

HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

“Fabricating Pharmaceutical Professionalism” —
the Career Prospects and Establishing
Professionalism of Pharmacists in Hong Kong

A New Practice for a New Era: Introducing
Certified Consultant Pharmacist Services in
Hong Kong

Coaching for Pharmacists (4) – Coaching Survey

Ulcerative Colitis and Crohn’s Disease – Current
and New Treatment Highlights

Endospores as Biological Indicator for the
Validation of Sterilization Process

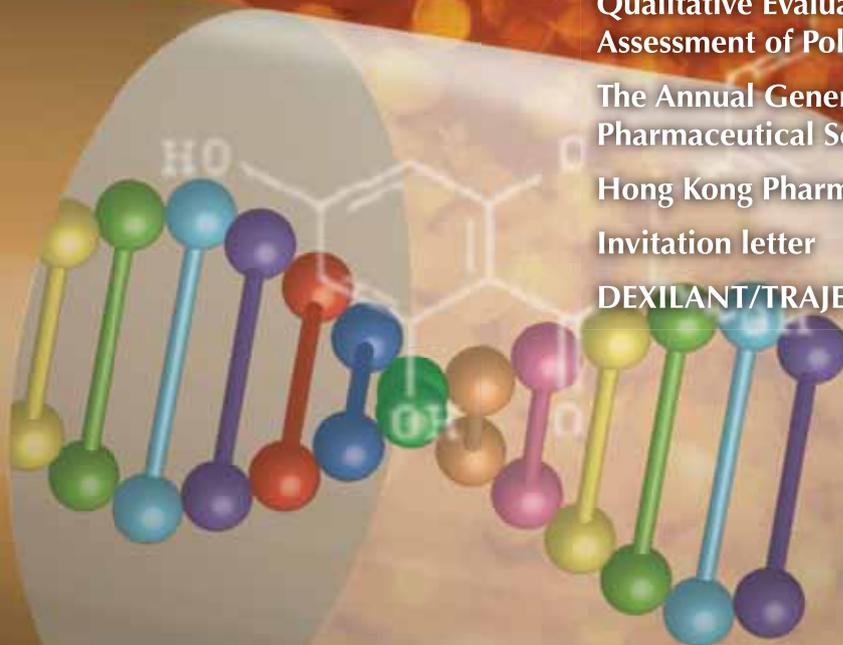
Qualitative Evaluation and Bioactivity
Assessment of *Polygonum bistorta* (拳參)

The Annual General Meeting of the
Pharmaceutical Society of Hong Kong

Hong Kong Pharmacy Conference 2013

Invitation letter

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

The Microbes Return



It's winter time again in Hong Kong! Accompanied by drastic changes in the climate are infectious diseases that are common during this cold season. As early as September 28, 2012, the Centre for Health Protection (CHP) of the

Department of Health (DH) urged the public to heed advice and take preventive measures against infection in this cold weather.⁽¹⁾ Although the winter influenza season has already commenced, the good thing is that, unlike in North America, the latest surveillance data shows that the influenza epidemic is still at the baseline level in Hong Kong. However, proper precautions have to be observed as always.

Nowadays, there are various emerging and re-emerging microbiological threats to public health. According to statistical analysis of news release by DH in the last three months, over 55% was health issues relevant to microbes. This phenomenon indicates that bacterial and viral diseases always pose a threat to a community. It may be iatrogenic or nosocomial infection brought about by implantation of heart pacemakers, prostheses, catheters, and even intravenous injection of drugs contaminated with microbes. These contaminated devices or drugs could lead to septic shock,⁽²⁾ spread of infectious diseases that may be asymptomatic⁽³⁾ or fatal subsequently.⁽²⁾ In spite of the use of antibiotics, transmission of living microbes is a problem for the use of medical devices and therapeutics. Eradication of microbes is not an easy task unless some assurances are incorporated into the sterilization. Biological indicators (BIs) have been recommended by many official compendia as an important tool for the validation of sterilization process. Their applications for the validation purposes have more than forty years' history in many advanced countries. Unfortunately, production of reliable BIs has not been described or disclosed. There are only some guidelines available for their production. Consequently, variations in their performances have been reported amongst different brands and leading to discrepant conclusion. Cheung in his article addressed this problem and reviewed the criteria for the use of spore crops as BIs.⁽⁴⁾

The safety of food and water has long been a public health concern not only in Hong Kong but worldwide. In

particular, water and food have been very vulnerable to be contaminated and become a reservoir of protozoa, bacteria, and viruses. Some people believed that organic foods are safer. Well, it may be true if the health concern is based on the view of residual pesticide. But microbiologically speaking, it is not safe. With the various selections of food hawkers or restaurants in Hong Kong, there has been a difficulty in monitoring food safety even though it becomes a more urgent task but limited number of inspectors is recruited to do the task. In addition, proper hygienic practices and environmental cleanliness should be maintained to avoid food poisoning and to destroy the reservoir of vectors (e.g. mosquitoes, snails, birds) of infectious agents (i.e. dengue virus, influenza virus, *Plasmodium* spp., *Schistosoma* spp. etc) simultaneously. However, up to now, no animal-borne, foodborne or waterborne diseases are completely eradicated. It is, therefore, a very challenging task for all of us to accomplish.

Microbial contamination of drug is another serious threat to public health that should not be ignored. In 2009, the Review Committee of the Regulation of Pharmaceutical Products in Hong Kong had recommended that local manufacturers should be required to conduct microbiological tests for non-sterile drugs in response to the incident of fungal contamination of drugs in the past years.⁽⁵⁾ A new model for microbiological monitoring, including the carrying out of microbiological tests on raw materials, limiting the time whereby the granules can be kept to not more than 48 hours, conducting microbiological tests on finished products and including microbiological testing in the stability studies of all products have been adopted. However, there are some shortages of supply of manpower who is competent to carry out the job as there is no such course offered in Hong Kong.

In another scenario, medical practitioners should strictly observe aseptic techniques in performing medical operations. It is very sad to note that the increasing number of cases of neonatal nosocomial sepsis and the emergence of multidrug resistant microbes (i.e. *Mycobacterium tuberculosis* & Methicillin Resistant *Staphylococcus aureus*) globally are so alarming. Public health education on the proper use and prescription of antibiotics should be strengthened. There are some medical doctors that based their prescriptions solely to the clinical manifestations of the disease rather than doing thorough parallel laboratory diagnostics (i.e. culture and sensitivity

tests) before antibiotic prescriptions. It is pretty good if the condition becomes better, if not, another higher dose of antibiotic is given exposing their clients to different antibiotics leading to multiple drug resistance. Thus, it is a must to establish a rigorous, strict, well-rounded, open-minded, and globally competitive training to maintain professionalism in medical and pharmaceutical practice.⁽⁶⁻⁸⁾ Zhang *et al* also suggested that modern methodologies should be applied to look for new antimicrobial compounds from Chinese Medicines, eg. *Polygonum bistorta* rhizome, as many of them remained unexplored.⁽⁹⁾

In recent years, every government has set their priorities in order to maintain a healthy living environment for their citizens. Most of the government have done their best to avoid whatever health risk for their citizens. They have introduced the most appropriate policy to provide adequate and affordable interventions of epidemic via basic research and promotion of public's awareness on microbial safety from different angles. Given by the fact that population of the world has been increased and most regions are urbanized, emerging and re-emerging of infectious diseases is highly possible. In the light of this trend, there is a need to produce more knowledgeable, well-trained and competent microbiologists with sufficient experiences to handle these unexpected infectious diseases. Strict surveillance systems based on clinical syndromes should be established and enhanced. Data collected should be shared instantly with local, regional, national, and global reference networks.

Cheung Hon-Yeung
Editor-in-Chief
 January 10, 2013

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- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

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

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Editorial

CHEUNG, Hon-Yeung 134

News & Short Communications

Scientific Committee Alerted the Public to the Emerge of a Novel Coronavirus Infection	136
Recall of Proprietary Chinese Medicine with Failed Microbial Limit	136
Three Cases of Septic Shock and Disseminated Intravascular Coagulopathy after Receiving Beauty Treatment	136
Dental Clinic Sorry for Not Proper Sterilization of Medical Devices	136
New Antibiotics for Resistant Bacteria Target DNA Pol III Alpha	137
Woman Arrested for Illegal Sale of Unregistered Pharmaceutical Product on the Internet	137
FDA Panel Endorses Novel Tuberculosis Drug	137
Long-Term Growth Hormone Treatment Ups Risk of Metabolic Syndrome	137
Oral Contraceptives May Increase VTE Risk in Women With PCOS	138
More Bacteria, Fungi Found in NECC Products	138
1,3-Dimethylamylamine Put Under Control as Pharmaceutical Product	138
Omega-3s Benefit Sickle-Cell Patients in Single-Center Study	138
Natamycin Superior to Voriconazole for Fungal Keratitis	139
Drug-Resistant Klebsiella pneumoniae Rises Across the US	139
Cancer Beats All Other Fields for New Drug Approvals in 2012	139
Probiotics Might Limit Infant Skin Problems	139
Pet Shop Raided for Selling Unregistered Pharmaceutical Products with Controlled Drug Ingredient	140
Fluoroquinolones First for Bacterial Keratitis	140
Study Links Milk-Producing Protein to Aggressive Breast Cancer	140
Results of Hong Kong Chinese Materia Medica Standards (Phase V) Announced	140

Pharmacy Education & Practice

"Fabricating Pharmaceutical Professionalism" — the Career Prospects and Establishing Professionalism of Pharmacists in Hong Kong
LEE, Carmen; CHENG, Lily 142

A New Practice for a New Era: Introducing Certified Consultant Pharmacist Services in Hong Kong
CHANG, Iris; SUNG, Christy; CHUNG, Rache; CHEUNG, Kin Man 146

Coaching for Pharmacists (4) – Coaching Survey
CHONG, WK Donald*; HUI, KW Jennifer 148

Drug & Therapeutics

Ulcerative Colitis and Crohn's Disease – Current and New Treatment Highlights
SUIEN, Lap-Hei Henry 151

Pharmaceutical Techniques & Technology

Endospores as Biological Indicator for the Validation of Sterilization Process
CHEUNG, Hon-Yeung 158

Herbal Medicines & Nutraceuticals

Qualitative Evaluation and Bioactivity Assessment of Polygonum bistorta (拳参)
ZHANG, Zhi-Feng; SHEN, Qing; CHEUNG, Hon-Yeung 166

Society Activities

The Annual General Meeting of the Pharmaceutical Society of Hong Kong
Hong Kong Pharmacy Conference 2013
Invitation letter 170

New Products

DEXILANT (Takeda) 174
TRAJENTA® (Boehringer Ingelheim)(Eli Lilly) 174
TROBALT™ (GlaxoSmithKline) 175

Scientific Committee Alerted the Public to the Emerge of a Novel Coronavirus Infection

Date: Sep. 28, 2012

The Scientific Committee on Emerging and Zoonotic Diseases of the Centre for Health Protection (CHP) of the Department of Health concurred after a meeting with the view that

surveillance for the latest spread of a novel coronavirus associated with severe respiratory syndrome is necessary. They urged local hospitals to take appropriate infection control

precautions when admitting patients suspected to have novel coronavirus infection.

Source: www.dh.gov.hk

Recall of Proprietary Chinese Medicine with Failed Microbial Limit

Date: Oct. 3, 2012

Huo Xiang Zheng Qi Wan is used for treating common cold, diarrhea, vomiting, summer heat-stroke and headache. The DH's market surveillance revealed that a batch (batch no. 20120603W) of

the aforementioned pCm was found to have a total bacterial count of 61,000 per gram, which was about six times of the registration criteria. The pCm was manufactured in the Mainland

and imported by a wholesaler for outer packaging before they were sold in Hong Kong.

Source: www.dh.gov.hk

Three Cases of Septic Shock and Disseminated Intravascular Coagulopathy after Receiving Beauty Treatment

Date: Oct. 4, 2012

Three women received treatment with intravenous infusions at a beauty treatment centre developed chills, headache, malaise, abdominal pain, vomiting, diarrhea, chest discomfort,

difficulty in breathing and back pain shortly after receiving treatment. One even developed diarrhoea, vomiting and numbness of both feet and was admitted to RH under intensive care in

critical condition. They were diagnosed to have septic shock and disseminated intravascular coagulopathy.

Source: www.dh.gov.hk

Dental Clinic Sorry for Not Proper Sterilization of Medical Devices

Date: Nov. 5, 2012

The University of Hong Kong has apologized to 250 students, teachers and their families treated with dental equipment not properly sterilized for four days in a row. University Council chairman Leong Che-hung Leung admitted failing to sterilize medical instruments is a serious matter and

he hopes the dental clinic will learn its lesson and prevent similar incidents from happening again. According to reports, some medical instruments at the HKU Health Service (Dental Unit) were not properly sterilized from October 30 to November 2. The dental clinic has since been in touch with 230 of 250 patients to

be tested for HIV and hepatitis B and C.

"It is said that the sterilization process was problematic, but they have followed the entire washing process," said Health Secretary Ko Wing-man.

Source: The Standard

New Antibiotics for Resistant Bacteria Target DNA Pol III Alpha

Date: Nov. 26, 2012

Belgian biotechnology group Galapagos is testing a new class of antibiotics that could be used to combat bacteria that have become resistant to other forms of medication. The group said that its new candidate drug, CAM 1, was tested against more than 250 different bacterial

strains and effectively killed 100% of all drug resistant *Staphylococcus aureus*, including methicillin-resistant *S. aureus*.

Galapagos says the drug works by inhibiting the target DNA pol III alpha,

an enzyme present in all bacteria and essential for their growth; this target is absent in humans. Galapagos said it hoped to enter clinical tests for CAM 1 in 2014.

Source: Medscape Pharmacists News

Woman Arrested for Illegal Sale of Unregistered Pharmaceutical Product on the Internet

Date: Nov. 28, 2012

A 47-year-old woman was arrested in a joint operation by the Police and the Department of Health (DH) in Wan Chai for suspected illegal sale in an Internet auction website of an unregistered

pharmaceutical product which claimed to contain glucosamine. Kirkland Signature Glucosamine and Chondroitin, labelled as containing glucosamine, is a pharmaceutical product which is

not registered with the Pharmacy and Poisons Board. Glucosamine is used as a dietary supplement.

Source: www.dh.gov.hk

FDA Panel Endorses Novel Tuberculosis Drug

Date: Nov. 29, 2012

The US Food and Drug Administration's (FDA's) Anti-Infective Drugs Advisory Committee agreed with Janssen Therapeutics, a division of Janssen Products, LP, that the manufacturer's drug bedaquiline could be approved on the basis of phase 2 data using the surrogate study endpoint of sputum

culture conversion rather than clinical cure because of the unmet treatment need.

Bedaquiline works via a novel mechanism of action: inhibition of a mycobacterial enzyme that is essential to the bacteria's action. The proposed

drug indication is a part of combination therapy for the treatment of pulmonary TB caused by MDR Mycobacterium tuberculosis in adults, to be administered under directly observed therapy.

Source: Medscape Pharmacists News

Long-Term Growth Hormone Treatment Ups Risk of Metabolic Syndrome

Date: Nov. 30, 2012

Adults with growth hormone deficiency (GHD) who take recombinant human growth hormone (rhGH) for 10 years or more are at increased risk of metabolic syndrome, a new study in 98 patients shows.

Given that improving cardiovascular risk is one of the major targets of rhGH therapy for adults with GHD, "the

effects of long-term rhGH therapy on overall cardiovascular profile needs to be established in a larger GHD cohort and should also be compared to healthy controls to control for the effect of aging," Dr. Kim M. J. A. Claessen of Leiden University Medical Center in The Netherlands, one of the study's authors said.

In the short term, rhGH therapy improved several cardiovascular risk factors, such as low-density lipoprotein (LDL) levels and body fat. However, there was some evidence that rhGH therapy could actually increase cardiovascular risk.

Source: J Clin Endocrinol Metab 2012.

Oral Contraceptives May Increase VTE Risk in Women With PCOS

Date: Dec. 3, 2012

Oral contraceptives, largely considered the most effective treatment to relieve symptoms for women with polycystic ovary syndrome (PCOS), might place patients at elevated risk for venous thromboembolism (VTE) events, according to a population-based study.

Risk for nonfatal VTE was 2 times greater among 43,506 women with a diagnosis of PCOS who were receiving

combined hormonal contraceptives (hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.41 - 3.24) compared with 43,506 matched control women who were taking contraceptives but did not have PCOS.

“Physicians should be aware of a potentially synergistic increase in venous thromboembolism risk in women with PCOS taking combined

oral contraceptives,” Steven T. Bird, PharmD, from the US Food and Drug Administrator (FDA) Center for Drug Evaluation and Research, and associates write in a report published online December 3 in the Canadian Medical Association Journal.

Source: CMAJ. Published online December 3, 2012

More Bacteria, Fungi Found in NECC Products

Date: Dec. 4, 2012

US federal health officials have identified additional microbial contamination in products distributed (and since recalled) by the New England Compounding Center (NECC) in Framingham, Massachusetts, the company at the center of the ongoing multistate fungal meningitis outbreak. As of today, 541 cases of fungal infections are linked

to contaminated methylprednisolone acetate injections made by NECC. This includes 363 cases of meningitis (with or without other infection), 153 paraspinal or spinal infections, and 17 peripheral joint infections. Thirty-six people have died.

In an update on their investigation issued today, they report identifying

additional bacteria and fungi in unopened vials of betamethasone, cardioplegia, and triamcinolone solutions. These include *Bacillus* bacteria, and fungal species including *Aspergillus tubingensis*, *A fumigatus*, *Cladosporium* species, and *Penicillium* species.

Source: www.fda.gov/medw

1,3-Dimethylamylamine Put Under Control as Pharmaceutical Product

Date: Dec. 6, 2012

The Department of Health (DH) drew public attention to the decision made by the Registration Committee of the Pharmacy and Poisons Board (the Committee) to regulate 1,3-Dimethylamylamine (DMAA) as a pharmaceutical product with effect from April 1, 2013.

DMAA is known to narrow the blood vessels, which can elevate blood pressure and may lead to cardiovascular

events ranging from shortness of breath and tightening in the chest to heart attack. Products containing DMAA have been gradually banned or removed from the market by overseas health authorities including the US, the United Kingdom, New Zealand, Finland, Canada and Australia.

Based on the recent findings of the potential adverse effects and the

overall risk assessment of DMAA, the Committee decided to regulate DMAA as a pharmaceutical product. Therefore, “Jack3d” and other products containing DMAA must be registered as pharmaceutical products with the Pharmacy and Poisons Board before they can be legally sold in the Hong Kong market.

Source: www.dh.gov.hk

Omega-3s Benefit Sickle-Cell Patients in Single-Center Study

Date: Dec. 7, 2012

Omega-3 fatty acid supplementation may be an effective, safe treatment for sickle cell anemia, the authors of a new single-center study suggest. Patients who took the supplements for a year

were significantly less likely than those on placebo to develop clinical vaso-occlusive events or severe anemia or to require blood transfusion. They also had a lower mean white blood cell count

than the patients on placebo and were less likely to miss school due to their illness.

Source: Am J Clin Nutr 2012

Natamycin Superior to Voriconazole for Fungal Keratitis

Date: Dec. 10, 2012

Topical natamycin, an older drug, was found superior to topical voriconazole for treating filamentous fungal

keratitis as reported by researcher Dr. Thomas M. Lietman from the University of California, San Francisco.

Source: Arch Ophthalmol 2012

Drug-Resistant *Klebsiella pneumoniae* Rises Across the US

Date: Dec. 12, 2012

Klebsiella pneumoniae drug resistance has significantly increased since 1998 for all antimicrobial agents except for tetracycline, according to a study published online December 12 and in the January issue of Emerging Infectious Diseases.

Guillermo V. Sanchez and his colleagues reported a total of more than 3.1 million *Klebsiella pneumoniae*

susceptibility cases for the years 1998 through 2010 in 200 institutions.

“Statistically significant increases in antimicrobial drug resistance to all agents ($p < 0.0001$) except tetracycline ($p = 0.0745$) were observed,” the researchers write. “Resistance to imipenem first appeared in TSN Database-USA in 2004 and rose gradually to 4.3%. In 2010, *K. pneumoniae* resistance to tigecycline

was 2.6%. The largest increases in antimicrobial drug resistance from 1998 to 2010 were observed for aztreonam (7.7% to 22.2%), ceftazidime (5.5% to 17.2%), and ciprofloxacin (5.5% to 16.8%)”, while smaller changes in resistance to tetracycline (14.2% to 16.7%) and amikacin (0.7% to 4.5%).

Source: Emerg Infect Dis. Published online December 12, 2012

Cancer Beats All Other Fields for New Drug Approvals in 2012

Date: Dec. 18, 2012

Eleven new drugs for the treatment of cancer were approved by the US Food and Drug Administration (FDA) in 2012 (so far). Only a few of these agents have been approved in Europe; most are still under review there. These eleven new drugs are:

Axitinib (Inlyta, Pfizer), Vismodegib (Erivedge, Genentech), Pertuzumab (Perjeta, Roche), Carfilzomib (Kyprolis, Onyx Pharmaceuticals), Ziv-aflibercept (Zaltrap), Enzalutamide (Xtandi, Astellas/Medivation), Regorafenib (Stivarga, Bayer), Bosutinib (Bosulif, Pfizer),

Omacetaxine mepesuccinate (Synribo, Teva Pharmaceuticals), Cabozantinib (Cometriq, Exelixis) and Ponatinib (Iclusig, Ariad).

Source: Medscape Pharmacists News

Probiotics Might Limit Infant Skin Problems

Date: Dec. 19, 2012

A few studies in which children at risk for developing eczema were given the bacteria *Lactobacillus rhapsodic* GG or *Lactobacillus rhamnosus* strain

HN001 found that the kids' chances of developing the skin condition were cut in half compared to kids given the placebo supplement. In addition, several other

studies that gave mixtures of probiotics to children also found the risk for eczema was at least halved.

Source: <http://bit.ly/XKg3hy>

Pet Shop Raided for Selling Unregistered Pharmaceutical Products with Controlled Drug Ingredient

Date: Dec. 21, 2012

Sale or possession of unregistered animal drugs is an offence under the Pharmacy and Poisons Ordinance (Cap 138). Upon the investigation of a complaint from a member of the public, the DH found two unregistered animal drugs, namely "Heartgard Plus Tablets" and "Tri-Heart Plus Tablets", both containing the antibiotic ivermectin inside a pet shop in Wan Chai. Hong Kong pharmaceutical

product registration number was not found on the products label. During the operation, the Police arrested the 42 year-old saleswoman of the pet shop for selling "Heartgard Plus Tablets". The two animal drugs are indicated for the prevention of heartworm disease and treatment of other parasite infections in dogs. They are both prescription drugs and should be used under the advice and instructions of veterinary surgeon.

Apart from the above two products, another two unregistered animal drugs, namely "Frontline Plus for Dogs" and "Frontline Plus for Cats", were found in another pet shop. Both Frontline Plus products, containing fipronil, are over-the-counter animal drugs indicated for the treatment of fleas and ticks in dogs or cats.

