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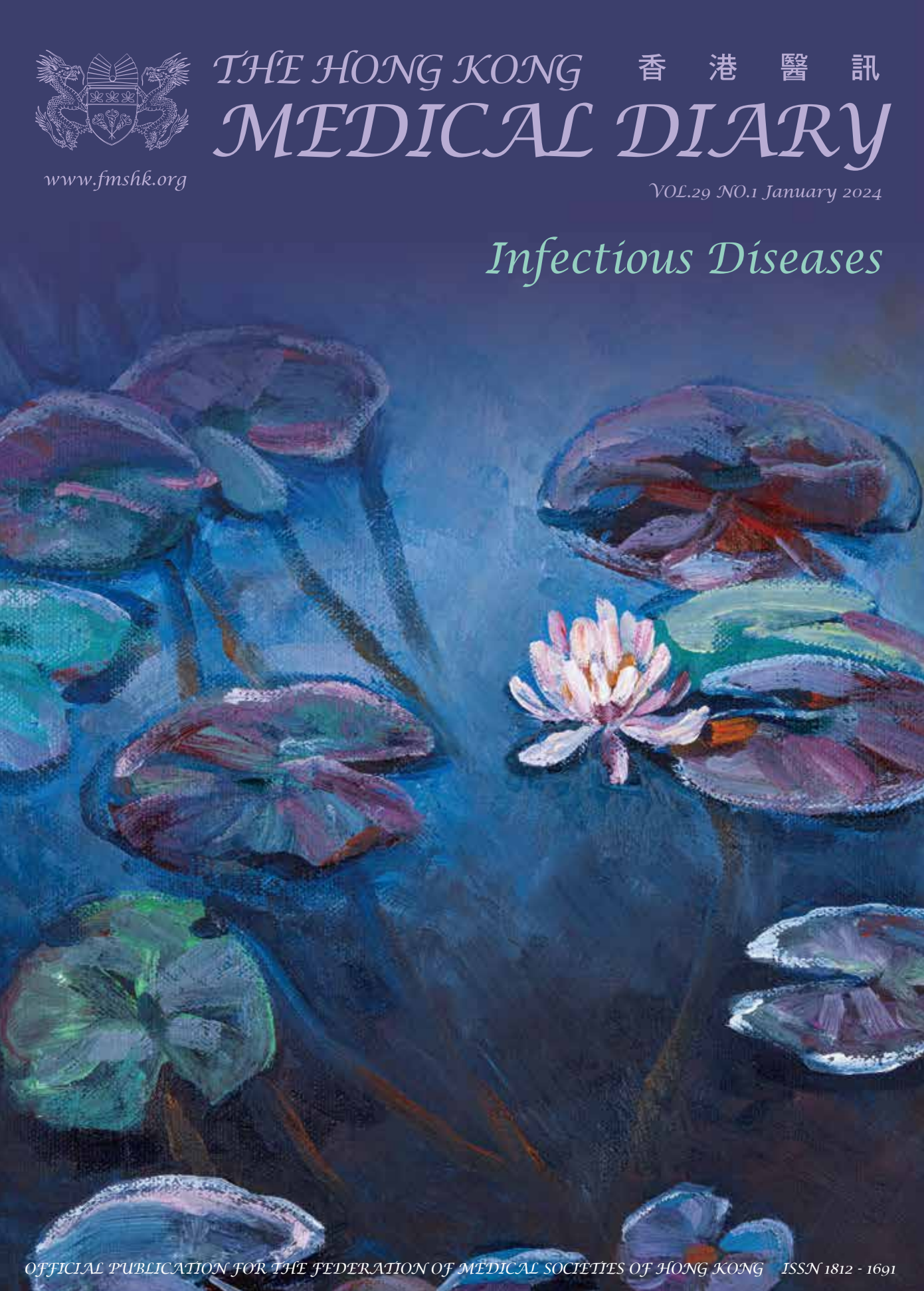
Infectious Diseases



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[#]Approved = Prevenar 20 is approved for the active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older.[1]

*Relative risk compared with younger (18–49 years), healthy adults.[2]

[†]At-risk conditions include alcoholism, asthma, chronic heart disease, chronic liver disease, chronic lung disease, chronic use of oral steroids, diabetes, neuromuscular/seizure disorders, rheumatoid arthritis, Crohn's disease, lupus, and smoking.

[§]The relevant figures are calculated based on the accumulative number of vaccinated persons aged ≥65 years (excluding those deceased) as of 26 February 2023.

References: 1. Prevenar 20 (Pneumococcal polysaccharide conjugate, 20-valent adsorbed) Prescribing Information. Pfizer Corporation Hong Kong Limited: Version December 2022. Available at: https://www.pfi.sr/wRb. Accessed 15 May 2023. **2.** Shea KM, et al. *Open Forum Infect Dis* 2014;1:ofu024. **3.** Centre for Health Protection. Statistics on Vaccination Programmes in the Past 3 years. Available at. https://www.chp.gov.hk/en/features/102226.html. Accessed 15 May 2023. **4.** Biyik MV, et al. *Prim Health Care Res Dev* 2020;21:e37.

https://www.pfi.sr/wRb

PREVENAR 20 Hong Kong Prescribing Information

The QR code/URL links to the latest Prescribing Information approved by the Department of Health in Hong Kong and may not be effective and the same as presented in the actual product package.

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The Cover Shot

蓮花清溫
Oil on Canvas (500 mm x 700 mm)

This oil painting was inspired by an event during the COVID-19 outbreak when I received a box of TCM formula Lianhua Qingwen from the Hong Kong Government. The medication claimed to have the effects of discharging heat and removing toxins.

In the painting, I depicted water lilies, which symbolise purity, peace, balance, and enlightenment, even in the midst of a murky water environment. Through the act of painting, I experienced immeasurable bliss and gained profound insights. Painting allows me to connect with deep emotions and find inner peace and tranquillity during challenging times.

Ms Carrie CHEUNG
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Amateur Artist

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Exactly four years ago, a previously unknown virus came into being to humankind which subsequently turned the world and our lives upside down. Today, very few people would have doubts about the power of a tiny virus which killed nearly 40 million people in 4 years' time. If the US Surgeon General William Steward, who proclaimed in 1969 that the time had come to 'close the book on infectious diseases', were still alive today, he would be shocked to witness the numerous emerging and re-emerging infectious diseases that happened in the past half a century. HIV/AIDS, SARS, MERS, dengue, tuberculosis, multi-drug resistant organisms, Ebola are just some of the most well-known diseases which plague the mankind. It is against this background that we have chosen to assemble this issue themed 'Infectious diseases' to illustrate the diversity and spectrum of problems faced by clinicians and the public, from epidemic to endemic diseases, from viral to bacterial infections, and from clinical management to public health preparedness.

