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VIATRIS

Somewhere Over the Rainbow!

On 1 July 2022, we have change in Government Office with the Chief Executive of Hong Kong changed from Ms. Carrie Lam to Mr. John Lee. The Policy Bureau of the Government Secretariat were re-organized on 1 July 2022. The policy portfolios such as environmental hygiene, food safety, public health on agriculture and fisheries previously belonged to Food and Health Bureau are assigned to the Environment and Ecology Bureau, leaving Health Bureau remaining the health portfolio to be in-charge. On 19 June 2022, the Central People's Government announced the appointment of Professor Lo Chung-mau, previously the Head of University of Hong Kong-Shenzhen Hospital, as the first Secretary for Health. As stated in the home page of the Health Bureau, Prof. Lo Chung-mau points out that in face of the challenges posed by ageing population, shortage of healthcare manpower and emerging diseases, our healthcare system must keep abreast of the times, make good use of technology and press ahead with reform and innovation to cope with the growing service demand of the community. We hope that the Health Bureau will be able to focus more on the matters pertaining to the health of the citizens of Hong Kong.

In order to avoid overburdening of the public hospitals, there is the urgent need to launch and promote primary healthcare services. A District Health Centre has already been set up in Kwai Tsing, and will be soon launched in Sham Shui Po, Wong Tai Sin, Tuen Mun, Southern District, Yuen Long and Tsuen Wan. District Health Centre Expresses have also been set up in another 11 districts. In these DHCs and DHC Expresses, the scope of work include health promotion and education, health risk factors assessment and chronic disease management. These "DHC Express" services will migrate as appropriate to the local DHC at a later stage. In time, we hope more pharmacists can take part in these District Health Centres and refer patients to the community pharmacists. Pharmacist can of course offer information and health advice on drugs. Other than health promotion and education, pharmacists can offer Medication Therapy Management and Medication Reconciliation Services.

In the Hospital setting, to relieve the manpower shortage of doctors and nurses, pharmacists has proceeded to specialization. Currently in the HA, there are pharmacists specializing in Oncology, Pediatrics, Internal Medicine and Infectious Diseases. I am delighted to include the article on page 41: "Management of Hospital-acquired Pneumonia and Ventilator-associated Pneumonia: The Conventional and Novel Antimicrobials" written by 2 Infectious Diseases Pharmacists: Chung, Ho-man Melissa and Ng Tsz-ming. It described that both Hospital-acquired Pneumonia (HAP) and Ventilator-associated Pneumonia (VAP) is a serious threat to patients, especially those that is caused by Multidrug-resistant organisms (MDROs). Physicians must be knowledgeable about local antibiogram and assessment on patient's risk factors for MDROs should be performed. Infectious diseases pharmacists have an important role in providing suggestions on the choice of antimicrobials, the monitoring required as well as measures to optimize the PK/PD property of the selected agent.

In the article on page 50, "Pharmacists' perspectives on the under-prescribing of oral anticoagulants among long-term aspirin users with atrial fibrillation: a preliminary report" written by NG, Vanessa W.S.; Wong, Ian C.K. and Lam, May P.S., it revealed some of the potential barriers of using OACs amongst the long-term aspirin users, which can be alleviated with the help from pharmacists in the community and highlighted the need of clinical service and education interventions.

In Hong Kong, there are many patients taking both Chinese medicine and western medicine, and there are possible Chinese herb-drug interactions which can lead to negative health impact for the patients. The article on page 35, "Review of Chinese Herb-Drug Interaction (CHDI) Databases" written by Chan, Philip Pan; Lam, Jason Chun-Sing; Li, Johnny Chun-Wing; Chow Tiffany Hoi-Yee and Chong, Donald Wing-kit provides an overview of 8 common databases that contain information on CHDI and compares their advantages and disadvantages. Pharmacists can consult multiple databases before making recommendations to patients or other healthcare professionals.

In recent years, we have heard that in healthy individuals, microbiome aids food digestion, regulates immunity, protects against pathogenic infection, and participates in the synthesis of vitamins and other nutrients. In diseased individuals, evidence shows an imbalance of beneficial and pathogenic microbes in the human microbiome, a phenomenon known as dysbiosis. In the article on page 54: "A Review on the role of Probiotics in the Management of Type II Diabetes Mellitus" written by KEI, Nelson; Chan Vegas; Ho Hoi Ying; IU, Pui Ching; Kwok, Yin Tai; YIN, Yingyi and SUN, Wai Yan Kiwi, it included 10 randomized clinical trials that evaluate the efficacy of probiotics. HbA1c was commonly used as the end-point parameter for evaluation, of which 4 showed a significant decrease. A definition conclusion could not be drawn due to the lack of standardization and specificity in these clinical trials and further investigation should be done before probiotics are used in the clinical setting.

I know many of you are engaged in the combat against the Covid-19 Pandemic, let's hope with the great majority of people being vaccinated, fewer people get infected, better vaccines and drugs being developed, we will be out of the pandemic by next year.

Hope you enjoy reading the articles. We welcome you to submit your research or review articles to enrich the HKPJ.

Mary Catherine Cheng
Managing Editor
5 September 2022

Prepared by Branson Fok and Chloe Ip

Tirzepatide Showed Substantial and Sustained Reductions in Body Weight for the Treatment of Obesity

Date: Jul 21, 2022

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist recently approved in the United States to treat type 2 diabetes mellitus. Phase 2 studies of tirzepatide have reported clinically relevant weight reduction in participants with diabetes, but its efficacy for weight reduction in those without diabetes has yet to be known.

This international, phase 3, double-blind, randomized, placebo-controlled trial investigated the efficacy and safety of tirzepatide in adults with obesity or overweight but without diabetes. A total of 2539 adults with a BMI of 30 or higher, or 27 or higher with at least one weight-related complication, were assigned in a 1:1:1:1 ratio to receive once-weekly subcutaneous tirzepatide at either one of three doses (5 mg, 10 mg, or 15 mg) or placebo, in addition to lifestyle interventions. Treatment lasted for 72 weeks including a 20-week dose-escalation period. The primary endpoints were the percentage change in weight from baseline to week 72 and a weight reduction of at least 5% by week 72.

Results for primary endpoints were in favour of all three doses of tirzepatide than with placebo. The mean percentage change in weight at week 72 was –15.0% (95% confidence interval [CI], −15.9 to −14.2) with 5-mg weekly doses of tirzepatide, −19.5% (95% CI, −20.4 to −18.5) with 10-mg doses, −20.9% (95% CI, −21.8 to −19.9) with 15-mg doses and −3.1% (95% CI, −4.3 to −1.9) with placebo (P<0.001 for all comparisons with placebo). The percentage of participants who had a weight reduction of at least 5% was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% (95% CI, 30 to 39) with placebo (P<0.001 for all comparisons with placebo). The most common adverse events seen with tirzepatide were transient gastrointestinal effects, which were mild to moderate in severity that mainly occurred during dose escalation.

In this 72-week trial in non-diabetic participants with obesity, tirzepatide (5 mg, 10 mg, or 15 mg) once weekly showed substantial and sustained reductions in body weight compared to placebo.

Source: www.nejm.org

Pembrolizumab plus Chemotherapy Resulted in Longer Overall Survival Among Patients with Advanced Triple-Negative Breast Cancer

Date: Jul 21, 2022

The interim analysis of the KEYNOTE-355 trial demonstrated that pembrolizumab plus chemotherapy resulted in longer progression-free survival than chemotherapy alone for patients with advanced triple-negative breast cancer whose tumors expressed a programmed death ligand 1 (PD-L1) combined positive score (CPS) of 10 or more. The results for overall survival whereas would be shown in the final analysis.

KEYNOTE-355 is an international phase 3, double-blind, randomized, placebo-controlled trial that examined the efficacy and safety of pembrolizumab plus chemotherapy among patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer. A total of 847 patients were assigned in a 2:1 ratio to receive chemotherapy in combination with either pembrolizumab 200 mg every 3 weeks for up to 35 infusions (n=566) or placebo (n=281). Primary endpoints included overall survival among patients whose tumors expressed PD-L1 with a CPS of 10 or more (CPS-10 subgroup), patients whose tumors expressed PD-L1 with a CPS of 1 or more (CPS-1 subgroup), and in the intention-to-treat population. The median follow-up was 44.1 months.

In the CPS-10 subgroup, overall survival was significantly longer with pembrolizumab-chemotherapy than with chemotherapy alone. The median overall survival was 23.0 and 16.1 months in the pembrolizumab and placebo groups respectively (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.55 to 0.95; two-sided P=0.0185). In the CPS-1 subgroup, the median overall survival was 17.6 and 16.0 months, respectively (hazard ratio, 0.86; 95% CI, 0.72 to 1.04; two-sided P=0.1125 [not significant]). In the intention-to-treat population, the median overall survival was 17.2 and 15.5 months, respectively (hazard ratio, 0.89; 95% CI, 0.76 to 1.05 [significance not tested]). The incidence of any adverse events was similar in the two groups. Adverse events of grade 3 or higher occurred in 68.1% and 66.9% in the two groups, respectively. The most common adverse events were anaemia, neutropenia, and nausea.

In conclusion, pembrolizumab plus chemotherapy achieved significantly longer overall survival than chemotherapy alone among patients with previously untreated advanced triple-negative breast cancer and PD-L1 expression scores of 10 or more.

Source: www.nejm.org

Review of Chinese Herb-Drug Interaction (CHDI) Databases

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ABSTRACT

Concurrent use of Chinese medicine and western medicine among patients is common in Hong Kong; however, Chinese herb-drug interactions (CHDI) are possible and can lead to negative impact on patients' health. Pharmacists have an important role in counselling patients regarding CHDI. Databases are needed for pharmacists to obtain such information and provide evidence-based advice to patients. This article provides an overview of 8 common databases that contain information on CHDI and compares their advantages and disadvantages. Pharmacists should consider the features of these databases and acknowledge their limitations when using them to assess CHDI. Consulting multiple databases is also suggested before making informed decisions and formulating recommendations to patients or other healthcare professionals. Future efforts including database development and research on CHDI are needed and pharmacists can play an important role to contribute.

Keywords: *Chinese Medicine, Herb-Drug Interaction, Databases, Chinese Herb-Drug Interaction Database*

INTRODUCTION

Concurrent use of Chinese and western medicine is common in Hong Kong. The Hong Kong Thematic Household Survey Report on Doctor Consultation in 2019 revealed that among the 1.5 million people who had consulted a doctor, 7.3% of them consulted both Chinese and western medicine doctors.[1] Also, Hong Kong Baptist University (HKBU) surveyed cancer patients in 2009, finding that more than 50% of cancer patients took Chinese herbs before, during, and after cancer treatment, and the majority did not tell their western doctors about the use of Chinese medicine.[2] In addition, with the government's continuous support, the role of Chinese medicine has been growing rapidly as well as the development of the Integrated Chinese-Western medicine program.[3,4] It is foreseeable that concurrent use of Chinese and western medicine will become more prevalent in Hong Kong.

However, co-administration of Chinese and Western Medicine may lead to **Chinese herb-drug interactions** (CHDI) and thus impose health threats to patients. The China Food and Drug Administration (renamed as National Medical Products Administration of China (NMPA) in 2018) received more than 13,000 reports of adverse events in 2016 solely regarding fixed-dose combinations of Chinese and western therapeutic ingredients, of which 34.2% of cases are suspected serious adverse reactions. In addition, it also revealed that the frequency of gastrointestinal adverse events is higher with the use of combination products than that of single agents.[5]

Chinese herb-drug interaction (CHDI) refers to an interaction between a Chinese herb and a drug that may increase or decrease the pharmacological or toxicological effects of either component.[6] The interaction can be pharmacokinetic or pharmacodynamic. For instance, Imai et al. suggested that glycyrrhizin, which is present in one commonly prescribed Chinese herb Gancao (甘草), may enhance drug absorption by increasing the permeability of intestinal epithelium and through inhibition of efflux transporter P-glycoprotein (P-gp) present in the intestine.[7]

Studies on the efficacy, safety, and interactions of Chinese medicine are often complicated by the complexity of formulation. Under the theory of traditional

Chinese medicine (TCM), herbs are seldom individually utilised as a significant medicinal effect from a single herb of high dose usually comes with high toxicity.[8] Instead, multiple herbs are used together in a formula for exerting additive or synergistic effects, reducing toxicities, or harmonizing their actions.[9] Decoction is the most common form of TCM that involves boiling the herbal formulae in water to facilitate absorption as most herbs cannot be directly swallowed. With the advancement of technology, Chinese herbs can now be formulated in a finished dose form as proprietary Chinese medicine (pCm) for direct consumption, available in mostly oral but also other routes of administration.[10]

Since patients often take Chinese and Western drugs together, there is an unmet need for evidence-based recommendations on handling interactions. As drug experts, pharmacists are ideally in the best position to reconcile patients' medications which include both Chinese and western medicines, and to give reliable advice. Nevertheless, as shown in a 2019 study, pharmacists still feel unconfident in effectively counselling patients on herbal medicines and rarely discuss the potential adverse effects or interactions with patients. Only 19% reported that they always discuss herb-drug interactions (HDIs) when patients used herbal medicines.[11] Generally, studies have shown that pharmacists have inadequate knowledge about HDI or adverse reactions of herbal medicines, and such knowledge gap may be due to inadequate education.[12-16] This may also be the case in Hong Kong where pharmacy graduates are not expected to be proficient in Chinese medicines such as knowing the indications, adverse effects, and potential interactions of Chinese herbs.

Reliable databases for checking CHDIs are thus important for pharmacists with the increasing popularity of integrative medicine. They allow pharmacists to scientifically assess potential interactions among the vast number of herb-drug combinations, handle related enquiries and make evidence-based decisions to ensure patient safety. This article serves to introduce currently available databases for checking CHDI and compare their features in order to discuss how pharmacists can utilise these databases in their clinical practice.

OVERVIEW OF CHDI DATABASES

This review discusses the features of 8 commonly used databases, but it is by no means exhaustive. Database features such as coverage, search languages, frequency of updates, the interaction assessments and whether they provided advice on the management of interactions are summarised in **Table 1**. The advantages and disadvantages of each database are explored in **Table 2**.

