and during surgery. The dose of corticosteroid replacement depends on patient's baseline glucocorticoid intake, duration of corticosteroid therapy, as well as the nature of surgery.[16]

Antibiotic prophylaxis[17-18]

Preoperative antibiotic prophylaxis is recommended in many types of surgery in order to prevent postoperative wound infections. Prophylactic antibiotics are usually given within 60-120 minutes before surgical incision or at induction of anaesthesia. A single dose of IV antibiotic or continuation up to 24 hours is generally sufficient. The efficacy of oral prophylactic antimicrobial agents has only been established in studies when used with mechanical bowel preparation for prophylaxis for colorectal procedures.

Efficacy, spectrum of activity, safety profile and cost of antimicrobial agents, as well as patient's medication allergies should be considered when selecting the appropriate antimicrobial agent for perioperative prophylaxis. In order to prevent surgical site infections, the selected antibiotic should target skin flora, including *Staphylococcus aureus* and *Staphylococcus epidermidis*. In clean-contaminated procedures, such as heart, kidney, and liver transplantations, the antibiotics should cover gram-negative rods and enterococci in addition to common skin flora. Antimicrobial agents with the narrowest spectrum of activity should be selected for surgical prophylaxis. Agents that are FDA-approved for use in surgical antimicrobial prophylaxis include cefazolin, cefuroxime, cefoxitin, cefotetan, ertapenem, and vancomycin **(Figure 3)**.

Cefazolin is the drug of choice for prophylaxis for most procedures, as it has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, and an excellent safety profile. A single dose of cefazolin 1g IV is recommended locally, and 2g is reserved for patients with body weight greater than 80 kg. In patients with beta-lactam allergy, clindamycin and vancomycin may be considered as alternatives. Routine use of vancomycin for prophylaxis is not recommended, and should only be considered in patients with known *Methicillin-resistant Staphylococcus aureus* (MRSA) colonization, at high risk for MRSA colonization (e.g. patients with recent hospitalization, nursing-home residents, haemodialysis patients), or true beta-lactam allergy.

Pre-operative MRSA screening and decolonization therapy[19-20]

Staphylococcal infection is not uncommon in hospitalized patients and is associated with substantial morbidity and mortality, including postoperative wound infections, nosocomial pneumonia and catheter-related bacteremia. To decrease the possibility of post-operative MRSA infections, a nasal swab may be performed and sent for conventional culture before the scheduled operation in high-risk patients. MRSA carriers will have to undergo MRSA de-colonization therapy before the operation to prevent unnecessary complications.

Mupirocin nasal ointment (Bactroban®) applied three times daily for 5 days is an effective, safe and relatively low-cost treatment for the eradication of MRSA and MSSA carriage. In addition, chlorhexidine gluconate 4% for bathing and shampooing should also be considered. The combination use of both agents was simple and had no major side effects. Upon repeated MRSA screening, patient can undergo operation as scheduled if he/she has 2 consecutive negative cultures. For persistent MRSA carriers, prophylactic vancomycin may be prescribed in the pre- and post-operative period.

POST-OPERATIVE MANAGEMENT

Acute pain management[21-23]

Pain is described by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage, or described in terms of such damage, and is always subjective".[21] The amount of pain a patient suffers after surgery is related to the extent of tissue damage and the site of surgery.[23] Patients should be assessed for their pain control using validated pain assessment tools in order to design the most appropriate postoperative pain management plan. Pain assessment helps to determine whether pain management is adequate, and whether analgesic or analgesic dose changes are required. Since pain is a subjective feeling, pain assessments are mainly based upon patient's self-report. Visual analogue scales and faces rating scales are examples of validated pain intensity assessment scales commonly used in practice. Apart from the pain intensity, onset and pattern, location, quality, any aggravating and relieving factors and response to previous treatment are also important elements in the pain assessment. For patients who cannot adequately report their pain because of cognitive deficits, sedation, developmental stage, or other factors, caregiver's input and behavioural assessment tools may be used.

Recommended Doses and Redosing Intervals for Commonly Used Antimicrobials for Surgical Prophylaxis				
	Recommended Dose		Half-life in Adults With Normal Renal Function, hr[19]	Recommended Redosing Interval (From Initiation of Preoperative Dose), hr[c]
Antimicrobial	Adults[a]	Pediatrics[b]		
Ampicillin-sulbactam	3 g (ampicillin 2 g/sulbactam 1 g)	50 mg/kg of the ampicillin component	0.8–1.3	2
Ampicillin	2 g	50 mg/kg	1–1.9	2
Aztreonam	2 g	30 mg/kg	1.3–2.4	4
Cefazolin	2 g, 3 g for pts weighing ≥120 kg	30 mg/kg	1.2–2.2	4
Cefuroxime	1.5 g	50 mg/kg	1–2	4
Cefotaxime	1 g[d]	50 mg/kg	0.9–1.7	3
Cefoxitin	2 g	40 mg/kg	0.7–1.1	2
Cefotetan	2 g	40 mg/kg	2.8–4.6	6
Ceftriaxone	2 g[e]	50–75 mg/kg	5.4–10.9	NA
Ciprofloxacin[f]	400 mg	10 mg/kg	3–7	NA
Clindamycin	900 mg	10 mg/kg	2–4	6
Ertapenem	1 g	15 mg/kg	3–5	NA
Fluconazole	400 mg	6 mg/kg	30	NA
Gentamicin[g]	5 mg/kg based on dosing weight (single dose)	2.5 mg/kg based on dosing weight	2–3	NA
Levofloxacin[f]	500 mg	10 mg/kg	6–8	NA
Metronidazole	500 mg	15 mg/kg Neonates weighing <1200 g should receive a single 7.5 mg/kg dose	6–8	NA
Moxifloxacin[f]	400 mg	10 mg/kg	8-15	NA
Piperacillin-tazobactam	3.375 g	Infants 2–9 mo: 80 mg/kg of the piperacillin component Children >9 mo and ≤40 kg: 100 mg/kg of the piperacillin component	0.7–1.2	2
Vancomycin	15 mg/kg	15 mg/kg	4–8	NA
Oral antibiotics for colorectal surgery prophylaxis (used in conjunction with a mechanical bowel preparation)				
Erythromycin base	1 g	20 mg/kg	0.8–3	NA
Metronidazole	1 g	15 mg/kg	6–10	NA
Neomycin	1 g	15 mg/kg	2–3 (3% absorbed under normal gastrointestinal conditions)	NA

Figure 3. *Recommended Doses and Dosing Intervals for Commonly Used Antimicrobials for Surgical Prophylaxis[17]*

Use of multimodal analgesics is recommended for postoperative pain management. Multimodal refers to the use of multiple agents that act by different mechanisms to provide analgesic effect. Round-the-clock analgesic is usually required in the immediate postoperative period. Paracetamol, NSAID/cyclooxygenase 2-selective (COX-2) inhibitors and opioids have different mechanisms of actions, and combination use may provide better pain control than either drug alone. Use of paracetamol or NSAIDs/COX-2 inhibitors in combination with opioids may offer synergistic pain control and opioid-sparing effect. Gabapentin and pregabalin are also effective in managing postoperative neuropathic pain. IV ketamine and IV lignocaine may also be added as part of multimodal analgesia.

Long-acting oral opioids are generally not recommended in the immediate postoperative period as the dose of analgesics may have to be frequently titrated at the beginning. Preoperative administration of opioids is also not recommended as it showed no clear benefit in improving pain control. Oral route is generally preferred over intravenous route for postoperative pain management, but IV boluses of opioids might be considered in the immediate postoperative period for more rapid pain relief and analgesic titration. For patients who cannot tolerate oral intake after surgery, use of intravenous patient-controlled analgesics (PCA) or epidural analgesics may also be considered. Intramuscular (IM) route should be avoided as it may cause significant pain and provides inconsistent analgesic effect due to erratic absorption.

When using multimodal analgesia, we should be aware of the different side effects of each agent. For instance, NSAIDs may increase the risk of gastrointestinal bleeding, renal dysfunction and cardiovascular events. Opioids may cause nausea and vomiting, constipation, sedation and respiratory depression. Opioids should be used with caution as there is also a potential for addiction and abuse.

Prophylaxis of Venous Thromboembolism (VTE)[24-25]

Venous thromboembolism, including deep venous thrombosis and pulmonary embolism, is common in postoperative setting. Appropriate interventions, both pharmacological and non-pharmacological, should be considered for VTE prophylaxis. Patients should be assessed for their risk of postoperative VTE prior to surgery, and the risk stratification is mainly based on the procedure type and patient's underlying VTE risk factors (e.g. previous VTE, immobility and malignancy). The risk of postoperative venous thromboembolism in orthopaedic patients, particularly those undergoing major hip and knee surgery, is highest among all surgical specialties. For patients at low risk of VTE, mechanical method of VTE prophylaxis, like graduated compression stockings, can be used. In patients with moderate to high risk VTE, use of heparin or DOAC is preferred. The duration of anticoagulation depends on surgery type, patient's history of VTE and patient's bleeding risk.

Intra-articular injection of tranexamic acid in total knee replacement surgery[26-27]

Tranexamic acid (TXA) is an anti-fibrinolytic agent that inhibits the activation of plasminogen to plasmin, which is an enzyme that degrades fibrin clots and fibrinogen. Through inhibiting tissue fibrinolysis, tranexamic acid stabilizes the possibility of clots entering the extravascular space and accumulating in tissues. Intra-articular tranexamic acid is given at the end of the operation to control blood loss and reduce the need for blood transfusion in total knee replacement surgery. When tranexamic acid is injected intravenously, only a small percentage of the drug reaches the target site. On the contrary, intra-articular tranexamic acid produces optimal concentration at the bleeding site with minimal systemic side effects. It also serves as an alternative route for patients, especially those with history of cardiac and cerebrovascular diseases, thromboembolism, and renal impairment.

