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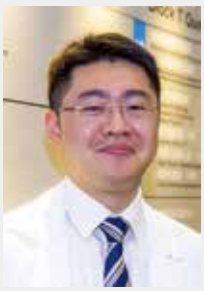
We never know or expect if there is a return before giving, but it is always more blessed to give than to receive.



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Integrative Chinese-Western Medicine in Hong Kong: Present and Future

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Today we celebrate the 20th anniversary of the Hong Kong Association for Integration of Chinese-Western Medicine (HKAIM). It constitutes the primary platform for the promotion of integrative medicine practice in the territory. The unexpected advent of the COVID-19 pandemic for over a year has rendered both huge challenge and precious opportunity for the augmentation of integrative medicine. On 26 January 2021, the Hospital Authority (HA) Chinese Medicine Department, under the leadership of Ms Rowena Wong, officially launched a scheme called "the Special Chinese Medicine Service for COVID-19 Patients in the Community Facilities". The scheme essentially allows Chinese medicine practitioners (CMPs) seconded from the tripartite Chinese medicine centres to serve the COVID patients admitted to the Asia-World Expo community facilities. Chinese medicine (CM) diagnosis and treatment strategies were, for the first time, made possible to the COVID patients as CMPs and western medicine (WM) doctors worked side by side under the same roof. This service set an important precedent in Hong Kong for the joint management of emerging infectious disease of pandemic scale integrating Chinese and Western medicine, despite the fact that integrative medicine has been used routinely in mainland China to combat COVID patients with exceptional results.

This scheme is an extension of the ongoing Integrated Chinese-Western Medicine (ICWM) programme where patients suffering from stroke, cancer and pain admitted to selected HA hospitals can opt for additional CM treatment (including acupuncture and herbal medicine) while they are under routine WM management. With Hong Kong's first Chinese Medicine Hospital (CMH) setting for operation soon, we at HKAIM have every reason to believe, and hope for, a new pinnacle in integrative Chinese and Western medicine practice in Hong Kong. The mode of "CM as the main treatment method, while WM provides assistance" has been designed for the operation of the CMH when it rolls out for services in 2025. The CMH will definitely be a perfect platform for the promotion of ICWM work. Here it is anticipated that CMPs will be working closely with WM doctors to provide holistic care for its inpatients and outpatients. The CMH will also be an excellent venue to carry out clinical research to evaluate the efficacy and safety of CM, including acupuncture and herbal medicine, for the management of common diseases. It is envisioned that WM methodology will be employed to determine the efficacy of CM treatment.

HKAIM has been steering integrative projects from education to research. Bridging the gap between CM and WM should improve the quality of healthcare service in general. The Integrative Joint Organizational Platform (IJOP), after review and interviews on the obstacles and their solutions surrounding CM-WM collaboration since 2015, has established a platform for exchanging experience and ideas as well as ways facilitating collaboration. It will also deliver integrative medicine to train CMPs and doctors. Besides interactive support backed by experts' understanding and a managed repertoire of knowledge on diseases, the IT platform offers other practice

enhancements with games for case collaboration. IJOP now has chosen diseases amenable for CM-WM collaboration with room for enhancing treatment efficacy. Clinical framework on diseases is built to facilitate CM-WM collaboration, combining medical evidence from the systemic reviews (SR) that we delegated to local universities and valuable insights from professional experts. In this issue, our experts and scholars present some integrative perspectives as background and materials for the interest of the WM profession. Striving for the best medical services for the public utilising the strengths of both CM and WM in an integrated setting with good procedures and methodology, medical experts and academic vanguards, with their faithful participation and invaluable contribution, have enabled the significant role of IJOP in Hong Kong. This venture, as we hope, would stimulate an atmosphere conducive to a collaborative environment. We have much confidence that integrative medicine is bound to flourish in the territory in the near future.

Developing the Integrative Joint Organizational Platform, IJOP

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INTRODUCTION

The common phenomenon that patients seek help simultaneously from both Chinese Medicine (CM) practitioners and Western Medicine (WM) doctors is well recognised. Our well-developed medical system should be supportive that patients in their illness suffer no more pains from inadequate CM-WM coordination and communication. CM has come a long way from its ancient roots, with governments around the world supporting CM research and practitioners being increasingly engaged in evidence-based practice[1]. Our platform is to create a conducive environment with channels for CM-WM collaboration, providing fine details for practice.

Efforts to address this need are not new. The Hong Kong Association for Integration of Chinese-Western Medicine (HKAIM) formed in 2001 has made many contributions.[2,3] There came increasing cross-disciplinary CM-WM interaction and development. Organisations including universities and the Hospital Authority (HA), steadfastly built up ways to develop Integrated Chinese-Western Medicine (ICWM) programmes, from education, service provision and research. Our people are fortunate that Chinese and Western cultures complement each other, as both CM and WM do produce remarkable medical outcomes despite their differences in clinical practice, methodology and standard. The essence of medicine is to enhance human health, reduce suffering from diseases, and make human life cope better with prosperity and longevity.

To improve our healthcare service, bridging the gap between CM and WM would be essential in improving the quality of healthcare service and enhancing medical practice as a whole. We felt obliged to make a useful and active step, resulting in the successful establishment of the Integrative Joint Organizational Platform (IJOP) since 2015. This milestone project was funded by the Innovation and Technology Commission (ITC). Survey and interviews on CM and WM practitioners, experts and scholars were conducted, and a systematic review on the obstacles and their solutions surrounding CM-WM collaboration was performed over: 1: System needs and Institution Development, 2: Safety during Collaboration, 3: Modes of Collaboration, 4: Issues with Evidence-based Medicine, 5: Barriers to Collaboration, 6: Education, 7: Chinese Medicine Hospital for Collaboration, and, 8: Collaboration Outcome. A positive atmosphere and rapport have been realised through a series of lectures, seminars and useful discussions. A good breadth of recommendations was made in the Report[4], providing a sound basis for further enhancing the level of ICWM. Thereafter, CM-WM collaboration is well recognised in the field.

Furthering IJOP, diseases with room for enhanced treatment efficacy amenable to CM-WM collaboration were chosen. The Disease Collaboration Consultant Panel, with the support of co-chairmanship from three universities, started inspiring discussions, scrutinising good rationale for prioritisation in choosing the diseases for action. ITC funding support was again obtained at this "IJOP-II - Disease Management Information Network".

IJOP VISIONS

IJOP aims to build a conducive environment and delineate details for CM-WM collaborative practice. To strengthen medical practice, creative approaches with fine details for practice are needed, wherewith exchanging experience and ideas, as well as establishing channels would help practitioners use both WM and CM services in delivering quality and effective medical care. Our model for the collaborative programme guides is shown in Fig. 1. Our IJOP web presence (www.hkaim.org.hk and www.ijopmed.org)[5] shares our philosophies and rationale on ICWM.

Fig. 1 IJOP collaborative model (Developed by author)

FURTHER DEVELOPMENT OF IJOP PROJECT

The IJOP phase 2 – the Disease Management Information Network was commissioned in March 2019 to:

A. Bring forward and share (共享) the facts, views and opinions about ICWM for the medical industry professionals through multi-platform, multi-media and multi-dimensional means.
B. Build bonds and forces (匯聚團結) for the sustainable development of ICWM, primarily for Hong Kong and subsequently generalisable for the world. The bond and forces are realised through various means in different perspectives and by many advisory and expert panels and a community network detailed below. Interpersonal core CM-WM bonding is bolstered by physical communication and our electronic platform, which allows various attractions and participation, including video production, virtual clinics (a game envisioning CM+WM integrative approaches), and webinars.
C. Confirm (引證) the validity of ICWM. For three selected disease groups (Stroke, Cancer and Eczema) where there are inadequate ICWM reviews, we further delegate Systematic Reviews to lead universities. A limited selection of disease groups (namely stroke, eczema and breast cancer) allows a concentrated effort to start with.
D. Seek consensus (共識) towards the clinical strategic framework (CSF) of CM+WM integration as a pilot to enable an effective method for bridging the gap between WM and CM.

These 4 elements are further elaborated below:

A. Bring Forward and Share ICWM Knowledge and Views

In creating CM-WM collaboration, concrete ideas and recommendations would first come from practitioners. IJOP provides warm collaborative channels to foster practitioners' initiatives. CM practitioners and WM doctors could call upon the support of a platform backed by experts' understanding and a managed repertoire of valuable knowledge on diseases. Multiple means such as seminars, videos, blogs, images, webinars and social platforms on collaborative approaches for disease problems through interviews and elaborations from expert practitioners and academic leaders should promote better mutual understanding.

Language and terminology have all along been a barrier to the exchange of views between CM and WM professionals. Effectively, we examined different sets of terminology in CM+WM and found that the translation between CM and WM terms available from the public web has much room for further improvement. We facilitate our members with an online platform tool "Search the Chinese Medicine Terms by Chinese or English"[6]. Besides keyword searches, it also provides classification browsing functions for understanding terms from basic medical theories, diagnostics, disease, therapeutics, acupuncture and medicinal treatment. With more content input, people who would like to learn in-depth can also make good use of our function as a starting point in CM+WM learning. This terminology search also aims to remove some obstacles in mutual understandings between CM and WM professionals. Mutual understanding is not impossible when the way is paved[7,8,9,10].

One good image is worth one thousand words, and one good video worth more. A video gallery for members offers a diversified collection from selected diseases to Covid-19 viewed from both CM and WM perspectives.

With many resources gathered, we organised a series of key IJOP webinars on specific diseases in late 2020. The medical industry sector welcomed them as each webinar attracted more than 500 doctors, CM practitioners and other medical professionals, with positive feedbacks. These covered:-

- STROKE: where Chinese medicine and Western medicine expertise matters
- ECZEMA: where Chinese medicine and Western medicine expertise matters
- BREAST CANCER: where Chinese medicine and Western medicine expertise matters

The success could be related to the strong line-up of speakers as well as in-depth CM+WM contents and specific useful ICWM collaborative directives. Significant CM+WM effectiveness over simply WM intervention was elaborated through Systemic Review (SR) studies. Heavy-weight speakers from the universities in Hong Kong, Guangzhou and USA, as well as disease specialists, gave good reviews and insights. Officiating top leaders include Dr WM Ko and Dr Donald KT Li, President of World Organization of Family Doctors, Dr Deacons TK Yeung from the Hospital Authority and Dr Cecilia WB Pang from the ITC, and a broad range of CM+WM leaders.

B. Build Bonds and Forces for Sustainable ICWM Development

In the formation of a coherent IJOP organisation, support from the top is cherished. National IM Masters Prof Chen Keji (陳可冀) and Prof Zhang Boli (張伯禮) act as IJOP Permanent Honorary Advisers. Besides, 16 top healthcare leaders and current CM and WM organisations steer our Honorary Advisers, and Advisory Committee, six overseas CM-WM vanguards as External Advisers, lead IJOP and three academic university leaders co-chaired the Disease Collaborative Consultant Panel. At the operation level, we have an embracive team of 70 from Eczema Experts, Stroke Experts and Breast Cancer Experts to form Expert Panels and Task Forces for each selected disease. We also form an Integrative Fellowship. This platform organisation is just the beginning of the emerging milestone, and will hopefully boost the history of ICWM in Hong Kong and beyond.

Physical meetings with these renowned CM and WM experts, committee, consultant panel, core group and task force leaders provided moments worth cherishing.

In the times of COVID-19, virtual meeting via Zoom facilitated more people joining in and more frequent communications with the task force and focus groups to work out solutions and frameworks. Project meetings with the universities kept quality on track with SR work. All were done with meaningful purposes and outcomes. Later, supported by this vibrant CM-WM integrative professional network, our webinars fostered a warm and friendly atmosphere between CM practitioners and WM doctors, with a thousand members joining. These webinars facilitated meaningful discussion and exchange of views and experience on the efficacy of ICWM on chosen diseases. In ongoing projects with expert interviews, our 70-member team, together with other community experts, bolsters our strength, bringing the questionnaire and associated beckoning call for closer CM-WM collaboration to various parts of the medical industry.

C. Confirm the Validity of Integrative Medicine

IJOP commissioned SR from the universities, Hong Kong Baptist University (HKBU) on Stroke, the University of Hong Kong (HKU) on Breast Cancer, and the Chinese University of Hong Kong (CUHK) on Eczema. Their appreciable strong commitment led to high academic standards. In addition, we are also pleased to have had WM experts, Dr Alexander YL Lau (neurologist), Dr Steven KF Loo (dermatologist) and Dr Tsz-him So (oncologist) to provide insightful feedback throughout the SR project process, further sharpening the outcomes.

Our SRs have accomplished some great successes. The publication generated from the SR on stroke is 1. 'Stroke Rehabilitation by Integrated Western and Traditional Chinese Medicine – a Systematic Review and Meta-analysis'[11]. SR papers on breast cancer include 2. 'Chinese Herbal Medicine for Reducing Chemotherapy-associated Side-effects in Breast Cancer Patients: A Systematic Review and Meta-Analysis'[12], 3. 'Treatment of Breast Cancer using Chinese Herbal Medicine: A Meta-analysis of Randomised Controlled Trials'[13], 4. 'Acupuncture of cancer-related symptom management in breast cancer patients- a systematic review and meta-analysis'[14], 5. 'Effectiveness of acupuncture as adjuvant therapy for side effects management on drug therapy-receiving breast cancer patients: a systematic review and meta-analysis of randomised controlled trials[15], and on eczema', 6. 'Systematic Review and Meta-analysis on Integrated Western and Chinese Medicine Interventions for Atopic Dermatitis'[16].

The results on the whole demonstrated that CM+WM is more effective in these specific diseases than WM alone. To recapitulate, 'The combined use of CM and WM has positive effects in stroke rehabilitation compared to the use of WM therapy alone'[11]. 'The potencies of CHM facilitate the management of chemotherapy toxicity application of CHM in clinic'[12]. 'Complementary use of CHM alongside western therapy was associated with better tumour response as well as prolonging survival'[13]. 'Acupuncture markedly alleviated pain, and psychological stress, moderately improved insomnia and fatigue, and mildly reduced hot flashes in breast cancer patients and survivors suggest acupuncture may be part of a multimodal approach to symptom management in breast cancer patients and survivors'[14]. 'A significant positive result was summarised from this meta-analysis, that acupuncture could effectively reduce the side effects induced by drug therapies on breast cancer patients. Positive responses are obtained with symptoms for gastrointestinal disorders, chemotherapy-induced peripheral neuropathy, aromatase inhibitor-associated arthralgia, aromatase inhibitor-associated joint symptoms, and cognitive impairment. The quality of life of patients has enhanced to a certain extent also. Without severe adverse events reported, it is recommended that suitable acupuncture treatments are considerable as adjuvant therapies with drug therapies on breast cancer patients[15]. 'Adopting IWCM may be superior to using WM alone in managing atopic dermatitis.'[16].

As demonstrated above, fruitful results have been achieved, providing strong buttresses for forming our upcoming Clinical Strategic Framework (CSF), as SR evidence is due to received comments from a wide range of CM and WM experts. Coupled with experience from our experts through a well-designed questionnaire, valuable inputs and professional insights could be incorporated into the CSF. This fundamental CSF can be further enhanced by use and experience during its publication to the wider medical community in Hong Kong.

D. Seek for Consensus, CM+WM Collaborative Framework

Through medical experience and competitive research with the changing world of new diseases and unbalanced health conditions, CM and WM are two mature, effective and important systems for healthcare. CM accumulated experience from thousands of years of practice, while WM has an edge with scientific research and methodological analysis. With both strengths integrated and setting organised among people, processes, methodology and system, we can strive for the best wisdom and medical services for precisional healthcare for the public. "在醫學中，既可藉西方科研方法學來研究分析，又可從中醫累積千年的思維及經驗中琢磨觀點。可望求同存異，發展和擴闊醫學精準療效，讓智慧重新，共識疾病治療和健康調理". This motto is the IJOP philosophy, a value proposition for further enlightenment on quality health for people. The benefit of having integrative medicine is obvious.

One of the most difficult parts is how to perform collaborative CM+WM practices in a clinical environment with due considerations on differences in medical theories, contradictions of views from medical experts, constraints of social rules for the locality and culture, and availability of agreeable expertise on both camps of medicine. Trying to establish protocols to standardise medical practices, a strategic framework could be a better way to bridge the gap in CM and WM to satisfy practitioners from both streams. A framework should be built not by any hardcore consensus unconvincing to either side, but by containment instead of elimination, flexibility of choice instead of hierarchical assignment, and experts' consensus instead of competition.

We believe with strong conviction that our CSF would be a breakthrough bedrock towards CM-WM integration. Particularly, we are not creating a top-down, dominant one-size-fits-all protocol. Instead, CSF demonstrates possibilities to allow peer experts to get inspiration for collaboration, upon which they may generate their frameworks for their niche modes of practice. Then more groups can incorporate at least some of the useful elements for their own application in practice. Experts and practitioners could choose what they need from several generated frameworks available. Secondly, our framework approach emphasises its efficiency and effectiveness. Among the many challenges, just a single guideline is insufficient for complex diseases and following a one-fits-all protocol is difficult in practice. Rather, a CSF fundamentally concise would stimulate CM and WM practitioners to seek collaboration based on needs through a pathway open to all so that they can proceed according to their niches and levels of practice. Another property of our CSF, being generated with a coherent voice within good CM+WM experts, would in time resonate with many more groups. The way they adapt it further for and under their standardisation can be feedback into the whole framework system so that the whole way of collaborative practice would enhance itself by feedback loops. Our CSF fundamentally is just a brace but also a humble attempt to be a beacon for others to develop their models. An area open to adjustment on CM-WM collaboration is left for further adaptation, for CM and WM practitioners of various specialities, professional training, practical experiences and under different healthcare systems. Essentially the useful elements with CSF fundamentals would be developed into further mutually inclusive frameworks, which demonstrate more adaptability, resilience and vitality than most strict guidelines and protocols.

To be strategic, a CSF needs to be specific for a disease group so that medical professionals could practically adopt it. The CSF provides options with sufficient information for CM and WM practitioners to assist their judgments in diagnosis and treatment. We operate in nine steps in developing a CSF in order to promote a better recognition of disease problems, facilitate CM and WM with a managed repertoire of valuable knowledge and views, collaborative approaches to disease problems, and gather good evidence-based clinical information, gather views from CM and WM practitioners' focus groups and Disease Experts, clarify gaps and demands in practice, and put forth drafted CSF Framework for feedback from community clinicians and restructuring the Framework for use so that this can be shared through warm, friendly and interactive, collaborative channels for CM and WM via an interactive multi-media platform. In IJOP currently, we have performed the above steps for the diseases with some success.