Some databases are freely accessible while others require subscription. In addition, with the advancement of technology, some new CHDI databases have even

Table 1. Comparison of CHDI Database Features

Database	Country of Origin	Focus on CHDI	Quantity of Individual Herbs Covered	Database Search Language	Search Language of Herbal Formula	Assessment of Interaction	Recommended Management for Interaction	Update Frequency
Freely Accessible Database								
CWMIIN	Taiwan	Yes	Fewer	Chinese	Chinese	Yes, by severity & evidence level	Yes	Unknown (Last in 2011)
CMSS	Taiwan	Yes	More	Chinese	Chinese	No	Yes	Unknown
SUPP.AI	US	No	More	English Latin	N/A	No	No	Unknown (Last in 2021/11)
Probot	Hong Kong	Yes	Still Under Development	Chinese English Latin	Chinese English	No	No	Unknown
CHDID	Hong Kong	Yes	Still Under Development	Chinese Latin	Chinese	Yes, by severity & evidence level	No	Quarterly
Commercially Accessible Database								
Natural Medicines	US	No	More	English Latin	English	Yes, by evidence level, severity level & likelihood of occurrence	Yes	Daily
Micromedex	US	No	Unknown	English	N/A	Yes, by severity level & degree of documentation	Yes	Daily
Stockley	UK	No	More	English Latin	N/A	Yes, by severity & evidence level	Yes	Quarterly

Table 2. Advantages and Disadvantages of CHDI Databases		
Database	**Advantages**	**Disadvantages**
CWMIIN	▪ Free ▪ Allows multiple search (including formulae)	▪ References are not critically appraised ▪ No management plan provided ▪ Outdated and narrow database
CMSS	▪ Free ▪ Allows search by different names (e.g., generic and brand names) ▪ Quick reference for management plan	▪ Do not support multiple search ▪ Unknown sources and unknown review process
SUPP.AI	▪ Free ▪ User-friendly search interface ▪ Vast database including supplements, food, medicines and herbs ▪ Allow search by multiple names of drugs	▪ Only as a secondary database without literature review ▪ May not include common Chinese herbs ▪ Not established by professional medical bodies ▪ Untraceable update ▪ Some automatically extracted results may not be accurate ▪ No management plan provided
Probot	▪ Source from Chinese literature databases, which include far more studies on Chinese medicines ▪ Allow search by herbal formulae as a whole ▪ Summary provided for each article included ▪ Allow automatic updates	▪ Subscription required for non-academics ▪ Most search results are interventional studies for adjuvant therapies ▪ No management plan provided
CHDID	▪ Wide coverage ▪ Seasonal update ▪ Free ▪ Allow search by formula ▪ Allow projection of unknown interactions from in-vitro CYP results	▪ Only in-vitro CYP interactions are documented so far. Do not support other PK/PD interactions yet ▪ The interactions are only screened by machine learning models from sources. The actual clinical significance is not known. ▪ No management plan provided
Natural Medicines	▪ Vast database ▪ Wide variety of interactions, can check for drug-herb-food-supplement interactions ▪ High information quality with authority ▪ Detailed information which facilitates management of HDI ▪ Have other built-in tools such as effectiveness ranking and pregnancy & lactation checker ▪ Supports multiple search	▪ Not cost-effective to most pharmacists by personal subscription ▪ Not focused on Chinese Medicines
Micromedex	▪ Wide variety of interactions, can check for drug-herb-food-supplement interactions ▪ Also checks for suitability in allergy, pregnancy, lactation, smoking and alcohol ▪ Instructions concise to follow ▪ Support multiple search	▪ Narrower sources (but articles are peer reviewed) compared to Natural Medicines Comprehensive Database ▪ Not focused on Chinese medicines
Stockley	▪ Vast database ▪ Check for drug-herb-food-supplement interactions ▪ Instructions concise to follow ▪ Support multiple search	▪ Not focusing on Chinese medicines ▪ Tied sale with other databases from Medicines Complete, which are usually basic but not mandatory for pharmacies.

utilised artificial intelligence (AI) technology to extract information from literature automatically and predict CHDI for database development and maintenance to save time and labour.

1. Freely accessible databases

The Chinese-Western Medicine Integrative Information Network (CWMIIN) (台灣中西藥交互作用資訊網) is a free database in TCM that retrieves CHDI-related literature from PubMed. It allows searching within a predefined list of TCM formulae, herbs and drugs. However, only either commercial or chemical name for western drugs is shown. While it only has a small coverage of herbs and drugs, it provides a brief summary on each interaction including the evidence supporting the interaction, evidence rating as well as some recommended actions.[17]

Taiwan Chi Mei Search System (CMSS) (台灣奇美醫學中心藥劑部中西藥交互作用查詢系統) is another CHDI database in Taiwan. It covers a total of 139 herbs and 52 TCM formulae, which results in 6,173 interaction pairs with western drugs. Although it provides the possible mechanisms of and some simple recommendations for each interaction, it does not list the sources of information or discuss the significance of each interaction.[18]

SUPP.AI is an AI supplement-drug interactions database. It automatically extracts supplement-drug interactions information from scientific literature and allows clinical professionals to access relevant studies easily. Based on the latest update in October 2021, it already covers 2,044 supplements, 2,866 drugs, and 59,096 interactions. Nevertheless, it does not assess the level of evidence or provide recommendations regarding the interaction.[19]

Probot Chinese Medicine–Drug Interaction Database (Probot) utilises an in-house programme to automatically retrieve and filter out CHDI-related abstracts from databases including "PubMed", "Wanfang", and "CNKI". Relevant interaction information is then extracted manually by pharmacists. It targets Chinese herbs and covers 6,292 interactions between 193 herbs/formulae and 726 western drugs as of July 2021. However, the database currently summarises relevant studies individually without stating the level of evidence or giving any recommended action. Also, most of the studies retrieved only focus on co-administration under specific indications, and hence the safety profile may not be generalised to all patients.[20]

Hong Kong Chinese Herb-Drug Interaction Database (CHDID) collects information from PubMed manually and predicts if a Chinese herb will inhibit/induce a cytochrome P450 (CYP) isoform by a machine learning model. It aims to cover 534 CM herbs stated in the Chapter 549 Chinese Medicine Ordinance of Hong Kong and 961 drugs approved for use in Hospital Authority (HA). Although it provides evidence rating, no corresponding recommendation is suggested.[21]

2. Commercially available databases (Subscription Required)

Commercially available databases are usually renowned for their vast sizes, high quality of evidence with editorial review and clear instructions for management on interactions.

Natural Medicines Comprehensive Database (Natural Medicines) provides a concise literature summary, scientifically-sound rating and recommended action for each CHDI. It is also updated regularly and is more useful when the patient is taking not only Chinese and western drugs but also other herbs and supplements such as bee venom and arginine.[22]

Micromedex is a comprehensive database commonly used in Hong Kong. It provides evidence-based and high-quality information, such as severity, mechanism and clinical management of interactions on a wide range of products not limited to Chinese drugs.[23]

Last but not least, **Stockley's Herbal Medicines Interactions (Stockley)** is published by Pharmaceutical Press, the publishing arm of the Royal Pharmaceutical Society. This database is not exclusive for Chinese medicines but mainly herbs and other supplements such as omega-3 and coenzyme Q10. Similar to Natural Medicines Comprehensive Database and Micromedex, it also provides evidence rating and recommended action for each CHDI. As of April 2022, there were 213 monographs on interactions involving herbal medicines.[24]

IMPLICATION FOR PHARMACISTS IN CHDI SEARCH

Pharmacists should consider the following points while assessing the potential for CHDI.

1. The interaction data in the existing databases often come from in vitro and in vivo studies, as well as case studies rather than clinical trials or cohorts. These databases only serve as a source of information to facilitate pharmacists' risk-and-benefit analysis instead of guidelines that provide direct recommendations. While pharmacists look at the conclusions/ratings in the databases, they still need to be aware of the level of evidence leading to such conclusions before making recommendations based on them. Critical appraisal is still required even with the assistance of databases.

2. Most drug interaction tools used in clinical practice focus largely on Western herbs, dietary supplements, and nutraceuticals with often only very limited coverage of Chinese medicines.

   For example, Danshen (*Salvia miltiorrhiza*) is a common "blood-activating and stasis-removing medicine" which is used for cardiovascular diseases in Chinese medicine. It is well-known for enhancing the anti-thrombotic effect of warfarin and avoidance of their combined use has been stressed in some literature.[25] Nevertheless, this interaction is not recorded in some of the well-known databases that are traditionally used for conventional drug interaction checking such as Lexi-comp (Natural Products Database). Therefore, it is helpful to be aware of the CHDI databases reviewed in this article.

3. One important characteristic of TCM is the use of "multi-herb formulae". Herbs are rarely used individually but rather in combination for their synergistic or complementary effects. Take "Siwutang" (四物湯) which is commonly used for "nourishing blood" and "regulating menstruation" as an example. It consists of four herbs, Shudihuang *(Rehmanniae Radix Praeparata)* (熟地黃), Baishao *(Paeoniae Radix Alba)* (白芍), Danggui *(Angelicae Sinensis Radix)* (當歸) and Chuanxiong *(Chuanxiong Rhizoma)* (川芎).

   Some databases, such as Micromedex and Stockley's Herbal Interactions, do not support keyword search of "multi-herb formulae name" due to multiple reasons such as inconsistency in the formulation of herbal

formulae and proprietary Chinese Medicines and the lack of corresponding studies on multi-herb formulae. Even when some databases contain information on herbal formulae, their coverage is often limited.

4. Most free databases are still growing or under development, so their credibility and coverage may not be sufficient for daily use. Pharmacist should take note of the recency of updates and included literature in the databases. If the latest update or available literature has been conducted some time ago from the time of search, it is prudent for pharmacist to perform a separate literature search.

5. These CHDI databases evaluate interactions based on different studies or assessment criteria. Where possible, pharmacists should consult two or more databases instead of just one interaction summary provided by a single database. In general, paid databases usually have more comprehensive descriptions on relatively well-studied interactions whereas the above-included free databases have wider coverage in terms of Chinese medicines.

6. For some herbs, processing (such as frying and decocting of *Aconitum carmichaelii Debx* (附子)) or different parts (such as bark and twigs of Cinnamomum cassia (肉桂)) of a plant may lead to differences in pharmacological actions toxicities, which may result in different interaction outcomes.

   Look-alike-sound-alike (LASA) errors can also occur in Chinese Medicine, especially if healthcare professionals (HCPs) are not familiar with botanical nomenclature. Whenever there are uncertainties, pharmacists should ask patients for more details about the herbs they are using before assessing potential interactions. A Chinese medicine prescription will be the best information source if available, or pharmacists can liaise with TCM practitioner to obtain more information. Identifying the differences arising from processing methods, plant parts, origin and species may help to choose the right searching terms.

7. Similar to western drugs, herbs also may have various names (common names, scientific names and Chinese Pinyin). Despite the efforts of some databases in including multiple names of the herbs, their lists may not be exhaustive. If there is no result from the search using the names of herbs provided by patients, pharmacists can try to search using other names of the herbs.

8. Similar to conventional drug interactions and drug counselling, it will only be possible to make suggestions when sufficient information regarding the drugs and herbs which patients are taking can be obtained. If the Chinese medicine prescriptions are not available, or if patients fail to provide enough information on the herbs they are taking or are going to take, pharmacists can counsel patients based on available information highlighting some major potential interactions between Chinese and western medicines, so that they can communicate with their Chinese Medicine practitioners and be aware before taking any Chinese Medicines.

9. While the role of Chinese medicine as a traditional, complementary and integrative medicine (TCIM) is recognised, more caution is required for patients under special care, such as those on chemotherapy.[26] Local guidelines and resources from authoritative institutions such as National Comprehensive Cancer Network should be consulted. If the use of Chinese medicine is not discouraged with reference to the guidelines, information from the databases can be used to make suitable recommendations regarding specific combinations.[27-28] The medical team needs to be aware that the patient is contemplating or using any Chinese medicines.

FUTURE DIRECTIONS

Various databases are now under development with the help of AI technology to ensure their comprehensiveness and timeliness; meanwhile, more information regarding the interactions between Chinese and western medicines is also needed. As drug experts, pharmacists can take up an important role. An interdisciplinary collaboration between healthcare providers and scientists is needed in developing and updating interaction databases, and pharmacists may contribute by assessing the clinical relevance of interactions. Pharmacists can also contribute to the reporting of CHDI. Case reports remain the major sources of clinical evidence of interactions in the databases; however, adverse drug reactions remain under-reported, especially of herbal medicines. Pharmacists can proactively report suspected interactions so that more data can be available for the assessment of interactions in the databases.

CONCLUSION

With increasing popularity of Chinese medicine, it is expected that more patients will take both western and Chinese herbal medicines to manage their diseases or improve overall health. Nevertheless, Chinese Medicine practitioners and western medicine doctors may not have in-depth knowledge on the medicines used by

their counterparts. Pharmacists are well-positioned to identify and assess the risk of potential CHDI to ensure efficacy and prevent adverse drug reactions. Numerous databases are available to screen for CHDI, each with its advantages and disadvantages. Pharmacists should be aware of these tools that may assist in making informed decisions and formulating recommendations to their patients or other HCPs regarding CHDI.

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Management of Hospital-acquired Pneumonia and Ventilator-associated Pneumonia: The Conventional and Novel Antimicrobials

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ABSTRACT

Hospital-acquired pneumonia (HAP) is a prevalent nosocomial infection, accounting for 21 cases per 1000 hospital admissions. Prompt and appropriate management of is therefore necessary to reduce the likelihood of intensive care admission, mechanical ventilation, long hospital stay, and risk of mortality. The emergence of multidrug-resistant organisms (MDROs), such as *Pseudomonas*, MRSA, *Acinetobacter spp.* etc., has complicated the management of HAP/ ventilator-associated pneumonia (VAP) and also led to higher mortality. Multiple factors interact with one another to increase the risk of multidrug-resistant HAP/VAP, which should be assessed with vigilance while deciding on the appropriate antimicrobial agent(s). This article provides an overview on the management HAP and VAP, including conventional and newer approaches and their therapeutic considerations.

Keywords: *Hospital-acquired pneumonia, ventilator-associated pneumonia, multidrug-resistant organisms*

INTRODUCTION

Despite advances in antimicrobial therapy, better supportive care, and preventative measures, pneumonia has remained an important cause of morbidity and mortality. In Hong Kong, the number of registered deaths were 9373, accounting for 18.5% of all registered deaths, and ranked 2nd amongst the Ten Leading Causes of Death in 2020.[1] Hospital-acquired pneumonia (HAP) is a common healthcare-acquired infection globally, with a prevalence of 21 cases per 1000 hospital admissions.[2] Compared to patients who did not develop HAP, patients who developed HAP were more likely to require intensive care, mechanical ventilation, have longer hospital stay, and even higher mortality.[3] Therefore, prompt and appropriate management of pneumonia is crucial.

This article provides an overview on the management of HAP and ventilator-associated pneumonia (VAP). This article highlights the use of various antimicrobials for empiric and definitive treatment of pneumonia, comprising conventional and newer approaches. Risk factors and therapeutic considerations will also be discussed on multidrug-resistant organisms (MDROs), including *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) Enterobacterales, and *Acinetobacter baumannii*.