CONCLUSION

Proper perioperative and postoperative management is crucial in minimizing unnecessary risk and in promoting early recovery from surgical procedures. Some medications should be continued throughout the peri-operative period to prevent disease relapse, while some medications have to be withheld or switched to alternatives before surgery. Appropriate perioperative antibiotic prophylaxis and screening for MRSA is recommended in order to prevent postoperative wound infections. Proper pain assessment and use of multimodal analgesics in the immediate postoperative period are essential for acute pain management associated with surgery.

Author's background

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Medication Management in Patients Undergoing Surgery

1. ***How long should aspirin be discontinued before surgery?***
   a. 1 day
   b. 3 days
   c. 5 days
   d. 7 days

2. ***Which of the following is INCORRECT?***
   a. Aspirin should be restarted as soon as adequate haemostasis has been achieved.
   b. Aspirin must be discontinued before all elective surgeries.
   c. Aspirin induces an irreversible inactivation of platelet cyclo-oxygenase (COX).
   d. Aspirin may increase the risk of postoperative bleeding.

3. ***The time of direct oral anticoagulants (DOAC) interruption before surgery depends on:***
   a. Patient's creatinine clearance
   b. Risk of bleeding
   c. Half-life of DOAC
   d. All of the above

4. ***Patient A is taking dabigatran and has a high bleeding risk. His recent creatinine clearance is 45 mL/min. How long should dabigatran be withheld before surgery?***
   a. 2 days
   b. 3 days
   c. 4 days
   d. 5 days

5. ***Which of the following may intensify the hypotensive effects of anesthesia?***
   a. Lisinopril
   b. Amlodipine
   c. Losartan
   d. a & c

6. ***The dose of corticosteroid replacement therapy depends on:***
   a. Indication of steroid therapy
   b. Duration of corticosteroid therapy
   c. Nature of surgery
   d. b & c

7. ***Which of the following is INCORRECT about antibiotic prophylaxis before surgery?***
   a. Perioperative antibiotic is required in all clean surgeries.
   b. Cefazolin is the drug of choice for prophylaxis in most procedures due to its spectrum of activity, duration of action and safety profile.
   c. Prophylactic antibiotics are usually given within 60 minutes before surgical incision or at induction of anaesthesia.
   d. Single dose of antibiotic is generally sufficient.

8. ***Which of the following is INCORRECT regarding Methicillin-resistant S. aureus (MRSA)?***
   a. Throat swab will be taken and sent for culture before scheduled operation to screen for MRSA.
   b. Nasal swab will be taken and sent for culture before scheduled operation to screen for MRSA.
   c. MRSA carriers should be preferably decolonized before the operation.
   d. There is an increasing trend of MRSA infection.

9. ***Which of the follow is INCORRECT regarding MRSA de-colonization therapy?***
   a. Chlorhexidine gluconate 4% may be added to mupirocin to eradicate MRSA.
   b. Patient can undergo operation as scheduled if there is one negative culture with nasal swab after completion of MRSA de-colonization therapy.
   c. If patient still have positive culture, the de-colonization culture should be repeated.
   d. Vancomycin may be used in persistent MRSA carriers.

10. ***Opioids should NOT be administered in which of the following routes in managing postoperative pain?***
    a. Oral
    b. Intravenous
    c. Intramuscular
    d. Epidural

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 264(D&T)

Review of Neurokinin-1 Receptor Antagonists in Chemotherapy-Induced Nausea and Vomiting

1. A 2. B 3. C 4. A 5. A 6. C 7. A 8. D 9. D 10. B

COVID-19: An Overview of its Transmission, Management and Prevention Strategies

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ABSTRACT

With the global pandemic threat of coronavirus disease 2019 (COVID-19) still upon us, researchers around the world are racing against time to find an effective treatment, and a vaccine in the longer-term to prevent and protect us from the threat of this novel infectious disease. A number of potential pharmacological options are undergoing trials. The results on Remdesivir from China and by Gilead have been conflicting. The combination of Lopinavir-ritonavir, Ribavirin and Interferon beta-1b are showing some early promises from an open-label study conducted in Hong Kong but there is no other good evidence as yet from other studies to show significant improvements, especially for patients with severe COVID-19. The data on Hydroxychloroquine and Chloroquine available so far were not of high quality and did not really show any good evidence on improvement. For Favipiravir, the data so far has been scarce and compared with another agent Umifenovir only, when some clinical improvement was shown. To date, it may be summarized that no antiviral therapy has been conclusively proven to be effective. Similar energies have been devoted concurrently in the search for a COVID-19 vaccine, and at the time of writing there are eight candidates going into Phase 1/2 clinical trials. However, despite extraordinary efforts and provided at least one of them is proven effective, a viable vaccine would take time before it is available on a commercial scale to meet the pandemic demand. While we are eagerly awaiting, in the intervening time, the best strategy to fend off COVID-19 infection is by adopting robust and effective preventive measures, in terms of: case isolation, contact tracing and quarantine, physical distancing, decontamination, hygiene measures including the wearing of masks and hand hygiene.

Keywords: *COVID-19, SARS-CoV-2, Coronavirus, Remdesivir, Lopinavir-Ritonavir, Ribavirin, Interferon, Hydroxychloroquine, Chloroquine, Favipiravir, Corticosteroids, Tocilizumab, Azithromycin, Vaccines*

INTRODUCTION

The alarm bell to the current pandemic of coronavirus disease 2019 (COVID-19) that threatens the world was first sounded when a pneumonia of unknown cause, detected in Wuhan, China was reported to the World Health Organization (WHO) Country Office in China on 31st December 2019.[1] The infectious culprit behind COVID-19 is now known to be severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single stranded RNA-virus. It is a beta-coronavirus, a genus of coronavirus where the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) also belong.[2] As it was reported that SARS-CoV shared 96% sequence identity with two bat-derived SARS-CoV, its origin from bats is highly suspected, although it is as yet unclear if any or what intermediate host might also be involved.[3] SARS-CoV-2 has around 80% resemblance in genetic sequence to SARS-CoV, and it is now known both viruses enter the host cells via angiotensin-converting enzyme 2 (ACE2).[4–6]

ACE2 is distributed and expressed in a wide variety of tissues within our body, including but not limited to our lungs, arteries, heart, kidneys and intestines.[7] While angiotensin converting enzyme (ACE) converts angiotensin I to the potent vasoconstrictor angiotensin II, ACE2 hydrolyses angiotensin II to angiotensin,[1-7] a vasodilator providing a counter-balance mechanism in the renin-angiotensin system (RAS).[8]

With the mode of entry into host cells in mind, the mode of transmission therefore is likely via respiratory droplets and direct contact (through hands then mucous membrane).[9] The SARS-CoV-2 viral titre in throat swab & sputum samples were reported to peak within 5 days after symptom onset,[10] which was different to SARS which peaked at around 10 days after onset. Notably some individuals could have positive viral titre before symptoms onset, indicating that a person could become infectious before they become symptomatic.[11] Compounding the issue, is that SARS-CoV-2 has emerged as more infectious than SARS-CoV, even though it may be less virulent.[12] The combined characteristics of SARS-CoV-2 is a recipe of pandemic potential.

In this article, the pharmacological management and prevention strategies of COVID-19 will be discussed with supporting evidence available up to the time of writing. The discussion on pharmacological management

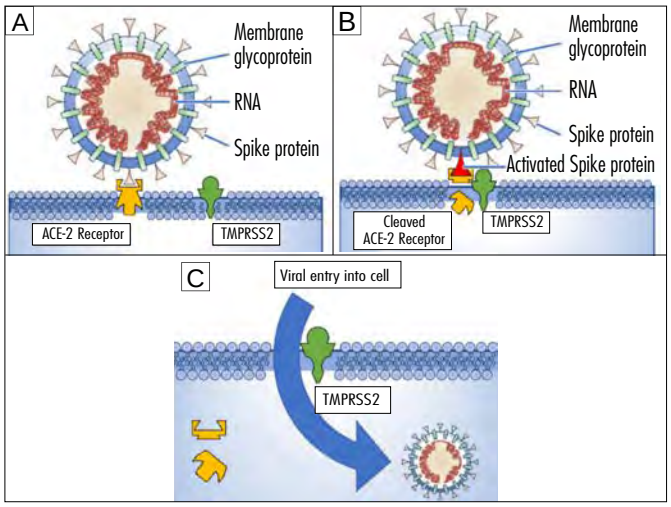

Figure 1. *Picture of SARS-CoV-2 illustrating interaction of viral spike protein with ACE2 receptors on host cell thereby gaining entry.* ***(A)*** *Spike proteins on the surface of the coronavirus bind to angiotensin-converting enzyme 2 (ACE-2) receptors on the surface of the target cell;* ***(B)*** *The type II transmembrane serine protease (TMPRSS2) binds to and cleaves the ACE-2 receptor. In the process, the spike protein is activated;* ***(C)*** *Cleaved ACE-2 and activated spike protein facilitate viral entry. TMPRSS2 expression increases cellular uptake of the coronavirus (Adapted from Rabi FA et al)*[6]

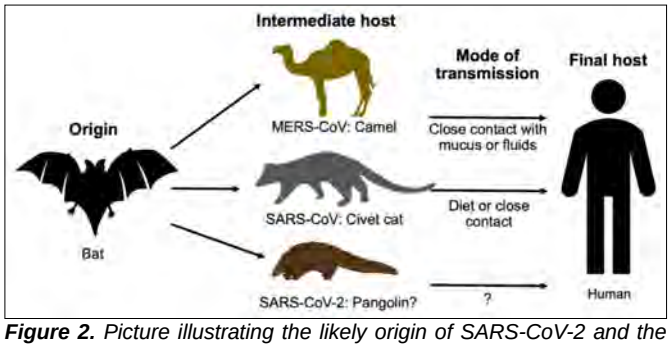

Figure 2. *Picture illustrating the likely origin of SARS-CoV-2 and the as yet uncertain intermediate host and mode of transmission. (Adapted from Yi et al)*[3]

will be limited to strategies that are available for use in public hospitals in Hong Kong so far.