DIRECTION FORWARD

Hong Kong Association for Integration of Chinese-Western Medicine (HKAIM) has been pursuing this good cause to bring CM and WM together, facilitate the exchange of academic knowledge between CM and WM, and advance their integration in health and clinical practice. IJOP made an advance to establish databases of the expertise of WM and CM practitioners to enhance the communications in disease managements for a better outcome. To start with, SRs provide the evidence that CM+WM can work better for specific diseases. Details need to be filled in from the experience of CM and WM experts. Eczema is a good example to illustrate this concept; good rapport and trust between CM and WM experts could lead to mutual referrals. We need to do more. Developing the CSF in eczema is to find more details for CM-WM collaboration, wherein we need to start from the very basics of how the skin actually reacts, no matter what the CM or WM perspective is (Fig. 2). After considerations for clinical steps, a tentative map or framework can be built with the strategic addition of CM elements in a WM acceptable frame. That can be improved step by step to become more systematic later with feedback from further use, interrogation and experience. A very encouraging result we share below is our draft CSF on eczema (Fig. 3).

In promoting collaboration, the development of this type of framework has emphasised disease-oriented research, bridging the gaps between CM practitioners

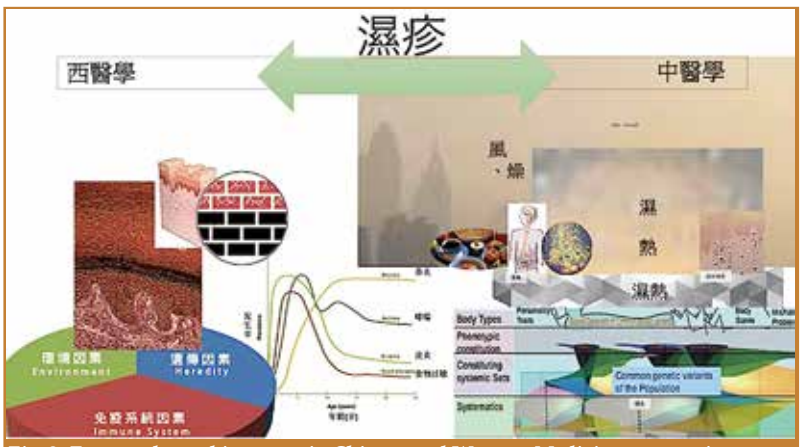

Fig. 2: Eczema, how skin reacts in Chinese and Western Medicine perspectives. It includes the skin and its structural functions, genetic immunological and environmental factors, the atopic march, reactions in stuffy humid weather as these are affected by diet and gut microbiome and the complex body constitution. (Developed by author)

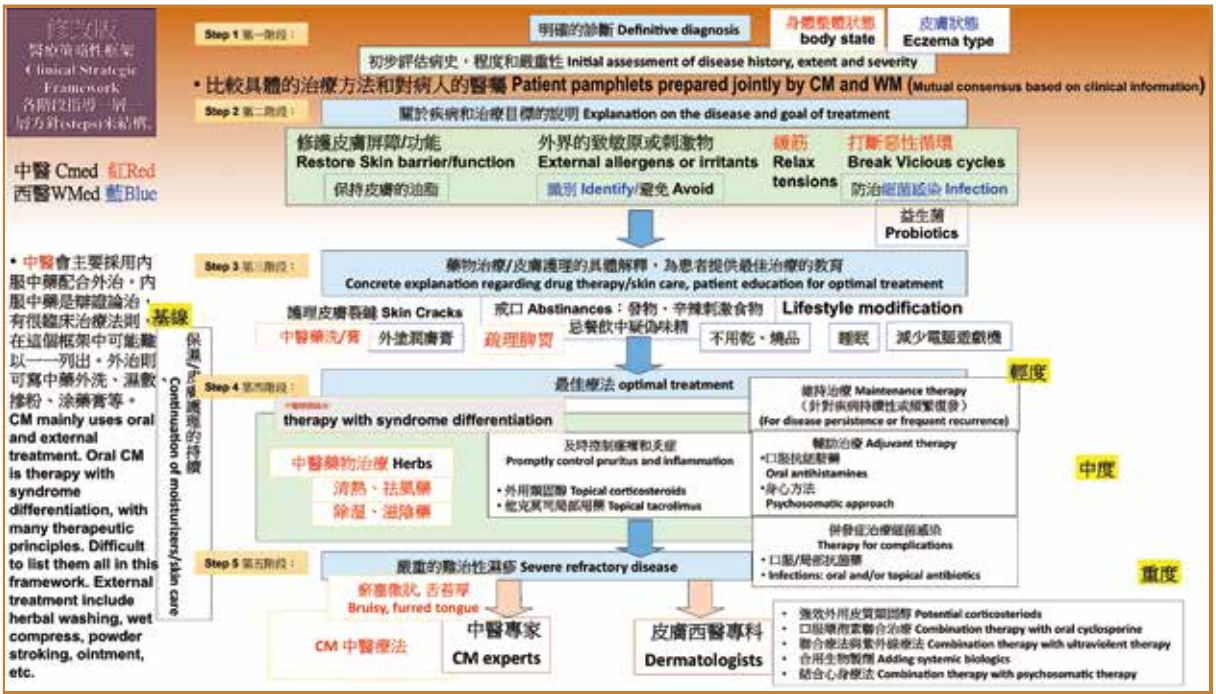

Fig. 3: Clinical Strategic Framework drafted for Eczema for collaborative practice. (Developed by author)

and WM doctors and facilitating a collaborative environment with professional resources about evidence-based medicine to enhance collaboration and practice. Framework as the base allows both CM and WM systems to find benefits of the other in the patient's journey. In IJOP as a platform for exchanging and enhancing practice methods, frameworks gathered from more users by their expertise and experience will fine-tune a wide usage of collaborative details. The faithful participation and priceless contribution of medical experts and leaders, as well as academic vanguards from universities, have enabled the significant role of IJOP in Hong Kong. This, as we hope, would stimulate an atmosphere conducive to a collaborative environment from which people can benefit.

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Development of Clinical Practice Guideline for Integrative Medicine

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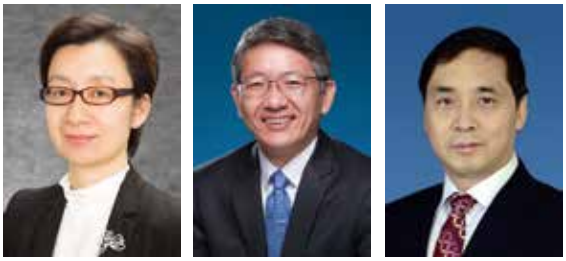

Dr Linda ZHONG Prof Zhaoxiang BIAN Prof LYU Aiping

Integrative medicine is widely used among the population across the globe. In Hong Kong and mainland China, the public often receives treatments from both Chinese medicine (CM) and Western medicine (WM)[1,2]. Although both medical systems have their specified regulatory authorities, there is a lack of standards to guide the safety and effectiveness of integrative use. Neither the patients nor general practitioners have clear guidance on seeking and providing integrative treatments. As a result, patients bear risks in searching for appropriate integrative treatments while practitioners need to handle the expectation mismatch of patients.

As a statutory body responsible for managing Hong Kong's public hospital services, the Hospital Authority (HA) has kept implementing and expanding the Integrated Chinese-Western Medicine Pilot Project since 2015[3]. The project selects eligible inpatients in public hospitals to receive both CM and WM treatment during hospitalisation and after discharge. However, this is an exploratory project with limited types of diseases (stroke, musculoskeletal pain, and cancer palliative care) and could not translate to guidelines for practitioners in Hong Kong.

Clinical practice guidelines (CPGs) are statements based on clinical research results and expert consensus to assist clinical decisions which aim to increase the value of the health care system. In 1990, CPG was defined by the Institute of Medicine (IOM) as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances". Later in 2011, IOM organised international expert meetings to update the definition of the CPG as "statements that include recommendations intended to optimise patient care. They are informed by systematic reviews of evidence and an assessment of the benefits and harms of alternative care options"[4].

Reliable CPGs can provide evidence-based treatment options applicable to daily practice and minimise potential conflicts between practitioners and patients. In the United States, CPGs are commonly found in institutions such as the American Gastroenterological Association (AGA) and the American Heart Association (AHA)[5,6]. In this article, we introduce clinical practice guidelines (CPGs) and their application to the development of integrative medicine in Hong Kong.

FORMATION OF CPGs

In recent decades, thousands of CPGs have been developed covering prevention, diagnosis, evaluation, treatment, and management of diseases[7]. One of the most recent CPG that received a wide range of discussion is the CPG developed by AHA in 2017, defining hypertension as 130/80 mm Hg[8]. Aiming to assist clinical decision by evidence, CPGs must be constructed rigorously with systematic processes including stakeholder analysis, data mining, prespecified selection, assessment of evidence, recommendation and expert review with an updated plan.

In the data mining step, researchers visit medical databases to systematically collect existing literature by using keywords. Then, the literature collected are being further filtered by prespecified selection criteria to exclude irrelevant articles. After available treatments are extracted from the literature, they are assessed and ranked by their quality of evidence to form recommendations. Next, the recommendations are structured and included in questionnaires for rounds of expert meetings to formulate the preliminary version of the CPG. After publication, the CPG would be reviewed and updated periodically.

CASE EXAMPLE

In 2019, we published a CPG for cancer palliative care using CM in Hong Kong[9]. Since the majority of palliative cancer patients would choose to receive WM and at the same time other supportive treatments, integrative treatment strategies are needed. The CPG for CM was constructed for practitioners and policymakers as a reference to develop integrative treatment strategies with herbal medicine, acupuncture, regulating and nursing processes. The whole CPG project was initiated in 2013 by the HA and underwent the following processes:

A. Data Query and Download

To avoid repetition of a clinical study and ensure efficiency, we chose the SinoMed database as the data source and identified clinical researches with CM treatment for cancer palliative care in SinoMed, which is the most comprehensive electronic medicine database in China. The time range is from 1979 to 1 January 2015. The following search terms were used: "cancer AND pain" OR "cancer AND insomnia" OR "cancer AND constipation" OR "cancer AND lymphedema" OR "cancer AND anorexia" OR "cancer AND lethargy" (in Chinese). As a result, 197,213 records for cancer palliative care were retrieved.

B. Data Mining Process

After retrieving data from SinoMed, we listed the data order by download order. There is a need to transfer the relevant data into the framework of structured file system, and a tool was developed (software copyright with submitted ID 0261882 and registered ID 2010SR073409) to transfer its plain TXT data into Microsoft® SQL Server® 2008 R2 Enterprise Edition. Then we used a data slicing algorithm "discrete derivatives", based on the calculation of frequency previously described[10], to filter high frequencies of 1. CM pattern classification and symptom differentiation; 2. herbal decoction; 3. acupuncture treatment. The data mining process was deployed on source data collected above with cancer and specified symptoms.

C. Existing Clinical Evidence Searching

The search strategy adopted was a combination of electronic and manual screening for systematic reviews of CM treatment on relevant symptoms. Cochrane guidelines were applied for methodological evaluation of literature quality. We used the grades of recommendations and the levels of evidence proposed by Professor Jianping Liu of China designed for traditional medicines[11].

D. Hong Kong Local Expert Consensus

On the key issues in the CPG, a Delphi survey was applied to collect professional advice from licensed CM practitioners in Hong Kong based on the literature search and documented clinical evidence. After two rounds of surveys, the consensus from Hong Kong local experts was obtained on the contents of the items, which served as one of the main sources for the formation of CPG.

E. Data Synthesis

Information from three aspects, 1. literature hotspots; 2. existing clinical evidence; and 3. local expert consensus, is summarised and listed for optional items in CPG. Items with insufficient data support were excluded.

F. Review and Consultation

A comprehensive review of the CPG was conducted through an expert consensus meeting, and items for inclusion was finalised for the CPG.

G. Drafting CPG

The guideline development group developed a framework and drafted the CPG accordingly.

H. Promotion

The electronic version of this study was published on the official websites of the HA and the Hong Kong Registered Chinese Medicine Practitioners Association. Also, publicity and promotion efforts were conducted to inform Hong Kong CM practitioners.

I. Execution

This example is the first guideline for CM clinical practice on cancer palliative care in Hong Kong. The production of this guide is just a beginning and an attempt. More experience and feedback are needed for future summaries.

J. Update

The CPG development panel will regularly entrust relevant professionals to review through collecting, collating, and analysing newly emerged evidence. CPG development panel has the responsibility and rights of decisions on the revision. In general, the CPGs need to be revised or updated in the following cases: 1. to include new intervention methods; 2. to provide evidence to prove that the existing intervention methods are the best, beneficial, or detrimental; 3. in adding conclusions that is important and relevant; 4. in generating new medical resources.

In summary, we applied standard methodology in our study with detailed descriptions of the methods used for the construction of the CPG. However, it is not optimal from the perspective of integrative medicine. One of the reasons is only CM experts were invited as members of the guideline development group. Without the participation of WM experts and their recommendations, the health benefits and potential risks of the integrative treatments are unclear.

APPLICATION OF CPGs FOR INTEGRATIVE MEDICINE

Hong Kong has a medical system different from mainland China, and thus the CPGs should be constructed separately. In mainland China, both CM and WM can commonly be prescribed by the same practitioner, while it is not the case in Hong Kong unless the practitioner has both CM and WM licenses. Without frequent communication between CM and WM practitioners, evidence-based referral becomes difficult, and therefore the existing system fails to respond to the needs of patients. On the other hand, CPGs can demonstrate the effectiveness and safety of the treatments from evidenced clinical research. Systematic review and meta-analysis results can be included in the CPGs as pooled estimation of the treatment effects.

CPGs for integrative medicine would not be a simple combination of CPGs of CM and WM. Instead of covering every disease, high quality CPGs with generalisability should aim on focusing on clinical questions that practitioners are truly interested in. In Hong Kong, the possible interaction between CM and WM treatments is under the spotlight since practitioners always need to deal with questions about integrative treatments. In the presence of CPGs for integrative medicine, practitioners can have a full picture of available integrative treatment options with references. In other words, the CPGs can provide insights and improve medical decisions based on comprehensive evidence from systematically collected literature and recommendations from clinical experts.

Furthermore, the public should also be considered as participants in the review process of the CPGs. Regarding integrative treatments, focuses from the public might not be the same as practitioners. With the involvement of the public, they will be able to reflect their concerns and increase the transparency of the CPGs from the perspective of potential patients.

POTENTIAL ISSUES AND CORRESPONDING SOLUTIONS

With an increasing number of CPGs being published in recent years[12], there are concerns about the quality of CPGs. As a result, statements such as AGREE II (Appraisal of Guidelines for Research and Evaluation II) and RIGHT (Essential Reporting Items for Practice Guidelines in Healthcare) were developed to provide frameworks aimed to improve the construction and report of CPGs[13,14]. These tools can increase the transparency of the CPGs reporting and the involvement of stakeholders for better impact and applicability.

The development of CPGs for integrative medicine could be challenging since the treatment combinations would be even more diversified. Moreover, the CPGs require opinions from experts of both CM and WM. As clinical research for integrative medicine is still in development, there are doubts that low quality evidence from literature would generate low quality CPGs. In fact, due to an evidence grading system in CPGs, readers can identify the quality of available treatments and make clinical decisions accordingly. In AGREE II and RIGHT, there is no statement on excluding any quality of evidence.

The application of CPGs is not popular among practitioners in Hong Kong. As the frontline of medical services, practitioners have the best understanding of patient needs. Therefore, to benefit from the CPGs, promotions and workshops targeting practitioners are necessary for notification and receiving feedback. It is also critical to increase the generalisability and prepare for future updates. From the perspective of public involvement, questionnaires based on the content of CPG can be designed for participation of the public.

Finally, due to the overwhelming number of CPGs worldwide, the management of CPGs for integrative medicine will be another issue in the future. As a result, a committee regarding maintenance and updates of CPGs is essential. Without proper monitoring, mass production of the CPGs with low methodology quality and out-of-date evidence could be a norm and harmful to the users.

CONCLUSION

Construction of CPGs regarding integrative treatments is necessary for Hong Kong. Well-developed CPGs facilitate decision making in clinical practice and enhance the trust between patients and practitioners. The formation of CPGs consists of consensus from shareholders in terms of quality and recommendations. Although there is still a long way to go, it will eventually benefit patients, practitioners, and policymakers to improve the quality and efficiency of medical services.

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HELPING TO REDEFINE SURVIVAL EXPECTATIONS FOR *MORE* PATIENTS WITH mNSCLC[1]

FIRST-LINE TREATMENT FOR *NONSQUAMOUS* AND *SQUAMOUS* mNSCLC[1]

Actor portayal; this is not an actual patient.

FIRST-LINE NONSQUAMOUS COMBINATION THERAPY:

KEYTRUDA® (pembrolizumab), in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no *EGFR* or *ALK* genomic tumor aberrations[1].

FIRST-LINE SQUAMOUS COMBINATION THERAPY:

KEYTRUDA®, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC[1].

FIRST-LINE MONOTHERAPY:

KEYTRUDA®, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%)] as determined by a validated test, with no *EGFR* or *ALK* genomic tumor aberrations, and is: stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic[1].