HIV/AIDS has killed nearly the same number of people as COVID-19 in the past 40 years (as of 2023). Dr Thomas Chik has shared two illustrative cases of acute HIV infection and highlighted the importance of early recognition to improving the prognosis of patients and enhancing disease control for public health control. Re-emerging diseases can take place when certain environmental factors are conducive to their re-emergence, and melioidosis is a case in point. Dr Kristine Luk has prepared a detailed account of the outbreak of melioidosis cases in Hong Kong in 2022 and its management. Another important bacterial disease in this part of the world is liver abscess caused by *Klebsiella pneumoniae* due to its propensity to cause metastatic infections. We have summarised the commonly encountered questions related to this disease in an article. Bacteraemia or septicaemia is still associated with high mortality, even in this era of medical advancement. Dr KM Yim has written a succinct article on the management of sepsis from an intensivist's and emergency physician's perspective. The WHO declared antimicrobial resistance a global emergency nearly 10 years ago. Lamentably, resistance is making the treatment of bacterial infections increasingly challenging. Dr Alan Wu's article is a timely summary of the state-of-the-art armamentarium against carbapenem resistant organisms. The battle against infectious disease relies heavily on rapid and accurate diagnostics. Professor Rosanna Peeling explained the role of diagnostics in the preparedness against 'Disease X', a term coined by the World Health Organization to refer to the known or potentially unknown pathogen that can cause large scale, serious pandemics leading to mass scale human disease. On a lighter side, Dr Thomas Tsang, one of the most famous legends in the public health battle against infectious diseases, shared with us his interesting hobby of rock and mineral collection.

The prevention, control and management of infectious diseases will need close collaboration between infectious disease physicians, laboratory and microbiology experts, doctors from different specialties, public health and paramedical professionals and the public. We hope that you are convinced that 'the book on infectious diseases' is far from closed and in fact, needs continuous updates. The wisdom from this book also needs to be put into actions for control to help our future generations. To end, we would like to express our sincere gratitude to all contributing authors and the editorial board and team for their unfailing support in making this multidisciplinary issue a reality.

LIBERATE YOUR PATIENTS FROM DAILY HIV THERAPY

with VOCABRIA + REKAMBYS, the first and only, complete long-acting injectable regimen, dosed once every 2 months, for virologically suppressed* patients[1,2]

First and only, complete long-acting regimen for HIV-1[1,2]

The efficacy you have come to expect from daily HIV regimens[1]

Preferred by 98% of patients over daily oral therapy in the ATLAS-2M clinical trial[3]

VOCABRIA cabotegravir suspension for injection + **REKAMBYS** rilpivirine suspension for injection

At Week 48, 98% of 306 patients with no prior exposure to VOCABRIA + REKAMBYS who responded to the questionnaire preferred every 2-month injections vs 1% of 306 patients who preferred the study daily oral lead-in (1% reported no preference).[3]

*HIV-1 RNA <50 copies/mL[1] in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior failure with agents of NNRTI and INI class.

Vocabria (cabotegravir 30mg film-coated tablets and 600mg prolonged-release suspension for injection in 3mL), and Rekambys (rilpivirine 900mg prolonged-release suspension for injection in 3mL).
Important Safety Information
Contraindications: • Hypersensitivity to any ingredient • Coadministration with rifampicin, rifapentine, rifabutin, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, systemic dexamethasone (except single dose) • St John's Wort **Warnings and Precautions:** • If discontinued, adopt a fully suppressive antiretroviral regimen no later than when the next injection would have been due • If virologic failure is suspected an alternative regimen should be adopted as soon as possible. Residual concentrations may remain for prolonged periods after discontinuation. • Increased risk of failure associated with 2 or more of: archived rilpivirine resistance mutations BMI ≥30 kg/m² or HIV-1 A6/A1 subtype • Caution if uncertain treatment history without pre-treatment resistance analyses, if BMI ≥30 kg/m², or HIV-1 A6/A1 subtype • Hypersensitivity reactions. Rare, serious post-injection reactions from accidental IV administration • Hepatotoxicity (monitor LFTs). Not recommended in hepatitis B • Limited data in hepatitis C, monitor LFTs • Opportunistic infections • Immune reactivation syndrome • QTc prolongation at supratherapeutic doses – caution with medicines associated with Torsade de Pointes • Not to be used with other antiretrovirals for HIV • Caution with narrow therapeutic index OAT1/3 substrates, e.g. methotrexate. If macrolide antibiotics required, consider azithromycin • Caution with oral treatments and H2 antagonists and antacids. • Limited data on the use of Vocabria in patients aged 65 years and over.
The following adverse events have been reported
Injection site reactions (generally mild/moderate) including cellulitis and abscess formation (uncommon), headache, pyrexia (mostly reported within one week of injection), depression, depressed mood, anxiety, abnormal dreams, insomnia/sleep disorder, somnolence, dizziness, dry mouth, decreased appetite, nausea, vomiting, abdominal pain/discomfort, flatulence, diarrhoea, fatigue, asthenia, malaise, rash, myalgia, weight increase, hepatotoxicity, pancreatitis, increased transaminases, increased bilirubin, decreases in white blood cells, haemoglobin and platelet count, increases in cholesterol, triglycerides, pancreatic amylase, and lipase Please refer to the full prescribing information for further information and prior to administration. Abbreviated Prescribing Information based on PI version: Vocabria 30mg film-coated tab- HK022021(GDS03/EU20210105); Vocabria 400mg, 600mg prolonged-release suspension for injection - version HK022021 (GDS03/EU20210105). For adverse events report, please call GlaxoSmithKline Limited at (852)3189 8989 or send an email to us at HKAdverseEvent@gsk.com.