DEFINITIONS

HAP and VAP are distinct entities: HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and not associated with mechanical ventilation, while VAP refers to pneumonia that occurs 48 hours or more after endotracheal intubation. In the past, pneumonia acquired outside the hospital by patients with significant contact with the healthcare system (e.g., nursing home, chronic dialysis, home wound care etc.) was termed 'healthcare-associated pneumonia' (HCAP). Patients with HCAP were presumed to be at high risk for MDROs, but this concept is no longer advocated. There is increasing evidence that many patients defined as having HCAP are not at high risk for MDROs, and underlying patient characteristics should be considered when determining the risk for MDROs, which will be discussed in the context below.[4]

PATHOGENESIS, ETIOLOGY AND RISK FACTORS

In general, pneumonia can be caused by bacteria, viruses, and/ or fungi. HAP and VAP are mostly caused by bacterial pathogens, including Gram-negative bacilli (e.g., *Pseudomonas aeruginosa*, *Escherichia coli*,

Klebsiella pneumoniae, Serratia marcescens, and *Acinetobacter species*; GNB) and Gram-positive cocci (e.g., Staphylococcus aureus). The flora of the oral tract rapidly shifts on admission from typical community respiratory organisms (e.g., *Streptococcus pneumonia*) toward nosocomial pathogens such as *S. aureus* and *P. aeruginosa.*

The development of nosocomial pneumonia can be multifactorial; risk factors can be categorised as patient-related, infection control-related, and intervention-related. Patient-related factors include advanced age, severe and/ or multiple comorbid illnesses (e.g., COPD, malignancy, alcoholism etc.), malnutrition, coma, and metabolic acidosis. Infection control-related risk factors include poor hygiene measures and the use of contaminated respiratory equipment. Intervention-related risk factors involve procedures (e.g., surgeries involving the chest and abdomen) and therapies (e.g., corticosteroids, cytotoxic agents, and immunosuppressants) that undermine normal host defences or predispose the host to heavy bacterial inoculum. Mechanical factors, for instance, intubation and enteral feeding, increase bacterial bioburden in the upper respiratory and orogastric tracts. All these factors interact with one another to increase the risk of micro-aspiration and the likelihood of pulmonary parenchymal colonisation and therefore invasive infection. Respiratory viruses including rhinoviruses, influenza, parainfluenza, adenoviruses, and RSV may also lead to nosocomial pneumonia and even occasional institutional outbreaks.[4,5]

CLINICAL PRESENTATION AND DIAGNOSIS

There are several clinical considerations when evaluating a patient suspected with pneumonia: (a) symptoms consistent with pneumonia, (b) the clinical setting in which the pneumonia takes place, (c) defects in host defence that could predispose to the development of pneumonia, and (d) possible exposures to specific pathogens. Patients can present with both respiratory and non-respiratory symptoms, including cough with or without sputum, chest discomfort, fever or hypothermia, fatigue, sweats, and headache etc.

Chest radiograph that shows a pulmonary infiltrate suggests the presence of pneumonia. Microbiologic tests, for example, culture of respiratory tract secretions (e.g., sputum, bronchoalveolar lavage, tracheal aspirate), blood culture and urine antigen tests, are important to identify the specific cause that causes pneumonia. These tests allow the physician to narrow the antibiotic spectrum by using fewer and more specific agents, thereby reducing unnecessary side effects and the development of resistance. Identifying specific causes may also help discover new agents, resistance patterns in established agents, and epidemiology of infectious outbreaks.[5]

The diagnosis of HAP and VAP can be challenging, as the clinical signs, such as new onset of fever, purulent sputum, leucocytosis, and impaired oxygenation, are neither sensitive nor specific. Although it is common for critically ill patients to present with pulmonary infiltrates on imaging, differential diagnosis, including atelectasis, acute respiratory pulmonary distress syndrome (ARDS), congestive heart failure (CHF), pulmonary haemorrhage, and pulmonary infarction can present with similar imaging.[6] Clinical Pulmonary Infection Score (CPIS) is a scoring system developed to aid diagnosis and guide the management of pneumonia **(Table 1)**. However, the quality of evidence demonstrated by several studies, which used CPIS as a diagnostic tool, was deemed to be low. Therefore, the 2016 Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) HAP/VAP guideline has recommended using clinical criteria alone, rather than clinical criteria plus CPIS or biomarkers (e.g., procalcitonin, C-reactive protein) to decide whether or not to initiate antibiotic therapy. Non-invasive sampling (e.g. endotracheal aspiration) is recommended for diagnosing HAP and VAP, rather than invasive sampling with quantitative cultures (e.g. bronchoscopy) **(Table 2)**.[4]

Table 1. Clinical Pulmonary Infection Score (CPIS)

Clinical Pulmonary Infection Score (CPIS)	0	1	2
Temperature, °C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
White blood cell count, per 10^9/L	≥ 4 or ≤ 11.0	< 4.0 or > 11.0	<4.0 or > 11.0 PLUS band forms ≥ 0.5
Tracheal secretions	Rare	Abundant	Abundant and purulent
Oxygenation (PaO_2 to FiO_2 ratio)	> 240 or ARDS		≤ 240 and no ARDS
Chest radiograph	No infiltrate	Diffused	Localised
Microbiology	Negative	Positive	Positive PLUS positive on Gram stain
Maximum score: 12			

ARDS, acute respiratory distress syndrome

Modified from Schurink CA, Van Nieuwenhoven CA, Jacobs JA, et al. Intensive Care Med. 2004;30:217-224

Table 2. Microbiologic tests suggested to diagnose HAP/VAP	
Microbiologic methods to diagnose HAP/VAP	**HAP/VAP**
Non-invasive respiratory sampling (e.g., sputum induction/ expectoration, nasotracheal suctioning, endotracheal aspiration in patients who require mechanical ventilation)	✓
Invasive respiratory sampling (e.g., BAL)	✗^
Blood culture	✓

^ Based on epidemiological risk factors
BAL, bronchoalveolar lavage; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia
Modified from Metlay JP, Waterer GW, Long AC, et al. Am J Respir Crit Care Med. 2019;200(7):e45-67.

TREATMENT

General principles

Appropriate and adequate antimicrobial therapy should be initiated promptly, as delayed or inadequate treatment is associated with increased duration of sickness, risk for complications and mortality. Local antibiogram should be utilised to guide the selection of empiric antimicrobial therapy. The antimicrobial therapy should be tailored according to the antimicrobial susceptibility tests, specific epidemiology of infection and the resistance patterns of the locale.

One of the primary considerations in selecting appropriate agents for treating pneumonia is the intrapulmonary penetration of the antimicrobial agents and their pharmacokinetic and pharmacodynamics characteristics. Most commercially available antimicrobials can achieve adequate intrapulmonary concentrations for treating pneumonia; daptomycin is an example of having low efficacy in treating pneumonia as it has been shown to bind to pulmonary surfactant. Toxicity considerations (e.g. drug interactions, side effects) and host factors (e.g. drug allergy, other co-existing comorbidities, age, renal and liver functions, immune status etc.) need to be considered when selecting the appropriate antimicrobial agent(s).[5]

HAP/VAP – Empiric treatment

When HAP or VAP is suspected, treatment should be started promptly **(Table 3)**. Sputum samples should be obtained from the lower respiratory tract for culture before beginning antibiotic therapy. However, initiation of antibiotic therapy should not be delayed for critically ill patients in order to obtain specimens. The risk factors for MDROs and mortality should be assessed. Broad spectrum antimicrobial therapy that covers MRSA and *Pseudomonas* should be considered in patients who present with risk factors (see 'Multidrug-resistant organisms (MDROs)'). Empiric antifungal and anaerobic coverage are not typically indicated.[4]

HAP/ VAP – Definitive treatment

Vancomycin and linezolid are both appropriate choices for empiric or definitive treatment of HAP/VAP caused by MRSA **(Table 4)**; clinical outcomes appear to be similar

Table 3. Empiric treatment of HAP/VAP			
	Preferred agent	**Alternatives**	**Special considerations**
HAP, onset < 4 days after admission + no previous antibiotics	I.V. / P.O. amoxicillin/clavulanate	I.V. ceftriaxone	
HAP, onset ≥ 4 days after admission + recent antibiotic use	I.V. piperacillin/tazobactam	I.V. imipenem/cilastatin or I.V. meropenem	➢ With ESBL concern: I.V. imipenem/ meropenem ➢ With MRSA concern: Add vancomycin
HAP, onset ≥ 5 days after admission			
Mechanical ventilation			

Suggested dosage (4): P.O. amoxicillin/clavulanate 1 g b.d., I.V. amoxicillin/clavulanate 1.2 g q8h, ceftriaxone 1-2 g daily, imipenem/cilastatin 500 mg q6h, meropenem 1 g q8h, piperacillin/tazobactam 4.5 g q6h, I.V. vancomycin 15 - 20 mg/kg q8-12h (consider a loading dose of 25 – 30 mg/kg x 1 for severe illness; dose adjusted to target 15 – 20 mg/mL of trough level)
ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*
Adapted from Ho PL, Wu TC, Chao DVK, et al. Reducing Bacterial Resistance with IMPACT, 5th Edition. Centre for Health Protection Hong Kong. 2017.

Table 4. Definitive treatment of HAP/VAP			
Organism	**Preferred agent**	**Alternatives**	**Remarks**
MRSA	I.V. vancomycin	I.V./P.O. linezolid in case of vancomycin-allergy or bacteraemia caused by MRSA with vancomycin ≥ 2 mcg/mL	Other useful adjuncts for deep-seated infections: Cotrimoxazole, fusidic acid or rifampicin, but not as monotherapy
Pseudomonas aeruginosa	I.V. piperacillin or ticarcillin/ clavulanate or piperacillin/ tazobactam + an aminoglycoside (e.g., amikacin)	➢ I.V. cefoperazone/sulbactam + aminoglycoside (mixed infection with Acinetobacter) ➢ I.V./ P.O. levofloxacin/ ciprofloxacin + an aminoglycoside (if allergic to penicillin)	Combination therapy recommended for all serious infection

Suggested dosage (4,28): Amikacin 15-20 mg/kg q24h, I.V. ciprofloxacin 400 mg q8h, cefoperazone/sulbactam 4g q12h, I.V. levofloxacin 750 mg q24h, I.V./ P.O. linezolid 600 mg q12h, piperacillin/tazobactam 4.5 g q6h, ticarcillin/clavulanate 3.1 g q4-6h, I.V. vancomycin 15 – 20 mg/kg q8-12h (consider a loading dose of 25 – 30 mg/kg x 1 for severe illness; dose adjusted to target 15 – 20 mg/mL of trough level)
MRSA, methicillin-resistant *Staphylococcus aureus*
Adapted from Ho PL, Wu TC, Chao DVK, et al. Reducing Bacterial Resistance with IMPACT, 5th Edition. Centre for Health Protection Hong Kong. 2017.

among these two agents.[7,8] While linezolid has superior lung penetration, is less nephrotoxic than vancomycin, and does not require renal dosage adjustment, it is more likely to cause thrombocytopenia and gastrointestinal symptoms, interact with other medications, and costs substantially more than vancomycin.[4,9]

Duration of treatment

Microbiologic tests should be obtained in patients on broad-spectrum empiric therapy. Based on respiratory and blood culture results, de-escalation should be considered at 48 hours if the patient is clinically improving.[10] For patients with HAP or VAP, the recommended duration of treatment is 7 days, including patients with non-fermenting Gram-negative bacteria, *Acinetobacter spp*., and MRSA with a good clinical response. However, there are situations that may require alternative duration (e.g., inappropriate empiric therapy initiated), depending on the rate of improvement of clinical, radiological, and laboratory parameters. It is recommended against routine treatment with antibiotics for 3 days or more in patients with low probability of HAP (i.e., CPIS 6 or with clinical presentation not highly suggestive of pneumonia) and no clinical deterioration within 72 hours of symptom onset.[4,11]

MULTIDRUG-RESISTANT ORGANISMS (MDROs)

MDROs – Risk factors and impact

The United States Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) has defined MDR as 'acquired non-susceptibility to at least one agent in three different antimicrobial classes'.[12] The emergence of MDROs, such as *Pseudomonas*, MRSA, *Acinetobacter spp*. etc., has complicated the management of HAP/VAP and also led to higher mortality. Numerous factors can contribute to a higher risk for MDROs **(Figure 1)**. *S. aureus* causes 13 - 40% of nosocomial pneumonia, and MRSA strains predominate in this setting. MDR Enterobacterales, which include those bacteria that produce AmpC enzymes, ESBL, carbapenemases, or a combination of these, is an important cause of difficult-to-treat nosocomial pneumonia. The management of pneumonia caused by carbapenem-resistant Enterobacterales (CRE) is particularly challenging, which could lead to an excess hospital mortality of 27%.[6]

MRSA and *P. aeruginosa*

The decision on whether empiric coverage for MRSA or *P. aeruginosa* is needed depends on the prevalence of these pathogens utilising the local antibiogram, as well as evaluating the risk factor(s) presented by the patient **(Figure 1)**. If empiric coverage for MRSA is indicated, the recommended agent is either vancomycin or linezolid, whilst two anti-pseudomonal antibiotics of different classes (i.e., one β-lactam-based agent plus one non-β-lactam based agent) are recommended in patients presented with one or more risk factors. Empirical treatment using aminoglycosides and colistin should be avoided if alternative agents with adequate Gram-negative activity are available.[4]

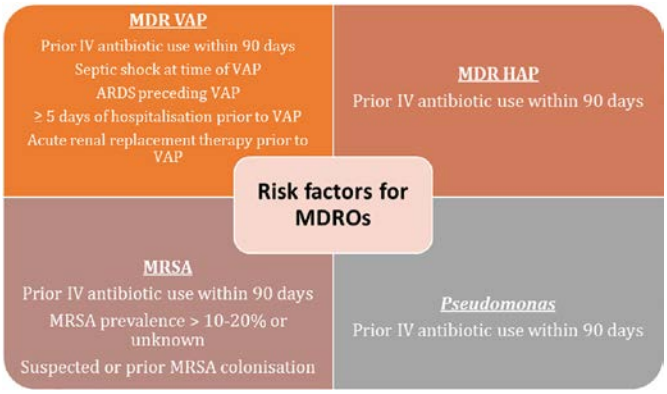

Figure 1. Risk factors for MDROs

ARDS, acute respiratory distress syndrome; HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant Staphylococcus aureus; VAP, ventilator-associated pneumonia

Modified from Kalil AC, Metersky ML, Klompas M, et al. Clin Infect Dis. 2016;63(5):e61-111.