PD-L1 = Programmed death-ligand1

Reference: 1. Hong Kong Product Circular (KEYTRUDA®, MSD)

Selected Safety Information for KEYTRUDA (pembrolizumab)
Indications: • **Melanoma-KEYTRUDA** (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma. • **KEYTRUDA** as monotherapy is indicated for the adjuvant treatment of patients with Stage **III** melanoma with involvement of lymph node(s) following complete resection. • **Non-Small Cell Lung Cancer-KEYTRUDA,** in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no *EGFR* or *ALK* genomic tumor aberrations. **KEYTRUDA,** in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC. **KEYTRUDA,** as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%)] as determined by a validated test, with no *EGFR* or *ALK* genomic tumor aberrations, and is: stage **III** where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic **KEYTRUDA,** as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. • **Urothelial Carcinoma-KEYTRUDA** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. **KEYTRUDA** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • **Classical Hodgkin Lymphoma-KEYTRUDA** as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • **Microsatellite Instability-High or Mismatch Repair Deficient Cancer-KEYTRUDA** is indicated for the treatment of adult patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. • **Renal Cell Carcinoma-KEYTRUDA,** in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC). **Dosage and administration:** Patient Selection: Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in stage **III** NSCLC who are not candidates for surgical resection or definitive chemoradiation, metastatic NSCLC or metastatic urothelial carcinoma; For MSI-H or dMMR Cancer, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens. • **Melanoma:** The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months in patients without disease recurrence. • **NSCLC:** For monotherapy or combination therapy, KEYTRUDA 200 mg should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate. • **Urothelial Carcinoma, Classical Hodgkin Lymphoma, MSI-H or dMMR Cancer:** 200 mg should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. • **Renal Cell Carcinoma:** KEYTRUDA 200 mg should be administered as an intravenous infusion over 30 minutes every 3 weeks in combination of axitinib 5 mg orally twice daily, until disease progression or unacceptable toxicity, or for KEYTRUDA up to 24 months in patients without disease progression. Dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer. **Contraindications:** None **Precautions:** • Immune-mediated pneumonitis • Immune-mediated colitis • Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib) • Immune-mediated endocrinopathies (adrenal insufficiency; hypophysitis; thyroid disorders - hyperthyroidism, hypothyroidism and thyroiditis; Type 1 diabetes mellitus) • Immune-mediated nephritis and renal dysfunction • Immune-mediated skin adverse reactions (SJS, TEN, exfoliative dermatitis and bullous pemphigoid) • Other immune-mediated adverse reactions • Infusion-related reactions (including hypersensitivity and anaphylaxis) • Complications of allogeneic HSCT in patients after or prior to treatment with KEYTRUDA treatment • Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone • Embryo-fetal toxicity **Adverse Events:** Most common adverse reactions (reported in ≥20% of patients) when KEYTRUDA was used as a single agent were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain; when KEYTRUDA was used in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis; when KEYTRUDA in combination with axitinib were diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. • Immune-mediated pneumonitis • Immune-mediated colitis • Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib) • Immune-mediated endocrinopathies • Immune-mediated nephritis and renal dysfunction • Immune-mediated skin adverse reactions • Other immune-mediated adverse reactions • Infusion-related reactions • As with all therapeutic proteins, there is the potential for immunogenicity. **For detailed precautions and adverse events, please consult the full prescribing information.**

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Radiology Quiz

Dr Hoi-to LAU
MBBS, FRCR

Dr Hoi-to LAU

Questions

1. What is the abnormality in this cervical spine X-ray? (Patient with trauma history)
2. What is the next investigation?

(See P.48 for answers)

The Use of Integrative Medicine for Treatment of COVID-19

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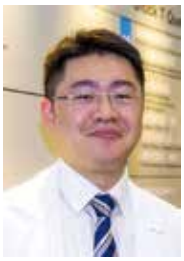


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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 June 2021.

CLINICAL PRESENTATION

Classical features of symptomatic COVID-19 cases include fever, new onset persistent cough and anosmia[1]. Later studies also showed distinctive mucocutaneous manifestations (e.g. transient lingual papillitis, glossitis with lateral indentations)[2]. Nevertheless, 28% to 59% of patients remained asymptomatic through the disease course[3], and patients may also present with common upper respiratory infection symptoms or non-specific symptoms such as fatigue, myalgia, rigour, headache or loss of appetite[1]. Being older, with underlying comorbidities (recent haematological malignancy, diabetes, chronic kidney disease, transplant history) and presenting with dyspnoea, anorexia and rash, are more prone to severe COVID-19[4,5]. In-hospital acute kidney injury has been shown to be associated with a prolonged course of disease and hospitalisation in HK[6]. "Long Covid-19" refers to the persistent symptoms of COVID-19, which commonly included fatigue, dyspnoea, joint pain, chest pain and cough[7]. A substantial increase in the prevalence of community depression has also been widely reported since the COVID-19 outbreak[8].

PATHOPHYSIOLOGY

The key pathophysiology of COVID-19 involves inflammatory infiltrates and microvascular thrombosis that leads to diffuse alveolar damage[5]. Laboratory findings showed that COVID-19 patients have a higher level of circulatory proinflammatory cytokines, e.g. IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α[9]. The immune response plays a critical role in the development of organ injury characterised by markedly elevated inflammatory markers (e.g. C-reactive protein and interleukins)[10].

The severe cases are associated with coagulation abnormality[11]. The higher level of D-Dimer, a product in the coagulation system, may serve as a predictor of severity and mortality[12,13]. A significant increase of neutrophil extracellular traps (NETs) triggered by soluble and cellular factors promoting thrombosis[14]. Autopsies show features of lung cell desquamation and formation of hyaline membrane, indicating the occurrence of acute respiratory distress syndrome[15] as well as the presence of thrombosis and micro-angiopathy with neutrophil-platelet clotting in vessels and capillaries of the lung[16,17].

TREATMENT STRATEGIES

The current strategy against COVID-19 focuses on public health interventions (e.g. social distancing, compulsory screening), trial treatment with licensed drugs and the development of new therapies and vaccines[5,18,19]. Social distancing was shown effective in reducing the transmission of COVID-19[20]. Although remdesivir[21] and interferon[22] have demonstrated a trend of shortened clinical course, their reduction in mortality was modest, and the efficacy varied across different populations[21,23]. The BLAZE-1 trial showed that combined bamlanivimab/estesevimab led to reduced viral load and hospitalisation/emergency visit rate[24] among moderate to severe cases, and corticosteroids have been shown to reduce mortality among severe cases[25,26]. A late phase II RCT from Oxford also demonstrated that budesonide, a conventional anti-asthmatic medication, led to 86.9% absolute risk reduction of hospitalisation or emergency service use which reconciles with the anti-asthmatic effect of herbs from CM[27].

PRESCRIPTION OF CHINESE MEDICINE (CM) FOR COVID-19

CM treatment integrated with conventional medicine has been recommended by the China National Clinical Practice Guideline (CPG) for COVID-19 infection since January 2020[28]. According to CM theory, COVID-19 is regarded as pestilential pathogens of warm and cold (溫疫, 寒疫) which usually invade the body with dampness pathogens (濕邪). These pathogens usually transform into heat-, phlegm-, and/or stasis- pathogens (熱, 痰, 瘀) from mild to severe stages, and resulting in deficiency and dryness (虛, 燥) during the convalescent stage[28].

According to the national CPG, over ten Chinese medicinal prescriptions are recommended based on syndrome differentiation of patients, and stages of CM pathogenesis in COVID-19 patients. The recommended

Fictional patient, for illustrative purposes only

For COPD patients on treatment with ICS/LABA or LAMA/LABA and at risk of exacerbation*[1]

*A worsening of symptoms or a history of exacerbation treated with antibiotics or oral corticosteroids in the past 12 months

It's the things you do today that make a big difference to their tomorrow[1-3]

TRELEGY Ellipta provides your patients with superior improvements in lung function and health-related quality of life, and reduction in annual rate of exacerbations vs. ICS/LABA and a LAMA/LABA (UMEC/VI)[1-3]

Start your patients on TRELEGY Ellipta today, expect more from tomorrow[1-3]

TRELEGY ELLIPTA
fluticasone furoate/umeclidinium/vilanterol

TRELEGY Ellipta (FF/UMEC/VI) 100mcg/62.5mcg/25mcg is indicated for maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA or a combination of a LAMA and a LABA[1]

Today. Tomorrow. TRELEGY.

FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; OD, once-daily; UMEC, umeclidinium, VI, vilanterol

REFERENCES: 1. Trelegy Hong Kong Prescribing Information, GDS05, Nov 2018 2. Lipson DA et al. Am J Respir Crit Care Med 2017; 196:438–446. 3. Lipson DA et al. N Engl J Med 2018; 378:1671–1680.

TRELEGY ELLIPTA (FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL)

SAFETY INFORMATION

- Trelegy Ellipta should not be used in patients with asthma since it has not been studied in this population
- Not for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy)
- Use with caution in patients with unstable or life threatening cardiovascular disease
- Do not stop therapy without physician supervision since symptoms may recur after discontinuation

PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT *TRELEGY ELLIPTA* **QUALITATIVE AND QUANTITIVATIVE COMPOSITION** Pre-dispensed dose of 100 micrograms of fluticasone furoate, 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate). Inhalation powder. **INDICATIONS** COPD (Chronic Obstructive Pulmonary Disease) *Trelegy Ellipta* 100 / 62.5 / 25 micrograms is indicated as a maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta$_2$-agonist or a combination of a long-acting beta$_2$-agonist and a long-acting muscarinic antagonist. **DOSAGE AND ADMINISTRATION** COPD Adults aged 18 years and over: One inhalation of *Trelegy Ellipta* 100 / 62.5 / 25 micrograms once daily. Paediatric population: There is no relevant use of *Trelegy Ellipta* in the paediatric population in the indication for COPD. Elderly patients (>65 years), patients with renal impairment or hepatic impairment: No dose adjustment. Trelegy Ellipta should be used with caution in patients with moderate to severe hepatic impairment. **CONTRAINDICATIONS** Hypersensitivity to the active substances or to any of the excipients **WARNINGS AND PRECAUTIONS** Asthma *Trelegy Ellipta* should not be used in patients with asthma since it has not been studied in this patient population. Deterioration of disease Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of disease control and patients should be reviewed by a physician. Patients should not stop therapy with *Trelegy Ellipta* without physician supervision since symptoms may recur after discontinuation. Not for acute use *Trelegy Ellipta* is not indicated for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation. Paradoxical bronchospasm As with other inhalation therapies, administration of *Trelegy Ellipta* may produce paradoxical bronchospasm that may be life-threatening. Treatment with *Trelegy Ellipta* should be discontinued immediately if paradoxical bronchospasm occurs. The patient should be assessed and alternative therapy instituted if necessary. Cardiovascular effects Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen with muscarinic receptor antagonists and sympathomimetics, including umeclidinium and vilanterol, respectively. *Trelegy Ellipta* should be used with caution in patients with unstable or life-threatening cardiovascular disease. Hepatic impairment Patients with moderate to severe hepatic impairment receiving *Trelegy Ellipta* should be monitored for systemic corticosteroid-related adverse reactions. Systemic corticosteroid effects Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Visual disturbance Patients with visual disturbance such as blurred vision receiving *Trelegy Ellipta* should be monitored for cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. Co-existing conditions *Trelegy Ellipta* should be used with caution in patients with convulsive disorders, thyrotoxicosis or pulmonary tuberculosis, or in patients with chronic or untreated infections. Anti-cholinergic activity *Trelegy Ellipta* should be used with caution in patients with narrow-angle glaucoma or urinary retention. Pneumonia in patients with COPD An increase in the incidence of pneumonia, including pneumonia requiring hospitalization has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index and severe COPD. Hypokalaemia beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. Caution should be exercised when *Trelegy Ellipta* is used with other medicinal products that have the potential to cause hypokalaemia. Hyperglycaemia beta$_2$-adrenergic agonists may produce transient hyperglycaemia in some patients. Patients with a history of diabetes mellitus receiving *Trelegy Ellipta* should be monitored more closely for hyperglycaemia. Excipients This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS** Interaction with beta-blockers beta$_2$-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Concurrent use of both non-selective and selective beta$_2$-adrenergic blockers should be avoided unless there are compelling reasons for their use. Interaction with CYP3A4 inhibitors Caution is advised when co-administering with strong CYP3A4 inhibitors as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol. Co-administration should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. Other antimuscarinics and beta$_2$-adrenergic agonists Co-administration of *Trelegy Ellipta* with other long-acting muscarinic antagonists or long-acting beta$_2$-adrenergic agonists has not been studied and is not recommended as it may potentiate the adverse reactions. **PREGNANCY AND LACTATION** Pregnancy Administration of *Trelegy Ellipta* to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. Breast-feeding A decision must be made whether to discontinue breast-feeding or to discontinue *Trelegy Ellipta* therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **ADVERSE REACTIONS** Common: Pneumonia, upper respiratory tract infection, pharyngitis, bronchitis,sinusitis, candidiasis of mouth and throat, urinary tract infection, constipation, oropharyngeal pain, rhinitis, influenza, nasopharyngitis, headache, cough, arthralgia, back pain; Uncommon:, viral respiratory tract infection, supraventricular tachyarrhythmia, tachycardia, atrial fibrillation, oropharyngeal pain, fractures, dysphonia, dry mouth. **OVERDOSE** An overdose of *Trelegy Ellipta* will likely produce signs, symptoms or adverse effects associated with the individual components' pharmacological actions. There is no specific treatment for an overdose with fluticasone furoate/vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Abbreviated Prescribing Information based on *Trelegy Ellipta* Prescribing Information, Hong Kong (HK122018, GDS05/EMA20181121). Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd. 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. For adverse events reporting, please call GlaxoSmithKline Limited at (852) 3189 8989 (Hong Kong) or email to HK Adverse Event mailbox: HKAdverseEvent@gsk.com

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Table 1. Chinese medicinal prescriptions for treating COVID-19 (The China National Clinical Practice Guideline for COVID-19 infection)(Adapted from national guideline)

Stage	Pattern of syndrome differentiation	Name of prescriptions or licensed proprietary Chinese Medicines for consideration
Mild, ordinary and severe	All patterns by adjusting herbs	**Qingfei Paidu (QFPD) decoction** (清肺排毒湯)
Mild (輕型)	Cold-dampness constraining the lung (寒濕鬱肺證)	Hanshiyi formula (寒濕疫方)
	Heat-dampness retaining in the lung (濕熱蘊肺證)	Modified Da Yuan yin* (達原飲加減)
Ordinary (普通型)	Dampness-toxin constraining the lung (濕毒鬱肺證)	Xuanfei Baidu (XFBD) formula (宣肺敗毒方)
	Cold-dampness obstructing the lung (寒濕阻肺證)	Modified Buhuanjing Zhenqi san* (不換金正氣散加減)
Severe (重型)	Pestilence-toxin obstructing the lung (疫毒閉肺證)	**Huashi Baidu (HSBD) formula (化濕敗毒方)**
	Dual blazes of Qi and Ying aspects (氣營兩燔證)	Modified Qingwen Baidu san* (清瘟敗毒散加減) Xiyanping injection (喜炎平), **Xuebijing (XBJ) injection (**血必淨**)**, Reduning injection (熱毒寧), Tanreqing injection (痰熱清), and Xingnaojing injection (醒腦靜)
Critical (危重型)	Internal blockage and external collapse (內閉外脫證)	Modified Sheng Fu decoction* (參附湯加減) Xuebijing (XBJ) injection (血必淨), Reduning injection (熱毒寧), Tanreqing injection (痰熱清), Xingnaojing injection (醒腦靜), Shenfu injection (參附注射液), Shengmai injection (生脈注射液), and Shenmai injection (參麥注射液)
Convalescent (恢復期)	Qi deficiency of the lung and spleen (脾肺氣虛證)	Modified Shenling Baizhu san and Yupingfeng san* (參苓白朮散合玉屏風散加減)
	Deficiency of Qi and Yin (氣陰兩虛證)	Shengmai yin and Zhuye Shigao decoction* (生脈飲合竹葉石膏湯加減)

* no name indicated in the China's guideline

"3-medicines-3-formulae" (3-M-3-F, 三藥三方) prescriptions consist of three Chinese medicines: Jinhua Qinggan (JHQG) granules 金花清感顆粒, Lianhua Qingwen (LHQW) capsules連花清瘟膠囊, and Xuebijing (XBJ) injection 血必淨 and three CM formulae: Qingfei Paidu (QFPD) decoction 清肺排毒湯, Huashi Baidu (HSBD) formula 化濕敗毒方, and Xuanfei Baidu (XFBD) formula 宣肺敗毒方. There are other modified formulae (e.g., Shengmai yin, Zhuye Shigao, Sijunzi decoction and Erchen decoction). These prescriptions could be employed as follows:

1. During Medical Observation (for Suspected Cases)

For patients who have mild flu symptoms or close contacts of confirmed cases, **JHQG金花清感** granules, or **LHQW連花清瘟 capsules** are recommended. Observational studies showed the two prescriptions improved symptoms of patients[29,30].

2. During Medical Treatment (for Confirmed Cases)

Once the diagnosis is confirmed, CM could be prescribed by syndrome differentiation of the patients (e.g. coldness, heat, dampness, phlegm, stasis, deficiency and dryness) according to the five stages of mild, ordinary, severe, critical, and convalescent as shown in Table 1.

CLINICAL EVIDENCE OF THE EFFECT OF INTEGRATIVE MEDICINE

CM has been used to treat COVID-19 since the early stage of the pandemic[5], with symptom-based differentiation into subtypes for the formulation of treatment[31]. For mild cases, a randomised controlled trial (RCT) led by Zhong Nan-shan (n=284) showed that **LHQW連花清瘟capsule**, a licensed proprietary CM for infectious diseases, increased the absolute overall recovery rate and chest computed tomography improvement rate by 9.1% (91.5% vs 82.4%, p = 0.022) and 19.7% (83.8% vs 64.1%, p < 0.001), respectively[32].

A large-scale national retrospective cohort study (n=8,939) showed that **QFPD清肺排毒decoction**, a combination of 4 classical CM formulations[33], was associated with 3.6% absolute risk (1.2% vs 4.8%) reduction in mortality. After adjusting for patient demographics and concomitant drug use, add-on QFPD decoction was associated with a 50% relative risk reduction of in-hospital mortality (HR = 0.50, 95% CI: 0.37 to 0.66, p < 0.001). The result is comparable to another retrospective cohort (n = 782), showing early administration of QFPD decoction was associated with a higher likelihood of recovery[34]. Apart from increasing recovery rate and reducing mortality in mild cases, a retrospective cohort (n=234) from Shanghai showed that earlier CM use was strongly associated with a shorter period of having SARS-CoV-2 swab and a shorter hospital stay[35].

A retrospective cohort (n=1,788) from 5 Wuhan hospitals showed that **add-on individualised CM** was associated with 58% risk reduction of mortality[31]. Among 317 severe/critical cases, add-on CM use was associated with 28.3% absolute risk reduction (18.6% vs 46.9%) of death. Propensity-score matched analysis showed a 66% (HR = 0.34, 95% CI: 0.15 to 0.76, p = 0.009) relative risk reduction in mortality, demonstrating a dose-dependent relationship with the duration of CM use. Severe/critical patients had a trend of stabilised D-dimer level after 3–7 days of add-on CM. Key CMs used in the cohort were anti-asthmatic, and immune-modulating drugs. CM users had comparable liver and renal function when compared to non-users.