ANTI-VIRAL TREATMENTS: RATIONALE AND EVIDENCE SO FAR

Remdesivir

Rationale of Use

Remdesivir is a broad-spectrum antiviral developed by Gilead originally for the treatment of Ebola virus disease. It is an adenosine nucleotide analogue prodrug. It binds to viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.

Remdesivir has shown *in vitro* activity against SARS-CoV-2.[13] In preclinical studies involving SARS-CoV and MERS-CoV, Remdesivir improved disease outcomes and reduced the viral level in mice.[14,15] Remdesivir initiated 24 hours prior to inoculation demonstrated prophylactic ability in a rhesus macaque model. When given 12 hours after MERS-CoV infection to rhesus macaques, Remdesivir reduced viral replication and the severity of lung disease compared to those in the control group.[16]

Clinical Trials

Several clinical trials using Remdesivir have been initiated globally.[17,18] The dosage of Remdesivir used was 200mg IV for 1 dose on day 1 followed by 100mg IV daily on Day 2-5 or Day 2-10. A randomized, double-blind, placebo-controlled, multicentre trial was conducted at 10 hospitals in Hubei, China.[19] The time to clinical improvement of patients in Remdesivir group did not show statistically significant difference from placebo group (hazard ratio 1.23; 95% CI 0.87-1.75). Clinical improvement rate at day 28 was 103/158 (65%) in Remdesivir group against 45/78 (58%) in placebo group (difference = 7.5%; 95% CI −5.7 to 20.7). 18/158 (12%) subjects discontinued Remdesivir due to adverse events while 4/78 (5%) discontinued placebo early.

Two other randomized, open label clinical trials called the SIMPLE trials were initiated by the drug manufacturer and have been conducted in multiple sites globally. On 24th April 2020, the preliminary results of the SIMPLE trial in severe COVID-19 patients were released in a press release.[20] Patients who received 10-day treatment of Remdesivir achieved similar improvement in clinical status compared to those randomized to a 5-day treatment course (odds ratio: 0.75; 95% CI 0.51 – 1.12) on Day 14. The time to clinical improvement for 50% of patients was 10 days in the 5-day treatment group and 11 days in the 10-day treatment group. In an exploratory analysis, patients who received Remdesivir earlier (within 10 days of symptom onset) had improved outcome compared to those who received Remdesivir later (after more than 10 days of symptom onset). 62% of patients treated early were discharged early compared to 49% who were treated late by day 14. The full data will be submitted to a peer-reviewed journal later.

The National Institute of Allergy and Infectious Diseases (NIAID) study has published their study results in a preliminary report on 22 May 2020. The study is designed as a randomized, controlled adaptive trial with multiple treatment arms.[21] The dosage of Remdesivir used in the study was the same as that in the China study. The data and safety monitoring board responsible for the study has recommended early unblinding of the results in view of shorter recovery time in the Remdesivir group. The preliminary results showed that patients who received Remdesivir had a faster time to recovery than those who received placebo, with a median of 11 days (95% CI 9 to 12) against 15 days (95% CI 13 to 19) respectively ($p<0.001$). Mortality rate according to the Kaplan-Meier estimate in the Remdesivir group was also lower compared to the placebo group (7.1% vs 11.9% respectively; hazard ratio for death, 0.70 (95% CI 0.47-1.04). The rate ratio in recovery was the greatest and statistically significant in patients with ordinal score 5 (hospitalized, requiring any supplemental oxygen) at baseline using Remdesivir.

Serious adverse events occurred in 21.1% in the Remdesivir group and 27.0% in the placebo group. Grade 3 and 4 events occurred in 28.8% in the Remdesivir group and in 33.0% in the placebo group. More patients receiving Remdesivir had pyrexia, decreased glomerular filtration rate, increased blood glucose, increased creatinine, prolonged prothrombin time, decreased blood albumin, alkalosis, dyspnoea and hypotension/hypertension than the placebo group. Serious adverse events such as cardiac arrest, atrial fibrillation, decreased glomerular filtration rate and shock occurred more frequently in Remdesivir group than placebo group. Otherwise, the incidence of adverse events was not significantly different between the Remdesivir group and the placebo group.

Lopinavir-Ritonavir, Ribavirin and Interferon

Rationale of Use

Lopinavir-Ritonavir inhibits coronavirus replication as a protease inhibitor. *In vitro* and animal studies show its activity for coronavirus including SARS-CoV and MERS-CoV.[22–24] The use of Lopinavir-Ritonavir, Ribavirin and Interferon (IFN) have been used in SARS and MERS with evidence of some clinical benefit.[22,25–27] It has also been extensively used in the treatment of HIV with known pharmacokinetics and safety profile.

Ribavirin targets viral RNA synthesis, inhibits viral RNA polymerase activities and guanosine triphosphate synthesis. It is suggested that Ribavirin is active against coronavirus in animal model mostly due to its indirect immunomodulatory effect rather than its weak anti-viral activity. *In vitro* activities of Ribavirin on SARS-CoV are variable and depends on the type of cells used in antiviral assay.[28,29] Ribavirin was seldom used as monotherapy in COVID-19 clinical trials.

Interferons bind to cellular surfaces' receptors and initiate JAK-STAT signaling cascades.[30] They exert immunomodulation effects,[31] and synergistic effects when used in combination with Ribavirin.[29,32] Interferons demonstrated anti-MERS-CoV and SARS-CoV activities *in vitro*.[14,33–35] Among the various types of Interferons, Interferon-beta appears to be the most active of the three classes of Interferons *in vitro* against SARS-CoV[29,33,34,36] and MERS-CoV.[14,34] Various clinical trials involving different types of Interferons are registered in clinicaltrials.gov,[17] which include α-Interferon nebulization and recombinant human Interferon α1β.

Clinical Trials

An open-label, randomized phase 2 clinical trial was conducted in Hong Kong comparing the combination of Lopinavir-Ritonavir 400mg/100mg Q12H, Ribavirin 400mg Q12H and Interferon beta-1b 8 units on alternate days for a maximum of 3 doses for 14 days against Lopinavir-Ritonavir alone.[37] The results showed that combination therapy had a significantly shorter median time to achieve negative SARS-CoV-2 nasopharyngeal swab than Lopinavir-Ritonavir monotherapy group (7 days and 12 days respectively, p=0.0010), a significantly shorter time to negative viral load in all specimens when assessed individually (8 days and 13 days respectively, p=0.001) and shorter duration of hospital stays (9 days and 14.5 days respectively, p=0.016). Interferon beta-1b was not initiated for patients who started treatment after >/= 7 days of symptom onset because of concerns regarding the pro-inflammatory effects of Interferon beta-1b in later stage of infection. The time to resolution of symptoms (defined as a NEWS2 of 0 maintained at 24 hours) was significantly shorter in the combination group than the control group (4 days and 8 days respectively, p<0.0001). Adverse events were self-limiting gastrointestinal symptoms with no difference between the groups.

In a randomized, open label study conducted in China, subjects with severe COVID-19 were assigned to receive either Lopinavir–Ritonavir 400mg/100mg Q12H plus standard of care against standard of care alone.[38] The median interval time between symptom onset and randomized was 13 days. The median days to clinical improvement were 15 days in the Lopinavir-Ritonavir group (n=96) and 16 days in the standard of care alone group (n=100). In the intention-to-treat population, Lopinavir-Ritonavir initiation within 12 days after symptom onset was not found to be associated with a shorter time to clinical improvement (hazard ratio, 1.39; 95% CI 1.00 - 1.91). No significant differences in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death were observed. Around 14% of subjects in the Lopinavir-Ritonavir group failed to finish the full 14-day course of administration primarily due to gastrointestinal adverse events.

Chloroquine and Hydroxychloroquine

Rationale of Use

Chloroquine and Hydroxychloroquine have both been extensively used in medicine with known pharmacokinetics and safety profile. Chloroquine has been used in the treatment of malaria, while Hydroxychloroquine has been used in the treatment of rheumatoid arthritis and malaria. They came to the spotlight in the treatment of COVID-19 mainly based on some *in vitro* studies. Both Chloroquine and Hydroxychloroquine have demonstrated *in vitro* activity against SARS-CoV-2, by reducing viral replication, and immunomodulating properties.[39–42] There is a report showing that Hydroxychloroquine may be more potent than Chloroquine *in vitro*; however, data are conflicting and additional studies are needed.[39,40]

Clinical Trials

Various clinical trials are initiated with different dosages. At least 23 clinical trials using Chloroquine/ Hydroxychloroquine in COVID-19 are ongoing in China

with more ongoing clinical trials in various countries.[43]

There are limited published clinical trials results evaluating the efficacy and toxicity of Chloroquine in COVID-19 treatment. According to a news briefing by the State Council of China in February 2020, Chloroquine had demonstrated superiority to the control treatment in inhibiting exacerbation of pneumonia, improving lung imaging findings, promoting virus-negative conversion and shortening of disease duration, with no obvious serious adverse effects, in more than 100 patients from various trials conducted in multiple centres in China.[44] However, no further information concerning the trial designs was reported and there is no published data of these clinical trials available for further review.[43]

Comparatively, Hydroxychloroquine has more clinical trial data published. Gautret et al. published an open-label non-randomized clinical trial including hospitalized patients with confirmed COVID-19 (n=36) in France. Virological clearance at day-6 post inclusion in patients who received Hydroxychloroquine and Azithromycin (HCQ+Azi, n=6), Hydroxychloroquine alone (HCQ, n=14) and no treatment (control, n=16) were compared. 100% in HCQ+Azi group, 57.1% in HCQ group and 12.5% in control group reached the primary outcome of virological clearance at day-6 ($p<0.001$).[45] There are several limitations for this trial though. Firstly, no information concerning the disease severity of patients assigned to each group is reported. Secondly, it only included a small sample size. Thirdly, 6 Hydroxychloroquine-treated patients were lost in follow-up because of early cessation of treatment, including 3 patients who were transferred to ICU and 1 patient who died. Also, Azithromycin was not originally intended for COVID-19 treatment, but added to prevent secondary bacterial infection as per clinical judgement.