Vocabria (cabotegravir 30mg film-coated tablets and 600mg prolonged-release suspension for injection in 3mL), and Rekambys (rilpivirine 900mg prolonged-release suspension for injection in 3mL).
Indication: Cabotegravir in combination with rilpivirine for treatment of HIV-1 in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior failure with agents of NNRTI and INI class. **Dosing:** *Adults (over 18 years)* carefully selected who agree to the injection schedule and are counselled about the importance of adherence. An oral lead in prior to the initiation of injections can be used to assess tolerability. For oral lead in: Prior to injections, once-daily oral dosing of cabotegravir 30mg tablet and rilpivirine 25mg tablet for approximately 1 month (at least 28 days) with food. Initiation injections following oral lead in: months 2 (final day of oral lead-in therapy) and 3. Separate intramuscular (gluteal) 3mL initiation injections of Vocabria and Rekambys. Continuation injections: Two months after the final initiation injections and every 2 months thereafter. Separate intramuscular (gluteal) 3mL injections of Vocabria and Rekambys. Injections may be administered up to 7 days before or after the due date. Please refer to the prescribing information for advice outside this window or missed injections. Caution in severe renal impairment or moderate hepatic impairment. Not recommended in severe hepatic impairment. **Contraindications:** Hypersensitivity to any ingredient. Coadministration with rifampicin, rifapentine, rifabutin, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, systemic dexamethasone (except single dose), St John's Wort. **Special warnings/precautions:** If discontinued, adopt a fully suppressive antiretroviral regimen no later than when the next injection would have been due. If virologic failure is suspected an alternative regimen should be adopted as soon as possible. Residual concentrations may remain for prolonged periods after discontinuation. Increased risk of failure associated with 2 or more of: archived rilpivirine resistance mutations BMI ≥30 kg/m² or HIV-1 A6/A1 subtype. Caution if uncertain treatment history without pre-treatment resistance analyses, if BMI ≥30 kg/m², or HIV-1 A6/A1 subtype. Hypersensitivity reactions. Rare, serious post-injection reactions from accidental IV administration. Hepatotoxicity (monitor LFTs). Not recommended in hepatitis B. Limited data in hepatitis C monitor LFTs. Opportunistic infections. Immune reactivation syndrome. QTc prolongation at supratherapeutic doses – caution with medicines associated with Torsade de Pointes. Not to be used with other antiretrovirals for HIV. Caution with narrow therapeutic index OAT1/3 substrates, e.g. methotrexate. If macrolide antibiotics required, consider azithromycin. Caution with oral treatments and antacids. Please refer to the prescribing information for full list of interactions. **Pregnancy/breast feeding:** Not recommended. **Side effects:** Please refer to prescribing information for full details. Injection site reactions (generally mild/moderate) including cellulitis and abscess formation (uncommon), headache, pyrexia (mostly reported within one week of injection), depression, depressed mood, anxiety, abnormal dreams, insomnia/sleep disorder, somnolence, dizziness, dry mouth, decreased appetite, nausea, vomiting, abdominal pain/discomfort, flatulence, diarrhoea, fatigue, asthenia, malaise, rash, myalgia, weight increase, hepatotoxicity, pancreatitis, increased transaminases, increased bilirubin, decreases in white blood cells, haemoglobin and platelet count, increases in cholesterol, triglycerides, pancreatic amylase, and lipase **Please read the full prescribing information prior to administration.** Full prescribing information is available on request from GlaxoSmithKline Ltd. 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information based on PI version: Vocabria 30mg film-coated tab- HK022021(GDS03/EU20210105); Vocabria 600mg prolonged-release suspension for injection - version HK022021 (GDS03/EU20210105); Rekambys 900mg prolonged-release suspension for injection - EU SmPC 28 July 2021; (Hong Kong Approval Date: 16.Dec.2021). For adverse events report, please call GlaxoSmithKline Limited at (852)3189 8989 or send an email to us at HKAdverseEvent@gsk.com

VOCABRIA injection is indicated, in combination with REKAMBYS injection, for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.[1]

HIV-1=human immunodeficiency virus type 1; **INI**=integrase inhibitor; **NNRTI**=non-nucleoside reverse transcriptase inhibitor.

References: 1. VOCABRIA Hong Kong Product Characteristics GDS03. **2.** REKAMBYS Summary of Product Characteristics. Janssen Healthcare; 2021. **3.** Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet. Published online ahead of print: Decem ber 9, 2020. doi: 10.1016/S0140-6736(20)32666-0.

GSK × ViiV Healthcare

Getting ahead of HIV together

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PM-HK-CBR-ADVT-220001
Date of Preparation: 13/02/2022 (02/24)

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Your Choice Matters. Consider CVD Risk and Weight Gain in HIV Management.[1,2]

Delstrigo®
doravirine/lamivudine/
tenofovir disoproxil fumarate

Indication: DELSTRIGO® is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir[3]

Abbreviations: ART: Antiretroviral therapy; CVD: Cardiovascular disease; HIV: Human immunodeficiency virus; RNA: Ribonucleic acid; NNRTI: Non-nucleoside reverse transcriptase inhibitor

References: 1. Kumar P, *et al.* Switching to DOR/3TC/TDF Maintains HIV-1 Virologic Suppression Through Week 144 in the DRIVE-SHIFT Trial. *J Acquir Immune Defic Syndr* 2021;87:801–805
2. European AIDS Clinical Society. EACS Guidelines. October 2021. Version 11.0. **3.** Delstrigo Hong Kong Product Circular.

Delstrigo Selected Safety Information

Indications: Delstrigo (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300mg) is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir.

Contraindications: • Hypersensitivity to the active substances or to any of the excipients. Co-administration with medicinal products that are strong cytochrome P450 (CYP)3A enzyme inducers is contraindicated as significant decreases in doravirine plasma concentrations are expected to occur. For the list of contraindicated medicines, please consult the full prescribing information.

Precautions: • NNRTI substitutions and use of doravirine - Doravirine has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. There is not sufficient clinical evidence to support the use of doravirine in patients infected with HIV-1 with evidence of resistance to the NNRTI class. • Severe acute exacerbation of hepatitis B in patients co-infected with HIV-1 and HBV - All patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. Patients who are co-infected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with Delstrigo. • New onset or worsening renal impairment - Delstrigo should be avoided with concurrent or recent use of nephrotoxic medicinal products (e.g., high-dose or multiple NSAIDs). Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at risk patients. • Bone loss and mineralisation defects - The effects of tenofovir disoproxil associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for HIV-1 infected adult patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. • Co-administration with other antiviral products - Doravirine/lamivudine/tenofovir disoproxil must not be co-administered with other medicinal products containing lamivudine, or with medicinal products containing tenofovir disoproxil, or tenofovir alafenamide, or with adefovir dipivoxil • Use with CYP3A inducers - Caution should be given to prescribing doravirine with medicinal products that may reduce the exposure of doravirine • Immune reactivation syndrome - Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy.
• Lactose - Delstrigo contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Adverse events: • The most frequently reported adverse reactions considered possibly or probably related to doravirine were nausea (4%) and headache (3%). Other common adverse events (≥1% to <10%) associated with doravirine/lamivudine/tenofovir disoproxil include abnormal dreams, insomnia, headache, dizziness, somnolence, cough, nasal symptoms, nausea, diarrhoea, abdominal pain, vomiting, flatulence, alopecia, rash, muscle disorders, fatigue, fever and alanine aminotransferase increased. For detailed side effects, please consult the full prescribing information.