Source: www.dh.gov.hk

Fluoroquinolones First for Bacterial Keratitis

Date: Dec. 28, 2012

Fluoroquinolones are a good first empiric treatment for patients with bacterial keratitis, according to a recent systematic review and meta-analysis conducted by Dr Marie-Sophie Hanet and CHU Mont-Godinne in the December issue of the Canadian Journal of Ophthalmology.

Fluoroquinolones are readily available and are well-tolerated by patients, the authors write. "Based on these data, it seems reasonable to consider fluoroquinolones as the initial empiric treatment in most cases of suspected bacterial keratitis, and the use of fortified antibiotics being

restricted to eyes unresponsive to initial treatment and to the cases for which a pathogen resistant to fluoroquinolones has been identified," the authors note.

Source: *Can J Ophthalmol.* 2012;47:493-499.

Study Links Milk-Producing Protein to Aggressive Breast Cancer

Date: Dec. 28, 2012

The discovery that a protein that triggers milk production in women may also be responsible for making breast cancers aggressive could open up new opportunities for treatment of the most

common and deadliest form of cancer among women. Found in all breast cells, the protein ELF5 tries to activate milk production even in breast cancer cells, which does not work and then

makes the cancer more aggressive, according to scientists from Australia and Britain.

Source: *PLOS Biology* 2012

Results of Hong Kong Chinese Materia Medica Standards (Phase V) Announced

Date: Dec. 31, 2012

The Department of Health (DH) published reference standards on safety and quality for 42 commonly used Chinese Materia Medica (CMM) in Phase V of the Hong Kong Chinese Materia Medica Standards (HKCMMS) in parallel with the growth of uses

of Chinese herbal medicine., "The development of reference standards not only constitutes an important foundation for the manufacture and quality assurance of herbal preparations, but also has greatly contributed to our understanding of Chinese medicine,"

a DH spokesman said.

The HKCMMS Volume V is accessible at the DH website (www.cmd.gov.hk/html/b5/service/hkcmms/vol5/main.html).

Source: www.dh.gov.hk



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“Fabricating Pharmaceutical Professionalism” — the Career Prospects and Establishing Professionalism of Pharmacists in Hong Kong

LEE, Carmen; CHENG, Lily

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BACKGROUND

Professor Ian CK Wong, the new Head of the Department of Pharmacology and Pharmacy, joined the Medical Faculty in June 2011. He had been studying Pharmacy in the United Kingdom and working in related fields since he was qualified in 1992. He developed interest in pharmacovigilance while looking at adverse drug reactions in his early practice. Devoting much effort in research and investigation, he was later awarded PhD from the University of Manchester for his research work on epileptic medication safety in patients. Professor Wong switched to the academic field after several years of clinical work, undertaking a teaching post as a Lecturer in the University of Bradford; and later Professor in the University of London where he set up the Centre for Paediatric Pharmacy Research. Growing up and studying in Hong Kong before entering the university, Professor Wong has now returned, bringing home the knowledge and experience from the United Kingdom.

The following statements are the dialogues between Professor Wong and the authors:

THE NEWLY ESTABLISHED PHARMACY CURRICULUM

With the first batch of Pharmacy students graduating from our school in June this year, our course has fulfilled the criteria of Pharmacy and Poisons Board of Hong Kong for a full accreditation. Like the counterparts from the Chinese University of Hong Kong, our graduates will also be exempted from the additional examinations of the Pharmacy and Poisons board. This is an advantage to local graduates since overseas pharmacists from, for example, the United Kingdom, Canada, Australia and

the United States, all need to pass the Board's written examination before they can practice in Hong Kong.

Career prospect

Pharmacy graduates will need to complete a year of internship organised in partnership with some future employers, before they can formally practise after their graduation. Professor Wong was optimistic about the prospects of our new graduates in view of the increasing demand for local pharmacists and the proficiency of our students.

Concerns about drug safety and monitoring arisen after scandals of contaminated drug formulations came up in the news in recent years. The Hospital Authority has also listed drug safety as one of the leading objectives to improve continuous healthcare services in the coming year. Due to the related plan to expand pharmacist coverage at general out-patient clinic pharmacies and to enhance aseptic dispensing service, pharmacist vacancies under the Department of Health and the Hospital Authority are expected to increase.

There are high demands for pharmacists in various fields in the community. Graduates may engage in pharmacovigilance under the Department of Health in inspecting the production of medicines, licensing and monitoring the selling of drugs, assessing reports of adverse drug reactions, and other relevant administrative work. They may also be employed under the Hospital Authority in doing dispensing or clinical work. Most of the community pharmacy services are currently provided by private organisations such as Watson's and Mannings' pharmacies, small entrepreneurs or charitable organisation like the Health Bank of the St James' Settlement. The pharmaceutical companies do hire pharmacists in

management and marketing, to ensure a good manufacturing practice (GMP) for quality and safety control in their production lines, but less for industrial research and development in Hong Kong.

Potential employers from the pharmaceutical industries, who co-organised the senior clerkship programmes, gave encouraging comments on our Pharmacy students, acknowledging their crucial skills in applying their knowledge flexibly, thinking creatively, and more impressively the ability in critical appraisal. Professor Wong therefore reiterated his confidence in our graduates, having faith that they will be competent future pharmacists. After all, the intrinsic knowledge and skills acquired during the school years are the qualities that will brace them up for challenges in their lifelong career.

SEPARATION OF PRESCRIBING FROM DISPENSING OF DRUGS

The uniqueness of pharmaceutical science

Medication is an agent encountered by both patient and healthcare provider and is the most frequent intervention used in the healthcare system. Doctors, nurses and many allied health professionals, however, often do not understand the technical knowledge about drug formulation and administration better than the pharmacists do. Disregarding the potential problem risks a loss of curative/therapeutic effect, and possibly causes toxic or even lethal effect in the patients. For this reason, drug-related matter is an exceptional issue that we have to deal with.

The chronically ill may fail to follow the directions of prescriptions due to various reasons. The inappropriate use of inhaler is a common example of low

medical compliance worldwide. In the treatment of asthma, it is common sense for physicians to prescribe medication in form of an inhaler. Yet, the significance of ensuring the proper way to apply the drug is often overlooked. Besides, particle size, spray generation, types of inhaler and other technical details in the formulation can also considerably affect the efficacy of the drug. Bearing in mind all the scientific bases behind, pharmacists in the United Kingdom are responsible for selecting suitable inhalers for the patients following a prescription. For example, auto-haler is more suitable for children since it does not require sophisticated hand-mouth coordination for administration. Medical doctors also value the professional recommendations of the pharmacists in planning for patient care.

While medical doctors are more specialised in making diagnosis, nurses are more focused on practical patient care; the pharmacy, pharmacology and formulations of medication are all unique for pharmacists who emphasises on a better use of medicine. When formulations are improved in account of the patients' and even their caretakers' perspectives, pharmacists' job can become more meaningful and humane than expected.

Drugs can often be absorbed via multiple routes such as oral, buccal, sublingual, subcutaneous, intramuscular, intravenous... Yet, not all forms are equally able to administer at times; just as the use of intrathecal drugs requires physicians' professional skills, and the application of rectal suppositories may not be acceptable in public areas. For instance, rectal diazepam for alleviating prolonged seizure is neither dignified nor convenient to use under many circumstances. New formulation of buccal midazolam was therefore invented as an alternative. Other routes of administrations including ingested, injected and inhaled formulae are also devised for different drugs and indications.

In one of Professor Wong's encounters during his practice in the United Kingdom, a mother was almost losing her child with an overdose of manually measured epileptic drugs. It was a terrifying experience for her to see that in addition to the cessation of seizure, her kid's respiration also faded. The child would have been gone if no appropriate treatment was not available. Quoting Dr Jacobus KF Ng, Honorary Associated Professor of the department, "Dangerous drugs should not be made too accessible

due to the increased hazard of misuse." Pharmacists, who work on research and development for better use of medicine, therefore include safety measures in their designs. As one of the pioneers, Professor Wong started the development of standard dosage oral prefilled syringe for buccal midazolam. Not only is it more convenient for caretakers to handle, its preparation is also available in age-standardised dosages. Once the correct ampoule is taken, any careless overdosing can be prevented even in the hand of non-professionals.

Prescribing error and drug safety

A study in the British Medical Journal reported the frequency of medical error in different countries. Despite the fact that there may be under-reporting, the average rate of errors is almost over 10% worldwide. One person in ten being the victim of a medical error is certainly not low! Vincent et al, (2001) estimated that one in two errors they examined were avoidable, while more than one third of them had resulted in serious sequelae such as death or disability.

Junior doctors are only allowed to perform surgery under the supervision of senior surgeon for safety reasons. Yet, any qualified doctors will have the right to make prescriptions independently. In fact, when talking about drug safety, any fault in the prescription, dispensing or administration could put the patient at risk. Current clinical guideline has incorporated a lot of safety measures to reduce drug-related medical error. One famous example is the "3 checks and 5 rights" in dispensing.

Yet, we have to admit that nobody can play God. Human error is inevitable. As all control measures fail, the "Swiss cheese theory" [1] demonstrates how the confluence of errors causes an undesirable healthcare outcome. And these are often accompanied with painful memories. Vincristine, as part of the chemotherapy for leukaemia, is supposed to be given by infusion. Intrathecal administration [2] is irreversible and fatal. Not until the National Health Service of the United Kingdom investigated on the death of a recovering 17-year-old boy [3], who died from his last course of chemotherapy; red flag on the potential hospital-based errors was raised.

A study [4] commissioned by the General Medical Council of the United Kingdom reported the prescribing error rate of around 8% in hospitals which is comparable to general practices. Even though it is quite clear that practitioners

take their prescribing very seriously, one in 20 prescription items had some sort of mistake and more than one in six patients who are put on medication are given a prescription containing an error. Even though most errors fell into oversights rather than mistakes, all practising doctors are equally susceptible due to their typically heavy workload. A good division of labour with pharmacists and a good medicine management system can avoid a lot of problem.

Clinical pharmacists are therefore here to spot and put right any errors when drugs are dispensed, making sure that the drug, dosages and route of administration are appropriate. They also take more comprehensive medication and allergic history to avoid duplication, possible drug interactions and adverse effects; and recommend alternative management plan in case of treatment failure or unbearable side effects in the patient. The role of pharmacists, as professionals excelling in the use of medicine, setup one more line of defence for potential medication offences in a hospital setting.

On one hand, drugs can be powerful and useful; on the other hand, they can be dangerous if mishandled. Healthcare directors worldwide, thus, consider medication safety as one of their priorities. There are certainly rooms for improvement in our hospital settings. By actively refining the second line of defence and proactively evaluating the existing challenges, the healthcare team is able to keep a vigilant eye in screening out the potential threat to the patients.

Role of pharmacists in primary healthcare

As healthcare has entered an era of specialisation, pharmacists will take care of the drug management of the patient, while doctors spend more time on their diagnostic specialty or other complicated diseases. This is also the approach adopted by many foreign countries in managing chronic diseases. Supplementary prescribers in the community provide prescribed drugs within sets of protocols. On the other hand, independent prescribers can treat wherever appropriate on top of a diagnosis, say, hypertension.

Professor Wong believed separating pharmacy from medicine is good, in simple terms, to scrutinise the best for our patients. To many physicians, making prescription is simply a standard

solution that comes with the diagnosis. The difficulties that patients experience might not be obvious if not particularly raised. Sometimes, the superior figure of medical doctors further prevents patient to confess their non-compliance, for example, in taking anti-diabetic medication. Community pharmacist not only refines the therapeutic solution for the patients, but also acts as a familiar person in dealing with omission, compliance and common adverse drug reactions that matter. For instance, constipation after taking anticholinergic drugs can be very distressing in the elderly who fails to seek a solution.

Community pharmacies are a more accessible and cost-effective mean to deliver primary care compared to public or private clinics. In the United Kingdom, pharmacists also take on several roles in primary and secondary preventions, including the regular monitoring of blood pressure and blood glucose level. These roles, at the same time, facilitate the long-term drug management of chronic patients in the locality. With government subsidies and reimbursement rewarding healthcare professionals in doing primary prevention, even smoking cessation programmes are moved out to the local pharmacies so as to alleviate the heavy workload in the hospitals.

Conflict of interest

In the United States, people don't really find drug sellers credible due to the conflict of interest between "gaining a profit from the business" and "providing the best drug to heal". In Hong Kong, such variance just happens to occur in the role of doctor. To many local citizens, medical consultation has to come with the corresponding medication which is thought to be included in the service charge. Unwittingly, it has become a routine practice which is very different from that in many Western countries. In the United Kingdom, doctors do not usually hand out drugs. Even if a dispensary is included in a clinic, a pharmacist will be solely in charge of the work.

You like it or not, local practitioners nowadays do prescribe quite a lot of items in a single consultation; though it is debatable for whether all listed in the prescription are necessary. As the mainstay of the healthcare profession and medical morality, the equitability of doctors' practice is seldom being challenged; even so, doctors are trained to be diagnostic specialists. They are not supposed to rely on drug profits for

their living, but should ingenuously be paid for their professional service of the medical consultation.

Whatever is the idealism, the reality is that doctors have already had a considerable share well-established in the drug market. There are by no means local pharmacists, who started sowing late, could survive from the ripe in others vineyard. They have no choice but to conglomerate the selling of necessities and groceries alongside with their pharmaceuticals.

In case of separation of prescribing from dispensing of drugs, pharmacists will dispense according to a prescription. They will have no control of what is being prescribed but only on what is being dispensed. As doctors prescribed, neither will they have control on the dispensing of drugs. The strategy safeguards the independence of both physicians and pharmacists while upholding the interdependence within the healthcare team for a common goal – the best treatment option for our patients.

The ageing population in Hong Kong

Growing up in Hong Kong, Professor Wong is genuinely amazed by Hong Kong's healthcare system in serving the enormous demand with such limited resources available. "The system has gradually evolved to a highly efficient one over the years," he said. But he did admit that in order to follow the sociodemographic changes in supporting the aged and one of the densest populations in the world, we have to establish a self-sustaining system.

In view of the ageing population, the healthcare system is anticipating an increase in demand on geriatric medicine. While more chronic diseases are foreseen, the upcoming complicated patients with multiple diseases are expected to give our healthcare workers more challenges ahead. Polypharmacy for the management of hypertension, stroke, renal disease, arthritis, diabetes... all require sophisticated monitoring to fine tune the drug dosages and look out for duplication and drug interactions. Yet, the high administration cost makes frequent hospital-based follow-up inefficient. Subsequent failure in secondary and tertiary disease preventions put further burden to the healthcare system, spiralling into a vicious cycle.

With reference to the example of the United Kingdom, continuous care that bases in the primary sector might make

things work better. Regular follow-ups with general practitioners or community pharmacists, who evaluate the efficacy of the repeated prescription, ensure a better use of medicine for disease management. Specialised clinics, such as warfarin clinics in some general out-patient services, have already been setup in Hong Kong as the pilot scheme to transfer the management of chronic diseases back to the community.

Alongside with the development of more ancillary services and facilities, like community centres and residential care homes, for the elderly, there will be increased need for local talents in providing professional pharmacy services; as it is unwise and unrealistic to allow untrained people to deal with all these drug issues. Since the proportion of senior citizens is growing steadily, changes might have to come faster to cope with the increasing need in the near future.

MOVING FORWARD TO PHARMACEUTICAL PROFESSIONALISM

Teamwork between different healthcare professionals

The current healthcare system in Hong Kong is like an ellipse constructed around two foci – the patients and the doctors. While the latter give, the former take. Nonetheless, no matter how serious the medical issue is, it seems to have nowhere to go but eventually come back to the doctors for a solution; or at least need a nod from them to proceed on certain simple procedures. Under such circumstances, resources could only circulate around the limited capacity within doctors' reach. This is undesirably risky owing to the workload from the large deal of acute cases they have to handle. A better distribution of resources with healthcare specialisation is needed.

Hong Kong has already got the talents and resources to maintain its healthcare system, but we need a better order to raise satisfaction and reduce burnout. In the United Kingdom, work not essential for the doctors, for example a treatment plan workable with nurses or pharmacists, is divided among other members of the healthcare team. This also promotes the rapid development in nursing, pharmacy and other allied health professions to a comparable status. This way, independent but related healthcare services would become more patient-oriented.

In Professor Wong's 20 years of pharmaceutical practice, he had never had a major conflict with the doctors. He appreciated that contributions from the nurses, pharmacists, and other allied health professionals are complementary to each other. With the cultural immersion in our Medical Faculty, division of labour within the healthcare team, yet, working together in coordination is perhaps not a dream. As also valued by our Dean, Professor SP Lee, our Medical School has gradually evolved to accommodate medical, nursing, Chinese medical and pharmacy students. Engagement from various international conferences, academic programmes, projects to day-to-day life has promoted mutual understandings between students, nurturing humble and receptive future healthcare professionals that could lay down their enormous ego to work as a team. Only by balancing and spreading the workload within the healthcare team, the system can be more sustainable.

How can the healthcare system transform

Examples from foreign countries

As a common phenomenon in most developed regions in the world, the ageing population defines the trend of future healthcare services; and changes in healthcare have been initiated in many foreign countries, like the United Kingdom, decades ago. While these forerunners serve as valuable references in guiding our current reform, it is, nonetheless, important for us to recognise the fundamental differences between the healthcare systems due to the distinct sociocultural and socioeconomic aspects.

In the United Kingdom, since the National Health Service is the largest player in the market, the government would certainly have the power to standardise the service charges at a reasonable price. On the other hand, healthcare services in Hong Kong are distinctly provided by the public and private sectors in which many primary care services are private. It should be understood that no service under capitalism will survive without adequate funding. It is, however, unsound to put healthcare on a consumer-driven service model which would end up with a lot of ethical and legal issues. Instead, a healthy physician-patient relationship should be built on mutual trust and medical professionalism.

The healthcare sector actually knows what has to be done and is also ready

for the change. But the general public is used to the overlapping roles between the doctors and the pharmacists. It is crucial to rectify such a deep-root concept and address the emerging worries as new policies and practices are implemented.

Empowerment to primary care

Effort has already been put to enhance pharmaceutical services. For instance, the Hong Kong Pharmaceutical Care Foundation provides professional pharmacy services to residential care homes for the elderly, in accordance to the ordinances and guidelines of the Social Welfare Department and the Department of Health. Besides, the charity project "Pharmaceutical Care Service for Patients", jointly organised by St. James' Settlement and the Society of Hospital Pharmacists of Hong Kong, also provides pharmaceutical care service to chronic patients and their family in the community on a voluntary basis. Some community pharmacists even volunteer to participate in home visits to elderly that lives alone.

In view of the huge demand for primary healthcare, these movements might become drops in the ocean only unless the relevant services are strengthened as a whole. Not only is it important to stretch the potential of individual professions, it is also worthwhile to extend teamwork conventionally in the hospital to the community in providing all-rounded primary care. What most private organisations have done, despite of their scattered pattern, was promising. What follows really depends on how the policy makers would understand the roles of different healthcare professionals, put the bits of sand together and empower them to work towards cost-effectiveness and sustainability.

CONCLUSION: THE NEW GENERATION

With the lot of breakthroughs made nowadays, it is important for us to keep up with the changes and be open to new ideas. Professor Wong also reminded us not to overlook our unique influence to the pharmaceutical development in mainland China. As a matter of fact, pharmaceutical industries, even pharmacy trainings, are less developed in East Asia than elsewhere. The emergence of local pharmacists following the set-up of Pharmacy courses two decades ago in the Chinese University of

Hong Kong and now in the University of Hong Kong was the first step.

"Hong Kong is the place. We have the freedom for development." Professor Wong sees the potential of Hong Kong to become the leading academic and research centre of Pharmacy in Asia. The Hospital Authority has been good in managing the local pharmacy system. Drugs from Hong Kong are less expensive than that from China because of a better budget control in the advanced system.

He further explained his point of view by extending to the electronic patient record system currently accessible in public hospital clusters. The idea and technology are mature. Promotion of "Public-Private Partnership" in the healthcare reform can further connect the existing Electronic Health Record (eHR) system among clinics, private and public hospitals. Valuable patient information can then be better circulated for various epidemiological studies and research in the future.

Witnessing the development of healthcare system in Hong Kong with the setup of Hospital Authority, and growing numbers of local doctors and nurses, Professor Wong looks forward to see his students establishing themselves and exerting to serve the community.

* (This article was originally published in Elixer 2011, University of Hong Kong)

Author's background

Both Miss LEE, Carmen and CHENG Lily are currently doing their medical professional trainings in the Faculty of Medicine, University of Hong Kong. They are belong to class M15.

Quotations

1. The Swiss cheese model, propounded by British psychologist James T Reason, compares human systems with multiple slices of Swiss cheese that stacked together side by side. The holes in the cheese slices represent individual weaknesses in the system. The system as a whole produces failure when the holes in the cheese align.
2. There were about 50 reported incidence of such error worldwide.
3. A 17-year-old boy receiving the last dose of vincristine for his leukaemia chemotherapy:
(1) A nurse just happened to have given him something to eat that morning, but have not noticed the empty stomach requirement of his chemotherapy.
(2) Since the boy needed to starve again, the chemotherapy treatment was delayed till most regular medical officers were off.
(3) A junior doctor, who started a new duty in the ward, injected vincristine intrathecally.
(4) Identical intravenous and intrathecal port increased the chance of medication error.
(5) The cytotoxic effect of the drug killed his brain cells and he died after a few days.]
4. "Study reveals scale of errors on doctors' prescriptions". The Guardian. 2nd May 2012.

A New Practice for a New Era: Introducing Certified Consultant Pharmacist Services in Hong Kong

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A NEW ADVANCED PRACTICE FOR A NEW ERA

In the 21st century, pharmacists in many parts of the world have advanced from the traditional roles of dispensing and counselling to expanded roles in providing advanced levels of direct patient care. As part of the advanced pharmacy practice learning program of the Global Drug Safety Conference and Exposition - Hong Kong 2011, The Drug Safety Consortium, The Practising Pharmacists Association of Hong Kong, the Hong Kong Academy of Pharmacy, and American Society of Consultant Pharmacists introduced the advanced practice of Patient-Centered Quality MTM (Medication Therapy Management) TM as a leading-edge international gold standard for managing the medication therapy management needs of patients.

NEW ROLES FOR PHARMACISTS

In advanced countries such as US and Australia, pharmacists in a new advanced role of the Certified Consultant Pharmacist have been playing an instrumental role in providing innovative ways to enable patients to become more willing and able to make safe and optimal use of medicines. Certified Consultant pharmacists, by nature of their work, need not be responsible to stay inside pharmacies to dispense medications, but may work outside of the pharmacy to provide advanced consultancy services including outcomes-based medication therapy management (MTM) and therapeutic lifestyle change (TLC) advisory services to patients. Therefore, consultancy pharmacy is considered as an advanced form of pharmacy practice by the global healthcare community and registered pharmacists, around the world, that may aspire to specialize in consultancy pharmacy practice are required to obtain further training and certification on the advanced practice of consultancy pharmacy practice to ensure that the highest attainable quality

of consultancy services are consistently provided to the public at large.

NEW CONSULTANCY PHARMACY PRACTICE MODEL OF "MTM"

The Origin of "MTM" in the USA

As the needs of the society evolve, patients expect more value from the services provided by the pharmacist. In the past decades, pharmacists in the USA and other advanced countries began to expand their traditional roles of dispensing and counselling and began to provide advanced consultancy services aiming to achieve optimization of medication therapies to achieve desired therapeutic goals.