Gautret et al. published another uncontrolled, non-comparative, observational study in a cohort of 80 relatively mildly infected inpatients treated with a combination of Hydroxychloroquine and Azithromycin over a period of at least 3 days with 3 main measurements: clinical outcome, contagiousness assessed by PCR and culture, and length of stay in infectious disease unit. Only 12 out of 80 patients required oxygen therapy and 3 patients required intensive care. Number of patients presumably contagious (with a PCR Ct value<34) steadily decreased overtime and reached zero on day 12. A rapid fall of viral load tested by qPCR was noted, with 83% negative at day 7, and 93% at day 8. Mean time from initiation to discharge was 4.1 days with a mean length of stay of 4.6 days. Several points to note are that almost all patients were considered low risk for clinical deterioration, including 4 asymptomatic carriers and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during the same time frame indeed. This is also an uncontrolled study and data presented cannot be used to determine whether a regimen of Hydroxychloroquine with Azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for patients with more severe disease.[46]

However, Molina et al reported different results from another prospective study in France. It assessed virologic and clinical outcomes of 11 consecutive hospitalized patients receiving the same dosing regimen of Hydroxychloroquine and Azithromycin as reported by the previous studies. In this study, 10 out of 11 of the patients had fever and received nasal oxygen therapy upon treatment initiation. Eight patients had comorbidities associated with poor outcomes. It showed that within 5 days, 1 patient died, 2 were transferred to the ICU. One patient discontinued the combination after 4 days due to QT prolongation. Eight out of 10 patients (excluding 1 died) were still positive for SARS-CoV-2 RNA in repeated nasopharyngeal swabs at days 5-6 after treatment initiation.[47]

A randomized, open-label study conducted in China also revealed insignificant clinical effects of Hydroxychloroquine. Thirty treatment-naïve patients with confirmed COVID-19 were randomized 1:1 to receive Hydroxychloroquine plus conventional treatment and conventional treatment only. A lower Hydroxychloroquine dose (400mg per day) compared to the dosage used in the French studies (600mg per day, Gautret et al. and Molina et al.) was used. On day 7, SARS-CoV-2 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the Hydroxychloroquine group and 14 (93.3%) cases in the control group ($p>0.05$).The median duration from hospitalization to virus nucleic acid negative conservation and the median time of temperature normalization were also similar in both groups.[48]

In conclusion, although Hydroxychloroquine and Chloroquine are included in some treatment guidelines, more evidence from ongoing clinical trials is needed to confirm the efficacy and safety of in the treatment of COVID-19. The US Food and Drug Administration has issued a safety communication cautioning against the use of Hydroxychloroquine or Chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to the risk of arrhythmias.[49] Optimal dosage of both agents is also unclear. There is currently no result from head-to-head comparison study between the two agents as well.

Favipiravir

Rationale of Use

Favipiravir is a RNA-dependent polymerase (RdRp) inhibitor that has been approved in Japan and China for the treatment of novel or re-emerging influenza virus infections in which other anti-influenza virus agents are not effective or insufficiently effective.[50] Favipiravir is converted into an active phosphoribosylated form (Favipiravir-RTP) in cells, which can be recognized as

a substrate by the viral RNA polymerase, thus inhibiting RNA polymerase activity. Favipiravir has been used in treating infections caused by RNA viruses, such as Ebola, in addition to influenza.[51,52]

In vitro study showed evidence of Favipiravir' s activity against SARS-CoV-2 in infected Vero E6 cells with high concentrations of drug.[13] Multiple clinical trials have been initiated in patients with COVID-19 in China, Japan, and other countries to evaluate Favipiravir alone or in conjunction with other antivirals or other agents.

Clinical Trials

A prospective, randomized, controlled, open-label multicenter trial was conducted, comparing conventional therapy plus Favipiravir (1600mg twice daily on the first day then 600mg twice daily thereafter for 7–10 days versus conventional therapy plus Umifenovir (200mg three times daily). Clinical recovery rate on day 7 did not significantly differ between Favipiravir group and Umifenovir group. Post-hoc analysis found that clinical recovery on day 7 was 62/111 (55.86%) in the Umifenovir group and 70/98 (71.43%) in the Favipiravir group (P=0.0199) for moderately ill patients with COVID-19. The latency to pyrexia reduction and cough relief in the Favipiravir group was significantly shorter than that in the Umifenovir group (P<0.0001).[53]

SUPPORTIVE TREATMENTS: RATIONALE AND EVIDENCE SO FAR

Apart from the intensive ongoing research aiming for an effective antiviral treatment for COVID-19, adjunctive treatment for COVID-19 is also another active area of research interest. In particular, the role of Corticosteroids and Tocilizumab in severe and critical COVID-19 patients has been widely discussed, and the intriguing use of Azithromycin in combination with Hydroxychloroquine is also being explored.

Corticosteroids

The use of Corticosteroids in COVID-19 is controversial. Although evidence of Corticosteroids use in COVID-19 is still limited, experience in other viral infections have been documented. It has been widely used during the outbreaks in the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) for its anti-inflammatory properties which might be useful in lung injury.[54] Yet, Corticosteroids will also inhibit immune responses and delay viral clearance, leading to prolonged viral shedding in the respiratory tract.[55] Observational studies on Corticosteroids use in patients with SARS and MERS had found an association of Corticosteroids use with delayed viral clearance from the respiratory tract and blood and high rates of complications including hyperglycemia, psychosis, and avascular necrosis, but no associations with improved survival.[56,57]

Recently, the use of Corticosteroids in suppressing cytokine storm or cytokine release syndrome (CRS)-like syndrome in COVID-19 is also under heated discussion. Studies had found that elevated levels of cytokines had been observed in severely ill patients with COVID-19[58] and the degree of increase was positively correlated with mortality rate and disease severity.[59,60] Cytokine release syndrome is an excessive immune response to external stimuli, which is closely related to the development and progression of acute respiratory distress syndrome (ARDS) and even fatality in severe or critical COVID-19 patients.[60] Corticosteroids, due to its anti-inflammatory property, have been used in combination with Tocilizumab or as monotherapy for the treatment of CRS induced by other conditions such as chimeric antigen receptor (CAR) T-cell therapy.[61] In COVID-19, the timely administration of a short course of glucocorticoids of no more than 1-2mg/kg of methylprednisolone or equivalent in critically ill patients might also inhibit excessive inflammation in the early stage of inflammatory cytokine storm and could effectively prevent the occurrence of ARDS and preserve patients' organ functions.[60] Thus, it is suggested that appropriate and short term use of Corticosteroids should be considered to inhibit cytokine storm and prevent disease progression in severe COVID-19 patients.[54]

The US National Institutes of Health currently recommend against the routine use of systemic Corticosteroids in mechanically ventilated patients with COVID-19 without ARDS, but recommend the use of low dose Corticosteroids in critically-ill COVID-19 patients with refractory shock. The use should be considered on a case-by-case basis.[62] Similar recommendation is also found in the Surviving Sepsis Campaign (SSC) guideline published by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, which recommends the use of Hydrocortisone 200mg per day.[63] Considering the scarce and conflicting evidence in COVID-19 and also the side effects associated with high dose Corticosteroids,[55] Corticosteroids must only be used when the benefits outweigh the risks in the treatment of COVID-19.

Tocilizumab

As mentioned earlier, elevation of cytokines levels including interleukin-6 (IL-6) have been observed in severely ill COVID-19 patients.[58] The release of a large amount of pro-inflammatory cytokines such as IL-6 , which is termed as cytokine storm, may result in undesirable outcomes such as ARDS.[64] Tocilizumab, being a recombinant humanized monoclonal antibody specific for the IL-6 receptor, has been suggested to have a role in attenuating cytokine storm in COVID-19 through its inhibition of IL-6, although the role of IL-6 in mediating cytokine storm in COVID-19 has not been established yet.[65]

At present, there is very limited published clinical trial evidence evaluating the safety or efficacy of Tocilizumab as supportive treatment for COVID-19. Available data

are limited to a retrospective, single-arm observational study of 21 patients with severe or critical COVID-19 pneumonia and case series/reports.[66,67] Multiple randomized controlled trials with an aim to address the safety and efficacy of this therapy in COVID-19 are now being planned or initiated globally.[68] Currently, the National Health Commission in China recommends Tocilizumab 4-8mg/kg once, which can be repeated for one more dose after 12 hours if initial dose is not effective, in patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in laboratory testing,[69] while the US National Institutes of Health and World Health Organization comment that there is insufficient data to make any recommendations yet. Before the availability of more supporting clinical data, the risks and benefits of using Tocilizumab in patients with COVID-19 should be carefully considered.