Several new antibiotics with activity against MDR *P. aeruginosa* have been approved by the FDA for the treatment of nosocomial pneumonia **(Table 5)**. The potent anti-pseudomonal activity of ceftolozane/tazobactam is attributed to its ability to evade the resistance mechanisms of *P. aeruginosa*. However, it lacks activity against Ambler class B enzymes, such as VIM and NDM. The approval of ceftazidime/avibactam for nosocomial pneumonia was based on the REPROVE trial, in which it showed broader activity against Gram-negative pathogens that were resistant to ceftazidime alone. Notably, it is also ineffective against metallo-β-lactamases (MBLs). The combination of aztreonam and ceftazidime/avibactam can be useful in targeting MBL-producers.[6,13] Cefiderocol has demonstrated potent activity against β-lactamase-producing *P. aeruginosa*, affirming its non-inferiority to high-dose extended infusion of meropenem.

MDR Enterobacterales

The management of pneumonia caused by MDR Enterobacterales is challenging, as AmpC and ESBL producers are usually resistant to most, if not all, cephalosporins. In the MERINO trial (Meropenem versus piperacillin/tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella spp.*),

the use of piperacillin/tazobactam was not shown to be non-inferior to meropenem in reducing 30-day mortality. Thus, the use of piperacillin/tazobactam as 'carbapenem-sparing therapy' was not supported.[14] Similarly, in a randomised trial comparing cefepime versus imipenem in the treatment of pneumonia, reduced efficacy of cefepime was observed in patients infected with ESBL-producing Enterobacterales.[15] Therefore, if local cefepime resistance rates among Gram-negatives associated with HAP or VAP are high (i.e., >10%), a carbapenem is generally recommended as the empirical choice for ESBL-producing Enterobacterales.

Prior to the availability of newer antibiotics, treatment of invasive CRE infections included the use of polymyxins, tigecycline, and aminoglycosides, often given in combination therapy. However, it is worth noticing that tigecycline is approved by the FDA for the treatment of community-acquired pneumonia (CAP), but not for CAP caused by MRSA nor HAP/VAP. A Boxed Warning was added to the label of tigecycline following the revelation of increased risk of death in patients treated with tigecycline when compared to other antimicrobials, and the risk was greatest in patients treated with tigecycline for VAP.[16] Despite the optimal treatment of CRE pneumonia is uncertain, several novel antibiotics, such as plazomicin, ceftazidime/avibactam, eravacycline, and meropenem/vaborbactam, have shown anti-CRE activity and may be considered for the management of CRE pneumonia **(Table 5).** Ceftazidime/avibactam is active against many carbapenemase-producing strains. The 30-day mortality in patients on colistin was 32% versus 9% in those on ceftazidime/avibactam for the treatment of CRE infections caused primarily caused by KPC producers. Nevertheless, literature data are still elusive regarding these newer options and specifically their clinical effectiveness in CRE infections.[6]

Acinetobacter baumannii

In patients with HAP/VAP caused by *Acinetobacter spp*., a carbapenem, commonly meropenem or imipenem, has been suggested if the isolate is susceptible to the agent. Ertapenem is not active against MRSA, *A. baumannii* and *P. aeruginosa*. Alternatively, cefoperazone/sulbactam and ticarcillin/clavulanate may also be considered for *Acinetobacter spp*. if susceptible. The β-lactamase inhibitor sulbactam has shown good antimicrobial activity against *Acinetobacter* strains; sulbactam can be combined with other antimicrobials such as carbapenems to treat extensively drug-resistant (XDR) *A. baumannii.* Although cefoperazone/sulbactam is not available in many countries, it is more frequently used for MDR *A. baumannii* infections in China, as it has shown lower resistance rates than ampicillin/sulbactam (12% vs 34%). The optimal dosage of sulbactam to treat MDR and XDR *A. baumannii* infections is unknown, but higher dose (i.e., 6 g of sulbactam/ day in divided doses, or even 8-9 g daily) has been suggested in patients with normal renal function.[17–20]

According to an epidemiologic survey conducted in China, *Acinetobacter spp*. was the most common pathogen of HAP and 76.8% of the *Acinetobacter* strains causing HAP were resistant to carbapenems. Combination of imipenem with colistin, ampicillin/ sulbactam, and amikacin appeared to have synergism against carbapenem-resistant *A. baumannii* (CRAB).[20] If the isolate is sensitive only to polymyxins, IV polymyxin and adjunctive inhaled colistin are recommended.[4,6] Previously, the paucity of novel antibiotics has led to a resurgence in the use of polymyxins, most commonly colistin. Although colistin has been advocated as a safe and effective agent for MDR *Acinetobacter* VAP, its use is associated with multiple clinical questions. For example, whether the concurrent use of I.V. colistin and aerosolised (AS) antibiotics (including AS colistin), or combined antimicrobial therapy with I.V. colistin, can improve the outcome of MDR *Acinetobacter* VAP, in contrast to I.V. colistin monotherapy. In a systemic review and meta-analysis, colistin was shown to be as effective as β-lactam antibiotics for the treatment of MDR *Acinetobacter* VAP, without an increased risk of nephrotoxicity. There have been conflicting findings in the clinical effectiveness of AS antibiotics for the treatment of Gram-negative pneumonia. IDSA has recommended against the use of AS antibiotics, due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications (e.g., bronchoconstriction) in 10 - 20% of patients receiving AS antibiotics.[19]

Although the results supporting the synergistic effect of the combination therapy of colistin with other antimicrobials have remained inconsistent, the option of colistin combined therapy should still be considered in order to reduce the risk of treatment failure and colistin resistance.[21] Combination therapy of rifampicin and colistin should be avoided in view of their potential adverse effects, as increased microbial eradication rate was not associated with improved clinical outcome.[4,6]

Notably, there is no clear 'standard of care' antimicrobial regimen for CRAB infections, as robust comparative studies on the efficacy of different agents are limited.[19] Since there can be a significant difference in the dosage range when indicated for infections of different severity (e.g., ampicillin/sulbactam 1.5 - 3 g every 6 hours for non-severe aspiration

Table 5. Novel antimicrobial agents targeting multidrug resistant organisms				
Antimicrobial agent	**Class**	**Dosage**	**Activity**	**FDA indication**
Aztreonam/ avibactam	Monobactam/ β-lactamase inhibitor	*Loading: I.V. 667 mg (500 mg AZT/167 mg AVI) over 30 mins* *Maintenance: I.V. 2 g over 3h q6h (1500 mg AZT/ 500 mg AVI)* [#a]	ESBL, KPC, class C β-lactamase, MBL	cIAI, cUTI, HABP/ VABP*
Cefiderocol	Siderophore cephalosporin	I.V. 2 g over 3h q8h	ESBL, CRE (class A, B, and D enzymes), carbapenem-resistant *P. aeruginosa, Stenotrophomonas maltophilia,* and *A. baumannii*	cUTI, HABP/VABP
Ceftazidime/ avibactam†	Cephalosporin/ β-lactamase inhibitor	I.V. 2.5 g (2g CTZD/ 0.5 g AVI) over 2h q8h	ESBL, KPC, AmpC, some class D serine β-lactamases	HABP/VABP, cIAI, cUTI
Ceftolozane/ tazobactam†	Cephalosporin/ β-lactamase inhibitor	**HABP/VABP:** I.V. 3 g (2 g CTOZ/1g TAZO) over 1h q8h	ESBL, MDR *P. aeruginosa*	cUTI, cIAI
Delafloxacin	Fluoroquinolone	I.V. 300 mg over 60 mins q12h, or P.O. 450 mg q12h	*K. pneumoniae,* including AmpC and class A ESBL-producers, ciprofloxacin-resistant *E. coli* and *A. baumannii*	ABSSSI, CABP
Eravacycline	Fluorocycline tetracycline	I.V. 1 mg/kg q12h	ESBL, CRE, MDR *A. baumannii*	cIAI
Imipenem/ cilastatin/ relebactam	Carbapenem/renal dehydropeptidase inhibitor/ β-lactamase inhibitor	I.V. 1.25 g (0.5 g IMI/ 0.5 g CILA/ 0.25 g RELE) over 30 mins q6h	KPC, MDR *P. aeruginosa*	cUTI, cIAI, HABP/ VABP
Meropenem/ vaborbactam	Carbapenem/boronic acid inhibitor	I.V. 4 g (2 g MERO/ 2 g VAB) over 3h q8h	CRE (class A and C enzymes)	cUTI
Meropenem/ nacubactam	Carbapenem/β-lactamase inhibitor	*I.V. 4 g (2 g MERO/ 2 g NACU) over 1.5 h*[#b]	CRE class A and C enzymes, MDR *P. aeruginosa*	Not applicable
Murepavadin	Cyclic peptide that targets outer membrane	*Doses up to 4.5 mg/kg as a single dose or 5 mg/kg in divided doses*[#c]	MDR *P. aeruginosa*	HABP/VABP, ABSSSI, BSI, cIAI*
Omadacycline	Aminomethylcycline	**CABP & ABSSSI:** Loading: I.V. 200 mg over 60 mins once, or 100 mg over 30 mins q12h on Day 1 Maintenance: I.V. 100 mg over 30 mins, or P.O. 300 mg daily **ABSSSI only:** Loading: P.O. 450 mg daily on Day 1 and 2 Maintenance: P.O. 300 mg daily	ESBL, *A. baumannii*	ABSSSI, CABP
Plazomicin	Aminoglycosides	I.V. 15 mg/kg over 30 mins daily	ESBL, CRE excluding NDM producers, *A. baumannii, P. aeruginosa*	cUTI

* Qualified Infectious Disease Product (QIDP) designation and Fast Track designation

[#a,b,c] Studied dose from NCT02655419 (29), NCT03182504 (30), and a Phase 1 trial (31), respectively.

† Registered in Hong Kong (Product recall of ceftolozane/tazobactam by the manufacturer in 2017; supply has not been resumed). *Drug Office. Department of Health, HKSAR. Available at* https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html (Accessed 28/12/21)

ABSSSI, acute bacterial skin and skin structure infection; AZT, aztreonam; AVI, avibactam; CABP, community-acquired bacterial pneumonia; cIAI, complicated intra-abdominal infection; CILA, cilastatin; CRE, carbapenem-resistant Enterobacterales; CTOZ , ceftolozane, CTZD, ceftazidime; cUTI, complicated urinary tract infection; ESBL, extended-spectrum β-lactamase; FDA, US Food and Drug Administration; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; MERO, meropenem; NACU, nacubactam, NDM, New Delhi metallo-β-lactamase; RELE, relebactam; TAZO, tazobactam; VAB, vaborbactam; VABP, ventilator-acquired bacterial pneumonia.

Modified from Watkins RR, Van Duin D. F1000Research. 2019;8(0):1–10.

pneumonia, whereas 3 g every 4 hours or even 9 g every 8 hours of ampicillin/sulbactam is required for HAP/ VAP caused by *Acinetobacter* spp.), there is a role in infectious diseases pharmacist to ensure that the prescribed dose is sufficient to target the bacterium in concern.

COMBINATION VERSUS MONOTHERAPY

There are debates whether a combination therapy will improve the outcome of Gram-negative pneumonia. Combination antibiotic therapy (i.e., the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, or polymyxin) is not routinely recommended for the treatment of CRE infections or 'difficult-to-treat' resistance-*P. aeruginosa*. Provided that the β-lactam agent has demonstrated *in vitro* activity, additional benefit was not shown with continued combination therapy, with an increased likelihood of antibiotic-associated adverse events caused by the continued use of a second agent. For the treatment of moderate to severe CRAB infections, combination therapy with at least two agents is suggested at least until an appropriate clinical response is observed.[22]

Overall, monotherapy has been suggested for the empirical therapy of HAP/VAP, unless patients are

presented with factors increasing the likelihood for *Pseudomonas* or other Gram-negative infection, or high mortality risk (e.g., need for ventilator support due to HAP and septic shock). For definitive treatment of HAP/VAP, the adoption of mono- or combination therapy should be guided by the risk factors of patients, e.g., presence of septic shock and risk for death. Combination therapy is deemed more appropriate in providing additive or synergistic action against serious infection and clinical failure **(Table 3 & 4)**.[4,9]

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) CONSIDERATIONS

Rather than conforming to the manufacturer's prescribing information, treatment should be optimised by tailoring antibiotic dosing using PK/PD data for the management of HAP/VAP. PK/PD-optimised dosing refers to the use of antibiotic blood concentrations, prolonged infusions (i.e., extended or continuous infusion), and weight-based dosing for certain antibiotics.[4]

Since β-lactams achieve bactericidal effect by its time-dependent property, prolonging the infusion of certain β-lactams is a potential strategy to optimise the PD effect of the given agent. Despite consistent results are lacking, a meta-analysis reported that patients who received prolonged infusion of antibiotics for the management of nosocomial pneumonia displayed higher clinical cure rates than those who received intermittent infusion.[23] Similarly, higher bactericidal exposure was achieved by prolonging the infusion time of cefepime, ceftazidime, and meropenem.[24] As critically ill patients are at high risk of acquiring pathogens with high MICs, classical intermittent dosing regimens may fail to achieve adequate PK/PD targets, leading to potential therapeutic failure or emergence of drug resistant pathogens. Therefore, prolonged infusion of β-lactams should be considered in critically ill patients with HAP or VAP, as well as for patients with HAP or VAP caused by Gram-negative bacilli with elevated but susceptible MICs.[23]

Over the last few decades, 'vancomycin creep' has appeared in HK, in which a silent and gradual increase in the vancomycin minimal inhibitory concentration (MIC) is observed.[9] Vancomycin MIC ≥ 2μg/mL has been associated with vancomycin treatment failure, therefore, alternative antibiotic has been recommended for isolates with vancomycin MIC ≥ 2μg/mL. Despite the lack of clinical data, vancomycin loading dose (i.e. 25 – 30 mg/kg, based on actual body weight) has been suggested for severe suspected or documented MRSA infections, including sepsis, meningitis, pneumonia, and endocarditis, to ensure early achievement of target trough concentration. There are limited robust clinical data to support higher target troughs (i.e., ≥ 15mg/L). However, for the purpose of optimising the PD of vancomycin, improving tissue penetration, and minimising selection of resistant strains, it is still recommended to target higher trough concentrations for serious infections due to MRSA.[25]

Historically, trough concentration was the sole monitoring parameter of vancomycin. Although trough-only monitoring is practical, the potential limitations surrounding the practice suggest that its use alone may be insufficient to guide vancomycin dosing. Although it is a consensus to maintain a high trough value (i.e. 15 – 20 mg/L) for serious infections, including those caused by MRSA, it has not been shown to correlate well with clinical benefits as expected. This is because the trough-only represents a single exposure point at the end of the dosing interval; an identical trough value can be yielded from a wide range of concentration-time profiles. In contrast, the 24-hour area under the curve (AUC) represents the average concentration during that dosing period. Thus, the use of the PD parameter, AUC to MIC ratio, has been advocated to be the best predictor as well as monitoring parameter of vancomycin efficacy. AUC/MIC ≥ 400 mg▪h/L was found to be associated with improved clinical response and microbiologic eradication in patients with ventilator-associated *S. aureus* pneumonia. Previously, the calculation of AUC using the linear-trapezoid rule required precise collection of vancomycin concentrations repeatedly, which made it impractical in busy healthcare institutions. The emergence of Bayesian software programmes has provided an alternative to this, which can estimate the vancomycin AUC value with minimal pharmacokinetic sampling and allow sampling within the 24 - 48 hours of vancomycin dosing rather than at steady-state.[26,27]

CONCLUSIONS

HAP and VAP, especially that is caused by MDROs, represent a serious threat to hospitalised patients. Physicians must be knowledgeable about local antibiogram and assessment on patient's risk factors for MDROs should be performed with vigilance. In cases where MDRO is suspected, infectious diseases physicians should be consulted to ensure appropriate and prompt management. To accomplish a successful antimicrobial stewardship, infectious diseases pharmacists also have a potential role in providing suggestions on the choice of antimicrobials, the monitoring required, as well as measures to optimise the PK/PD property of the selected agent.