Due to the lack of a standardized service delivery model for consultant pharmacists to provide health and medication management advisory services to the public, the quality of the advice provided by the consultant pharmacists could not be effectively measured and evaluated to generate best value for patients using those services.

With the aim to develop a standardized pharmacy consultancy service delivery model for pharmacists to follow, the American Society of Consultant Pharmacists started to work with other national pharmacy associations in the USA to develop a brand new medication therapy management advisory service model called "**MTM**" (*Medication Therapy Management*) and established a core elements framework, standardized processes, and consensus definitions so that the pharmacy profession could offer a consistent approach for providing "MTM" services to all patients who might receive those services.

Consensus definition for "MTM" was achieved in July 2005 and the core elements for providing "MTM" services were established in 2006 to "maximize both effectiveness and efficiency of "MTM" service delivery across pharmacy

settings in an effort to improve quality of care and patient outcomes.

The published definition of "MTM" below has become a standard for the USA and overseas pharmacy profession to follow: **Consensus Definition of MTM:** "*MTM is a distinct group of services that optimize therapeutic outcomes for individual patients. MTM services are independent of, but can occur in conjunction with, the provision of a medication product. MTM services encompass a broad range of professional activities and responsibilities of the qualified pharmacist.*"

Since 2006, MTM consultancy services has become a standard pharmacy consultancy service reimbursed through the Medicare and Medicaid government health programs. Since the invention of the initial "MTM" model in the USA, great efforts have been made by the pharmacy profession to improve the original practice model to more advanced levels to attain better performance results through ensuring consistency in certification standards of MTM consultant pharmacists, improving MTM service effectiveness in the ability to achieve outcomes, attaining a higher level of patient-centered quality, and achieving greater customer satisfaction.

The advanced form of "MTM" was developed as the "**Patient-Centered Quality MTM (Medication Therapy Management) TM**" model with an aim to provide the highest attainable level of quality and performance outcomes to any patient that may be provided with professional services from Certified MTM Consultant Pharmacists.

Pioneering of Certified MTM Consultancy Services in Hong Kong

In order to professionally and properly introduce the Certified MTM Consultant Pharmacists Services to Hong Kong and to duly respect the copyrights and intellectual property rights of

the American Society of Consultant Pharmacists as the key originator of the MTM practice model, the American Society of Consultant Pharmacists was appointed to provide official certification training, in accordance to the internationally recognized certification standards of MTM practice, for the first teams of Certified MTM Consultant Pharmacists in Hong Kong in 2011.

The first teams of Certified Consultant Pharmacists, having obtained official certification in the advanced practice of Patient-Centered Quality MTM TM, have started their new professional practice to provide internationally recognized and high quality medication therapy management services to the public in Hong Kong through the “**I Love MTM**” Program (TM). In this issue of the Hong Kong Pharmaceutical Journal, we are thankful for the contribution from the advanced professional practice of Cheung, Chung, and Law, Certified Consultant Pharmacists to share some of their very interesting experiences in the “I Love MTM” Program (TM) patient consultations for our professional learning.

Examples of Patient Benefits from the “I Love MTM” Program (TM)

Patient-Centered Quality MTM (TM) Case Study

A 43 year-old woman presented with newly diagnosed diabetes was prescribed by her doctor metformin three times daily with meals to manage her diabetes condition. After the patient reported prolonged diarrhea after starting metformin therapy, her doctor stopped her metformin therapy and started her on sitagliptin 100mg once daily. After starting sitagliptin therapy, the patient experienced discomfort and dizziness. After attending a diabetes education seminar, the patient learned that diabetes in its early stages may be controlled with diet modification and weight management. In view of the intolerance to her prescribed medication therapy, she decided to stop the medication therapy on her own and started herself on a low calorie diet.

After not achieving much success in weight reduction on her own, the patient asked for the advice of the Certified MTM Consultant Pharmacist through the “I Love MTM” (tm) Program. During the MTM Patient Interview Meeting, the patient insisted on not wanting to take any medications for her diabetic condition. Therefore, it was agreed between the

patient, her doctor, and the Certified MTM Consultant Pharmacist that the MTM goals should focus on achieving personalized Therapeutic Lifestyle Change objectives for the optimal management of the diabetic condition.

Through the use of Motivational Interviewing⁽¹⁾ processes, the patient was able to demonstrate significant behaviour changes to result in increased exercise activity and achievement in weight reduction. With the additional use of an easy-to-manage healthy eating diet plan designed by a Registered Dietician and follow-up by the MTM Consultant Pharmacist for a period of 6 weeks, the patient was able to achieve the desired BMI (Body Mass Index) and reached target glycemic control. When the patient returned to the doctor for a follow-up visit, the doctor reviewed her HbA1C and regular blood glucose testing results. It was agreed by the doctor and the patient that it was no longer necessary for the patient to take any medications for her diabetes condition, mainly due to her success in maintaining healthy diet and regular exercise activity. The patient was delighted to hear of the good news from her doctor and thanked the professional team of the “I Love MTM” (tm) Program for the support over the six week regimen.

TAKE HOME MESSAGE

Respect for the patient’s preferences in deciding their choice of health management and medication therapies is of paramount importance to the success of the Patient-Centered Quality MTM (TM) Consultation Services.

In this case study, the adverse drug reactions experienced by the patient may result in the patient’s refusal to accept prescribed drug therapies to treat her diabetic condition. Therefore, it was important for the Certified MTM Consultant Pharmacist to address both the patient’s biological needs as well as psychological reactions in the design of personalized diabetes management strategies.

In the general case of diabetes patients, the inclusion of TLCs (Therapeutic Lifestyle Changes) and the effective use of Motivational Interviewing techniques would be one of the most important elements in the MAP (medication action plan) to support patients to achieve optimal control of the diabetes condition.

The “I Love MTM” Program (TM) seems to be able to offer a new choice for patients that may need more innovation in the kind of support provided by healthcare professionals that are willing and able to work according to the patient’s preferred choice of health and medication management therapies.

You Can Also Join the “I Love MTM” Program (TM)

Registered Pharmacists in Hong Kong can become a Certified MTM Consultant Pharmacist and support the “**I Love MTM**” Program (TM) after obtaining the required advanced practice training and fulfilling the internationally recognized certification standards in the practice of Patient-Centered Quality MTM (TM) consultancy practice. As with overseas counterparts, Certified Consultant Pharmacists are required to comply with the Consultant Pharmacists Code of Ethics and have professional indemnity insurance necessary for consultant pharmacy practice to protect the best interests of patients.

The next Certification Training for Pharmacists on Patient-Centered Quality MTM (Medication Therapy Management) TM conducted by trainers from the American Society of Consultant Pharmacists is scheduled to be in June 2013 in the location of Hong Kong. Please contact the registration team for more information at hkconsultantpharmacists@gmail.com

Authors’ background

CHANG Iris is a registered pharmacist in HK and USA and is currently the President of The Practising Pharmacists Association of HK. She is currently practising as a community pharmacist and a Certified Primary Healthcare Consultant Pharmacist in HK. She has championed many pharmacy advancement initiatives, including MTM (Medication Therapy Management), Patient-Centered Quality Primary Healthcare, and the Global Drug Safety Day. She has received recognitions on a local and global level for her contributions and recently has been awarded with an Honorary Membership from the Royal Pharmaceutical Society in the UK. **SUNG, Christy** is a Registered Pharmacist in both HK & USA. He was trained as a PharmD in the States. **CHUNG, Rache** and **CHEUNG Kin Man** are Registered Pharmacists in HK & in Aust/NZ. Both of them are Certified MTM Consultant Pharmacist (ASCP).

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Coaching for Pharmacists (4) – Coaching Survey

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ABSTRACT

In recent years, coaching has been getting more attention due to the benefits it brings to personal and organizational development. However, not many pharmacists in Hong Kong may be aware of the concept of coaching. A survey was therefore conducted to investigate pharmacists' experience of and attitude towards coaching. This article will highlight the results and analysis of the survey, the obstacles of coaching amongst pharmacists in Hong Kong, the benefits of coaching in hospital, community and industrial settings, and ways to make pharmacists change.

Keywords: *coaching; pharmacists; coaching survey; obstacles; benefits.*

INTRODUCTION

In the last quarter century, pharmacy has expanded its role within the health care delivery system from a profession focusing on preparation and dispensing of medications to patients to one in which pharmacists provide a range of patient-oriented services to maximize the medicine's effectiveness. The constantly changing environment of the pharmacy profession requires pharmacists to be equipped with essential skills and competencies to cope with all the challenges and uncertainties. Coaching does not only bring personal and organizational benefits, but also leads to better healthcare for patients in the community.

As discussed in the previous article Coaching for Pharmacists (3) – Technical Coaching, there are different types of coaching models, skills and tools. Coaching can be practiced effectively if pharmacists are familiar with these elements of coaching.

However, we believe that not many pharmacists in Hong Kong are aware of the concept of coaching. Therefore, we designed a survey on coaching for pharmacists. This article will highlight the results and analysis of the survey, the obstacles of coaching amongst pharmacists in Hong Kong, the benefits of coaching in hospital, community and industrial settings, and ways to make pharmacists change.

SURVEY ON COACHING

A survey on coaching was conducted among pharmacists in Hong Kong. The aim of the survey was to investigate pharmacists' experience of and attitude towards coaching. 16 pharmacists were interviewed on the phone including 4 hospital pharmacists, 5 community pharmacists, and 4 industrial pharmacists working in various teams, namely drug safety, regulatory affairs, medical affairs and clinical operations of multinational pharmaceutical companies.

Ten of the interviewees have received training on coaching. 7 of them have been coached and 10 have coached others before. 9 agreed that coaching is a work-related learning which is applicable to all kinds of professions including the healthcare profession. 4 believed that coaching will help to create a better relationship between superiors and colleagues. 1 believed that it can improve interpersonal skills. 3 believed that it has the potential to maximize their productivity. 3 believed that it will give a right direction to set their future goal. 4 believed that it will improve work-life balance. 2 believed it will improve solution of problem solving and decision making. 6 believed that it will improve all the above mentioned areas. 6, 5, 11, 9 and 15 of them thought that EQ (emotional quotient), NLP (Neuro Linguistic Programming), goal setting, questioning and listening

are important in coaching respectively. 11 of them were willing to coaching their colleagues/staff.

The results obtained were quite satisfactory in the way that a lot of the interviewees have come across coaching before. However, they were not sure about the advantages of coaching. In fact, coaching can improve the relationship between superiors and colleagues, enhance interpersonal skills, maximize productivity, give a right direction to set future goal, and improve work-life balance, solution of problem solving and decision making. Only 37.5% (n=6) of the interviewees correctly recognized that coaching can improve all of the above mentioned areas. Listening is the skill/tool identified by most of the interviewees as important in coaching. Not many of them believed EQ, NLP, and questioning are important in coaching. This shows that they may not be clear about the skills/tools used in coaching.

OBSTACLES OF COACHING AMONGST PHARMACISTS IN HONG KONG

This extensive training and strong academic background of pharmacists make them the most knowledgeable healthcare professional when it comes to medicines and their use. Some pharmacists may therefore be arrogant and believe that they do not have the need to be coached. On the other hand, some may have low self-esteem and feel that they don't have the ability to coach their colleagues or staff.

Currently, there are three pharmacists' societies/associations in Hong Kong, namely the Pharmaceutical Society of Hong Kong, the Society of Hospital Pharmacists of Hong Kong and the Practising Pharmacists Association of Hong Kong. Registered pharmacists

in Hong Kong may only be the member of one or two societies/associations. Therefore, if one society/association provides training on coaching, only its members, but not all the pharmacists in Hong Kong, can benefit from it.

Moreover, staff shortages have put pharmacies at some public hospitals with heavy workload and long working hours. Supply of manpower in pharmacy is limited as there are only 30 graduates each year from the Chinese University of Hong Kong and another 20 graduates from a new pharmacy program by the University of Hong Kong next year. Despite the tight manpower, the Hospital Authority is planning to introduce 24-hour pharmacy services in some hospitals. Hong Kong also has fewer pharmacists per capita than some overseas countries. The number of pharmacists in Hong Kong is 24 per 100,000 people, compared with 78 in the UK, 25 in Taiwan and 179 in Japan. The heavy workload and long working hours render coaching difficult to be practiced in the work setting.

Besides, the curricula of the two pharmacy programs in Hong Kong focus on knowledge of pharmacy and do not provide courses in leadership or coaching skills to prepare for students' future work.^(1,2) Furthermore, different work settings, such as the Hospital Authority, community chain pharmacies or pharmaceutical companies, seldom provide training on leadership or coaching. Therefore, there is a lack of coaching concept in pharmacists' education and training in Hong Kong. In the United States, the American Pharmacists Association launched a Leadership Training Series in 2007. It is for members who want to develop their leadership potential. It consists of four parts that will be offered over four years of student pharmacist's education. Upon completion of the series, participants will receive a Recognition of Participation.⁽³⁾

BENEFITS OF COACHING IN HOSPITAL, COMMUNITY AND INDUSTRIAL SETTINGS

In general, coaching ensures that coachees learn every essential task they will have to accomplish on their own. Coaching therefore allows them to blend into the work setting faster. Coaching also enables coaches to

spot the coachees' strengths and weaknesses, let coachees learn more about their strengths and turn their weaknesses into strengths. If the coach thinks that the coach has the potential to be a good leader, more leadership training can be provided. Furthermore, coaching allows the coach to train their own people management skills and organization skills in preparing training materials to train the coachees.

Through coaching, questioning and listening skills are developed and self-awareness is increased in order to enhance the pharmacists' emotional and social intelligence. The outcome is an increased capacity to be present with patients, curious about their perspective, and using a better-trained ear. An improved pharmacist-patient relationship results in better overall patient care. Patients noted that the pharmacists "took time to understand what I am saying" and "explained so I understood my illness".

Once pharmacists acquire the skills of coaching, apart from coaching their staff or colleagues, they can also coach patients. We may think that having a heart attack would be enough to persuade a man to quit smoking, change his diet, exercise more often and take his medication. We may think that hangovers, auto crashes, memory blackouts and damaged relationships would be enough to convince a woman to stop drinking. We may think that the threats of blindness, amputations and all the other complications that come with diabetes would be enough to motivate a patient to manage their weight, check their blood sugars and take their medications. However, this may not be true. Difficulties in making changes are an expected part of the coaching process. Pharmacists can work with multiple strategies to problem-solve around barriers and move forward. They must go beyond simple information delivery and be trained in health behavior change, motivational interviewing and self-management education. Motivational interviewing is about helping an individual identify where they are in terms of readiness to change and to use helpful strategies to facilitate them moving toward the next step. Pharmacists should coach patients to build confidence in their ability to make change and to meet them where they are in the process of change. Collaborative

goal setting and action planning can be carried out for chronic diseases and conditions.

HOW TO MAKE PHARMACISTS CHANGE

Some pharmacists may be reluctant to coach or to be coached. An essential core issue of making changes is motivation. A lot of work has been done to determine why some people are motivated and why some people aren't. There are currently four notions about why people don't change – either they don't see, they don't know, they don't know how to or they just do not care. Giving them insights can make them see, giving them knowledge can make them know enough, giving them skills can teach them how to change.⁽⁴⁾

Research says that "change talk" can be used to draw out behavior change. Change talk is when the individuals think about and express their desire to change, their ability to change, their reasons to change or their need to change. The research has shown that the more they talk about that, the greater the strength of their commitment toward their plan or the behavior change.

We cannot just give people information about doing certain things and tell them to do these. Instead, we have to understand why they struggle with change and understand the pressures and challenges they are facing that keep them stuck.

It is more effective to approach people in a way that is based on what works and why people change. Motivational interviewing works because it approaches people in a way that expresses empathy. It establishes the rapport and helps people to get out of self-protective mode. It supports their autonomy, which allows them to put aside their suspicion and be creative in terms of their problem solving. It helps them recognize an inconsistency between where they are and where they would like to be. It helps them understand their ambivalence and elicit change talk. This is a good way of supporting their self-efficacy. It helps them strengthen their belief that they can make the change and provides assistance while developing a plan of action that is both practical and sustainable.

SUMMARY

Issues in profession	<ul style="list-style-type: none"> - Lack of coaching concept in the training - Short staffing and heavy workload - Split-up of societies/associations - Arrogance of pharmacists - Work life imbalance - Insufficient communication with colleagues and superiors - Insufficient further development for personal strength - Low self-esteem
How coaching is important in general	<ul style="list-style-type: none"> - Stimulates and supports growth in an individual's performance - Provides directions for any individual - Allowing one to utilizing their potential to maximize their productivity and achieve their personal growth. - A tremendous support in work-related learning - An intervention to stimulate thinking and make advancements - Involves reflection on performance, clarification of individual thoughts, behavioral patterns, motivation for works and career development
Why coaching can address these challenges	<ul style="list-style-type: none"> - Coaching is a way to demonstrate one's approach towards problem solving, interaction with patients, and one's general ability to communicate. - Coaches help pharmacists to take hold of job responsibilities, improve performance, establish new skills and excel to a higher career level. - Coaching enables pharmacists to identify their individual strengths and weaknesses, and then be able to link them to their personal and career aspirations. - Coaches play roles in the way to encourage pharmacists to establish long-term developmental goals and help them conceptualize a strategy to attain them. - Through coaching, pharmacists can contribute to the independent development individuals and encourage improvement through self learning. - It stimulates thinking and planning which can bring out best performance of a coachee, helping them to focus, breaking down tasks and clarifying their values.
Roadmap to get this "done" or "achieved"	<ul style="list-style-type: none"> - Increase awareness of coaching training practice goal setting reflection/feedback

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Ulcerative Colitis and Crohn's Disease – Current and New Treatment Highlights

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ABSTRACT

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic and relapsing inflammatory disorders involving the gastrointestinal tract. The incidence and prevalence of UC in Hong Kong had a six-fold and three-fold increase respectively in the past decades, while the incidence and prevalence of CD in Hong Kong had a three-fold and five-fold respectively. In this article the author addresses and discusses the current treatment methods and some new therapies that are being developed.

Keywords: Ulcerative Colitis, Crohn's disease, HK incidence, HK prevalence, therapeutic treatment.

INTRODUCTION

Ulcerative colitis

Ulcerative Colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon. It is the continuous inflammation extending from the distal rectum proximally involve part or all of the large intestine.^(1,2) The clinical symptoms of UC involve bloody diarrhea, often with prominent symptoms of rectal urgency and tenesmus.^(1,2) The goal of therapy is to induce and maintain remission of symptoms, improve quality of life, reduce the need for long-term corticosteroids and minimize the risk of having cancer.⁽²⁾

Crohn's disease

Crohn's disease (CD) is a disease characterized by deeper and discontinuous focal ulceration which may occur anywhere throughout the GI tract.^(1,3) It is characterized by focal, asymmetric, transmural, and granulomatous inflammation throughout the GI tract.^(1,3) CD is a chronic inflammatory disease

that is not medically or surgically curable; therefore the goal of therapy is to induce and maintain symptomatic control, improve quality of life and minimize potential toxicity and complications.⁽³⁾

INCIDENCE AND PREVALENCE IN HONG KONG

Reported cases of ulcerative colitis

There were two long term cohort studies investigating the prevalence and incidence of Chinese UC patients in Hong Kong. One study suggested that the point prevalence of UC was 26.5 (95% CI: 22.6-30.9) per 100,000 in 2006. The annual age-specific incidence rate was 0.3 (95% CI: 0-0.9) per 100,000 in the period of 1986-1988, and the incidence rate was 1.8 (95% CI: 0.8-3.1) in the period of 2004-2006 (Fig. 1); therefore there was a six-fold increase for the incidence of UC in Hong Kong in the past two decades.⁽⁴⁾ The other study suggested that the crude prevalence rate of UC was 2.26 per 100,000 in 1997, and it was 6.30 per 100,000 in 2006 (Fig. 2).⁽⁵⁾ Therefore there was a three-fold increase for the prevalence of UC in Hong Kong in a 10-year period.⁽⁵⁾ The results of the above studies suggest that the incidence of prevalence of UC in Hong Kong is increasing.

The incidence and prevalence of UC in Hong Kong were comparable to other Asian countries, such as Japan (1.95 and 18.12 per 100,000 respectively), and South Korea (1.51 and 30.87 per 100,000 respectively).⁽⁴⁾

However, according to the cohort study, the complication, colorectal cancer and colectomy rates were relatively low compared to Western countries.^(4,5) Only a minority of patients developed medically refractory disease, colorectal cancer (negligible) or required colectomy (2.4% and 7.6% at 1 and 10 years).⁽⁴⁾ This may

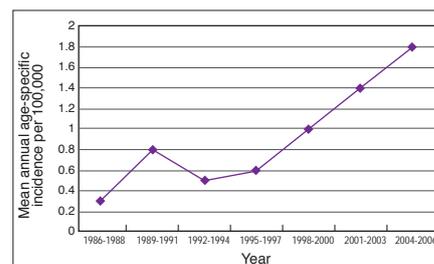


Figure 1. The temporal trend of mean annual age-specific incidence of ulcerative colitis in Hong Kong, 1986-2006. Adapted from Chow DKL et al.⁽⁴⁾

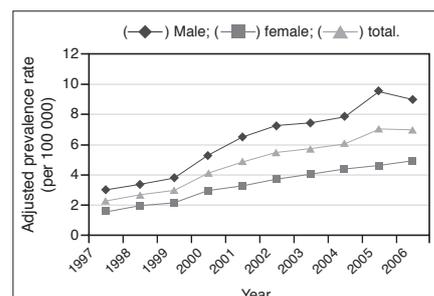


Figure 2. Adjusted prevalence rate of Chinese ulcerative colitis from 1997-2006. Adapted from Lok KH et al.⁽⁵⁾

suggest that the disease course is milder for Chinese patients.^(4,5)

Reported cases of Crohn's disease

There were two long term cohort studies investigating the prevalence and incidence of Chinese CD patients in Hong Kong. One study suggested that the annual incidence rate was 0.3 per 100,000 in 1989, and the incidence rate was 1.0 (95% CI: 0.8-1.1) per 100,000 in 2004 (Fig. 3); therefore there was a three-fold increase for the incidence of CD in Hong Kong in the past two decades.⁽⁶⁾ The greatest rate of rise was noted in mid to late 1990's.⁽⁶⁾ The other study suggested that the crude incidence rate of CD was 0.12 per 100,000 in 1991, and it was 0.25 per 100,000 in 2006, whilst the crude prevalence rate of CD was 0.39 per 100,000 in 1991, and it was 2.70 per 100,000 in 2006 (Fig. 4).⁽⁷⁾ Therefore, there was a two-fold increase for the

crude incidence rate and a five-fold increase for the crude prevalence rate in the study period.⁽⁷⁾ The results of the above studies suggest that the incidence and prevalence of CD in Hong Kong is increasing. There is no comparison with other Asian countries on the incidence and prevalence of CD.

