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Advance Therapy in Respiratory Diseases

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TRELEGY ELLIPTA

fluticasone furoate/umeclidinium/vilanterol

GSK

嶄新 乾粉吸入器

一開 一吸[1]

95%患者 都話易用易吸[2]

實話易吸

SAWADEE

TRELEGY ELLIPTA (fluticasone furoate/umeclidinium/vilanterol) Safety Information • Trelegy Ellipta should not be used in patients with asthma since it has not been studied in this population • Not for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy) • Use with caution in patients with unstable or life threatening cardiovascular disease • Do not stop therapy without physician supervision since symptoms may recur after discontinuation • Common adverse events: Pneumonia, sinusitis, headache, cough, arthralgia

References: 1. AC Grant, et al. J Aerosol Med Pulm Drug Deliv. 2015 Dec 1; 28(6): 474-485. **2.** Siler TM, et al. PLoS ONE. 2022 17(8): e0273170.

PM-HK-FVU-ADVT-230001 (01/2025) Date of preparation: 13/02/2023

HK65911 – Trelegy Ellipta inhalation powder pre-dispensed 100mcg/62.5mcg/25mcg

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Disclaimer

The Cover Shot

Kyoto is famous for its fall foliage in autumn, and millions of tourists are heading toward the oldest city in Japan to feast one's eyes in autumn. The combination of fall foliage and different temples and shrines with profound historical heritage provided an exceptionally breathtaking scene. Eikan-dō Zenrin-ji Temple (永觀堂禪林寺) is located in Sakyō-ku of Kyoto and was first established in 853. In autumn, the garden and temple were surrounded by splendid shades of orange and red. It is one of the autumn scenery that should not be missed. The cover photo was taken in Eikan-dō Zenrin-ji Temple in 2018. The glowing appearance of the maple leaves with the sunlight made it stand out from other fall foliage.

Dr YIP Wing-ho
Associate Consultant,
Medicine and Therapeutic Department,
Prince of Wales Hospital

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Editorial

Dr YEUNG Yiu-cheong
MBBS, MPH, MRCP, FHKCP, FHKAM, FRCP (Edin, Glasg)
President
CHEST Delegation Hong Kong and Macau

Dr Jenny CL NGAI
MBChB, MRCP, FHKCP, FHKAM, FRCP (Edin)
President
Hong Kong Thoracic Society

Co-Editors


Dr YEUNG Yiu-cheong Dr Jenny CL NGAI

It is our pleasure to introduce this issue of Hong Kong Medical Diary on "Advance Therapy in Respiratory Diseases". In the June 2022 issue of the Hong Kong Medical Diary, Dr CK Ng had brought us comprehensive coverage in the area of difficult and severe asthma. Like many other specialties, there is much advance in the field of respiratory medicine. In the present issue, we have covered five respiratory topics, including lung cancer, pleural disease, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease and MDR-TB.

Lung cancer is the most common cancer in Hong Kong and is the leading cause of cancer-related deaths. Dr Lynn YW Shong, and Dr David CL Lam, will give us an up-to-date review of the latest therapies for advanced non-small cell lung cancer, with a special emphasis on target therapies, angiogenesis inhibitors and immunotherapies.

Pleural diseases are common diseases presented to the Emergency Department requiring hospitalisation. The article “Advances in Pleural Medicine” by Dr Chan Ka -pang will give a general overview of the recent developments in the diagnosis and management of several major categories of pleural disease. This article will also be the CME article of the present issue of Medical Diary.

Idiopathic pulmonary fibrosis (IPF) is a progressive disease associated with significant morbidities and mortalities. The article "Update on Management of IPF" by Dr Se Hoi-ue and Dr Law Wai-lam will cover the area of diagnosis, drug therapy, points to note before starting anti-fibrotic drugs and acute exacerbations of IPF.

Chronic obstructive pulmonary disease is a chronic respiratory disease with significant morbidity and mortality. In the article on updates in the management COPD by Dr MC Chan and Dr YH Chan, the latest concepts on pathogenesis, diagnosis and updates in combined GOLD assessment were discussed. An update in pharmacological and non-pharmacological treatment in stable COPD and COPD exacerbation will be reviewed.

Remarkable progress in the treatment of MDR-TB/Rifampicin-resistant tuberculosis comes from the advent of new drugs such as bedaquiline and pretomanid and repurposed drugs such as linezolids. Dr Alan CK Chan, and Dr Maria SN Lee, will give a review of the scientific evidence behind the latest WHO guideline in 2022.

We sincerely hope this issue of the Medical Diary will provide useful information to readers. Finally, we would like to express my gratitude to all the contributing authors for their invaluable support.

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

Annual Scientific Meeting 2023

Revolutionising Healthcare Through Innovations

Date: 22 October 2023, Sunday **Time:** 09:00-17:00

Format: Hybrid 1) Online: Zoom Webinar
2) Onsite: The Ballroom, 7/F, Cordis, Hong Kong
555 Shanghai Street, Mong Kok, Kowloon

09:00-09:30 **Onsite and Online Reception**

09:30-10:00 **Opening Ceremony**

10:00-11:00 **Session 1** (Plenary Session)

- **中國人口老齡化現狀、挑戰與老年醫學發展機遇**
  王建業教授
  中華醫學會, 老年病學分會主任委員
- **Medical Advance in Exoskeleton for Neurorehabilitation**
  Prof. Raymond Kai-yu TONG
  Professor and Founding Chairman, Department of Biomedical Engineering, CUHK

11:20-12:20 **Session 2** (AstraZeneca Session - Advances in Management of Asthma and Chronic Kidney Disease)

- **Practice Changing Update in GINA 2023**
  Dr. Terence Chi-chun TAM
  Honorary Clinical Assistant Professor, Department of Medicine, HKU
- **Advancing the Management in Chronic Kidney Disease - From Primary to Collaborative Care**
  Dr. Winston Wing-shing FUNG
  Associate Consultant, Department of Nephrology & Medicine, Prince of Wales Hospital

12:20-13:20 **Lunch Symposium** (Keynote Lecture)

- **Modernising Chinese Medicine**
  Prof. BIAN Zhaoxiang
  Associate Vice-President (Chinese Medicine Development), HKBU

13:20-14:20 **Session 3A** (Otsuka Session – New Advances in Management of Leukaemia)

- **Unmet Needs in the Management of Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndromes (MDS)**
  Dr. Harinder Singh Harry GILL
  Clinical Associate Professor, Department of Medicine, School of Clinical Medicine, HKU
- **Tyrosine Kinase Inhibitors in CML and Ph+ ALL**
  Dr. Garret Man-kit LEUNG
  Associate Consultant, Department of Medicine, Queen Mary Hospital

Session 3B (Advances in Bladder and Rectal Diseases Disorders)

- **Hemorrhoidal Crisis - How Can Be Treated and Avoided?**
  Dr. Philip Ming-ho KAM
  Specialist in General Surgery
- **Overactive Bladder Treatment Strategies: Insights from the OAB Consensus Statement**
  Dr. Peggy Sau-kwan CHU
  Consultant Urologist, Department of Surgery, Tuen Mun Hospital

14:20-15:20 **Session 4A** (Advances in Paediatric Neuro-developmental Disorders)

- **Holistic Care in Paediatric Pharmaco Resistant Epilepsy in Era of Genomics: Etiologies Based Medical, Dietary and Surgical Intervention & Neuropsychology**
  Dr. Mario Wai-kwong CHAK
  Associate Consultant, Department of Paediatric and Adolescent Medicine, Tuen Mun Hospital
  Ms. Vitti Wai-kei POON
  Clinical Psychologist, Child Assessment Center, Tuen Mun Hospital
- **Breakthrough In Early Identification of Autism: Genomic and Neural Encoding Testing**
  Dr. Fanny Wai-fan LAM
  Honorary Clinical Assistant Professor, Paediatrics and Adolescent Medicine, HKU

Session 4B (Chinese Medicine Session)

- **Potential Role of Evidence-based Herbal Medicines in Cancer Management**
  Prof. Clara Bik-san LAU
  Associate Director, Institute of Chinese Medicine,
  State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants, CUHK

15:40-16:40 **Session 5** (Advances in Allergy & Immunology Session)

- **Recent Advances in House Dust Mite Allergy Immunotherapy** ***(Lecture via Zoom)***
  Prof. Eike Gunther WÜSTENBERG
  Specialist in Otorhinolaryngology and Allergology, Professor of Medicine
- **Innovative Management Strategies for Type 2 Inflammatory Diseases**
  Dr. Alson Wai-ming CHAN
  Specialist in Paediatric Immunology, Allergy & Infectious Diseases

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健道同行

Partnering in the Health Journey

攜手共建香港基層醫療

Let's join hands to strengthen Primary Healthcare in Hong Kong

《基層醫療指南》(《指南》)是一個以網絡模式建立的電子資料庫，旨在便利公眾根據基層醫療服務提供者的執業資料尋找合適的基層醫療服務。

Primary Care Directory (PCD) is a web-based database set up to facilitate the public to search for suitable primary care service providers according to their practice information.

基層醫療指南
Primary Care Directory

由2023年10月6日起，醫生需要載列於《指南》，才能參與政府資助的基層醫療計劃。

Being listed in the PCD is a pre-requisite for doctors to enrol in Government-subsidised Primary Healthcare (PHC) programmes with effect from 6 October 2023.

涵蓋的計劃包括地區康健中心服務、疫苗資助計劃、院舍防疫注射計劃、長者醫療券計劃、大腸癌篩查計劃、普通科門診公私營協作計劃、慢性疾病共同治理先導計劃，以及將來推出的政府資助的基層醫療計劃。

Involved programmes include the District Health Centre services, Vaccination Subsidy Scheme and Residential Care Home Vaccination Programme, Elderly Health Care Voucher Scheme, Colorectal Cancer Screening Programme, General Outpatient Clinic Public-Private Partnership Programme, Chronic Disease Co-care Pilot Scheme and subsequent new PHC initiatives.

我們歡迎普通科或有興趣提供基層醫療的專科醫生加入《指南》。醫生可以選擇在《指南》內提供他們的專業資格讓公眾參考。如果是專科醫生，其專科醫生身分也可以在《指南》內顯示。

General practitioners (GP) and specialists interested in providing PHC are welcome to join PCD. Doctors may choose to provide their professional qualifications in the PCD for public reference. For specialists, their status as specialists can also be shown in the PCD.

如有興趣登記加入《指南》，請瀏覽以下網址、掃描二維碼、致電熱線3576 3658或發送電郵至pho@healthbureau.gov.hk。

If you are interested in enrolling in PCD, please visit the website below, scan the QR code, call the hotline at 3576 3658 or email to pho@healthbureau.gov.hk.

www.pcdirectory.gov.hk

慢性疾病共同治理先導計劃
Chronic Disease Co-care Pilot Scheme

家庭醫生配對 促進長久醫患關係
Family Doctor Pairing cultivates long-term doctor-patient relationship

在「慢性疾病共同治理先導計劃」（「慢病共治計劃」）下，每位參與計劃的市民均會與自選的家庭醫生進行配對。政府會向市民提供資助，讓市民透過家庭醫生，在私營醫療界別進行篩查、治療和管理目標慢性疾病(例如高血壓、糖尿病和血糖偏高)。

Under the Chronic Disease Co-care Pilot Scheme (CDCC Pilot Scheme), all participating citizens will be paired with self-selected Family Doctors. Subsidies will be provided to citizens for screening, treatment and management of target chronic diseases, such as hypertension, diabetes mellitis and pre-diabetic condition, through the paired Family Doctors in the private healthcare sector.

家庭醫生透過長久醫患關係，為配對病人提供全面的醫療服務，包括提供疫苗接種和癌症篩查等其他基層醫療服務，以及在地區康健中心的支援和協助下，為市民制定健康人生計劃。

Through long-term doctor-patient relationship, Family Doctors will provide holistic healthcare to their paired patients, including vaccination and cancer screening, as well as developing life course preventive care with the support and assistance from District Health Centres.

計劃主要元素
Key elements of the Scheme

資助 Subsidies	家庭醫生在篩查和治療時可獲資助。配對參加者也可獲安排資助的化驗 Subsidies are provided to Family Doctors for screening and treatment of their paired participants. Their paired participants can also receive subsidised laboratory tests
共付模式 Co-payment	配對參加者在篩查階段應診，需向家庭醫生支付指定的共付費用。在治療階段的受資助診症，則配對參加者需付家庭醫生就參加計劃時訂明的診症共付額（由家庭醫生釐定） Paired participants need to pay a fixed co-payment to Family Doctors during screening phase and a flexible co-payment (determined by the Family Doctors) during treatment phase
社區藥物名冊 Community Drug Formulary	家庭醫生可以優惠價格訂購社區藥物名冊內特定的藥物 Family Doctors can order specified drugs in the Community Drug Formulary at low prices
按服務表現付費獎勵 Pay-for-Performance incentives	如配對病人能夠達到健康目標，家庭醫生可獲得獎勵 Family Doctors can be awarded with incentives by achieving health targets for their paired patients
雙向轉介機制 Bi-directional referral mechanism	家庭醫生可按準則為配對病人轉介至醫管局接受一次指定的專科諮詢服務 Family Doctors can initiate a request for a specialist consultation by the Hospital Authority for their paired patients based on specified criteria
團隊合作 Teamwork	如有需要，家庭醫生可安排配對參加者接受護士診所、視光師和物理治療師等專業人士跟進 If necessary, Family Doctors could arrange follow-up by professionals such as Nurse Clinic, Optometrists and Physiotherapists for the paired participants

如想了解更多或成為家庭醫生及參加「慢病共治計劃」，請瀏覽以下網址、致電熱線 2157 0500 或發送電郵至cdccdoctor@healthbureau.gov.hk。

If you want to know more or become a Family Doctor and join the CDCC Pilot Scheme, please visit the website below, call the hotline at 2157 0500 or email to cdccdoctor@healthbureau.gov.hk.

www.primaryhealthcare.gov.hk/cdcc

Update on Medical Treatment of Multidrug-resistant/Rifampicin-resistant Tuberculosis

Dr Alan CK CHAN
MRCP(UK), FHKAM(Medicine)
Specialist in Respiratory Medicine
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health, Hong Kong

Dr Maria SN LEE
MRCP(UK), FHKAM(Medicine)
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health, Hong Kong


Dr Alan CK CHAN Dr Maria SN LEE

INTRODUCTION

Multidrug-resistant (MDR-TB) tuberculosis (defined as Mycobacterium tuberculosis with resistance to at least isoniazid and rifampicin) and rifampicin-resistant tuberculosis (RR-TB) remain a global health challenge nowadays. According to the latest World Health Organization (WHO) report, there were an estimated 450,000 incident cases of MDR/RR-TB in 2021 globally, up 3.1 % from 437,000 in 2020[1]. An estimated 191,000 deaths occurred due to MDR/RR-TB in 2021[1]. Promising progress has been made in the management of MDR/RR-TB in recent years, thanks to the advent of new drugs such as bedaquiline and pretomanid and repurposed drugs such as linezolid[2 - 3]. The data from several observational studies and clinical trials on the safety and effectiveness of regimens incorporating these drugs have bolstered the armamentarium against MDR/RR-TB. Based on the results of these trials, the World Health Organization (WHO) has updated its guidelines on the management of MDR/RR-TB on a number of occasions in recent years, including the most updated guideline published in December 2022.