Drug interactions: Delstrigo is a complete regimen for the treatment of HIV-1 infection; therefore, Delstrigo should not be administered with other antiretroviral medicinal products. *Effects of other medicinal products on doravirine, lamivudine, and tenofovir disoproxil* • Doravirine - Doravirine is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of doravirine • Lamivudine - Because lamivudine is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine. • Tenofovir disoproxil - Because tenofovir is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion via OAT1, OAT3 or MRP4 may increase serum concentrations of tenofovir. *Effects of doravirine, lamivudine, and tenofovir disoproxil on other medicinal products* • Doravirine - Doravirine at a dose of 100 mg once daily is not likely to have a clinically relevant effect on the plasma concentrations of medicinal products that are dependent on transport proteins for absorption and/or elimination or that are metabolised by CYP enzymes. • Lamivudine - Lamivudine does not inhibit or induce CYP enzymes. • Tenofovir - Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low. **Before prescribing, please consult the full prescribing information.**

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Carbapenem Resistant Bacteria and an Overview of Existing and Novel Treatment Options

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Dr Alan KL WU

Antimicrobial resistance (AMR) remains one of the most important and imminent challenges to global health and development. A widely-cited report from UK in 2016 estimated that AMR could potentially lead to the loss of 10 million lives per year by 2050 and cause substantial economic impact[1]. More recently, a major report highlighted the scale of AMR worldwide, with drug-resistant infections directly causing 1.27 million deaths in 2019 and contributing to the deaths of a further 4.95 million[2]. Preliminary data suggests that AMR has worsened globally as a result of the COVID-19 pandemic, with various countries reporting alarming increases in antibiotic use and a parallel rise in the incidence of drug-resistant infections in hospital and community settings[3, 4]. The latest data from the Hospital Authority of Hong Kong likewise revealed a rising rate of healthcare-associated MRSA bacteremia and also an increasing prevalence of multi-drug resistant (MDR) gram-negative organisms in hospitalised patients, with numerous outbreaks reported since the start of the pandemic[5].

Carbapenems are widely considered the drugs of choice for combating antibiotic-resistant infections. They are stable against beta-lactam degrading enzymes produced by bacteria, such as extended-spectrum beta-lactamases (ESBL) or AmpC beta-lactamases. Although resistance to carbapenems has been recognised since these drugs were first used, the recent emergence of such resistance worldwide, particularly for gram-negative bacteria, has led to much concern. In 2017 and 2013 (updated in 2019), the WHO and CDC released their lists of antibiotic-resistant priority organisms respectively, and MDR-gram-negatives resistant to carbapenems are listed among those which posed the greatest threats[6]. It is also worrying that there has not been an increase in new treatment options against these organisms. Of all the antibiotics that initiated new drug applications in the 2000s, only 17 % earned FDA approval within 12 years, while 62 % were discontinued[7]. Since 2014, several new antibiotics with proven or potential activities against drug resistant gram-negative organisms have been approved (Table 1)[6, 8, 9, 10]. It is important for clinicians to have a better understanding of carbapenem resistance, and both the existing and newer treatment options available to ensure their proper use in clinical practice.

CARBAPENEMS - AN OVERVIEW AND SPECTRUM OF ACTIVITY[11]

As members of the β-lactam family, carbapenems act by inhibiting bacterial cell-wall synthesis. Modifications of thienamycin, a compound first isolated from the bacteria *Streptomyces cattleya* in 1976, have yielded a number of agents including imipenem (used in combination with cilastatin), meropenem, ertapenem, doripenem, biapenem and tebipenem; only the first three agents are registered in Hong Kong. Tebipenem, the only oral carbapenem, is currently under development in the USA and only approved for use in Japan.

As a group, carbapenems possess potent activities against a range of pathogens, including aerobic Gram-negatives [i.e. Enterobacterales, e.g. *Escherichia coli (E. Coli), Klebsiella pneumoniae (K. pneumoniae) and Enterobacter* spp.; non-fermenters, such as *Pseudomonas aeruginosa (P. aeruginosa) and Acinetobacter spp.*)], Gram-positives (e.g. *Staphylococcus and Streptococcus* spp.) as well as anaerobes. Imipenem is more active against gram-positive cocci when compared to meropenem (e.g. ampicillin-susceptible *Enterococcus faecalis* is considered susceptible to imipenem), whereas meropenem has higher activity against gram-negatives (e.g. *Proteus* and *Providentia* spp, as well as *Morganella morganii* are less susceptible to imipenem). Against *P. aeruginosa*, doripenem is the most active agent, whereas ertapenem is ineffective against *P. aeruginosa, Acinetobacter and Enterococcus* species.

MECHANISMS OF CARBAPENEM RESISTANCE AND ORGANISMS OF CONCERN[11, 12, 13, 14]

Carbapenems act by inhibiting penicillin-binding proteins (PBPs), enzymes involved in bacterial cell wall synthesis. Inhibition of peptidoglycan crosslinking results in cell lysis and death. For Gram-negative bacteria, in order to access the site of action, carbapenems need to cross the outer membrane, a process which is facilitated by membrane proteins known as porins. Once inside the bacteria, carbapenems need to be able to withstand degradation by beta-lactamases and active removal by efflux drug pumps in order to exert their effect.

Resistance to carbapenems can be intrinsic (i.e. universal for a particular bacterial species) or acquired, and may be mediated by four main mechanisms:

1) **Production of altered, low-affinity PBPs**: main mechanism for resistance in Gram-positive organisms; may be acquired by horizontal gene transfer from related species - examples include PBP2a in methicillin-resistant *Staphylococcus aureus* (MRSA), and also PBP5 in *Enterococcus faecium* (90 % of strains resistant to ampicillin and carbapenems).