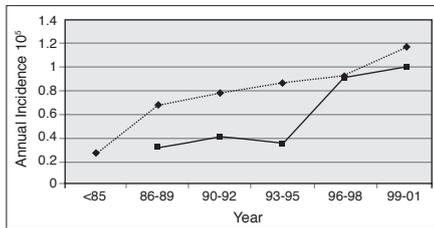


Figure 3. The temporal trend of the incidence of Chinese Crohn's Disease (solid line) and ulcerative colitis (dotted line) up to 2001. Adapted from Leong RWL et al.⁽⁶⁾

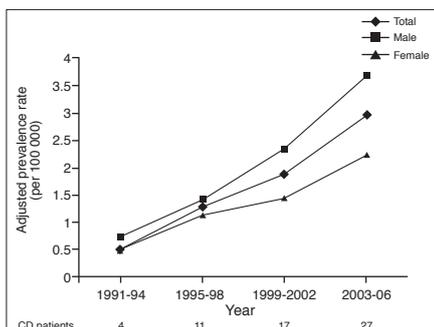


Figure 4. Age-adjusted prevalence rates of Crohn's Disease from 1991-2006. Adapted from Lok KH et al.⁽⁷⁾

It was also found that Chinese population with CD had a higher chance of having upper gastrointestinal tract (GIT) disease (19%) when compared to Caucasians (0.5-13%). They were found to have more proximal small bowel obstruction and perforations, which suggests that small bowel CD complications were more common in Chinese.⁽⁶⁾ On the other hand, Chinese population had a lower chance of having isolated terminal ileal disease (4%) when compared to Caucasians (30%). Moreover, it is also found that the Chinese population had a higher chance of having penetrating (45%) and stricturing complications (18%), and they tended to have more ankylosing spondylitis (9%) when compared to Koreans (1.9%) in CD patients.⁽⁶⁾

CLINICAL MANIFESTATION

Ulcerative colitis

Table 1 summarizes the feature and staging of UC. The hallmark clinical symptoms of UC include bloody diarrhea, rectal urgency or tenesmus.^(1,2) In a patient with persistent symptoms, stool examination, sigmoidoscopy, colonoscopy, or biopsy should be performed. These diagnostic

tests help indicate the presence of colitis and exclude the presence of infectious or non-infectious causes.⁽²⁾

Crohn's disease

Table 2 summarizes the feature and staging of CD. CD has overlapping features with other inflammatory bowel diseases; therefore it is difficult to diagnose CD.⁽³⁾ Characteristic symptoms of chronic or nocturnal diarrhea, abdominal pain, weight loss, fever, rectal bleeding may reflect the underlying inflammation, but clinical signs such as pallor, cachexia, abdominal mass or tenderness, perianal fissures, fistula or abscess may also help identify CD.^(1,3) Endoscopy, radiography, and pathological findings may help document focal asymmetric, transmural or granulomatous features.⁽³⁾

Table 3 summarizes the differences between UC and CD.

DIAGNOSIS

Table 4 summarizes the common laboratory tests and diagnostics tools for UC and CD and their functions.

Laboratory tests and diagnosis of ulcerative colitis

For UC, sigmoidoscopy or colonoscopy may help evaluate the mucosal changes characteristics of UC, such as loss of typical vascular structure, granularity, friability and ulceration.⁽²⁾ These changes proceed proximally in a symmetric, continuous, and circumferential pattern to involve part or all parts of the colon. The mucosal biopsy may also help identify UC from other colitis, since the mucosa may show separation, distortion, atrophy of crypts, and lymphoid aggregation.⁽²⁾

Laboratory tests and diagnosis of Crohn's disease

For CD, endoscopy is used to confirm the diagnosis of CD, assess disease location or obtain tissue for pathological evaluation. Radiography such as ultrasound, CT, or MRI, is used to confirm disease location and intestinal complications.⁽³⁾ Serological studies evaluating antibodies may provide adjunctive support for the diagnosis of CD.⁽³⁾

Table 1. Different stages of UC: Signs and Symptoms.⁽²⁾

Feature	Mild	Moderate	Severe	Fulminant
No. of stools/ day	<4 (with or without blood)	>4 (with or without blood)	>6 with blood	>10 with blood
Systemic toxicity	No	Minimal	Yes (fever, tachycardia, anemia)	Yes (fever, tachycardia, anemia)
Erythrocyte sedimentation rate	Normal	Normal	Elevated	Elevated
Other symptoms	N/A	N/A	Toxic megacolon	Abdominal tenderness, abdominal distention, toxic megacolon

Table 2. Different stages of CD: Signs and Symptoms.⁽³⁾

Feature	Mild-moderate	Moderate-Severe	Severe-fulminant
Fever	Mild	Yes	Severe
Abdominal pain or tenderness	Yes	Yes	Severe, intestinal obstruction
Other symptoms	Dehydration	Dehydration, weight loss	Dehydration, weight loss
Respond to drug treatment		Fail to respond to treatment for mild-moderate disease	Fail to respond to conventional corticosteroid or biologic agents

Table 3. Features for differentiating between UC and CD. Adapted from Bernstein CN et al.⁽¹⁾

	Typical UC features	Typical CD features
Clinical	Frequent small-volume diarrhea with urgency Predominantly bloody diarrhea	Diarrhea accompanied by abdominal pain and malnutrition Stomatitis Abdominal mass Perianal lesions
Endoscopic and radiological	Diffuse superficial colonic inflammation Involvement of rectum, but this can be patchy Shallow erosions and ulcers Spontaneous bleeding	Discontinuous transmural asymmetric lesions Mainly involving ileum and right-sided colon Cobblestone appearance Longitudinal ulcer Deep fissures
Histopathological	Diffuse inflammation in mucosa or submucosa Crypt architecture distortion	Granulomatous inflammation Fissures or aphthous ulcers can be seen; often transmural inflammation
Serological markers	Antineutrophil cytoplasmic antibodies	Anti- <i>Saccharomyces cerevisiae</i> antibodies

Table 4. Common laboratory tests and diagnostic tools for UC and CD.⁽¹⁾

Category	Test	Function
Stool examination	Fecal examination	- Eliminate bacterial, viral or parasitic cause of diarrhea
	Fecal blood examination	- Indicate presence of occult blood or fecal leukocyte in the stool to strengthen the indication for endoscopy
	<i>Clostridium difficile</i>	- Positive result suggests other possible causes of the disease
	Cytomegalovirus	- Positive result suggests other possible causes of the disease
Blood examination	Complete blood count, liver function test and human immunodeficiency virus	- Basic information
	Erythrocyte sedimentation rate, C-reactive protein and orosomucoid	- Suggest the inflammation and disease activity
	Electrolytes, albumin, ferritin, calcium, magnesium, vitamin B12, cobalamin	- Suggest possible malabsorption
	Serum ferritin and transferrin	- Suggest possible iron deficiency and anemia
Intestinal tuberculosis (TB) examination	Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) test	- Positive p-ANCA antigen and negative ASCA tests possibly suggest UC - Negative p-ANCA antigen and positive ASCA tests possibly suggest CD
	Tuberculin purified protein derivative (PPD) skin test	- Eliminate intestinal TB cause of the disease
Imaging and endoscopy	Serum PPD antibody test	- Eliminate intestinal TB cause of the disease
	Plain abdominal radiography	- Establish the presence of colitis and the extent - Use when bowel obstruction or perforation is expected - Exclude toxic megacolon
	Barium double-contrast enema or barium small-bowel radiography	- Assess the gastrointestinal tract and distal small bowel - Delineate the length of a stricture - Help to assess the areas in which there is no access to endoscopy or when colonoscopy is incomplete
	Sigmoidoscopy and colonoscopy	- Assess ulcers, inflammation, bleeding and stenoses - Perform multiple biopsies - Assess for CMV infection in patients receiving chronic immunosuppressant medication or positive <i>C. difficile</i> infection in stools
	Computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI)	- Determine the disease extent and severity - Assess for perforating complications
	Push enteroscopy and double enteroscopy	- Assess for small-bowel disease by reaching small-bowel with balloon dilation

CURRENT TREATMENT

The American College of Gastroenterology and the World Gastroenterology Organization, two reputable authorities on inflammatory bowel diseases, have issued treatment guidelines on UC and CD. Table 5 summarizes the treatment of different stages of the diseases.

Therapies for ulcerative colitis – mild to moderate distal colitis

For patients with mild to moderate

distal colitis, there are several first-line therapies, including oral aminosalicylates, topical aminosalicylates, and topical steroid.^(1,2) Clinical findings show that topical aminosalicylates is superior to oral aminosalicylates or topical steroid, and the combination of oral and topical aminosalicylates is more effective than either alone.⁽²⁾

For topical aminosalicylates, mesalamine⁺ suppositories at a dose of 500 mg twice daily or 1000 mg once daily are effective for treating the disease and

maintaining remission, while mesalamine⁺ enema in doses of 1-4 g is also effective in inducing and maintaining remission.⁽²⁾ Alternatively, oral aminosalicylates can be used, such as sulfasalazine at a dose of 4-6 g per day in four divided doses, mesalamine⁺ at a dose of 2-4.8 g per day in three divided doses, balsalazide[#] 6.75 g per day in three divided doses, olsalazine[#] 1.5-3 g per day in two divided doses, or mesalamine⁺ with a multimatrix formulation at a dose of 2.4-4.8 g per day.⁽²⁾ They are effective in treating the disease and the therapeutic effects are observed in 2 to 4 weeks' time. Meanwhile, topical corticosteroid can also be considered, such as 100 mg hydrocortisone enema, 10% hydrocortisone foam, as effective treatment for acute distal colitis.⁽²⁾ For patients that have difficulty in retaining enema, they should choose the foam formulation. Combination therapy may give better response in some patients, and they may consider using a combination of oral mesalamine⁺ 2.4 g and mesalamine⁺ enema 4 g per day.⁽²⁾

For patients that are not responding to the first-line therapy, they may consider using alternative treatment, such as oral prednisolone at a dose of 40-60 mg per day, or infliximab with an induction regimen of 5 mg/kg at weeks 0, 2 and 6.⁽²⁾

Table 6 summarizes the maintenance therapy for mild to moderate distal colitis.

Therapies for ulcerative colitis – mild to moderate extensive colitis

For the UC patients with mild to moderate colitis, they are often treated with oral aminosalicylate.^(1,2) The first-line therapy is traditionally sulfasalazine at a dose of 4-6 g daily in clinical practice.⁽²⁾ Alternatively, patients can be treated with alternate aminosalicylate at a dose up to 4.8 g daily of the active 5-aminosalicylate acid (5-ASA) moiety, including some "newer" aminosalicylates, such as balsalazide[#], olsalazine[#], Eudragit-S-coated, pH-dependent mesalamine⁺, ethylcellulose-coated mesalamine⁺, multimatrix-release mesalamine⁺.⁽²⁾ They are all equivalent to sulfasalazine in terms of therapeutic efficacy.

For those patients who are not responding to oral aminosalicylates, they can be treated with oral steroids. Prednisolone at a dose of 40-60 mg daily is given to the patients until clinical signs of improvement occur.⁽²⁾ After achieving clinical response, the oral steroid is tapered off 5-10 mg weekly until reaching a daily dose of 20 mg. Then the oral steroid is further tapered off 2.5 mg weekly.⁽²⁾ Oral steroid is also indicated for patients who demand rapid improvement.^(1,2)

Table 5. Overview of disease status and common drug therapy. Adapted from Bernstein CN et al.⁽¹⁾

	Distal UC	Extensive UC	CD
Mild	Rectal or oral 5-ASA Rectal GCS	Topical and oral 5-ASA	Sulfasalazine or other 5-ASA for colonic disease only Metronidazole or ciprofloxacin for perineal disease BUD for ileal and/or right colon disease
Moderate	Rectal or oral 5-ASA Rectal GCS	Topical and oral 5-ASA	Oral GCS AZA or 6-MP MTX Anti-TNF
Severe	Rectal or oral 5-ASA Oral or intravenous GCS Rectal GCS	i.v. GCS i.v. CSA or i.v. infliximab	Oral or i.v. GCS Subcutaneous (s.c.) or i.m. MTX i.v. infliximab or s.c. adalimumab or s.c. certolizumab

Notes: 5-ASA, 5-aminosalicylates. 6-MP, 6-mercaptopurine. Anti-TNF, anti-tumor necrosis factor. AZA, azathioprine. BUD, budesonide. CSA, cyclosporine. GCS, glucocorticosteroids. MTX, methotrexate.

Table 6. Ulcerative colitis: maintenance therapy for mild to moderate distal colitis.⁽²⁾

Drug	Dose
<i>First-line agents</i>	
Mesalamine ⁺ suppository	500 mg daily or twice daily
Mesalamine ⁺ enema	2-4 g daily, every two days or every three days
Sulfasalazine	2 g daily
Olsalazine [#]	1 g daily
Eudragit-S-coated mesalamine ⁺	3.2 g daily
Balsalazide [#]	2-6 g daily
Granulated extended release mesalamine ⁺ capsules	1.5 g daily
Oral mesalamine ⁺ + mesalamine ⁺ enema	1.6 g daily + 4 g twice weekly
<i>Second-line agents</i>	
Azathioprine	
6-mercaptopurine	
Infliximab	

For those patients who are not responding to oral steroids, they can be treated with thiopurines, such as azathioprine at a dose of 1.5-2.5 mg/kg daily or 6-mercaptopurine.^(1,2) However, these agents have slow onset of reaction, requiring 3 to 6 months to exhibit their optimal effect.⁽²⁾ Meanwhile, infliximab is another agent that can be used to treat patients who are not responding to oral steroids. Infliximab, a monoclonal antibody to tumor necrosis factor- α , is effective in inducing response and remission for patients with moderate to severe UC.^(1,2) The drug is administered intravenously with an induction dose of 5 mg/kg at weeks 0, 2 and 6, and the infusion is administered over a 2-hour period to prevent infusion reactions.⁽²⁾

Table 7 summarizes the maintenance therapy for mild to moderate extensive colitis.

Therapies for ulcerative colitis – severe extensive colitis

For severe UC patients who do not respond to optimal doses of oral aminosallylates (4-6 g sulfasalazine, 4.8 g mesalamine⁺, or 6.75 g balsalazide[#]), oral steroids (40-60 mg daily of prednisolone) or topical treatment, and do not require immediate hospitalization, they can be treated with infliximab infusion at a dose of 5 mg/kg.⁽²⁾ For those patients that require immediate hospitalization, they can be treated with intravenous steroid at a dose

equivalent to 300 mg hydrocortisone or 60 mg methylprednisolone daily.^(1,2) There is no further benefit to using a higher dose of steroids. Moreover, broad spectrum antibiotics, such as oral vancomycin, intravenous metronidazole, or ciprofloxacin, should be added to intravenous steroids to prevent infection for patients presenting with signs of toxicity and worsening of symptoms.⁽²⁾

For patients who do not respond significantly to the initial maximal medical therapy after 3 to 5 days, they are unlikely to benefit from continuation of therapy. Therefore, they can be considered for treatment with intravenous cyclosporine, tacrolimus or infliximab, or being referred for surgery.^(1,2) Patients can be treated with cyclosporine at a dose of 2-4 mg/kg per day, or using tacrolimus with dose targeting to trough levels of 5-15 ng/mL.⁽²⁾ However the clinical use of tacrolimus is still not well-established. Meanwhile, infliximab at a dose of 5 mg/kg can also be considered, but there are only limited data regarding the use of infliximab in patients with severe UC refractory to intravenous steroid. Any further deterioration in clinical, laboratory or radiological response on drug therapy indicates the induction of immediate surgery.⁽²⁾

Therapies for Crohn's disease – mild to moderate

For ileal, ileocolonic or colonic active

CD patients, they are often treated with oral mesalamine⁺ 3.2-4 g daily in clinical practice.^(1,3) Alternatively, for ileocolonic or colonic active CD patients, they can be treated with sulfasalazine 3-6 g daily in divided dose.^(1,3)

For those patients that are irresponsive to the first-line treatment, alternative treatment can be used. For example, some patients are treated with metronidazole at a dose of 10-20 mg/kg per day if they are irresponsive to sulfasalazine.^(1,3) Alternatively, controlled-release budesonide at a dose of 9 mg daily can be used for patients with CD confined to the ileum and/or the right colon, and it has similar efficacy when compared to conventional oral corticosteroid, which is another choice for treating mild to moderate CD.⁽³⁾

Some clinical trials are investigating the effects of antibiotics on treating mild to moderate CD. For example, one of the clinical trials demonstrated that the use of ciprofloxacin 1 g gave statistically significant improvement on the ongoing treatment of CD. Another trial also demonstrated that the use of rifaximin 200 mg t.i.d. gave beneficial results in a 16-week therapy.⁽³⁾ However, the clinical trials have not consistently demonstrated efficacy; therefore the use of antibiotics in treating mild to moderate CD is somewhat questionable.⁽³⁾

Therapies for Crohn's disease – moderate to severe

For patients with moderate to severe CD, they are generally first treated with prednisolone 40-60 mg daily, generally in a 7-28 day period, until their symptoms are relieved.^(1,3) Clinical studies show that higher dose of prednisolone or methyl prednisolone may give a higher response rate.⁽³⁾ If there is any sign of infection or abscess, appropriate antibiotics therapy, percutaneous drainage or surgical drainage should be performed.⁽³⁾ For maintenance therapy, either azathioprine at a dose of 2.0-3.0 mg per day, or 6-mercaptopurine at a dose of 1.0-1.5 mg per day, can be used to maintain the steroid-induced remission, or parenteral methotrexate at a dose of 25 mg per week can be used for steroid-dependent or steroid-refractory CD.⁽³⁾

For those patients that are not responding to the first-line therapy, including aminosallylates, antibiotics, corticosteroids or immunomodulators, the anti-TNF monoclonal antibodies, such as infliximab, adalimumab and certolizumab pegol[#], can be used. Infliximab infusion at a dose of 5 mg/kg, or an induction regimen of 5 mg/kg infusions at weeks

Table 7. Ulcerative colitis: maintenance therapy for mild to moderate extensive colitis.⁽²⁾

Drug	Dose	Footnotes
<i>First-line agents</i>		
Sulfasalazine	2-4 g daily	For the 4 g daily dose, patients may not tolerate the side effects. Therefore adjust the dose by observing patients' response.
Mesalamine ⁺	4 g daily	Larger dose of the agent is generally well-tolerated.
Olsalazine [#]	4 g daily	Larger dose of the agent is generally well-tolerated.
Balsalazide [#]	4 g daily	Larger dose of the agent is generally well-tolerated.
<i>Second-line agents</i>		
Azathioprine		
6-mercaptopurine		
Infliximab IV	5 mg/kg every 8 weeks	Infliximab monotherapy or infliximab-azathioprine combined therapy is more effective than azathioprine monotherapy.

0, 2, 6, followed by maintenance therapy, is effective in treating moderate to severe CD.^(1,3) Moreover, it is found that infliximab monotherapy and infliximab-azathioprine combined therapy are more effective than azathioprine monotherapy in patients that are not responding to the first-line treatments.⁽³⁾

Adalimumab with an induction dose of 160 mg and 80 mg after 2 weeks, followed by a maintenance dose of 40 mg every other week, can be used in patients who have lost response to infliximab.⁽³⁾ Alternatively, certolizumab pegol[#] 400 mg subcutaneously can also be used.⁽³⁾

For those patients that are not responding to the first-line therapy, including aminosalicylates, antibiotics, corticosteroids or immunomodulators, or even anti-TNF monoclonal antibodies, the humanized monoclonal antibody to $\alpha 4$ integrin, natalizumab[#], can be used. The dosage regimen of 300 mg infusions at weeks 0, 4, 8 is recommended.⁽³⁾

Therapies for Crohn's disease – severe/ fulminant

Surgical evaluation is given to patients with intestinal obstruction or tender abdominal mass, such as ultrasound, MRI scan and CT scan.⁽³⁾ If an abscess is confirmed, percutaneous or surgical drainage is performed to remove the abscess. If the presence of an abscess is excluded, the patient should be administered parental corticosteroid equivalent to prednisolone at a dose of 40-60 mg.^(1,3)

Nutritional support such as elemental feeding can be given to patients if they are unable to maintain their nutritional requirements. Fluid and electrolyte supportive therapy is also indicated for dehydrated patients. If the patients are presented with anemia or active hemorrhage, transfusion is also indicated.

It is also suggested that if findings from MRI or CT scan confirm the presence of inflammatory mass, broad-spectrum antibiotics should also be given along with corticosteroid to prevent potential infection.⁽³⁾

For those patients that are not responding to parenteral corticosteroid, parenteral cyclosporine or tacrolimus can be given to the patients as the second-line therapy.^(1,3) If the patients still fail to respond to these treatments, surgical intervention should be considered to prevent the worsening of the symptoms.⁽³⁾

Table 8 summarizes the maintenance therapy for CD.

Table 8. Crohn's disease: maintenance therapy. ⁽³⁾		
Drug	Dose	Footnotes
<i>First-line agents</i>		
Sulfasalazine		Do not have consistent maintenance therapeutic effect.
Mesalamine*		Do not have consistent maintenance therapeutic effect.
Prednisolone		Have side effects such as decreased bone mineral density and steroid related toxicity if used for long time. Therefore it is not recommended for long-term use.
Budesonide	6 mg daily	Effective in reducing the time to relapse in ileal and/or right colonic CD.
Azathioprine	2.0-2.5 mg/kg	Clinical trials show that effective in maintaining remission for at least 4 years.
6-mercaptopurine	1.5 mg/kg	Clinical trials show that effective in maintaining remission for at least 4 years.
Methotrexate IM	15 mg weekly	Effective to maintain methotrexate-induced remission.
<i>Second-line agents</i>		
Infliximab	Every 8 weeks	Infliximab monotherapy or infliximab-azathioprine combined therapy is more effective than azathioprine monotherapy.
Adalimumab SC	40 mg every week or every other week	
Certolizumab pegol SC [#]	400 mg every 4 weeks	
Natalizumab [#]	300 mg every 4 weeks	Effective to maintain natalizumab-induced remission.

NEW TREATMENT

Figure 5 demonstrates various new therapeutic targets for inflammatory bowel disease.

Blockade of pro-inflammatory cytokines - Tofacitinib

One of the new treatments in treating inflammatory bowel diseases involves the use of Janus Kinases (JAK) inhibitors. JAK receptors, namely JAK1, JAK2 and JAK3, play an important role in cell growth, survival, development and differentiation of immune cells.⁽⁸⁾ Therefore, blocking these cytokine receptors may help block the downstream signaling pathway and reduce the inflammatory response.

Tofacitinib (CP-690, 550) is a small molecule inhibitor of JAK3, which is undergoing phase II clinical trials for various immune diseases, including

UC and CD.^(10,11) Studies show that this substrate interferes with Th2 and Th17 cell differentiation; therefore blocking the production of IL-17 and IL-22 (Fig. 6).⁽⁸⁾ It helps with the downstream suppression of the pathological immune responses that occur in UC and CD.

