Advance Therapy in Respiratory Diseases
實話易吸

 TRELEGY ELLIPTA (fluticasone furoate/umeclidinium/vilanterol) Safety Information - Trilogy E 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 treatment without physician supervision since symptoms may recur after discontinuation - Common adverse events: Pneumonia, sinusitis, rhinosinusitis, cough, asthmapnea

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 (永観堂禅林寺) 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.

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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 this 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 antifibrotic 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 linezolid. 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.
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 Kei-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

12:20-13:30 Lunch Symposium (Keynote Lecture)
- Modernising Chinese Medicine
  Prof. BIAN Zhaoxiang
  Associate Vice-President (Chinese Medicine Development), HKBU

13:20-14:40 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. Haninder 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

14:10-15:20 Session 4A (Advances in Paediatric Neuro-developmental Disorders)
- Holistic Care in Paediatric Pharmaco Resistant Epilepsy in Era of Genomics: Etologies Based Medical, Dietary and Surgical Intervention & Neuropsychology
  Dr. Mario Wai-kwong CHAK
  Associate Consultant, Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital
  Ms, Vivi Wai-kee 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

15:40-16:40 Session 5 (Advances in Allergy & Immunology Session)
- Recent Advances in House Dust Mite Allergy Immunotherapy (Lecture via Zoom)
  Prof. Elke Günther WUESTENBERG
  Specialist in Otolaryngology and Allergology, Professor of Medicine
- Innovative Management Strategies for Type 2 Inflammatory Diseases
  Dr. Alston Wai-ming CHAN
  Specialist in Paediatric immunology, Allergy & Infectious Diseases

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$400 for Non-members of FMSHK Member Societies
Online: Free of charge

Registration
Application of CME / CNE accreditation is in progress.
Enquiry: 2527 8898  Ms. Lucy Lau

Online Registration
https://forms.gle/yAKcN&Bq6zCW6ErL8
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.

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.
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 mellitus 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

<table>
<thead>
<tr>
<th>項目</th>
<th>內容</th>
</tr>
</thead>
<tbody>
<tr>
<td>資助 Subsidies</td>
<td>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.</td>
</tr>
<tr>
<td>共付模式 Co-payment</td>
<td>配對參加者在篩查階段應按，需向家庭醫生支付指定的共付費用。在治療階段的資助，則對參加者需付家庭醫生就參加計劃的診斷共付額（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.</td>
</tr>
<tr>
<td>社區藥物名冊 Community Drug Formulary</td>
<td>家庭醫生可以優惠價格訂購社區藥物名冊內指定的藥物。Family Doctors can order specified drugs in the Community Drug Formulary at low prices.</td>
</tr>
<tr>
<td>按服務表現付費獎勵 Pay-for-Performance incentives</td>
<td>如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.</td>
</tr>
<tr>
<td>雙向轉介機制 Bi-directional referral mechanism</td>
<td>家庭醫生可按參數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.</td>
</tr>
<tr>
<td>團隊合作 Teamwork</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

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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. An estimated 191,000 deaths occurred due to MDR/RR-TB in 2021. 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. 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. 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. 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. 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. In that document, the WHO also recommended replacing the injectable agent, kanamycin or capreomycin, with amikacin. 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. 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. The Nix-TB study, which was a single-arm uncontrolled open-label intervention study that investigated the BPaL regimen for patients with MDR-TB in the intention-to-treat population achieved favourable outcomes at six months, at the expense of high frequency of adverse events. 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. 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 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. In the TB-PRACTICAL, which was a Phase 2, 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...
moxifloxacin for the treatment of MDR/RR-TB in recent years (Adapted from reference 16 & 17)

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)