Table 1: Summary of antibacterial drugs with potential activity against WHO critical priority pathogens that gained market authorisation between Dec 2014 and June 2023[a]

Name (trade name) [Market authorisation holder(s)]	Agency/agencies granting approval + indication	Antibacterial class	Registered in Department of Health of HKSAR (as at 1st Sept 2023)	Expected activity against carbapenem-resistant gram- negative organisms[b]			
				CRAB	CRPA	CPE	STM
Vaborbactam + meropenem (Vabomere) [Melinta (Menarini, EU)]	FDA approved for cUTI EMA approved for cUTI, HAP and VAP, and for the treatment Gram negative infections with limited treatment options	Boronate BLI + β-lactam (carbapenem)	No	X	X	√ KPC X MBL/ OXA-48	X
Plazomicin (Zemdri) [Achaogen (Cipla USA / QiLu Antibiotics, China)]	FDA approved for cUTI EMA application withdrawn	Aminoglycoside	No	X	?	√ KPC / OXA-48 ? MBL	X
Eravacycline (Xerava) [Tetraphase (La Jolla, Everest Medicines)]	FDA and EMA approved for cIAI	Tetracycline	Yes	?	X	√ KPC/ MBL/ OXA-48	√
Relebactam + imipenem/ cilastatin (Recarbrio) [MSD]	FDA approved for cUTI and cIAI EMA approved for HAP and VAP and for BSI with a suspected respiratory source, and for treatment of Gram-negative infections with limited treatment options	DBO-BLI + β-lactam (carbapenem)/ degradation inhibitor	No	X	? (if non-MBL mediated)	√ KPC X MBL/ OXA-48	X
Cefiderocol (Fetroja) [Shionogi]	FDA approved for cUTI, HAP and VAP EMA approved for treatment of infections due to aerobic Gram-negative organisms in adults with limited options	Siderophore β-lactam (cephalosporin)	No	√	√	√	√
Avibactam + ceftazidime (Avycaz) [Abbvie]	FDA and EMA approved for cIAI[c] and cUTI, HAP and VAP, and (in EMA only) for the treatment of Gram-negative infections with limited options	BLI + β-lactam (cephalosporin)	Yes	X	√ (if non-MBL mediated)	√ KPC / OXA-48 X MBL	X
Tazobactam + Ceftolozane (Xerbaxa) [MSD]	FDA and EMA approved for cUTI, cIAI[c], HAP and VAP	BLI + β-lactam (cephalosporin)	Yes	X	√ (if non-MBL mediated)	X	X
Sulbactam + durlobactam (Xacduro) [Innoviva Specialty Therapeutics]	FDA approved for HAP / VAP caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus complex*	BLI + β-lactam	No	√	X	X	X

Adapted from references: 6, 8, 9, 10.
Abbreviations: BLI, beta-lactamase inhibitor; BSI, bloodstream infection; cIAI, complicated intrabdominal infection; CRAB, carbapenem-resistant Acinetobacter baumannii; CPE, carbapenemase-producing Enterobacterales; CRPA, carbapenem-resistant Pseudomonas aeruginosa; cUTI, complicated urinary tract infection; DBO, diazabicyclooctane; EMA, European Medicines Agency; FDA, Food and Drug Administration (USA); HAP, hospital-acquired pneumonia; i.v., intravenous; KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamases; OXA-48, oxacillinase-48 like enzymes; STM, Stenotrophomonas maltophilia, VAP, ventilator-acquired pneumonia.

Pathogen activity: √, active; ? possibly active; X not or insufficiently active [c]In combination with metronidazole.

2) **Downregulated production or absence of porins due to genetic mutations**: Decreased penetration of carbapenems caused by porin loss (e.g. OprD in *P. aeruginosa*, OmpK35/K36 in *K. pneumoniae* and OmpC/F in *Enterobacter* spp.) has been associated with carbapenem resistance, especially when in combination with hyperproduction of AmpC beta-lactamases; individual carbapenems may be affected differently (e.g. imipenem more affected than meropenem and doripenem in P. aeruginosa with OprD loss; ertapenem more affected than imipenem and meropenem by AmpC hyperproduction plus decreased permeability in Enterobacterales).

3) **Upregulation of multi-drug efflux systems**: Drug efflux systems are capable of expelling antibiotics that have penetrated through the outer membrane. As an example, meropenem and doripenem are substrates of MexA-MexB-OprM in *P. aeruginosa*, and upregulation of this system augments resistance to meropenem and doripenem but not imipenem.

4) **Enzyme hydrolysis**: One key resistance mechanism is hydrolysis by carbapenemases, which may be chromosomal (intrinsic) or encoded on high-transmissible plasmids (acquired). Carbapenemases are beta-lactamases classified under Ambler classes

A / D (serine-β-lactamases) and B (metallo-β-lactamases) that are capable of conferring resistance to carbapenems in gram-negative organisms and are endemic in certain parts of the world (refer to Table 2 for details).

Table 2: Examples of clinically-significant carbapenemases[a]

Carbapenemases	Examples	Endemic area
Class A	KPC	North-eastern USA, Greece, Israel, Colombia and Puerto Rico. Nosocomial outbreak
Class B metallo-β-lactamases (MBLs)	VIM NDM IMP	Southern Europe, Indian subcontinent. Also reported in China, Australia, USA, Canada, Europe & Balkan region Spread in hospital & community
Class D oxacillinases	OXA	Turkey, North Africa, Gulf region and India. Outbreaks have occurred in Europe

Adapted from reference 14.
[a]Abbreviations: Klebsiella pneumoniae carbapenemase (KPC); Verona Integron-Mediated Metallo-β-lactamase (VIM); New Delhi Metallo-beta-lactamase (NDM); Imipenemase Metallo-beta-lactamase (IMP); carbapenem-hydrolyzing oxacillinase (OXA).

OVERVIEW OF CARBAPENEMASE-PRODUCING GRAM-NEGATIVE ORGANISMS[8]

Enterobacterales - Carbapenemase-producing Enterobacterales (CPE), a subset of organisms within the group of carbapenem-resistant Enterobacterales (CRE), have emerged globally since the 2000s. Different enzyme types are associated with distinct geographical locations, with *K. pneumoniae* carbapenemases (KPC) mainly causing infections in the US and Israel, while New Delhi metallo-β-lactamses (NDM) have been reported to cause UTI, pneumonia and bloodstream infections in India and Pakistan. CPE is now being increasingly detected in surveillance samples in patients admitted to hospitals in Hong Kong, but invasive infections are still uncommon[5, 15]. According to a recent study, the predominant enzyme types found in Hong Kong belong to Class B (mainly NDM, and less commonly IMP), followed by Class D (OXA)[16].