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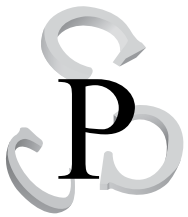
Questions for Pharmacy Central Continuing Education Committee Program

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



2 CE Units

Management of Hospital-acquired Pneumonia and Ventilator-associated Pneumonia: The Conventional and Novel Antimicrobials

1. ***Which of the following pathogens are likely to cause hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)?***
   i. *Streptococcus pneumoniae*
   ii. *Pseudomonas aeruginosa*
   iii. *Staphylococcus aureus*
   iv. *Chlamydia pneumoniae*
   a. i and iv
   b. ii and iii
   c. ii, iii and iv
   d. All of above

2. ***Which of the following procedures are considered appropriate for diagnosing nosocomial pneumonia?***
   i. Chest radiograph
   ii. Respiratory sampling by sputum induction or expectoration
   iii. Routine sampling by bronchoalveolar lavage
   iv. Blood culture
   a. i and ii
   b. ii and iii
   c. i, ii and iv
   d. All of above

3. ***Which of the following patients presents with the lowest risk for multidrug-resistant organism(s) (MDROs)?***
   a. A 45-year-old patient with good past health and has just been diagnosed with influenza and CAP.
   b. An 80-year-old patient who was treated with I.V. meropenem one month ago.
   c. A 60-year-old patient who is being treated in an institution where MRSA prevalence is found to be >20%.
   d. A 33-year-old patient who is presented with septic shock and has been hospitalised for 10 days before being diagnosed with VAP.

4. ***Which of the following antimicrobials is the LEAST appropriate for the treatment of HAP?***
   a. P.O. amoxicillin/clavulanate 1g bd
   b. I.V. daptomycin 6mg/kg once daily
   c. I.V. meropenem 1g q8h
   d. I.V. imipenem/cilastatin 500 mg q6h

5. ***What is the recommended duration of treatment for HAP and VAP?***
   a. Less than 5 days
   b. 14 days
   c. 7 days
   d. At least 10 days

6. ***A 68-year-old lady was presented with persistent fever (38.8°C), shortness of breath and purulent sputum, 5 days after hospital admission. Localised infiltration was shown on chest radiograph; white cell count and C-reactive protein were found to be 9.0 per 10^9/L and 17 mg/L respectively. Her past medical history included chronic obstructive pulmonary disease, ishaemic heart disease, and hyperlipidemia; MRSA decolonisation therapy was given two weeks ago. Last month, she received a course of I.V. hydrocortisone and I.V. amoxicillin/clavulanate due to exacerbated COPD. Which of the following antimicrobial(s) is the most appropriate empirical treatment for this lady?***
   a. I.V. ceftriaxone 1g daily + P.O. levofloxacin 750mg daily
   b. I.V. piperacillin/tazobactam 4.5g q8h + I.V. vancomycin 1g q12h
   c. I.V. amoxicillin/clavulanate 1.2g q8h + P.O. doxycycline 100mg bd + I.V. linezolid 600mg q12h
   d. I.V. cefepime 2g q8h

7. ***Which of the following statements is INCORRECT regarding multidrug-resistant organisms (MDROs)?***
   a. According to the the United States Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC), multidrug resistance is defined as 'acquired non-susceptibility to one broad-spectrum antimicrobial'.
   b. MDR Enterobacteriaceae, such as AmpC and ESBL producers, are usually resistant to most, if not all, cephalosporins.
   c. In patients presented with one or more risk factors for MDROs, empiric coverage using vancomycin or linezolid for MRSA, and two anti-pseudomonal antibiotics of different classes for *P. aeruginosa*, should be considered.
   d. An antibiotic with activity against MSSA is recommended for patients with HAP/VAP who are being treated empirically and have no risk factors for MRSA infection and are not at high risk of mortality

8. ***Which of the following statements is correct regarding the novel antimicrobial agents targeting MDROs?***
   a. The addition of avibactam to ceftazidime extends the spectrum of activity to include most Enterobacteriaceae (including AmpC, ESBL, some *K. pneumoniae* and OXA-type carbapenemases), as well as *Acinetobacter* species with high MICs to ceftazidime alone.
   b. Ceftolozane/tazobactam demonstrates potent activity against *P. aeruginosa* and Ambler class B enzymes, such as VIM and NDM.
   c. Cefiderocol was shown to be inferior to high-dose extended infusion of meropenem, despite its potent activity against β-lactamase-producing *P. aeruginosa.*
   d. Tigecycline is not approved by the FDA for the treatment of HAP/VAP as it was found to increase risk of death in patients treated for VAP when compared to other antimicrobials.

9. ***Which of the followings strategies is/are to optimise the treatment of HAP/VAP?***
   i. Combination therapy is recommended in patients suspected with Gram-negative HAP/VAP and presented with risk factors, such as septic shock and risk of death.
   ii. The concurrent use of aerosolised and I.V. colistin may be considered as last resort in cases of MDR *Acinetobacter* VAP.
   iii. For critically ill patients with HAP/VAP, or HAP/VAP caused by Gram-negative bacilli with elevated but susceptible MICs, prolonged infusions of β-lactams should be considered, provided that there is no compatibility and stability issue.
   iv. Based on respiratory and blood culture results, de-escalation should be considered at 48 hours if the patient is clinically improving.
   a. iii only
   b. i and iii
   c. ii and iv
   d. All of above

10. ***Which of the following statements is INCORRECT regarding the use of vancomycin?***
    a. Alternative antibiotic is recommended for isolates with vancomycin MIC 2μg/mL to avoid treatment failure.
    b. Higher vancomycin trough concentrations (i.e. 15 – 20 mg/L) should be targeted for serious infections due to MRSA, in light of optimising the pharmacodynamics of vancomycin, improving tissue penetration, and minimising selection of resistant strains.
    c. AUC/MIC 600 mg•h/L was found to be associated with improved clinical response and microbiologic eradication in patients with ventilator-associated *S. aureus* pneumonia.
    d. Trough-only monitoring is insufficient to guide vancomycin dosing, as it barely represents a single exposure point at the end of the dosing interval, which can be yielded from a wide range of concentration-time profiles.

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 291(D&T)

Recent Development of Lipid Management: PCSK9 Inhibitors and Inclisiran

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

Pharmacists' perspectives on the under-prescribing of oral anticoagulants among long-term aspirin users with atrial fibrillation: a preliminary report

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ABSTRACT

Despite the increasing evidence of the superior efficacy of oral anticoagulants (OACs) compared to antiplatelet therapy (aspirin and/or clopidogrel) for stroke prevention, their improved safety profiles and current clinical recommendations, OACs are underused whereas antiplatelet therapy remains high in Asia compared to western countries. Prior studies identified the barriers of using OACs from the view of patients with atrial fibrillation (AF) and clinicians but the perception of pharmacists on this aspect remains under-examined. Therefore, this qualitative study aimed to investigate the attitudes of the local pharmacists on the issue of under-prescribing OACs to patients with AF.

Face-to-face interviews were conducted with six eligible pharmacists via Zoom using a validated semi-structured interview guide from 2019-2020. All interview recordings were transcribed verbatim and data were analyzed based on thematic approach. A total of five themes were derived, namely 1) physical characteristics of long-term aspirin users with AF, 2) concerns on the adverse effects from the patients with AF, 3) worries and concerns from caregivers, 4) patients' compliance to the anticoagulation treatment, and 5) Role of aspirin in stroke prophylaxis. Majority of the pharmacists agreed that worries and concerns from patients and caregivers were mainly on the risk of bleeding and lifestyle adjustment brought by the OACs, which adversely affect patients' compliance to treatment and hence the willingness to receive OACs.

These preliminary findings revealed some of the potential barriers of using OACs among the long-term aspirin users, which can be alleviated with the help from the pharmacists in the community and highlighted the need of clinical pharmacy service and education interventions.

Keywords: *atrial fibrillation, barriers, oral anticoagulants, aspirin*

INTRODUCTION

Oral anticoagulants (OACs) have been recommended as a long-term prophylaxis to patients with atrial fibrillation (AF) who are at high risk of stroke in the international clinical guidelines.[1-4] For more than decades ago, warfarin as a vitamin K antagonist, was used to be the only available OAC indicated for stroke prevention. Since 2010, non-vitamin K antagonist OACs (NOACs) including dabigatran, rivaroxaban, apixaban and edoxaban, were approved by the Food and Drug Administration and introduced to the market as alternatives to warfarin. The latest international clinical guidelines now discourage the use of antiplatelet monotherapy (aspirin or clopidogrel) as a large body of research showed that OACs was more superior to antiplatelet monotherapy in terms of risk reduction in stroke and all-cause mortality but demonstrated a comparable risk of gastrointestinal bleeding.[1-8]

Despite the change of the international clinical guidelines on the stroke prevention, the proportion of patients with AF receiving antiplatelet therapy in Hong Kong still doubled as those receiving OACs (43% vs 26%) in recent years.[7] Several studies have been conducted to investigate the attitudes on the barriers of using OACs for stroke prevention from the perspectives of patients and physicians and the findings have been consistent in both western and Asian countries.[9-14] However, the perception from the pharmacists remains unclear due to

limited studies in literature. Pharmacists are often the first point of contact in the community and play an important role of promoting the quality use of medicine. Therefore, it is crucial to understand pharmacists' point of view on the issue of under-prescribing of OACs among long-term aspirin users with AF. We performed a local study to obtain some preliminary results.

METHOD

Recruitment and procedure

Participants were eligible to take part in this study if they are registered pharmacists in Hong Kong and have prior experience of dispensing OACs and/or aspirin to patients with AF for stroke prevention. They were excluded if they were unable to communicate in Cantonese or English. Eligible participants were recruited either through recommendations from pharmacy managers or through the word of mouth of researchers' personal network. Patient information leaflets and written consent forms prepared by two researchers (VN and ML) were given to the participants for their consideration once they accepted our invitation. Ethics approvals were sought and obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW18–580).

Interviews between the researchers (VN and ML) and the participants were conducted either face-to-face or through Zoom due to the outbreak of COVID-19. A semi-structured interview guide was developed and validated by our multidisciplinary research team (e.g. pharmacists, cardiologists and geriatricians). The interview questions focused on the understanding of characteristics which patients with AF were more likely to be prescribed aspirin monotherapy from their clinical experience, and their opinions on why doctors would prefer aspirin over OACs. Informed consent was obtained before the interview for each participant. All interviews were audio-taped with participants' permission along with the field notes to record interviewees' facial expressions, speaking tone and emotions.

Data analysis

All interview recordings were transcribed verbatim and anonymized. Data was then analyzed according to the principles of thematic analysis. Each transcript was coded line by line and codes with similar meanings were categorized to form different themes.[15] Data collection and analysis were conducted concurrently so any themes identified from existing data could be followed up when interviewing new patients.[16] Several meta-themes were developed after systematic and repetitive analysis on the sub-themes. Data collection stopped when data saturation was achieved, i.e. where no more new themes were identified. NVivo (QSR International Pty Ltd., Version 12, 2019, Victoria, Australia) was used to facilitate the identification and refinement of patterns and themes. Data was analyzed by two researchers (VN and ML) independently and mutual agreement was reached on coding and themes.

RESULTS

Between January 2019 and March 2020, we had face-to-face interviews with a total of 6 participating pharmacists. Five meta-themes were derived: 1) physical characteristics of long-term aspirin users with AF; 2) concerns from the patients with AF; 3) worries and concerns from caregivers; 4) patients' compliance to the anticoagulation treatment; and 5) role of aspirin in stroke prophylaxis

Theme 1: physical characteristics of long-term aspirin users with AF

More than half of the pharmacists mentioned that patients with advancing age were more likely to be prescribed aspirin instead of OACs and they defined advancing age as 85 years or above. Elderly patients are often fragile. On top of advancing age, multiple comorbidities, high bleeding risk and history of bleeding are also the common characteristics of patients with AF that doctors would consider prescribing aspirin. *("Patients usually have many comorbidities, more often advancing age like at least 85 years or above. They might as well have high bleeding risk, known history of GI bleeding. To conclude, majority of the patients that I have encountered are elderly people and history of GI bleeding, doctors would probably not consider anticoagulation but aspirin instead." **P3**).*

Theme 2: concerns on the adverse effects from the patients with AF

It is well established that bleeding is a common adverse event from OACs. In general, from patients' perspective, bleeding is perceived as a serious complication, which makes patients over-worrying about the occurrence of bleeding. *("Most of the time bleeding is something that patients are scared of. No matter how you assure them that the number (risk of bleeding) is just a theoretical risk and the bleeding symptoms would not be very severe, but patients are usually very concerned. From patients' point of view, bleeding is something very serious, so some of them will refuse once they know bleeding is a side effect." **P1**)*. Furthermore, the signs of bleeding are observable such that patients are aware of

their bleeding situation, which makes them hesitate their decisions on using OACs. *("The signs of bleeding are pretty obvious in warfarin compared to aspirin, such as bruising. Patients would aware that they actually bleed a lot and they feel very panic." **P6**).*

Theme 3: worries and concerns from caregivers

Family members are often the major caregivers of most elderly patients and hence the decision-maker of the treatment agents if any changes are warranted. From the pharmacists' experience, most caregivers they have encountered expressed the concern that it would be difficult for them to help patients comply with their anticoagulation treatment, especially where there are different lifestyle adjustments necessitated by OACs, such as diet restriction, frequent change of dosages, complex dosing regimen, and regular blood tests required. The most common example raised by the pharmacists is the inconvenience arisen from the regular blood tests which are often clashed with their jobs. *("Carers and patients find the regular blood tests very annoying. Since the elderly patients can't come to hospitals by themselves, their family members need to take days off to accompany the patients every 8 weeks. This is a huge challenge to them!" **P6**).*

Theme 4: patients' compliance to the anticoagulation treatment

There are more lifestyle adjustments necessary resulting from the use of OACs compared to aspirin, which might potentially bring inconvenience to patients' daily lives and hence affecting their compliance and adherence to the anticoagulation, particularly warfarin. Half of the pharmacists mentioned that regular blood tests is frequently cited by patients as the reasons of refusing OACs. *("Actually, patients found the blood tests the most annoying and they have to come back every 8 weeks. Younger patients often encounter this problem as they need to work during the day. How would you expect them to come back from 9-5 during weekdays just for the blood tests? So, INR monitoring is the most challenging barrier!" **P6**)*. Diet restriction is another concern from the patients raised by the pharmacists. In a Chinese society, Chinese herbal medicines and regimen have become popular and are often used as complementary and alternative remedy without doctors' prescriptions. There might be potential drug interactions with OACs and Chinese herbal medicines and thus adversely affecting the effectiveness of the OACs. *("I think the biggest challenge is diet. Chinese patients love having Chinese herbal medicines where they can get over-the-counter, or adding some Chinese medicines to the dish. All these might interact with warfarin." **P2**).*

Theme 5: Role of aspirin in stroke prophylaxis

Most pharmacists perceived that aspirin is an alternative to patients with AF only if they are contra-indicated to any of the anticoagulants or insist not to opt for anticoagulation. *("It (aspirin) is better than nothing to patients!" **P1**).* Since aspirin was recommended to patients with low risk of stroke before the clinical guidelines was updated in 2018, they believed that aspirin might have tiny protection when patients did not receive any stroke prevention therapy. However, they also emphasized that current evidence showed the superiority of OACs over aspirin monotherapy and clinical guidelines do not recommend the use of aspirin monotherapy.