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Description</th>
<th>Setting</th>
<th>Experimental arms</th>
<th>Control arm</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nix-TB[2]</td>
<td>A single-arm uncontrolled unblinded intervention study</td>
<td>South Africa</td>
<td>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</td>
<td>No standard of care control group</td>
<td>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 %)</td>
</tr>
<tr>
<td>ZeNix[3]</td>
<td>A partially blinded randomised controlled trial</td>
<td>South Africa, Georgia, Moldova, the Russian Federation</td>
<td>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</td>
<td>No standard of care control group</td>
<td>Overall risk-benefit ratio favoured the arm that received linezolid at a dose of 600 mg for 26 weeks</td>
</tr>
<tr>
<td>TB-PRACTICAL[4]</td>
<td>A phase 2 -3, open-label randomised controlled trial</td>
<td>South Africa, Belarus, Uzbekistan</td>
<td>15 years and older patients who had RR-TB, investigating three different 24-week regimens containing BPaL with or without moxifloxacin or clofazimine</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Age &lt; 14 years</th>
<th>MDR/RR-TB fluoroquinolone susceptible</th>
<th>Pre-XDR-TB</th>
<th>XDR-TB</th>
<th>Extensive pulmonary TB</th>
<th>Extrapulmonary TB</th>
<th>Persons living with HIV</th>
<th>Pregnant/ breastfeeding women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter 6-month regimen</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes except CNS, miliary and osteoarticular</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BPaLM[1]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPaL[2]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes except CNS, miliary and osteoarticular</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Shorter 9-month all oral regimen</td>
<td>4 - 6 Bdg(6 m)-Lfx/Mfx-Cfz-Z-E-Hb/Eto/5 Lfx/Mfx-Cfz-Z</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes except meningitis, miliary, pericardial and osteoarticular</td>
<td>Yes</td>
</tr>
<tr>
<td>4 - 6 Bdg(6 m)-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hb/5 Lfx/Mfx-Cfz-Z</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes except meningitis, miliary, pericardial and osteoarticular</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Longer 18 - 20-month individualised regimens[3]</td>
<td>18 - 20-month regimens based on the WHO drug grouping A, B, and C[4]</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (with exceptions, see footnote)[8]</td>
</tr>
</tbody>
</table>

Bdg: bedaquiline; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; Cfz: clofazimine; CNS: central nervous system; E: ethambutol; Eto: ethionamide; H: high dose isoniazid; L: 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-cliaitasin 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 as 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 pregnancy/breastfeeding 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. 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.

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). 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 breastfeeding 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). The 9-month all-oral regimen comprises bedaquiline, pretomanid, linezolid (at a daily dose of 600 mg), 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. 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). 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. In particular, there should be sufficient companion drugs to protect not only
fluous quinolones 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.

**References**


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In the clinical trial programme for BREZTRI, inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) refers to budesonide/formoterol fumarate, and long-acting muscarinic antagonist (LAMA)/LABA refers to glycopyrronium/formoterol fumarate.

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


ABBREVIATED PRESCRIBING INFORMATION

Presentation: Aerosphere pressurised inhalation suspension budesonide 300μg/glycopyrronium 72 μg/formoterol fumarate 4.6 μg 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-agonist or combination of a long-acting muscarinic antagonist. Dosage: Two inhalations daily (one inhalation in the morning and one inhalation in the evening). Contraindications: Hypersensitivity to the active substances, tetracyclines, Ld-diketoxyxyllic acid-schachtin, calcium chandelates. Precautions: Not for acute use. Should be discontinued immediately if paradoxical bronchospasm occurs. It is recommended that treatment should not be stopped abruptly. Caution to patients with clinically significant uncontrolled and severe cardiovascular disease, bronchial asthma, or with known thoracic surgery. Used with caution in patients with thyrotoxicosis, symptomatic prostatism, pyloric obstruction or with variable angina pectoris, severe renal impairment and severe hepatic impairment. Co-administration with other bronchodilators is not recommended. No or limited data on pregnancy, breastfeeding & fertility. Interactions: Strong CYP3A inhibitors, rifampicin, ritonavir, not recommended for use with other inhalers. May antagonise effect of beta-agonists. Other beta-adrenergic, anticholinergic, lithium, theophylline. Avoid use with monoamine oxidase inhibitors. Undesirable effects: Pneumonia, headache, urinary tract infection, rash and dizziness, hypersensitivity, bronchospasm, breathlessness, dysphonia, cough, nasal, coryza, sneezing, nasal. Full local prescribing information is available upon request. AY000532122

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**References:**

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

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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\(^4\). The overall survival rates remain low due to late-stage diagnosis\(^5\)–\(^4\). 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\(^6\). 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)\(^7\).