There are 2 phase II clinical trials evaluating the effects of tofacitinib on UC and CD. The study evaluating the efficacy and safety of tofacitinib on UC was conducted on patients with moderate-severe stage at an 8-week therapy. It is expected the drug delivers therapeutic effects by blocking signaling through common δ chain-containing cytokines, including IL-2, -4, -7, -9, -15, and -21.⁽¹⁰⁾ For the results (Table 9), the clinical response rate of patients using placebo was 42%, while the clinical response rate of patients using 0.5, 3, 10, or 15 mg drugs were 32%, 39%, 61% and 78%, respectively.⁽¹⁰⁾ The clinical

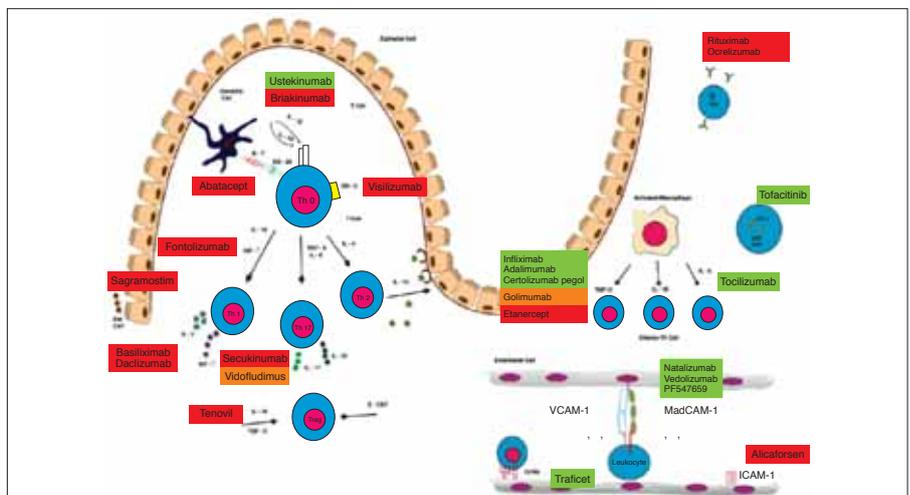


Figure 5. Successful and unsuccessful new therapeutic programs in inflammatory bowel disease. (Green: programmes with a positive outcome. Orange: potentially effective or ongoing programmes. Red: programmes failed.) Adapted from Danese S.⁽⁸⁾

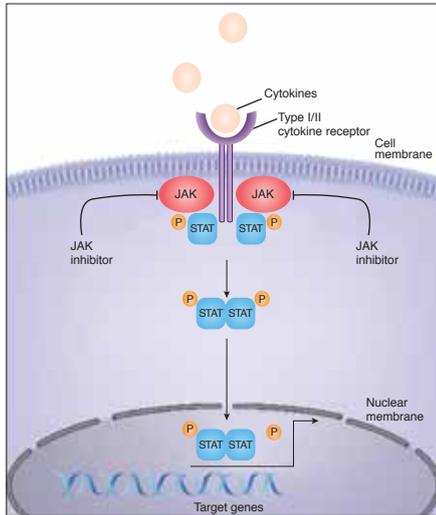


Figure 6. Suggested mechanism of tofacitinib. Adapted from Garber K.⁽⁹⁾

remission rate of patients using placebo was 10%, while the clinical remission rate of patients using 0.5 mg, 3 mg, 10 mg, 15 mg drugs were 13%, 33%, 49% and 41%, respectively.⁽¹⁰⁾ The incidences of adverse events were similar between placebo-treated and drug-treated patients. Therefore, it is concluded that there is a dose-dependent increase in clinical response and remission rates for patients using tofacitinib for treating moderate-severe UC. Moreover, the drug is generally well-tolerated.⁽¹⁰⁾

The study evaluating the efficacy and safety of tofacitinib on CD was conducted on patients with moderate-severe stage for 4 weeks. It is expected the drug delivers therapeutic effects by blocking signaling through common γ chain-containing cytokines, including IL-2, -4, -7, -9, -15, and -21.⁽¹¹⁾ For the results (Table 10), the response 70 rate of patients using placebo was 47.1%, while the response 70 rate of patients using 1, 5 and 15 mg drugs were 36.1%, 57.6 and 45.7%, respectively.⁽¹¹⁾ The response 100 rate of patients using placebo was 29.4%, while the response 100 rate of patients using 1 mg, 5 mg and 15 mg drugs were 30.6%, 45.5 and 37.1% respectively.⁽¹¹⁾ The clinical remission rate of patients using placebo was 20.6%, while the clinical remission rate of patients using 1, 5 and 15 mg drugs were 30.6%, 24.2%, and 14.3% respectively.⁽¹¹⁾ The incidences of adverse events were similar between placebo-treated and drug-treated patients. Therefore, it is concluded that there is no significant clinical effect within 4 weeks for patients using tofacitinib for treating moderate-severe CD. However, the drug is generally well-tolerated.⁽¹¹⁾

To conclude, the phase II trial of tofacitinib on moderate-severe UC shows promising results. Further experiments and investigations are needed to confirm

the potential efficacy of tofacitinib in treating UC.

Preventing leukocyte infiltration of endothelium - Vedolizumab

One of the new major routes to treat UC and CD is to develop inhibitors of different elements in the leukocyte infiltration process. T cells and neutrophils migrate from the systemic circulation into the intestinal mucosa once they are activated. This infiltration process is governed by the expression of integrins and chemokine receptors (CCR) on leukocytes and adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and mucosal addressin cell adhesion molecule 1 (MAdCAM-1).⁽⁸⁾ Some biological agents target integrins and the adhesion molecules and affect the interactions between leukocytes and endothelial cells. For example, vedolizumab targets integrin $\alpha 4\beta 7$ which interacts with MAdCAM-1 and mediates the interaction between leukocytes and endothelial cells, preventing the leukocytes infiltration (Fig. 7).⁽⁸⁾ It is undergoing phase III clinical trials for both UC and CD, since favorable results were obtained in phase II clinical trials and other early phase trials.

There are 2 phase II clinical trials evaluating the clinical benefits of vedolizumab on UC and CD.^(13,14) The study evaluating the efficacy and safety of vedolizumab on UC was conducted on patients after 6 weeks of therapy. It is expected the drug delivers therapeutic effects by inhibiting the migration of leukocytes into the inflamed GI tissue by blocking the cellular adhesion molecules.^(13,14) Integrin $\alpha 4\beta 7$ presents on the cell-surface of some circulating T lymphocytes, and they are involved in recruiting leukocytes to the GI gut. The integrin may react with MAdCAM-1 which expresses in intestinal vasculature and inflamed tissues.^(13,14) Vedolizumab may block the interaction and effectively treat the inflamed disease. For the results (Fig. 8), the clinical remission rate of patients using placebo at week 6 was 14%, while the clinical remission rate of patients using 0.5mg and 2mg of drugs at week 6 were 33% and 32% respectively.⁽¹³⁾ The percentage of patients who improved by 3 points on the UC clinical scores were 33%, 66% and 53% for patients using placebo, 0.5 mg and 2 mg drug respectively.⁽¹³⁾ There were no serious adverse events reported. Therefore, it is concluded that vedolizumab is more effective in inducing remission than placebo in patients with UC in a short term therapy, and the drug is generally well-tolerated.⁽¹³⁾

Table 9. Results of the Phase 2 Study of CP-690, 550, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis. (Adapted from Sandborn WJ et al).⁽¹⁰⁾ FeC, fecal calprotectin. CRP, C-reactive protein. BL, base line.

	CP-690.550				
	PBO n=48	0.5 MG BID n=31	3 mg BID n=33	10 mg BID n=33	15 mg BID n=49
BL					
Mayo score, median (range)	8 (4-11)	9 (6-12)	8 (6-12)	8 (3-11)	8 (5-11)
FeC, mg/kg, geometric mean	635	665	718	366	720
CRP, mg/l, geometric mean	4.5	6.6	6.3	4.7	5.7
Wk8					
Clinical response, %*	42	32	49	61	78
Clinical remission, %*	10	13	33	49	41
Endoscopic response, %*	46	52	58	67	78
Endoscopic remission, %*	2	10	18	30	27
FeC, % change from BL**	-23	-31	-51	-62	-69
CRP, % change from BL**	-33	-23	-55	-42	-73

* ITT population; **observed population

Table 10. Results of the Phase 2 Randomized Study of CP-690, 550, an Oral Janus Kinase Inhibitor, in Active Crohn's Disease. (Adapted from Sandborn et al).⁽¹¹⁾ FeC, fecal calprotectin. CRP, C-reactive protein. BL, base line.

	PBO n=34	CP-690.550		
		1 mg BID n=36	5 mg BID n=35	15 mg BID n=35
BL				
CDAI score, mean	306.4	300.3	397.7	308
FeC, mg/kg, geometric mean	522	397	290	420
CRP, mg/kg, geometric mean	8.2	6.6	8.4	10.4
Week 4				
Response 70 ¹ , %	47.1	36.1	57.6	45.7
Response 100 ¹ , %	29.4	30.6	45.5	37.1
Remission ¹ , %	20.6	30.6	24.2	14.3
FeC, % change from BL ¹	16	32	14	-49*
CRP, % change from BL ²	-9	-21	-34	-59**

¹ITT population; ²observed population; *pc0.05; **pc0.01

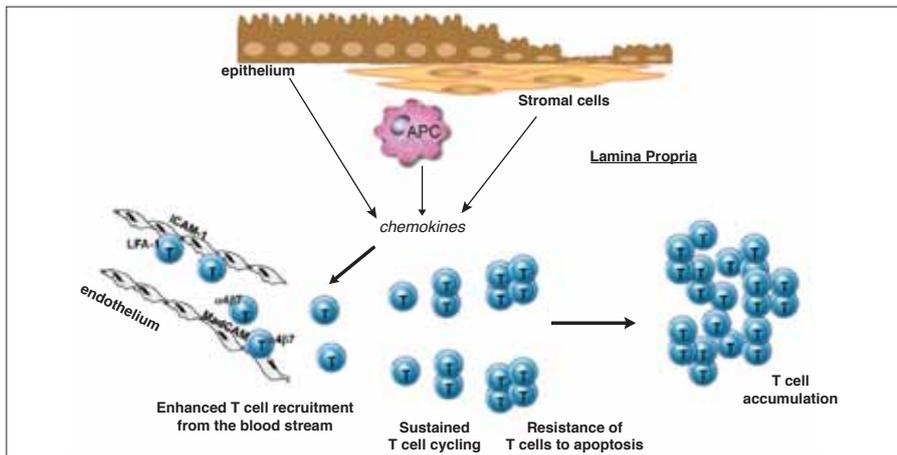


Figure 7. Mechanism of leukocyte infiltration and the suggested mechanism of vedolizumab. Adapted from Monteleone G et al.⁽¹²⁾

The study evaluating the efficacy and safety of vedolizumab on CD was conducted on patients at a 2-month therapy. It is expected that the drug delivers similar therapeutic effects as the part mentioned above. For the results (Fig. 9), the clinical response rate of patients using placebo at day 57 was 41%, while the patients using 0.5 mg/kg and 2 mg/kg drugs were 49% and 53% respectively.⁽¹⁴⁾ The clinical remission rate of patients using placebo at day 57 was 21%, while the clinical remission rate of patients using 0.5 mg/kg and 2 mg/kg drugs were 30% and 37% respectively.⁽¹⁴⁾ The most common observed adverse events were the worsening of CD.⁽¹⁴⁾ Therefore, it is concluded that there is a dose-dependent therapeutic effect for patients using vedolizumab treating CD in a short-term therapy. There is a significant effect on clinical remission. The drug is also considered as generally well-tolerated.⁽¹⁴⁾

To conclude, the phase II trials of vedolizumab on UC and CD show promising results. Further experiments and investigations are to be performed to confirm the potential efficacy of vedolizumab on treating UC and CD.

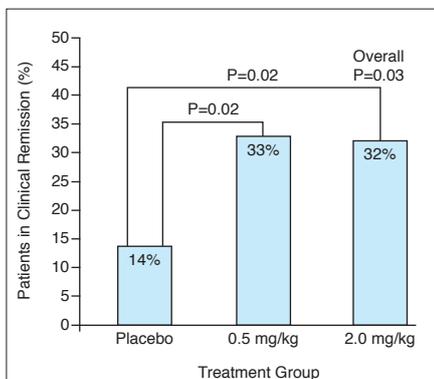


Figure 8. Percentage of Patients in Clinical Remission at Week 6 in the Phase 2 study of Vedolizumab on Ulcerative Colitis. Adapted from Feagan BG.⁽¹³⁾

CONCLUSION

Ulcerative colitis and Crohn's disease are chronic and relapsing inflammatory disorders involving the gastrointestinal tract, and these diseases severely reduce patients' quality of life. The main goal of therapy for these diseases is to improve quality of life and maintain long-term remission. The common agents used in treating such diseases include aminosaliclylate (mesalamine[#], sulfasalazine, olsalazine[#], balsalazide[#], etc.), corticosteroids (prednisolone, methylprednisolone, hydrocortisone), antibiotics (metronidazole, ciprofloxacin), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) and monoclonal antibody against tumor necrosis factors (infliximab, adalimumab, certolizumab[#], natalizumab[#]). Guidelines and instructions on the treatment of different stages or severity of disease are available.^(1,2,3)

For the development of potential therapies for UC and CD, although there are many areas to explore, there is no single "magic bullet" being discovered. It is suggested that the patients with UC and CD may be born with one or more

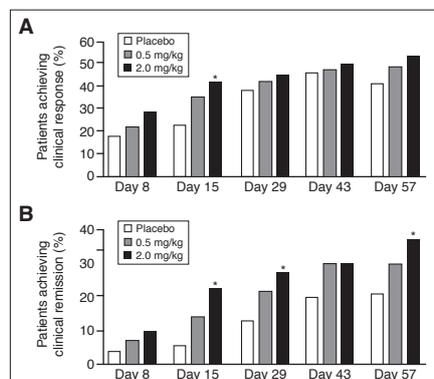


Figure 9. Percentage of patients achieving (A) clinical response and (B) clinical remission in the phase 2 study of Vedolizumab on Crohn's Disease. Adapted from Feagan BG.⁽¹⁴⁾

range of genetic deficiency, and at some points in the patients' life, the abnormal immunological balance may break out followed by a triggering event and result in disease progression.⁽⁶⁾ Therefore, it is important to investigate different pathways involved in the immunological imbalance and develop different targeted therapies. Moreover, combination approach can be considered since it may be more effective to suppress the inflammation by simultaneously tackling more than one pathway.⁽⁸⁾

Author's background

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Endospores as Biological Indicator for the Validation of Sterilization Process

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ABSTRACT

Sterilization refers to any process by which materials, objects or environments may be rendered sterile and absolutely free from microbials. To check whether a sterilization process functions effectively or not, specific types of bacterial spores have been recommended as biological indicator (BI) for in-process validation of the process. The reason why spores are chosen is because they are highly resistant to heat, radiation and sterilant. There are different types of BI for monitoring different sterilization processes. Although many commercially available BIs provide excellent means to validate different sterilization processes, the performance of BI is affected by both intrinsic characteristics of the organism as well as some environmental parameters before and after their production. In this article, the selection, preparation, employment and storage conditions of BIs are briefly reviewed. As BIs play an important role in the evaluation of sterilization process, the importance of their reliable quality is pointed out and discussed. It is recommended that in-depth investigations and control of their preparation are necessary before they are used for this purpose.

Keywords: microbial contamination; sterilization; quality assurance; endospore; biological indicators; in-process biovalidation; resistance performance tests

INTRODUCTION

In biomedical, pharmaceutical fields and food industries, a lot of things including materials, devices and equipment as well as wastes have to be sterilized in order

to prevent any potential degradation of a product or minimize the chance of spreading a disease due to the presence of microbial cells. There are different sterilization methods currently available for elimination of microorganisms. To check whether a lot of thing is sterile, a test on every unit would seem desirable. However, this is impossible since the sterility test is a destructive procedure.

Confidence of sterility test

In the early days sterility test was carried out by picking up samples randomly and testing them indirectly. But Statisticians have pointed out that this approach of testing does not really test all items that are to be use,^(7,10,24) and the untested materials are only assumed to meet the sterility standard in the batch. Furthermore, this method may not be able to detect low levels of contamination. Brown and Gilbert (1977) have statistically shown that official sterility tests offer low degrees of

assurance of sterility.⁽³⁾

Table 1 and 2 illustrate how levels of contamination in a lot of treated products may escape detection by the sterility-test procedures.⁽¹⁰⁾ In Table 1 the probability data are calculated for lots with various degrees of assumed contamination when 10 random samples per lot are tested. If a lot has one contaminated in each 1000 items (i.e. 0.1% contamination) could be passed as satisfactory in 99 tests out of 100. Even at the 10% contamination level, contamination would be detected, only 2 out of 3 times (i.e. 0.651%). Table 2 shows the difficulty in attempting to improve the reliability of sterility tests by increasing sample size. For contamination levels as low as 0.1%, increasing the sample size from 10 to 100 only increases the probability of rejection from 0.01 to 0.09. Even a sample size of 500 would result in erroneously accepting a lot six times out of ten. Hence, it is clear that product sterility testing is a poor method of validating sterilization procedures.

Table 1. Probabilities for sterility testing of articles with assumed levels of contamination⁽¹⁰⁾

"True" % contamination	Probability of designated positives out of 10 samples tested			
	0	1	5	10
0.1	0.990	(Total = 0.01)		
1.0	0.904	0.091		
5.0	0.599	0.315		
10.0	0.349	0.387	0.001	
30.0	0.028	0.121	0.103	
50.0	0.001	0.010	0.246	0.001

Table 2. Relationship of probabilities of acceptance of lots of varying assumed degrees of contamination to sample size⁽¹⁰⁾

Number of samples tested (n)	Probability of no positive growth "True" % contamination of lot					
	0.1	1	5	10	15	20
10	0.99	0.91	0.60	0.35	0.20	0.11
20	0.98	0.82	0.36	0.12	0.04	0.01
50	0.95	0.61	0.08	0.007		
100	0.91	0.37	0.01	0.00		
300	0.74	0.05				
500	0.61	0.01				

The concept of biovalidation of sterilization process for sterility assurance

Ideally, a lot of so called sterilized items should contain nil contaminated items. However, inspection is not and never can be 100 percent in practical case, so batches containing a small proportion of contaminated items may be passed by a sterility test as discussed above. There are documented incidents where batches of infusion fluid were found contaminated after "autoclaving" and passing routine tests.^(5,29) Therefore, the concept of sterility assurance and an alternated method of monitoring and controlling sterilization process were introduced. This method is called **In-process Biovalidation of Sterilization**, which involves the usage of specific microorganisms to monitor the sterilization cycles in terms of their biological lethality. These specific microorganisms used in such a way are called biological indicators (BIs). In practice, almost all current biological indicators are bacterial spores.^(7,32) The reasons why spores are chosen as biological indicators are based on their unique property. Comparing to vegetative cells, spores are more resistant to heat, to radiation and to sterilant (Table 3). Although some viruses and certain radiation-resistant non-spore forming bacteria are also equally resistant or even more resistant to a specific sterilization process, bacterial spores still have a higher tolerance to all these antimicrobial factors. In addition, bacterial spores have longer storage time than vegetative cells and are easily to handle. Hence, they are recommended for use as BIs in sterilization monitoring.

HISTORICAL BACKGROUND

Actually, the term "biological indicators"

have different meanings in various aspects. In ecological field, biological indicators are referred to certain kinds of organism that can provide an indication of the quality of their environment. This concept is very similar to the BIs used in pharmaceutical industry which implies the using of special types of microorganism in monitoring of a sterilization process. According to United States Pharmacopeia XXXIV (2011), a biological indicator is a characterized preparation of specific microorganism, usually spores of selected resistant strains to a particular sterilization process.⁽³¹⁾ It can be defined as a unit which carrying known concentration of microorganisms and resistance to a given sterilizing agent, that can be expected to follow a predictable death rate when exposed to certain physical or chemical parameters.⁽²³⁾ The purpose of using a BI is to assess the efficacy of the operation of a sterilization apparatus, to develop and establish a validated sterilization process, in addition to monitoring sterilization cycle periodically.

In the early days, sterility determination was simply carried out by standing flasks of culture to one side, or incubated for several days to see whether there was any survived bacterial. If bacterial growth was not detected in the flasks (i.e. the culture did not turn cloudy), they could be used for the later works. So the contaminants became the BIs in this situation. In the 19th century, the monitoring of sterilization in food industries was carried out by examining the food products directly. Occasionally, spoilage microorganism could be used as a form of BI because if any spoilage appeared, it indicates that the sterilizing process is not functioned as expected. However, this is not a proper method for sterilization monitoring, since a period of time waiting for any bacterial

growth noticed is needed. Also, the heat resistant bacteria such as *Clostridium botulinum* may not be detected by visual inspection. For the medical aspect, the concept of using BIs was introduced at the end of the 19th century. The tiny materials were inoculated with spore forming organisms, and then treated by the sterilizing process. After the treatment is completed, the test pieces would be cultured for later inspection. Those "tiny materials" represent the forerunners of BIs used nowadays. It is interesting that in the early days of Europe, some hospitals took some garden soil, put it into surgical packs and subjected it to the sterilizing process. If the materials showed microbial growth, the sterilization process was failure and needed to be verified again. This similar approach was also found in can industry.⁽²⁴⁾

CRITERIA FOR SPORES USED AS BIOLOGICAL INDICATORS

As mentioned above, sterilization is a biological destruction or removal process. It takes a big risk to assume that certain procedures can achieve such destruction without adequate demonstration. Hence any physical parameters used must be integrated with biological indicators. Uses of BIs provide excellent monitoring means because all known and unknown factors affecting the efficacy of a sterilization process are included. This practice has been incorporated during process development, qualification or validation.⁽³⁰⁾ The selection of an organism as the biological indicator is based on its ecological, morphological and physiological characteristics, all these nature characteristics may determine the effectiveness of organism for the evaluation purpose.⁽⁷⁾ Therefore, a particular organism with defined resistance would be used in specific sterilization procedures.

Basic requirements of BIs

As early as in 1968, the United States Public Health Service Regulations had already specifically stated out five requirements for biological indicators. These requirements are: (1) they cannot be pathogenic for men, (2) they cannot produce pyrogen or toxins, (3) they cannot grow at or below 37°C within a two week incubation period, (4) they have good resistance to specific sterilization procedure and (5) they should be stored well for long periods.⁽⁷⁾ Similar requirements also be published in British Pharmacopeia 1993,⁽²⁾ all BI should be met these basic criteria.