BASIC RESEARCH ON CHINESE MEDICINE FORMULAE AND HERBS

QFPD清肺排毒decoction were studied regarding their pharmacological activities, supported by network pharmacology[33]. The anti-viral effects were: 1. direct on viral replication, 2. modulation of host pathways like TLRs, RGL, RLH, AMPK, P/13K/AKT, MAPK/ERK signal pathways, 3. promotion of defence via T and B cell functions, 4. free radical scavenging activities by enhancing SOD, CAT and GPX. Blockage of ACE2 receptors and prevention of binding of SARS-CoV-2 via spike protein S1 subunit was shown.

Prevention of cytokine storm induced micro-vascular thrombotic cascade was shown to be due to inhibition of inflammation associated genes, reduction of inflammatory factors, regulation of signal pathways and balance of cytokines. Pulmonary vasculopathy and fibrosis were shown to be prevented by regulatory effects on the endothelium and coagulation mechanism.

The above actions were found in 6 key herbs in combination with 14 others, viz: *Ephedra Sinensis* (Ma Huang麻黃), *Bupleurum Chinense* (Chai-hu柴胡), *Pogostemon Cablin* (Guang -huo-xiang廣藿香), *Cinnamomum Cassia* (Gui-zhi桂枝), *Scutellariae Baicalensis* (Huang-qin 黃芩), and *Glycyrrhiza Uralensis* (Gan-cao 甘草). Another study revealed that two compounds (kaempferol and quercetin) from **QFPD清肺排毒decoction** directly suppress SARS-CoV-2 replication by inhibiting papain-like protease (PLpro) and 3C-like protease (3CLpro), and it is involved in the regulation of viral infection and inflammation/cytokine pathways[36].

Network analysis of **LHQW連花清瘟capsule** showed that it regulates proteins co-expressed with ACE2 receptor of COVID-19, suggesting the potential effects against SARS-CoV-2 infection[37]. Zhong Nan-shan's research team showed that the LHQW capsule and Liu Shen capsule inhibited the replication of SARS-CoV-2 in Vero E6 cells and suppressed expressions of cytokine genes (e.g., TNF-α, IL-6, MCP-1) in Huh-7 cells[38,39]. In silico screening showed that *Lonicerae Japonicae Flos* (Jin-yin-hua 金銀花) and *Forsythiae Fructus* (Lian-qiao連翹), two key herbs of LHQW, worked against COVID-19 by targeting 3CLpro and ACE2[40]. *Phillyrin* from Lian-qiao 連翹, significantly suppressed viral infection and pro-inflammatory cytokines in cells via attenuating NF-κB signalling pathway[41].

One major component in **QFPD and LHQW**, *Scutellariae Baicalensis* (Huang-qin 黃芩) and its compound, baicalein, reduced the morphological damage of SARS-CoV-2 infected Vero E6 cells, inhibited inflammatory cell infiltration in the lung, and reduced serum cytokines (IL-1â and TNF-α) in rats[42]. Consistently, baicalein inhibited SARS-CoV-2 replication via inhibiting 3CLpro activity in *vitro*[43].

Network pharmacology analysis on **XBJ血必淨injection** showed that it could benefit COVID-19 patients with immuno-thrombosis by targeting PI3K-Akt, TNF, IL-4, IL-10, IL-13, IL-17, HIF-1, apoptosis, and platelet activation & aggregation pathway.

XBJ inhibited the level of IL-6, TNF-α in serum in the methicillin-resistant staphylococcus aureus-induced sepsis mice, and suppressed inflammatory response by down-regulating the activation of NF-κB, MAPK, and PI3K/Akt pathways in Pam3CSK4-stimulated mouse macrophages[44]. It inhibited the expression of HIF-1á (to attenuate hypoxia-induced injuries) in lungs of paraquat-induced pulmonary injury mouse[45], and up-regulated the expression of IL-10 (an anti-inflammatory cytokine) in the acute lung injury/sepsis model animals[46,47]. XBJ and its compounds *Carthami Flos* (Hong-hua 紅花), *Paeoniae Radix Rubra* (Chi-shao 赤芍), *Chuanxiong Rhizoma* (Chuan-xiong 川芎), *Salviae Miltiorrhizae Radix* (Dan-shen 丹參) and *Angelicae Sinensis Radix* (Dang-gui 當歸) have anticoagulant and anti-thrombotic effects. Animal studies indicated that XBJ prevented pulmonary thrombosis by inhibiting P-selectin in lung endothelial cells[48], and some herbs in XBJ had anti-platelet and antithrombotic effects by reducing thromboxane B2 formation[49].

DISCUSSION & CONCLUSION

We have identified the anti-oxidative, anti-viral, anti-inflammatory, anti-thrombotic, anti-asthmatic and immunity and ACE2 receptor binding modulating effect of the key herbs in the three formulae (**LHQW, QFPD and XBJ**) being used for COVID-19. The evolution of the use of CM in treating patients with COVID-19 has just been published[50].

There is substantial clinical evidence on the effectiveness of **QFPD** and **LHQW** with or without combination with western medicine. *In silico, in vitro* and *in vivo* studies supported by network pharmacology, have shown the mechanisms of action of key compounds and herbs alone or in different combinations, resulting in the multi-target effects of the formulae. It is noteworthy that CM has also been demonstrated to reduce mortality in severe/critical cases according to the best available clinical evidence currently.

The National Institute of Health has just announced an investment of US$ 1 billion to address the emergence of "Long Covid-19". The potential of using CM for the prevention and treatment of microvascular thrombosis in different organs and tissues should be explored, not only for its immediate clinical effect but for alleviation of long-term side effects.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "The Use of Integrative Medicine for Treatment of COVID-19" by Dr CHAN Kam-wa,Dr CHEN Haiyong, Prof FENG Yibin and Dr Vivian WONG TAAM and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 June 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. Tinnitus is a common clinical presentation of COVID-19.
2. Age is not related to the severe presentation of COVID-19.
3. All COVID-19 patients recovered well with no sequelae.
4. Mass vaccination is one of the current strategies for COVID-19 management.
5. Hydroxychloroquine is well supported by clinical evidence to have a therapeutic effect on COVID-19.
6. For early and mild symptoms, Chinese medicines could be effective with their antiviral properties.
7. For severe COVID-19, there is some evidence that Chinese medicines could be effective through immunomodulation.
8. Evidence from in vitro, in vivo, network pharmacology studies, and randomised controlled trials supports the use of Lianhua Qingwen (連花清瘟) capsule for COVID-19 management.
9. Evidence from in vitro, in vivo, network pharmacology and cohort studies support the use of Qingfei Paidu (清肺排毒) decoction for COVID-19 management.
10. Overall, the possible benefits of Chinese medicine include reducing mortality, shortening the hospitalisation period, symptom alleviation and increasing the recovery rate.

ANSWER SHEET FOR JUNE 2021

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

The Use of Integrative Medicine for Treatment of COVID-19

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

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

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

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to May 2021 Issue

Advances in Sepsis Management

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

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How may Integrative Medicine be Useful in Stroke Care?

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Dr Chong-ching CHAN Dr Alexander Yuk-lun LAU Dr Edwin Chau-leung YU Prof Jian-gang SHEN

INTRODUCTION

Stroke is a leading cause of mortality and morbidity worldwide. Western Medicine (WM) focuses on early diagnosis for revascularisation, post-stroke rehabilitation and secondary prevention, while Chinese Medicine (CM) places emphasis on holistically restoring the internal homeostasis and eliminating pathogens (扶正驅邪).

Integrative Medicine aims to optimise patient outcome and well-being by basing upon the best understanding of both WM and CM. The development of artemisinin for the treatment of malaria and the use of arsenic for acute promyelocytic leukaemia based on CM has revolutionised WM practice, but integrative medicine is more than the simple incorporation of CM medicinal materials into mainstream medical practice. Integrative medicine should take advantage of the strengths of both WM and CM to produce synergistic effects and yield better therapeutic outcome.

CM Syndrome Differentiation: A Holistic Approach and Personalised Medicine

From inspection (望診), auscultation or olfaction (聞診), inquiry (問診) and palpation (切診), CM diagnosis emphasises disease diagnosis (辨病), syndrome differentiation (辨証) and body constitution discretion (辨體).

CM syndrome differentiation (Fig. 1) analyses a patient's symptoms and signs together with the body constitution, personality, mental status, lifestyle, and environmental factors, to provide an integrated diagnostic summary for personalised care. This process is used in identifying the disease aetiology (病因), location (病位), and nature (病性), followed by the assessment of its severity (病情), disease course and prognosis (病勢) for the explanation of the disease mechanism (病機).

Fig. 1. Chinese Medicine (CM) Syndrome Differentiation (Adapted from 中醫診斷學 (page 235), by 朱文鋒 . 2002. 中國中醫藥出版社 .)

CM DIAGNOSTICS AND THERAPEUTICS IN STROKE

Why is Stroke called 'Wind Stroke' (中風) in CM?

According to the Yellow Emperor's Inner Classics《黃帝內經》, the pathogenic factor of 'Wind' has the characteristics of having a sudden onset, quick changes ('風者，善行而數變') and attacking the upper part of the body ('傷於風者，上先受之')[1], corresponding to the nature of acute neurological dysfunction in stroke.

CM relates the pathological basis of stroke to the dysfunction of 'Zangfu Organs (臟腑)' or 'Meridian/ Collateral channels (經絡)'. CM elements producing stroke syndromes include 'Heat (火)', 'Phlegm (痰)', 'Blood stasis (血瘀)', 'Qi stagnation (氣滯)' and 'Qi-Blood or Yin-Yang deficiency (氣血陰陽不足)' as the interplay between external pathogens and the host condition. The 'Phlegm-Heat' syndrome, being the most common CM syndrome in acute stroke patients[2], has been shown to be associated with the inflammatory response,

hypercoagulability and hyperhomocysteinaemia[3] – corresponding to the risk factors and pathogenesis of stroke.

Brief Introduction of CM Syndrome Differentiation in Stroke

According to CM theory, stroke is classified according to the patient's clinical patterns into the 'Meridian/ Collateral Channel stroke syndrome (中經絡証)' or the 'Zangfu Organ stroke syndrome (中臟腑証)'. In essence, the former has neurological deficit with preserved consciousness, whereas the latter has impaired conscious level. Those stroke patients with impaired consciousness ('Zangfu Organ Stroke syndrome') can be further classified into the 'Collapse syndrome (脫証)' or the 'Blockade Syndrome (閉証)'. The 'Blockade syndrome' can be sub-typed into the syndromes of 'Yang Blockade (陽閉証)' or 'Yin Blockade (陰閉証)' (Fig. 2).

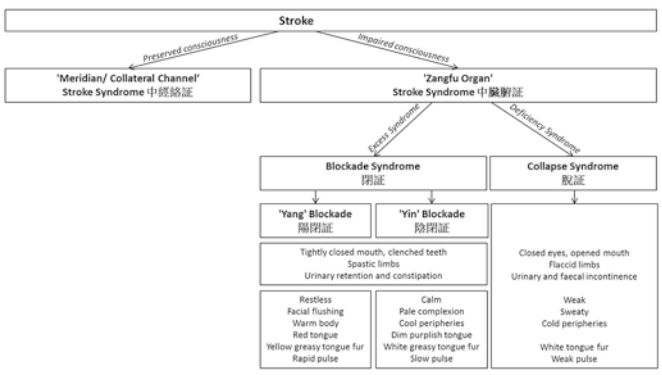

Fig. 2. CM Syndrome Differentiation in Stroke (Developed by authors)

CM Formulation (中藥)

CM formulations have multifactorial effects in stroke treatment, including antioxidant, anti-inflammatory, anti-apoptotic, neuroprotective, and vascular protective properties[4]. A CM formulation should be prescribed with the guidance of CM theory so that the different medicinal materials can work synergistically to maximise treatment effect and minimise adverse effects.

Angong Niuhuang Wan (AGNH Pill 安宮牛黃丸) is a well-known CM formula often used for acute and critically ill patients with impaired consciousness due to stroke, meningitis, encephalitis, toxic encephalopathy or septicaemia[5,6]. It contains 11 medicinal materials working synergistically to clear 'Heat', eliminate toxins and restore consciousness[5,6]. The pill contains *Bovis Calculus* (牛黃) 100g, *Bubali Cornu* (水牛角) 200g, *Artificial Moschus* (人工麝香) 25g, *Margarita* (珍珠) 50g, *Cinnabaris* (朱砂) 100g, *Realgar* (雄黃) 100g, *Coptidis Rhizoma* (黃連) 100g, *Scutellariae Radix* (黃芩) 100g, *Gardeniae Fructus* (梔子) 100g, *Curcumae Radix* (郁金) 100g, and *Broneolum Syntheticum* (冰片) 25g. These materials are ground into a fine powder, then mixed and formed into a honey pill and wrapped with gold foil[5,6]. The AGNH Pill has been named as one of the three treasures in CM as a first-aid medicine in CM practice.

In the AGNH Pill, the chief medicinal materials (君藥) are *Bovis Calculus*, *Bubali Cornu* and *Moschus* which provide the principal curative effect to clear 'Heat', clear the 'CM Heart'[7] and restore consciousness[6]. The deputy medicinal materials (臣藥) strengthen the formulation's principal effect, with *Coptidis Rhizoma*, *Scutellariae Radix* and *Gardeniae Fructus* clearing 'Heat' and removing toxins from the body, while *Curcumae Radix* and *Broneolum Syntheticum* dispel filth, clear blockage and improve consciousness[6]. The assistant medicinal materials (佐藥) either support the principal curative action, treat the secondary syndrome, temper the potency or toxicity of the chief or deputy medicinal materials, or act conversely to other materials to help the body not rejecting the CM formulation. In the AGNH Pill, these are *Cinnabaris* and *Margarita*, which tranquilise and unblock the 'CM Heart', *Realgar* which helps *Bovis Calculus* eliminate 'Phlegm' and remove toxins, and gold foil which calms the 'CM Mind'[6]. Last but not least, the envoy medicinal material (使藥) may direct treatment effect to the target site or harmonise different materials in a formulation. The use of honey harmonises and protects the 'CM Stomach' from strong effects of the AGNH Pill[6] (Fig. 3).

Pre-clinical and clinical trials have studied the use of AGNH Pill in different stages of acute stroke. Experimentally, AGNH Pill exerted its neuroprotective effects via its antioxidant and anti-inflammatory properties in rat models of cerebral ischaemia injury[8]. Clinically, add-on treatment of AGNH Pill to conventional medicine showed beneficial effects over conventional medicine alone in both ischaemic and haemorrhagic stroke[9-11].

There have been safety concerns for the AGNH Pill because of its mercury- and arsenic-containing materials, including *Cinnabaris* (mercuric sulfide, > 96% HgS) and *Realgar* (arsenic sulfide, > 90% As_4S_4). *Cinnabaris* and *Realgar* have neuroprotective effects against cerebral ischaemia-reperfusion injury[12], by inhibiting oxidative or nitrative stress-mediated matrix metalloproteinase activation and protecting tight junction proteins in the ischaemic brains[13]. Clinically, short-term use of AGNH Pill has been shown to improve consciousness, neurological impairment, and outcome in stroke patients without liver or renal toxicity[12-16]. It has been proved that treatment with one AGNH Pill daily for one week would not induce liver or renal toxicity[12]. A study reviewing adverse events associated with the AGNH Pill yielded only 49 incidents reported in the period of 1974 - 2015, which were attributed to improper use such as overdose for children or concurrent use with incompatible drugs[17]. There is an ongoing randomised double-blind placebo-controlled trial in Hong Kong to review the use of AGNH Pill in stroke[18].

Notably, according to CM principle, the AGNH Pill is only useful in acute stroke with the 'Yang Blockade syndrome (陽閉証)' but is contraindicated in the 'Yin Blockade syndrome (陰閉証)', 'Collapse syndrome (脫証)' or the 'Meridian/Collateral Channel stroke syndrome (中經絡証)' (Fig. 2). AGNH Pill is contraindicated in pregnant ladies and athletes and should be used with caution in patients with liver and renal impairment. It is recommended that the AGNH Pill should be used at the dose of one pill daily for not more than one week

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End-of-Life Care for Older People in the Context of COVID-19

Topics:

Prof Rowan Harwood

Honorary Consultant Geriatrician

Professor of Palliative and End-of-life Care,
The University of Nottingham

End-of-life Care of Older People Living in the Community (Home and Residential Care Settings): Achieving a Balance between Compassionate Care and Public Health Measures

Older people may face difficulties to access and look for the End-of-life (EOL) care resources in the community. The topic will include the sharing from UK on community-based EOL care to achieve a balance between compassionate care for older people and public health measures and also the barriers encountered during COVID-19.

Dr Raymond Lo

Specialist in Geriatrics

Clinical Professor (Hon),
Department of Medicine and Therapeutics,
The Chinese University of Hong Kong

End-of-life Care during COVID-19 in Palliative Care Wards

In the COVID-19 pandemic, EOL care is more important than ever. Patients presenting COVID-19 symptoms with severe condition may need referral to palliative care ward. The topic will explore how to apply better EOL care to the patients under sudden exacerbation in health condition and the importance of advance care planning to determine the care preference and treatment goals.

Date: 6 July 2021 (Tuesday)
Time: 4:00pm – 5:30pm (HKT)
Language: English
(with simultaneous interpretation to Cantonese)

Online via ZOOM
Registration Deadline: 28 June 2021

Dr James Luk

Specialist in Geriatrics

Past President,
The Hong Kong Geriatrics Society

Chairman,
End-of-life Care Special Interest Group,
The Hong Kong Geriatrics Society

End-of-life Care during COVID-19 in Residential Care Settings

EOL care is a complex yet pressing issue and becomes more challenging to older people in residential care settings during COVID-19. The topic will cover how patient holistic needs be affected and the psychological and social implications to the patients and their caregivers with respect to the physical isolation and other restrictions during the pandemic.