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ORAL EGFR-TYROSINE KINASE INHIBITORS (EGFR-TKIs)

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 afatinib, 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-vmjj is a bispecific human antibody to EGFR and MET receptors that bypasses resistance to EGFR-TKIs and has immune-cell directing activity. Mobocertinib is an oral TKI that selectively inhibits diverse EGFR and ERBB2 (HER2) exon 20 insertion mutations. The NCCN NSCLC Panel recommends amivantamab as a subsequent therapy option for patients with EGFR exon 20 insertion mutation metastatic NSCLC. 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.

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. 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. 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. Lorlatinib is also recommended as a subsequent therapeutic option for ALK-positive metastatic NSCLC after progression on either alectinib, brigatinib, or ceritinib.

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. 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. 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 METex14 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 METex14 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 METex14 skipping mutation-positive metastatic NSCLC. Crizotinib or systemic therapy (e.g., carboplatin plus paclitaxel) is useful in certain circumstances as a first-line therapy option for METex14 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. 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 %.

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/ERK pathway. Dabrafenib specifically inhibits BRAF p.V600E mutations, while trametinib inhibits MEK 1/2, which is downstream of BRAF signalling. 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

NTRK1/2/3 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. 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.

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 deruxtcan-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. The NCCN NSCLC Panel recommends fam-trastuzumab deruxtcan-nxki or ado-trastuzumab emtansine as a subsequent therapy option for patients with metastatic NSCLC and ERBB2 (HER2) mutations.

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. 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 panel recommends ramucirumab plus docetaxel as a subsequent therapy option for patients with metastatic NSCLC, regardless of histology. 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).

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 use of immune checkpoint inhibitors as 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.
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 the need to develop individualized 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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1. World Health Organization key facts in cancer. 2020
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Advances in Pleural Medicine

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

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). 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. Skilled operators can also identify the relevant anatomical landmarks neighbouring the puncture site, and minimise the risk of accidental pneumothorax, bleeding and organ puncture. The sonographic findings also supplement additional clinical information in guiding the diagnosis of pleural effusion, for example, identifications of pleural septations in complicated parapneumonic effusion (CPPE) and irregular nodularity on the diaphragm in malignant pleural effusion (MPE).

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.

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

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. 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%. 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. 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. 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. 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. This regimen can provide satisfactory radiographic improvements, reduce the need for surgical referral and shorten the hospital stay in pleural infection. 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. 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. 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). Concurrent injection of tPA and DNase may be preferred due to convenience and similar efficacy. 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 talc pleurodesis (median four days vs two days). However, the study outcomes should be interpreted with caution due to its limited sample size (32 patients in total) 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, and is an important pleural disease that consumes many healthcare resources. In the US, there was a steady upward trend of emergency visits, and 30-day readmission was observed from 2010 through 2016. 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. 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. 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.

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. Pleurodesis with talc slurry through the pleural drain can offer successful MPE control in around 70 % of patients. When comparing talc slurry with tPA/DNase instillation of tissue plasminogen activator (tPA), the pleurodesis failure rate at 90 days was equivalent in the TAPPS trial. In eligible patients, IPC offer similar control of dyspnoea, and quality of life but shorter hospital stay than talc pleurodesis. IPC-related infection is always a concern for IPC, and it typically happens at least 6 to 8 weeks after IPC implantation. 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 %. 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. Despite the concern of infection, IPC is not a contraindication for chemotherapy, as it does not increase the risk of IPC-related infection. 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. The chance of auto-pleurodesis can be enhanced by frequent drainage and talc instillation through IPC. 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. 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.

Although surgical pleurodesis is an option, it is usually not widely adopted due to the patient’s ineligibility. Indeed, video-assisted thorascopic 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. 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.

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 pneumothorax48. 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 group44. 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 option25.

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 groups46.

A persistent air leak (PAL) in pneumothorax represents an air leak lasting more than 5 to 7 days48. PALs are more common and less likely to resolve with SSPs than PSPs52. In a local, single-centre retrospective study, the prevalence of PAL for more than seven days was 43.3 % of 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 group44. 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 option25.