Table 3. Resistance of spores and cells of <i>Bacillus subtilis</i> to various treatments ⁽¹²⁾		
Treatment	Cells	Wild-type spores
(1) Hydrogen peroxide resistance		
Time of Treatment (min)	% survival after 10% hydrogen peroxide treatments	
1	11	--
2.5	0.3	92
5	--	88
20	--	60
(2) UV Resistance		
UV dose to kill 90% of population (J/m ²)	40	315
(3) Heat Resistance (D values)		
D ₉₅ ^o	--	14 min
D ₈₅ ^o	--	320 min
D ₆₅ ^o	<15 s	105 h
D ₂₂ ^o	--	2.5 yrs

Logarithmic death kinetics of microorganism

In any typical sterilization treatment, the death of contaminating microorganisms usually proceed as a logarithmic progression.^(1,23,24) It means that a constant proportion of microorganisms will die in each unit of time during exposure to a sterilant. Therefore, a plot of such death kinetics of microorganism is expressed as negative logarithms and indicates that sterilization is a probability function.^(7,23) The probability concept of survival is the foundation of acceptable assurance of sterility for a sterilized product. Since BI is the key to this inactivation kinetics, it should be reliable to provide predictable and reproducible in order to assure that the sterilization cycle is being accurately evaluated.⁽²³⁾

Characterization of death kinetics of BI by D-value, Z-value and F-value

Because of the significance of reliability, calibration of the biological indicator, in terms of population and resistance, is a critical step for its appropriate use.⁽¹⁸⁾ Resistance of BI is defined by Decimal Reduction Time (i.e. D-value), which is the time required for the tenfold or one logarithm reduction in spore population. In other words, it is equivalent to 90% kill. The more resistant of spores to a sterilant, the larger D-value they are. So the selection of BI for a particular sterilization cycle includes determination of D-values.⁽¹⁵⁾ Likewise, the appropriate use of BI may vary in different situations, because it depends on whether it is being used for cycle development, cycle validation or routine monitoring. The method for determination of D-value of the BI in different sterilization process is published in the USP XXXIV (2011), and the appropriate range of D-values for selecting a suitable BI in different sterilization mode are listed in Table 4 (radiation sterilization is not included). Another important factor in the selection and use of BI for the overkill method is the number of degrees of temperature change needed to change the D-value by one logarithm, which is termed as the Z-value. The Z-value is the measuring of the change in thermal resistance of the spore population over a given temperature range. Thus the higher Z-value means the less vary in D-value respect to temperature changes. Occasionally the F-value, which is the measuring of the microbial inactivation capability of a heat sterilization process and is defined in unit of time, may also

be used to express the lethality of the spores.⁽²³⁾ Assuming that the Z-value of a spore is 10°C, and if the D-value of the BI is one minute at 121°C, a F₀ of 10 minutes would reduce by 10 logarithms of the spore population.

Common bacterial spore strains (B1s) use in different sterilization processes

There are different BIs have been used in different method of sterilization. In all pharmacopeia of advanced countries, it has been specified that only spores of certain bacterial strains could be used in the validation of moist heat sterilization, ethylene oxide sterilization (EtO sterilization) or dry heat sterilization. For moist heat sterilization, spores of specific strain of *Bacillus stearothermophilus* are used. For EtO sterilization and dry heat sterilization, spores of *Bacillus subtilis* var niger are recommended (Figure 1).

According to the British Pharmacopoeia (1993), spores of *Bacillus pumilus* could be used to monitor radiation sterilization.⁽²⁾ But in the pharmaceutical and medical device industries, some people still rely primarily on physical devices, such as dosimeters. It seems that the BI has not been commonly adopted.⁽²³⁾ However, some people argue that sterilization is a process to eliminate living organisms, using a physical devices instead of a living organism is an irrational approach.

COMMERCIAL PACKAGING OF BIOLOGICAL INDICATORS

There are 4 forms of biological indicators commercially available; namely spore suspension, vial self-contained BI, paper strip BI and bulky packaging of spores. These different forms of commercially available BIs are shown in Figure 2.

Table 4. Typical characteristics for commercially supplied biological indicator systems as recommended in USP⁽³¹⁾

Sterilization Mode		Example of a Typical D-Value (min)	Range of D-Values for Selecting a Suitable BI (min)	Limits for a Suitable Resistance (Depending on the Particular D-Value) (min)	
				Survival Time	Kill Time
Dry Heat	160°C	1.9	Min. 1.0 Max. 3.0	Min. 4.0 Max. 12.0	10.0 32.0
	121°C*	5.0	Min 2.0 Max. 3.0	Min. 8.0 Max. 30.0	20.0 15.0
Ethylene Oxide (600 mg/L)	54°C, 60 RH%	3.5	Min. 2.5 Max. 5.8	Min. 10.0 Max. 27.0	25.0 68.0
Moist Heat	121°C	1.9	Min. 1.5 Max. 3.0	Min. 4.5 Max. 14.0	13.5 32.0

* This sterilization mode was included in an earlier version of the compendium (USP XXII, 1990) but not included in the latest version.

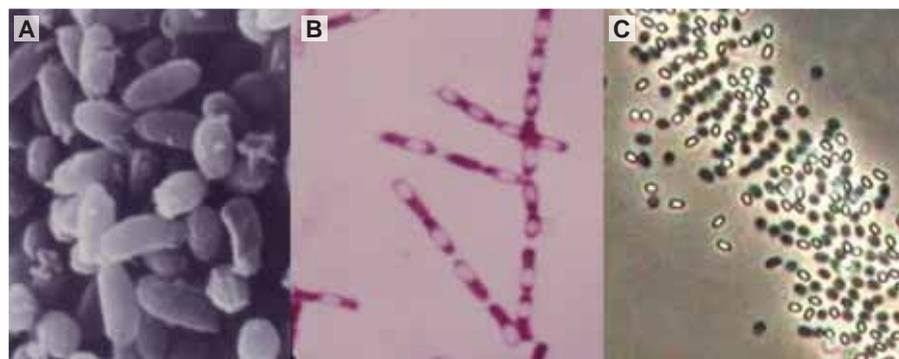


Figure 1. Spores of *Bacillus stearothermophilus* (Plate A), simple safranin stain of spores of *B. subtilis* var niger (Plate B) and *B. pumilus* (Plate C).



Figure 2. Different types of packaging of biological indicators. (From left to right): self-contained ampules, self-contained vial, paper strips inoculated with spores and bulky packaging of spores.

Paper strip BI

The paper strip BI is inoculated with a defined number of selected bacterial spore, which has known spore resistance and is individually packaged in a container that is readily penetrable by sterilant. After being exposure to the sterilant, the paper strip BI can be transferred aseptically from its container to the suitable recovery media for incubation. The result of test is simply detected by the observing whether there is any bacterial growth or not. The advantages of using paper strip BI are that they are relatively cheap, small in size and easy to handle. However, it is possible that the BI will get contaminated during the transferring a culturing medium after the sterilization. Although aseptic technique is applied, the inadvertent contamination may occur.⁽⁸⁾

Vial or ampule self-contained BI

For those vial or ampule self-contained BIs, they can be further subdivided into two types. One of them is referring to the plastic vials containing spore paper carriers (e.g. bacterial spores of *B. stearothermophilus* and/or *B. subtilis*), with crushable glass ampules of bacteriological culture media. After the sterilization cycle, the self-contained BI can be taken out from its sterilization chamber and then the ampules can be broken to permit the flow of the media towards the inoculated carrier. Then the unit is activated, which is followed by the incubation procedure. Last of all, the color change of the unit is checked for a positive or negative result. The advantage of self-contained BI over the paper strip one is no aseptic technique required, so the chance of inadvertent contamination is eliminated. But the size of a vial self-contained BI is relatively large when compared with the paper one, thus they may not fit in small locations. The other type of self-contained monitor is consisting seal glass ampule with *B. stearothermophilus* spores suspended in recovery medium, which is very similar to the one previously mentioned. But it is used for steam sterilization only, especially for the evaluation of sterilization of liquids.⁽²³⁾

Spore suspension

The last type of BI is the spore suspension containing selected bacterial spore strain. Normally the suspension media are sterile distilled water, buffer or ethanol/water solution. The spore suspension is directly inoculated on

the items to be sterilized, after the sterilization is completed, the items can be aseptically removed to culture medium for incubation. There are several events we should be aware of the items or products for inoculation do not affect the characteristics of the given spore strain, and the spore concentration in suspension is able to give a high density of spore after drying. The production of this form of BI may be easier than others, but the clumping of spores is likely to appear, particularly on hydrophobic surfaces. The occluded spores on pitted or crazed materials may magnify the given spore resistance subject to the sterilant.⁽²³⁾ Further discussions about the current factors affecting the accuracy of the use of BI will be noticed in the next section.

CURRENT PROBLEMS OF COMMERCIAL SPORES USED IN STERILIZATION PROECESS

As mentioned before, biological indicators are used for the monitoring sterilization procedures, so it is a kind of quality control tool and should be subjected to rigid standardization for quality assurance of their performance. Thus a stable reproducible test piece with an appropriate end point is needed. In other words, the performance of an indicator is of primary importance and that the bacterial count is of secondary importance.⁽⁷⁾

Different resistance and viable counts of commercial BIs

Actually, various companies adopt different production methods of biological indicators, resulting in different resistances for given spore spores⁽¹³⁾ or viable counts per indicator.⁽⁷⁾ Consequently, it is not surprising that the resistance performance tests of BIs give different results between various companies. In our studies, we found that even though spore crops were prepared from the same strain, they could exhibit different heat resistance properties if their preparation methods were different (Figure 3). It is obvious that spores prepared from Methods A (●) exhibited a linear relationship to heat inactivation while those from method B (■) gave different phenotypical properties; i.e. exhibiting a biphasic response to heat inactivation and more resistant to heat for a small portion of the spore crop. This phenomenon explain why different brands of BI products and even the same brand but because of inconsistent

production approach, it may lead to inconsistent results of assurance of sterilization. The typical characteristics of biological indicators have been published in the USP XXXIV (Table 4), the manufacturers should follow the suggestions for the production of BIs.

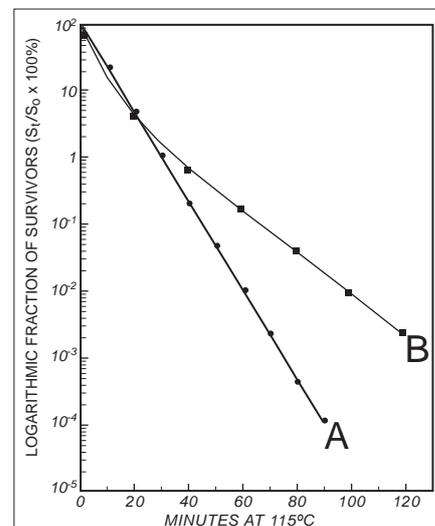


Figure 3. Heat inactivation curves of spore crops prepared from media containing different limiting component. Method A (●) was carbon-limiting medium while Method B (■) was sulphur-limiting medium.

Contamination of commercial BIs before used

We cannot exclude the possibility of the contamination of commercial BIs before used, although so far no actual cases have been reported. The presumptive contamination may be caused by the poor aseptic operations in the production area, in other words, the personnel problem is involved.⁽²⁶⁾

Reliability of BIs performance data in early days

Due to the limitation of ordinary autoclaves, the accuracy of most performance data obtained by the ordinary autoclaves in early days would be questionable.⁽²⁶⁾ It is because the time required to achieve the sterilization temperature is varies in autoclave cycles, the long heat-up operation to reach 121°C in autoclaves might cause the significant killing of spores.⁽⁷⁾ These variable cycles for heat up obviously had certain effect on BIs calibration results. Nowadays some special instruments have been developed for quality assurance of BIs.

The biological indicator evaluator resistometers (BIER) for steam or ethylene oxide sterilization are available for the determination of the D-value, and the Association for the Advancement of

Medical Instrumentation (AAMI) has listed the minimum performance standards for BIER vessels. The brief descriptions of the BIER vessels standard are shown in Table 5 and Table 6. The evaluations of the *B. pumilus* BIs for radiation sterilization should be contracted out by the BI manufacturers to a commercial irradiation facility or the National Institute of Standards and Technology.⁽²³⁾

Confidence in D-values and inactivation kinetics

The unwarranted confidence in D-values and inactivation kinetics of a BI may lead to a disastrous sterilizer failure.⁽²⁴⁾ During the sterilization process, the constant death rate of microorganisms is assumed throughout the cycle, until the safety margin is achieved. However, in actual practice, killing-curves often show deviations from straight lines.^(6,24) These deviations may cause the unpredictable survivors remain on the products although the sterilization cycle finished.

PARAMETERS AFFECTING THE PERFORMANCE OF BIOLOGICAL INDICATORS

In fact, the reliability and performance of BIs not only dependent on inherent characteristics, but also involve environmental parameters. A number of literature have reported the effects of environmental factors on their performance.^(8,16,20-22) There are 4 main aspects that should be carefully considered whenever using BI for validation of sterilization process;

namely preparation procedures, storage condition, positioning of BI in sterilization chamber and post-exposure of BI handling.

Preparation procedures

The preparation procedures are critical steps affecting the resistance characteristics of spore, which involve the composition of sporulation media,⁽¹⁴⁾ variation in temperature and humidity conditions during spore propagation, length of incubation, suspension harvest and cleaning procedures, the age of the spore suspension and the inoculation on suitable carrier for later use.⁽²³⁾ The composition of sporulation media must contain sufficient nutritional requirements since nutritional deficient cells may not be capable of synthesizing sufficient spore components related to the resistance ability. Normally the basic compositions of sporulation media are a limited amount of glucose together with various kinds of cation.⁽³⁰⁾ After the bacterial sporulation; the next critical step is the cleaning of spores. According to the investigation by Gerhardt and Black,⁽²³⁾ permeability of spores lead to the accumulation of low molecular weight nutrients such as amino acids and glucose, resulting the spores to lose heat resistance and initiated spore germination. Moreover, the remains from vegetative cells in suspension may affect the resistance characteristics of spore, in turn affecting the accuracy of the evaluation result. So during harvest, spores are removed from broth or agar by refrigerated centrifugation, and then repeated water rinses and centrifugation, alcohol or an alcohol and

water mixture may be used to destroy the remaining vegetative cells or other contaminants. Sometimes lysozyme or trypsin treatment is applied to remove cellular debris deposited.^(7,23) In some cases, alcohol-water mixture, such as methanol/water is used as a suspending medium, but the present of methanol may induce the changes of spore resistance. For example, spores dried on aluminum foil from 90% methanol / 10% water suspension were less resistant than those dried from distilled water suspension.⁽⁶⁾ Apart from these, the carrier nature of BIs also has significant influence on BIs performance.^(7,9,19,23,27) The D values of *Bacillus subtilis* var niger spores with plastic carrier were different from the aluminum and paper one.⁽¹⁹⁾ The D values for paper, aluminum and plastics are 4.370, 6.143 and 12.300, respectively, which indicates that plastics possess the highest resistance among the three testing materials (Figure 4).

The different drying condition for spore suspension on supporting medium (e.g. aluminum foils strips) may also cause different extent of spore resistance of *Bacillus subtilis* var niger. The spore that were dried at higher temperatures (56°C) over anhydrous CaCl₂ had more resistant than those dried at room temperature.⁽⁶⁾ The study by Shintani demonstrated that the effect of salt in the suspension during drying and the entrapment of microorganisms in salt crystal by pores in the cotton yarn carrier material would increase spore resistance.⁽²⁷⁾

Table 5. Performance requirements of Steam BIER Vessel ⁽²³⁾	
Performance Parameter	Requirement
1. Time to achieve desired temperature	≤ 10 seconds
2. Accuracy of pressure monitoring device	± 0.5 psig
3. Accuracy of temperature control device	± 0.5°C
4. Graduation of timers	
Precision	± 1 second
Repeatability	± 1%
5. Time to exhaust	≤ 5 seconds (reproducible)

Table 6. Performance requirements of Ethylene Oxide BIER Vessel ⁽²³⁾	
Performance Parameter	Requirement
1. Time to achieve sterilant concentration	≤ 1 minute (reproducible)
2. Operating values	
Temperature	± 1°C
Relative humidity	± 10 %
Sterilant concentration	± 15 %
3. Accuracy of temperature control device	± 0.5°C
4. Accuracy of pressure monitoring devices	± 6.35 mm Hg
5. Precision of timers	± 1 second
6. Time to exhaust	< 1 min (reproducible with ± 1 second)
7. Leakage of an evacuated chamber (125 mm Hg)	< 10 mm Hg/hr

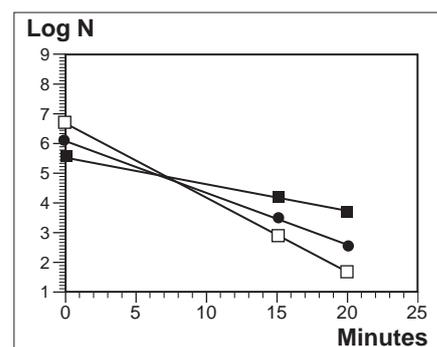


Figure 4. Lethality curves of *Bacillus subtilis* var niger spores on paper (□), aluminum (●) and plastic (■) groups as carrier. N = CFU/ carrier; D value of spore on paper = 4.370; aluminum = 6.143; plastic = 12.300.

Storage condition

After the preparation and inoculation procedures are completed, the storage of BIs should also be taken into account. The storage time, relative humidity (RH) and temperature are the environmental factors affecting HIs

performance.^(8,20,21,22) Reich et al. in 1979 reported on the declining of resistance of several commercially available *B. stearothermophilus* as a function of time. So in order to maintain the resistance of spores, Reich suggested to store the spore strips in the freezer because such storage helps to restrain the loss of heat resistance and germination ability, together to avoid any type of heat shock.⁽²²⁾ His later works with Morien in 1982 also demonstrated the influence of environment storage relative humidity on BI. There was a statistically significant decrease in moist heat resistance when the *B. stearothermophilus* BI was stored at 20°C under 0 or 20% RH.⁽²¹⁾ Also the *B. subtilis* BI has a significant increase in ethylene oxide resistance when they were placed at 20°C with 0% RH. However, Gillis gave different opinions on the storage of *B. stearothermophilus* BIs.⁽¹¹⁾ He pointed out that the stability of *B. stearothermophilus* BIs could remain over 17 months at 20 to 30°C and under 35% RH.

A study on some in-house paper strips revealed the resistance of spore to moist heat was increased when the spores were stored extensively under refrigeration with RH maintained less than 30%, while storage temperature, no matter at the ambient or at refrigerated environment, has no obvious effect on the performance of BIs on paper strips used in EtO sterilization even after two years of storage.⁽²⁰⁾ Similar results were found in *B. pumilus* strips used in gamma sterilization after a year of storage. The spore suspension placed at -20°C for 10 months and exposed on aluminum foil possessed a higher ethylene oxide resistance than those kept at 4°C or those freshly prepared.⁽⁸⁾ Nevertheless, storage time and condition of BIs should be recommended by the manufacturer.

Positioning of BIs during the evaluation process

Proper placing of BIs in the sterilization chamber is another important issue that should be contemplated, e.g., vertically, sideways, to assure maximum penetration of the substrate.⁽³¹⁾ For instance, when using the self-contained biological indicators in downward displacement steam sterilizers, be careful to ensure the steam could pass through the cap to the spore strip in the container. This is especially important for the high temperature and short exposure time of steam sterilization; improper placing of BIs may give a false positive result.⁽¹⁵⁾

Post exposure handling of BIs

After the exposure to sterilant, an appropriate recovery medium should be employed for the recovery of survival spores on BI. The formulation of recovery medium should provide conditions favoring cellular repair and spore germination as the survival spores might receive sub-lethal damage after the sterilization process.⁽⁷⁾ Basically, the recovery medium should include a nitrogen source, vitamins and minerals. As early in 1960, Cook and Brown proved that the medium used for the recovery process of heat damaged spores is an important issue.⁽⁷⁾ In 1968, Doyle et al. mentioned about the poor recovery was noted in sterilant-damaged spores suspended in fluid thioglycollate.⁽⁹⁾ Subsequent studies by Labbe in 1979 proved that certain compositions in recovery medium could give better recovery rate.⁽¹⁶⁾ It has been shown that addition of starch or charcoal to the medium was able to enhance the recovery of thermal injuries of *B. stearothermophilus* spores, while the TPDP medium (i.e. medium composed of trypticase, phytone, dextrose and phosphate) had no effect. Contrary, trypticase soy agar and dextrose tryptone agar were markedly inferiors.⁽¹⁶⁾ although the USP XXII (1990) recommended the use of soybean casein digest broth (SCDB) as a recovery medium. The discrepancy has been suggested as a consequent of different brands of SCDB which affect the D-value of BIs and in turns, swaying the accuracy of the BI sterility test.^(17,23) Since the nutritional value of SCDB or any medium obtained from different biological sources may vary greatly from each other. In the

standing point of the manufacturers, it would be impossible to carry out a complete analysis and the quality control of complex medium. Not only because it is expensive to do the analysis but also technically difficult.

On the other aspect, the prolonged post-sterilization hold time (the delay between the end of sterilant exposure and the starting of BI recovery testing) may affect the recovery ability on sterilant-damaged spores [4]. Caputo et al. showed the effect of storage temperature before recovery procedure for EtO-damaged *B. subtilis* and steam-impared *B. stearothermophilus* spores. Those spores stored at 20 to 25°C for 2 days before recovery treatments had 90% reduction in growth when compared to those were refrigerated at 2 to 5°C for the same period of time. But this phenomenon does not seem universal for BIs. In reviewing data presented in Table 7 and 8, no obvious trends on the decreasing of spore viability due to the prolonged post-sterilization hold time or storage temperature,⁽²³⁾ so further investigations are needed in this aspects.

Presence of pH indicator in self-contained BIs

Furthermore, the presence of pH indicator in some self-contained BIs which is for detecting bacterial growth may give certain effects on spore resistance.⁽²³⁾ A decreased D-value for *B. stearothermophilus* paper strips grew in SCDB with bromocresol purple was reported. Subsequently, the American Sterilizer Company carried out the test and revealed that using 0.03 g/liter of phenol red as a pH indicator does not

Table 7. Steam BI Post-sterilization Hold Study.⁽²³⁾

Post-hold Days	Spordi® (paper strip BI)		Proof Plus® (self-contained BI)	
	D ₁₂₁ (20 to 25°C)	D ₁₂₁ (32 to 35°C)	D ₁₂₁ (20 to 25°C)	D ₁₂₁ (32 to 35°C)
0	2.2	2.2	1.9	1.9
1	2.2 (0%)*	2.3 (4.5%)	2.0 (5.3%)	1.9 (0%)
2	2.2 (0%)*	2.2 (0%)	1.9(0%)	1.9 (0%)
3	2.0 (9.1%)	2.1 (4.5%)	1.9 (0%)	1.9 (0%)
4	2.2 (0%)	2.2 (0%)	1.7 (10.5%)	1.9 (0%)
5	2.1 (4.5%)	2.1 (4.5%)	1.8 (5.3%)	1.9 (0%)

* % different from baseline ("0 hold") D-value

Table 8. Ethylene Oxide BI Post-sterilization Hold Study.⁽²³⁾

Post-hold Days	Spordi® (paper strip BI)		Proof Plus® (self-contained BI)	
	D ₁₂₁ (20 to 25°C)	D ₁₂₁ (32 to 35°C)	D ₁₂₁ (20 to 25°C)	D ₁₂₁ (32 to 35°C)
0	3.2	3.2	4.1	4.1
1	3.1 (3.1%)*	3.1 (3.1%)	4.1 (0%)	4.3 (4.9%)
2	3.2 (0%)*	3.1 (0%)	4.0(0%)	4.1 (0%)
3	3.1 (3.1%)	3.2 (0%)	4.1 (0%)	4.0 (2.4%)
4	3.2 (0%)	3.1 (3.1%)	4.0 (2.4%)	4.2 (2.4%)
5	3.1 (3.1%)	3.1 (3.1%)	4.1 (0%)	4.4 (7.3%)

* % different from baseline ("0 hold") D-value

inhibit the outgrowth of low numbers of compromised spores.⁽²³⁾ This gives a reference to BI manufacturers in choosing proper pH indicator.