LANDMARK INITIATIVES TO TREAT PATIENTS WITH SHORTER REGIMENS

Historically, patients with MDR/RR-TB were treated with long and arduous regimens that were often poorly tolerated. The interest in reducing the duration of treatment for MDR/RR-TB has driven several initiatives in recent years to treat patients with shorter regimens. The results from observational studies conducted in Bangladesh, Cameroon and Niger using standardised regimens lasting 12 months or less have shown a higher likelihood of treatment success compared with longer regimens when treating selected patients who have not been previously exposed or do not have additional resistance to second-line drugs[4 - 5]. Given the published data and potential impact of shorter regimens on treatment cost and affordability, the WHO recommended for the first time in 2016 a standardised 9 - 12-month injectable-containing shorter MDR-TB regimen for eligible patients[6]. Two years later, the results of the randomised STREAM Stage 1 trial that demonstrated non-inferiority of shorter regimens versus longer regimens with respect to efficacy outcome were made available to the WHO[7]. Based on the data from the STREAM trial, and individual patient data (IPD) collected from national authorities and technical agencies, the WHO released a revised recommendation on the use of a shorter MDR-TB regimen that reinforced the importance of excluding resistance to the fluoroquinolones and second line injectable agents before a shorter regimen is considered[8]. In that document, the WHO also recommended replacing the injectable agent, kanamycin or capreomycin, with amikacin[8]. To address the problem of toxicity of injectable agents, and in light of observational data on an all-oral bedaquiline-containing shorter regimen of 9 months duration from the South Africa TB Programme, the WHO recommended an injectable-sparing regimen of 9 months duration (with bedaquiline replacing the injectable drug and given for six months) for the treatment of selected patients with MDR-TB in December 2019[9 - 11]. The continuous quest for shorter, less toxic regimens has motivated a number of further studies designed to test new regimens comprising bedaquiline, pretomanid and linezolid (BPaL)-based regimens in subsequent years (Table 1)[12 - 14]. In the Nix-TB study, which was a single-arm uncontrolled open-label intervention study that investigated the BPaL with high dose linezolid (1,200 mg daily) conducted from 2015 to 2017, 63/71 (89 %) patients with extensively drug-resistant TB (XDR-TB) (defined as MDR-TB with additional resistance to any fluoroquinolone and at least one injectable (amikacin, capreomycin, or kanamycin) according to the then prevailing WHO definition and 35/38 (92 %) patients with MDR-TB in the intention-to-treat population achieved favourable outcomes at six months, at the expense of high frequency (peripheral neuropathy 81 %, myelosuppression 48 %) of adverse effects from linezolid[12]. Based on the data from the Nix-TB study, the WHO recommended in December 2019 the use of the BPaL regimen in XDR-TB patients under operational research conditions[11]. In the follow-up study (ZeNix), which was a partially blinded randomised controlled trial testing four different arms of the 26-week BPaL regimen with different doses (600 mg vs 1,200 mg) and durations (9 or 26 weeks) of linezolid, the overall risk-benefit ratio favoured the arm that received linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer linezolid dose modifications.[13] In the TB-PRACTECAL, which was a Phase 2 - 3, open-label randomised controlled trial of patients 15 years of age or older who had RR-TB, investigating three different 24-week regimens containing BPaL with or without moxifloxacin or clofazimine, showed that the 24-week BPaL plus moxifloxacin (BPaLM) regimen was non-inferior to the locally approved standard of care that was based on WHO recommendations at the time of

Table 1. Main clinical trials on shorter regimens comprising bedaquiline, pretomanid and linezolid and/or moxifloxacin for the treatment of MDR/RR-TB in recent years (Adapted from reference 16)

Trial name	Description	Setting	Experimental arms	Control arm	Remarks
Nix-TB[12]	A single-arm uncontrolled unblinded intervention study	South Africa	14 years and older XDR-TB or treatment intolerant/ nonresponsive MDR-TB receiving BPaL with high dose linezolid (1,200 mg daily) for 6 - 9 months	No standard of care control group	63/71 (89 %) patients with XDR-TB and 35/38 (92 %) patients with MDR-TB achieved favourable outcomes at six months; the frequency of adverse effects from linezolid was high (periphery neuropathy 81 %, myelosuppression 48 %)
ZeNix[13]	A partially blinded randomised controlled trial	South Africa, Georgia, Moldova, the Russian Federation	14 years and older XDR-TB, pre-XDR-TB or intolerant/ nonresponsive MDR/RR-TB, investigating four different arms of the 26-week BPaL regimen with different doses (600 mg vs 1,200 mg) and durations (9 or 26 weeks) of linezolid	No standard of care control group No standard of care control group	Overall risk-benefit ratio favoured the arm that received linezolid at a dose of 600 mg for 26 weeks
TB-PRACTECAL[14]	A phase 2 -3, open-label randomised controlled trial	South Africa, Belarus, Uzbekistan	15 years and older patients who had RR-TB, investigating three different 24-week regimens containing BPaL with or without moxifloxacin or clofazimine	Multiple local standards of care, including 9 - 12-month injectable-containing regimen, 18 - 24-month WHO-recommended regimen (pre-2019), 9 - 12-month all-oral regimen, 18 - 20-month all-oral regimen	The 24-week BPaL + moxifloxacin (BPaLM) regimen was non-inferior to the locally approved standard of care that was based on WHO recommendations at the time of the study

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; MDR-TB: multidrug-resistant tuberculosis; RR-TB: rifampicin-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis

Table 2. Summary of new regimen options for treatment of patients with MDR/RR-TB (Adapted from reference 16 & 17)

Regimen		Age < 14 years	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB[7]	Extrapulmonary TB	Persons living with HIV	Pregnant/ breast feeding women
Shorter 6-month regimen	BPaLM[1]	No	Yes	No	No	Yes	Yes except CNS, miliary and osteoarticular	Yes	No
	BPAL[2]	No	No	Yes	No	Yes	Yes except CNS, miliary and osteoarticular	Yes	No
Shorter 9-month all oral regimen	4 - 6 Bdq(6 m)-Lfx/ Mfx-Cfz-Z-E-Hh-Eto/5 Lfx/Mfx-Cfz-Z-E[3]	Yes	Yes	No	No	No	Yes except meningitis, miliary, pericardial and osteoarticular	Yes	No
	4 - 6 Bdq(6 m)-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hh/5 Lfx/Mfx-Cfz-Z-E[4]	Yes	Yes	No	No	No	Yes except meningitis, miliary, pericardial and osteoarticular	Yes	Yes
Longer 18 - 20-month individualised regimens[5]	18 - 20-month regimens based on the WHO drug grouping A, B, and C[6]	Yes	Yes/No	Yes/No	Yes	Yes	Yes	Yes	Yes (with exceptions, see footnote)[8]

Bdq: bedaquiline; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; Cfz: clofazimine; CNS: central nervous system; E: ethambutol; Eto: ethionamide; Hh: high dose isoniazid; Lfx: levofloxacin; Lzd: linezolid; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; Mfx: moxifloxacin; Pre-XDR-TB: MDR-TB that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid) (revised WHO definition as in January 2021); Z: pyrazinamide

[1] No documented or suspected resistance to bedaquiline, pretomanid, linezolid, fluoroquinolone
[2] No documented or suspected resistance to bedaquiline, pretomanid, linezolid
[3] No documented or suspected resistance to fluoroquinolone, bedaquiline, clofazimine, ethionamide
[4] No documented or suspected resistance to fluoroquinolone, bedaquiline, clofazimine, linezolid
[5] When 6-month BPaLM/BPaL and 9-month regimens could not be used
[6] Group A: levofloxacin or moxifloxacin, bedaquiline, and linezolid; Group B: clofazimine, and cycloserine or terizidone; Group C: ethambutol, delamanid, pyrazinamide, imipenem–cilastatin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and p-aminosalicylic acid
[7] Extensive disease in adults defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography; in children aged below 15 years, extensive disease is defined by the presence of cavities or bilateral disease on chest radiograph
[8] Ethionamide is contraindicated in pregnancy because animal reproduction studies have shown an adverse effect on the foetus; amikacin and streptomycin are teratogenic and should be avoided in pregnant/breast feeding women; dosing and safety data to support the optimal use of second-line TB drugs such as bedaquiline and linezolid during pregnancy are sparse; the benefits of providing effective MDR/RR-TB treatment with bedaquiline and linezolid to the parent is considered to outweigh the potential risks posed to the in-utero foetus or the breastfed infant

the study[14]. The results of the TB-PRACTECAL and the ZeNix study have prompted the WHO to further update its recommendations on the treatment of MDR/RR-TB in 2022[15-17].

HIGHLIGHTS OF NEW MDR/RR-TB TREATMENT OPTIONS

Based on the evidence provided by the TB-PRACTECAL trial and ZeNix trial, the WHO suggested in 2022 the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (at a daily dose of 600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients (Conditional recommendation, very low certainty of evidence) (Table 2)[15-17]. The recommendation applies to patients aged 14 years and older with MDR/RR-TB with presumed or documented fluoroquinolone susceptibility involving the lung and extrapulmonary sites other than the central nervous system, osteoarticular and disseminated (miliary) forms, irrespective of HIV status. The recommendation does not apply to pregnant and breast feeding women as evidence on the safety of pretomanid in these sub-groups of patients is limited. In cases of documented resistance to fluoroquinolones before the start of treatment, a regimen composed of bedaquiline, pretomanid and linezolid (BPaL) can be initiated, or if fluoroquinolone resistance is known while a patient is on BPaLM, moxifloxacin should be dropped from the regimen and treatment continued with BPaL. The duration of BPaLM regimen is standardised for six months (26 weeks). For BPaL, it is possible to extend the duration of treatment to 9 months (39 weeks) if sputum cultures are positive between months 4 and 6. Irrespective of whether BPaLM or BPaL is used, response to treatment should be closely monitored with monthly sputum smear microscopy and culture. Patients should undergo appropriate evaluation for adverse events, including cardiotoxicity (especially prolonged QTc interval), hepatotoxicity, marrow toxicity and peripheral neuropathy at the beginning, during and after treatment to ensure patient safety.

For patients not eligible for the 6-month BPaLM/BPaL regimen (or when the BPaLM/BPaL regimen is not available), the WHO suggests the use of a 9-month all-oral regimen rather than the longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded (Conditional recommendation, very low certainty of evidence) (Table 2)[15 - 17]. The 9-month all-oral regimen comprises bedaquiline (used for six months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid[16]. There should be no documented or suspected resistance to bedaquiline, fluoroquinolones, clofazimine, ethionamide, or linezolid (whichever is considered for inclusion in the regimen). The recommendation applies to both adults and children with no extensive or severe pulmonary TB and no severe extrapulmonary TB, irrespective of HIV status. Unlike the 6-month BPaLM/BPaL regimen, the 9-month all-oral regimen containing linezolid (but not the ethionamide-containing 9-month regimen) may be considered for women who are pregnant or breastfeeding.

Some patients with MDR/RR-TB may not be eligible for either the above-mentioned 6-month or 9-month regimens. Examples include those with severe extrapulmonary TB, those with additional resistance to key drugs of the 6-month or 9-month regimens, children aged below 14 years who cannot be treated with BPaLM/BPaL, or who, for whatever reason, cannot opt for the 9-month regimen. There may also be occasions that patients do not respond well while on a 6-month or 9-month regimen or have significant intolerance to key components of the above-mentioned regimens. Under these scenarios, the WHO suggests the use of longer individualised regimens (Conditional recommendation, very low certainty of evidence) (Table 2)[15 - 17]. These regimens generally have a duration of at least 18 months. The regimens are individually designed based on a hierarchical grouping (Group A to C) of second-line TB drugs and the drug-resistance profile (Table 2). To tailor an effective regimen, all three Group A drugs and at least one Group B drug should be included. If only one or two Group A drugs are used due to either drug resistance or drug intolerance, both Group B drugs are to be included. If the regimen cannot be composed of drugs from Groups A and B alone, Group C drugs are added to make up an adequate regimen. It is necessary to ensure that treatment starts with at least four TB drugs likely to be effective, and that at least three drugs are included for the rest of the treatment if bedaquiline (which is normally used for 24 weeks) is stopped. As with patients on shorter 6-month or 9-month regimens, patients on longer individualised regimens need to be monitored closely for response to treatment and for adverse events, including cardiotoxicity (especially prolonged QTc interval), hepatotoxicity, marrow toxicity, peripheral neuropathy or other central nervous system side effects from drugs where appropriate.

CAVEATS IN MANAGEMENT OF MDR/RR-TB

The advent of new and repurposed drugs, as well as the data from the recent clinical trials demonstrating the efficacy and safety of shorter regimens, bring new optimism and new hope to the treatment of MDR/RR-TB. Nevertheless, there are some caveats for the use of the shorter regimens. First, proper patient selection and adherence to the principles of use of these regimens, as recommended by the WHO is mandatory. Second, treatment should be administered under closely monitored conditions, and measures need to be put in place to ensure the early detection and timely reporting of potential adverse events. Third, given that resistance to new TB drugs such as bedaquiline is emerging globally, access to drug susceptibility tests, rational use of these drugs in terms of careful tailoring of an adequate regimen, and patient support to enable full adherence to treatment is imperative to prevent the acquisition of additional resistance and loss of the new effective regimens[18 - 20]. In particular, there should be sufficient companion drugs to protect not only

fluoroquinolones but also bedaquiline, pretomanid, and linezolid. Since MDR/RR-TB may pose a great impact on public health, a treatment regimen for each MDR/RR-TB case should be initiated by specialist physicians, who have in-depth experience in the management of MDR/RR-TB, after a thorough review of the case history and investigation findings. Regular review and discussion of the management of MDR/RR-TB cases among specialists is also advocated.

CONCLUSION

Remarkable progress has been made in the treatment of MDR/RR-TB in recent years. The latest WHO guideline represents a milestone in MDR/RR-TB treatment development by providing the basis for shorter, all-oral regimens. Selected patients with MDR/RR-TB fulfilling the inclusion criteria as recommended by the WHO can be cured by shorter 6 - 9 month regimens. However, the fight against MDR/RR-TB is far from over. Further studies are urgently needed to further advance optimised regimen compositions, identify factors that may predict responses to treatment and the optimal regimens for subgroups of patients such as those with chronic kidney disease and chronic liver disease, as well as the best strategies to prevent development of drug resistance. Additional research for new drugs and new regimens is needed in order that the global TB targets of the United Nations Sustainable Development Goals (SDGs) and the WHO End TB Strategy can be achieved. The treatment landscape of MDR/RR-TB is rapidly changing. Readers should refer to the relevant and appropriate international guidelines, such as those from the WHO, which constantly update their recommendations on the use of different regimens for treating MDR/RR-TB.

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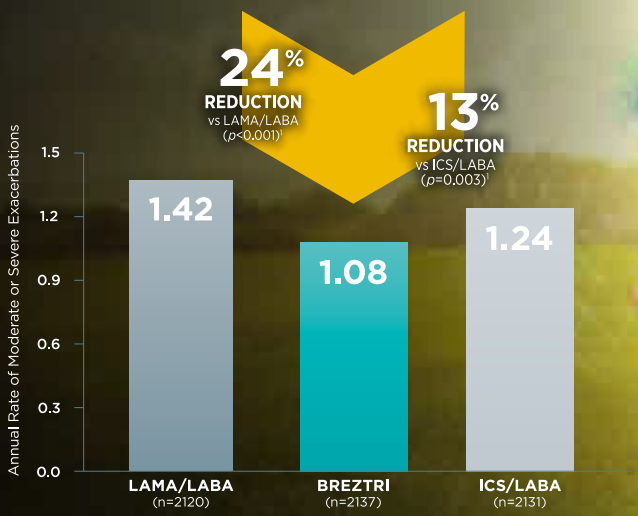

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Budesonide/glycopyrronium/formoterol fumarate dihydrate 160/14.4/10µg is not an approved dose.

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COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist.

References: 1. Rabe KF, et al. N Engl J Med. 2020;383:35-48. **2.** Breztri Aerosphere. Hong Kong Summary of Product Characteristics. Version Oct 2022.

ABBREVIATED PRESCRIBING INFORMATION
Presentation: Aerosphere pressurised inhalation, suspension budesonide 160µg/glycopyrronium 7.2µg/formoterol fumarate dihydrate 5µg per inhalation. **Indications:** As a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta$_2$-agonist or combination of a long-acting beta$_2$-agonist and a long-acting muscarinic antagonist. **Dosage:** Two inhalations twice daily (two inhalations in the morning and two inhalations in the evening). **Contraindications:** Hypersensitivity to the active substances, norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine, calcium chloride. **Precautions:** Not for acute use. Should be discontinued immediately if paradoxical bronchospasm occurs. It is recommended that treatment should not be stopped abruptly. Caution in patients with clinically significant uncontrolled and severe cardiovascular disease. Potential systemic effects of inhaled corticosteroid. Particular care is needed in patients transferring from oral steroids. Increase in the incidence of pneumonia in patients with COPD. Risk in visual disturbance, hypokalaemia, hyperglycaemia. Used with caution in patients with thyrotoxicosis, symptomatic prostatic hyperplasia, urinary retention or with narrow-angle glaucoma, severe renal impairment and severe hepatic impairment. Co-administration with other anticholinergic is not recommended. No or limited data on pregnancy, breast-feeding & fertility. **Interactions:** Strong CYP3A inhibitors, itraconazole, cimetidine, not recommended other anticholinergic and/or long-acting β2-adrenergic agonist. Other beta-adrenergic, xanthine derivatives, steroids and non-potassium sparing diuretics, β-adrenergic blockers, quinidine, disopyramide, procainamide, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines. L-dopa, L-thyroxine, oxytocin and alcohol. **Undesirable effects:** Pneumonia, headache, urinary tract infection, oral candidiasis, hyperglycaemia, anxiety, insomnia, palpitations, dysphonia, cough, nausea, muscle spasms. **Full local prescribing information is available upon request.** API.HK.BRE.1022

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Presentation: Benralizumab 30 mg solution for injection in pre-filled pen. Indications: Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS/LABA. Dosage: Subcutaneous injection, 30 mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Precautions: Should not be used to treat acute asthma exacerbations; Seek medical advice if asthma remains uncontrolled or worsens after initiation of treatment; Abrupt discontinuation of corticosteroids after initiation of Benralizumab is not recommended. Reduction in corticosteroid doses should be gradual and performed under the supervision of a physician; Patients with pre-existing helminth infections should be treated before initiating therapy of Benralizumab. Interactions: No formal drug interaction studies have been conducted. Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of Benralizumab. Undesirable Effects: Headache, pharyngitis, hypersensitivity reactions, pyrexia and injection site reaction. Full local prescribing information is available upon request. APLHK.FAS.0521

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New Therapies for Advanced Non-Small Cell Lung Cancer: An Overview

Dr Lynn YW SHONG

Bachelor of Medicine, PhD, MRCP(HK), FHKCP, FHKAM (Medicine)
Specialist in Respiratory Medicine
Associate Consultant, Division of Respiratory Medicine, Department of Medicine, Queen Mary Hospital

Dr David CL LAM

MBBS, BSc (BiomedSc), MD, PhD, FHKCP, FHKAM (Medicine), FRCP (Edin, Glasg, Lond)
Specialist in Respiratory Medicine
Clinical Associate Professor, Division of Respiratory Medicine, Department of Medicine, The University of Hong Kong

Dr Lynn YW SHONG Dr David CL LAM

ABSTRACT

Lung cancer is one of the leading causes of cancer-related deaths globally. There have been significant advancements in lung cancer treatment over the past decade, and newer and more effective therapies are continuously being developed. This article offers an up-to-date review of the latest therapies for advanced non-small cell lung cancer, with a special emphasis on targeted therapies, angiogenesis inhibitors and immunotherapies.