Moderator

Prof Jean Woo

Director, Jockey Club Institute of Ageing,
The Chinese University of Hong Kong

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Initiated and Funded by:
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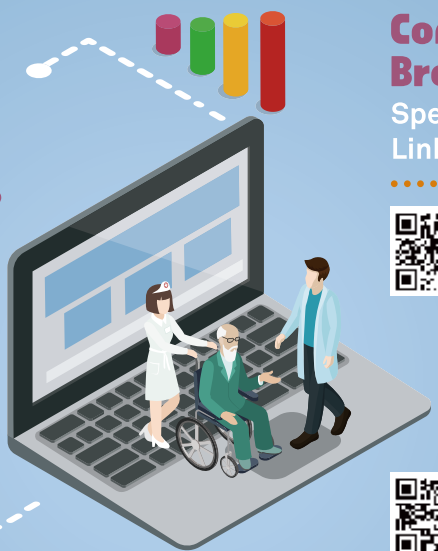
E-learning period:
15 May - 30 Oct 2021
Duration: 1 hour



Advance Care Planning: What, Why, When, How?
Speaker: Dr. Kong Tak Kwan
Link: https://bit.ly/392BZD0

Communications for Breaking Bad News
Speaker: Dr. Christopher Lum
Link: https://bit.ly/2QkU60b

Ethics of Clinical Decision-making for End-of-life Patients
Speaker: Dr. Derrick Au
Link: https://bit.ly/2OYyoyG

How People with Pre-Existing Palliative Care Needs are Affected by the COVID-19 Pandemic
Speaker: Dr. James Luk
Link: https://bit.ly/3a2scxg

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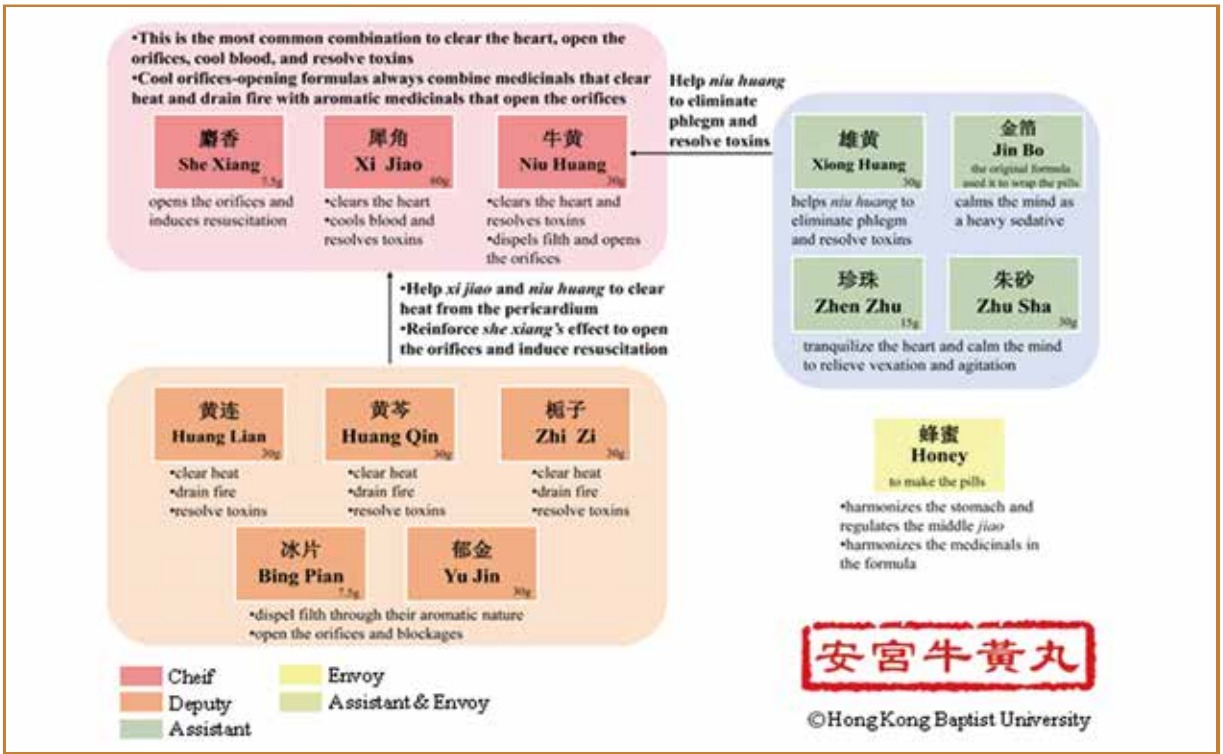

Fig. 3. Combination and Roles of Medicinal Materials in the Angong Niuhuang Pill (安宮牛黃丸)
(Excepted from Hong Kong Baptist University School of Chinese Medicine Chinese Medicine Formula Database. 2012.[6])

in acute stroke patients. The AGNH Pill would not be suitable for prevention or health enhancement because the risks of mercury and arsenic toxicity in long-term use remain to be investigated.

For post-stroke rehabilitation, the Buyang Huanwu Decoction (BYHWD 補陽還五湯) can be used. It was first described in the Corrective Errors in Medicine《醫林改錯》, and is a representative formula for boosting 'Qi (氣)' and promoting blood circulation. BYHWD consists of *Astragali Radix* (黃芪) 120g, *Angelicae Sinensis Radix* (當歸) 6g, *Paeoniae Radix Rubra* (赤芍) 4.5g, *Chuanxiong Rhizoma* (川芎) 3g, *Carthami Flos* (紅花) 3g, *Persicae Semen* (桃仁) 3g, and *Pheretima* (地龍) 3g. *Astragali Radix* functions as the mega-chief medicinal material to invigorate 'Qi' and enhance 'Yang-Qi (陽氣)'. *Angelicae Sinensis Radix, Paeoniae Radix Rubra, Chuanxiong Rhizoma, Carthami Flos* and *Persicae Semen* are the deputy and assistant medicinal materials for promoting blood circulation and replenishing 'Qi-Blood (氣血)'. *Pheretima* serves as the envoy medicinal material to smoothen the movement of 'Qi-Blood' in the body.

Clinical trials have revealed that BYHWD has neuroprotective and neurogenic effects on ischaemic brain injury. BYHWD has been shown to inhibit neuronal apoptosis, promote the proliferation and differentiation of neural stem cells and neurite formation, and enhance the recovery of learning and memory functions in rat ischaemic stroke model through the regulation of multiple cellular signalling pathways[19]. Systematic review and meta-analysis have demonstrated that BYHWD could improve neurological deficits and is safe in patients with acute ischaemic stroke[20].

In short, for stroke patients with appropriate CM syndromes, the AGNH Pill is useful in acute stroke, while the BYHWD is effective in post stroke management.

Acupuncture and Moxibustion (針灸)

Acupuncture and moxibustion regulate the flow of the body's life energy called 'Qi' and restore the body's balance through acupuncture points located along specific pathways of the body known as the 'meridian and collateral channels'. Acupuncture exerts its effect on the body by local action, segmental and extra-segmental analgesia, central regulation, and myofascial trigger points effects[21].

Acupuncture in stroke rehabilitation has several effects, including promotion of neurogenesis and cell proliferation in the central nervous system, anti-apoptosis effect and regulation of cerebral blood flow in the ischaemic area, regulation of neurochemicals, and improvement of the impaired long-term potentiation and memory in the brain[22]. Clinical studies have demonstrated that acupuncture can reduce mortality and neurological deficit in severe ischaemic stroke[23]. The beneficial effects of acupuncture in post-stroke rehabilitation include reducing spasticity[24] and shoulder-hand syndrome[25], improving muscle strength and motor function[26], balance[27], dysphagia[28] and speech disturbance[29], depression[30] and cognitive dysfunction[31], as well as the general well-being of stroke patients.

The Ottawa Evidence-Based Clinical Practice Guidelines for Post-Stroke Rehabilitation recommended in 2006 that there is 'good scientific evidence to consider

acupuncture as an adjunct to standard stroke rehabilitation to improve walking ability, range of motion and balance'[32]. This recommendation was acknowledged by the American Heart Association and American Stroke Association Guideline in 2016[33]. The Cochrane Stroke Group reviewed the evidence and concluded in their review in 2016 that acupuncture 'may have beneficial effects on improving dependency and global neurological deficiency'[34].

INTEGRATIVE MEDICINE IN STROKE

Acute Stroke Management

'Time is brain'. In ischaemic stroke within the therapeutic time window, reperfusion therapies (which include intravenous thrombolysis and mechanical endovascular thrombectomy) should be given as soon as possible. The aim is to recanalise the blocked blood vessels, and restore blood flow to the viable ischaemic penumbra, which can reduce brain damage and neurological deficit. In haemorrhagic stroke, immediate reversal of anticoagulation and rapid control of blood pressure can prevent haematoma expansion and improve stroke outcomes. Patients should be admitted to an acute stroke unit under the care of a multidisciplinary stroke team.

CM has a role in acute stroke management, but an accurate CM syndrome differentiation is essential. One interesting acute CM treatment for patients with the 'Blockade syndrome' is blood-letting from the EX-UE11 acupuncture points (十宣放血) to release the 'Heat' toxin. These ten acupuncture points are located just distal to each fingernail. Pricking and releasing a small amount of blood from EX-UE11 is known to help revive consciousness in patients with coma, acute stroke, or epilepsy. Acupuncture points useful for the 'Zangfu Organ stroke syndrome' include the GV20 (百會), GV26 (水溝), and LI4 (合谷) acupuncture points[35]. Additional acupuncture points for patients with the 'Blockade syndrome' include the LI11 (曲池) and ST40 (豐隆) acupuncture points[35]. Other commonly used acupuncture points in stroke include ST36 (足三里) and GV14 (大椎) acupuncture points.

As discussed before, AGNH Pill can be used in acute stroke patients with the 'Yang Blockade syndrome'. Patients with the 'Yin Blockade syndrome' should need another pill, the Su He Xiang Wan (蘇合香丸)[35]. On the other hand, ginseng may be helpful for stroke patients with the 'Collapse syndrome'[35].

Furthermore, recent studies indicated that CM formulation could reduce haemorrhagic transformation and reduce morbidity and mortality in acute ischaemic stroke with delayed intravenous thrombolysis[36,37]. Thus adjunct therapy with CM treatment has the potential to extend the therapeutic window for thrombolysis, prevent haemorrhagic transformation and improve neurological outcome in stroke. These novel approaches for WM are time-tested for CM and now more evidence-based.

Post-Stroke Management and Rehabilitation

After the acute phase of stroke, WM management focuses on secondary stroke prevention, prevention and management of comorbidities and complications, as well as stroke rehabilitation. The contemporary guideline-based stroke rehabilitation recommends a multidisciplinary approach involving patients, their family and caregivers, stroke physicians and nurses, physiotherapists, occupational therapists, speech-language therapists, dietitians, psychologists, and social workers[38]. Many patients also consult CM practitioners and acupuncturists for post-stroke management, and these should be well collaborated. Depending on the patients' stroke severity, neurological recovery and social support, rehabilitation can be hospital- or community-based. A comprehensive stroke rehabilitation programme should be goal-directed and personalised, with an aim to minimise disabilities, enhance functional recovery, promote social reintegration and the resumption of roles in the home, family, recreational and vocational domains[39].

Evidence-based WM rehabilitation strategies for the hemiplegic upper limb include constraint-induced movement therapy, mirror therapy and mental imagery[40]. Interventions for post stroke mobility impairment include task-specific training, therapeutic exercise by strength, resistance, balance, cardiovascular and aerobic training, electromechanical and robotic assisted mobility training[41,42], as well as the use of games and virtual reality. Besides, brain stimulation (repetitive transcranial magnetic stimulation and transcranial direct current stimulation) also facilitates stroke recovery by altering neural activity and modulating cortical excitability[40,41,43,44].

On the other hand, CM practice utilises a holistic approach and can have a significant contribution in stroke rehabilitation. CM considers not only the patient's stroke severity, conscious level, and neurological deficit, but also considers the comorbidities and medical complications, such as respiratory symptoms or infection, chest pain or palpitation, gastrointestinal symptoms (including dyspepsia, nausea or vomiting, constipation or diarrhoea), urinary tract infection or urinary retention, headache, or dizziness, as well as joint or back pain. As a result, CM treatment regimen not only varies among different patients, but is also modified according to the different disease stages in a patient.

CM therapeutics useful for post-stroke care include CM formulation, acupuncture and moxibustion, tuina (推拿) and fumigation-washing therapy (薰洗療法). CM formulation such as the BYHWD (補陽還五湯) promotes neural stem cell growth and enhances neurological recovery[19,20] by invigorating 'Qi', activating 'Blood' and clearing the 'collateral channels'.

Tuina is a special type of massage based on the CM theory of 'meridian and collateral channels' to regulate 'Qi-Blood'. Tuina can relieve pain, improve spasticity, increase the range of motion of joints, and promote recovery of motor function in stroke patients[46]. Fumigation-washing therapy treats patients

by fumigation and washing of the diseased areas with hot CM decoction. The heat and the CM medicinal materials work together to dredge the 'external pathogens' through the 'body surface', activate and harmonise the 'meridian and collateral channels' and regulate 'Qi-Blood'. Fumigation-washing therapy has the effect of relieving pain and reducing swelling[46].

Evidence-based recommendations of CM treatment modalities in stroke have been published in 2020 after systemic literature reviews and multidisciplinary expert review[46]. In summary, an integrative approach in stroke care may yield better outcomes in the neuroprotection, neurogenesis, and functional recovery in stroke patients in both acute and rehabilitation phases.

FUTURE DIRECTIONS FOR INTEGRATIVE MEDICINE DEVELOPMENT

Directions for Integrative Medicine Research

A systemic review and meta-analysis on stroke rehabilitation by integrative medicine has been performed in 2020 under the Integrative Joint Organizational Platform (IJOP) of the Hong Kong Association for Integration of Chinese-Western Medicine. The group analysed 77 randomised controlled trials and quasi-randomised controlled trials on stroke rehabilitation comparing WM and CM interventions[47]. In particular, it was found that the addition of acupuncture to WM may result in significant improvement in stroke patients' dependency and swallowing function, and the use of CM with WM may result in significant improvement in post-stroke depression[47].

Clinical research in CM is challenging because CM treatment emphasises individualised care and the holistic approach. Integrative medicine resesarch must consider both the patients' WM diagnosis and CM syndrome differentiation while balancing issues of CM heterogenicity and sample size. A pragmatic approach to clinical integrative medicine research is to group patients with a particular WM diagnosis into CM syndrome subgroups. Semi-individualised CM treatment can then be given to balance personalisation and standardisation, to maximise disease sampling and reflect actual clinical practice[48].

Future Integrative Medicine Development

CM has been used for health maintenance, disease prevention and treatment for centuries. It is not only widely accepted by the Chinese population but has also accumulated its reputation worldwide. The World Health Organization (WHO) has recognised traditional medicine as an important and often underestimated part of health care and has updated its traditional medicine strategy[49]. The strategic objectives are to build the knowledge base and formulate national policies, as well as to strengthen safety, quality, and effectiveness through regulation[49]. Recognising that traditional medicine is an integral part of health services, WHO has included a new chapter on traditional medicine in the new International Classification of Diseases (ICD-11), incorporating information on CM symptomatology, patient constitution, aetiology, course and outcome, or treatment response[50]. Including CM information into this global diagnostic standard will not only facilitate research and evaluation of the safety and efficacy of traditional medicine but will also promote the development of integrative medicine internationally[50].

In Hong Kong, CM has been gradually incorporated into the public healthcare system over the years. With collaborative efforts from the government, academia, industry and the community, integrative medicine is developing in different levels – pre-clinical and clinical research, education and training, clinical service, and law-based regulation[51]. The Integrated Chinese-Western Medicine Pilot Programme, launched by the Hospital Authority in Hong Kong in 2014, has accumulated experience for CM inpatient services and outpatient follow-up in stroke care. The way forward is to include CM practitioners in the stroke multidisciplinary team and further develop stroke units into Integrative Stroke Units providing both WM and CM service. In this regard, the imminent establishment of the first Chinese Medicine Hospital in Hong Kong can provide an ideal platform to provide clinical service to stroke patients, and further development of training and research opportunities in integrative medicine.

CONCLUSION

WM and CM approach diseases from different angles but with the same aim to restore health. WM advancements in stroke have focused on the reduction of brain damage and neurological disabilities with revascularisation therapies. CM emphasises holistic care by managing stroke, comorbidities and optimising the host conditions. Integrative medicine can achieve synergistic effect to reduce patient's disabilities, enhance stroke recovery, and improve their quality of life.

The authors would like to thank Dr Peng Zengfu for his contribution to the acupuncture section.

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Integrative Cancer Care in Hong Kong - Are we ready?

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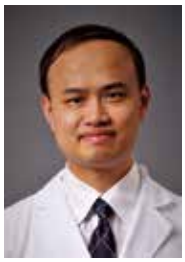
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INTRODUCTION: CANCER BURDEN IN HONG KONG

According to the Hong Kong Cancer Strategy published by the Department of Health in 2020 and data from the Cancer Registry of Hospital Authority (HA), all cancers have increased by 16% from 2005 to 2016. Total annual new cases are expected to increase from 29,110 to 42,190 by 2030[1,2]. The trend can be attributed to an ageing population, increased surveillance and an unhealthy lifestyle. On the other hand, cancer-related mortality accounts for one-third of all deaths in Hong Kong. The associated health and socioeconomic impact should not be underestimated. The increase in incidence and prevalence of cancers puts additional stress on the existing shortage of cancer service providers. It is expected that such shortage will worsen in the future due to inadequate resources allocated to staff training, cancer prevention, treatment and palliative care service[3,4].

In Hong Kong, Chinese Medicine (CM) plays a significant role in cancer care. According to HA, about 18% of cancer patients would concurrently consult private Chinese Medicine Practitioners (CMP) during conventional cancer care. Despite the implementation of Integrated Chinese-Western Medicine Pilot Project for Palliative Care for Cancer led by HA's Chinese Medicine Department, the role of CMP in the Cancer Case Manager (CCM) Programme remains ambiguous. The latter programme has already provided service to more than 13,900 breast cancer and 16,600 colorectal cancer new cases, respectively[1,3].