AUDIT OF BI MANUFACTURING

Auditing the manufacture of BI is an important issue for the application of BI. It is because not every user has its own BI verification facilities, certificate of product performance should be provided with each lot of BIs to ensure proper standard. The following information should be always included in the process of spore certification; namely (1) name of the BI manufacturer, (2) name and strain of the inoculated indicator organism(s), (3) the mode of sterilization to be monitored, (4) the product lot number, (5) the heat shock spore population level(s), (6) Products resistance characteristics at specified conditions using a stated methodology, (7) the expiration date, (8) recommended storage conditions and, (9) a method for safe disposal.⁽²³⁾

CONCLUSION

In consideration of the above problems described, it seems that biological indicators still should not be used alone in the evaluation of sterilization. So the use of BI plus the Good Manufacturing Practices and accepted practices for cycle development and validation is necessary. The chemical indicator can be used as a supplement to BI in the routinely monitoring in the sterilization process.⁽²³⁾ Nevertheless, biological indicators still have their significant value and are recognized as being the closest to ideal monitors to determine the efficacy of sterilization process.^(23,25) Thus, the standardization of media and procedure in manufacturing process of BI are needed in order to maximize or enhance the values and effectiveness of BIs.⁽⁷⁾

The audit of BI manufacturers and the quality audit (QA) help to assure the commercial BI is up to an acceptable standard. In the article by Graham and Boris, they have summed up 13 points for performing the QA test of BI. These points are concerning on the manufacturing procedure and its maintenance, the standard of operation process, the components in the QA test, personnel qualification and training and, shipping consideration etc. Furthermore, the FDA audits industrial BI users

approximately every second year, in turn to ensure the users have proper BI handling skills.⁽²³⁾ In recent year, a rapid readout biological indicator for steam sterilization has been developed, and it is able to monitor sterilization effectiveness within 3 hours while those conventional BIs require 48 hours to get the test result. Rutala et al (1996) also proved that the sensitivity of this rapid readout BI is equivalent to a standard 48-hour BI.⁽²⁵⁾ So such improvement gives users much convenience and enhances working efficiency.

In conclusion, further investigation and improvements of conventional BIs are necessary in order to promote the routine use of BIs for validating sterilization process.

Author's background

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*Result from PLATO study - BRILINTA™ reduced CV deaths vs clopidogrel without increasing overall major or fatal bleeding but have an increase in non-CABG major & minor bleeding.

ACS= acute coronary syndrome †OAP= oral antiplatelet

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Qualitative Evaluation and Bioactivity Assessment of *Polygonum bistorta* (拳參)

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Botanical Name: *Polygonum bistorta* L.

Plant Family: Polygonaceae

Pharmacopoeia Name: Bistortae Rhizoma

Chinese Name: 拳參 (Quanshen)

Other Names: Caoheche, Dao Jianyao, Di Xia, Hong Zaoxiu, Hui Toushen, Po Shanyao, Shan Liuliu, Shan Xiazi, Tong Luo, Zishen, Adderwort, Common Bistort, Easter Ledges, Easter Mangian, Knotweed, Oderwort, Osterick, Patience Dock, Snakeroot, Snakeweed, Twice Writhen

Part Used: Dried leaves or the root and rhizome

Common Uses: Clearing away heat and toxic materials, detumescence hemostatic

an important herbal drug. It is listed in the Pharmacopoeia of the People's Republic of China, and is frequently dispensed in many Traditional Chinese Medicines. It has been reported that the alcoholic extract of the rhizome exhibited some antibacterial, anti-inflammatory and anti-mutation activities. This herb has been used for the treatment of dysentery with bloody stools, diarrhoea in acute gastroenteritis, acute respiratory infection with cough; carbuncles, scrofula, aphthous ulcer, haematemesis, epistaxis, haemorrhoidal bleeding and venomous snake bite. Several triterpenoids, flavones and phenolic acids in the extract of *P. bistorta* have been isolated and structurally determined.

ABSTRACT

Polygonum bistorta L. is rich in starch and has been roasted and consumed by people as vegetable. The rhizome of this plant is also

Keywords: *Polygonum bistorta* L.; microscopic identification; chemical components; dysentery; antimicrobial activity; anti-inflammatory

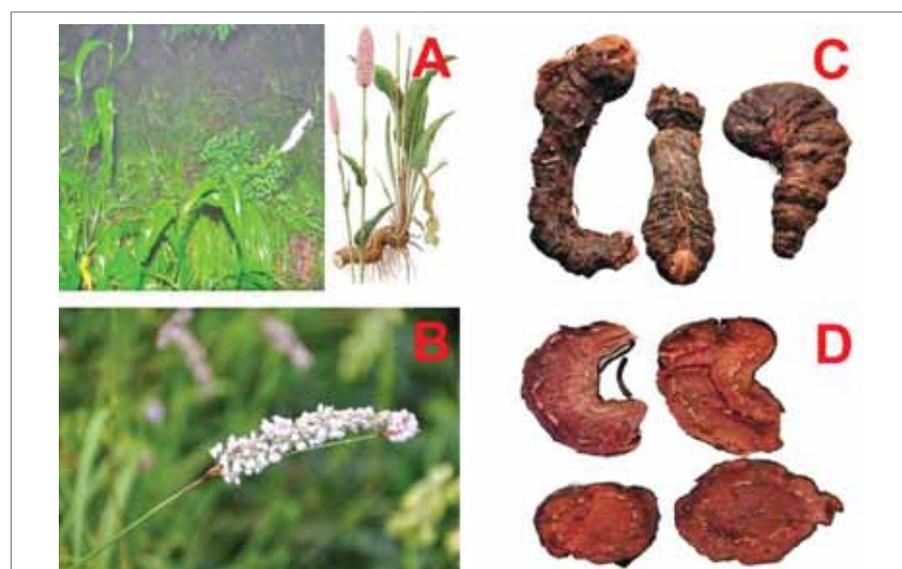


Figure 1. Morphological features of Bistorta. Plate A = whole plant photo (left) and sketch (right) of *Polygonum bistorta* L.; Plate B = flowers of *Polygonum bistorta* L., Plate C = rhizomes with all rootlets removed, Plate D = Decoction slices of rhizomes.



Contraindications

No obvious contraindications reported. Avoid its' uses in pregnant or breast-feeding women.

Undesirable Effects

No obvious toxicity reported but patients may experience stomach upset and GI irritation. Hepatic dysfunction may occur as well.

Interaction with Conventional Drugs

None reported. But combining it with certain drugs may alter their action or produce unwanted side effects.

INTRODUCTION

Polygonum bistorta L. (拳參), as shown in Figure 1, is one of the most important herbs in the genus of *Polygonum* (Polygonaceae) which is comprised of 300 species. This herb distributes worldwide; they could be found in north temperate regions such as Europe and North America,⁽¹⁾ where the herb is commonly known as adderwort, bistorta or knotweed. In China, it is called Quanshen and is especially abundant in the southwest region; over 120 species have already been identified and more than 80 species have reported medicinal uses. *Polygonum bistorta* L., which is widely grown in Hebei, Liaoning and Inner Mongolia in China, was firstly documented in "Tu Jing Ben Cao" (圖經本草).⁽¹⁾ The rhizomes of this herb have been used in Traditional Chinese Medicine to treat dysentery with bloody stools, diarrhoea in acute gastroenteritis, acute respiratory infection with cough; carbuncles, scrofula, aphthous ulcer, haematemesis, epistaxis, haemorrhoidal bleeding and venomous snake bite.⁽²⁾ However, its' uses are often mixed because of its appearances similar to

“chonglou” and “caoxuejie”.⁽³⁾ Therefore, authentication of bistorta for medicinal uses is particularly important. for antiinflammation, promoting blood circulation, dysentery, diuretic and hemorrhage.⁽⁴⁾

The plants of genus *Polygonum* contain many phenolic compounds; some of which show interesting biological activities. In recent years, some other compounds such as triterpenoids, flavonoids, phlobaphene and a trace of emodin have also been isolated from the rhizome of *P. bistorta* L. It has been reported that this crude herb exhibited antibacterial, anti-inflammatory and anti-mutational activity. Aqueous extracts of this herb are rich in tannins.

DESCRIPTION AND IDENTIFICATION

Figure 1C & D is the photos of Bistortae Rhizoma which is the dried rhizome of *Polygonum bistorta* L. (*Polygonaceae*). The rhizome is collected in spring upon budding or during autumn when stem and leaf withered. Soil, residual leaf and stem should be removed. After it has been dried under the sun, the rootlet should also be removed to obtain the Bistortae Rhizoma.

The herb is compressed-cylindrical and usually curved into a shrimp-like shape, with obtuse or slightly narrowed ends and about 2-11 cm long and 8-25 mm in diameter. Its external appearance is purple brown and dark brown, with one side protuberant and the other side flat or slightly furrowed. The surface consists of

thick annulated striations and remnants of rootlets or root scars. Its texture is hard. Fracture surface is roundish or nearly reniform, pale brown to brown with dotted, yellowish-white vascular bundles which are arranged interruptedly in a ring. The herb has slight odor and taste bitter and astringent. However, its mixture (including *Paleaceum Rhizoma*, *Paridis Rhizoma*) possess some similar characters,⁽³⁾ making it difficult to distinguish.

In this review, the differences between some macroscopic features of Bistortae Rhizoma and that of its counterfeit are reviewed. The detailed differences are summarized in Table 1.

Microscopic appearance

The transverse section of Bistortae Rhizoma appears to be hard, roundish and nearly reniform. Under the microscope, the cork is found to have several layers of brown cells containing some brown masses. The cortex occupies about 1/4 of the rhizome. Vascular bundles are collateral and arranged in an interrupted ring. The xylem consists of vessels and fibres while the phloem is narrow. The pith is broad and parenchymatous cells contain clusters of calcium oxalate.

Some important features in the powder of the crude herb could also be found under the microscope. For instance, the color of the powder is pale brownish-red. Starch granules are fairly abundant. They are broadly ovoid, long ellipsoid or subspheroid with a diameter of about 2-13 μ m. Their boundary is hilum pointed, V-shaped or slit-shaped and striation

distinct under a light microscope but appear black and cruciate-shaped under the polarized microscope. Compound starch granules are rare. If they are found, they are composed of 2-3 units. Clusters of calcium oxalate are numerous and scattered singly with 19-65 μ m in diameter. They appear as polychromatic under the polarized microscope. Vessels are mainly bordered-pitted. Spiral vessels are occasionally visible. Their diameter is around 10-55 μ m. Fibres are scattered or in bundles and their diameter is 6-30 μ m. The wall of this herb is relatively thick and pit canals are distinct. Cork cells are subsquare containing brownish-red masses.

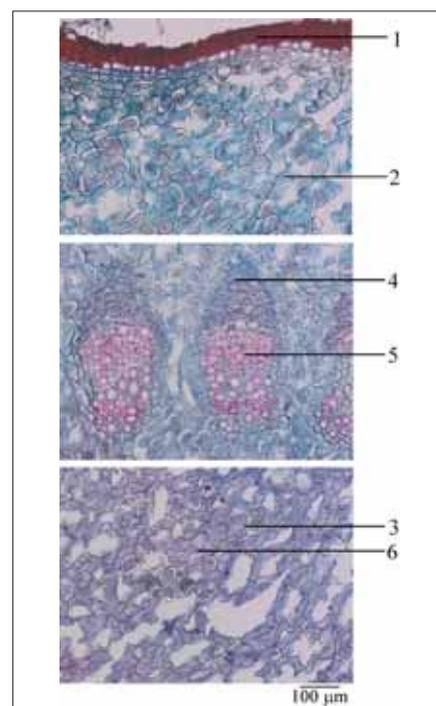


Figure 2. Microscopic features of transverse section of Bistortae Rhizoma. 1 = Cork, 2 = Cortex, 3 = Clusters of calcium oxalate, 4 = Phloem, 5 = Xylem, 6 = Pith

CHEMICAL COMPONENTS

Besides plenty abundant of starch as mentioned above, Bistortae Rhizoma also contains around 8.7-25% tannins. It is, indeed, one of the strongest botanical astringent for poultices. More recently, some secondary compounds have been isolated and structurally determined from the herb (Fig. 4). These include four new compounds, namely, 24(E)-ethylidenecycloartanone (Compound 1) and 24(E)-ethylidenecycloartan-3a-ol (Compound 2), (3-methoxycarbonylamino-4-methyl-phenyl)-cabamic acid methylester (Compound 10), and (3-methoxycarbonylamino-2-methyl-phenyl)-cabamic acid metylester (Compound 11) together with

Features	Bistortae Rhizoma	Paleaceum Rhizoma	Paridis Rhizoma
Shape	Compressed-cylindrical, usually curved into a shrimp-like shape, both ends obtuse or slightly narrowed	Triangular kidney shape, cylindrical	Nodositas compressed-cylindrical, slightly curved
Size	2-11 cm long, 8-25 mm in diameter	About 3 cm long, 8-20 mm in diameter	5-12 cm long, 10-45 mm in diameter
External color	Externally purple brown to dark brown	Externally purple brown to dark brown	Brown to greyish-brown
Surface	Rough, one side protuberant and the other side flat or slightly furrowed, with thick annulated striations and remnants of rootlets or root scars	Rough, one side protuberant and the other side flat, with thick annulated striations and ring-tailed or root scars	One side with significant nodositas, the other with many fibrous root scars. With ring-tailed protuberance.
Texture	Hard. Fracture roundish or nearly reniform, pale brown to brown, dotted vascular bundles yellowish-white, arranged interruptedly in a ring.	Hard. Fracture brown to greyish brown, dotted vascular bundles yellowish-white, arranged interruptedly in a ring.	Hard. Fracture white to brown, starchy
Odour and taste	Odour slight; taste bitter and astringent	Odour slight; taste bitter and astringent	Odorless, slightly bitter
Function attending	Clearing away heat and toxic materials, Detumescence, hemostatic	Scattered stasis hemostatic, Gas under pain	Clearing away heat and toxic materials, Detumescence, hemostatic, Cool liver spasm

seven known compounds including cycloartane-3, 24-dione (Compound 3), 24-methylenecycloartanone (Compound 4), *c*-sitosterol (Compound 5), β -sitosterol (Compound 6), β -sitosterone (Compound 7), friedelin (Compound 8) and 3β -friedelinol (Compound 9). All the cycloartane type triterpenoids, compounds 7 and 8 are reported for the first time from *Bistortae Rhizoma*.⁽⁵⁻⁹⁾

QUALITY ASSESSMENT OF BISTORTAE RHIZOMA

Although many secondary compounds have been isolated from *Bistortae rhizoma*, little attention was paid to the quality control with regard to bioactive constituents. Until now, the only quality criteria is recorded in the latest edition of Chinese Pharmacopoeia (2010 ed). Nevertheless, it only requires analyzing the contents of total ash, water, acid-insoluble ash and hot ethanol extract

(Committee of National Pharmacopoeia, 2010). None of the representative compounds was recommended as the marker for identification or assay with the specific chromatographic method (i.e., HPLC and TLC). Cecotti^(10,11) reported that fresh aerial parts of this plant species were collected in the Western Italian Alps during the summer at three different phenological stages, namely vegetative, flowering, and fruiting, and steam-distilled in a Clevenger-type apparatus. The oils accounted for 0.004 to 0.010% of the fresh plant material, and their compositions were determined by GC/FID and GC/MS. The composition of the oils during the vegetative period varied both in quantity and quality. Several classes of compounds were found with a predominance of alcohols in the vegetative phase, terpenes and linear-chained saturated hydrocarbons in the flowering phase, while saturated aliphatic acids and their methyl esters were predominant in fruiting phase. The most

abundant compounds were 3-methylbut-3-en-1-ol in the vegetative phase, linalool in the flowering phase, and dodecanoic acid and its methyl ester in the fruiting phase. Huang Jiabao and Xia Jing⁽¹¹⁾ also reported the determination of catecholic acid and gallic acid by HPLC. However, catecholic acid and gallic acid are very common in many plant medicines. Up to now, no special marker was selected for quality control of *Bistortae Rhizoma*.

BIOLOGICAL EFFECTS

Anti-bacterial activity

Liu Chunqi⁽¹²⁾ found that different concentrations of the ethanol extract on *Staphylococcus aureus* and *Escherichia coli* have dose dependent inhibitory activity. But it has no inhibition effect on dysentery bacillus. Liu et al reported that their study revealed the ethyl extract had inhibitory effect to *Bacillus subtilis*, *Proteus sp*, *Pseudomonas aeruginosa* and *Streptococcus pneumonia*.⁽¹³⁾ The inhibitory effect is attributed to gallic acid present in the herb.

Analgesic activity

The water extract of *Bistortae Rhizoma* could significantly reduce continuous pain stimulus by increasing the pain threshold of mice. When naloxone, an opioid receptor antagonist, was applied, it could not antagonize the analgesic action of *Bistortae Rhizoma* extract in rats. This phenomenon suggests the analgesic property of the herb has different mechanism. However, we have little knowledge about its pharmacological effects and further explorations are required.⁽¹⁴⁾

Anti-inflammatory activity

The aqueous ethanol extracts of *Bistortae Rhizoma* was screened for anti-inflammatory activity with various species.⁽¹⁵⁾ Administered (100 and 200 mg.kg⁻¹, p.o.) before the induction of carrageenan rat paw oedema, extracts of *P. bistorta* significantly suppressed both the maximal oedema response and the total edema response (monitored as area under the time course curve). *Bistortae Rhizoma* significantly inhibited both the acute and chronic phases of the adjuvant-induced rat paw swelling. Further studies on *Bistortae Rhizoma* (100-800 mg.kg⁻¹) revealed a dose-dependent inhibition of the carrageenan-induced rat paw oedema over the dose

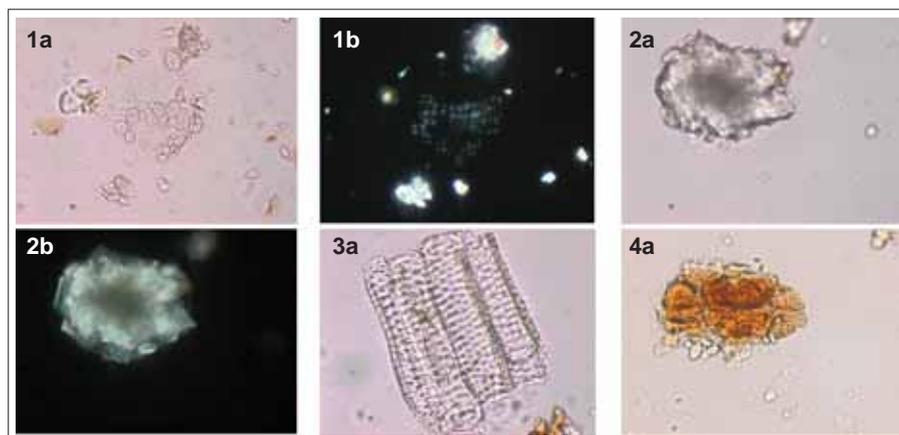


Figure 3. Microscopic features of powder of *Bistortae Rhizoma*. 1 = Starch granules; 2 = Clusters of calcium oxalate; 3 = Bordered-pitted vessel; 4 = Cork cells. a = Features under the light microscope; b = Features under the polarized microscope.

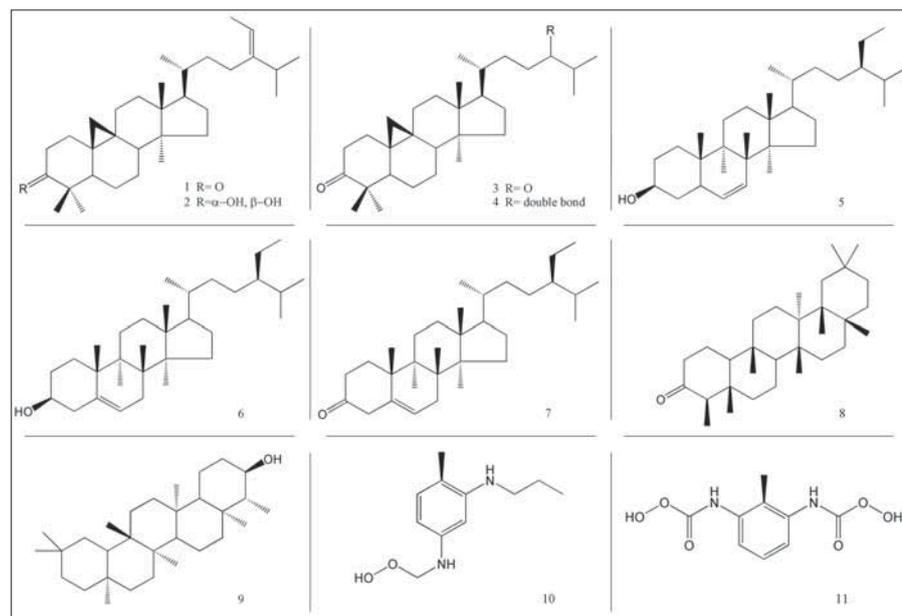


Figure 4. Chemical structure of some compounds isolated from *Bistortae Rhizoma*.

range 100-400 mg.kg⁻¹ and the ED₅₀ value was approximately 158.5 mg.kg⁻¹. The extract (200 mg.kg⁻¹), administered after the onset of the inflammatory responses reversed the course of both the carrageenan- and adjuvant-induced rat paw swelling. The results confirm that the extracts of *Bistortae Rhizoma* contain anti-inflammatory substances.

Anticancer activity

The chloroform, hexane fraction and the sub-fractions of *Bistortae Rhizoma* extracts were evaluated for their cytotoxic activity against P338 (Murine lymphocytic leukaemia), HepG2 (Hepatocellular carcinoma), J82 (Bladder transitional carcinoma), HL60 (Human leukaemia), MCF7 (Human breast cancer) and LL2 (Lewis lung carcinoma) cancer cell lines in culture.⁽¹⁶⁾ The extracts showed moderate to very good activity against P388, HL60 and LL2 cancer cell lines.

Effect on circulatory system

The biological effect of *Bistortae Rhizoma* on cardiovascular system was the focus of studies in recent years. Li et al found that the n-butyl alcohol extract of *Bistortae Rhizoma* could significantly reduce the contraction amplitude, velocity and diastolic velocity of the stereo right atrium of the guinea pig.⁽¹⁷⁾ They also found that different concentrations of butyl alcohol extract have a dual effect; it may activate the K⁺ channels or may inactivate the Ca₂⁺ channel. Consequently, it can inhibit or promote smooth muscle cell membrane voltage dependent calcium channel.

In another scenario, Ye Heyang et al showed that the protective effect of extract exerted acute myocardial ischemia in rat.⁽¹⁸⁾ It was noted that the activity of superoxide dismutase was improved in the rat's myocardial tissue after given the extract. Consequently, level of malondialdehyde in the tissue was reduced. As a result of these changes, radicals were also removed and lipid peroxidation was prevented, leading to some protective effects on myocardium. All these results demonstrated that the n-butyl alcohol extract of *Bistortae Rhizoma* has a remedy effect on myocardial ischemia.