INTRODUCTION

Lung cancer is the most lethal and the second most common cancer worldwide in 2020[1, 2]. It is the most common cancer in Hong Kong, with 5,422 new cases in 2020 and the leading cause of cancer-related deaths over the past decade[3]. As the population in Hong Kong ages, the burden of lung cancer is expected to increase. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 85 % of all lung cancers[3]. The overall survival rates remain low due to late-stage diagnosis[3, 4]. Advanced stage lung cancers are also metastatic lung cancers, where primary lung cancer has spread from the lungs to other parts of the body.

Treatment for advanced lung cancer may include chemotherapy, radiation therapy, targeted therapy, immunotherapy, or a combination of these treatments. While advanced lung cancer is often difficult to treat, these treatments can help to slow the progression of the disease and improve quality of life. With substantial improvements in understanding disease biology and identifying oncogenic genomic alterations, newer therapies, such as targeted therapies and immunotherapies, have improved outcomes[5]. A decline in the age-standardised death rate of around 1 % each year in Hong Kong had been observed over 2015 - 2020[3]. This article provides an overview of advances in the treatment of advanced NSCLC, focusing on targeted therapies, angiogenesis inhibitors and immunotherapies.

TARGETED THERAPIES IN ADVANCED NSCLC

Targeted therapies are designed to specifically target cancer cells by disrupting the molecular pathways that drive tumour growth and survival. Clinical trials have shown that targeted therapies can be more effective and better tolerated than chemotherapy regimens for patients with specific genetic mutations in advanced stage NSCLC. Currently, targeted therapies are available for epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) rearrangement, *ROS1* rearrangement, *MET* alterations, *BRAF* mutations, *RET* and *NTRK* translocation. Targeted therapy is the preferred therapeutic option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations (Table 1)[6].

Table 1. Specific targeted therapies are available for the treatment of eligible patients with advanced NSCLC (Summarised by authors)

Drug	Target(s)
Alectinib	*ALK* and *RET* rearrangements
Brigatinib	Various *ALK* rearrangements and other targets
Ceritinib	*ALK* and *ROS1* rearrangements
Crizotinib	*ALK* rearrangements, *ROS1* rearrangements, *MET* tyrosine kinases (high-level *MET* amplification, *MET*ex14 skipping)
Erlotinib	*EGFR* mutations (exon 19 deletions, exon 21 L858R, exon 18 G719X, exon 21 L861Q, exon 20 S768I)
Gefitinib	*EGFR* mutations (exon 19 deletions, exon 21 L858R, exon 18 G719X, exon 21 L861Q, exon 20 S768I)
Afatinib	*EGFR* mutations (exon 19 deletions, exon 21 L858R, exon 18 G719X, exon 21 L861Q, exon 20 S768I)
Dacomitinib	*EGFR* mutations (exon 19 deletions, exon 21 L858R, exon 18 G719X, exon 21 L861Q, exon 20 S768I)
Osimertinib	*EGFR* mutations and T790M
Lorlatinib	*ALK* and *ROS1* rearrangements
Dabrafenib	*BRAF* p.V600E mutations
Trametinib	MEK
Entrectinib	*ROS1* and TRK fusion proteins
Larotrectinib	TRK fusion proteins
Capmatinib	*MET* tyrosine kinases (*MET*ex14 skipping mutations, high-level *MET* amplification)
Tepotinib	*MET* tyrosine kinases (*MET*ex14 skipping mutations, high-level *MET* amplification)
Selpercatinib	*RET* rearrangements
Pralsetinib	*RET* rearrangements
Cabozantinib	*RET* rearrangements
Adagrasib	*KRAS* G12C mutations
Sotorasib	*KRAS* G12C mutations
Bevacizumab	VEGF
Ramucirumab	VEGF receptor
Cetuximab	*EGFR*

ORAL *EGFR*-TYROSINE KINASE INHIBITORS (EGFR-TKLs)

EGFR (also known as *ERBB1* or *HER1*) alteration is the most common driver mutation, present in approximately 10 - 20 % of Caucasian NSCLC patients and over 50 % of Asian NSCLC patients. The development of oral *EGFR* tyrosine kinase inhibitors (TKIs) has significantly improved the survival of patients with advanced stage *EGFR*-mutant NSCLC. Currently, there are three generations of TKIs available. The first generation includes drugs like gefitinib and erlotinib, while the

second generation includes afatinib and dacomitinib, which bind irreversibly to *EGFR*. The third generation is represented by osimertinib, which targets the *EGFR* T790M mutation.

The National Comprehensive Cancer Network (NCCN) NSCLC Panel recommends erlotinib, gefitinib, and dacomitinib as first-line therapeutic options in patients with metastatic non-squamous NSCLC and common *EGFR* mutations, including exon 19 deletions and *EGFR* exon 21 L858R mutations regardless of their performance status. Erlotinib, gefitinib, afatinib, and dacomitinib are also recommended for patients with uncommon *EGFR* mutations, such as S768I, L861Q, and/or G719X mutations. Osimertinib has shown remarkable efficacy in patients with *EGFR* T790M-mutated NSCLC that has progressed after first- or second-generation *EGFR*-TKI therapy and is now the preferred first-line therapy for patients with common or uncommon *EGFR* mutations, regardless of their T790M mutation status, especially for patients with progressive disease with brain metastasis or leptomeningeal disease. However, most *EGFR* exon 20 mutations do not respond to *EGFR* TKIs, and first-line platinum-based chemotherapy is typically recommended for most patients with *EGFR* exon 20 insertion-positive metastatic NSCLC. Some *EGFR* exon 20 alterations, such as p.A763_Y764insFQEA, are sensitive to *EGFR* TKIs; p.A763_Y764insLQEA may be sensitive to first and third-generation *EGFR* TKIs. Amivantamab-vmjw is a bispecific human antibody to *EGFR* and MET receptors that bypasses resistance to *EGFR*-TKIs and has immune-cell directing activity[7]. Mobocertinib is an oral TKI that selectively inhibits diverse *EGFR* and *ERBB2* (*HER2*) exon 20 insertion mutations[8]. The NCCN NSCLC Panel recommends amivantamab as a subsequent therapy option for patients with *EGFR* exon 20 insertion mutation metastatic NSCLC[9]. Mobocertinib or amivantamab can be used as third-line or beyond therapy if the patient has previously received only one or none of these agents.

MONOCLONAL ANTIBODY THAT INHIBITS EGFR

Cetuximab is a monoclonal antibody that targets *EGFR*. Afatinib plus cetuximab can be considered as an option for patients with disease progression after receiving afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), or gefitinib and after chemotherapy.

ORAL AGENTS THAT INHIBIT KRAS MUTATIONS

KRAS is responsible for synthesising a G-protein with GTPase activity that is part of the MAP/ERK pathway, and point mutations in *KRAS* most commonly occur at codon 12. *KRAS*-mutated NSCLC accounts for 23 - 35 % and 13 - 20 % of all NSCLCs in Caucasian patients and East Asians, respectively. The prevalence of *KRAS* mutations is associated with cigarette smoking. Adagrasib and sotorasib are oral RAS-GTPase family inhibitors that target *KRAS* G12C mutations. The NCCN NSCLC Panel recommends adagrasib as a subsequent therapeutic option for selected patients with metastatic NSCLC and *KRAS* G12C mutations who have disease progression after treatment with platinum-based chemotherapy[10, 11].

ORAL TKIs THAT INHIBIT ALK REARRANGEMENTS

ALK rearrangements occur in approximately 3 - 7 % of NSCLC patients. Crizotinib was the first *ALK* inhibitor approved for the treatment of *ALK*-positive advanced NSCLC. It is an oral TKI that inhibits *ALK* rearrangements, *ROS1* rearrangements, and some MET tyrosine kinases, and it is approved for patients with metastatic NSCLC who have *ALK* or *ROS1* rearrangements[9]. Subsequently, more potent and selective *ALK* inhibitors have been developed, such as ceritinib, a second-generation oral TKI that inhibits *ALK* and *ROS1* rearrangements, or alectinib and brigatinib, being second-generation oral TKIs that inhibit *ALK* rearrangements; and lorlatinib, which is an oral third-generation TKI that targets *ALK* and *ROS1* tyrosine kinases. Alectinib demonstrated superior efficacy and better tolerability compared to crizotinib for *ALK*-positive NSCLC patients. Lorlatinib has good CNS penetration and inhibits a broad range of *ALK* resistance mutations that develop after treatment with first- and second-generation *ALK* inhibitors[9]. The NCCN NSCLC Panel decided that alectinib, brigatinib, and lorlatinib are preferred first-line therapies for *ALK*-positive metastatic NSCLC, while ceritinib is "other recommended" and crizotinib is conditionally useful[6]. Lorlatinib is also recommended as a subsequent therapeutic option for *ALK*-positive metastatic NSCLC after progression on either alectinib, brigatinib, or ceritinib[9].

ORAL TKIs THAT INHIBIT ROS1 REARRANGEMENTS

c-ROS oncogene 1 (*ROS1*) is a receptor tyrosine kinase that, when genetically translocated and fused with designated partner genes, acts as a driver oncogene in 1 - 2 % of NSCLCs. Although *ROS1* is a distinct receptor tyrosine kinase, it behaves very similar to *ALK*. *ROS1*-positive NSCLC is associated with features such as adenocarcinoma, younger patients and never-smokers. The NCCN NSCLC panel recommends four agents for patients with *ROS1*-positive metastatic NSCLC: ceritinib, crizotinib, entrectinib, and lorlatinib. Entrectinib is an oral TKI that inhibits several tyrosine kinases, including *ROS1* and TRK. Although entrectinib has better CNS penetration than crizotinib, it is more toxic, with nervous system disorders (3 %) and cardiac disorders (2 %) reported[9]. The NCCN NSCLC Panel recommends ceritinib as a first-line therapy option for patients with *ROS1*-positive metastatic NSCLC. Crizotinib and entrectinib are preferred agents for first-line therapy in patients with *ROS1*-positive metastatic NSCLC, compared with ceritinib, because they are better tolerated. Lorlatinib is recommended as a subsequent therapy option in patients with *ROS1*-positive metastatic NSCLC whose disease becomes resistant to ceritinib, crizotinib, or entrectinib[9]. Entrectinib and lorlatinib are recommended as subsequent therapeutic options for patients with CNS progression after crizotinib or ceritinib.

ORAL TKIs THAT INHIBIT METex14 SKIPPING MUTATIONS

MET alterations include *MET*ex14 skipping mutations, which occur in 3 - 4 % of NSCLCs, *MET* GCN gain or amplification, occurring in 1 - 5 % of NSCLCs, and MET protein overexpression. Capmatinib and Tepotinib are

oral TKIs that selectively inhibit *MET*ex14 skipping mutations and high-level *MET* amplification. The NCCN NSCLC Panel recommends capmatinib and tepotinib as preferred first-line therapy or subsequent therapy options for patients with *MET*ex14 skipping mutation-positive metastatic NSCLC[12]. Crizotinib or systemic therapy (e.g., carboplatin plus paclitaxel) is useful in certain circumstances as a first-line therapy option for *MET*ex14 skipping mutation. The NCCN Panel recommends capmatinib, crizotinib, and tepotinib for patients with metastatic NSCLC and high-level MET amplification (gene copy number of ≥ 10).

ORAL TKIs THAT INHIBIT RET REARRANGEMENTS

The rearranged during transfection (*RET*) gene encodes a tyrosine kinase receptor responsible for normal cell proliferation and differentiation in various tissues. Rearrangements between *RET* and various fusion partners have been identified in 1.4 - 2.5 % of NSCLCs. They are primarily seen in young patients with poorly differentiated lung adenocarcinoma who do not smoke or have a history of light smoking[13]. Cabozantinib is an oral TKI that inhibits *RET* rearrangements and other kinases. Pralsetinib and selpercatinib are oral TKIs that selectively inhibit *RET* rearrangements, with first-line therapy yielding an overall response rate of 70 - 85 %[6]. The NCCN NSCLC Panel recommends selpercatinib (preferred), pralsetinib (preferred), or cabozantinib as first-line or subsequent therapeutic options for *RET* rearrangement–positive metastatic NSCLC.

ORAL AGENTS THAT INHIBIT BRAF MUTATIONS

The *BRAF* p.V600E mutation is the most common type of *BRAF* point mutation and occurs in 1 - 2 % of patients with lung adenocarcinoma. Dabrafenib and trametinib inhibit kinases in the RAS/RAF/MEK/ERK pathway[9]. Dabrafenib specifically inhibits *BRAF* p.V600E mutations, while trametinib inhibits MEK 1/2, which is downstream of *BRAF* signalling[9]. The NCCN NSCLC Panel decided that: 1) dabrafenib plus trametinib is the preferred option; 2) systemic therapy regimens are other recommended options; and 3) single-agent dabrafenib or vemurafenib may be useful in certain circumstances.

ORAL TKIs THAT INHIBIT NTRK1/2/3 GENE FUSIONS

*NTRK*1/2/3 gene fusions encode TRK fusion proteins that act as oncoproteins for various solid tumours, including lung cancer and are very rare (< 1 % prevalence) in NSCLC[9]. Entrectinib and Larotrectinib are oral TKIs that inhibit TRK fusion proteins in patients with *NTRK* gene fusion-positive disease. The NCCN NSCLC Panel recommends entrectinib or larotrectinib as preferred first-line or subsequent therapy options for *NTRK1/2/3* gene fusion-positive metastatic NSCLC[6].

MONOCLONAL ANTIBODY-DRUG CONJUGATES THAT INHIBIT ERBB2 (HER2) MUTATIONS

Human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) - activating mutations occur in 2 % of lung cancers. The NCCN panel recommends first-line therapy with platinum-based chemotherapy with or without immunotherapy for patients with metastatic NSCLC and *ERBB2* (*HER2*) mutations. Ado-trastuzumab emtansine (also known as T-DM1) is a humanised antibody-drug conjugate consisting of trastuzumab, an antibody (immunoglobulin G1) targeting *HER2*, and emtansine, a microtubule inhibitor. Fam-trastuzumab deruxtecan-nxki is another humanised monoclonal antibody-drug conjugate consisting of trastuzumab linked to deruxtecan, a topoisomerase I inhibitor; the agent remains stable until it is cleaved by peptidase in cancer cells[14]. The NCCN NSCLC Panel recommends fam-trastuzumab deruxtecan-nxki or ado-trastuzumab emtansine as a subsequent therapy option for patients with metastatic NSCLC and *ERBB2* (*HER2*) mutations[6, 14, 15].

AGENTS THAT INHIBIT VEGF OR VEGF RECEPTORS

Bevacizumab is a recombinant monoclonal antibody that targets VEGF, while ramucirumab is a recombinant monoclonal antibody that targets VEGF receptors[9]. Bevacizumab in combination with a PD-L1 inhibitor plus chemotherapy (e.g., IMpower150 regime ABCP) is another recommended first-line therapeutic option regardless of PD-L1 expression for patients with good performance status (PS), non-squamous NSCLC, without actionable driver mutations or a recent history of hemoptysis. Combination therapy with ABCP may be a therapeutic option in eligible patients with *EGFR* mutations who failed primary *EGFR*-TKI. The NCCN NSCLC Panel recommends ramucirumab plus docetaxel as a subsequent therapy option for patients with metastatic NSCLC, regardless of histology[9]. Treatment with erlotinib plus bevacizumab or ramucirumab is recommended as a first-line therapy option for eligible patients with metastatic non-squamous NSCLC and common *EGFR* mutations (other recommended)[6].

IMMUNE CHECKPOINT INHIBITORS

Immunotherapies have transformed the treatment of lung cancer by utilising the patient's immune system to identify and eliminate cancer cells. The cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed death 1 (PD-1) immune checkpoints are negative regulators of T cell immune function. Inhibition of these targets results in increased activation of the immune system. The most common immune checkpoint inhibitors (ICIs) are human monoclonal antibodies, including cemiplimab-rwlc, nivolumab, pembrolizumab, which inhibit PD-1 receptors on T cells, atezolizumab and durvalumab which inhibit PD-L1, tremelimumab-actl and ipilimumab which inhibit CTLA-4. ICIs are associated with unique immune-mediated adverse events. Contraindications for treatment with PD-1/PD-L1 inhibitors may include autoimmune diseases, the use of immunosuppressive agents, and some oncogenic drivers. ICIs have a delayed effect compared to targeted therapy or cytotoxic chemotherapy. Traditional RECIST criteria may not be applicable due to the phenomenon of pseudoprogression, where effective tumour killing causes inflammatory swelling of tumours, leading to apparent enlargement of lung tumour sizes on imaging.

Single-agent pembrolizumab, atezolizumab, cemiplimab-rwlc or nivolumab plus ipilimumab (useful in certain circumstances, e.g. renal impairment) are recommended as first-line therapeutic options for eligible patients with metastatic NSCLC with PD-L1 expression levels of 50 % or more, and negative test results for actionable driver mutations[16]. Single-agent pembrolizumab, or nivolumab plus ipilimumab, is a first-line therapy option in patients with metastatic NSCLC with PD-L1 levels of 1% to 49 %, and negative test results for actionable driver mutations.