Risk factors for colonisation or infection due to CPE include: Prior use of antibiotics in recent three months (broad spectrum cephalosporins and/or carbapenems); prior colonisation or infection with a CPE; recent travel within 12 months to endemic countries (e.g. India, Greece, Pakistan, Turkey, Croatia), particularly if health care exposure occurred; trauma; underlying immunosuppression; mechanical ventilation; use of indwelling devices (e.g. urinary or venous catheters); and residence in a long-term care facility[17].

Non-fermenters: *P. aeruginosa and Acinetobacter* spp. may develop resistance to carbapenems through the acquisition of Class B (e.g. VIM) and D (OXA) enzymes respectively, and if combined with other mechanisms, may lead to MDR phenotypes. There is evidence that MDR *Acinetobactor baumannii (A. baumannii)* is now increasingly encountered in Hong Kong[18]. Other organisms in this group, such as *Stenotrophomonas maltophilia (S. maltophilia)* and *Elizabethkingia meningoseptica (E. meningoseptica)*, are intrinsically resistant to carbapenems due to the production of chromosomally encoded Class B MBLs.

Anaerobic bacteria: Carbapenem resistance in anaerobes was detected soon after the drug was introduced. It is most well recognised for the species *Bacteroides fragilis (B. fragilis)*, and the mechanism of resistance is the upregulation of expression of an MBL encoded by the *cfiA* gene, with ertapenem being the most affected. Resistance risk factors include prolonged exposure to carbapenems and β-lactam-β-lactamase combinations. While resistance rates have remained low in most countries, growing resistance in Asia has been noted, with moderate to high imipenem resistance in Japan (3 - 10 %), and very high resistance in Pakistan (24.1 %) and Mongolia (38.5 %)[19].

LABORATORY DIAGNOSIS OF CARBAPENEM RESISTANCE

When faced with a patient with risk factors for carbapenem-resistant organisms (e.g. known history of prior colonisation or infection due to carbapenem-resistant organisms, relevant travel history to endemic areas etc.), clinicians should arrange to send suitable screening samples to laboratories (e.g. stool or rectal swabs, wound swabs, drain fluids etc.) to allow prompt diagnosis for infection control and treatment purposes. In patients with a history of prolonged exposure to carbapenems or other broad-spectrum antibiotics, clinicians should maintain a high index of suspicion for the possible emergence or acquisition of carbapenem-resistant pathogens during therapy, and should consider discussing with a clinical microbiologist specific testing of bacterial isolates for carbapenem resistance, as this might not be routinely performed for certain types of bacteria (e.g. anaerobes such as *B. fragilis*). When clinically indicated, bacterial isolates should be tested for susceptibility against each carbapenem, as it is possible to resist one agent but not the others. Laboratory directors should ensure that their laboratories are following the latest testing protocols and susceptibility breakpoints for optimal detection and reporting of carbapenem-resistant organisms (e.g. those recommended by CLSI[20]). For all newly diagnosed CRE isolates, further genotypic tests should be performed in the laboratory to determine the presence of carbapenemase genes as well as the exact enzyme type involved, as this will have important implications on the selection of suitable treatment options.

TREATMENT OPTION FOR CARBAPENEM-RESISTANT GRAM-NEGATIVES: RE-PURPOSING EXISTING ANTIBIOTICS[21]

Existing antibiotics may retain activity against carbapenem-resistant organisms and can be considered for certain infections if in-vitro susceptibility is demonstrated. Examples include metronidazole for carbapenem-resistant *Bacteroides fragilis*, ampicillin-sulbactam for carbapenem-resistant *A. baumanii* (CRAB), oral fosfomycin for treatment of cystitis caused by some carbapenem-resistant Enterobacterales (CRE),

and amikacin for treatment of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Meropenem and/or imipenem-cilastatin can be used to treat ertapenem-resistant CRE if in-vitro susceptibility is confirmed, and carbapenemase genes are not detected. The polymyxin group of antibiotics (colistin and polymyxin B), with their broad-spectrum activities against most Enterobacterales (except *Serratia marcescens*, *Proteus*, *Providencia, Morganella,* and *Hafnia species*) as well as *P. aeruginosa, A. baumannii* and some *S. maltophilia* strains, has re-emerged as a potential option in recent years; yet drug toxicity, uncertain pharmacokinetics and concerns with suboptimal efficacy have limited their use. Refer to Table 3 for an overview of available options and dosing for the treatment of specific target organisms.

TREATMENT OPTIONS FOR CARBAPENEM-RESISTANT GRAM NEGATIVES: NEWER ANTIBIOTICS

Since 2014, at least eight new antibiotics have been approved for the treatment of carbapenem-resistant organisms globally, of which three are currently registered in Hong Kong (refer to Table 1). Most of them were developed specifically to target CPE, CRPA and CRAB.

Ceftazidime-avibactam: Avibactam is a diazabicyclooctane beta-lactamase inhibitor (BLI) that was approved in combination with ceftazidime for the treatment of cUTI, cIAI, HAP/VAP, as well as Gram-negative infections with limited treatment options. Avibactam reversibly inhibits class A β-lactamases, class C β-lactamases, and certain oxacillinases. Although not active against organisms producing Class B MBLs on its own, it may be combined with aztreonam for this purpose. It has been associated with higher rates of clinical success and survival in CPE infections compared with colistin or aminoglycoside containing regimes.

Ceftolozane-tazobactam: Ceftolozane is a new 3-aminopyrazolium cephalosporin with robust activity against *P. aeruginosa*; it is stable against AmpC type β-lactamases and the added tazobactam further improves its antipseudomonal activity. It is not active against CPE, CRAB or STM, and in CRPA harbouring class B MBLs. It is approved for cUTI, cIAI, HAP/VAP.

Meropenem-vaborbactam: Vaborbactam is the first boronic acid BLI, a group known to reversibly and competitively inhibit serine-β-lactamases. It inhibits class A β-lactamases but not class B MBLs or class D β-lactamases. It is approved for cUTI, HAP and VAP, and treating Gram-negative infections with limited options.