HETEROGENEOUS LOCAL PRACTICE

With advances in knowledge of pleural medicine, there were major updates in guidelines for managing pleural diseases25. 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 hospitalins in Hong Kong, significant heterogeneity in the management of pleural diseases among respiratory versus non-respiratory clinicians was observed53. 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 wakening or training, limited accessibility of drugs, devices, and dedicated service support may contribute to the observed heterogeneity53. 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.

References

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 MCHK CME Programme (for non-specialists) for answering the MCHK CME programme. Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2023 for answering the MCHK CME programme. Please return the completed answer sheet 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/F, 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

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Answers to September 2023 Issue
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AE, adverse event; FVC, forced vital capacity; GI, gastrointestinal; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

Footnotes:
¹OFEV® (Nintedanib) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF) and idiopathic pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease (SSc-ILD) in adults. Dosed simplicity: One capsule twice daily.
²OFEV® (Nintedanib) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phase, and for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) in adults. Dosed simplicity: One capsule twice daily.
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-association of ILD with a progressive fibrosing phenotype, 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
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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.

lims, peanut or soya, or to any of the excipients. Pregnancy. Special warnings and precautions: Diarrhoea was the most frequent gastrointestinal event reported. Diarrhoea should

reported gastrointestinal adverse reactions. Arterial thromboembolic events were infrequently reported. Use caution when treating patients at higher cardiovascular risk including

ased risk of venous thromboembolism was observed in nintedanib treated patients. Treatment with OFEV® may increase blood pressure. Systemic blood pressure should be

ild 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

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

ould 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

ators 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 GCT 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


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- Polyneuropathy
- Family history of TTR amyloidosis

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

**References:**

**Vyndamax Abbreviated Prescribing Information**

1. **Trade Name:** Vyndamax™ Capsules (Tafamidis 60 mg). 2. **Presentation:** Elong 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 60 mg (tafamidis orally once daily). 5. **Contraindications:** Hypersensitivity to the active substance or 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, midostaurin), substrates of uptake transporters OCT1 and OAT3 (organic anion transporters, e.g., non-steroidal anti-inflammatory drugs, bumetamide, furosemide, lansoprazole, methotrexate, oseltamivir, paroxetine, venlafaxine, zidovudine, ritonavir), 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:** Fatigue 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: VNX1120 FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.
Update on Management of IPF

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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. 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. 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. 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 over five years, and studies showed an overall mean survival of 4 years for patients diagnosed with IPF after ten years of follow-up.

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. 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. Definite UIP pattern consists of subpleural, basal predominant reticular abnormality with honeycombing on HRCT. 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.

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). 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.
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) side effects from nintedanib, and they include 1) low risk factors for the development of gastrointestinal impairment (Child Pugh A). Raised liver transaminases (LFT) 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 IPF

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.

CONCLUSION

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

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

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Nintedanib</th>
<th>Pirfenidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular tyrosine kinase inhibition targeting growth factor receptors involved in pulmonary fibrosis: ATP-competitive inhibitor of FGFR1 / VEGFR2 / PDGFR-α &amp; β</td>
<td>Inhibition of TGF-β production and downstream signalling, collagen synthesis, and fibroblast proliferation</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>-Annual FVC decline</td>
<td>-113.6 ml vs -223.5 ml (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-216 ml vs -363 ml (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>-On-treatment mortality</td>
<td>HR 0.57, p = 0.0274</td>
</tr>
<tr>
<td>Dosage</td>
<td>150 mg bd oral</td>
<td>801 mg tds oral</td>
</tr>
<tr>
<td>Common side effects</td>
<td>Diarrhea, nausea and vomiting, abdominal pain, decreased appetite, weight loss, deranged LFT</td>
<td>Nausea, rash, diarrhoea, dyspepsia, deranged LFT, photosensitivity</td>
</tr>
</tbody>
</table>

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

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

References
3. Lam GSM, EYY Sze, WH Yip. Casebook of interstitial lung disease. 2023

Radiology Quiz
Dr Thomas WL YIP
MBChB, FRCR

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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#於PROVENT研究中，使用EUVUSHELD組合與使用安慰劑組所發生的不良事件比例相似。

*55.5％相比92.4％的受試者中產生免疫反應。

参考資料：
病從鼻入
保護從鼻起
有效減輕流感症狀

噴鼻式疫苗
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Updates in the Management of COPD

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DEFINITION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease worldwide, with significant morbidity and mortality. It is a heterogeneous lung condition characterised 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. 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. 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.