Azithromycin

Azithromycin is a macrolide antibiotic commonly used in the treatment of different bacterial infections. Interestingly, apart from its anti-bacterial property,[70] Azithromycin has also demonstrated *in vitro* activity against certain viruses such as H1N1[71] and Zika.[72–74] Recently, there has been report suggesting that the combination of Hydroxychloroquine and Azithromycin might have synergistic effect *in vitro* on SARS-CoV-2.[75] The rationale behind such proposed use of Azithromycin in COVID-19 is probably due its immunomodulatory and anti-inflammatory properties.[76] While the mechanism of such properties are yet to be confirmed, it is most frequently and consistently reported as contributed by reduced neutrophilic inflammation, interleukin-1beta and interleukin-8, which are pro-inflammatory cytokines.[77]

Clinical findings regarding the use of Azithromycin in combination with Hydroxychloroquine in the treatment of COVID-19 have been conflicting, with some trials demonstrated beneficial evidence of such combination,[45,46] while some did not.[47] Therefore, these results have to be further evaluated and confirmed in randomized controlled trials with larger sample size. There is insufficient data to confirm the clinical benefits of such combination at this moment. Also, as both Azithromycin and Hydroxychloroquine are QT-prolonging agents, concomitant use may enhance QT-prolonging effect and close monitoring for such effect and ventricular arrhythmias is required.[78] In view of the controversial data and potential toxicities, the US National Institutes of Health states that the combination of Azithromycin plus Hydroxychloroquine is not recommended for use in COVID-19.[62]

CURRENT STATUS OF VACCINE DEVELOPMENT

While the hunt for an effective COVID-19 treatment is still on, vaccination may be the ultimate solution for the COVID-19 pandemic. The production of a useful and viable vaccine is fraught with difficulties, not only in that it is expensive and an often huge investment risk, traditionally it also typically takes years to develop. For a new viral vaccine such as for COVID-19, a number of steps or hurdles will need to be overcome before it may be generally available.

The general steps involved would be no less than the following:[79]

(1) Viral sequencing – this could take an uncertain period of time provided the viral culprit was identified. For COVID-19, this turned out to be solved with the sharing of the genetic sequence of the novel coronavirus involved by China's National Health Commission to the WHO on 12 January 2020.[80]
(2) Need for a technological model – development of a technological model for production of vaccine prototype is required. This depends on the type of vaccine targeted. If for a DNA- or RNA-based vaccine, the time required may be shorter since synthetic processes are used and no culture or fermentation is involved. However, no such process has been validated or licensed.
(3) Animal model for testing vaccine – a suitable animal model will need to be found so as to proceed to rigorous safety testing in trials. This is necessary since vaccine candidates may exacerbate lung disease either directly by themselves or as a result of antibody-dependent enhancement.
(4) Elicitation of consistent immune response – the candidate vaccine(s) would need to be able to elicit a consistent immune response when administered. However, the potential duration of immunity and the number of doses required to produce an adequate level of immunity is unknown and needed to be worked out.
(5) Ability to scale up production – although the novel platform technology may produce a vaccine prototype, the candidate vaccine must be suitable for scaling up to large-scale manufacture in order to meet the demands in a pandemic.

In light of the pandemic, with the backing of government and non-government funding, researchers all around the world have been working hard to develop a vaccine against COVID-19 at record speed, hoping to curb the further spread of the disease. Up till 13th May, there are over 100 candidate vaccines all over the world, with 8 candidates in clinical evaluation.[81]

SARS-CoV-2 harbors a linear single-stranded positive sense RNA genome, encoding 4 structural proteins (spike (S), envelope (E), membrane (M), and nucleocapsid (N)] of which S is a major protective antigen that elicits highly potent neutralizing antibodies (NAbs). A variety of mechanisms and formulations have been employed in the development of vaccine against COVID-19, such as DNA-, RNA-based formulations, recombinant-subunits containing viral epitopes, adenovirus-based vectors and purified inactivated virus.

The table below summarized the candidate vaccines in clinical evaluation.[81]				
Platform	**Type of Candidate Vaccine**	**Developer**	**Mechanism**	**Stage of development**
Non-replicating viral vector	Adenovirus Type 5 vector	CanSino Biological Inc./ Beijing Institute of Biotechnology	- A genetically engineered vaccine which includes a replication-defective adenovirus type 5 as the vector expressing SARS-CoV-2 full length spike (S) protein[82]	Phase 2 trial in April 2020 (Active but not recruiting)
	ChAdOx1 (a chimpanzee adenovirus vaccine)	University of Oxford	- A genetically engineered vaccine which includes a replication-deficient common cold virus (adenovirus) from chimpanzees as vector express SARS-COV-2 spike (S) protein[83]	Phase 1/2 trial started in March 2020
DNA vaccine	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals	- Composed of optimized DNA plasmids, which are small circles of double-stranded DNA that are synthesized or reorganized by a computer sequencing technology and designed to produce a specific immune response in the body[84] - The DNA vaccines deliver optimized plasmids directly into cells intradermally using Inovio's proprietary hand-held smart device called CELLECTRA®. CELLECTRA® uses a brief electrical pulse to open small pores in the cell reversibly to allow the plasmids to enter, overcoming a key limitation of other DNA and mRNA approaches[84] - Once inside the cell, the plasmids are used by the cell's own machinery to generate specific coded antigens, which then stimulate an immune response[84]	Phase 1 trial started in early April 2020
Inactivated Vaccine	Inactivated	Beijing Institute of Biological Products/ Sinopharm	- Vaccines with purified inactivated SARS-COV-2 viruses - Selected strains of SARS-CoV-2 being grown on Vero cell line and purified - Induce SARS-CoV-2-specific neutralizing antibodies, especially the more effective Spike(S)- and receptor binding domain (RBD) antibodies - RBD-specific immunoglobulin accounts for part of the S-induced antibody responses[85]	Phase 1/2 trial started in April 2020
		Wuhan Institute of Biological Products/ Sinopharm		
	Inactivated + alum	Sinovac		Phase 1/2 trial started in April 2020
RNA	mRNA	BioNTech/ Fosun Pharma/ Pfizer	- The trial consists of 4 vaccine candidates, each representing different mRNA formats and target antigens[86] - Each mRNA format is combined with a lipid nanoparticle (LNP) formulation[86] - Two candidates include the large spike sequence, while the other two candidates include the smaller optimized receptor binding domain from the spike protein[86] - Expression of the mRNA by the cells would elicit the immune response	Phase 1/2 trial started in late April 2020
	LNP encapsulated mRNA	Moderna/ National Institute of Allergy and Infectious Diseases	- LNP encapsulated mRNA based vaccine - Encodes a prefusion-stabilized form of the SARS-COV-2 spike protein[87] - Cells will be directed to express the spike protein, which would elicit the immune response[88]	Phase 1 trial started in March 2020; Phase 2 trial has obtained approval from FDA

CONCLUDING REMARKS

The information or evidence on the management and prevention of COVID-19 are expanding exponentially with data becoming outdated almost as soon as they are published. It is clear, however, that to date conclusive evidence supporting an effective treatment for COVID-19 is still wanting, while an effective and viable vaccine is an uncertain distance down the road on the horizon. Until such a vaccine is finally available, the only practical approach to fend off COVID-19 infection is by adopting robust and effective preventive measures, in terms of: case isolation, contact tracing and quarantine, physical distancing, decontamination, hygiene measures including the wearing of masks and hand hygiene by frequent hand washings.[12]

For readers who are interested in more information on treatment or supportive therapies, they may use the QR-code provided to access a handbook with relevant interim information.

Author's background

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

COVID-19: An Overview of its Transmission, Management and Prevention Strategies

1. ***Which of the following is true about SARS-CoV-2?***
   (i) It is a double stranded DNA virus with close resemblance to SARS-CoV.
   (ii) It belongs to the same genus as SARS-CoV and Middle East respiratory syndrome virus.
   (iii) It enters through the host cells via angiotensin-converting enzyme 2.
   A. (i) and (ii)
   B. (ii) and (iii)
   C. (i) and (iii)
   D. (i), (ii) and (iii)

2. ***Which of the following explains the mechanism of action for remdesivir?***
   A. It is an adenosine nucleotide analog, which inhibits viral replication through premature termination of RNA transcription.
   B. It is a protease inhibitor with in vitro activity against various coronaviruses.
   C. It binds to cellular surfaces' receptors and initiate JAK-STAT signaling cascades.
   D. It is a partial agonist to the ACE2 receptor, hence inhibiting entry of virus into host cells.

3. ***Which of the following statement(s) about lopinavir-ritonavir is/ are true?***
   (i) It is a protease inhibitor which inhibits coronavirus replication.
   (ii) It was widely used in the management of SARS although in vitro activity against SARS-CoV was not demonstrated.
   (iii) It has been widely used for the treatment of HIV with known pharmacokinetics and safety profile.
   A. (i) only
   B. (i) and (ii)
   C. (i) and (iii)
   D. (ii) and (iii)

4. ***Which of the following statements is correct?***
   A. Interferon-alpha is proved to be most active among different classes of interferons against SARS-CoV.
   B. Ribavirin shows strong antiviral activity against all genus of coronavirus.
   C. When used for the treatment of COVID-19, ribavirin is usually used as monotherapy to reduce the incidence of adverse reactions.
   D. None of the above.

5. ***Which of the following is true regarding the use of hydroxychloroquine in COVID-19 management?***
   A. Studies consistently showed that hydroxychloroquine is more effective than remdesivir in the management of severe COVID-19 cases.
   B. Hydroxychloroquine can counteract the QT prolonging effect of azithromycin when used as combination therapy.
   C. Chloroquine is less toxic than hydroxychloroquine, although it is less potent than hydroxcyhloroquine against SARS-Co-V in in vitro studies.
   D. None of the above.