Plazomicin: Plazomicin is a newly developed aminoglycoside that is resistant to modification by many aminoglycoside-modifying enzymes, and is broadly active against the CRE/CPE, including strains that are resistant to existing aminoglycosides (amikacin, gentamicin, tobramycin); however, it is not active against many CPE strains producing NDM type of carbapenemases, because of frequent coproduction of 16S ribosomal RNA (rRNA) methyltransferases which confer high-level resistance to all existing

Table 3: Suggested dosing of antibiotics for the treatment of infections caused by carbapenem-resistant organisms if testing confirmed susceptible

Agent	Adult Dosage (assuming normal renal and liver function[b])	Target Organisms / infections
Amikacin	**Cystitis**: 15 mg/kg/dose IV x 1 **All other infections**: 15 mg/kg/dose IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	CRE/CPE, CRPA
Ampicillin-sulbactam	Total daily dose 6-9g of sulbactam Potential infusion strategies: 9 g IV q8h over 4 hours; 27 g IV q24h as a continuous infusion; 3g IV q4h over 30 mins	CRAB
Cefiderocol	2 g IV q8h, infused over 3 hours	CRE/CPE, CRPA, CRAB, STM
Ceftazidime-avibactam	2.5 g IV q8h, infused over 3 hours	CRE/CPE, CRPA
Ceftazidime-avibactam and aztreonam	***Ceftazidime-avibactam***: 2.5 g IV q8h, infused over 3 hours *PLUS* **Aztreonam**: 2 g IV q6-8h, infused over 3 hours	CPE (MBL-producing), STM
Ceftolozane-tazobactam	**Cystitis**: 1.5 g IV q8h, infused over 1 hour **All other infections**: 3 g IV q8h, infused over 3 hours	CRPA
Ciprofloxacin	**Uncomplicated cystitis**: 400mg IV q12h or 500mg PO q12h **All other infections**: 400 mg IV q8h OR 750 mg PO q12h	CRPA
Colistin	Refer to international consensus guidelines on polymyxins[c]	CRE/CPE, CRPA, CRAB
Eravacycline	1 mg/kg/dose IV q12h	CRE/CPE, CRAB
Fosfomycin	**Cystitis**: 3 g PO x 1 dose	CRE/CPE *(E. coli)*, limited to cystitis
Gentamicin	**Cystitis**: 5 mg/kg/dose x 1 **Pyelonephritis or complicated UTI**: 7 mg/kg/dose IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	CRE/CPE, CRPA
Imipenem-cilastatin	**Uncomplicated cystitis**: 500 mg IV every 6 h, infused over 30 min **All other infections**: 500 mg IV every 6 h, infused over 3 h (if possible)	CRE (resistant to ertapenem only, carbapenemase gene not etected)
Imipenem-cilastatin-relebactam	1.25 g IV q6h, infused over 30 minutes	CRE/CPE, CRPA
Levofloxacin	750 mg IV/PO q24h	STM
Meropenem	**Uncomplicated cystitis**: 1 g IV every 8 h, infused over 30 min **All other infections**: 2 g IV every 8 h, infused over 3 h (if possible)	CRE (resistant to ertapenem only, carbapenemase gene not detected)
Meropenem-vaborbactam	4 g IV q8h, infused over 3 hours	CRE/CPE
Minocycline	200 mg IV/PO q12h	CRAB, STM
Nitrofurantoin	Macrocrystal/monohydrate (Macrobid®) 100 mg PO q12h Oral suspension: 50 mg PO q6h	CRE (cystitis only)
Plazomicin	**Cystitis**: 15 mg/kg d IV x 1 dose **All other infections**: 15 mg/kg c IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	CRE/CPE, CRPA
Polymyxin B	Refer to international consensus guidelines on polymyxins[c]	CRE/CPE, CRPA, CRAB
Tigecycline	200 mg IV x 1 dose, then 100 mg IV q12h	CRE/CPE, CRAB, STM
Tobramycin	**Cystitis**: 5 mg/kg/dose IV x 1 **Pyelonephriris or complicated UTI**: 7 mg/kg/dose IV x 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation	CRE/CPE, CRPA
Trimethoprim-sulfamethoxazole	**Cystitis:** 160 mg (trimethoprim component) IV/PO q12h **Other infections:** 8-12 mg/kg/day (trimethoprim component) IV/PO divided q8-12h (consider maximum dose of 960 mg trimethoprim component per day)	CRE/CPE, STM

Adapted from reference 21.
[a]Abbreviations: CRAB: Carbapenem-resistant Acinetobacter baumannii; CRE: Carbapenem-resistant Enterobacterales; CPE: Carbapenamase producing Enterobacterales; CRPA: Carbapenem-resistant Pseudomonas aeruginosa; E. coli: Escherichia coli; IV: Intravenous; MBL: Metallo-β-lactamases; MIC: Minimum inhibitory concentration; PO: By mouth; q4h: Every 4 hours; q6h: Every 6 hours; q8h: Every 8 hours; q12h: Every 12 hours; q24h: Every 24 hours; STM: Stenotrophomonas maltophilia
[b]Dosing suggested for several agents in table differs from dosing recommended by the US Food and Drug Administration.
[c]Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019; 39(1): 10-39.

aminoglycosides. It is currently approved for the treatment of cUTI.

Eravacycline: Eravacycline is a new synthetic tetracycline that is not affected by ribosome protection proteins such as TetM and less prone to efflux mechanisms. It has broad activity against gram-negative pathogens including CRE/CPE, CRPA and *Stenotrophomonas maltophilia*, but not *Pseudomonas aeruginosa*. It is also active against gram-positive pathogens (including methicillin-resistant S. aureus and vancomycin-resistant enterococci) and many clinically relevant anaerobes. It is currently approved for the treatment of cIAI.

Imipenem-Cilastatin-Relebactam: Relebactam is a new BLI with a diazabicyclooctane core, similar to avibactam. It inhibits classes A/C but not classes B/D β-lactamases. It is active against most KPC-producing CRE strains and some strains of CRPA, but not CRAB or *S. maltophilia*. It is currently approved for the treatment of cUTI, cIAI, HAP /VAP, BSI with a suspected respiratory source, and for the treatment of Gram-negative infections with limited treatment options.