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. 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. 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. 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. Another subtype receiving attention is preserved ratio impaired spirometry (PRISm), with FEV1/FVC ratio ≥ 0.7 and FEV1 < 80 %. PRISm has been proposed to be a transitional state and is associated with increased risk of cardiopulmonary disease and all-cause mortality. 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.

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. However, spirometry has been underutilised in the management of COPD worldwide. 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.

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. (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, characterised with a history of at least two moderate exacerbations or at least one exacerbation leading to hospitalisation, regardless of symptom level.
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\textsuperscript{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\textsuperscript{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\textsuperscript{18}. The number of different inhaler devices should be minimised to reduce the error during application and improve compliance\textsuperscript{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. 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.

Until recently, mortality benefit has not been demonstrated in pharmacological treatments of COPD, possibly due to the heterogeneity of COPD population. 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. 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. Better characterisation of the complex and heterogeneous COPD population according to the underlying pathophysiology and endotypes may identify more efficacious treatments.

**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. 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.

Vaccinations are another important treatment strategy to prevent exacerbations and pneumonia. GOLD guideline suggested influenza vaccination and SARS-CoV-2 vaccination for COPD patients. 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.

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. CHP currently recommends one dose of PCV13 followed by one dose of 23vPPV one year later. Those who had 23vPPV beforehand 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.

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. 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 hospitalisation history or PaCO2) remain unclear. On the other hand; there are randomised controlled trials that suggested no survival benefits of home NPPV. Various factors may account for these discrepancies: differences in patient selection, underpowered studies, NPPV settings incapable of achieving adequate ventilation, and poor adherence. 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. 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\textsuperscript{41, 42}. Adverse effects in the endobronchial valve treatment group included pneumothorax, valve removal or valve replacement\textsuperscript{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 %)\textsuperscript{28}.

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\textsuperscript{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\textsuperscript{60}. 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\textsuperscript{49}.

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\textsuperscript{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\textsuperscript{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\textsuperscript{47}. Postulated mechanism would include alteration in breathing pattern that diminishes development of dynamic hyperinflation or to a change in perception of breathlessness\textsuperscript{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 have 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 %\textsuperscript{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\textsuperscript{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\textsuperscript{50}. There is evidence for an association between COPD and lung cancer that has been systematically confirmed in several epidemiological and observational cohort studies\textsuperscript{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\textsuperscript{52}. Locally, Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) from CHP has last updated their recommendation in June 2023\textsuperscript{53}. 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\textsuperscript{50}. There is evidence for an association between COPD and lung cancer that has been systematically confirmed in several epidemiological and observational cohort studies\textsuperscript{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\textsuperscript{52}. Locally, Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) from CHP has last updated their recommendation in June 2023\textsuperscript{53}. 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\textsuperscript{54}.

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 characterized by dyspnea and/or cough and sputum that worsens 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 antibiotics54, 55. Outpatient management should be considered for mild ECOPD. The potential indications for a hospitalisation 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 comorbidities2. 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.

References

Fig. 3: Suggested approach to patient suspected COPD exacerbation (ECOPD) (Excerpted from reference 53)
How to Pick Up Running as a Habit

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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, 呉師傅 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. 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)
AN ADD-ON MAINTENANCE TREATMENT FOR PATIENTS (12+ YEARS) WITH INADEQUATELY CONTROLLED SEVERE ASTHMA WITH TYPE 2 INFLAMMATION

AN ADD-ON MAINTENANCE TREATMENT FOR PATIENTS (12+ YEARS) WITH INADEQUATELY CONTROLLED SEVERE ASTHMA WITH TYPE 2 INFLAMMATION

A CLEAR PATH TO ASTHMA CONTROL

UP TO 72% REDUCTION
SIGNIFICANT EXACERBATION REDUCTION

IN annualized severe exacerbations at Week 24
with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (P=0.0003)†