To date, many patients suffering from cancer associated symptoms and treatment side effects are not adequately addressed by the current model of oncology care[4-7]. Advanced stage of the disease is associated with poor quality of life[8]. In this connection, the formal introduction of CM into the oncology clinical pathway might improve the patient journey. In fact, the use of CM in cancer patients is common, ranging from 14.2% in US, 55% in Mainland China, extending to 64% in Taiwan[9-11]. A recent systematic review and meta-analysis involving 83 randomised-control trials (RCTs) of cancer patients on CM have shown that some herbal medicine could decrease the incidence of leukopenia and has a potential prophylactic benefit for white blood counts[12]. Some herbs were effective in improving quality of life, relieving side-effects of chemotherapy and radiation therapy such as poor appetite, diarrhoea or radiation-induced pneumonitis[13-18]. In vitro and in vivo studies also confirmed that some herbal medicine could inhibit colorectal cancer (CRC) growth[19-21], decrease cancer cell viability[22], suppress metastasis[23], reverse drug resistance[24], increase animal survival[25], and enhance chemotherapy potency[26]. However, the concurrent use of CM in cancer treatment remains controversial. Some herbs (e.g. St. John's wort or Gingko Blioba 銀杏 or Panax Ginseng人蔘) could interfere with the effect of chemotherapy, and inappropriate use could lead to toxicity[27-29]. Although there are some exciting results found in the above, the quality of evidence of these studies still lack of blinding, randomisation and publication bias[14,30] or syndrome differentiation not being incorporated according to the CONSORT guidelines of clinical guidelines of Chinese Medicine[31], thus limiting its clinical implication.

Despite the popularity of CM among cancer patients, a recent survey suggested that less than 5% of cancer patients would report the use of CM to their oncologists, while 77% of their oncologists had asked the history of taking CM[31]. Due to the lack of an inter-professional referral system in Hong Kong, the concurrent use of CM and conventional cancer care is often self-initiated by patients. Some patients are reluctant to reveal the use of CM to their physicians. Not directly facing the use of CM, doctors would jeopardise good medical care, and the WM profession would lose patients' trust. Suppose CM can be considered as part of the oncology management plan in that case, the patient outcome could be improved via a coordinated multi-disciplinary approach, and patient safety could be safeguarded via minimising potential drug-herb interaction.

To this end, this article serves as a medium to 1. outline the training available for service providers who are dedicated to using integrative approach to offer cancer care in Hong Kong; 2. review the current status of clinical practice guidelines (CPG) in Mainland China, US and Taiwan to understand the benefits of an integrative approach in cancer care; 3. and review the latest version of CM CPG in cancer pain developed in Hong Kong.

Good Clinical Practice for Chinese Medicine Practitioners in Cancer Care

Cancer treatment is emphasised by the Universities, and top CM experts have been recruited from Mainland China into their Schools of Chinese Medicine to further develop patient care and research areas. An organised

curriculum of Chinese medicine oncology had been built in postgraduate level of the schools of Chinese Medicine in the universities. The HA Chinese Medicine Department has also provided a senior fellowship training programme for CMPs to further advance knowledge and skills in cancer care[32,33]. Under this programme, trainees are sent to Chinese medicine hospitals of Mainland China for 1,500 hours in both inpatient and outpatient cancer bedside training. Some of these trainees opted for a formal qualification under the universities (i.e. professional diploma, taught master, MPhil or PhD degrees). These programmes are provided by local universities, professional associations, or jointly organised with non-local educational institutions[34,35]. In particular, the Hong Kong Association for Integration of Chinese-Western Medicine (HKAIM) has been offering certificate courses that include 8-14 learning hours for vocational CMP and western medical doctors who registered interests in cancer care since 2010[36].

Without any infrastructure of specialty training[37], the Chinese Medicine Development Fund of the government support the Hong Kong Institute of Integrative Medicine of The Chinese University of Hong Kong and HKAIM to launch the first professional diploma programme in enhancing the latest knowledge in cancer care for CMPs. This course is taught by a team of oncologists, family physicians, surgeons, medical social workers, palliative care nurses and renowned CM experts of Mainland China and Hong Kong. The course aims to train up to 100 CMPs with a focus on cancer care. In time, these graduates could contribute to cancer service in the future Chinese Medicine Hospital or the community for outpatients and inpatients settings. This project should serve as a platform for key stakeholders, including local universities, HA, medical specialist colleges, CMPs, local and international experts, to formulate a CM speciality training model in oncology that may involve a 3+3 pathway (resembling of the western oncologists training in Hong Kong). It could benchmark the clinical practice standard with the counterparts of Mainland China[38].

Is the Evidence Enough for us to Join Hands for the Benefit of the Survival of Cancer Patient?

In Mainland China, CMPs can prescribe western medications and technology in CM hospitals. This practice allows hospitals to keep up-to-date with the international CPG and latest development in cancer treatment while involving CM from early to advance or late-stage cancer diseases[39-41]. Hospital-based CPG is therefore developed to serve this purpose. Overall, the strategy is to offer surgery to those who are indicated and incorporate CM to 1. increase surgical recovery, decrease rate of complication, and recurrence or metastasis; 2. decrease adverse effects of conventional therapies (such as neurotoxicity caused by chemotherapy); 3. increase compliance to chemotherapy; 4. improve health-related quality of life of patients; and 5. increase the 5-years survival of late stage cancers.

The counterparts in US also established guidelines via the National Comprehensive Cancer Network (NCCN). At present, 5 out of 11 NCCN CPG recommend acupuncture as one of the interventions for adult cancer pain, increasing survival, palliative care, cancer-related fatigue and antiemesis[42].

The way Taiwan promotes integrative care is different by means of the inclusion of CM in National Health Insurance (NHI). Interestingly, data from NHI suggested that concurrent use of CM and western medicine could increase the median survival of pancreatic cancer from 8 months to 19 months[41,43]. Other cancers from adult or paediatric population studies also reported similar effects[44]. Surprisingly, overall treatment cost could be reduced by 81.9% by adding CM to treat leukaemia patients (combined treatment: NT$870,694,519; western medicine treatment alone: NT$6,211,043,099)[45]. Using network pharmacology, more than 18 herbs have been identified to improve survival when they are used according to CM syndrome differentiation and diagnosis. This implies that the effectiveness of Chinese herbs need precise diagnosis and clinical application for identifying specific herbs that need to be used in cancer care to increase clinical application[40,46].

Hong Kong Chinese Medicine Clinical Practice Guideline for Cancer Pain

One of the most important aspects of treating and managing cancers is pain control. Cancer pain can be caused by complications of cancer, such as bone metastasis, cancer infiltration and/or nerve compression. Chemotherapy-induced peripheral neuropathy and mucositis; radiotherapy-induced mucositis, dermatitis and enteritis; post-operative wound and scar tissue can all cause treatment-related pain. It can affect patients throughout and after the course of the disease and its treatment[47]. It is estimated that one-quarter of cancer patients experience cancer pain at diagnosis, one-third during treatment, and three-quarters during advanced stages[48,49].

If the cancer pain is not relieved, patients may suffer from fatigue, anxiety, depression, loss of appetite, and other symptoms, and seriously affect the patient's daily activities, self-care ability, and overall quality of life[50]. Therefore, managing symptoms is as important as treating cancers.

Cancer pain has long been recorded in ancient CM literature with various descriptions and naming of the symptoms. Additionally, much evidence from reviews and clinical trials have now shown that CM treatments are associated with cancer pain relief as well as improving quality of life[50-58]. A recent meta-analysis involving 920 patients published on JAMA Oncology confirmed that high quality RCTs are available to support the use of acupuncture[59]. Notably, seven sham-controlled RCTs were rated high quality and judged to have a low risk of bias for all of their domains and showed that real (compared with sham) acupuncture was associated with reduced pain intensity (mean difference [MD], -1.38 points; 95%CI, -2.13 to -0.64 points; I2 = 81%). A favourable association was also seen when acupuncture and acupressure were combined with analgesic therapy in 6 RCTs for reducing pain intensity (MD, -1.44 points; 95%CI, -1.98 to -0.89; I2 = 92%[60].

The Joint Commission[58], American College of Physicians[59], NCCN[61] and American Society of Clinical Oncology guidelines[62] all recommend a combination of pharmacologic and non-pharmacologic modalities, including acupuncture. In Hong Kong, a CM CPG for cancer pain with sound scientific methodology was developed by Hong Kong Baptist University to collaborate with other parties[63]. It suggested the following treatment regime for consideration (Table 1).

Table 1: Disease patterns and associated treatment as suggested by the Hong Kong's Chinese Medicine Clinical Practice Guideline (Adapted from Lam, N.C., et al.[63])

Pattern	Herbal medicine	Acupuncture
All patterns	NA	He Gu (LI4), Tai Chong (LR3), A Shi points (合谷, 太衝, 亞是穴) Grading of recommendation: B Level of evidence: IIa
Qi movement stagnation (氣滯)	Modified Chai Hu Shu Gan San (柴胡疏肝散加減: 枳殼、甘草、柴胡、白芍、陳皮、香附、川芎), Modified Si Ni San (四苓散加減: 白、澤瀉、豬苓、茯苓) Grading of recommendation: A Level of evidence: Ib	Nei Guan (PC6), Gong Sun (SP4), Qi Men (LR14), Zhong Wan (RN12), Zhi Gou (SJ6) (內關, 公孫, 氣門, 中脘, 支溝) Grading of recommendation: C Level of evidence: IV
Phlegm-dampness congealing (痰濕凝滯)	Modified Ting Li Da Zao Xie Fei Tang (葶藶大瀉心湯加減:葶藶子、大棗) Grading of recommendation: C Level of evidence: IV	Zu San Li (ST36), Feng Long (ST40), Yin Ling Quan (SP9) (足三里, 豐隆, 陰陵泉) Grading of recommendation: C Level of evidence: IV
Static blood obstructing (瘀血內阻)	Modified Tao Hong Si Wu Tang (桃紅四物湯加減:桃仁、紅花、熟地、白芍、川芎、當歸), Modified Fu Yuan Huo Xue Tang (復元活血湯加減:大黃、柴胡、當歸、桃仁、紅花、穿山甲、瓜蔞根、甘草) Grading of recommendation: B Level of evidence: IIa	Xue Hai (SP10), Ge Shu (BL17), Dan Zhong (RN17), San Yin Jiao (SP6), Nei Guan (PC6) (血海, 膈俞, 膻中, 三陰交, 內關) Grading of recommendation: C Level of evidence: IV
Qi stagnation and blood stasis (氣滯血瘀)	Modified Ge Xia Zhu Yu Tang (膈下逐瘀湯加減:五靈脂、當歸、川芎、桃仁、丹皮、赤芍、烏藥、延胡索、甘草、香附、紅花、枳殼), Modified Xue Fu Zhu Yu Tang (血府逐瘀湯加減:當歸、生地、桃仁、紅花、赤芍、川芎、枳殼、甘草、柴胡、牛膝、桔梗) Grading of recommendation: B Level of evidence: IIa	Nei Guan (PC6), Xue Hai (SP10), Ge Shu (BL17), Liang Qiu (ST34) (內關, 血海, 膈俞, 梁丘) Grading of recommendation: C Level of evidence: IV
Combination of phlegm and blood stasis (痰瘀互結)	Modified Wen Dan Tang (溫膽湯加減:竹茹、枳實、橘紅、制半夏、茯苓、甘草、生薑、大棗), Modified Xue Fu Zhu Yu Tang (血府逐瘀湯加減:當歸、生地、桃仁、紅花、赤芍、川芎、枳殼、甘草、柴胡、牛膝、桔梗), Modified Si Wu Tang plus Er Chen Tang (四物湯加二陳湯加減: 熟地、白芍、川芎、當歸、橘紅、制半夏、茯苓、甘草) Grading of recommendation: B Level of evidence: IIa	Feng Long (ST40), Xue Hai (SP10), Zu San Li (ST36), San Yin Jiao (SP6), Nei Guan (PC6) (豐隆, 血海, 足三里, 三陰交, 內關) Grading of recommendation: C Level of evidence: IV
Qi and blood deficiency (氣血虧虛)	Modified Si Wu Tang (四物湯加減: 熟地、白芍、川芎、當歸) Grading of recommendation: C Level of evidence: IV	Qi Hai (RN6), Zhong Wan (RN12), Zu San Li (ST36), Xue Hai (SP10), Pi Shu (BL20), Fei Shu (BL13), San Yin Jiao (SP6) (氣海, 中脘, 足三里, 血海, 脾俞, 肺俞, 三陰交) Grading of recommendation: C Level of evidence: IV

INTEGRATIVE JOINT ORGANIZATIONAL PLATFORM (IJOP) IN FOSTERING THE EVIDENCE INTO PRACTICE

IJOP, with the support of the Innovation and Technology Commission of the HKSAR Government, systematic reviews and meta-analysis of pooling published clinical trials have shown that Chinese Medicine or acupuncture could reduce chemotherapy-associated side-effects in breast cancer patients[64]. Available literature indicated that the adjunctive use of CHM with chemotherapy might reduce the chemotherapeutic agents-associated adverse events (including nausea and vomiting, diarrhoea, alopecia, myelosuppression, and impaired immune function). We are looking forward to subsequent research reports on the impact of the adjuvant use of Chinese medicine or acupuncture as these may be particularly considered for chemo-brain, in triple-negative breast cancer, and in improving the micro-environments of chemotherapy and target therapy for increasing tolerance of conventional treatment.

CONCLUSION

In view of the heavy cancer burden, we have a track record of making an effort in education, research and establishing some clinical guidelines for cancer care. With the new initiatives in the first Hong Kong Chinese Medicine Hospital, the integrative multi-disciplinary approaches will benchmark the enhancement of quality of care.

Summary and Bring Home Messages.

(1) The burden of cancer diseases is increasing in Hong Kong, but cancer care in the hospital setting is driven by western conventional cancer care without the formal involvement of Chinese Medicine.

(2) Vocational Education of Chinese Medicine Practitioners on cancer care is in progress with the support of the Hong Kong Chinese Medicine Development Fund. The quality of education will be strengthened by an inter-disciplinary approach.

(3) Some Clinical Practice Guidelines support the use of acupuncture in cancer care, particularly cancer pain. Hong Kong also has its own Chinese Medicine Clinical Practice Guideline for cancer pain.

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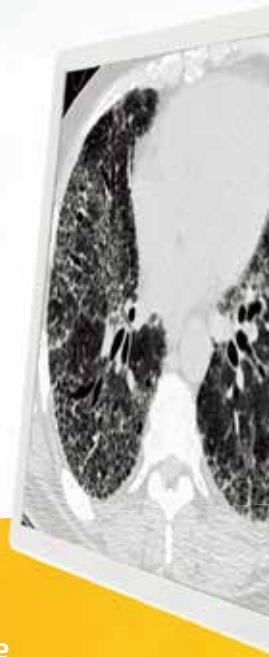
and modify ILD progression by slowing lung function decline[1]



As many as 18% to 32% of patients with non-IPF ILDs are estimated to be at risk for developing a progressive fibrosing phenotype[2]

OFEV® was shown to modify ILD progression across a broad range of patients with a progressive fibrosing phenotype by slowing decline in FVC by 57% over 52 weeks[1]

In INBUILD®, patients taking OFEV® had a 33% reduction in risk of acute exacerbations or death over the full study duration[1,3*]

The most common AEs observed with OFEV® in INBUILD® were GI-related, mild-to-moderate, and could be effectively managed in most patients with progressive fibrosing ILDs[1]

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Dosing simplicity: Just 1 capsule taken twice daily[1]

▼ **OFEV API [API_OFE_16-17_V1]**
Presentation: Nintedanib esilate, Capsule, 150 or 100mg **Indications:** For the treatment of Idiopathic Pulmonary Fibrosis in adults; To slow the rate of decline in pulmonary function in patients with systemic sclerosis associated interstitial lung disease; for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype (also known as progressive fibrosing ILD) **Dosage and administration:** The recommended dose is 150 mg twice daily administered approximately 12 hours apart. The management of adverse reactions to OFEV® could include dose reduction (to 100mg twice daily) and temporary interruption. Treatment may be resumed at the full recommended dose (150mg twice daily) or a reduced dose (100mg twice daily). In patients with mild hepatic impairment (Child Pugh A), the recommended dose is 100mg twice daily approximately 12 hours apart. Treatment of patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment is not recommended. The capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed. **Contraindication:** Hypersensitivity to nintedanib, peanut or soya, or to any of the excipients; Pregnancy. **Special warnings and precautions:** Diarrhea was the most frequent gastrointestinal event reported. Diarrhea should be treated at first signs with adequate hydration and anti-diarrheal medication and may require dose reduction or treatment interruption. Nausea and vomiting were frequently reported gastrointestinal adverse reactions. Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischemia. In clinical trials, no increased risk of venous thromboembolism was observed in nintedanib treated patients. Treatment with OFEV® may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated. Use OFEV® in patients with clinically significant pulmonary hypertension only if the anticipated benefit outweighs the potential risk. Weight loss has been reported. Physicians should monitor patients' weight, and when appropriate, encourage increased caloric intake if weight loss is considered to be of clinical significance. Only use OFEV® in patients with a known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk. Therapy with OFEV® should be permanently discontinued in patients who develop gastrointestinal perforation. Based on mechanism of action, OFEV® increases risk of bleeding. Use OFEV® in patients with known risk of bleeding only if anticipated benefit outweighs the potential risk. Cases of drug-induced liver injury have been observed with nintedanib treatment in both clinical trials and post-marketing surveillance database. Administration of OFEV® was associated with elevations of liver enzymes and bilirubin. Hepatic transaminase and bilirubin levels should be investigated just before initiation of treatment, then at regular intervals (monthly) during the first three months and periodically thereafter or as clinically indicated. The safety, efficacy and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30ml/min CrCl). No increased frequency of impaired wound healing was observed in the clinical trials. It is not known if nintedanib or its metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue treatment with OFEV, taking into account the benefits of breast-feeding for the child and of OFEV® treatment for the mother. **Interactions:** Nintedanib is a substrate of P-gp and to a minor extent CYP3A4. Coadministration with the potent P-gp s and CYP3A4 inhibitor ketoconazole increased exposure to nintedanib. Potent P-gp and CYP3A4 inducers decreased exposure to nintedanib. **Adverse reactions:** Common(>3% in nintedanib group and >1.5% more frequently than placebo): Diarrhea, Nausea, Vomiting, Constipation, Abdominal pain, Gastroesophageal reflux disease, Flatulence, Weight decreased, Liver enzyme elevation, Decreased appetite, Headache, Hypertension, Pneumonia, Musculoskeletal pain, Fatigue, Dizziness, Urinary tract infection. Less Common(<3%): Hyperbilirubinemia, Alopecia **Storage conditions:** Please refer to outer packaging for storage condition. **Note:** Before prescribing, please consult full prescribing information (OFE_16-17_V1).