Chemotherapy plus pembrolizumab or cemiplimab-rwlc or nivolumab plus ipilimumab or tremelimumab-actl plus durvalumab are recommended as first-line therapy options in patients with metastatic NSCLC and negative test results for actionable driver mutations, regardless of PD-L1 expression levels. The NCCN NSCLC Panel recommends the pembrolizumab plus chemotherapy regimens over the ABCP regimen due to their favourable tolerability and greater experience with these regimens. The recommended chemotherapy for metastatic nonsquamous NSCLC is pemetrexed with either cisplatin or carboplatin; the recommended chemotherapy for metastatic squamous NSCLC is paclitaxel with carboplatin.

Maintenance therapy with cemiplimab-rwlc with or without pemetrexed, or pembrolizumab with pemetrexed or atezolizumab and bevacizumab or durvalumab with or without pemetrexed for non-squamous NSCLCL or pembrolizumab or durvalumab for squamous NSCLC is also recommended. Maintenance immunotherapy is recommended for up to 2 years, if tolerated, for all first-line immunotherapy (± chemotherapy) regimens. Single-agent pembrolizumab is recommended as a subsequent therapy option for selected patients with metastatic NSCLC and PD-L1 levels greater than 1 %; nivolumab or atezolizumab is recommended as a subsequent monotherapy option for selected patients with metastatic NSCLC regardless of PD-L1 levels based on improved overall survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy[17].

NOVEL APPROACHES

Innovative treatment strategies, such as chimeric antigen receptor (CAR) T-cell therapy, cancer vaccines, oncolytic viruses, adoptive cell therapy using tumour-infiltrating lymphocytes (TILs), and combined therapies are being explored in lung cancer. CAR T-cell therapy genetically engineers a patient's T cells to target cancer cells expressing specific antigens; however, its application in lung cancer is challenging due to the tumour microenvironment and antigen heterogeneity. Early-phase clinical trials evaluating the safety and efficacy of CAR T-cell therapy in lung cancer are ongoing[18]. Antibody-Drug Conjugates (ADCs) are a novel therapeutics class combining monoclonal antibodies' specificity with chemotherapy agents' cytotoxicity. Sacituzumab govitecan is a Trop-2-directed antibody and topoisomerase inhibitor drug conjugate and has demonstrated encouraging antitumour activity in early-phase clinical trials[19]. Integrating newer therapies with traditional modalities, such as surgery, radiation therapy, and chemotherapy, may lead to better outcomes for a broader range of lung cancer patients.

CONCLUSIONS

The landscape of lung cancer treatment has undergone a significant transformation with the emergence of targeted therapies and immunotherapies, resulting in improved outcomes for patients with specific genetic alterations or biomarkers. However, several challenges persist, including resistance to targeted therapies and variable response rates to immunotherapies. Ongoing research efforts are focused on identifying novel targets, optimising existing therapies to overcome these challenges. Biomarker discovery and implementing precision medicine strategies are crucial in ensuring that the right patients receive the appropriate therapy at the right time. It is imperative to continue the discovery and development of novel therapies to enhance the quality of life and survival of lung cancer patients.

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Consistent Benefits Over ICS/LABA[1]

↓78% risk of escalating to triple therapy

↓24% risk of COPD exacerbation

↓26% risk of pneumonia requiring hospitalization

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$ agonist; LAMA: long-acting muscarinic antagonist.

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SPIOLTO API [API_SPIO_02&04_V1]

Presentation: 2.5 microgram tiotropium (as bromide monohydrate) and 2.5 microgram olodaterol (as hydrochloride) per puff. Indications: Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). Dosage and administration: The recommended dose is 5 microgram tiotropium and 5 microgram olodaterol given as two puffs from the Respimat inhaler once daily, at the same time of the day. Contraindication: Hypersensitivity to the active substances, atropine or its derivatives, e.g. ipratropium or oxitropium, or any of the excipients. Special warnings and precautions: Should not be used in asthma. Not for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. Inhaled medicines may result in paradoxical bronchospasm and should be discontinued immediately and alternative therapy substituted. Caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. Caution to avoid getting the spray into their eyes. Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries. In patients with moderate to severe renal mpairment (creatinine clearance of ≤ 50 ml/min), use only if the expected benefit outweighs the potential risk. Caution in patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalized for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (> 100 beats per minute). Beta2-adrenergic agonists may produce a clinically significant cardiovascular effect as measured by increases in pulse rate, blood pressure and/or symptoms. Caution in patients with cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm, in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval (e.g. QT > 0.44 s), and in patients who are unusually responsive to sympathomimetic amines. Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Caution needs to be taken in case of a planned operation with halogenated hydrocarbon anaesthetics. Should not be used in conjunction with any other medications containing long-acting beta2-adrenergic agonists. As with all medications, immediate hypersensitivity reactions may occur after administration. Should not be used more frequently than once daily. Interactions: Concomitant administration of other adrenergic agents (alone or as part of combination therapy) may potentiate the undesirable effects. Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalemic effect of adrenergic agonists. Beta-adrenergic blockers may weaken or antagonise the effect of olodaterol. Monamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of SPIOLTO RESPIMAT on the cardiovascular system. Adverse reactions: Uncommon: Dizziness, headache, tachycardia, cough, dysphonia, dry mouth. Rare: Insomnia, vision blurred, atrial fibrillation, palpitations, supraventricular tachycardia, hypertension, laryngitis, pharyngitis, epistaxis, bronchospasm, constipation, oropharyngeal candidiasis, gingivitis, nausea, stomatitis, hypersensitivity, angioedema, urticaria, pruritus, rash, arthralgia, back pain, joint swelling, urinary retention, urinary tract infection and dysuria. Storage conditions: Please refer to outer packaging. Note: Before prescribing, please consult full prescribing information (SPIO_02&04_V1).

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Boehringer Ingelheim Hong Kong Limited
Suites 1504-9, Great Eagle Centre, 23 Harbour Road, Wanchai, Hong Kong
Tel: 2596 0033 Fax: 2827 0162
Website: www.boehringer-ingelheim.com.hk

Advances in Pleural Medicine

Dr CHAN Ka-pang

MBChB (CUHK), FRCP (Glasgow), FHKCP, FHKAM

Specialist in Respiratory Medicine
Clinical Lecturer, Department of Medicine & Therapeutics, The Chinese University of Hong Kong

Dr CHAN Ka-pang

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 October 2023.

INTRODUCTION

Pleural diseases are common diseases presented to the Emergency Department, and hospitalisation is usually warranted. The disease burden should not be underestimated. Based on a retrospective cohort study using Healthcare Utilization Project databases in the United States (US), 361,270 hospitalisations occurred due to pleural diseases in adults, resulting in national costs of USD 10.1 billion in 2016. 64,174 readmissions were identified with the highest mean proportion in patients with malignant pleural mesothelioma (49 %) and malignant pleural effusion (45 %). Secondary spontaneous pneumothorax (SSP) had the shortest time to readmission[1]. Similarly, in a multicentrre, cross-sectional study from 50 municipalities in China, the prevalence of pleural effusion was estimated to be 4,684 per 1 million adults, with tuberculosis, malignancy and parapneumonic effusion/empyema considered as the most common causes in different age groups[2].

There have been many exciting advances in the diagnosis and management of pleural diseases in the past decade. This article serves as a general overview of the recent development in the diagnosis and management of several major categories of pleural disease.

UTILISATION OF THORACIC ULTRASOUND

The advances and wide adoption of point-of-care thoracic ultrasound (TUS) have revolutionised the practice of pleural medicine. The TUS is reliable in detecting small amounts of pleural effusion, with a high sensitivity of 93 % and specificity of 96 % compared to chest X-ray (CXR)[3]. TUS allows the operator to appreciate the extent of pleural effusion and presence of loculation, and thus decide the optimal needle puncture site during the pleural intervention[4, 5]. Skilled operators can also identify the relevant anatomical landmarks neighbouring the puncture site, and minimise the risk of accidental pneumothorax, bleeding and organ puncture[6 - 8]. The sonographic findings also supplement additional clinical information in guiding the diagnosis of pleural effusion[4, 7], for example, identifications of pleural septations in complicated parapneumonic effusion (CPPE)[9] and irregular nodularity on the diaphragm in malignant pleural effusion (MPE)[10].

In contrast to pleural effusion, the utility of TUS in diagnosing pneumothorax was mainly reported in prospective case series involving patients with trauma, post-image guided biopsy or in critical care. Although it was shown that TUS has a better sensitivity for pneumothorax compared with CXR, the clinical effect or outcome was not proven by any randomised controlled trial[4].

With its easy availability and benefits, TUS is now widely adopted by clinicians and is considered a core skill for trainees[4, 11]. The latest guidelines also emphasised the mandatory use of TUS in pleural procedures whenever available[4, 12].

PLEURAL INFECTION

Parapneumonic effusion is common among patients presenting with pneumonia, and its presence leads to a worse prognosis. CPPE and empyema, collectively known as pleural infection, are associated with an increased mortality and consumption of healthcare resources[13, 14]. Patients with pleural infection should receive timely administration of appropriate antibiotics and pleural drainage.

The microbiological diagnosis of pleural fluid in pleural infection is crucial in guiding the choice of antibiotics, but the yield is usually limited by prior use of antibiotics and the fastidious nature of microorganisms. One of the ways to increase the diagnostic yield is to inoculate the pleural fluid into blood culture bottles, which can enhance the yield by 15 %[15]. The AUDIO study, a proof-of-concept study, suggested that TUS-guided pleural biopsies could increase the microbiological yield by 25 % in addition to pleural fluid and blood samples[16]. Alongside culture, the high throughput next-generation sequencing (NGS) technology may provide additional metagenomic information, which was reported by the exploratory TORPIDS study. In this study, pleural infection was predominately polymicrobial, with mixed anaerobes and other Gram-negative bacteria predominating in community-acquired polymicrobial infection, whereas Streptococcus pneumoniae prevailed in monomicrobial cases. High mortality was associated with Staphylococcus aureus and Enterobacteriaceae infection[17]. NGS has the potential to identify the complete microbiome, but prospective validation of this technology is warranted for its clinical utility. In addition, geographical variations of bacteriological

patterns in pleural infection have been reported[18]. Therefore, the results of the TORPIDS study may not be directly applicable to other geographical regions.

Adequate drainage of infected pleural fluid is another pillar of management. Since the publication of the MIST-2 trial in 2011, sequential intrapleural instillation of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) progressively become the standard medical management to enhance fluid drainage[12]. This regimen can provide satisfactory radiographic improvements, reduce the need for surgical referral and shorten the hospital stay in pleural infection[19]. The risk of severe bleeding remains low and, most of the time, can be managed conservatively. However, controversies have been raised for the MIST-2 regimens as the dose of tPA (10 mg) was empirically chosen without pharmacokinetic assessment, and the sequential injection is tedious and at risk of iatrogenic infection[20]. Small observational series employing lower dosing regimens of tPA at 2.5 mg and 5 mg as the starting dose have shown similar safety and efficacy. Subsequent escalation to 10 mg can be considered if the pleural infection cannot be controlled clinically[21, 22]. This reduced tPA dose regimen may be considered in patients with a potentially higher bleeding risk (e.g., on therapeutic anticoagulation, which cannot be temporarily ceased)[12]. Concurrent injection of tPA and DNase may be preferred due to convenience and similar efficacy[20]. However, these two modifications had not been validated by high-quality randomised controlled trials.

Although pleuroscopy is considered one of the standard investigations for exudative effusion, its therapeutic role in pleural infection is not very well established. In a recent multicentre, randomised controlled trial comparing pleuroscopy and intrapleural fibrinolytic for patients with pleural infection. Patients who underwent pleuroscopy had a shorter length of hospital stay than those who received intrapleural fibrinolytic (median four days vs two days)[23]. However, the study outcomes should be interpreted with caution due to its limited sample size (32 patients in total)[20] and the procedure success rate is also operator dependent.

MALIGNANT PLEURAL EFFUSION

MPE could be found in as many as 15 % of patients who died from malignancy[24, 25], and is an important pleural disease that consumes many healthcare resources[26]. In the US, there was a steady upward trend of emergency visits, and 30-day readmission was observed from 2010 through 2016[1]. MPE can recur quickly after therapeutic drainage. Around 90 % of patients with MPE would develop symptomatic recurrence within one month after therapeutic thoracentesis, without definitive treatment[27]. In a Canadian retrospective cohort study using the Nationwide Readmissions Database, it was found that the 30-day unplanned readmission rate after various pleural drainage methods (ranged from thoracentesis, chest drain insertion with and without pleurodesis to thoracoscopy with and without pleurodesis) was 25.6 %, and the mortality rate during readmission was 17.3 %. Abundant evidence has shown that non-definitive management with thoracentesis could lead to more readmissions and subsequent procedures[28, 29]. This evidence highlights the need for definitive treatment to reduce symptomatic recurrence and, thus, unscheduled readmissions in MPE.

As MPE represents a status of stage 4 malignancy, the treatment for the malignancy itself and pleural effusion would both be palliative intent. There is an ongoing trend of managing patients with MPE based on personalised needs and disease phenotype, targeting the patient's symptoms, and quality of life instead of radiographical recurrence[30, 31].

Pleurodesis and indwelling pleural catheter (IPC) are considered definitive treatments for MPE, in addition to effective oncological treatment, if there is no evidence of trapped (non-expandable) lung[12, 30]. Pleurodesis with talc slurry through the pleural drain can offer successful MPE control in around 70 % of patients[32, 33]. When comparing talc slurry with talc poudrage through pleuroscopy, the pleurodesis failure rate at 90 days was equivalent in the TAPPS trial[33]. In eligible patients, IPC offer similar control of dyspnoea, and quality of life but shorter hospital stay than talc pleurodesis[34, 35]. IPC-related infection is always a concern for IPC, and it typically happens at least 6 to 8 weeks after IPC implantation[36]. A large-scale study involving 1,021 patients found that only 4.9 % developed IPC-related pleural infection. Most of these could be successfully controlled with antibiotics, and the overall mortality risk was only 0.29 %[37]. In cases of complicated pleural infection, intrapleural tPA/DNase can also be instilled via IPC and is not associated with additional major morbidity and mortality[38]. Despite the concern of infection, IPC is not a contraindication for chemotherapy, as it does not increase the risk of IPC-related infection[39]. IPC also offers a chance of auto-pleurodesis ranging from 24 - 47 %, depending on the nature of the cohort, and IPC can be removed once its occurrence[30]. The chance of auto-pleurodesis can be enhanced by frequent drainage[40] and talc instillation through IPC[41]. In patients with MPE and trapped lung, which is contraindicated for talc pleurodesis, IPC is the only definitive treatment of choice, and auto-pleurodesis can still happen[40]. In the latest international guideline, talc pleurodesis and IPC can both be offered to eligible patients, and ultimately, it is a shared decision between patients and physicians depending on patient choice, resource availability and physician familiarity[12, 30].

Although surgical pleurodesis is an option, it is usually not widely adopted due to the patient's ineligibility. Indeed, video-assisted thoracoscopic partial pleurectomy could not provide longer overall survival, but more complications and longer hospital stay than talc pleurodesis in patients with malignant mesothelioma in the MesoVATS study[42]. Whether there is an absolute benefit of surgical pleurodesis over IPC (and/or talc pleurodesis) remains to be solved, which will be answered by the ongoing AMPLE-3 trial[43].

PNEUMOTHORAX

Pneumothorax can be broadly classified into primary and secondary spontaneous pneumothorax, and traumatic pneumothorax that includes iatrogenic causes. Patients with primary spontaneous pneumothorax (PSP) usually present with pain as the primary symptom, instead of breathlessness, as they

usually have good lung reserve in the contralateral fully expanded lung. Hence, there is considerable heterogeneity in the management of PSP. Conservative treatment may be considered to allow slow resolution of the pneumothorax and avoid painful pleural drainage procedures. Based on this, the recently published PSP trial may change the treatment paradigms for primary pneumothorax[44]. In this trial, patients with moderate to large PSP without unstable physiological features were randomised to receive small-bore (12 French or smaller) Seldinger-style chest drain or conservative management with closed CXR monitoring. Patients randomised to the conservative management group may be discharged with analgesia and written instructions if no oxygen was required and they were walking comfortably. The radiographic resolution within eight weeks for patients who received conservative management was non-inferior to interventional management. Conservative management also spared 85 % of the patients from an invasive intervention and resulted in fewer hospitalisation days and adverse events than interventional management. The percentage of patients with early pneumothorax recurrence was also lower in the conservative-management group[44]. Therefore, the latest guideline suggested considering conservative management for the treatment of minimally symptomatic (i.e., no significant pain or breathlessness and no physiological compromise) or asymptomatic PSP in adults regardless of size in centres with available expertise. It is a good practice that all treatment options should be discussed with the patient to determine their main priority, with consideration for the least invasive option[12].

Contrary to PSP, secondary spontaneous pneumothorax (SSP) is traditionally managed with pleural drainage by chest drain with an underwater seal drain (UWSD). As SSP is usually associated with prolonged hospitalisation, it was postulated that an ambulatory care model with a flutter valve might shorten the hospitalisation. However, in an open-label randomised controlled trial which randomised patients with SSP to either a chest drain with UWSD or ambulatory care with a flutter valve, there was no difference in the length of hospital stay between the two groups[45].