200 mL IMPROVEMENT
RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION

at Week 52 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (P=0.0001)†

86% OF PATIENTS
REDUCED OR NO INCREASE IN THEIR OCS DOSE
by Week 24 with DUPIXENT 300 mg Q2W + SOC vs 68% with placebo + SOC (P=0.0001)†

UP TO 75% OF PATIENTS
HIGH RESPONDER MEASURES

IN Asthma Control Questionnaire measures of sleep, activity limitations, and breathing†

NOW AVAILABLE

LIBERTY ASTHMA VENTURE Study Design: 310 patients were randomly assigned with one glucocorticosteroid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks. After a glucocorticosteroid dose-adjustment period before randomization, glucocorticosteroid 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 proportion of patients with a reduction in the glucocorticosteroid dose at week 24. Key secondary end points were the proportion of patients who were 2x with a reduction of at least 19% in the glucocorticosteroid dose and the proportion of patients with a reduction in a glucocorticosteroid dose of less than 0.5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study Design: 1,902 patients who were 52 years of age or older with uncontrolled asthma were randomly assigned in a 2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 mg or 300 mg every 2 weeks or matched-volume placebo for 24 weeks. The primary end points were the annualized rate of severe exacerbations and the absolute change from baseline to week 24 in the forced expiratory volume in 1 second (FEV1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV1, in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophilic; FEKQ, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroid; Q2W, every 2 weeks; SOC, standard of care

References: 1. Dupixent: Summary of Product Characteristics. May 2020. 2. Jane EF, Nuy P, Brusilow C, et al. Efficacy and safety of dupilumab in glucocorticosteroid-dependent severe asthma. N Engl J Med. 2018;378(2):1247-1258. 3. Castro M, Corren J, Fiazzi D, et al. dupilumab: efficacy and safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(2):1238-1246. 4. LIBERTY ASTHMA VENTURE: 310 patients were randomly assigned with one glucocorticosteroid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks. After a glucocorticosteroid dose-adjustment period before randomization, glucocorticosteroid 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 proportion of patients with a reduction in the glucocorticosteroid dose at week 24. Key secondary end points were the proportion of patients who were 2x with a reduction of at least 19% in the glucocorticosteroid dose and the proportion of patients with a reduction in a glucocorticosteroid dose of less than 0.5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV1) before bronchodilator use were also assessed.

SELF-INJECTABLE Convenient subcutaneous injection†

Sanofi Hong Kong Limited
1/F B Section 212 on 3/F, AXA SOUTHISIDE, 38 WONG CHUK HANG ROAD, WONG CHUK HANG, HONG KONG
Tel: (852) 2506 8333 Fax: (852) 2506 2537