6. ***Which of the following statements is most accurate regarding the current situation of antiviral treatment of COVID-19?***
   A. Hydroxychloroquine has the most promising results among all antiviral treatments investigated so far.
   B. Remdesivir consistently demonstrates superiority over placebo for the time to clinical improvement for patients with COVID-19.
   C. Favipiravir is shown to have the highest clinical recovery rate when compared with remdesivir and hydroxychloroquine.
   D. To the date of publishing, no effective antiviral treatment has been identified yet.

7. ***Which of the following statements is true regarding the use of corticosteroids?***
   (i) The United States National Institutes of Health currently recommend against the routine use of systemic corticosteroids in mechanically ventilated patients with COIVD-19 without ARDS, but recommend the use of low dose corticosteroids in critically-ill COVID-19 patients with refractory shock.
   (ii) Hyperglycemia, psychosis and avascular necrosis are some of the potential side effects when used in high dose for the management of COVID-19.
   (iii) The use of corticosteroids in COVID-19 management may lead to delayed viral clearance.
   A. (i) only
   B. (ii) only
   C. (ii) and (iii) only
   D. (i), (ii) and (iii)

8. ***Which of the following is true about tocilizumab?***
   A. It is a monoclonal antibody found to have in vitro antiviral activity against coronaviruses.
   B. It is indicated for the treatment of cytokine release syndrome and other inflammatory conditions, such as rheumatoid arthritis.
   C. It is specific for the IL-1 and IL-6 receptors.
   D. Studies showed that the use of tocilizumab may be beneficial in COVID-19 patients who presented with reduced level of IL-6.

9. ***Which of the following correctly describes the challenges for COVID-19 vaccine development?***
   (i) The potential duration of immunity and number of doses needed to produce adequate immunity need to be determined.
   (ii) The genetic sequence of SARS-CoV-2 is not yet identified.
   (iii) The vaccine, once proven to be safe and effective, needs to be mass produced in order to meet the demands in the pandemic.
   A. (i) only
   B. (iii) only
   C. (i) and (iii) only
   D. (i), (ii) and (iii)

10. ***Which of the following are platforms used in development of candidate vaccines for COVID-19?***
    A. Non-replicating viral vector
    B. Inactivated vaccine
    C. DNA vaccine
    D. All of the above

Answers will be released in the next issue of HKPJ.

Nutritional Intervention and Pharmacotherapy in Malnourished Cancer Patients

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ABSTRACT

Malnutrition is a common condition in cancer patients. Cancer-related anorexia/cachexia syndrome results in decreased nutritional intake and unintentional weight loss. This may contribute to poor prognosis. Nutritional intervention is recommended for those cancer patients who can eat but are unable to maintain weight. Nutritional intervention consisting of dietary counselling and nutritional support aims to improve nutritional status. In addition, pharmaconutrients and pharmacological agents may play a role in improving clinical outcomes in cancer patients. This review summarizes the current practices of nutritional interventions and pharmacotherapy against cancer-related anorexia/ cachexia syndrome.

Keywords: *Malnutrition, cachexia, nutritional intervention, dietary counselling, pharmaconutrition*

INTRODUCTION

Malnutrition is a common condition affecting cancer patients. Literature reported that approximately 26% to 85% of cancer patients were malnourished.[1-4] Nutritional status of cancer patients significantly affects prognosis and their quality of life (QOL). Adequate nutrients including proteins and calories are important for healing and fighting against infections during cancer treatments. Protein-calorie malnutrition (PCM) can retard the healing process and increase risk of infection, leading to progressive wasting. It is also associated with decreased overall survival (OS) and decreased QOL.[5,6] Therefore, early detection and correction of malnutrition is crucial to improve OS and QOL of the patients.

MALNUTRITION DUE TO CANCER

Cancer may lead to malnutrition due to anorexia and cachexia. Anorexia, defined as the loss of desire to eat, is resulted from tumor-induced metabolic changes in cancer state.[7,8] Cancer can alter the taste and smell of food and therefore diminishes appetite.[9] Psychological stress also contributes to the development of anorexia in cancer patients.[10] Cachexia is another alarming condition in cancer patients. Cachexia is defined as a progressive irreversible wasting syndrome characterized by loss of body weight and muscle in a marked and gradual manner.[11] Statistically, cachexia is responsible of 22% death in cancer patients.[12] The etiology of cancer cachexia is not well studied. It has been proposed that tumour products impose catabolic effects on host tissues, leading to breakdown of the tissues and hence unintentional weight loss.[13-15]

MALNUTRITION DUE TO CANCER TREATMENT

Chemotherapy is the systemic treatment of cancers, which can result in systemic toxicity even at therapeutic doses as the drugs are widely distributed throughout the body.[16,17] The most common side effects include anorexia, taste changes, nausea, vomiting, diarrhea and mucositis.[18] These side effects can lead to decreased desire of food intake and therefore malnutrition. In addition, malnutrition can attenuate the ability to recover between chemotherapy cycles. Patients may be unable to adhere to chemotherapy schedule if their blood counts are suboptimal before next dosing.[19]

Radiotherapy is a relatively localized cancer treatment with fewer systemic side effects. Head and neck irradiation causes taste alteration, xerostomia and mucositis due to salivary gland dysfunction.[20-22] Thoracic irradiation causes esophagitis whereas abdominal irradiation may cause nausea and vomiting.[23] Pelvic irradiation can cause small bowel disease and radiation enteritis.[24,25] These complications can lead to decreased oral intake, decreased nutrients uptake and eventually malnutrition.

Surgery is one of the major modalities of cancer treatment. Some types of procedures can create mechanical barriers to nutrient uptake.[26] Bowel resection, as a common surgical treatment in gastrointestinal cancers, can lead to a shortened gastrointestinal tract and hinder nutrients absorption.[27,28]

Surgery itself is traumatic to patients and therefore adequate nutrients are essential for the healing process. Literature reported that malnutrition at the time of surgery portends poorer prognosis.[29]

NUTRITIONAL INTERVENTION IN CANCER PATIENTS

Nutritional intervention, recommended for cancer patients who can still eat but are at risk of malnutrition, aims to improve nutritional status.[30] Nutritional intervention includes dietary counselling and nutritional support. Dietary counselling is the first-line option to improve adherence to daily diet. Nutritional support is the next step to promote nutritional intake in cancer patients if they are unable to maintain normal diet. When oral nutritional support is not feasible, artificial nutrition is adopted to improve nutritional status.

Nutrition-related side effects of cancer treatments can cause dysphagia and malabsorption of nutrients. Lifestyle modification encourages nutritional intake and hence improves nutritional status. A systematic review showed that dietary counselling increases QOL of cancer patients, yet results failed to reach statistical insignificance.[31] Dietary counselling may serve a minor role in improving QOL in cancer patients by symptomatic management.

Nutritional support is recommended when cancer patients are unable to obtain adequate nutrition from diet.[30] Oral nutrition is the first-line choice. However, oral nutritional supplementation may not be feasible when oral intake or food transport is impaired. Therefore, enteral nutrition may serve as another option to improve nutritional status.[32,33] Percutaneous endoscopic gastrostomy (PEG) feeding and nasogastric tube feeding are the two major options in administering enteral nutrition. In case of severe gastrointestinal function impairment, parenteral nutrition is adopted to provide nutrition[30,34,35] However, it is associated with increased cost and risk of infectious complications.[36,37] In general, parenteral nutrition is only recommended if intestinal function is impaired and prognosis is more than two months.[30] A systematic review by the American Gastroenterological Association (AGA) revealed that the use of parenteral nutrition in cancer patients did not provide significant survival benefits but was associated with increased rate of complication.[38] Therefore, it is recommended that parenteral nutrition is only reasonable when conventional oral nutrition is inadequate.[30]

PHARMACONUTRITION

Pharmaconutrition refers to the use of nutrients in pharmacological doses to exert metabolic effects, resulting in clinical outcomes.[39,40] These pharmaconutrients are used as an adjunct to conventional nutritional support, aiming to manage cancer cachexia. These agents are easily accessible in community pharmacy.

Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) is a kind of polyunsaturated long chain omega-3 fatty acid and is largely abundant in fish oil.[41] Previous studies suggested that EPA may play a role in suppressing systemic inflammatory responses in cancer patients.[42-46] High dose of omega-3 fatty acids (more than 2 g/day) was reported to have clinical anti-inflammatory effects.[47] European Society for Parenteral and Enteral Nutrition (ESPEN) and American Society for Parenteral and Enteral Nutrition (ASPEN) suggest the use of omega-3 fatty acids in cancer patients at risk of malnutrition.[30,48]

To date, EPA supplementation in cancer patients is not supported by robust clinical evidence. Six clinical trials studying effects of fish oil supplements (with EPA content 0.4 – 2.2 g/day) in advanced stage cancer patients showed improvement in appetite, energy intake, body weight, lean body mass and QOL.[44,49-53] The results of a randomized control trial on 92 patients with advanced lung cancer undergoing chemotherapy showed that EPA supplementation was associated with maintained body weight and less anorectic symptoms.[52] However, the sample size of these studies was small. Nevertheless, four trials with sample sizes ranging between 60 and 518 patients suggested that there was no significant clinical benefits in cancer patients under fish oil supplementation.[47,54-56] Recent systematic review concluded that omega-3 fatty acids supplement was beneficial for cancer patients undergoing chemotherapy and radiotherapy by preserving body composition.[57]

Glutamine

Glutamine belongs to the class of non-essential amino acid and is important for nucleotide synthesis.[58] It is important to intestinal mucosal integrity by facilitating gastrointestinal mucosal healing, especially for damage due to cancer treatment.[59] The major reported benefits of glutamine include improvement of radiation enteritis, stomatitis, esophagitis and skin toxicity.[30] Therefore, glutamine was believed to have beneficial effects on relieving chemotherapy toxicity. However, a narrative review suggested that the clinical evidence of glutamine supplementation was not strong.[60] Only 8 out of 24 studies using oral glutamine supplementation and 6 out of 12 studies using parenteral glutamine supplementation showed clinical benefits in cancer patients. There is currently no international guideline recommending supplementation of glutamine to cancer patients.