A persistent air leak (PAL) in pneumothorax represents an air leak lasting more than 5 to 7 days[46]. PALs are more common and less likely to resolve with SSPs than PSPs[47]. In a local, single-centre retrospective study, the prevalence of PAL for more than seven days was 43.3 % among non-surgical SSP patients. PAL was associated with longer hospitalisation in the index episode and higher recurrence rates up to two-year post-discharge[48]. Observational study found that 61 % of patients with SSPs and PALs would resolve at seven days, and 81 % would resolve by 14 days with conservative management[49]. In patients with SSP and PAL, surgical referrals can be initiated to consider surgical treatment, as early as on day 2 of air leak. However, for those who are not surgical candidates, chemical pleurodesis, autologous blood patch, and bronchoscopic blockage of bronchi with endobronchial valves (EBV)[12, 50, 51] have been described. During the EBV insertion, the culprit lobe or lung segment of leakage is identified and followed by the deployment of the EBV. The one-way valve works by blocking the influx of air into the leakage site, and subsequent collapse of that particular lobe or segment. Once there is a cessation of air leakage and resolution of pneumothorax, the EBV can be removed later. In a local retrospective study involving 37 patients with PAL, the air leak ceased within 72 hours for only eight patients (22 %), with immediate air-leak cessation after completion of EBV implantation. Patients with fewer medical co-morbidities and immediate air-leak cessation after EBV implantation have a higher likelihood of success[52]. Due to the paucity of high-quality evidence, a large prospective randomised controlled trial is required to inform the optimal patient selection strategy and definite benefits of EBV over other pleural interventions.

HETEROGENEOUS LOCAL PRACTICE

With advances in knowledge of pleural medicine, there were major updates in guidelines for managing pleural diseases[12]. However, the recognition of pleural disease as an important disease category remains suboptimal. In a recent cross-sectional questionnaire survey targeting clinicians of various subspecialties in internal medicine and levels of experience (basic and higher trainees, specialists) from twelve regional hospitalsin Hong Kong, significant heterogeneity in the management of pleural diseases among respiratory versus non-respiratory clinicians was observed[53]. A significant proportion of clinicians were unaware of pleuroscopy for investigating exudative pleural effusion, intrapleural tPA / DNase for pleural infection and IPC for recurrent MPE. The lack of a wareness or training, limited accessibility of drugs, devices, and dedicated service support may contribute to the observed heterogeneity[53]. This urges better training on managing pleural diseases in general medical and respiratory physicians.

CONCLUSION

There have been rapid developments in pleural medicine in the past few decades, ranging from using TUS and different intervention strategies to optimising patient care and minimising the need for surgery. Although gaps exist between research and real-life application, the momentum of high-quality research in pleural medicine will slowly solve the areas of uncertainty.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Advances in Pleural Medicine" by Dr CHAN Ka-pang and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 October 2023. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/Fl., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

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

1. Thoracic ultrasound (TUS) is less sensitive and specific than chest X-ray (CXR) to detect small amounts of pleural effusion.
2. TUS can supplement additional clinical information in guiding the diagnosis of complicated parapneumonic effusion (CPPE) and malignant pleural effusion (MPE).
3. Inoculating pleural fluid into blood culture bottles can enhance the bacterial culture positivity rate by 15 % compared to transferring the pleural fluid into plain bottles.
4. Intravenous antibiotic alone is adequate for treating CPPE and empyema.
5. For CPPE and empyema that are incompletely drained, intrapleural instillation of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) can improve radiographic outcomes, reduce the need for surgical referral and shorten the hospital stay.
6. Malignant pleural effusion (MPE) seldom recurs after pleural drainage, even without any oncological treatment.
7. Talc pleurodesis and indwelling pleural catheter (IPC) are considered definitive treatments for MPE in eligible patients.
8. Frequent IPC drainage and instillation of talc through IPC can enhance the chance of auto-pleurodesis.
9. For patients with primary spontaneous pneumothorax who are asymptomatic and with stable physiological features, conservative management by closed observation is an alternative to chest drain insertion.
10. Insertion of the endobronchial valve is not a therapeutic option for pneumothorax with persistent air leaks.

ANSWER SHEET FOR OCTOBER 2023

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2023 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Advances in Pleural Medicine

Dr CHAN Ka-pang
MBChB (CUHK), FRCP (Glasgow), FHKCP, FHKAM
Specialist in Respiratory Medicine
Clinical Lecturer, Department of Medicine & Therapeutics, The Chinese University of Hong Kong

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

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

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Answers to September 2023 Issue

The Story of Vaccines

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

NOW APPROVED FOR THE TREATMENT OF PROGRESSIVE FIBROSING ILDs, SSc-ILD AND IPF[1]

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and modify ILD progression by slowing lung function decline[2]

Dosing simplicity: Just 1 caps

AE, adverse event; **FVC**, forced vital capacity; **GI**, gastrointestinal; **ILD**, interstitial lung disease; **IPF**, idiopathic pulmonary fibrosis; **SSc-ILD**, systemic sclerosis-ass

References: 1. Ofev, Hong Kong Prescribing Information. **2.** Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: da lung disease (PF-ILD): the patient journey. Am J Respir Crit Care Med. 2018;197:1-2.

OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive p

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Presentation: Nintedanib esilate, Capsule, 150 or 100mg **Indications:** For the treatment of Idiopathic Pulmonary Fibrosis in adults; for the treatment of systemic sclerosis associat recommended dose is 150 mg twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolera be resumed at the full recommended dose (150mg twice daily) or a reduced dose (100mg twice daily). In patients with mild hepatic impairment (Child Pugh A), the recommende OFEV® is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed. **Contraindication:** Hypersensitivity to nintedа be treated at first signs with adequate hydration and anti-diarrheal medication and may require dose reduction or treatment interruption. Nausea and vomiting were frequently r known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischemia. In clinical trials, no inc measured periodically and as clinically indicated. OFEV® should not be used in patients with severe pulmonary hypertension. Close monitoring is recommended in patients with diverticular disease or receiving concomitant corticosteroids or NSAIDs. OFEV® should only be initiated at least 4 weeks after abdominal surgery. Therapy with OFEV® should ischaemic colitis and careful assessment of patient's condition and other risk factors. Based on mechanism of action, OFEV® increases risk of bleeding. Use OFEV® in patients wit trials and post-marketing surveillance database. Administration of OFEV® was associated with elevations of liver enzymes and bilirubin. Hepatic transaminase and bilirubin levels sh two months of treatment and periodically thereafter. Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk fac pharmacokinetics of nintedanib have not been studies in patients with severe renal impairment (<30ml/min CrCl). No increased frequency of impaired wound healing was observe carry an enhanced risk for severe reactions to soya preparations. **Interactions:**Nintedanib is a substrate of P-gp and to a minor extent CYP3A4. Co-administration with the pote common (≥1/10) and Common (≥ 1/100 to < 1/10): Weight decreased, Decreased appetite, Bleeding, Diarrhea, Nausea, Abdominal pain, Vomiting, Hepatic enzyme increased, Rash induced liver injury (Common in PF-ILD), Hyperbilirubinemia, Pruritus, Alopecia, Proteinuria; Not known: Aneurysms and artery dissections, Renal failure. **Storage conditions:** Do

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As many as 18% to 32% of patients with non-IPF ILDs are estimated to be at risk for developing a progressive fibrosing phenotype[3]

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sule taken twice daily[1]

sociated interstitial lung disease.

ata from the whole INBUILD trial. Eur Respir J 2022; 59: 2004538. **3.** Wijsenbeek M, Kreuter M, Fischer A, et al. Non-IPF progressive fibrosing interstitial

henotype, and systemic sclerosis associated interstitial lung disease (SSc-ILD).[1]

ed interstitial lung disease in adults; for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype in adults **Dosage and administration:** The te the 150 mg twice daily dose. The management of adverse reactions to OFEV® could include dose reduction (to 100mg twice daily) and temporary interruption. Treatment may d dose is 100mg twice daily approximately 12 hours apart. Treatment of patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment is not recommended. anib, peanut or soya, or to any of the excipients; Pregnancy. **Special warnings and precautions:** Diarrhea was the most frequent gastrointestinal event reported. Diarrhea should eported gastrointestinal adverse reactions. Arterial thromboembolic events were infrequently reported. Use caution when treating patients at higher cardiovascular risk including reased risk of venous thromboembolism was observed in nintedanib treated patients. Treatment with OFEV® may increase blood pressure. Systemic blood pressure should be mild to moderate pulmonary hypertension. Particular caution should be exercised when treating patients with previous abdominal surgery, previous history of peptic ulceration, be permanently discontinued in patients who develop gastrointestinal perforation or ischaemic colitis. Exceptionally, OFEV® can be reintroduced after complete resolution of h known risk of bleeding only if anticipated benefit outweighs the potential risk. Cases of drug-induced liver injury have been observed with nintedanib treatment in both clinical hould be investigated before treatment initiation and during the first month of treatment with OFEV®. Patients should then be monitored at regular intervals during the subsequent tors for renal impairment/failure. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome. The safety, efficacy and ed in the clinical trials. Caution should be exercised when nintedanib is administered in patients who may develop QTc prolongation. Patients with known allergy to peanut protein nt P-gp s and CYP3A4 inhibitor ketoconazole increased exposure to nintedanib. Potent P-gp and CYP3A4 inducers decreased exposure to nintedanib. **Adverse reactions:** Very n, Headache; Uncommon (≥ 1/1,000 to < 1/100): Thrombocytopenia, Dehydration, Myocardial infarction, Hypertension (Common in PF-ILD and SSc-ILD), Pancreatitis, Colitis, Drug not store above 25°C. Store in the original package in order to protect from moisture. **Note:** Before prescribing, please consult full prescribing information (OFE_15_18-21_V3).

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- HFpEF[2]
- HF therapy intolerance*[3]
  *The standard therapies for HF, including ACEI, ARB, and BB[3]
- LVH on Echo[2]
- Imaging and ECG discrepancy**[2]
  **Imaging finding of LVH and normal/low QRS voltage on ECG[2]

Non-cardiac:

- Orthopaedic syndromes (e.g carpal tunnel syndrome, lumbar spinal stenosis and bicep tendon rupture)[2]
- Polyneuropathy[2]
- Family history of TTR amyloidosis[4]

Abbreviations: ACEI: Angiotensin-converting enzyme inhibitors; **ARB:** Angiotensin-receptor blockers; **ATTR-CM:** Transthyretin amyloid cardiomyopathy; **BB:** Beta blockers; **ECG:** Electrocardiogram; **Echo:** Echocardiography; **HF:** Heart failure; **HFpEF:** Heart failure with preserved ejection fraction; **LVH:** Left ventricular hypertrophy; **TTR:** Transthyretin

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VYNDAMAX ABBREVIATED PRESCRIBING INFORMATION

1. TRADE NAME: Vyndamax™ capsules (Tafamidis 61 mg) **2. PRESENTATION:** 61mg soft capsules **3. INDICATIONS**: Vyndamax is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). **4. DOSAGE**: The recommended dose is one capsule of Vyndamax 61 mg (tafamidis) orally once daily. **5. CONTRAINDICATIONS**: Hypersensitivity to the active substances or to any of the excipients of the drug (Please refer to the full prescribing information for details). **6. WARNINGS & PRECAUTIONS:** Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis. Tafamidis should be added to the standard of care for the treatment of patients with transthyretin amyloidosis. Physicians should monitor patients and continue to assess the need for other therapy, including the need for organ transplantation, as part of this standard of care. Tafamidis should be discontinued in patients who undergo organ transplantation. **7. INTERACTIONS:** Substrates of efflux transporter BCRP (breast cancer resistant protein; e.g., methotrexate, rosuvastatin, imatinib); substrates of uptake transporters OAT1 and OAT3 (organic anion transporters; e.g., non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine). **8. PREGNANCY AND LACTATION:** Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception. Tafamidis should not be used during breast-feeding. **9. SIDE EFFECTS:** Flatulence and liver function test increased. A causal relationship has not been established. Reference: Prescribing Information HK PI (Version Jul 2020) Date of preparation: Nov 2020 Identifier number: VYNX1120 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

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Update on Management of IPF

Dr SE Hoi-ue
MBBS, MRCP(UK), FHKCP, FHKAM (Medicine)
Specialist in Respiratory Medicine
Resident Specialist, Department of Medicine, Queen Elizabeth Hospital

Dr LAW Wai-lam
MBChB (CUHK), MRCP(UK), FHKCP, FHKAM (Medicine), FRCP(Edin)
Specialist in Respiratory Medicine
Associate Consultant, Department of Medicine, Queen Elizabeth Hospital
Vice-President, Hong Kong Thoracic Society


Dr SE Hoi-ue Dr LAW Wai-lam

INTRODUCTION

Interstitial lung disease (ILD) is an umbrella term encompassing a broad spectrum of diseases affecting primarily the pulmonary interstitium. Over 200 separate disorders range from rare diseases like lymphangioleiomyomatosis to more common diseases like idiopathic pulmonary fibrosis. They could be classified into idiopathic (primary), autoimmune-related, exposure-related (including iatrogenic), interstitial lung diseases with cysts or airspace filling, sarcoidosis, and orphan diseases. Diagnosis of ILD is based on a combination of clinical, radiological and sometimes pathological features. In more than two-thirds of patients, clinical-radiological features are sufficient in making a diagnosis[1]. It is worth mentioning that primary and secondary interstitial lung diseases share the same radiological and pathological features. That highlights the importance of careful clinical history taking and physical examinations to identify secondary causes, as treatment would be drastically different. Appropriate blood tests, such as autoimmune markers could also provide important clues in whether the patient is suffering from autoimmune diseases. In the remaining patients, bronchoscopy with bronchoalveolar lavage and lung biopsy could offer additional information to aid in diagnosing ILD.

EPIDEMIOLOGY AND DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS (IPF)

Of all primary interstitial lung diseases, idiopathic pulmonary fibrosis (IPF) is the most common and is the most researched. In the literature, reported incidence of IPF ranges from 1.2 to 7.44 per 100,000 per year. In databases from East Asia, its incidence was reported to be 1.2 to 4.16 per 100,000 per year[2]. According to a local retrospective study conducted in all major hospitals in Hong Kong from 1 January 2013 to 31 December 2017, the period prevalence of IPF in Hong Kong is 7.41 per 100,000 people[3]. The disease is progressive and leads to significant morbidity due to decline in lung function. Without anti-fibrotic treatment, patients' mortality rate is up to 31 % at or over five years, and studies showed an overall mean survival of 4 years for patients diagnosed with IPF after ten years of follow-up[4].

Patients with IPF classically present with unexplained exertional dyspnoea for months to years, chronic dry cough, Velcro-like crackles on examination. Chest X-ray and lung function tests, including spirometry, lung volume and diffusion capacity of the lung for carbon monoxide, should be performed. Classical findings are bilateral lower zone reticular infiltrate on chest X-ray and reduced lung volume, FVC and diffusion capacity on lung function test[4]. However, in early disease, these could be normal. Diagnosis of IPF relies heavily on the interpretation of high resolution CT (HRCT) findings and exclusion of alternative diagnoses such as connective tissue disease. According to the latest ATS/ERS/JRS/ALAT guideline updated in 2022, a diagnosis of IPF can be made without further lung biopsy or invasive investigations, including bronchoscopy in patients with HRCT pattern of usual interstitial pneumonia (UIP), after appropriate exclusion of differential diagnoses[5]. Definite UIP pattern consists of subpleural, basal predominant reticular abnormality with honeycombing on HRCT[4]. In cases where there are atypical findings or where clinical features are not diagnostic, a management plan should be discussed in multidisciplinary meetings to determine the appropriate subsequent action, including the need for lung biopsy. In the past, surgical lung biopsy was always warranted whenever there was doubt in the diagnosis of interstitial lung disease (ILD). However, with the recent advances in endoscopic technique and the increase in amount of evidence of transbronchial cryobiopsy (TBCB) in the diagnosis of ILD, there was an update in the guideline in 2022. In centres where the appropriate expertise is available, TBCB is an acceptable alternative to traditional surgical lung biopsy as the two showed great histopathological concordance but with better safety profile[5, 6].

DRUG THERAPY FOR IPF

Nintedanib and Pirfenidone are the two approved pharmacological agents for the treatment of IPF. Their approval was based on landmark studies including INPULSIS, CAPACITY and ASCEND, which proved their efficacy in slowing decline in pulmonary function, measured by annual FVC decline, while having a tolerable side effect profile (Table 1) [8 - 12]. Nintedanib is included in the Hospital Authority Drug Formulary and experience in its use has been growing in the past few years. Despite multiple studies lending support for the use of Pirfenidone in IPF, clinical experience in its use is lacking due to its unavailability in Hong Kong.