Sanofi (dupilumab) Injection
200mg - 300mg
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<th>Sunday</th>
<th>Monday</th>
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<td><strong>Zoom Live</strong>&lt;br&gt;Topic: Latest Psoriatic Disease Management - What Is Achievable Today?</td>
<td><strong>Certificate Course on Respiratory Medicine 2023 (Video Lectures)</strong></td>
<td><strong>In-person</strong>&lt;br&gt;The HKMA District Health Network (Kowloon East) CME Lecture in Physical Attendance Mode Topic: IBS and Overlapping FGID Symptoms</td>
<td><strong>Certificate Course on Renal Medicine 2023 (Video Lectures)</strong></td>
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<td><strong>The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed</strong>&lt;br&gt;<strong>In-person / Zoom Live</strong>&lt;br&gt;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</td>
<td><strong>Certificate Course on Renal Medicine 2023 (Video Lectures)</strong></td>
<td><strong>Zoom Live</strong>&lt;br&gt;HKMA Adult Immunisation Campaign 2023 Topic: The Hidden Disease Burden of HPV-Related Head and Neck Cancers in Hong Kong</td>
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<td><strong>In-person / Zoom Live</strong>&lt;br&gt;HKMA-GHK CME Programme 2023 (Physical Lecture + Online) Topic: To-be-confirmed</td>
<td><strong>Certificate Course on Respiratory Medicine 2023 (Video Lectures)</strong></td>
<td><strong>Certificate Course on Renal Medicine 2023 (Video Lectures)</strong>&lt;br&gt;<strong>HKFMS Foundation Meeting</strong>&lt;br&gt;<strong>FMHSH Executive Committee Meeting</strong></td>
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<td><strong>Certificate Course on Healthcare Mediation 2023 (Video Lectures)</strong></td>
<td><strong>In-person</strong>&lt;br&gt;The HKMA District Health Network (Sha Tin) CME Lecture in Physical Attendance Mode Topic: Improving CV Prognosis With Early And Massive LDL-C Reduction</td>
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<td><strong>Zoom Live</strong>&lt;br&gt;HKMA Adult Immunisation Campaign 2023 Topic: The Impact of Introducing Higher Pneumococcal Conjugate Vaccine</td>
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<td><strong>Certificate Course on Healthcare Mediation 2023 (Video Lectures)</strong></td>
<td><strong>In-person / Zoom Live</strong>&lt;br&gt;HKMA-HKSIP CME Programme 2023 (Physical Lecture + Online) Topic: ID Microbes Using Metagenomic and Big Data Bioinformatics</td>
<td><strong>Certificate Course on Renal Medicine 2023 (Video Lectures)</strong></td>
<td><strong>Certificate Course on Renal Medicine 2023 (Video Lectures)</strong>&lt;br&gt;<strong>The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed</strong>&lt;br&gt;The Hong Kong Neurosurgical Society Meeting - To be confirmed</td>
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<td>3 TUE 1:00 PM</td>
<td>Zoom Live Topic: Latest Psoriatic Disease Management - What Is Achievable Today? Organiser: The Hong Kong Medical Association Speaker: Dr Victor Tak-lung WONG</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<td>4 WED 7:00 PM</td>
<td>Certificate Course on Respiratory Medicine 2023 (Video Lectures) S/F, The HKMA District Health Network Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr IUN Chung-tat</td>
<td>Ms Vienna LAM Tel: 2527 8898</td>
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<td>5 THU 2:00 PM</td>
<td>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 Tung Tak Street, Tseung Kwan O, Hong Kong</td>
<td>The HKMA District Health Network Dept. Tel: 3108 2514 1 CME Point</td>
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<td>9 MON 2:00 PM</td>
<td>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</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<td>11 WED 7:30 AM</td>
<td>The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed Organiser: The Hong Kong Neurosurgical Society Speaker: Dr Jessamin Wunche YE Chairman: Dr CHEUNG Fung-ching Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting</td>
<td>College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2995 4536 Fax. No.: 2995 4061 1.5 CME Point</td>
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<td>11 WED 2:00 PM</td>
<td>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 Shui Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<td>11 WED 7:00 PM</td>
<td>Certificate Course on Respiratory Medicine 2023 (Video Lectures) Organiser: The Federation of Medical Societies of Hong Kong Speaker: Mr NG Shu-wah, Ms Maggie LAM</td>
<td>Ms Vienna LAM Tel: 2527 8898</td>
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<td>12 THU 7:00 PM</td>
<td>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</td>
<td>Ms Vienna LAM Tel: 2527 8898</td>
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<td>13 FRI 2:00 PM</td>
<td>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</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<td>17 TUE 2:00 PM</td>
<td>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 Shui Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<td>18 WED 1:00 PM</td>
<td>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</td>
<td>The HKMA District Health Network Dept. Tel: 3108 2507 1 CME Point</td>
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<td>19 THU 7:00 PM</td>
<td>Certificate Course on Renal Medicine 2023 (Video Lectures) Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Sam LAU, Dr Lorraine KWAN</td>
<td>Ms Vienna LAM Tel: 2527 8898</td>
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<td>19 THU 7:00 PM</td>
<td>HKFMS Foundation Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Winord Social Service Building, 19 Hennessy Road, Wan chai, Hong Kong</td>
<td>Ms Nancy CHAN Tel: 2527 8898</td>
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<td>19 THU 8:00 PM</td>
<td>FSMHK Executive Committee Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windord Social Service Building, 19 Hennessy Road, Wan chai, Hong Kong</td>
<td>Ms Nancy CHAN Tel: 2527 8898</td>
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<td>20 FRI 1:00 PM</td>
<td>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, Hung hom, Kowloon</td>
<td>The HKMA District Health Network Dept. Tel: 3108 2514 1 CME Point</td>
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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, micurition urgency, pelvic pain, and urge incontinence. 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.