PHARMACOLOGICAL AGENTS

Pharmacological agents may have a role in improving nutrition in cancer patients. Corticosteroid and

progestin are recommended by ESPEN guidelines as pharmacological agents on nutrition in cancer patients to improve clinical outcomes.[30]

Corticosteroids

Corticosteroids are associated with increased appetite, which may serve as a potential appetite stimulant in oncologic patients.[61] The use of corticosteroids was demonstrated with significant improvements in appetite and QOL in six studies with a total of 637 cancer patients.[62] There was insufficient evidence to show superiority of any specific corticosteroid over another.[63] Nevertheless, corticosteroids are well-known for causing insulin resistance, myopathy, immunosuppression, and osteoporosis. Therefore, the use of corticosteroids to increase appetite should only be limited to a short period of time.[30]

Progestins

Progestins including megestrol acetate and medroxyprogesterone acetate were shown to stimulate appetite and induce weight gain.[64,65] The use of progestin was associated with improvement of appetite, energy intake and weight in a systematic review with 29 trials with a total of 4139 cancer patients. However, improvement in QOL was minimal.[62] In terms of side effect profile, adverse effects of progestin include impotence, vaginal spotting, edema and thromboembolism.[66,67] These potential side effects have to be taken into consideration when using progestins as appetite stimulants in cancer patients.

CONCLUSION

Cancer patients often require special nutritional needs. Dietary counselling to cancer patients is associated with improvement in QOL but only with questionable significance. Oral nutritional supplementation improves QOL but not providing survival benefits. In serious circumstances, invasive feeding including enteral and parenteral nutrition may be the option but they provide no improvement in survival yet increased complication rates. Although pharmaconutrients are recommended in international guidelines, clinical evidence is not robust and consistent data are lacking. Further research is warranted to explore the role of these agents in the management of malnutrition in cancer patients. In the meantime, pharmacological agents remains to be the reliable option in improving nutritional status and thus are recommended for use after balancing the benefits against the potential side effects.

Author's background

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SHPHK: Thank you Pharmacists

*Reported by **LEUNG, Vienna***
Pharmacist of the Society of Hospital Pharmacists of Hong Kong

These are uncertain times for all of us.

The Hong Kong health system has been facing an unprecedented challenge with COVID-19. Healthcare professionals are working selflessly day and night to safeguard the health of patients. The Society of Hospital Pharmacists of Hong Kong (SHPHK) would like to take this opportunity to thank its Members for working tirelessly and maintaining their professionalism during the COVID-19 epidemic.

COVID-19 Myths Debunked - Equipping Hong Kong Citizens with the Correct Knowledge to Fight the Virus

In the past few months, the Society has been trying to deliver correct messages about COVID-19 to Hong Kong citizens through media interviews and article publications in different newspaper columns, hoping to provide the latest evidence-based advice regarding COVID-19 to the general public. For example, the Society has earlier talked about the safety of ibuprofen for fever-associated COVID-19, the ingredients of different alcohol sanitizers and the experimental treatments for COVID-19 in various media interviews.

In view of the fierce virus outbreak, the Drug Education Resources Centre (DERC) has also launched a brand new column, namely 抗疫專欄 in its website. In this column, you may find all Society's interviews with different media regarding COVID-19, as well as a series of COVID-19 related articles written by the DERC editors. The DERC team will continue to do their best to promote the safe and effective use of medications by the public.

To learn more about 抗疫專欄, please go to: www.derc.org.hk.

Never Stop Learning – SHPHK Educational Events 2020

As COVID-19 continues to spread, most of the live educational seminars have been postponed or cancelled, but this should not be an excuse for us to stop learning!

To help its Members to maintain their continuing professional development, SHPHK will be hosting a series of webcasts on different clinical topics in the coming months.

The first webcast on **'The Role of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease Care'** will be held on 15th April 2020. The webcast will offer two sessions, both covering the same materials, so you may choose a session that best suits your schedule. There will also be a webcast on **'The Frontline Perspective on Implementing Preferred Reliever'** and **'Update on Biologics'** in May and June, respectively.

More details will be announced through the SHPHK News Reporter Channel in due course.

The 33rd SHPHK Annual General Meeting

Due to the outbreak of COVID-19, the Committee of SHPHK has decided to postpone the Annual General Meeting (AGM) of the Society until mid-June 2020, as advised by the Society's legal advisor. We will provide another update on the AGM in mid-May. Please stay tuned!

We hope we would be able to see you all again very soon. Take care for now!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

香港藥學會全力支持政制及內地事務局「爲有緊急藥物需要的港人送遞處方藥物特別計劃」

在新型冠狀病毒疫情肆虐下，不少港人被逼滯留內地，當中有不少長期病患者需要定期到醫院覆診，但因無法親身回港覆診取藥而面臨斷藥問題；另外，亦有親友嘗試寄藥給內地的港人遇到困難，如不能透過郵寄或速遞公司等協助。有見及此，政府及不少機構都希望能為有需要的市民出一分力，而政制及內地事務局則考慮推行「為有緊急藥物需要的港人送遞處方藥物特別計劃」。故此，香港藥學會被邀請參與這個試驗計劃，並協助設計整個審核及重整藥物的流程以讓各政府部門考慮是否可行。香港藥學會會長龐愛蘭在整個試行的過程中，與各政府部門不斷交流及改善，最終獲得認可，並由局方在2月24日正式向外公佈落實計劃。是次的寄藥行動，由政制及內地事務局推行，工聯會統籌，香港藥學會藥劑師審核藥物，並由社會福利處人員負責寄出。

寄藥行動由二月開始，每逢星期一、四全日服務，至今已完成超過六千多個個案，計劃預計會於五月結束。藥劑師在過程中會義務審核港人親友代從醫管局、衛生署、私家醫生診所或透過醫生紙到藥房取得的藥物是否屬「醫生處方藥物」；檢查藥物的劑量是否恰當、種類是否齊全、有沒有漏藥；遇到沒有藥物標籤的藥物，會即時透過醫健通核實醫生是否處方該藥物給患者，重新整理其藥物及列明用藥方法；解答親友在藥物方面的疑難，讓他們向患者轉達用藥需要注意的事項。

香港藥學會衷心感謝每一位義務參與的藥劑師，您無私的付出及專業精神是大家有目共睹的，很多市民亦向我們表達了感激之情。是次計劃充份體現了在疫情之下，大家仍然能守望相助，令人感動。

圖一：前食物及衛生局局長到訪寄藥計劃現場，為藥劑師打氣。


圖二：香港藥學會義務藥劑師合照。


圖三及圖四：藥劑師正審核親友帶來的處方藥物。

Change of Capsule Colour

PRADAXA®
(Boehringer Ingelheim)

Prepared and edited by Ivy Chan

Active Ingredient:
Dabigatran etexilate (as mesilate)

Presentations:
Each hard capsule contains 75 mg, 110 mg or 150 mg of dabigatran etexilate (as mesilate).

75mg: Capsules with white, opaque cap and white, opaque body (size 2)

110mg: Capsules with light blue, opaque cap and light blue, opaque body (size 1)

150mg: Capsules with light blue, opaque cap and white, opaque body (size 0)

Pharmacological Properties:
Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.

Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Indications:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Forensic Classification:
P1S1S3

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: ***Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drugs & Therapeutics; Primary Care; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology*** and ***New Products***. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular four issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

Submission of Manuscript

Submission of a paper implies that it has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors are specifically discouraged from submitting papers as fragmented studies of a particular topic. A manuscript must be indicated which section it is belonged. Upon received, it will be screened by a **Sectional Editor** of HKPJ for initial consideration before it is sent out for further review or comment.

For online submission:
Authors are encouraged to submit manuscripts using the online submission system. Access to the system, and full instructions on its use, can be found on the HKPS website at: http://www.HKPS.org/HKPJ/Guidelines. In creating the electronic version of their manuscript, authors are requested to follow the guidelines for submitting files. The paper should be submitted as a single file, prepared with a standard word-processor such as Microsoft Word, with embedded tables and graphics. Please note that any embedded graphics must also be submitted as separate, original files. The preferred formats for graphics files are tiff or postscript. All correspondence between Editor and author is performed by email. Authors are reminded that the copyright of their article or paper is automatically transferred to HKPJ once it is accepted for publication in the journal.

For hardcopy submission:
Three copies of the manuscript are required on either 8.5"x11" or A4 paper (two copies are used for review purposes and the original is kept on file at the Section Editor). Copies must be produced on a high-quality printer, and originals and copies of all Figures and Schemes must be fully legible. Initially only send hard copies of the paper; when it has been refereed, revised if necessary, and accepted, you will be requested to send a disk containing the final version with the final hard copy to the appropriate Editor. Make sure that the disk and the hard copy match exactly. The revised manuscript must be returned to the Editors within one month, otherwise it may be deemed to be new and subject to further review. When submitting the final version with a disk please label all disks with "HKPJ", your name, software (e.g. word 2000), hardware used (e.g. PC or Macintosh) and file names with the correct extension (e.g. Fig 1.cdx, Table 1-6. xls). Save text on a separate disk from the graphics, include the text and tables in one file, and provide graphics and structures in separate numbered files. Please remember to keep a backup copy of both the electronic files and original manuscript for reference and safety since we cannot accept responsibility for damage or loss of papers. Original manuscripts are discarded three months after publication unless the Publisher is asked to return original material after use.