DISCUSSION

AF is a common cardiac arrhythmia in elderly people and its prevalence has been increasing with aging of the population.[17] In our study, most participated pharmacists mentioned that advancing age (>85 years old) is an important consideration to prescribe OACs or aspirin to patients at advancing age. Our findings were consistent with current evidence from the qualitative studies.[18] Advancing age is a risk factor of developing multiple comorbidities, bleeding complications, falls and cognitive impairment, which are the common reasons cited by doctors hesitating the prescribing decision of OACs.[18] Therefore, doctors might be more leaning to prescribe aspirin, as reflected from the pharmacists' observations and experience.

Regarding the use of OACs, there is a dilemma between balancing the benefits of stroke prophylaxis and risk of bleeding. From what pharmacists observed in our study, the reluctance of using OACs is often due to the patients' deep-rooted perception of bleeding as a serious complication, which might be arisen from poor understanding of OACs and the importance of stroke prevention.[13] Some patients might be overwhelmed by the signs of bleeding (e.g. bruising, blood in urine) and hence amplify their fear of re-occurrence of bleeding when they are prescribed OACs as suggested by pharmacists in our study. The participated pharmacists also encountered difficulty in assuring the patients on the safety of OACs and this reflected the problem of patients lacking knowledge on the AF stroke prevention management. Therefore, it is crucial to help patients enhance their understanding to their illness and the importance of the treatment.

Similar to the findings from prior studies, the lifestyle adjustment necessitated by OACs is cited as one of the barriers of using OACs, such as diet restriction, regular therapeutic drug monitoring and complex dosing regimen.[9, 10, 13] Both patients and their

caregivers are concerned about the inconvenience arisen from the lifestyle changes and might hinder the adherence and compliance to the treatment. In the recent decade, patients who were newly diagnosed with AF were prescribed NOACs unless contraindication since the introduction of NOACs into the market but this barrier is still a major challenge for people who have been taking warfarin long-term or contraindicated to NOACs.

It is believed that our preliminary findings could shed some light on the needs of clinical pharmacy services and patient education for patients with AF in Hong Kong. Currently, anticoagulation clinics led by multidisciplinary teams have been set up in some of the public hospitals in Hong Kong. In the clinics, pharmacists work with different healthcare professionals to form an interdisciplinary team. Pharmacists play a key role in improving the quality of prescribing OACs by addressing and minimizing any potential drug-related problems, such as checking adherence to treatment, identifying any drug-drug interactions, and dose adjustment of OACs. However, the current scope of service is only limited to patients taking warfarin so long-term aspirin users with AF would not be able to access this service at the moment. Furthermore, pharmacists can also serve as an educator by organizing seminars and workshops for patients with AF and their caregivers, which help establish a strong basis of understanding to their illness and the importance of AF management. Pharmacists in community settings, as the first point of contact of the primary care, could set up a face-to-face or online consultation platform to provide timely assistance to patients with any drug-related enquiries.

CONCLUSION

This study reflected the potential barriers of using OACs from pharmacists' observation and clinical experience and implicated the need for clinical pharmacy service and patient education for patients with AF and their caregivers. Pharmacists are recommended to be more proactive in engaging in clinical services and delivering patient-centered care.

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A Review on the Role of Probiotics in the Management of Type II Diabetes Mellitus

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ABSTRACT

The prevalence of Type II Diabetes Mellitus (T2DM) is increasing at an alarming rate worldwide. Poor management of T2DM could lead to serious complications. Conventional management of T2DM involves various pharmacological treatments and lifestyle modifications. Disrupted gut microbiota has been linked to the pathogenesis of T2DM. Using probiotics as a novel alternative to alleviate T2DM has gained wide attention due to their potential to improve gut dysbiosis. This review focuses on exploring the research trend of the use of probiotics as an adjuvant agent to the drug regimen for glycemic control improvement. We included 10 randomized clinical trials that evaluated the efficacy of probiotics. HbA1c was commonly used as the end-point parameter for evaluation, of which 4 showed a significant decrease. Although minor adverse events were shown in clinical trials, serious side effects should not be ruled out in vulnerable groups of patients. However, a definitive conclusion could not be drawn due to the lack of standardization and specificity in these clinical trials. Further investigation should be done before probiotics are used in the clinical setting.

***Keywords**: Diabetes Mellitus, gut dysbiosis, glycemic control, probiotics*

INTRODUCTION

Diabetes is a main cause of morbidity and mortality in Hong Kong, which accounts for 1.0% of all deaths.[1] It is noteworthy that diabetic patients are exposed to a higher risk of cardiovascular disease, nephropathy and neuropathy.[2] Adequate management of diabetes are crucial to prevent or delay the onset of different complications, thereby improving the quality of life and alleviating the economic burden on the healthcare system.

Type II Diabetes Mellitus (T2DM) is a condition when insulin secretory defect with insulin resistance occurs, accounting for more than 85% of all diabetes cases.[3] Metformin is the most commonly prescribed medication for T2DM under the class of biguanide. It inhibits hepatic glucose output without causing hypoglycemia. Other drug options for T2DM include sulfonylureas, thiazolidinediones, alpha-glucosides inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, dipeptidyl peptidase (DPP)-4 inhibitors, sodium–glucose cotransporter (SGLT)-2 inhibitors, and insulins. Various pharmacological treatments, together with dietary and lifestyle modification are the standard pragmatism to improve glycemic control in patients with T2DM. However, these strategies may have limited efficacy at advanced-stages of T2DM.[4] Therefore, there has been a growing interest in exploring various treatment options for T2DM. Dysbiosis of the gut microbiota is associated with T2DM.[5] Restoration of the disrupted gut microbial community by probiotics to facilitate glycemic management in diabetic patients has been increasingly studied in recent years. Probiotics are defined as live microorganisms that when administered in adequate amounts confer a health benefit on the host.[6] They are commonly used to alleviate gastrointestinal conditions by reducing the colonization of pathogenic bacteria in the gut.[7] The potential health benefits of probiotics in treating or preventing different human diseases, such as irritable bowel syndrome, inflammatory bowel disease, dental

caries, pediatric respiratory infections, and dermatitis have been shown.[8] Despite the broad potential clinical application of probiotics, no probiotic products have been approved by the US Food and Drug Administration (FDA) for the treatment of a specific disease.[9]

Probiotics as a treatment option for T2DM has gained wide attentions in the past decade. Demonstrating the efficacy of probiotics to revert the misconfigured microbial community and to assist in glycemic management in diabetic patients has been the goal of those research. Probiotics might alleviate T2DM through several mechanisms: (i) reduction of inflammation via reduced lipopolysaccharides and pro-inflammatory cytokines in the bloodstream; (ii) improvement of glycemic and insulin metabolism; (iii) decrease in insulin resistance; and (iv) prevention of pancreatic β-cell destruction.[3] Based on the above, the functions and efficacy of probiotics in T2DM are worth studying. This article describes the link between gut microbiota and pathogenesis of T2DM, the underlying mechanisms of the probiotics, and clinical evidence on the efficacy and safety of the use of probiotics in T2DM patients.

RESULTS AND DISCUSSION

Microbiota composition in human gut

The gastrointestinal tract of a healthy adult is harbored with approximately 500 to 1000 species of bacteria, in which 90% of the bacterial species belonging to the phyla Bacteroidetes and Firmicutes. Gut microbiota participates in digestion, synthesis of metabolites, and water-soluble vitamins. Healthy gut microbiota can provide maintenance of intestinal barrier integrity and protection against pathogens.[10]

The ratio of Bacteroidetes to Firmicutes was positively correlated with the reduction in glucose tolerance.[11] *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, and *Roseburia* were identified to be negatively associated with T2DM.[12] A key signature of gut microbiota in T2DM patients is the reduced abundance of butyrate-producing bacteria, especially *Roseburia* and *Faecalibacterium*.[12] Butyrate produced by these bacteria might decrease gut permeability through serotonin transporters and peroxisome proliferator-activated receptor gamma (PPAR-γ) pathways in healthy individuals.[13] Furthermore, a higher ratio of *Bacteroides-Prevotella* group versus class *Clostridia* and *C. coccoides-E.rectale* group was found in T2DM individuals. The increase in *Bacteroides* and *Prevotella* species were associated with metabolic endotoxemia and inflammation in T2DM. The inflammation could elevate oxidative stress, hence causing damage to the pancreatic β-cells that are responsible for the production and release of insulin.[14] Increased abundance of *Bacilli* and *Lactobacillus* group were observed in T2DM mice and obese humans. Evidence supported that the genus *Lactobacillus* could contribute to chronic inflammation in T2DM subjects due to its immunomodulating properties.[11]

Link between gut microbiota and T2DM

The gut-brain axis (GBA) is the major signaling pathway to control glucose homeostasis. Disturbance of this axis is suggested to positively correlated with a T2DM phenotype. Recently, the bidirectional interactions within the GBA were highlighted.[15] The signaling mechanism from the gut microbiota to the central nervous system is proved to be the parallel and interacting channels that involve the nervous, endocrine, and immune systems. The signals are transmitted from the gut microbiota to the brain through neuroimmune and neuroendocrine mechanisms mediated by the vagus nerve. Signaling molecules include gut microbiota metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan metabolites.[16] On the other hand, signals are transmitted from the brain to the gut microbiota via the autonomic nervous system. These signals are responsible for the regulation of gut permeability, gut motility, and luminal release of hormones, modulating the community structure and function of the gut microbiota.[16]

Moderate dysbiosis and pro-inflammatory environment as indicated by the upregulation of microbial genes involved in oxidative stress, increased serum lipopolysaccharides (LPS) concentration and intestinal permeability were the major characteristics of gut microbiota in T2DM.[17] Dysbiosis attributed to environmental and genetic factors might increase intestinal permeability and alter mucosal immune response, which could lead to the onset or worsening of T2DM.[17,18] Butyrate is an important SCFA in attenuating T2DM. Insulin sensitivity and secretion could be improved by butyrate through stimulation of glucagon-like peptide-1 (GLP-1) secretion and reduction of inflammation in adipocytes.[18] Elevated concentration of LPS could activate toll-like receptors, inducing the release of inflammatory cytokines that stimulate the inactive immune system. The increase in intestinal permeability due to reduced expression of tight junction proteins was shown to favor LPS translocation, resulting in metabolic endotoxemia and insulin resistance.[19] Also, increased LPS could activate the nuclear factor kappa-B and c-Jun N-terminal kinase pathways. Consequently, insulin resistance and insulin signaling deficiency in the muscle, adipose tissue, liver, and hypothalamus would be formed.

Proposed mechanisms of probiotics against T2DM

Evidence showed that the intake of probiotics could bring positive effects to the gut microbiota, leading to an increase in the production of SCFAs and improvement of the intestinal barrier function.[18] Species of *Bifidobacterium* and *Lactobacillus* are commonly used as probiotics.[18] In rats, alleviation of T2DM was demonstrated after 12-week supplementation of probiotic *Lactobacillus paracasei* NL41. Pancreatic β-cell loss could be inhibited by this probiotic, enhancing insulin secretion and contributing to hyperglycemia reduction.[20] Moreover, the hypoglycemic property of probiotic *L. paracasei* HII01 reported in T2DM rats might be explained by SCFA-induced AMPK activation and improved inflammation-disturbed insulin signaling.[21] Improvement of intestinal barrier function was considered as a possible mechanism of *Bifidobacterium animalis* subsp. *lactis* 420 to improve glucose tolerance in high-fat diet (HFD)-fed mice.[22] However, the anti-diabetic mechanisms shown by lactobacilli are still limited for bifidobacteria.

Efficacy of probiotics in the treatment of T2DM

To evaluate the efficacy of probiotics in T2DM treatment via modulation of the gut microbiota, a literature search for relevant randomized clinical trials (RCTs) in recent years was conducted. We summarized 10 RCTs as shown in **Table 1** and **Table 2**. Results of the common diabetic outcomes such as glycated hemoglobin A1c (HbA1c), fasting blood glucose (FBG), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG) in the studies were reviewed **(Table 3)**. Also, recent meta-analyses integrating the findings on this topic were included for discussion.