Table 1. Comparison of anti-fibrotic agents. (Adapted from reference 8 - 12)

	Nintedanib	Pirfenidone
Mechanism of action	Intracellular tyrosine kinase inhibition targeting growth factor receptors involved in pulmonary fibrosis: ATP-competitive inhibitor of FGFR-1 / VEGFR2 /PDGFR-α & β	Inhibition of TGF-β production and downstream signalling, collagen synthesis, and fibroblast proliferation
Efficacy		
-Annual FVC decline	-113.6 ml vs -223.5 ml ($p < 0.001$)	-216 ml vs -363 ml ($p < 0.001$)
-On-treatment mortality	HR 0.57, p = 0.0274	
Dosage	150 mg bd oral	801 mg tds oral
Common side effects	Diarrhea, nausea and vomiting, abdominal pain, decreased appetite, weight loss, deranged LFT	Nausea, rash, diarrhoea, dyspepsia, deranged LFT, photosensitivity

POINTS TO NOTE BEFORE STARTING NINTEDANIB

Gastrointestinal adverse effects (diarrhoea, nausea and raised liver transaminases) are the commonest adverse effects experienced by patients taking nintedanib. In INPULSIS and INBUILD trials, diarrhoea was the most reported adverse event (62.4 % and 66.9 %, respectively) [8, 12]. Attempts have been made to identify risk factors for the development of gastrointestinal side effects from nintedanib, and they include 1) low body mass index, 2) full dose at 300 mg per day, 3) poor performance status; and 4) low serum albumin[13]. Despite its frequent occurrence, it is rare that these adverse effects by themselves will lead to permanent discontinuation of the anti-fibrotic agent. There are two strategies commonly employed when a patient develops diarrhoea. Antidiarrheal agents, most commonly loperamide, are frequently prescribed. Up to 55.3 % of patients require antidiarrheal agents to mitigate the side effects[14]. In one study, 78.6 % of patients developing diarrhoea had resolution of symptoms without the need for dose reduction or treatment interruption[14]. However, if the symptom persists, temporary treatment interruption and dose reduction from 150 to 100 mg bd are viable strategies used to reduce side effects. A study has shown that nintedanib dose reduction and the use of multiple antidiarrheal agents are two factors proven to have positive effects on the continuation of nintedanib. Dose reduction has also been shown to have no apparent effect on FVC decline, which is the major treatment outcome measure of nintedanib[14]. Only 4.4 % of patients taking nintedanib required permanent discontinuation of medication due to diarrhoea[15]. Nausea and loss of appetite are also commonly reported (24.5 % in INPULSIS trial). However, most events were mild to moderate and were self-limiting.

Nintedanib is mainly metabolised by the liver. Its use is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) cirrhosis. Low dose should be used for patients with mild hepatic impairment (Child Pugh A). Raised liver transaminases are not uncommonly encountered with the use of anti-fibrotic agents. However, in many instances, liver function recovered within four weeks, and most patients with mild liver dysfunction remained asymptomatic without clinically apparent liver injury.

Nevertheless, liver function should be monitored closely during the initial few months of starting anti-fibrotic treatment (every four weeks of the first three months, then every three months afterwards), as 70 % of patients developed abnormal liver function in the first three months. Treatment should be discontinued if the patient develops symptoms of acute liver injury or liver transaminases rise above five times the upper limit of normal (ULN). A lower dose of nintedanib can be considered if the patient is asymptomatic and liver transaminases are above three times but less than five times the ULN.

Some authorities would suggest the starting dose of nintedanib to be 100 mg bd in patients with low BMI and poor performance status for the above reasons[15]. Managing expectations and warning patients of its potential side effects is another aspect that is integral to ensuring the effectiveness of anti-fibrotic agents, as compliance is the key to success. As opposed to treatment of most other diseases, taking anti-fibrotic agents would not lead to symptomatic relief as their effect mainly lies in halting disease progression. A realistic portrayal of drug effects on patients during counselling is essential in ensuring good compliance with treatment.

ACUTE EXACERBATION OF IPD

Apart from declines in lung function and dyspnoea scores, acute exacerbation of IPF (AE-IPF) has long been recognised as a major contributor to mortality in IPF. AE-IPF is defined as an acute, clinically significant respiratory deterioration without an identifiable cause. Up to one in five IPF patients experience an exacerbation each year, and the median survival from an AE-IPF is 100 days only[16]. The etiology of AE-IPF remains uncertain. Treatment of AE-IPF is largely supportive with oxygen and non-invasive ventilatory support. Invasive ventilation and extracorporeal membrane oxygenation (ECMO) are reserved for selected cases as a bridge to lung transplantation. Numerous specific treatment strategies have been attempted, but none has been proven beneficial in randomised studies[17]. The latest guideline recommended the use of systemic corticosteroids but evidence is lacking. The global heterogeneity in treatment strategies of AE-IPF by respiratory physicians with ILD expertise was recently described by an international survey[18]. Hopefully, future studies will provide more guidance on this aspect.

CONCLUUSION

IPF is an evolving disease. There have been drastic changes in its understanding in recent years, from how it is diagnosed to how it is best managed. The anti-fibrotic agent is an essential part of treatment as it is currently the most evidence-based pharmacological treatment in the management of IPF. Other aspects

of the disease, for example, management of AE-IPF warrant more research.

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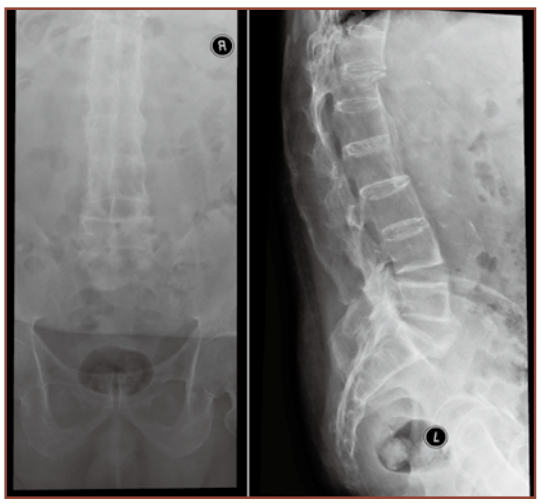
Radiology Quiz

Dr Thomas WL YIP

MBChB, FRCR

Dr Thomas WL YIP



A 70-year-old male who fell from height had XR lumbosacral spine done at the emergency department.

Questions

1. What type of arthritis is this patient likely suffering from?
2. What is the associated complication seen on this set of radiographs?
3. What is the next step of the investigation?

(See P.44 for answers)

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Updates in the Management of COPD

Dr CHAN Ming-chiu
MBBS(HK), MRCP(UK), FHKAM, FHKCP
Associate Consultant, Department of Medicine and Geriatrics, Princess Margaret Hospital

Dr CHAN Yu-hong
MBBS(HK), MRCP(UK), FHKAM, FHKCP, FRCP(Edin)
Associate Consultant, Department of Medicine and Geriatrics, Princess Margaret Hospital

Dr CHAN Ming-chiu Dr CHAN Yu-hong

DEFINITION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease worldwide with significant morbidity and mortality[1]. It is a heterogeneous lung condition scharacterised by chronic respiratory symptoms (dyspnea, cough, expectoration, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction[2]. Locally in Hong Kong, the prevalence of COPD in the elderly population greater than or equal to 60-year-old was found to be 25.9 % and 12.4 % using post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio and lower limit of normal cutoff respectively[3]. COPD also posed a significant health care burden, and was responsible for over 19,000 admissions in 2014. However, it has been shown that the COPD admissions had a decreasing trend. This might be due to a decline in the prevalence of smoking and tuberculosis, and increased use of long-acting bronchodilators[4].

PATHOGENESIS AND PRE-COPD

The understanding of disease pathogenesis of COPD has been evolving. COPD is not only associated with cigarette smoking, but also with other environmental exposures such as biomass fuels, occupational dust and fumes[5]. Moreover, in the past, the disease has been considered as the consequence of accelerated decline of the lung function, but now there is no evidence that childhood disadvantages, such as genetic factors, early-life events and infections, can result in low maximally attained lung function in adulthood and cause COPD despite a normal rate of lung function decline[6]. This pathway was responsible for about half of the COPD development in an analysis of 3 large cohorts. Researchers were also trying to identify patients at risk of developing COPD. They proposed the group of Pre-COPD, for patients with chronic respiratory symptoms, with or without structural and/or functional abnormalities, but without airflow obstruction on spirometry[7]. Similar to COPD patients, subjects of pre-COPD are heterogeneous. Various tools, including symptom assessments, lung function tests, lung function trajectories and imaging modalities, have been used to characterise different subtypes of pre-COPD and identify the risk of progression. For example, chronic bronchitis symptoms were predictors for subsequent COPD developments in multiple cohorts[8]. Another subtype receiving attention is preserved ratio impaired spirometry (PRISm), with FEV1/FVC ratio ≥ 0.7 and FEV1 < 80 %[9]. PRISm has been proposed to be a transitional state and is associated with increased risk of cardiopulmonary disease and all-cause mortality10. Studies are needed to explore treatments that can ameliorate symptoms or even risk of COPD progression in these populations. Subjects with Pre-COPD or PRISm are at risk of developing airflow obstruction over time, but not all of them do[8,9].

DIAGNOSIS OF COPD AND UPDATE IN COMBINED GOLD ASSESSMENT

In patients who have risk factors of COPD illustrated above present with chronic respiratory symptoms of dyspnea, cough, sputum production or history of recurrent lower respiratory tract infection, the diagnosis of COPD should be considered and confirmed with spirometry post bronchodilator FEV1/FVC < 0.72. The degree of airflow limitation should be assessed with FEV1 on spirometry. Patients who have disproportionate symptoms with FEV1 impairment should prompt the physician to revisit the diagnosis, evaluate the comorbidities and consider further testing, such as a full lung function test and imaging to elucidate lung mechanics[2]. However, spirometry has been underutilised in the management of COPD worldwide[5]. Previous studies in Hong Kong also demonstrated the underuse of spirometry in general outpatient clinic and even in hospital-based medical clinic, and physicians should be aware of the clinical use of spirometry to facilitate COPD management[11].

After confirming the presence of airflow obstruction and assessing its degree, the Global Initiative for Obstructive Lung Disease (GOLD) recommends dividing the patients according to the degree of dyspnea and exacerbation risk, and to guide initial pharmacological treatment[2]. (Fig. 1) In 2023, the GOLD report revised the initial COPD assessment tool to stress on the importance of exacerbation and divided COPD patients into three categories. Group A patients have few symptoms (modified Medical Research Council mMRC 0-1 or COPD Assessment Test CAT < 10) and up to 1 moderate annual exacerbation, while group B patients have a higher symptom burden (mMRC ≥ 2 or CAT ≥ 10) and up to 1 moderate annual exacerbation. In contrast with the old version of the tool, groups C and D have merged into group E, scharacterised with a history of at least two moderate exacerbations or at least one exacerbation leading to hospitalisation, regardless of symptom level.

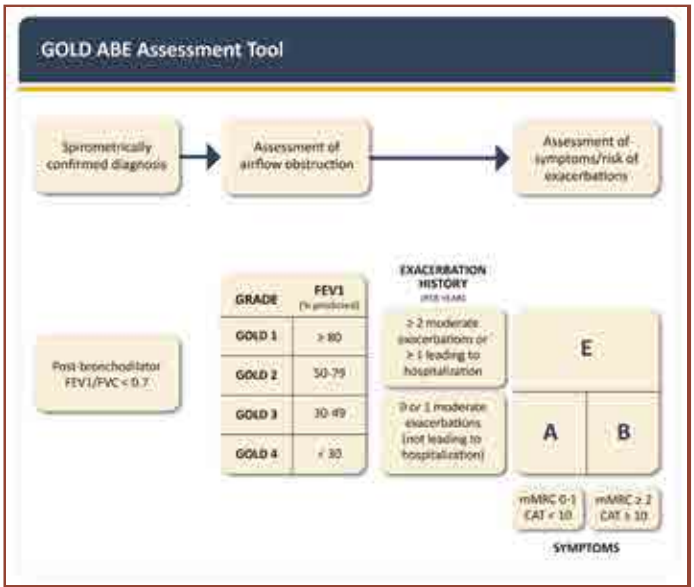

Fig. 1: Updated ABE Assessment Tool of COPD (Excerpted from GOLD guideline 2023[2])

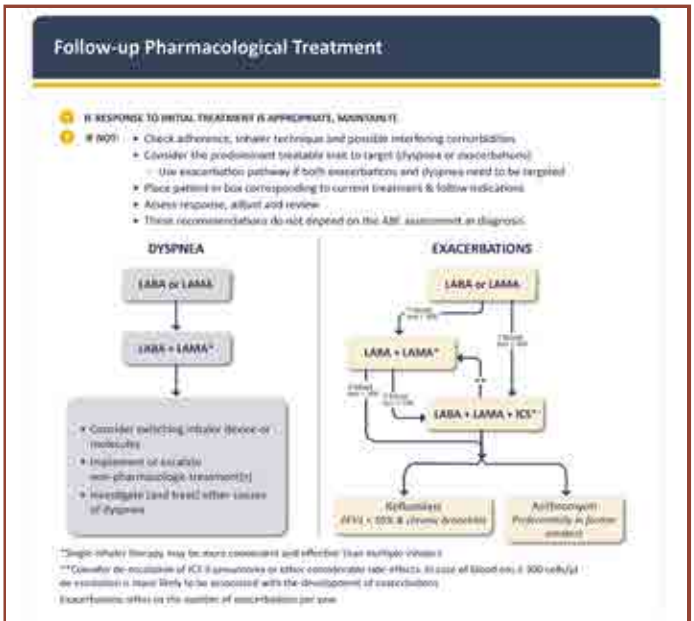

Fig. 2: Choice of pharmacological treatment of stable COPD (Excerpted from GOLD guideline 2023[2])

PHARMACOLOGICAL TREATMENT OF STABLE COPD PATIENTS

Initial pharmacological treatment in Group A patients would be a bronchodilator, preferably a long-acting beta-agonist (LABA) or long-acting muscarinic antagonist (LAMA), while in Group B, a combination of LABA and LAMA is recommended for better lung function improvement and symptom relief[12,13]. In Group E, again dual bronchodilators are recommended for better exacerbation reduction than monotherapy, and inhaled corticosteroid (ICS) should be added if peripheral blood eosinophil is greater than 300 cells/μL as increasing blood eosinophil predicts ICS efficacy for exacerbation reduction[14 - 17].

When choosing an inhaler device, factors to be considered include the requirement of flow rate, coordination, manual dexterity, patient's preference and cost[18]. The number of different inhaler devices should be minimised to reduce the error during application and improve compliance[19]. Physicians should provide education and ensure acceptable inhaler technique upon first prescription and check the puffing technique and compliance during follow-up visits. In the GOLD report, subsequent COPD management depends on two treatable traits of a patient: persistent dyspnea and recurrent exacerbations. (Fig. 2)

In patients with persistent dyspnea, a single bronchodilator can be stepped up to dual bronchodilators for better efficacy in symptom relief while considering non-pharmacological treatment and alternative causes of dyspnea. In patients with recurrent exacerbations on bronchodilator, if peripheral blood eosinophil is elevated, treatment should be stepped up to triple therapy, as discussed previously. Roflumilast, a phosphodiesterase-4 inhibitor, and azithromycin may also be considered in specific COPD patient groups with persistent exacerbations[20, 21]. GOLD report also advised physicians to consider de-escalating the inhaler regimen and remove ICS if pneumonia or other side effects were observed, though increased exacerbations may be observed, especially in patients with high blood eosinophil count[22 - 24].

Until recently, mortality benefit has not been demonstrated in pharmacological treatments of COPD, possibly due to the heterogeneity of COPD population[5]. However, two randomised controlled trials have demonstrated that triple therapy of LABA, LAMA and ICS, compared with dual bronchodilators, can reduce mortality in moderate to severe COPD patients with a history of exacerbations[25, 26]. Recently, encouraging data was also seen in biologics treatment in COPD. An intriguing study was published this year demonstrating that dupilumab could reduce exacerbation and improve lung function and symptoms in a subset of COPD patients with blood eosinophil of at least 300 cells/μL signifying type 2 inflammation, despite the fact that the conflicting results of previous studies using biologics targeting interleukin-5 pathway in COPD patients[27 - 29]. Better characterisation of the complex and heterogeneous COPD population according to the underlying pathophysiology and endotypes may identify more efficacious treatments[5].

NON-PHARMACOLOGICAL TREATMENT OF STABLE COPD PATIENTS

Pharmacological treatment has gained a lot of attention over the last decade due to major advancements in inhalation devices and long-acting agents, as well as improvement in our understanding of the role of ICS. Nonetheless, non-pharmacological treatment is still the essential modality in COPD management, and is easily overlooked.

Smoking cessation is by far the most efficient method in reducing mortality in COPD. A combination of behavioural treatment and pharmacotherapy for smoking cessation is shown to be effective. There is no convincing evidence of choosing which type of agent according to a systemic review[30]. The absolute reductions in mortality risk after quitting smoking ranged 32 - 84 % compared with continuing smokers. This magnitude of mortality reduction is greater than all currently available pharmacological therapy. Smoking cessation slows down lung function decline (ΔFEV1 -1.8 versus -31.4 mL/year) and reduces morbidities, especially those related to atherosclerosis[31].

Vaccinations are another important treatment strategy to prevent exacerbations and pneumonia. GOLD guideline suggested influenza vaccination and SARS-CoV-2 vaccination for COPD patients[2]. For pneumococcal vaccination, the latest updated recommendation from the Centre for Disease Control and Prevention (CDC) in the US is PCV15 followed by PPSV23, or one dose of PCV20. Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥ one year after their last PPSV23 dose[32].

In Hong Kong, the Centre for Health Protection (CHP) has provided a subsidy scheme for influenza and pneumococcal vaccinations in the elderly and those with chronic diseases[33]. CHP currently recommends one dose of PCV13 followed by one dose of 23vPPV one year later. Those who had 23vPPV beforeshould receive a single dose of PCV13 1 year after the previous 23vPPV vaccination.

In adults with COPD, the CDC also recommends the Tdap vaccination (also called dTaP/dTPa) to protect against pertussis (whooping cough), tetanus and diphtheria, in those who were not vaccinated in adolescence. CDC also advises routine uses of shingles vaccine in age greater than 50 years old[34].

Long term oxygen therapy (LTOT) was demonstrated to provide survival benefit in COPD. The studies in the early 1980s laid the foundation for long-term domiciliary management of hypoxemia. Two major RCTs using LTOT in COPD patients with resting PaO2 ≤ 55 mmHg or < 60 mmHg with cor pulmonale or secondary polycythemia showed a survival benefit[35, 36].