Suggested Referees

Please submit, with your manuscript, the names and addresses of 2 potential referees. You may also mention persons who you would prefer not to review your paper.

Editorial Authority

The Editors of HKPJ reserve the right to make alterations to manuscripts submitted for publication. Such alterations will be made if manuscripts do not conform with accepted scientific standards or if they contain matter which in the opinion of the Editors is unnecessarily verbose or unclear. Alterations may be queried, but this will inevitably delay publication.

Preparation of manuscript

The manuscript is required to be written in English, with numbered pages, single-spaced, using Arial 9 point font, and in a suitable word-processing format. Each page should have adequate margins (4 cm) and liberal spaces at top and bottom of the manuscript. All textual elements should begin flush left, with the second paragraphs onwards indent, and should use the wrap-around end-of-line feature, i.e. no returns at the end of each line. Place two returns after every element such as title, headings, paragraphs, figure and table call-outs. Most formatting codes will be removed or replaced on processing your article. Please do not use options such as automatic word breaking, justified layout, double columns or automatic paragraph numbering (especially for numbered references). However do use bold face, italic, subscripts, superscripts etc. The Editors reserve the right to adjust style to certain standards of uniformity. If authors are unfamiliar with HKPJ, they should consult a recent copy (or the free online sample copy available from www.HKPS.com/HKPJ) to see the conventions currently followed for guidance in preparing submissions.

The content of manuscripts must be arranged as follows: (1) a Title Page with authors name(s) and address(es); (2) an Abstract, in which contents are briefly stated; (3) a 4 to 6 Key Word Index, (4) Introduction, and (5) the Results and Discussion (preferably combined). Although each section may be separated by headings, they should form one continuous narrative and only include details essential to the arguments presented. If a discussion is separately provided, it should not include a repetition of the results, but only indicate conclusions reached on the basis of them, and those from other referred works; (6) Conclusions or Concluding Remarks; (7) the Experimental should include brief details of the methods used such that a competent researcher in the field may be able to repeat the work; (8) Acknowledgments; (9) References; (10) Legends, Formulae, Tables and Figures.

Title Page and Author Names: Titles must be as brief as possible, consistent with clarity, and should not exceed 10 words in length. Uninformative phrases such as "Chemical examination of", "Studies on", "Survey of", "New", "Novel" etc. will be deleted. If a paper is part of a series, this must not be given in the heading, but referred to in a footnote in the form: *Part 9 in the series "The Role of Pharmacists in Medical Care of Patients" followed by a numbered reference to the previous part. Author names should be typed right underneath the article title. Each author should identify himself or herself with Surname in capital letters, followed by the first name. All names are separated by a semicolon (;). An asterisk should be placed following the name of the author to whom correspondence inquiries should be made. Full postal addresses must be given for all co-authors. Superscript letters; a, b, c should be used to identify authors located at different addresses.

An **Author's background box** at the end of each article is mandatory to include the author's job title and the affiliated institutle or organization. Full details of telephone, fax numbers and e-mail address should also be indicated for the corresponding authors. No academic or professional membership title is allowed.

ABSTRACT: The abstract should be on a separate page and briefly describe the results obtained and conclusions reached, not the methods used, or speculations on any other matter. They are not expected to be a complete summary but only an outline of the main findings. The abstract should be contained within 250 words and should be readable without reference to the rest of the paper.

Key Words: Authors must give four to six "key words" or phrases, which identify the most important subjects covered by the paper.

INTRODUCTION should give the minimum historical data needed to give appropriate context to the author's investigation and its relationship to other similar research previously or currently being conducted. Only information essential to the arguments should be presented. Much data can be taken for granted or quoted in abbreviated form. Specific term (genus, species, authority) of all experimental works must be given at first mention and preferably be in the form adopted by the International Scientific Community.

RESULTS AND DISCUSSION: These sections should be carefully prepared with discussions of the results being compared with existing and/or previous knowledge within the field. Authors are, however, encouraged to combine the Results and Discussion sections wherever possible.

EXPERIMENTAL: Subsections on the Experimental Procedures should be italicized and inserted as part of the first line of the text to which they apply. HKPJ encourages an extensive use of abbreviations (these are listed at the back of the Instructions to Authors, or the reader is referred to other sources). The Experimental should begin with a subsection entitled General Experimental Procedures. This subsection will typically contain brief details of instruments used, and identification of sources of specialized chemicals, biochemicals and molecular biology kits. The next subsection describes the source(s) and documentation of biological materials used, whether in reference to whole plants or parts there from, crude drugs, or any other plant material from which identifiable chemical substances are obtained for the first time. Documentation must also include a reference to voucher specimen(s) and voucher number(s) of the compounds, plants or other material examined. If available, authors should quote the name and address of the authority who identified each sample investigated. Specimens should preferentially be deposited in a major regional herbarium where the collection is maintained by state or private institution and which permits loan of such materials. With other microorganisms, the culture collection from which they were either accessed and/ or deposited should be included, together with identification of the strain designation code. The Experimental Procedures employed should be concise but sufficiently detailed that a qualified researcher will be able to repeat the studies undertaken, and these should emphasize either truly new procedures or essential modifications of existing procedures. Experimental details normally omitted include: (I) method of preparation of common chemical and biochemical derivatives, (2) excessive details of separation of compounds, proteins and enzymes, e.g. preparation of columns, TLC plates, column and fraction size. Compound Characterization: Physical and spectroscopic data for new compounds must be comprehensive, and follow the order shown below: compound name (and assigned number in text); physical state of compound (e.g. oil, crystal, liquid, etc.), melting and/or boiling point; optical rotation and/or circular dichroism measurements, if optically active; UV; JR, IH NMR; 13C NMR; MS. For all new compounds, either high-resolution mass spectral or elemental analysis data is required. See later section for method of data presentation.

Nomenclature: Chemical nomenclature, abbreviations and symbols must follow IUPAC rules. Whenever possible, avoid coining new trivial names; every effort should be made to modify an existing name. For example, when a new compound is described, it should be given a full systematic name according to IUPAC nomenclature and this should be cited in the Abstract or in the Experimental section.

ACKNOWLEDGMENTS: This section is used to provide brief credit for scientific and technical assistance, and in recognition of sponsorship through financial support and any other appropriate form of recognition.

References: All publications cited in the text should be presented in a list of references following the text of the manuscript. In the text refer to the author's name (without initials) and year of publication (e.g. "Since Peterson (1993) has shown that ..." or "This is in agreement with results obtained later by Kramer.[4]" For two authors both authors are to be listed, with "and" separating the two authors. For more than two authors, use the first author's surname followed by et al. The list of references should be arranged according to the order of their appearance in the text with no more than three authors listed. If number of authors of a reference exceeds three, "et al" is used followed by year of publication in bracket after the first author. Journal titles should be completely shown followed by the volume, issue number in bracket if included, colon and start – final page number. The manuscript should be carefully checked to ensure that the spelling of authors' names and dates are exactly the same in the text as in the reference list. Some examples of references are shown below:

(1) Cabello-Hurtado F, Durst F, Jorrin JV, Werck-Reichhart D. et al. (1998). Coumarins in Helianthus tuberosus: characterization, induced accumulation and biosynthesis. *Biochemistry,* 49(1):1029-1036.

(2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids.* 2nd Ed, pp. 79-105. Springer Verlag, New York.

(3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn 0, (Eds.), *Comprehensive Natural Products Chemistry,* Vol. 8. pp. 137-196. Pergamon, Oxford.

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Abbreviations
About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), μM, mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min^{-1})
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ^{1}H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, μm, mm, cm, m
Literature: lit.
Mass spectrometry: m/z $[M]^{+}$ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M_r
Nuclear magnetic resonance: ^{1}H NMR, ^{13}C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or $^{-1}$
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation $sec^{-1)}$
Repetitive manipulations: once, twice, x3, x4, etc.
RR_t (relative retention time), R_1 (Kovat's retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H_2O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: 1, (litre), μ1, ml
Weight: wt, pg, ng, μg, mg, g, kg

Inorganics, e.g. $AlCl_3$ (aluminum chloride), BF_3 (boron trifluoride), Cl., CO_3, H_2, HCl, $HClO_4$ (perchloric acid), HNO_3. H_2O, H_2O_2, H_2SO_4, H_3B0_3 (boric acid), He, $KHCO_3$ (potassium bicarbonate), $KMn0_4$ (potassium permanganate;), KOH, K-Pi buffer (potassium phosphate buffer), $LiAlH_4$ (lithium aluminium hydride), Mg^{2+}, $MgCl_2$, N_2, NH_3, $(NH_4)_2S0_4$, Na^{+}, $NaBH_4$ (sodium borohydride), NaCl, $NaI0_4$ (sodium periodate), NaOH, Na_2S0_3 (sodium sulphite), Na_2S0_4 (sodium sulphate), $Na_2S_20_3$ (sodium thiosulphate), 0_3, PPi (inorganic phosphate), SO_4^{2-}., Tris (buffer).

Organics, e.g. Ac_20 (acetic anhydride), n-BuOH (butanol), C_6H_6 (benzene), CCl_4 (carbon tetrachloride), CH_2Cl_2 (methylene chloride), $CHCl_3$ (chloroform), CH_2N_2 (diazo-methane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetra-acetic acid), Et_20 (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), $HC0_2H$ (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me_2CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran). ^{1}H NMR solvents and standards: $CDCl_3$ (deutero-chloroform), D_2O, DMSO-d_6 [deuterodimethylsulphoxide not $(CD_3)_2S0$], pyridine-d_5 (deuteropyridine), TMS (tetramethylsilane).

For further terms used in biochemistry and molecular biology the authors should see the websites of the nomenclature committees (www.chem.qmul.ac.uk/iubmb/).

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