Patients have a better recovery experience than TURP, with durable results and no new and lasting sexual dysfunction*. 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

Rapid relief and recovery in days, not months*

Lowest catheter rate of the leading BPH procedures*

The only leading BPH procedure that does not destroy tissue

Proven durability through 5 years*

Real world outcomes consistent with randomised controlled data*

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

I am a urologist.
I am a patient.

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

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Calendar of Events

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<tr>
<th>Date</th>
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<th>Speaker/Details</th>
<th>Enquiry/Remarks</th>
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<tr>
<td>24</td>
<td>7:00 PM</td>
<td><strong>Certificate Course on Healthcare Mediation 2023 (Video Lectures)</strong></td>
<td>The Federation of Medical Societies of Hong Kong</td>
<td>Dr. CHOO Kah-lin, Consultant in Medicine, Accredited Mediator</td>
<td>Ms Vienna LAM</td>
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<td>24</td>
<td>2:00 PM</td>
<td><strong>In-person / Zoom Live</strong></td>
<td>HKMA-HKSTP CME Programme 2023 (Physical Lecture + Online)</td>
<td>Dr. YE Bin, Speaker</td>
<td>HKMA CME Dept.</td>
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<tr>
<td>26</td>
<td>7:00 PM</td>
<td><strong>Certificate Course on Renal Medicine 2023 (Video Lectures)</strong></td>
<td>The Federation of Medical Societies of Hong Kong</td>
<td>Prof. Paul Bo-san LAI, Speaker</td>
<td>Ms Vienna LAM</td>
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<td>27</td>
<td>2:00 PM</td>
<td><strong>Zoom Live</strong></td>
<td>HKMA Adult Immunisation Campaign 2023</td>
<td>Speaker, Dr. WONG King-ying</td>
<td>HKMA CME Dept.</td>
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<td>31</td>
<td>2:00 PM</td>
<td><strong>Certificate Course on Healthcare Mediation 2023 (Video Lectures)</strong></td>
<td>The Federation of Medical Societies of Hong Kong</td>
<td>Dr. CHAN Kit-ying Sandy, Registered Nurse, Accredited Mediator</td>
<td>Ms Vienna LAM</td>
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<td><strong>Certificate Course on Healthcare Mediation 2023 (Video Lectures)</strong></td>
<td>The Federation of Medical Societies of Hong Kong</td>
<td>Dr. CHAN Kit-ying Sandy, Registered Nurse, Accredited Mediator</td>
<td>Ms Vienna LAM</td>
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**Certificate Course for Doctors, Nurses, Paramedics and Allied Health Workers**

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
SYMBICORT™
ANTI-INFLAMMATORY RELIEVER
DELIVERS EFFICACY WHEN IT MATTERS
REDUCES EXACERBATIONS, ALONE OR WITH MAINTENANCE.1,2
NOW INDICATED FOR MILD, MODERATE AND SEVERE PATIENTS.3

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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References:

Presentation: Budenoseide/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 5) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 168/4.8 mg Turbuhaler Adult & Adolescent ≥ 12 yr: 1 inhalation 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 (Adults & Adolescents ≥ 12 yr): Patients should take 1 inhalation of Symbicort Turbuhaler 168/4.8 mg 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 4 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and 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 168/4.8 mg Turbuhaler Adult & Adolescent ≥ 12 yr: 2 inhalations b.d. Max daily dose is 4 inhalations. COPD 168/4.8 mg 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 sympathetic mimics, cardiovascular disorders, hyperkalemia, diabetes, pneumonia, lactase, 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-2-adrenergic blockers, other sympathomimetic agents, Xanthine derivatives, minocycline, terbinafine and diuretics. Monamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines. Undesirable effects: Prolactin, Candida infections in the oropharynx, headache, tremor; mild irritation in the throat, coughing, hoarseness. Full formal prescribing information is available upon request. APL1HK.SYM.07.21

Please visit contactmedicalastrazeneca.com, for (1) enquiring Medical Information (MI), (2) reporting Individual Case Safety Report (ICSR) and/or (3) reporting product quality complaint (PQC) to AstraZeneca Hong Kong Limited.

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