For COPD patients with persistent hypercapnia, domiciliary non-invasive positive pressure ventilation (NPPV) may be considered. A systematic review and meta-analysis of these studies confirms that NPPV decreases mortality and risk of hospitalisation. The best candidate subgroups (by recent shospitalisation history or PaCO2) remain unclear[37]. On the other hand; there are randomised controlled trials that suggested no survival benefits of home NPPV[38]. Various factors may account for these discrepancies: differences in patient selection, underpowered studies, NPPV settings incapable of achieving adequate ventilation, and poor adherence[39]. Therefore, the decision to start home NPPV should be made by a specialised team, with careful titration of setting and adequate training provided to patients and their caregivers.

In selected patients, interventional bronchoscopy and surgery may be beneficial after optimising the medical care. Examples of such techniques included surgical bullectomy, endobronchial valves (EBV), lung coils or vapour ablation. In selected cases, we may consider lung transplantation referral.

When there is a bulla that occupies more than one-third of a hemithorax and compresses adjacent viable lung tissue, surgical bullectomy can lead to reductions in dyspnea and improvements in exercise tolerance[40]. In cases of predominant emphysema and hyperinflation (significant increase in total lung capacity and residual volume), EBV are the most studied therapy of all the endoscopic lung volume reduction (ELVR) techniques. In subjects with hyperinflation and absence of interlobar collateral ventilation (by CT scan and bronchoscopy),

randomised controlled trials showed significant increases in FEV1 and 6-minute walk distance as well as health status compared to the control group at 6 and 12 months[41, 42]. Adverse effects in the endobronchial valve treatment group included pneumothorax, valve removal or valve replacement[41]. Pneumothorax could be seen in up to 26.6 % of subjects treated with the endobronchial valve and happens usually within the first 72 hours of the procedure (76 %)[42].

PULMONARY REHABILITATION

Pulmonary rehabilitation is appropriate for most people with COPD; improved functional exercise capacity and health related quality of life have been demonstrated across all grades of COPD severity, with the effect best shown in moderate to severe disease[2]. The currently available evidence suggests that programs lasting 6 to 8 weeks would give the best results, while extending beyond 12 weeks would not yield additional benefits[43]. It should be a patient-tailored program that includes, but is not limited to, exercise training, education, self-management intervention. It aims at behaviour change, improving the physical and psychological condition and promoting the long-term adherence to health-enhancing behaviours[44].

SUPPORTIVE TREATMENT AND PALLIATIVE CARE

Even when receiving optimal medical therapy, many COPD patients continue to experience distressing breathlessness, impaired exercise capacity, fatigue, and suffer from panic, anxiety and depression[45]. Many of these symptoms can be improved by wider use of palliative approaches.

Opiates, neuromuscular electrical stimulation (NMES), and chest wall vibration (CWV) can relieve dyspnea; for example, morphine is shown to improve the health status of COPD patients[46]. These approaches are effective but will need careful titration and often specialist assessment. One simple approach that has gained attention is utilising a small hand-held fan. Applying air current to patient's face, can help improve exercise capacity[47]. Postulated mechanism would include alteration in breathing pattern that diminishes development of dynamic hyperinflation or to a change in perception of breathlessness[47]. Since a small fan can be obtained readily with low cost, this method has been incorporated into rehabilitation programmes by many hospitals in Hong Kong.

Other important areas to manage for the more severe COPD patients would also include nutritional and psychological support.

SEARCH FOR COMORBIDITIES

COPD patients often have other diseases (comorbidities). Some of these are related to COPD by sharing risk factors (e.g. cigarette smoking), or affected by severity (e.g. from chronic inflammation), or arising independently (ageing related). Comorbidities can bave impact on prognosis of COPD.

Cardiovascular diseases, namely heart failure, ischaemic heart disease and arrhythmia, are a major cause of mortality in COPD patients. The prevalence of systolic or diastolic heart failure in COPD patients ranges from 20 % to 70 %[48]. The symptoms of heart failure and COPD overlap and mimic each other, or accompanies acute exacerbation. Treatment with selective β1-blockers improves survival in heart failure and is proven to be safe in patients with heart failure who also have COPD[2, 49].

The other major comorbidity is lung cancer. Lung cancer is currently the leading cancer (both incidence and mortality) according to the latest Hong Kong Cancer Registry 2020[50]. There is evidence for an association between COPD and lung cancer that has been systematically confirmed in several epidemiological and observational cohort studies[51]. These two diseases appear to share more than tobacco exposure as their common origin. One particular interest is whether a screening program for lung cancer is feasible in COPD patients. Several studies involving the use of low-dose chest computed tomography (LDCT) screening have shown improved survival. The GOLD guideline would suggest annual low-dose CT scan (LDCT) for lung cancer screening in people with COPD due to smoking according to recommendations for the general population, but not in COPD not due to smoking due to insufficient data to establish benefit over harm[2]. Locally, Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) from CHP has last updated their recommendation in June 2023[52]. For asymptomatic population at average risk, routine lung cancer screening is not recommended. For high risks individuals, as the local applicability of these screening criteria has not been sufficiently characterised, doctors are advised to balance the benefits and harms (including false-positive findings and potential follow up investigations) of LDCT screening before making an informed and sindividualised decision. Local studies, such as the International Lung Screening Trial (ILST), are ongoing and will give us more insight on the issue[52].

Therefore, there is no good literature support for routine lung cancer screening in COPD patients locally. A careful risk and benefit assessment is needed, as COPD patients may have more false-positive findings on screening CT and are also prone to complications from extra investigations for abnormal lung shadow. As this is a rapidly evolving area, readers are suggested to stay tuned for newer updates on this matter.

Other important comorbidities would include but are not limited to, gastroesophageal reflux, osteoporosis, obstructive sleep apnea, metabolic syndrome, anxiety and depression[2].

REVISED DEFINITION OF COPD EXACERBATIONS (ECOPD)

The older definition of an acute exacerbation was the acute worsening of respiratory symptoms, resulting in additional pharmacotherapy. This definition is more likely research tools than clinical help, as the definition is based on the post facto use of healthcare resources. It also did not take into account various confounders or comorbidities.

The latest GOLD guideline proposes the Rome proposal to define ECOPD as: "in a patient with COPD, an exacerbation is an event scharacterised by dyspnea and/or cough and sputum that worsen over ≤ 14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the airways"[53]. Although this statement is not fully validated by large scale study yet, it gives us a more clinically relevant way to label patients as ECOPD and give treatment accordingly. The severity of an ECOPD has also been discussed in this Delphi statement and incorporated into GOLD guidelines. (Fig. 3)

More than 80 % of ECOPD can be managed on an outpatient basis with pharmacological therapies, including bronchodilators, corticosteroids, and antibiotics[54, 55]. Outpatient management should be considered for mild ECOPD. The potential indications for a shospitalisation would include severe symptoms (such as tachypnea, desaturation, altered mental state), acute respiratory failure, the onset of new physical signs (such as cyanosis and peripheral oedema), failure to respond to initial treatment and, the presence of severe comorbidities[2]. As most of COPD patients are elderly patients, adequate social support should also be factored into the treatment setting considerations.

CONCLUSION

There have been a number of exciting updates on diagnosis, assessment and treatment of COPD recently. Both pharmacological and non-pharmacological treatment are important in helping our COPD patients. Knowing the different inhaler devices would be essential to empower patient self-management and improve patient adherence. Comorbidities screening and exacerbation treatment are important aspects of COPD management.

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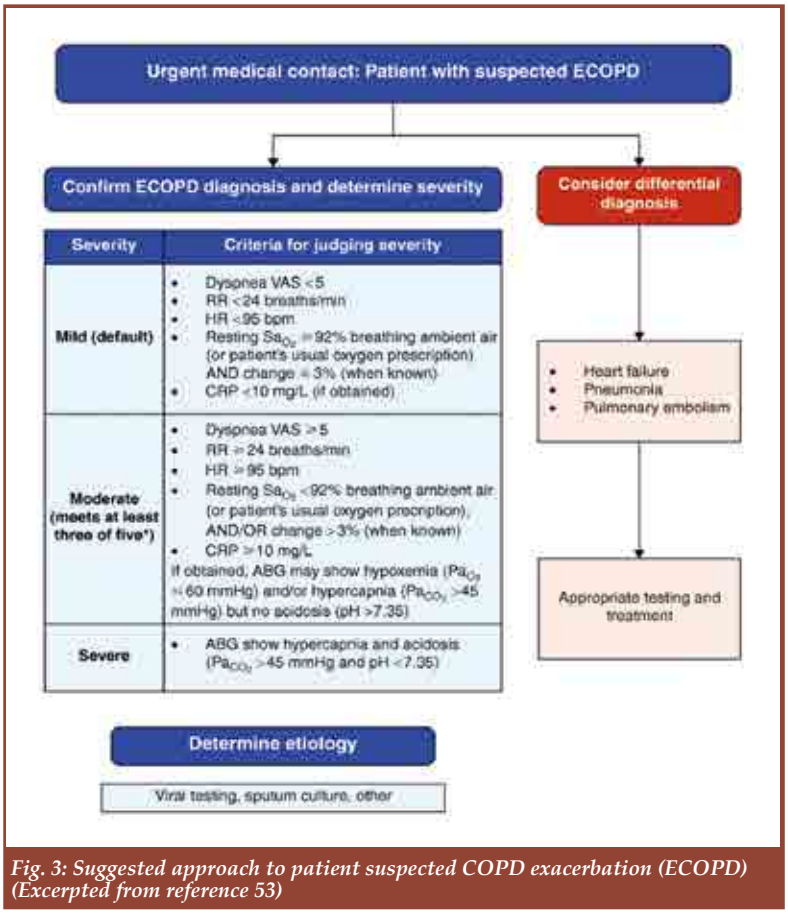

Fig. 3: Suggested approach to patient suspected COPD exacerbation (ECOPD) (Excerpted from reference 53)

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How to Pick Up Running as a Habit

Dr YEUNG Yiu-cheong
MBBS (HK), MPH, MRCP, FHKAM, FHKCP, FRCP (Edin, Glasg)
Consultant Physician
Respiratory team
Department of Medicine and Geriatrics
Princess Margaret Hospital

Dr YEUNG Yiu-cheong

Medical professionals are always busy helping people. We might be busy and may not have time to take care of our own health.

I seldom exercise before 2018. My journey of running started in late 2018, after I registered for the Diabetes Hong Kong Healthy Run held on 19/1/2019. Without any idea of what a 10 km distance is about and did not even have a pair of proper running shoes, I tried to get professional support by joining the running club "NSF Distance Running Club" in October 2018. Through a structured training program, I have learned the importance of proper warm up, stretching exercises and cool down before and after running exercises. Regular training interval running, tempo running and long distance running have helped build up the body for running longer and longer while minimising injury. My big thanks to my coach, 吳師傅 who has given me valuable advice and tips in running. 吳輝揚師傅 is the former Chinese marathon recorder holder in Hong Kong for 26 years (1992 - 2018). In the NSF Running Club. I have also met friends like Dr Kevin Kwok and Dr Iris Li, who are experienced runners and have given me a lot of encouragement when I get exhausted from running.

In six months, I can see changes in my body, with weight reduced by 30 pounds and BMI dropped from 27 kg/m² in 2018 to 22.5 kg/m² in 2019. I managed to complete two half-marathons in Hong Kong and the Fuji Marathon in 2019. On the other side, I have tasted what Iliotibial band syndrome, plantar fasciitis and painful callosity.

Running is also a good group exercise. Eight colleagues of our department formed two teams in the "Sower Action Challenge 12 hours" Trail run in Oct 2019, a charity marathon event with an aim to promote education in rural regions for orphans and underprivileged children.

Since early 2020, the regular running club activities were suspended due to the COVID-19 epidemic. However, my running practice did not stop. In order to keep social distancing, I run alone from Science Park to Tai Po along the seaside. This gives me a good time to get fresh air after wearing N95 Mask for the whole day. The tranquillity of the path with Ma On Shan and Pat Sin Leng as a backdrop has never bored me.

During these few years, I also started hiking and trail running. Trail running is different from road running and requires more coordination and stability. The joy is when we immerse ourselves in the natural beauty, and a good trail running may not be defined by data or timing. I have good accompanies with Dr Harold Lee and Dr Nicole Chau in the HK100 Trail run in 2020.

Here are some personal tips for developing a running habit:

1. Try to join some competitions, start with a short distance like a 10 kilometres run. This will help you to develop a target and motivate yourself to practice.
2. Do it incrementally; start with a 15 - 20 minutes run first. When you feel fine with the distance, you can gradually increase the distance and duration.
3. Try to join a running club, where you will meet people with a common interest and it will motivate you to run regularly every week. The feeling is excellent when running in a group. You can learn the steps in warm up, stretching and post running cool down exercise.
4. Keep a record of your running and pacing. You can monitor your progress, which is important for keeping yourself motivated in the running. Nowadays, a sport watch and smartphone Apps will help you to keep your running record.

In summary, running is a good exercise; you can do it alone or in groups.

"We are what we repeatedly do. Running is not a sport, but a habit" - Unknown.

Fig. 1 DM run 19/1/2019 (Personal collection)

Fig. 2 Photo with師傅, Dr Iris Li and Dr Kevin Kwok (Personal collection)

Fig. 3 27/10/2019 Sower Action Challenge 12 hrs (Personal collection)

Fig. 4 Beautiful red leaves in Mt. Fuji Marathon 2019 (Personal collection)

Fig. 5 Tranquility in Science Park 2022 (Personal collection)

Fig. 6 HK100 2020 with Nicole and Harold (Personal collection)

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LIBERTY ASTHMA VENTURE Study Design[2]: 210 patients were randomly assigned with oral glucocorticoid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study Design[3]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Summary of Product Characteristics. May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg- initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <12 years not been established. Not to be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** AD: Most common adverse reactions reported- injection site reactions, conjunctivitis, blepharitis and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reaction reported- injection site erythema. For other undesirable effects, please refer to the full prescribing information. Preparation: 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-20.05

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200mg · 300mg

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2	★Zoom Live Topic: Latest Psoriatic Disease Management- What Is Achievable Today? 3	★Certificate Course on Respiratory Medicine 2023 (Video Lectures) 4	★In-person The HKMA District Health Network (Kowloon East) CME Lecture in Physical Attendance Mode Topic: IBS and Overlapping FGID Symptoms ★Certificate Course on Renal Medicine 2023 (Video Lectures) 5	6	7
8	★Zoom Live Topic: Recent Advancement of Microbiome Research and Its Application in Infection, Vaccination and Quality of Life Management 9	10	★The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed ★In-person / Zoom Live HKMA-CUHK Medical Centre CME Programme 2023 (Physical Lecture + Online) Common health problems for the elderly Topic: How To Fight Common Elderly Health Problems -Dementia and Sarcopenia ★Certificate Course on Respiratory Medicine 2023 (Video Lectures) 11	★Certificate Course on Renal Medicine 2023 (Video Lectures) 12	★Zoom Live HKMA Adult Immunisation Campaign 2023 Topic: The Hidden Disease Burden of HPV-Related Head and Neck Cancers in Hong Kong 13	14
15	16	★In-person / Zoom Live HKMA-GHK CME Programme 2023 (Physical Lecture + Online) Topic: To-be-confirmed ★Certificate Course on Healthcare Mediation 2023 (Video Lectures) 17	★In-person The HKMA District Health Network (Sha Tin) CME Lecture in Physical Attendance Mode Topic: Improving CV Prognosis With Early And Massive LDL-C Reduction 18	★Certificate Course on Renal Medicine 2023 (Video Lectures) ★HKFMS Foundation Meeting ★FMSHK Executive Committee Meeting 19	★In-person The HKMA District Health Network (Kowloon City) CME Lecture in Physical Attendance Mode Topic: The Contemporary Management on Typical and Atypical Diabetes Mellitus 20	21
22	23	★Certificate Course on Healthcare Mediation 2023 (Video Lectures) 24	25	★In-person / Zoom Live HKMA-HKSTP CME Programme 2023 (Physical Lecture + Online) Topic: ID Microbes Using Metagenomic and Big Data Bioinformatics ★Certificate Course on Renal Medicine 2023 (Video Lectures) 26	★Zoom Live HKMA Adult Immunisation Campaign 2023 Topic: The Impact of Introducing Higher Pneumococcal Conjugate Vaccine 27	28
29	30	★Zoom Live Topic: Prevention and Risk Reduction of CRC with the Recent Advancement of Gut Microbiome Research and Guideline ★Certificate Course on Healthcare Mediation 2023 (Video Lectures) 31				

ZERBAXA®
ceftolozane and tazobactam
for injection

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

FIGHT IT NOW
CHOOSE ZERBAXA®

Consider ZERBAXA® for ventilated patients

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

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

ZERBAXA® in vHAP/VAP[2]

PRIMARY ENDPOINT

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

FAVOURABLE SUBGROUPS

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

MICROBIOLOGICAL RESPONSE RATE

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

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

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

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

Zerbaxa® Selected Safety Information

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

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

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

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

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

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

- Hypersensitivity reactions
  Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.
  Before initiating therapy with ZERBAXA®, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. If this product is to be given to a patient with a cephalosporin, penicillin, or other beta-lactam allergy, exercise caution because cross sensitivity has been established. If an anaphylactic reaction to ZERBAXA® occurs, discontinue the drug and institute appropriate therapy.
- *Clostridium difficile*-associated diarrhea
  Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZERBAXA®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.
  If CDAD is confirmed, discontinue antibacterials not directed against *C. difficile*, if possible. Manage fluid and electrolyte levels as appropriate, supplement protein intake monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.
- Development of Drug-Resistant Bacteria
  Prescribing ZERBAXA® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Adverse Events:
- Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis
  The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA® were nausea, diarrhea, headache, and pyrexia.
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)
  The most common adverse reactions (2% or greater) occurring in patients receiving ZERBAXA® were hepatic transaminase increased[1], renal impairment/renal failure[2], diarrhea, intracranial hemorrhage[3], vomiting, clostridium difficile colitis[4].