AE, adverse event; **FVC**, forced vital capacity; **GI**, gastrointestinal; **ILD**, interstitial lung disease; **IPF**, idiopathic pulmonary fibrosis; **SSc-ILD**, systemic sclerosis-associated interstitial lung disease.
*Using data up to the second database lock. 95% CI=0.46, 0.98 (*P*=0.04).

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OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, and systemic sclerosis associated interstitial lung disease (SSc-ILD).[1]

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PC-HK-100400(10/2020)

Conquering Atopic Dermatitis with Integrative Medicine: Synergy between the East and the West

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CURRENT LANDSCAPE FOR ATOPIC DERMATITIS

Atopic dermatitis (AD) is the most common inflammatory skin condition seen in dermatology practice.[1] Its prevalence in the past twenty years has been steadily increasing. This condition negatively impacts the quality of life for affected children and their caregivers. It can lead to a significant decrease in self-esteem, as well as increased rates of depression, anxiety, and suicidal ideation.[2]

Tremendous progress has been made in the understanding of the complex nature of AD over the past decades. The pathophysiology of AD is multifactorial, including strong genetic susceptibility, important contributions of immune dysregulation due to excessive T-helper (Th)2 and Th22 activity, with variable contributions of Th1/Th17, skin barrier dysfunction, and both cutaneous and gut microbiome dysbiosis.[3] Cutaneous inflammation is characterised by upregulated type 2 cytokines, such as IL-4, IL-13, and IL-31, heightened IgE sensitisation to various allergens, risk of food allergy, airway hyperreactivity, all of which may eventually contribute to the atopic march.[4]

The primary aim of AD management is to improve symptoms and achieve long-term eczema control with a multistep approach tailored according to disease severity (Fig. 1).[5] For all patients, basic management consists of continuous epidermal barrier repair with emollients and avoidance of individual triggers. In moderate-to-severe AD, topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCI) are the mainstays of treatment. However, patients with more severe AD often require treatment with systemic anti-inflammatory drugs, e.g. cyclosporin A, azathioprine, methotrexate and mycophenolate, which may potentially lead to significant side effects and hence treatment cessation.[6] Therefore, before the recent introduction of targeted biologic therapies, poor patient satisfaction with the treatment is common. Paller et al. (2002) found that less than one-third of patients reported satisfaction with their current treatment regimens.[7] There is interest in complementary and integrative medicine (CIM) for the treatment of AD, with over 40% of patients with AD reporting the use of integrative medicine approaches, including Chinese medicine (CM). CM has a long history in the management of various skin diseases, including AD.[8,9] Small scale clinical trials showed that CM might be beneficial in reducing disease severity in a subgroup of AD patients with certain CM syndromes.[10]

The advancement of targeted biologic therapies has revolutionised the therapeutic landscape of AD with high efficacy and favourable side effect profiles.[11] Clear therapeutic goal could now be achieved with improved patient satisfaction and quality of life.[12] The problem for biologics is their high cost, hopefully reduced in later products. Dupilumab, the first FDA approved biologics for AD, was consistently shown to have high efficacy. More than half of the patients achieved a 75% reduction of Eczema Area and Severity Index (EASI75) in different phase III clinical trials.[13] More highly efficacious therapeutic pipelines for AD are expected to

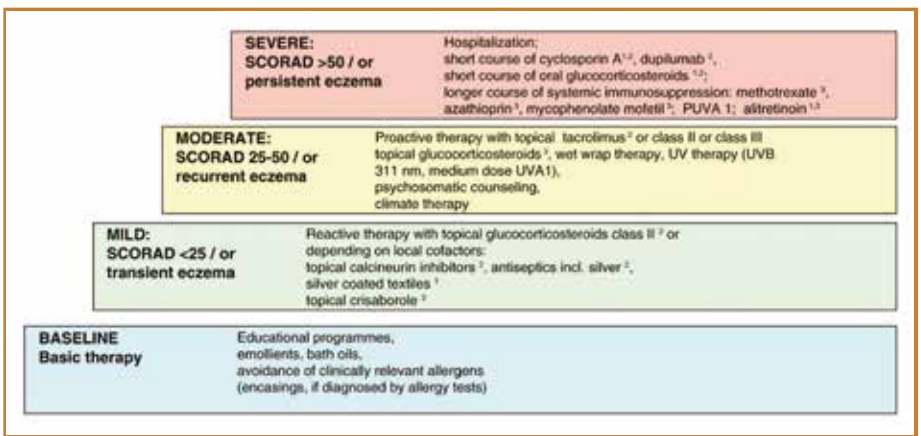

Fig. 1. European Academy of Dermatology and Venereology (EADV) treatment consensus for atopic dermatitis. Modified and adapted from Wollenberg et al.[12]

be approved and available for clinical use in the coming years.[14] Some clinicians may dispute the value of CM in the current molecular era of AD. In fact, there are still a lot of unmet needs in the complicated journey of patients with AD.

TREATMENT GOAL AND POTENTIAL SYNERGIES IN THE AD JOURNEY

The clear therapeutic goal of management and expectation could improve the treatment satisfaction in AD. The treatment goal for AD includes high treatment efficacy, long term remission, improvement of non-specific symptoms relief and prevention of disease progression.

We need to appreciate the strength and weakness of individual therapies of western and Chinese medicine. The big question is whether the combination of conventional western medicine with CM could further enhance the efficacy. As CM could approach the management of AD through a different angle by modulating the body constitution, choosing the best combination modality in different disease context could maximise the potential benefit of integrative therapies.

Treatment Efficacy Endpoint

The objective standard of adequate disease control of AD is a 50 - 75 % reduction in EASI score in conventional clinical trials for western medicine.[15] Currently, most published clinical trials of CM in AD with reasonable publication quality only showed modest efficacy in mild to moderate disease.[16] Use of CM in mild to moderate disease may be comparable with conventional western medicine, and clinical studies with a larger sample size will be desirable. However, clinical trials assessing the efficacy of CM in severe complicated disease are generally lacking.[17] From a treatment efficacy standpoint, it would be interesting to know whether concurrent use of CM with conventional western medicines across a patient with different disease severity could increase the therapeutic efficacy and symptom control.

Long Term Disease Control and Remission

After the patient has good disease control (EASI75), the next step is to maintain the treatment efficacy and minimise the episode and severity of relapse. In the conventional treatment approach, "proactive management" is adopted. CM could play an important role in proactive management in AD, particularly during stepping down from conventional western therapies. Common triggering factors include exposure to dust mites, concomitant food allergy or delayed type food reaction, stress, and poor sleep quality. CM could play a role in reducing the severity of triggers by modulation of body constitution. In addition, some Chinese herbs and Chinese herbal formulas have been shown to exert potent anti-allergic and anti-inflammatory actions on experimental models of AD.[18,19,20,21]

Non-Specific Symptoms Control

Non-specific psychosomatic symptoms, such as poor sleep, nervousness, bloating, constipation, diarrhoea, and lack of energy, are common among patients with AD. There are limited treatment options in western medicine. CM may play a role for symptomatic relief.[22]

Disease Prevention

Both primary and secondary preventions of AD are hot research topics. Studies showed that the use of probiotics during pregnancy and intensive use of moisturising cream during infancy could prevent high risk infant from AD development. Early adequate interventions of atopic dermatitis were found to reduce the risk of the development of food allergy.[23]

However, there is limited evidence for treatment to prevent patients with early mild AD from progressing to severe AD. Researchers are actively investigating the role of early intervention and adequate disease control in order to improve long term prognosis and prevention of development of severe disease in later life. CM may play a potential role in secondary prevention of AD progression to severe disease by early modulation of body constitution and suboptimal body status.[24]

IS THERE ANY SCIENTIFIC BASIS TO THINK THAT INTEGRATIVE MANAGEMENT WILL PROVIDE MORE EFFECTIVE IN REACHING THERAPEUTIC GOALS?

Although there are huge unmet needs and room for combining conventional management with CM, high quality clinical trials and systematic reviews regarding integrative therapy of CM with conventional therapies are unfortunately few and far between. Most of the studies regarding the integration of CM only assess the short term treatment efficacy in active disease management with integration of topical treatment or antihistamine only. Efficacy and safety in the integrative treatment with conventional systemic anti-inflammatories and biologics are unknown. There is currently no evidence regarding long term remission and prevention of disease progression for CM use.[9, 25]

Further clinical studies using a pragmatic clinical trial approach will be more suitable to assess the real efficacy of integrative management. Nonetheless, the Integrative Joint Organizational Platform (IJOP) from the Hong Kong Association for Integration of Chinese-Western Medicine (HKAIM) has launched the systematic review project and tried to answer the big question: whether a combination of CM and western conventional treatment will provide a better outcome to our patient with AD? The preliminary results are promising, and there are ongoing high-quality clinical trials in the local university setting.[26] Hopefully, we could provide a better scientific evidence of integrative treatment in the coming future.

HOW COULD WE INTEGRATE CM WITH OUR CONVENTIONAL HEALTH CARE SYSTEM?

To facilitate the integration of CM with conventional therapies in real life health care system, we need to build a bridge to connect the gap. Mutual understanding and respect of all parties will be of utmost importance. Academic meetings and seminars are held regularly by local organisations like HKAIM, aiming to facilitate the understanding and standardisation of the diagnosis language, and treatment philosophy will be useful for integration between the east and west.

To implement integrative care in our current system, it would be desirable to have a professional institute and organisation to uphold the risk management, safety monitoring, clinical governance and quality reassurance of the integrative care.

After initial implementation, pragmatic trials with solid outcome and cost-effectiveness measures will be the next step to reinforce the value of integrative management. Stratification of the AD patients into different CM syndrome groups with evidence-based, protocol-driven diagnosis and management supported by pragmatic trials with appropriate outcome measures will be essential to the final implementation into our healthcare system.

Currently, the IJOP aims to build a conducive environment and map out details for the collaborative practice of Chinese medicine and western medicine. There will be a lot of challenges ahead for the integration. Nonetheless, collaborative efforts from experts and local organisations such as HKAIM, IJOP and universities are evidenced; communication, education, and integrative medicine research are ongoing. Hopefully, we could bring the best therapies to relieve our AD patients' sufferings and finally conquer this distressing and life ruining skin disease in the near future.

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Integrative Chinese-Western Approach for Irritable Bowel Syndrome: From Basic Science, Translational Study to New Drug Development

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BACKGROUND

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, which is diagnosed on the basis of recurrent abdominal pain related to defecation or in association with a change in stool frequency and form. Based on the Rome IV criteria, IBS is classified into four subtypes by predominant stool pattern: IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), IBS with mixed symptoms of constipation and diarrhoea (IBS-M) and un-subtyped (IBS-U). The management of this condition is not satisfactory because there is no clear understanding of the pathogenesis. The last two decades witnessed the efforts and progress on the pathophysiological mechanism about this condition. It is currently believed that IBS is multifactorial, including psychological factors, changes in gastrointestinal motility, neural and endocrine influences, infection, diet, and drugs. Under the influences of the above factors, the intestinal function is disturbed, resulting in abdominal pain, abdominal bloating, constipation or diarrhoea; and central nervous system function is disturbed, such that psychiatric co-morbidity, e.g. depression and anxiety are overrepresented in individuals with IBS. The overall effects of the conventional treatment currently in common use for patients are not satisfactory.

Due to unsatisfactory results from conventional treatment, Chinese Medicine including herbal medicine and acupuncture, are increasingly popular treatment alternatives for IBS sufferers. Unfortunately, most clinical trials related to Chinese Medicine in this area have been of poor quality, and some of the systematic reviews or meta-analyses provide uncertain results, although there are some positive results from such an evidence-based approach[1]. Furthermore, the mechanisms of the Chinese medicines for IBS have not been systematically and well studied. Indeed, there are no new Chinese herbal drugs for IBS on the market.

IBS sufferers demonstrate the clinical phenotypes from different organs, not just the gut-brain axis. Such system-based condition may need a systems approach to manage the symptoms. Chinese Medicine is a different medical system based on the holistic approach to managing the disease. The approach of western medicine, which aims to understand the pathophysiology and the underlying mechanisms, should be integrated with the holistic approach of Chinese medicine to further the understanding of the development of the condition. Then, developing a thoroughly innovative approach for IBS is one of the goals for such research approaches.

With the Innovative Commission Scheme's support, researchers from the Chinese University of Hong Kong and Hong Kong Baptist University have worked together during the last two decades to investigate the basic mechanisms and Chinese herbal medicine-based new drug development for IBS. The major research findings from the team shed light on the understanding of IBS and new drug development. Several pieces of works are briefly introduced herewith:

ENVIRONMENTAL STRESSORS IN EARLY LIFE AND ITS CONTRIBUTION TO THE DEVELOPMENT OF IBS

An epidemiological study showed that environmental stressors in early childhood could have a detrimental impact later in life, manifesting in functional gastrointestinal disorders, including IBS. The phenomenon is also observed in rodents, where neonatal-maternal separation (NMS), a model of early life stress, induces phenotypes similar to IBS. However, the underlying mechanisms remain unelucidated. We believe this is a critical step to understand, at least for some patients with IBS, why the stressor can predispose the patients to develop IBS symptoms. Our study showed that NMS induces the increase of intestinal stem cells (ISCs) and their differentiation toward secretory lineages, including enterochromaffin (EC) and Paneth cells, leading to EC hyperplasia[2]. EC hyperplasia results in the increased serotonin production, and increased visceral pain. Such changes after NMS treatment could be reversed by inhibition of nerve growth factor (NGF)-mediated tropomyosin receptor kinase A (TrkA) signalling. More interestingly, NGF treatment recapitulates the intestinal phenotype of NMS mice and in mouse intestinal organoids. Furthermore, NGF transactivates Wnt/β-catenin signalling. In addition, NGF and serotonin are positively correlated in the sera of diarrhoea-predominant IBS patients. These findings provide mechanistic insights into early life stress-induced intestinal changes. These findings come

from animal studies but do shed light on IBS in patients. In future, there is a need to provide more evidence to explain the linkage of environmental stressors with the development of IBS, including but not limited to the following areas: 1. A prospective longitudinal study is needed to investigate how many patients with earlier life stressor may develop IBS, and any other co-factors affecting the process; 2. Based on the first step study, follow-up studies are needed to elucidate whether and how the development process is enhanced or eliminated in the life span, thus to find out how to deal with the condition; 3. In the animal study, inhibition of NGF-mediated trkA signalling has been shown to have effects on IBS symptoms. There is a need to have a clinical trial to test whether such treatment can help IBS sufferers in a well-designed randomised clinical trial. 4. Any difference in the effects of different stressors on the development of IBS? In the study, NMS has been demonstrated as a trigger to induce the development of IBS in the adult. How about another type of stressors? Whether these stressors could be a trigger for the worsening of the symptoms of IBS? If yes, whether the mechanisms are similar? These studies will share the light on the understanding of the mechanism of IBS, and further facilitate the drug discovery and symptoms management for IBS patients.

GUT MICROBIOME AND THEIR CONTRIBUTION TO IBS

During the last decade, the exciting and growing research on the contribution of gut microbiota in functional gastrointestinal diseases, including IBS, steadily increased, but the knowledge about the exact contribution to the development and management of IBS based on gut microbiome manipulation is still a big challenge. During last two decades, our research team has focused on investigating the gut microbiome specific metabolites in the development of IBS and aimed to investigate whether Chinese medicine can help to find a solution from a gut microbiome angle.

In our studies on the mechanism of the excessive bile acid (BA) excretion in IBS-D[3], we analysed the percentage of IBS-D with excessive BA excretion and the mechanism of such changes. Based on our observational study, we performed BA-related metabolic and metagenomic analyses in 290 IBS-D patients and 89 healthy volunteers; the results showed that 24.5% of IBS-D patients exhibited excessive excretion of total BAs and alteration of BA-transforming bacteria in faeces[3]. Significantly, the increase in Clostridia bacteria (e.g., C. scindens) was positively associated with the levels of faecal total BAs and serum 7α-hydroxy-4-cholesten-3-one (C4), which is BA precursor, but negatively correlated with serum fibroblast growth factor 19 (FGF19) concentration[3].

In the colonisation study with Clostridia-rich IBS-D faecal microbiota or C. scindens, the results showed that these treatments individually enhanced serum C4 and hepatic conjugated BAs but reduced ileal FGF19 expression in mice. Inhibition of Clostridium species with vancomycin yielded opposite results[3]. Furthermore, Clostridia-derived BAs suppressed the intestinal FGF19 expression in vitro and in vivo. These data demonstrate that the Clostridia-rich microbiota contributes to excessive BA excretion in IBS-D patients, which provides a mechanistic hypothesis with testable clinical implications[3]. This study also suggested that integrating the gut microbiota analysis with the metabolic analysis is necessary, not only in clinical research but also in practice. Future studies are also needed in the following areas, at least, to transfer the findings to clinical application. Firstly, there is a need for a study involving IBS-C, IBS-M and non-BA excessive diarrhoea, thus confirming the relationship between the Clostridia-rich gut microbiome and their contribution to excessive BA excretion. Secondly, a clinical study is needed to verify whether modulation of Clostridia in IBS-D can help manage IBS symptoms. Thirdly, whether traditional Chinese Medicine can help to modulate such gut microbiome-induced IBS symptoms.

JCM1602 AS A NEW DRUG FOR DIARRHOEA-PREDOMINANT IBS

Chinese herbal therapies have been used for thousands of years in Eastern Asia and have been used by IBS sufferers, and in some clinical trials, they are effective in relieving symptoms among IBS patients. Generally, traditional Chinese herbal formulae (CHF) consisting of CHM can be easily adjusted in accordance with concrete conditions, which means that the treatment is based on syndrome differentiation and varied from individual to individual. Meanwhile, CHF/CHM containing many different ingredients may act on multiple sites/pathways with potential synergistic effects and chemical reactions, which is coherent with the system approach for IBS management.

During IBS treatment with Chinese Medicine, previous studies suggested that standardisation of the diagnosis and treatment is a key issue in practice. The researchers from our team showed that variations in diagnosis and treatment principles for IBS do exist among Traditional Chinese Medicine practitioners. Concordant diagnosis can be reached by mutual understanding and converging opinion among Traditional Chinese Medicine practitioners[4].