Glycemic outcomes:

HbA1c

HbA1c levels indicate the extent of haemoglobin glycation in red blood cells, which is an important indicator of glycemic control over two to three months.[23] Of 10 RCTs, 4 studies showed a significant decrease in HbA1c when compared to the placebo group. Only 2 studies did not include HbA1c as one of the glycemic outcomes.[24,25] Tonucci (2017) reported a significant reduction in HbA1c in T2DM patients (P= 0.02) when compared to placebo after 6-week consumption of fermented goat milk containing *L. acidophilus* La-5 and *B. animalis* subsp. *lactis* BB-12 at a dose of 10^9 colony-forming units (CFUs)/day for each probiotic strain.[26] This is consistent with another trial which involved the largest sample size (n=136) among the 10 RCTs to investigate the 12-week effect of multi-strain probiotic supplementation containing *L. acidophilus, L. casei, L. lactis, B. bifidum, B. longum,* and *B.* infantis (10^{10} CFUs/

Table 1. Summary of the reviewed randomized clinical trials

Study	Type of trial	Country participated	Patient group	Duration of treatment
Firouzi et al., 2016[27]	Single centre, randomized, double-blind, parallel, placebo-controlled	Malaysia	T2DM diagnosed at least 6 months; HbA1c: 6.5 - 12 %; FBG < 15mmol/L; not on insulin and antibiotics	12 weeks
Hsieh et al., 2018[31]	Single centre, randomized, double-blind, placebo-controlled	Taiwan	T2DM diagnosed more than 6 months; HbA1c: 7 - 10%	9 months
Kobyliak et al., 2018[30]	Single centre, randomized, double-blind, placebo-controlled	Ukraine	T2DM diagnosed for at least 6 months; HbA1c: 6.5 - 11.0%; treated with diet and exercise alone or metformin, sulphonylureas and insulin on a stabilized dose for at least 3 months	8 weeks
Madempudi et al., 2019[28]	Single centre, randomized double-blind placebo-controlled	India	T2DM; on stable metformin 500mg monotherapy for 8 weeks prior to screening	12 weeks
Mobini et al., 2016[32]	Commercially recruited, parallel, randomized, double-blind, placebo-controlled	Sweden	T2DM diagnosed more than 6 months; HbA1c: 6.7 - 10.4%	12 weeks
Palacios et al., 2020[33]	Single centre, randomized, double blind, placebo-controlled	Australia	Prediabetes or T2DM diagnosed within the previous 12 months	12 weeks
Razmpoosh et al., 2019[24]	Single centre, randomized, double-blind	Iran	T2DM diagnosed at least 10 months; controlled glucose and lipid profile levels of participants; without any antibiotic or hormone replacement therapy such as insulin	6 weeks
Sabico et al., 2018[25]	Single centre, randomized, double-blind, placebo-controlled	Saudi Arabia	T2DM diagnosed less than 6 months without diabetes complications; HbA1c: > 7%	6 months
Soleimani et al., 2017[29]	Single centre, parallel, randomized, double-blind, placebo-controlled	Iran	Diabetic hemodialysis patients	12 weeks
Tonucci et al., 2017[26]	Single centre, randomized, double-blind, placebo-controlled trial	Brazil	T2DM diagnosed at least one year	6 weeks

Table 2. Characteristics and methods of the reviewed randomized clinical trials

Study	Sample size & intervention	Microorganisms in probiotics & dose	Delivery vehicle/ Dosage form
Firouzi et al., 2016[27]	Total: n = 136 C: n = 68, one placebo sachet per day Pro: n = 68, one probiotic sachet per day	*Lactobacillus acidophilus* *Lactobacillus casei* *Lactobacillus lactis* *Bifidobacterium bifidum* *Bifidobacterium longum* *Bifidobacterium infantis* (3×10^{10} CFU per species)	Sachet
Hsieh et al., 2018[31]	Total: n = 74 C: n = 24, two placebo capsules per day Pro 1: n = 25, two *L. reuteri* ADR-1 capsules per day Pro 2: n = 25, two heat-killed *L. reuteri* ADR-3 capsules per day	Pro 1: Live *Lactobacillus reuteri* ADR-1: 2×10^9 CFU per capsule Pro 2: Heat-killed *Lactobacillus reuteri* ADR-3: 1×10^{10} cells per capsule	Capsule
Kobyliak et al., 2018[30]	Total: n = 53 C: n = 22, one placebo sachet per day Pro: n = 31, one probiotic sachet per day	*Lactobacillus* + *Lactococcus* (6×10^{10} CFU/g) *Bifidobacterium* (1×10^{10}/g) *Propionibacterium* (3×10^{10}/g) *Acetobacter* (1×10^6/g) 10g per sachet	Sachet
Madempudi et al., 2019[28]	Total: n = 79 C: n = 39, two capsules per day after any principal meal Pro: n = 40, two capsules per day after any principal meal	*Lactobacillus salivarius* UBLS22 *Lactobacillus casei* UBLC42 *Lactobacillus plantarum* UBLP40 *Lactobacillus acidophilus* UBLA34 *Bifidobacterium breve* UBBr01 *Bifidobacterium coagulans* Unique IS2 (5×10^6 CFU per strain)	Capsule
Mobini et al., 2016[32]	Total: n = 44 C: n = 15, one placebo capsule per day Pro 1: n = 15, one capsule of 10^8 CFU *L. reuteri* DSM 17938 per day Pro 2: n = 14, one capsule of 10^{10} CFU *L. reuteri* DSM 17938 per day	*Lactobacillus reuteri* DSM 17938 (10^8 CFU or 10^{10} CFU)	Capsule
Palacios et al., 2020[33]	Total: n = 60 C: n = 30 (14 on metformin), two placebo capsules per day Pro: n = 30 (14 on metformin), two probiotic capsule per day	*Lactobacillus plantarum* Lp-115 (6×10^9 CFU) *Lactobacillus bulgaricus* Lb-64 (3×10^9 CFU) *Lactobacillus gasseri* Lg-36 (18×10^9 CFU) *Bifidobacterium breve* Bb-03 (7.5×10^9 CFU) *Bifidobacterium animalis* subsp. *lactis* Bi-07 (8×10^9 CFU) *Bifidobacterium bifidum* Bb-06 (7×10^9 CFU) *Streptococcus thermophilus* St-21 (450×10^6 CFU) *Saccharomyces boulardii* DBVPG 6763 (45×10^6 CFU)	Capsule
Razmpoosh et al., 2019[24]	Total: n = 68 C: n = 34, two placebo capsules per day Pro: n = 34, two probiotics capsules per day	*Lactobacillus acidophilus* (2×10^9 CFU) *Lactobacillus casei* (7×10^9 CFU) *Lactobacillus rhamnosus* (1.5×10^9 CFU) *Lactobacillus bulgaricus* (2×10^8 CFU) *Bifidobacterium breve* (3×10^{10} CFU) *Bifidobacterium longum* (7×10^9 CFU) *Streptococcus thermophilus* (1.5×10^9 CFU)	Capsule
Sabico et al., 2018[25]	Total: n = 61 C: n = 30, Two placebo sachets per day Pro: n = 31, Two probiotics sachets per day	*Bifidobacterium bifidum* W23 *Bifidobacterium lactis* W52 *Lactobacillus acidophilus* W37 *Lactobacillus brevis* W63 *Lactobacillus casei* W56 *Lactobacillus salivarius* W24 *Lactococcus lactis* W19 *Lactococcus lactis* W58 (2.5×10^9 CFU/g, 2g per sachet)	Sachet
Soleimani et al., 2017[29]	Total: n = 55 C: n = 27, one placebo capsule per day Pro: n = 28, one probiotic capsule per day	*Lactobacillus acidophilus* *Lactobacillus casei* *Bifidobacterium bifidum* (2×10^9 CFU/g per species)	Capsule
Tonucci et al., 2017[26]	Total: n = 45 C: n = 22, 120g goat milk per day Pro: n = 23, 120g goat milk with probiotics added per day	*Lactobacillus acidophilus* La-5 *Bifidobacterium animalis* subsp *lactis* BB-12 (10^9 CFU per strain)	Fermented goat milk

Abbreviation: C, Control group; Pro, Probiotic group

Table 3. Results of the reviewed randomized clinical trials

Study	Results*						
	HbA1c	FBG	HOMA-IR	HDL-C	LDL-C	TG	TC
Firouzi et al., 2016[27]	Within Pro: N/A Between: P = 0.795 (NS)	Within Pro: N/A Between: P = 0.600 (NS)	Within Pro: N/A Between: P = 0.419 (NS)	Within Pro: N/A Between: P = 0.398 (NS)	Within Pro: N/A Between: P = 0.670 (NS)	Within Pro: N/A Between: P = 0.721 (NS)	Within Pro: N/A Between: P = 0.504 (NS)
Hsieh et al., 2018[31]	Pro 1: Within Pro: N/A Between: 3rd month: P = 0.0321 (S, Decrease) 6th month: P = 0.0212 (S, Decrease) Pro 2: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS)	N/A	Pro 1: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS) Pro 2: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS)	Pro 1: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS) Pro 2: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS)	Pro1: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS) Pro 2: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS)	Pro1: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS) Pro 2: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS)	Pro1: Within Pro: N/A Between: 3rd month: P = 0.0467 (S, Decrease) 6th month: P > 0.05 (NS) Pro 2: Within Pro: N/A Between: 3rd month: P > 0.05 (NS) 6th month: P > 0.05 (NS)
Kobyliak et al., 2018[30]	Within Pro: P = 0.068 (NS) Between: P = 0.367 (NS)	Within Pro: P = 0.384 (NS) Between: P = 0.878(NS)	Within Pro: P = 0.047 (S) Between: P = 0.063 (NS)	N/A	N/A	N/A	N/A
Madempudi et al., 2019[28]	Within Pro: P = 0.0150 (S, Decrease) Between: P < 0.001 (S, Decrease)	Within Pro: P = 0.0174 (S, Decrease) Between: P = 0.0169 (S, Decrease)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)
Mobini et al., 2016[32]	Pro 1: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS) Pro 2: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Pro 1: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS) Pro 2: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	N/A	Pro 1: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS) Pro 2: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Pro 1: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS) Pro 2: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Pro 1: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS) Pro 2: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Pro 1: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS) Pro 2: Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)
Palacios et al., 2020[33]	Within Pro: N/A Between: P = 0.73 (NS) Sub-group of patients on metformin: Within Pro: N/A Between: P = 0.036 (S, Decrease)	Within Pro: N/A Between: P = 0.48 (NS) Sub-group of patients on metformin: Within Pro: N/A Between: P = 0.048 (S, Decrease)	Within Pro: N/A Between: P = 0.18 (NS) Sub-group of patients on metformin: Within Pro: N/A Between: P = 0.033 (S, Decrease)	N/A	N/A	N/A	N/A
Razmpoosh et al., 2019[24]	N/A	Within Pro: P = 0.001 (S, Decrease) Between: P = 0.12 (NS)	Within Pro: P = 0.47 (NS) Between: P = 0.43 (NS)	Within Pro: P = 0.002 (S, Increase) Between: P = 0.47 (NS)	Within Pro: P = 0.19 (NS) Between: P = 0.61 (NS)	Within Pro: P = 0.13 (NS) Between: P = 0.79 (NS)	Within Pro: P = 0.52 (NS) Between: P = 0.80 (NS)
Sabico et al., 2018[25]	N/A	Within Pro: P < 0.05 (S, Decrease) Between: P > 0.05 (NS)	Within Pro: P < 0.05 (S, Decrease) Between: P < 0.05 (S, Decrease)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Within Pro: P > 0.05 (NS) Between: P > 0.05 (NS)	Within Pro: P < 0.05 (S, Decrease) Between: P > 0.05 (NS)	Within Pro: P < 0.05 (S, Decrease) Between: P > 0.05 (NS)
Soleimani et al., 2017[29]	Within Pro: P = 0.01 (S, Decrease) Between: P = 0.02 (S, Decrease)	Within Pro: P = 0.01 (S, Decrease) Between: P = 0.006 (S, Decrease)	Within Pro: P < 0.001 (S, Decrease) Between: P < 0.001 (S, Decrease)	Within Pro: P = 0.66 (NS) Between: P = 0.32 (NS)	Within Pro: P = 0.2 (NS) Between: P = 0.86 (NS)	Within Pro: P = 0.53 (NS) Between: P = 0.81 (NS)	Within Pro: P = 0.05 (S, Increase) Between: P = 0.9 (NS)
Tonucci et al., 2017[26]	Within Pro: P = 0.06 (S, Decrease) Between: P = 0.02 (S, Decrease)	Within Pro: P = 0.52 (NS) Between: P = 0.48 (NS)	Within Pro: P = 0.02 (S, Increase) Between: P = 0.77 (NS)	Within Pro: P = 0.5 (NS) Between: P = 0.38 (NS)	Within Pro: P = 0.31 (NS) Between: P = 0.03 (S, Decrease)	N/A	Within Pro: P = 0.52 (NS) Between: P = 0.04 (S, Decrease)

Abbreviation: C, Control group; N/A, Not available; NS, Not significant; S, Significant; Pro, Probiotic group

*The result part summarizes each parameter for (1) the within-group P value for probiotic group (comparison between baseline and endpoint values in probiotic group); (2) the between-group P value (comparison of endpoint values between probiotic group and control group)

day, each).[27] Madempudi (2019) conducted a RCT to understand the role of a multi-strain probiotic capsule, UB0316 (*L. salivarius* UBLS22, *L. casei* UBLC42, *L. plantarum* UBLP40, *L. acidophilus* UBLA34, *B. breve* UBBr01, *B. coagulans* Unique IS2, 5 × 10^9 CFUs each and fructo-oligosaccharides, 100 mg), as an adjuvant to metformin therapy in diabetic management. HbA1c was significantly reduced after 12-week combined UB0316 supplementation and metformin therapy in T2DM patients as compared to placebo.[28] Soleimani (2017) performed a study that focused on T2DM patients with end-stage kidney failure on hemodialysis. The trial lasted for 12 weeks and the probiotic supplement was in form of a capsule containing *L. acidophilus, L. casei,* and *B. bifidum* (2 x 10^9 CFUs/day, each). The result showed a significant reduction in HbA1c (P= 0.02), suggesting that probiotics might have beneficial effects on glycemic control of hemodialysis patients, delaying protein–energy malnutrition and vascular complications.[29]

Theoretically, multi-strain probiotic products would provide better efficacy than that of single-strained. Supplementation of different species of probiotic bacteria in mixtures could establish mutualistic interactions and produce diverse metabolites. This accounts for the greater synergistic effect of multi-strain probiotics in promoting intestinal and metabolic health.[30] However, this assumption is not consistent with the results of the four RCTs that we reviewed. Hsieh (2018) specifically studied the effects of live vs heat-killed *L. reuteri*, and was unable to show a significant reduction in HbA1c in the latter.[31] Another RCT that studied the effect of low dose and high dose of *L. reuteri* DSM 17938 showed no significant difference in HbA1c between the groups at baseline and after 12 weeks of intervention.[32] No HbA1c reduction was demonstrated in two other studies using multi-strained probiotics.[30,33] Interestingly, these two studies included the greatest number of probiotic strains among the 10 reviewed RCTs. Other genera of bacteria were selected in addition to *Lactobacillus* and *Bifidobacterium*. The probiotic formulation adopted in Kobyliak (2018) included *Propionibacterium*, and *Acetobacter* while that of Palacios (2020) contained *Streptococcus* and *Saccharomyces*.[30,33] However, it is noteworthy that HbA1c was significantly decreased in a sub-group of T2DM participants taking metformin and multi-strain probiotic.[33] This result cohered with the findings of Madempudi (2019) that showing probiotics could be adjunctive to metformin for the management of T2DM.[28]

FBG:

Of the 10 RCTs, 8 studied the effect of probiotics on blood glucose by analysing the FBG level. However, a significant reduction in FBG (P= 0.006) was only shown in one study.[29] Although the result of FBG in T2DM patients was insignificant, a significant reduction of FBG was demonstrated after conducting sub-group analysis among patients taking metformin.[33] Nevertheless, controversial findings were seen between meta-analyses. A significant decrease (P< 0.05) and a borderline reduction (P= 0.05) in FBG were found in meta-analyses of probiotic consumption conducted in 2016 and 2018, respectively.[34,35]

HOMA-IR:

The homeostatic model assessment (HOMA) is a frequently used method in clinical studies to assess insulin resistance (IR) from fasting plasma insulin and glucose concentrations. HOMA-IR values negatively correlate with insulin sensitivity and positively correlate with insulin resistance.[36]

Six studies of the selected articles assessed insulin resistance using HOMA-IR, in which only one of them showed a significant reduction in HOMA-IR value when compared with baseline. The study on haemodialytic patients conducted by Soleimani (2017) showed a corresponding significant reduction in both HOMA-IR value and other glycemic parameters such as HbA1c and FBG.[29] Kobyliak (2018) demonstrated a significant reduction in HOMA-IR in the probiotic group from its corresponding baseline but not significant when compared to the placebo group.[30] Conflicting results were found when reviewing meta-analyses of the effect of probiotics on HOMA-IR. A meta-analysis conducted by Li (2016), which included 12 RCTs with 368 participants also showed no significant difference in HOMA-IR between the probiotic-treated group and control group.[37] In contrast, a significant difference was shown when pooling the HOMO-IR data from 4 RCTs (P= 0.002) in another meta-analysis. However, the heterogenicity was reported to be high.[34]

Lipid profile outcomes

Dyslipidemia is a common feature in T2DM patients, which is characterized by elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides levels.[38] Five of the reviewed RCTs assessed dyslipidemia parameters, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides. Only one RCT using multi-strain probiotic-containing goat milk showed a significant reduction in LDL-C (P= 0.03) and TC level (P= 0.04) when compared to the placebo group.[26] The positive results may be in part, due to the high BMI at baseline (placebo group: 27.94 ± 4.15 kg/m^2; treatment group: 27.49 ± 3.97 kg/m^2). The dose of probiotics in this study was comparable to that of other RCTs but showed negative results. Madempudi (2019)

explained the insignificant results in lipid profile could result from metformin-induced lipid-balancing effects at baseline.[28] While dyslipidemia is a multifactorial condition, Hsieh (2018) attributed the negative result in lipid profile to the lack of consideration of cofactors such as diet, exercise, and stress during data collection.[31]

Safety concerns

Although probiotics are generally safe to use in healthy individuals, T2DM patients may be at-risk due to their dysbiotic gut microbiota. There are a few studies conducted to evaluate the safety of the use of probiotics in T2DM patients. A meta-analysis showed 15 out of 28 RCTs had reported adverse events but none of them was serious. Minor adverse events included abdominal cramping, dyspepsia and diarrhea.[14]

The potential risks of probiotic-associated infections and antibiotic resistance are postulated by case reports. T2DM has been identified as a risk factor for lactobacilli infection.[39] A case of *Lactobacillus paracasei*-induced liver abscess and bacteremia in a 65-year-old T2DM patient was reported. Probiotic consumption was believed to be the source of the infection as confirmed by strain identification, suggesting that overdose of probiotics should be avoided in immunocompromised patients.[40] In addition, it was reported that unrestrained consumption of non-specific probiotics with the usage of broad-spectrum antibiotics would increase selective pressure on the gut microbiota, potentially generating multi-resistant bacteria or yeast. The use of antibiotic-resistant probiotic strains might transfer antibiotic-resistant genes to commensal bacteria inhabiting in the gastrointestinal tract. *Lactococcus lactis* was reported to transfer antibiotic-resistant genes to *Enterococcus faecalis*.[41] As a result, the translocation of antibiotic-resistant genes may affect the future choices of antibiotics.

Practice points for pharmacists

Different strains, doses, and treatment durations of probiotics could affect the efficacy. Microorganisms of the genera *Bifidobacterium, Lactobacillus, Lactococcus,* and *Propionibacterium* are the most commonly studied probiotics.[12,14] The proportion of *Bifidobacterium* in the gut microbiota was reported to be lower in T2DM patients than that in healthy adults across different studies.[42-44] However, *Bifidobacterium* is usually combined with other probiotics such as the *Lactobacillus* spps. as the formulation in human trials. It is noteworthy that human studies that dedicated to *Bifidobacterium* spps. are rare, possibly due to its insignificant anti-diabetic effects in T2DM patients when they are used alone.[45]

Probiotics dosage and treatment duration should be considered carefully. Meta-analysis that summarized 17 RCTs showed no association between the daily dose of $<10^{11}$ CFUs of probiotics and change in FBG, insulin or HOMA-IR.[46] Trials using a higher probiotic dose ($\geq 10^{9}$ CFU) was not better in HbA1c reduction when compared to lower dose trials ($p < 0.05$).[47] Thus, taking more than the manufacturer's recommended doses do not provide futher benefits of glycermic control.

Several studies highlighted the importance of the duration of probiotic therapy for diabetes, but statistical analyses are lacking.[48,49] According to Ruan (2015), reduction of FBG and HOMA-IR were only observed in RCTs that conducted more than 8 weeks.[46] The result is in line with another randomized, double-blind, placebo-controlled trial that T2DM patients had a significant reduction in HbA1c after taking probiotics for three months when compared to the placebo group ($P = 0.0494$).[31]

CONCLUSION

This review described the proposed mechanism of action, efficacy and safety profile of probiotic use in T2DM patients. It is believed that probiotics are safe to use and may have certain efficacy in the context of T2DM treatment. Most probiotics mentioned in this review could lower HbA1C, but not have as much effect on FBG or HOMA-IR. Different probiotic regimens are also investigated and the studies mainly focused on the genera *Bifidobacterium, Lactobacillus, Lactococcus,* and *Propionibacterium*. Also, the mixed ratio of these probiotics was adopted across different studies. As most studies used multi-strain probiotics, the efficacy of the individual probiotic bacteria could not be confirmed. Further studies are required to unravel the long-term effects of probiotic supplementation on gut microbiota composition and clinical outcomes in T2DM patients.

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The Activities of the Pharmaceutical Society of Hong Kong

與立法會醫療及衞生界林哲玄議員見面會

六位香港藥學會的代表與立法會議員林哲玄醫生及其顧問醫生們於2022年5月3日進行了一場會議，在會議中討論了藥劑行業目前面對的情況並提出了以下的建議：

1. 藥劑師應可成為醫療券的服務提供者，提供藥物管理服務。
2. 藥劑師可在各層面推動健康教育及檢測等工作。
3. 藥劑師絕對勝任並應參與疫苗注射計劃。
4. 推動公私營合作計劃，將醫管局穩定的病人，交由社區藥劑師配藥及負責藥物管理。此計劃可增加病人服藥的依從性，從而減少藥餘。
5. 對老人院舍的監管應作出深入探討，社署及衞生署應成立跨部門組織，並加強與藥劑師合作，增強藥物管理能力，從而減少重複用藥及病人出入醫院的頻率。
6. 要求醫管局加強臨床培訓，聘請兩所大學的藥劑系畢業生至少兩年，以增加其臨床經驗。
7. 「藥」字應被法例要求為指定字眼，只能只用於藥房。其他無牌商店如藥店、藥妝等不允許使用。
8. 藥行乃以前藥劑師不足時代的產物，現應如診療所一樣不再發牌，使其自然流失。
9. 公營醫療醫院內的藥物補充診所應該聘用藥劑師為穩定病情的長期病人評估藥物及解答藥物上的問題，從而減低醫生的工作量。
10. 醫院的醫療外展隊（現有醫生，護士或物理治療師）應加入藥劑師為病人處理使用藥物上的問題。

立法會議員林哲玄醫生與香港藥學會代表合照(上)；林議員及本會會長沈明達藥劑師(下)

持續專業發展課程

本年度學會的首個香港衞生署外包裝品質授權人持續專業發展課程「基礎藥品包裝」已於2022年7月30日舉行，當日的課程全場滿座。

The Activities of the Society of Hospital Pharmacists of Hong Kong

The 35th Annual General Meeting of SHPHK

The 35th Annual General Meeting (AGM) of the Society of Hospital Pharmacists of Hong Kong (SHPHK) was successfully held on 15th July 2022 (Friday) at The Mira Hong Kong, Tsim Sha Tsui.

Congratulations to all elected General Committee Members! SHPHK will continue to work with different parties, including different medical professional bodies, patient groups, educational institutions, pharmaceutical partners, NGO, etc., to promote health and medication safety in the community.

Prior to the AGM, a lecture on 'COVID-19 Pre-Exposure Prophylaxis for Immunocompromised Patients' was delivered by *Dr. Anthony Raymond Tam*, Associate Consultant and Infectious Disease Specialist, Department of Medicine, Queen Mary Hospital and *Mr. Vincent Wong*, General Committee Member of SHPHK. The Society would like to thank Dr. Tam and Vincent for taking time from their busy schedule to be the guest speakers at this lecture. The recording of the lecture has now been uploaded to the SHPHK website. Members who were not able to attend the lecture physically can now watch the recorded lecture online (Member login required).

SHPHK AGM 2022

From left: Mr. Vincent Wong, General Committee Member of SHPHK; Mr. William Chui, President of SHPHK and; Dr. Anthony Raymond Tam, Associate Consultant and Infectious Disease Specialist, Department of Medicine, Queen Mary Hospital

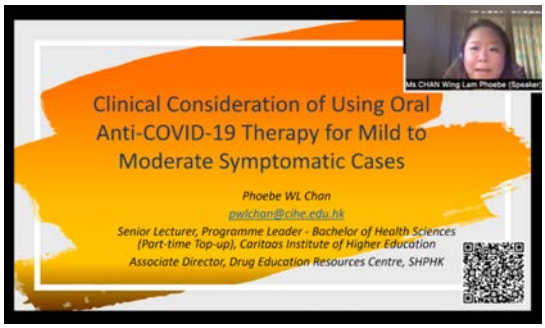
Activities of SHPHK (May to August 2022)

1. COVID-19 Webinar for Dispensers

The Society not only organises educational talks for pharmacists, but also for dispensers, nurses, pharmacy students, other healthcare professionals, teachers, parents and the general public.

A webinar on 'Clinical Consideration of Using Oral Antiviral Therapy for Symptomatic Mild to Moderate COVID-19 Cases' was organised on 28 May 2022. This is the 3rd and final webinar of the COVID-19 series on oral anti-COVID-19 therapy. The aim of this webinar was to equip dispensers with the knowledge and skills to dispense the two available oral COVID-19 antivirals to patients with confidence.

The Society would like to thank *Ms. Phoebe Chan*, Associate Director of the Drug Education Resources Centre for sharing with us her clinical experience in counselling patients on the administration of the two oral COVID-19 antivirals during the 5th COVID-19 wave in Hong Kong.



Ms. Phoebe Chan, Associate Director of the Drug Education Resources Centre

2. Webinar on 'Introducing Personalised Cardiovascular Disease Risk Assessment for Chinese (P-CARDIAC)'

According to the World Health Organisation, cardiovascular disease (CVD) is the leading cause of death globally. Commonly used CVD risk assessment models, e.g., Framingham risk score, Pooled Cohort Equations (PCE), QRISK3 and TRS 2°P, are derived from western populations. To predict and prevent CVD in Chinese population in Hong Kong, a local CVD risk assessment model is needed. Recently, the Innovation and Technology Bureau of the HKSAR Government and four divisions of The University of Hong Kong, namely the LKS Faculty of Medicine, School of Nursing, School of Public Health and Department of Computer Science, have jointly developed P-CARDIAC*, the first personalised, Chinese-specific risk assessment model for cardiovascular and cerebrovascular diseases, aiming to accurately predict the CVD risk of Chinese population in Hong Kong.

A webinar on P-CARDIAC was held on 11 July 2022 to introduce this newly developed CVD risk assessment model to pharmacists. The Society would like to thank *Prof. Ian CK Wong*, Lo Shiu Kwan Kan Po Ling Professor in Pharmacy, Head of Department of Pharmacology & Pharmacy, The University of Hong Kong and *Dr. Sze Ling Celine Chui*, Assistant Professor, School of Nursing, LKS Faculty of Medicine, The University of Hong Kong for providing the latest update on the current CVD situation in Hong Kong, explaining the limitations of the existing risk assessment models and demonstrating how pharmacists could apply the P-CARDIAC model in their daily practice in Hong Kong in the webinar.

* The P-CARDIAC project was supported by The University of Nottingham, The University of London, U.K., and Amgen Hong Kong.

From left: Prof. Ian CK Wong, Lo Shiu Kwan Kan Po Ling Professor in Pharmacy, Head of Department of Pharmacology & Pharmacy, The University of Hong Kong; Dr Sze Ling Celine Chui, Assistant Professor, School of Nursing, LKS Faculty of Medicine, The University of Hong Kong and; Mr. Vincent Wong, General Committee Member of SHPHK.

3. The 30th Annual Scientific Congress of the Hong Kong College of Cardiology (HKCC ACS 2022)

As one of the supporting organisations of HKCC ACS 2022, our President Hon. Assoc. Prof. William Chui and our Member Ms. Amy Chan were invited to share their insights into the clinical considerations of using oral antiviral drugs for the treatment of COVID-19 at the Allied Cardiovascular Health Professional Symposium on 9 July 2022.

On-demand video recordings of the scientific session will be available at the Congress Website (www.hkccasc.com) soon. You may contact the Congress Secretariat directly via email (info@hkccasc.com) for details.

From left: Ms. Amy Chan (Co-Chair), Member of SHPHK; Mr. Man-pan Li (Co-Chair); Dr. Jonathan G Sung (Co-Chair) and; Mr. William Chui (Guest Speaker), President of SHPHK

You are most welcome to follow the Society's Facebook page (@SHPHK) and Instagram (@SHPHK1987) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

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IQPP = International Quality Plasma Program. QSEAL = Quality Standards of Excellence, Assurance and Leadership.

Indication: Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.

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Abbreviated product information (EU Aug17-HK Aug17)
Human Albumin 200 g/l [Baxter/Baxalta] Solution for Infusion
Indication: Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate. **Dosage:** The dose required depends on the size of the patient, the severity of trauma or illness and on continuing fluid and protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required. **Contraindications:** Hypersensitivity to albumin preparations or to any of the excipients. **Warnings and Precautions:** Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented. Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients. Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patient´s circulatory situation. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. Fertility, pregnancy and lactation Clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. **Adverse Reaction:** Nausea, flushing, skin rash, fever, anaphylactic shock, hypersensitivity/allergic reactions, headache, dysguesia, myocardial infarction, atrial fibrillation, tachycardia, hypotension, pulmonary edema, dyspnea, vomiting, urticaria, pruritis, chills

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