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

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

Before prescribing, please consult the full prescribing information

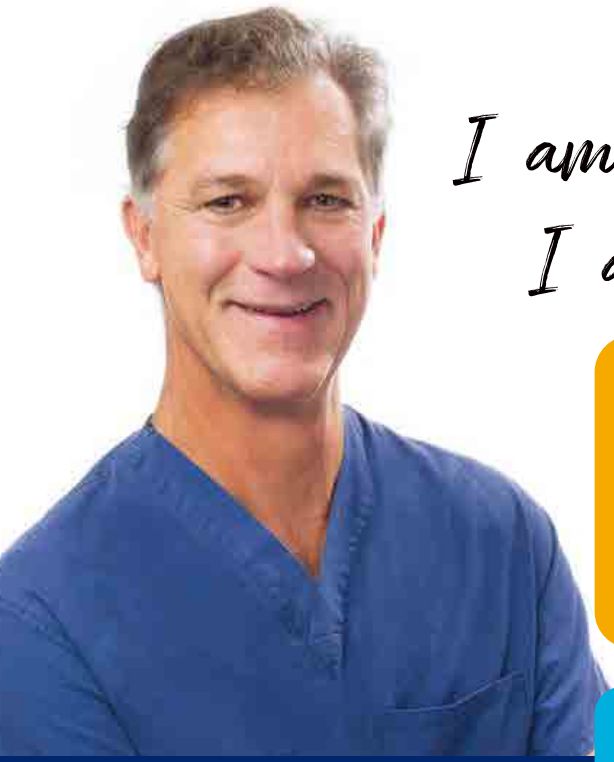
MSD

Merck Sharp & Dohme (Asia) Ltd.
29/F, Low Block, 39 Yun Ping Road, Causeway Bay, Hong Kong.
Tel: (852) 2811 2000 Fax: (852) 2834 0758
Website: www.msd.com.hk

HK-ZER-200035 Oct 2020

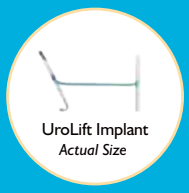
Date / Time	Function	Enquiry / Remarks
3 TUE 1:00 PM	**Zoom Live** **Topic: Latest Psoriatic Disease Management- What Is Achievable Today?** Organiser: The Hong Kong Medical Association Speaker: Dr Victor Tak-lung WONG	HKMA CME Dept. Tel: 3108 2507 1 CME Point
4 WED 7:00 PM	**Certificate Course on Respiratory Medicine 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr LUN Chung-tat	Ms Vienna LAM Tel: 2527 8898
5 THU 2:00 PM	**In-person** **The HKMA District Health Network (Kowloon East) CME Lecture in Physical Attendance Mode** **Topic: IBS and Overlapping FGID Symptoms** Organiser: The HKMA District Health Network Speaker: Dr CHEUNG Sai-wah Venue: Crowne Plaza Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O, Hong Kong	The HKMA District Health Network Dept. Tel: 3108 2514 1 CME Point
9 MON 2:00 PM	**Zoom Live** **Topic: Recent Advancement of Microbiome Research and Its Application in Infection, Vaccination and Quality of Life Management** Organiser: The Hong Kong Medical Association Speaker: Dr Norma Nor CHAN	HKMA CME Dept. Tel: 3108 2507 1 CME Point
11 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** **Organizer: Hong Kong Neurosurgical Society** Speaker: Dr Jessamin Wenzhe YE Chairman: Dr CHEUNG Fung-ching Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061 1.5 CME Point
2:00 PM	**In-person / Zoom Live** **HKMA-CUHK Medical Centre CME Programme 2023 (Physical Lecture + Online)** **Common health problems for the elderly** **Topic: How To Fight Common Elderly Health Problems -Dementia and Sarcopenia** Organiser: The Hong Kong Medical Association and CUHK-Medical Centre Speaker: Dr Wency Wan-sze HO Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Respiratory Medicine 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Mr NG Shu-wah, Ms Maggie LIT	Ms Vienna LAM Tel: 2527 8898
12 THU 7:00 PM	**Certificate Course on Renal Medicine 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Andrew LUK, Dr Joseph Ho-sing WONG	Ms Vienna LAM Tel: 2527 8898
13 FRI 2:00 PM	**Zoom Live** **HKMA Adult Immunisation Campaign 2023** **Topic: The Hidden Disease Burden of HPV-Related Head and Neck Cancers in Hong Kong** Organiser: The Hong Kong Medical Association Speaker: Dr Eddy Wai-hung LAM	HKMA CME Dept. Tel: 3108 2507 1 CME Point
17 TUE 2:00 PM	**In-person / Zoom Live** **HKMA-GHK CME Programme 2023 (Physical Lecture + Online)** **Topic: To-be-confirmed** Organiser: The Hong Kong Medical Association and the Gleneagles Hong Kong Hospital Speaker: To-be-confirmed Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Healthcare Mediation 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHOO Kah-lin	Ms Vienna LAM Tel: 2527 8898
18 WED 1:00 PM	**In-person** **The HKMA District Health Network (Sha Tin) CME Lecture in Physical Attendance Mode** **Topic: Improving CV Prognosis With Early And Massive LDL-C Reduction** Organiser: The HKMA District Health Network Speaker: Dr Steven Siu-lung LI Venue: Courtyard by Marriott Hong Kong Sha Tin, 1 On Ping Street, Sha Tin New Territories, Hong Kong	The HKMA District Health Network Dept. Tel: 3108 2514 1 CME Point
19 THU 7:00 PM	**Certificate Course on Renal Medicine 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Sam LAU, Dr Lorraine KWAN	Ms Vienna LAM Tel: 2527 8898
7:00 PM	**HKFMS Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
20 FRI 1:00 PM	**In-person** **The HKMA District Health Network (Kowloon City) CME Lecture in Physical Attendance Mode** Topic: The Contemporary Management on Typical and Atypical Diabetes Mellitus Organiser: The HKMA District Health Network Speaker: Dr Cheuk-lik WONG Venue: Spotlight Recreation Club (博藝會), 4/F., Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	The HKMA District Health Network Dept. Tel: 3108 2514 1 CME Point

UROLIFT



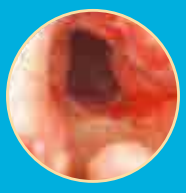
I am a urologist.
I am a patient.

> "I went from getting up 3 times a night to sleeping through 6-8 hours! What a difference it has made at work as well. I can now complete longer surgeries without urgency to void."
>
> **Philip Butler, M.D., F.A.C.S.*** *Genesis Healthcare Partners* and UROLIFT SYSTEM PATIENT



UroLift Implant
Actual Size

PRE-PROCEDURE



POST-PROCEDURE

FDA cleared to treat patients with prostate volumes up to 100cc

MAIN REASONS I CHOSE THE UROLIFT SYSTEM AND RECOMMEND IT TO MY PATIENTS

Patients have a better recovery experience than TURP, with durable results and no new and lasting sexual dysfunction**[1,7,9]

Rapid relief and recovery in days, not months[1,6]

Lowest catheter rate of the leading BPH procedures[2,5-7,9,10]

The only leading BPH procedure that does not destroy tissue

Proven durability through 5 years[7]

Real world outcomes consistent with randomised controlled data[8]

Check out the data at **UroLift.com**
For more information, email to **UroLift.hk@teleflex.com** or contact **+852 5523 7854** *(WhatsApp Only)*

Indicated for the treatment of symptoms of an enlarged prostate up to 100cc in men 50 years or older. As with any medical procedure, individual results may vary. Most common side effects are temporary and include haematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence.[1] Rare side effects, including bleeding and infection, may lead to a serious outcome and may require intervention. Consult the Instructions for Use (IFU) for more information.

*Dr. Butler is a paid consultant of NeoTract|Teleflex. Results may vary.
**No instances of new, sustained erectile or ejaculatory dysfunction in the L.I.F.T. pivotal study.

1. Roehrborn, J Urol 2013 2. Bachmann, Eur Urol 2013; 3. AUA BPH Guidelines 2003, 2010, 2018 4. Naspro, *Eur Urol* 2009 5. Montorsi, *J Urol* 2008; McVary, *J Sex Med* 2016 6. Shore Can J Urol 2014 7. Roehrborn et al. *Can J Urol* 2017 8. Eure et al J Endourol 2019 9. Mollengarden, Prostate Cancer Prostatic Dis 2018; 10. Gilling, J Urol 2017

Teleflex
INTERVENTIONAL UROLOGY

Date / Time	Function	Enquiry / Remarks
24 TUE 7:00 PM	**Certificate Course on Healthcare Mediation 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Peter Chi-wang PANG	Ms Vienna LAM Tel: 2527 8898
26 THU 2:00 PM	**In-person / Zoom Live** **HKMA-HKSTP CME Programme 2023 (Physical Lecture + Online)** **Topic: ID Microbes Using Metagenomic and Big Data Bioinformatics** Organiser: The Hong Kong Medical Association and the Hong Kong Science Park Speaker: Dr YE Bin Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Renal Medicine 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr HO Lo-yi, Dr Ivy Lok-yan WONG	Ms Vienna LAM Tel: 2527 8898
27 FRI 2:00 PM	**Zoom Live** **HKMA Adult Immunisation Campaign 2023** **Topic: The Impact of Introducing Higher Pneumococcal Conjugate Vaccine** Organiser: The Hong Kong Medical Association Speaker: Dr WONG King-ying	HKMA CME Dept. Tel: 3108 2507 1 CME Point
31 TUE 2:00 PM	**Zoom Live** **Topic: Prevention and Risk Reduction of CRC with the Recent Advancement of Gut Microbiome Research and Guideline** Organiser: The Hong Kong Medical Association Speaker: Dr Norman Nor CHAN	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Healthcare Mediation 2023 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Prof Paul Bo-san LAI	Ms Vienna LAM Tel: 2527 8898

Certificate Course for Doctors, Nurses, Paramedics and Allied Health Workers **Course No. C401** **CME/CNE Course**

Certificate Course on
Healthcare Mediation 2023
醫護調解課程 *(Video Lectures)*

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society for Healthcare Mediation

Date	Topics	Speakers
17 Oct 2023	Mediation & Healthcare	Dr. CHOO Kah-lin 俞佳琳醫生 Consultant (Medicine) Accredited Mediator
24 Oct 2023	DOs and DON'Ts in Healthcare Mediation	Dr. PANG Chi Wang Peter 彭志宏醫生 Surgeon in private practice Accredited Mediator
31 Oct 2023	Listening Skills & Use of Body Language	Prof. LAI Bo Sang Paul 賴寶山醫生 Professor, Department of Surgery Accredited Mediator
7 Nov 2023	Perception Check, Paraphrasing & Summarizing Skills	Dr. TSOI Chun-hing Ludwig 蔡振興醫生 Consultant (Emergency Medicine) Accredited Mediator
14 Nov 2023	Reframing & Facilitative Skills	Dr. ONG Kim-lian 王金蓮醫生 Consultant (Emergency Medicine) Accredited Mediator
21 Nov 2023	Negotiation Skills & Empowerment	Dr. CHAN Kit-ying Sandy 陳潔瑩博士 Registered Nurse Accredited Mediator

Date : 17, 24, 31 October & 7, 14, 21 November 2023 (Tuesday)
Duration of session : 1.5 hours (6 sessions)
Time : 7:00 pm – 8:30 pm
Course Feature : Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors : DOCTORS are required to complete a quiz after the completion of each lecture
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline : 11 October 2023
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

Online Application from website: http://www.fmshk.org

Answers to Radiology Quiz

Answers:

1. The patient suffers from ankylosing spondylitis. It is evidenced by the fusion of bilateral sacroiliac joints (blue arrow), diffuse syndesmophytic ankylosis with "bamboo spine" appearance and interspinous ligament ossification giving a "dagger spine" appearance (yellow arrow).

2. The lateral radiograph shows the three-column-fracture traversing T12 vertebral body with associated spinal canal narrowing (green arrow).

3. The patient needs an urgent orthopaedic referral. Urgent MRI can be arranged to assess possible spinal cord injury.

Dr Thomas WL YIP
MBChB, FRCR

MSD

TAKE ON THE CHALLENGES OF COVID-19[1]

TEST. TREAT. TAKE CHARGE.

molnupiravir

Reference: 1. molnupiravir US EUA Product Insert

MOLNUPIRAVIR Selected Safety Information

Authorized Use

1. Molnupiravir is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults:
   - with positive results of direct SARS-CoV-2 viral testing, and
   - who are at high risk for progression to severe COVID-19, including hospitalization or death, and
   - for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate
2. Molnupiravir is not approved for any use, including the treatment of COVID-19, but is authorized for emergency use by the FDA under an Emergency Use Authorization (EUA).
3. The emergency use of molnupiravir is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

Limitations of Authorized Use

4. Molnupiravir is not authorized:
   - for use in patients who are less than 18 years of age
   - for initiation of treatment in patients hospitalized due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
   - for use for longer than 5 consecutive days
   - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19
5. Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

Contraindications

6. No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.

Warnings and Precautions

7. There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.
8. Molnupiravir is not recommended for use during pregnancy. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
9. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual.
10. Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently during treatment with molnupiravir and for 4 days after the last dose.
11. Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.
12. Hypersensitivity reactions, including anaphylaxis, have been reported with molnupiravir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue molnupiravir and initiate appropriate medications and/or supportive care.
13. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. The safety and efficacy of molnupiravir have not been established in pediatric patients.

Adverse Reactions

14. The most common adverse reactions occurring in ≥1% of subjects in the molnupiravir treatment group in the Phase 3 double-blind MOVe-OUT study were diarrhea (2% versus placebo at 2%), nausea (1% versus placebo at 1%), and dizziness (1% versus placebo at 1%) all of which were Grade 1 (mild) or Grade 2 (moderate). Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (≤1%) of the subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo.

Drug Interactions

15. No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild to moderate COVID-19, have been conducted.

Breastfeeding

16. There are no data on the presence of molnupiravir or its metabolites in human milk. It is unknown whether molnupiravir has an effect on the breastfed infant or affects breast milk production. Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.

Males of Reproductive Potential

17. Nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir. The risk beyond three months after the last dose of molnupiravir is unknown.

Before prescribing, please consult the full prescribing information.

MSD

Merck Sharp & Dohme (Asia) Ltd.
[illegible]

HK-ANV-00006 May/2022

The FIRST Anti-Inflammatory Reliever

SYMBICORT™
ANTI-INFLAMMATORY RELIEVER
DELIVERS EFFICACY WHEN IT MATTERS

REDUCES EXACERBATIONS, ALONE OR WITH MAINTENANCE.[1-7]

NOW INDICATED FOR MILD, MODERATE AND SEVERE PATIENTS[8]

References: 1. O'Byrne PM et al. N Engl J Med 2018; 378: 1865-76. **2.** Bateman ED et al. N Engl J Med 2018; 378: 1877-87. **3.** Beasley R et al. N Engl J Med 2019; DOI: 10.1056/NEJMoa1901963. **4.** Hardy J et al. Lancet 2019; Published online Aug 23, 2019; http://dx.doi.org/10.1016/S0140-6736(19)31948-8. **5.** Kuna P et al. Int J Clin Pract 2007 (May); 61(5): 725 – 36. **6.** Bousquet J et al. Respir Med 2007; 101: 2437 – 46. **7.** Sobieraj DM et al. JAMA 2018; doi: 10.1001/jama.2018.2769. **8.** Symbicort Hong Kong Package Insert. Feb 2021.

Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** In adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations. Symptomatic treatment of moderate to severe COPD in adults. **Dosage:** **Asthma** ***1) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1 inhalations as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***2) Symbicort maintenance and reliever therapy*** *Adult & Adolescent ≥ 12yr:* Patients should take 1 inhalation of Symbicort Turbuhaler 160/4.5 mcg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and some may need 2 inhalations b.d.. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***3) Symbicort maintenance therapy 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1-2 inhalations b.d.. Max daily dose is 4 inhalations. **COPD** ***160/4.5 mcg Turbuhaler*** *Adult:* 2 inhalations b.d.. Max daily dose is 4 inhalations. **Contraindications:** Hypersensitivity to budesonide, formoterol or lactose. **Precautions:** Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS, HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/tuberculosis, sensitivity to sympathomimetic amines, cardiovascular disorders, hypokalaemia, diabetes, pneumonia, lactose, pregnancy & lactation. Not recommended for children below 12 years of age. Incidence of candidiasis can be minimized by having patients rinse their mouth out with water after inhaling their maintenance dose. **Interactions:** CYP3A4 inhibitors, beta-receptor blocking agents, other sympathomimetic agents, Xanthine derivatives, mineralocorticosteroids and diuretics, Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines. **Undesirable effects:** Palpitations, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request.** API.HK.SYM.0721

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Further information is available on request:

AstraZeneca Hong Kong Limited
Unit 1-3, 11/F, 18 King Wah Road,
North Point, Hong Kong.
Tel: (852) 2420 7388 Fax: (852) 2422 6788

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Symbicort® budesonide/formoterol **EFFICACY WHEN IT MATTERS**