JCM-16021, a Chinese herbal formula composed of seven herbs, is modified based on a traditional formula (Tongxie Yaofang) for diarrhoea and abdominal pain with Liver QI stagnation and Spleen Qi deficiency. According to the TCM theory, the Liver governs the free flow of Qi. Liver Qi Stagnation may violate the proper operation of the Spleen. The rise of Spleen Qi is to maintain the transportation of water and nutrient throughout the whole body. When the Spleen is offended by Liver Qi Stagnation, diarrhoea will be induced. Therefore, the Liver Qi Stagnation and Spleen Qi deficiency (LSSD) is believed to be the major mechanism of IBS-D, and the treatment for this subtype should be based on soothing the Liver Qi and strengthening the Spleen Qi. JCM-16021 is designed to treat the IBS-D with the LSSD pattern. Our previous small scale study indicated that JCM-16021 has a potential therapeutic effect of relieving IBS symptoms by comparing with Holopon and placebo[5].

Further, JCM-16021 can dose-dependently attenuate visceral hyperalgesia in neonatal maternal separation rats by changing the synthesis and metabolism of 5-HT in the colons of rats[6]. Another study also has indicated that JCM-16021 can reduce the EC cell hyperplasia and 5-HT availability and upregulate the decreased levels of certain mucosal cytokines, especially the Th1-related cytokines in PI-IBS rats[6]. Furthermore, a larger scale and rigorous clinical trial to further investigate the efficacy and safety of JCM-16021 for IBS-D with 392 volunteers has been completed recently. The data analysis is ongoing now, and the results should be released soon. We hope the results will support this remedy to be marketed in the near future.

Integrative Chinese-Western approaches for irritable bowel syndrome are alternatives for IBS, especially from basic science, translational study to new drug development. It is expected that a comprehensive management strategy will soon be developed for this complicated condition.

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Western Medicine Clinicians as Pioneers in Integrative Medicine

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Integrative Medicine (IM) in the Hospital Authority (HA) was launched by HKAIM's former Presidents, Drs WM Ko & Vivian Wong. In 2003, when HK was hit by SARS, they facilitated the invitation of Prof Lin Lin & Prof Yang Zhimin from Guangdong Provincial Hospital of Chinese Medicine (CM) to treat patients in HA hospitals, starting with the Intensive Care Unit. Prof PC Leung also used CM for the prevention of SARS. The results were published in international peer-reviewed journals[1,2]. Dr PK Hui and the HA SARS Collaborative Group recorded our experience in the treatment and rehabilitation of pulmonary fibrosis. Prof Derrick Au discussed the "Role of CM in Treating SARS Patients: Evidence in Context" in a chapter in the book "Challenges of SARS", coedited by Drs Jane Chan & Vivian Wong, published by Saunders Elsevier in 2006[3].

To address the key concerns of our western medicine (WM) colleagues, we made sure that CM was vetted by the same Research Ethics Committee as WM. A Toxicology Reference Laboratory was established at Princess Margaret Hospital under the leadership of Drs Albert Chan and Tony Mak, to explore potential herbal toxicity. The HA Chief Pharmacist's Office was responsible for vetting procurement and testing of herbal products. A Drug-Herb Interaction Database was created and made available to all HA staff as well as those on Private Public Partnership (PPP)[4]. Dr ML Tse has been updating and enhancing its functions[5]. A special website 中醫動 was launched for public education, professional training and research sharing[6].

The Government initially funded 18 district-based CM clinics which were upgraded to the present CM Clinics cum Teaching & Research Centres (CMCTR). The CMCTRs next to the major HA Cancer Centres were staffed by CM oncologists who were given access to the HA Clinical Management System (CMS) via the PPP Programme. Dr Tung Yuk chaired the Committee. A pilot IM primary healthcare (PHC) clinic was started at Queen Elizabeth Hospital with the co-operation of Kowloon Central Cluster Family Medicine consultant Dr David Chao and the School of Chinese Medicine (SCM) of HKBU.

Courses in CM have been run annually for doctors, nurses and allied health colleagues to facilitate better dialogue in the clinical setting. CM graduates from our 3 Universities were recruited to a 3-year CM training programme based in the CMCTRs, with structured preservice & in-service courses in WM clinical practice and continued CM clinical training during the three years. Those with high potential were given scholarships for training at the best centres in China where IM is practised. The plan was to develop CM specialist-training through the acquisition of advanced WM and CM knowledge in parallel. In the field of Psychiatry for Family Medicine, Prof Lam Tai-pong of HKU organised courses for CM trainees in collaboration with Dr Yip Ka-chee of Kowloon Hospital.

In Tung Wah Hospital, Dr Yuen Wai-ki ran a liver cancer ward with the CM team, holding regular grand rounds for students and trainees. Drs Lo Wai-kei and Lui Sing-leung ran IM renal clinics. Dr Leonard Lee worked on stroke rehabilitation with the CM experts. Ms Kathy Lee, the General Manager (Nursing), was a qualified CMP. She designed IM nursing charts that were approved by the HA Central Nursing Committee for use in all hospitals. The "protocol driven" IM practice was well established in Kwong Wah Hospital where Drs Andrew Yip & MH Chan facilitated such in Departments of Medicine, Surgery, O & T and O & G. Dr Hung Kwan-ngai, the neurosurgeon in Queen Mary Hospital, sent post-operative patients to the MacLehose Medical Rehabilitation Centre for IM rehabilitation, which included acupuncture treatment by HKU professors.

EVIDENCE-BASED INTEGRATIVE MEDICINE (EBIM) DRIVEN BY CLINICIANS

The CMCTRs, collaborating with the SCM from HKU, CUHK & HKBU, were used as hubs for development of EBIM. Based on systematic review of publications and/or expert opinion, more than 20 integrative medicine protocols were developed and piloted in different clusters under HA. The Chinese Medicine Department of HA funded the reviews resulting in 23 publications in peer review journals[7-29]. Through the HA Central Co-ordination Committees, the cross-referral mechanism and the clinical documentation within hospitals were endorsed.

Research studies were prioritised for the major disease burdens in which existing regimens do not produce satisfactory results, but CM has some scientific evidence of possible advantage. HA funded projects such as pharmacology of herbal medicine to treat influenza viral infection by CUHK[30-33], use of computer imaging for tongue diagnosis by Poly U, and management of obesity by HKBU[34]. Dr Roger Ng of Kowloon Hospital steered the study on post-stroke depression[35,36], and Prof KF Chung of HKU lead the post-partum depression study. The latter was greatly supported by Dr KY Leung of Queen Elizabeth Hospital[37].

At CUHK, Prof PC Leung pioneered studies on the diabetic foot[38] , Prof Thomas Chan on herbal pharmacology and Prof Julian Chan on obesity[7]. Prof Joseph Sung & Prof Justin Wu initiated work on Irritable Bowel Syndrome, expanding to Crohn's Disease and Ulcerative Colitis, receiving recurrent grants from NIH, USA. CM diagnostics in 望聞問切 were also explored. The HK Institute of Integrative Medicine and the Institute of CM, CUHK, were both started by these western medicine (WM) clinicians. The Li Dak Sum Yip Yio Chin R & D Centre for Chinese Medicine, and the State Key Laboratory for Research on Bioactivities and Clinical Applcations of Medicineal Plants under Prof PC Shaw, Prof PC Leung & Prof Clara Lau are steered by western bio-pharmacological theory and practice.

At HKU, a Molecular Chinese Medicine Laboratory was run by the paediatricians, the late Prof Alan Lau, Prof YL Lau and Prof Godfrey Chan, in turn. Prof Cindy Lam of Family Medicine did collaborative work with Guangdong and Taiwan on the Body Constitutions (體質)[39-40]. Prof Virginia Wong researched acupuncture for cerebral palsy at the Duchess of Kent Children's Hospital. Prof Raymond Cheung used CT scan of the brain to document acupuncture stimulation effects in post stroke patients. Prof KF Chung conducted a number of projects in depression and insomnia[16-18,29,36,37]. Prof PC Ho studied the use of acupuncture for In Vitro Fertilisation. The Vivian Taam Wong Endowed Professorship in Integrative Medicine was established. Prof MF Yuen is now engaged in a multi-centre trial of herbal formula YIV-906, approved by US FDA for phase 3 trial, used in conjunction with chemotherapy for late stage liver cancer.

RESEARCH & EDUCATION IN IM PIONEERED BY HKAIM

In 2013-15, HKAIM was funded by the Professional Services Development Assistance Scheme (PSDAS), to organise Primary Healthcare Courses in WM for CM practitioners (CMP) in private practice. It covered common conditions in the community, prevention, rehabilitation, diagnostics, geriatrics, paediatrics, gynaecology and psychiatry. When the funding ended, we were in the position to organise more in-depth training, with broader perspectives, enabling the interaction of WM and CMPs.

Diabetes affects 9% of the population, with limited therapeutic options from WM for prevention and treatment of the associated kidney disease. HKAIM obtained funding from Fu Tak Iam (FTI) Foundation in 2014-16 to start a service-research programme with the 3 SCMs, on chronic kidney disease with diabetes[41]. Our programme demonstrated the potential in using individualised therapy offered by CMPs. This laid the foundation for a subsequent randomised controlled trial funded by the HMRF and coordinated by Prof Sydney Tang of the Department of Medicine, HKU[42].

In public health education, we have used different media to deliver IM healthcare messages. Since 2013, Dr Vivian Wong, as Hon President of HKAIM, has co-hosted the weekly RTHK radio programme 精靈一点 (on RTHK 31 TV since 2018), with the invitation of CMPs to share different perspectives on common healthcare practices. During the COVID-19 pandemic, a total of 22 newspaper articles have been published. Those on the use of CM are important introductions for the practice of IM in the eyes of the community.

EPILOGUE - FROM SARS TO COVID-19

Integrative Medicine started in China because Chairman Mao invited the best WM doctors to learn CM, more than 60 years ago. Twenty years ago, HK introduced CM to our WM doctors via education, research and clinical practice of EBIM. Communication and collaboration are the keys to success. I have listed 39 outstanding clinicians and researchers as pioneers in this endeavour, but I wish to apologise to those who have escaped my failing memory. Equally remarkable are the CM professors, post-graduate students, researchers who are named in the 44 references.

The challenges of SARS are different from COVID-19. Given the large amount of research output on the effectiveness of IM in the management of COVID-19, we are happy that HA has started a pilot to use IM for the early and mild cases in the Asia Expo Community Treatment Facility. As shown in the article in this edition of the Hong Kong Medical Diary on "The Use of Integrative Medicine for treatment of Covid-19", there is substantial evidence from pharmacological, in vivo, in vitro and clinical studies that CM formulae, alone or in combination with standard WM treatment, provide a better outcome in terms of admissions, use of ICU and death rates.

The IM teams from HKU and HKBU were quick off the mark in such scientific exploration with publications in March and July 2020[43,44]. Is it time that we allow CMPs to work with our expert physicians and intensivists in an effort to improve the outcome of our patients in HK, as we did in 2003 during the SARS crisis? For "long Covid-19", should we organise a proper IM study better than our small scale study in 2003?

The historical account in the article remains a personal description by the author.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		* Live Lecture HKMA - HKS&H CME Programme 2021 Topic: Common Upper Limb Fractures and Options of Treatment **1**	* Live Lecture COVID Vaccine & Patients with Chronic Diseases: Evidences from Clinical Trials & Real-world Data * Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures) **2**	* Live Lecture Herpes Zoster in Adults and New Vaccine Development **3**	* Live Lecture Updates On Vaccine Technologies And Corresponding Data - Online * Certificate Course on Mental Health 2021 (Video Lectures) **4**	**5**
6	**7**	* Live Lecture Right Choice at the Right Time for BPH LUTs Management **8**	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed * Live Lecture Management of Migraine * Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures) **9**	* Live Lecture Importance of Glycemic Control on T2DM in Changing Environment **10**	* Live Lecture Structural Heart Intervention for Stroke Prevention: Role of Left Atrial Appendage Occlusion (LAAO) Patent Foramen Ovale (PFO) Closure * Certificate Course on Mental Health 2021 (Video Lectures) **11**	**12**
13	**14**	* Live Lecture Reproductive Genetics **15**	* Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures) **16**	**17**	* Certificate Course on Mental Health 2021 (Video Lectures) **18**	**19**
20	**21**	* Live Lecture HKMA-GHK CME Programme 2020 Topic: Management on Musculoskeletal Tumor **22**	* Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures) **23**	* Live Lecture New Strategy to Protect Infants' Pertussis from Caregivers **24**	* Certificate Course on Mental Health 2021 (Video Lectures) **25**	**26**
27	**28**	**29**	* Live Lecture Sympathetic Overdrive and the Role of Beta Blockers * Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures) **30**			

Date / Time	Function	Enquiry / Remarks
1 TUE 2:00 PM	**Live Lecture** **HKMA - HKS&H CME Programme 2021** **Topic: Common Upper Limb Fractures and Options of Treatment** Organiser: Hong Kong Medical Association; Hong Kong Sanatorium & Hospital; Speaker: Dr KOU Sio-kei	HKMA CME Dept. Tel: 3108 2507 1 CME Point
2 WED 2:00 PM	**Live Lecture** **COVID Vaccine & Patients with Chronic Diseases: Evidences from Clinical Trials & Real-world Data** Organiser: Hong Kong Medical Association; Speaker: Dr Lars POHLMEIER	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Charleen Sze-yan CHEUNG	Ms Vienna LAM Tel: 2527 8898
3 THU 2:00 PM	**Live Lecture** **Herpes Zoster in Adults and New Vaccine Development** Organiser: HKMA-KLN East Community Network; Speaker: Dr WONG Chun-por	Ms. Antonia Lee Tel: 3108 2514 1 CME Point
4 FRI 2:00 PM	**Live Lecture** **Updates On Vaccine Technologies And Corresponding Data - Online** Organiser: Hong Kong Medical Association; Speaker: Dr Wilson LAM	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Mental Health 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Yee-him WONG	Ms Vienna LAM Tel: 2527 8898
8 TUE 2:00 PM	**Live Lecture** **Right Choice at the Right Time for BPH LUTs Management** Organiser: HKMA-KLN West Community Network; Speaker: Dr HO Lap-yin	Ms. Antonia Lee Tel: 3108 2514 1 CME Point
9 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society; Speaker(s): Dr Jennie Shu-yan YEUNG; Chairman: Dr YAM Kwong-yui; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	1.5 points College of Surgeons of Hong Kong Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
2:00 PM	**Live Lecture** **Management of Migraine** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr TSANG Kin-lun	Ms. Antonia Lee Tel: 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr FUNG Tak-yuen	Ms Vienna LAM Tel: 2527 8898
10 THU 2:00 PM	**Live Lecture** **Importance of Glycemic Control on T2DM in Changing Environment** Organiser: HKMA-Hong Kong East Community Network; Speaker: Dr CHAN Chi-pun	Ms. Candice Tong Tel: 3108 2513 1 CME Point
11 FRI 2:00 PM	**Live Lecture** **Structural Heart Intervention for Stroke Prevention: Role of Left Atrial Appendage Occlusion (LAAO) Patent Foramen Ovale (PFO) Closure** Organiser: HKMA-KLN City Community Network; Speaker: Dr Gary Shing-him CHEUNG	Ms. Candice Tong Tel: 3108 2513 1 CME Point
7:00 PM	**Certificate Course on Mental Health 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Queenie CHIN	Ms Vienna LAM Tel: 2527 8898
15 TUE 2:00 PM	**Live Lecture** **Reproductive Genetics** Organiser: HKMA-YTM Community Network; Speaker: Dr Vivian Chi-yan LEE	Ms. Candice Tong Tel: 3108 2513 1 CME Point
16 WED 7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Kwok-yin LEUNG	Ms Vienna LAM Tel: 2527 8898
18 FRI 7:00 PM	**Certificate Course on Mental Health 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Lai-wah CHAN	Ms Vienna LAM Tel: 2527 8898
22 TUE 2:00 PM	**Live Lecture** **HKMA-GHK CME Programme 2020** **Topic: Management on Musculoskeletal Tumor** Organiser: Hong Kong Medical Association; Gleneagles Hong Kong Hospital; Speaker: Dr Timothy Yat-cheong SO	HKMA CME Dept. Tel: 2527 8452 1 CME Point
23 WED 7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Ben Chong-pun CHAN	Ms Vienna LAM Tel: 2527 8898
24 THU 2:00 PM	**Live Lecture** **New Strategy to Protect Infants' Pertussis from Caregivers** Organiser: HKMA-New Territories West Community Network; Speaker: Dr Helene WAN	Ms. Antonia Lee Tel: 3108 2514 1 CME Point
25 FRI 7:00 PM	**Certificate Course on Mental Health 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Dicky CHUNG	Ms Vienna LAM Tel: 2527 8898
30 WED 2:00 PM	**Live Lecture** **Sympathetic Overdrive and the Role of Beta Blockers** Organiser: Hong Kong Medical Association; Speaker: Dr CHEONG Yan-yue, Adrian Piers	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Amelia Pui-wah HUI	Ms Vienna LAM Tel: 2527 8898

Answers to Radiology Quiz

Answers:

1. There is abnormal bony alignment at C4/5 level, with incongruent facet joints articulations at C4/5 level. Underlying bilateral C4/5 facet joints subluxation is suggested. The abnormal bony alignment with angulation at the C4/5 level is likely to be due to underlying ligamentous injury and disruption. The overall picture suggests significant cervical spine injury.

2. Urgent referral to CT cervical spine to look for any unstable fractures should be done. If the patient has neurological symptoms, the MRI cervical spine should also be performed to look for epidural hematoma and cord compression.

Dr Hoi-to LAU
MBBS, FRCR

以岭

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Approved for children ≥ 2 years

References :
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http://www.espen.org/espenguidelines.html

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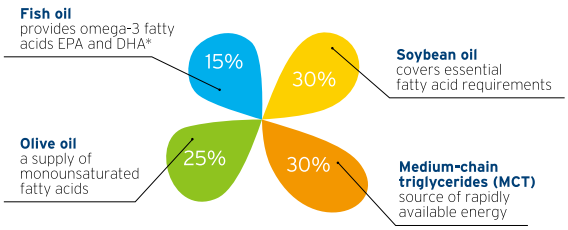

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