Immunoregulatory Function of *Bistortae Rhizoma* Ethanol Extract.⁽¹⁹⁾

Li and Luan reported the immunoregulatory function of the ethanol extract of *Bistortae Rhizoma*.⁽¹⁹⁾

Their results demonstrated that the extract can enhance mononuclear macrophages phagocytic capacity of normal mice, promote T lymphocytes proliferation, increased serum hemolysin level and IL-2 in mice.

MODE OF ADMINISTRATION & DOSAGE

Quanshen is one of the strongest botanical astringents known. It comes as dried powder, slice root and tea. To prepare the decoction, some herbalists suggest mixing a teaspoon of the powdered root with 1 to 1½ cups of boiling water and taken orally not more than 3 cups per day for the treatment of diarrhea. The herb should not be continuously taken for more than 3 weeks a time.

CONCLUSION

Bistortae Rhizoma is an important Traditional Chinese Medicine and has been reported to exert various biological effects based on animal and cell model. It comes as dried powder, slice root and tea form. Internally, *bistort* is used to treat dysentery, gastric and pulmonary haemorrhage, irritable bowel syndrome, jaundice, peptic ulcers, and ulcerative colitis. It has also been used as an anthelmintic, an antidote for certain poisons, and a douche for excessive vaginal discharge or bleeding. Externally, it has been used for haemorrhoids, insect bites, measles, snakebites, and small burn or wounds. It is also included in mouthwash or gargle for canker sores, gum problems, laryngitis and sore throat. There are lots of data indicating that it has antibacterial, anti-inflammatory activity, anticancer and immune-regulatory function. Nevertheless, its underlying molecular mechanisms are still missing and not fully understood. Therefore, it is strongly suggested that modern methodologies should be applied to prepare its bioactive compounds and further studies on the pharmacological mechanism of these compounds should be encouraged.

ACKNOWLEDGEMENTS

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Authors' background

Dr. ZHANG Zhifeng, received his PhD degree from the Sichuan University of China and is currently a Postdoctoral Fellow at the City University of Hong Kong. **Mr SHEN Qing** is a PhD student at the same institute. He works on a project relevant to the effect of herbal extract on the lipidomic profile of organisms. He received his BSc and MSc trainings in China. **Dr. CHEUNG Hon-Yeung**, who is an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong, is a manufacturing pharmacist and biotechnologist. He has more than 40 years of work experience in industry, academic and consultancy jobs. He has been an expert witness in court and a member of the Biotechnology Committee for Hong Kong and Shenzhen Government. Dr. Cheung has published more than 200 papers and articles in many prestigious international journals. His email address: bhhyun@cityu.edu.hk

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The Annual General Meeting of the Pharmaceutical Society of Hong Kong

The Extraordinary General Meeting and Annual General Meeting of the Pharmaceutical Society of Hong Kong were held on 15 Dec 2012 at 5.00 p.m. at the PSHK Club House. The EGM is for the purpose of revising the M&A of PSHK in order to add one more Vice-President in the General Council. All voting members agreed to the revision. The president, Mrs. Mary Catherine Cheng reported on the activities for 2012 and the Treasurer, Ms. Candy Tai reported on the financial standing of PSHK. The GC member election began at 6.00p.m. Last year's President and the three Pharmacy & Poisons Board Representatives naturally become GC members and 11 General Council members were elected by ballots.

Seven old GC members stayed on and four new GC members were elected for the coming term. The meeting was followed by dinner at Majesty Seafood Restaurant [金御海鮮酒家] at 7.00 p.m. The food was great and everyone has the

opportunity to catch up with old friends and also meet new ones.

We look forward to a new year of vitality and advancement for the Pharmacy profession.

General Council of the Pharmaceutical Society of Hong Kong 2012			
President	Mrs. CHENG Mary Catherine		
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Hong Kong Pharmay Conference 2013

Date: 23rd – 24th March, 2013

Venue: Hong Kong Convention & Exhibition Centre, Wanchai, Hong Kong

Programme Rundown:

Day 1 (23rd March, 2013)

Time	Topics
1:30pm	Registration 註冊
2:30pm – 2:40pm	Opening ceremony (Room S221) 開幕儀式
2:40pm – 2:50pm	Welcome speech by Mr. Michael Ling, the Chairman of the Conference 會議主席致歡迎辭
2:50pm – 3:00pm	Keynote Speech By Dr. Wing Man KO (TBC) (Hong Kong SAR), Secretary for Food & Health Government of HKSAR 開幕辭
3:00pm – 3:40pm	Theme 1: Partnership with Government to Improve Pharmaceutical Care By Ms. Fatimah Moideen KUTTY (Singapore) 主題一：與政府合作改善藥物服務
3:40pm – 4:00pm	Coffee Break – Poster & Exhibition 休息·海報展覽
4:00pm – 4:40pm	Theme 2: Clinical Pharmacy Services in Emergency Medicine – getting things started at the front door By Dr. Simone TAYLOR (Australia) 主題二：開展急症室藥劑服務
4:40pm – 5:20pm	Theme 3: Adopting Hong Kong Pharmacy Management in China: an experience By Mr. Jian ZHANG (China) 主題三：在中國採用香港的藥劑部管理 — 經驗分享
5:20pm – 6:00pm	Theme 4: The Elephant in our Old Age Homes – why should we, pharmacist, care By Mrs. Mary CHENG (Hong Kong SAR) 主題四：安老院舍之藥物服務
6:00pm – 10:00pm	Conference Dinner (Chancellor Room, 4/F) 會議晚宴

Day 2 (24th March, 2013)

Concurrent Session	I	II	III
8:30am - 9:10am	<p>Therapeutic Debates 治療辯論</p> <p>Mr. Kenneth CHEUNG, Ms. Ritchie KWOK, Ms. Elaine LO;</p> <p>Ms. Phoebe CHAN, Mr. Jacky CHUNG, Mr. Eric YAU;</p>	<p>Clinical Service Implementation: the Planning, Process and Outcome 如何計劃推行新藥劑服務</p> <p>By Dr. Jennifer YU (Hong Kong SAR)</p>	<p>Medication Reconciliation – Inpatient & Outpatient Setting, Employing Technology to Create a Hassel-free System 使用智能科技進行藥物重組</p> <p>By Ms. Shakira ZAINUDIN (Singapore)</p>
9:10am – 9:50am	<p>Dr. Wilson LEUNG, Mr. Raymond MAK, Dr. Simon SO (Hong Kong SAR)</p>	<p>Pharmacist & Dietitian Collaboration in Community Pharmacy 社區藥劑師與營養師合作的模式</p> <p>By Mr. Vincent KWOK (Manning's District Pharmacist) & Mr. Edmund LUK (Manning's Dietitian) (Hong Kong SAR)</p>	<p>Unit-dose Dispensing – Good and Evil 單位配藥</p> <p>By Ms. Janet PANG (Hong Kong SAR)</p>
9:50am – 10:30am		<p>Veterinary Pharmacist 寵物藥劑服務</p> <p>By Mr. Rob MORRIS (United Kingdom)</p>	<p>Decentralised Automated Dispensing System in St. Teresa's Hospital 智能配藥 — 香港的經驗</p> <p>Mr. Eric WONG (Hong Kong SAR)</p>
10:30am – 11:00am	<p>Coffee Break – Poster & Exhibition 休息，海報展覽</p>		
11:00am – 11:40am	<p>Cancer in Children and Young People – Treatment, Symptom Management and Palliative Care 兒童與青少年之癌症治療</p> <p>By Ms. Julie MYCOFT (United Kingdom)</p>	<p>Building Professional Image in Pharmacy 如何為藥劑師打造專業形象</p> <p>By Ms. Mary NG (Hong Kong SAR)</p>	<p>“My E-drug Management” – Your most wanted Health App 「我最喜愛的健康程序」</p> <p>By Ms. S. C. CHIANG, Mr. Johnny WONG, Ms. Phoebe CHAN (Hong Kong SAR)</p>
11:40am – 12:20pm	<p>Future of Paediatric Formulation: an European experience 兒科劑型的未來 — 歐洲的經驗分享</p> <p>By Prof. Olivier BOURDON (France)</p>	<p>Transforming your Pharmacy Career – Leadership Lessons Along the Way 您的藥劑事業 — 改善領導能力</p> <p>By Ms. Grace LAU (Hong Kong SAR)</p>	<p>A Hong Kong Pharmacist in China: a New Model 香港藥劑師在中國：新管理模式</p> <p>By Mr. Bill LEUNG (Hong Kong SAR)</p>
12:20pm – 2:00pm	<p>Lunch – Poster & Exhibition, Multi-media Show 午餐及海報展覽，多媒體放映</p>		
2:00pm – 2:40pm	<p>Topical Treatment Respiratory Diseases in Paediatric Patients 兒童呼吸系統疾病之治療及管理</p> <p>By Dr. Daniel NG (Hong Kong SAR)</p>	<p>A day in the life of an Emergency Medicine pharmacist – Some Interactive Clinical Vignettes 在急症室的一天 — 個案分享</p> <p>By Dr. Simone TAYLOR (Australia)</p>	<p>Advanced Services in Primary Care Pharmacy 進階的基層藥劑服務：如何求同存異</p> <p>UK: Mr. William KWAN USA: Dr. Jennifer YU Aus: Ms. Cadence YAN/Mr. Arthur CHAN HK: Ms. Iris CHANG Sing: Ms. Fatimah Moideen KUTTY</p>
2:40pm – 3:20pm	<p>Biosimilars – a Pharmacist's Perspective 從藥劑師角度看生物仿製製藥</p> <p>By Prof. TROUVIN (France)</p>	<p>Limited admission Prior registration required 需於登記櫃檯預先註冊</p>	<p>Mod: Jason Chen</p>
3:20pm – 5:00pm	<p>Plenary Session: Man-power Review – Where do we go from here? 主題會議：藥劑的人力檢討</p> <p>Representatives from CUHK, DH, HA, HKU, Mannings, Watson's the Chemist</p>		
5:00pm – 5:15pm	<p>Closing by Ms. S. C. CHIANG, Vice Chairlady 副主席閉幕發言</p>		



Dear pharmacists, friends and colleagues,

It is my great pleasure to invite you to join us in the Hong Kong Pharmacy Conference 2013 – *the Silver Jubilee* !

The theme title of the Conference this year is “**TransPharmAction**”. The word is coined to convey the important message for **pharmacy** service to be **transformed** for the betterment of our clients, with positive and proactive **actions**.

Indeed the pharmacy profession has been evolving alongside our society and the healthcare industry in Hong Kong. Even our very Conference has transformed itself during the past 25 years, starting from a single organizing body - the Society of Hospital Pharmacists of Hong Kong - to a happy party of seven. We are particularly joyous to welcome the **University of Hong Kong** to join the family that already include **The Pharmaceutical Society of Hong Kong**, **The Practicing Pharmacists Association of Hong Kong**, **The Society of Hospital Pharmacists of Hong Kong**, **The Chinese University of Hong Kong**, **The Department of Health**, and **The Hospital Authority**.

This year we have paid particular attention to cater for the interest of our participants coming from all sectors of the profession. **Day One** comprises a plenary session with experts from different countries, reporting on their latest, transformative services, which will surely stimulate us to transform our own. The plenary will start off with a keynote speech by our new Secretary of Food and Health, the Government of HKSAR.

Day Two is filled with an assortment of exciting and relevant topics ensuring that our participants have many favorite ones to choose from. For **hospital pharmacy practice**, we feature medication reconciliation, unit dose dispensing, and automated, decentralized drug supply. There will be a sharing by a Hong Kong pharmacist setting up and running a mainland hospital pharmacy. Likewise, an Australian pharmacist will tell us of their innovative service in the area of emergency medicine.

For **clinical pharmacists**, there is a dedicated session for paediatrics, covering important areas such as oncology, respiratory diseases and drug formulations. To make it more interesting to learn clinical pharmacy, there will be 3 “therapeutic debates”, where local, iconic clinical pharmacists will discuss controversial topics and bring out the pros and cons of important drug therapy regimens/practices. The hot topic of Biosimilars, which is transforming the industry of drug development, will also be addressed.

For **community and primary care pharmacists**, they will find it interesting to come to the discussion where practice models from different countries are shared. We have also invited a dietitian and a veterinary pharmacist to add an extra flavor to our conference.

In **management**, we offer lectures about new service planning, professional image and leadership for success. If all these topics are not transformative enough for you, you should come to the presentation about the newest smart phone “app” called “My e-drug management”, which is developed to empower patients to manage their own medication profile.

In order to be able to enact the transformation, an adequate and well utilized workforce is instrumental to success. The grand finale of our Conference is a plenary discussion of the **Manpower Review** being undertaken by the initiative of the Hong Kong Government.

We hope the Conference 2013 – *the Silver Jubilee* will live up to its title – “**TransPharmAction**” ! See you all in the Hong Kong Convention and Exhibition Centre on 23 and 24 March, 2013.

Yours faithfully,

Mr. Michael Ling
Chairperson,
Hong Kong Pharmacy Conference 2013 – *the Silver Jubilee*

For full information, please visit the following site: <http://www.pharmacyconference.org/>

CE Questions Answer for 193(D&T)

The Use of Biologics (Anti-TNF) in Immunologic Diseases

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

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- **Renal Clear Cell Carcinoma (ccRCC): SUTENT[®] is the only agent to demonstrate more than 2 years' median OS in an ITT population of patients with metastatic clear cell RCC in a randomized phase 3 trial¹**
- **SUTENT[®] significantly improved time to progression, progression free survival and objective response rate vs. placebo in gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate²**
- **Most common adverse events included fatigue, diarrhoea, nausea, vomiting, hypertension, bleeding, mucositis, skin abnormalities, altered taste³**

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SUTENT ABBREVIATED PACKAGE INSERT

- TRADE NAME:** SUTENT[®]
- PRESENTATION:** Each capsule contains 12.5, 25, or 50mg of sunitinib (as malate).
- INDICATIONS:** For the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and the treatment of advanced renal cell carcinoma (RCC).
- DOSE:** Recommended dose for GIST and advanced RCC are 50 mg orally once daily, on a 4 weeks on treatment followed by 2 weeks off schedule (Schedule 4/2), with or without food. **Dose Modification:** Dose increase/reduction of 12.5-mg increments is recommended based on individual safety and tolerability. A dose reduction for SUTENT to a minimum of 37.5mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor. A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.
- CONTRAINDICATIONS:** None
- WARNINGS & PRECAUTIONS:** **Left Ventricular Dysfunction:** Discontinue SUTENT if clinical manifestations of CHF are present. Patients should be monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluation of left ventricular ejection fraction should also be considered. Baseline evaluation of ejection fraction should be considered in patients without cardiac risk factors. **QT Interval Prolongation & Torsade de Pointes:** Use with caution in patients with a history of QT interval prolongation; patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Periodic monitoring with on-treatment ECG and electrolytes should be considered. **Hypertension:** Monitoring and treatment as needed with standard anti-hypertensive therapy. Temporary suspension of SUTENT is recommended in case of severe hypertension, until hypertension is controlled. **Haemorrhagic events:** Clinical assessment should include CBCs and physical examinations. Epistaxis was the most common haemorrhagic adverse event reported in clinical studies. **Thyroid dysfunction:** Baseline thyroid function measurement recommended. Patients with hypothyroidism/hyperthyroidism should be treated as per standard practice before starting SUTENT. Close observation of signs & symptoms recommended. **Adrenal Insufficiency:** Monitor for adrenal insufficiency in patients who experience stress (e.g. surgery, trauma/severe infection). **Lab Test:** CBCs with platelet count and serum chemistries including phosphate should be performed before each treatment cycle.
- INTERACTIONS:** Co-admin. of CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflavin, ritonavir, saquinavir, telithromycin, voriconazole) & grapefruit increases sunitinib concentration, dose reduction for SUTENT is recommended. Co-admin. of CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease SUTENT plasma concentrations unpredictably, patients receiving SUTENT should not take St. John's Wort concomitantly, dose increase for SUTENT should be considered.
- PREGNANCY AND LACTATION:** **Pregnancy:** Category D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT. **Lactation:** It is not known whether SUTENT or its primary active metabolite are excreted in human milk, women should be advised against breastfeeding while taking SUTENT.
- SIDE EFFECTS:** AE >20%: fatigue, anhedonia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia and bleeding. Potentially serious AE: left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension and adrenal function.

Reference: SUTENT HK PI (version MARCH 2009)
Date of preparation: Oct 2010

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

References:

- Muller AJ et al. *Journal of Clinical Oncology* 2009; 27: 2584-90
- Demetri GD et al. *Lancet* 2006; 368: 1329-36
- SUTENT Hong Kong Prescribing Information Version: 16 March, 2009.



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NEW PRODUCTS

DEXILANT (Takeda)

Active Ingredient:

Dexlansoprazole 30 mg or 60 mg

Presentation:

14 delayed-release capsules of 30 mg or 60 mg

Pharmacological Properties:

Dexlansoprazole is the *R*-enantiomer of lansoprazole (a racemic mixture of the *R*- and *S*-enantiomers).

DEXILANT is supplied as a dual delayed release formulation in capsules for oral administration. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles

The dual delayed release formulation of DEXILANT results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours. Dexlansoprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the (H⁺,K⁺)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid production.

Indications:

Healing of all grades of erosive esophagitis (EE) for up to 8 weeks.

Maintain healing of EE for up to 6 months.

Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks

Dosage & Administration:

Adults:

Healing of EE: Recommended Dose: 60 mg once daily for up to 8 weeks.

Maintenance of Healed EE: Recommended Dose: 30 mg once daily; controlled studies did not extend beyond 6 months.

Symptomatic Non-Erosive GERD: Recommended Dose: 30 mg once daily for 4 weeks.

Elderly: No dosage adjustment is necessary for elderly patients

Hepatic Impairment: No adjustment for Dexilant is necessary for patients with mild hepatic impairment (Child-Pugh class A). Consider a maximum daily dose of 30 mg for patients with moderate hepatic impairment (Child-Pugh class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh class C)

Renal Impairment: No dosage adjustment is necessary for patients with renal impairment (see Renal Impairment under Pharmacokinetics under Actions).

Missed Dose: Take the dose as soon as remembered. If it is almost time for the next dose, skip the missed dose and take the next dose at the usual time. Do not double the dose to make up for the missed dose.

Administration:

Dexilant can be taken without regard to food.

Dexilant should be swallowed whole.

Alternatively, Dexilant capsules can be opened and administered as follows:

Open capsule; sprinkle intact granules on 1 tablespoon of applesauce; swallow immediately. Granules should not be chewed. Do not store for later use.

Contraindications:

DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT

Precautions:

Gastric malignancy, bone fracture, hypomagnesemia, increased risk of gastrointestinal infections

Drug Interactions:

Dexilant causes inhibition of gastric acid secretion. It is likely to substantially decrease the systemic concentrations of the HIV protease-inhibitor atazanavir, which is dependent upon the presence of gastric

acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, Dexilant should not be co-administered with atazanavir.

It is theoretically possible that Dexilant may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (eg, ampicillin esters, digoxin, iron salts, ketoconazole).

Warfarin: Co-administration of Dexilant 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR (see Drug-Drug Interactions under Pharmacokinetics under Actions). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with Dexilant and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Tacrolimus: Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Side Effects:

Diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, flatulence

Forensic Classification:

P1S1S3

TRAJENTA® (Boehringer Ingelheim) (Eli Lilly)

Active Ingredient:

Linagliptin

Presentation:

Each film-coated tablet contains 5 mg of linagliptin

Pharmacological Properties:

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4, EC 3.4.14.5) an enzyme which is involved in the inactivation of the

incretin hormones GLP-1 and GIP (glucagon-like peptide1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000 fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

Indications:

Trajenta is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:

as monotherapy

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

as combination therapy

- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Dosage & Administration:

The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be

maintained, and linagliptin administered concomitantly. When linagliptin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia

Trajenta can be taken with or without a meal at any time of the day.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

Precautions:

Trajenta should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.

In clinical trials of linagliptin as part of combination therapy with medicinal products not known to cause hypoglycaemia (metformin) rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.

When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo.

Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.

Drug Interactions:

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.

Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Side Effects:

The most frequently reported adverse reaction was

hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea

Forensic Classification:

P1S1S3



Active Ingredient:

Retigabine

Presentation:

TROBALT 50 mg, 100 mg, 200 mg, 300 mg and 400 mg film-coated tablets

Pharmacological Properties:

Retigabine acts primarily through opening neuronal potassium channels (KCNQ2 [Kv7.2] and KCNQ3 [Kv7.3]). This stabilizes the resting membrane potential and controls the sub-threshold electrical excitability in neurons, thus preventing the initiation of epileptiform action potential bursts. Mutations in the KCNQ channels underlie several human inheritable disorders, including epilepsy (KCNQ2 and 3). However other mechanisms by which retigabine may assert an antiepileptic effect have yet to be fully elucidated. In a range of seizure models, retigabine increased the threshold for seizure induction produced by maximal electroshock, pentylenetetrazol, picrotoxin and N-methyl-D-aspartate (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models, for example, in the fully kindled state and in some cases during the kindling development.

Indications:

Retigabine is indicated as adjunctive treatment of partial onset seizures with or without secondary generalization in adults aged 18 years and above with epilepsy.

Dosage and Administration:

Retigabine must be titrated, according to individual patient response, in order to optimize the balance between efficacy and tolerability. The maximum total daily starting dose is 300 mg (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week, according to the individual patient

response and tolerability. An effective maintenance dose is expected to be between 600 mg/day and 1,200 mg/day. The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established. If patients miss one dose or more, it is recommended that they take a single dose as soon as they remember. After taking a missed dose, at least 3 hours should be allowed before the next dose and then the normal dosing schedule should be resumed. When withdrawing Retigabine, the dose must be gradually reduced.

Renal Impairment

A 50% reduction in the initial and maintenance dose is recommended in patients with moderate to severe renal impairment. The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose is increased by 50 mg every week, to a maximum total dose of 600 mg/day.

Hepatic Impairment

A 50% reduction in the initial and maintenance dose is recommended in patients with moderate to severe hepatic impairment. The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose is increased by 50 mg every week, to a maximum total dose of 600 mg/day. Retigabine is not recommended during pregnancy and in women of childbearing age, not using contraception.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

Precautions:

Urinary retention

Urinary retention, dysuria and urinary hesitation were reported generally within the first 8 weeks of treatment and must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT prolonging effect. Caution should be taken when retigabine is prescribed with medicinal products known

to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment and in those with a corrected QT interval >440ms at baseline, an ECG should be recorded on reaching the maintenance dose.

Psychiatric disorders

Confusional state, psychotic disorders and hallucinations were reported. These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients.

Suicide risk

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. Therefore patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice if signs of suicidal ideation or behavior emerge.

Withdrawal seizures

As with other antiepileptic drugs, retigabine must be withdrawn gradually to minimize the potential for rebound seizures. It is recommended that the dose is reduced over a period of at least 3 weeks, unless safety concerns require an abrupt withdrawal.

Drug Interactions:

Retigabine can be reduced by Carbamazepine and Phenytoin and may increase digoxin serum concentrations and the duration of anesthesia induced by some anaesthetics. Alcohol may increase the visual blurring. Clinical laboratory assays of both serum and urine bilirubin may be falsely elevated

Side Effects:

Dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation.

Forensic Classification:

P1S1S3