Cefiderocol: Cefiderocol is a novel siderophore cephalosporin in which the catechol side chain forms a chelated complex with ferric iron. This mechanism enables cefiderocol to actively cross the outer membrane of gram-negative bacteria using a receptor-mediated bacterial iron transport system. In addition, cefiderocol is stable against hydrolysis by a variety of carbapenamases, including those from classes A, B and D. As a result, it is active against a wide range of carbapenem-resistant gram-negative bacteria ranging from CRE/CPE to CRPA, CRAB, and *S. maltophilia*. It is currently approved for the treatment of cUTI, HAP and VAP, and infections due to aerobic Gram-negative organisms in adults with limited options.

Sulbactam-durlobactam[9]: Sulbactam, initially developed as a BLI used in combination with other beta-lactams, was later found to have potent intrinsic activity against *Acinetobacter* species. However, as it is readily degraded by carbapenamases, it does not have clinically useful activity against CRAB. The addition of durlobactam, a novel diazabicyclooctane (DBO) BLI with an inhibition profile against Class D carbapenemases commonly produced by *Acinetobacter* spp, effectively restores the activity of sulbactam towards CRAB. In April 2023 the drug was approved by FDA for treatment of HAP/VAP caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex.

When faced with patients with complicated infections due to carbapenem-resistant organisms, source-control measures such as drainage of abscesses and/or surgical debridement of infected tissues should be attempted in order to decrease the overall bacterial load and reduce the chance of emergence of further resistance during therapy. In addition, a combination of antibiotics guided by in-vitro susceptibilities and potential synergism would often be needed, as opposed to monotherapy using one of the newer agents, to increase the likelihood of a successful outcome. Patients with such infections should preferably be managed with infectious disease specialists or clinical microbiologists.

CONCLUSION

Carbapenem-resistant pathogens have emerged as a significant healthcare burden in the 21st century, and treatment options have been limited to agents such as colistin in combination with other antibiotics. Fortunately, several new agents with activity against carbapenem-resistant pathogens have been approved. These newer agents will become important additions to the currently limited armamentarium and are expected to improve the outcome of patients affected by carbapenem-resistant pathogens. As each new agent has its strengths and limitations, antimicrobial stewardship will continue to play a crucial role in ensuring its optimal and rational use in the coming years.

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ZERBAXA®
ceftolozane and tazobactam
for injection

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

FIGHT IT NOW
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Consider ZERBAXA® for ventilated patients

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

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

ZERBAXA® in vHAP/VAP

PRIMARY ENDPOINT

Non-inferior to meropenem in 28-day all-cause mortality in ITT population[2]

FAVOURABLE SUBGROUPS

Favourable 28-day all-cause mortality for the subgroups of vHAP and previous failure of antibiotics for current nosocomial pneumonia episode[2]

MICROBIOLOGICAL RESPONSE RATE

Numerically higher microbiologic eradication rates in ME population with *P. aeruginosa*[3]

Study Design: A randomized, controlled, double-blind, non-inferiority trial conducted between Jan 16, 2015 and April 27, 2018 at 263 hospitals in 34 countries. Patients (n=726) were randomly assigned (1:1), and stratified by type of nosocomial pneumonia (either VAP or vHAP) and age (<65 years vs ≥65 years), to receive either 3 g ZERBAXA® (n=364) or 1 g meropenem intravenously every 8 h (n=362) for 8–14 days. The primary endpoint was 28-Day all-cause mortality (at a 10% non-inferiority margin). ME population: patients with key gram-negative lower respiratory tract pathogens at baseline

Reference: 1. ZERBAXA® Hong Kong Product Circular. **2.** Kollef MH *et al.* Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *The Lancet, Infectious Diseases.* 2018;19(12):1299–1311. **3.** Martin-Loeches I et al. Clinical and microbiological outcomes, by causative pathogen, in the ASPECT-NP randomized, controlled, Phase 3 trial comparing ceftolozane/tazobactam and meropenem for treatment of hospital-acquired/ventilatorassociated bacterial pneumonia, *J ntimicrob Chemother,* 2022;77(4):1166–1177.

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

Zerbaxa® Selected Safety Information

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

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

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

Precautions:
- Decreased Efficacy in Patients with Baseline Creatinine Clearance of 30 to 50 mL/min

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

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

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

- Hypersensitivity reactions

  Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.
  Before initiating therapy with ZERBAXA®, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. If this product is to be given to a patient with a cephalosporin, penicillin, or other beta-lactam allergy, exercise caution because cross sensitivity has been established. If an anaphylactic reaction to ZERBAXA® occurs, discontinue the drug and institute appropriate therapy.
- *Clostridium difficile*-associated diarrhea

  Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZERBAXA®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.
  If CDAD is confirmed, discontinue antibacterials not directed against *C. difficile*, if possible. Manage fluid and electrolyte levels as appropriate, supplement protein intake monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.
- Development of Drug-Resistant Bacteria

  Prescribing ZERBAXA® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Adverse Events:
- Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis

  The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA® were nausea, diarrhea, headache, and pyrexia.
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

  The most common adverse reactions (2% or greater) occurring in patients receiving ZERBAXA® were hepatic transaminase increased[1], renal impairment/renal failure[2], diarrhea, intracraninal hemorrhage[3], vomiting, clostridium difficile colitis[4].

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

- Laboratory Values

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

Before prescribing, please consult the full prescribing information

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Two Cases of Acute Retroviral Syndrome

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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 January 2024.

CASE 1

A thirty years old gentleman, without significant past medical history, presented with a 5-day history of fever with chills and rigours and poor appetite. Systemic review was negative. He was sexually active, an MSM (man having sex with a man), in a monogamous relationship and residing with his partner. He denied recreational drug use. Physical examination showed multiple cervical lymphadenopathy, bilateral tonsillar exudates, oral thrush, and a macular rash over the trunk and limbs.

The chest radiograph was clear. His haemoglobin level was normal. Platelet count was slightly low (135 x 10^9 /L) and there was lymphopenia (0.37 x 10^9 /L). The nasopharyngeal swab for viral panel PCR was negative, and blood culture showed no growth. Hepatitis B and C serologies were negative. The monospot test was negative. EBV serology was positive for IgG but not IgM. Quantiferon TB was negative. The procalcitonin level was not elevated. He was started empirically on ceftriaxone and doxycycline. Ceftriaxone was stepped up to ertapenem and micafungin was added for persistent high fever and a rising C reactive protein (CRP).

Blood for HIV was checked and was positive for p24 antigen. HIV antibody was negative. HIV RNA was 3 x 10^7 copies/mL. CD4 count was 219 cells/uL. High fever and upper respiratory tract symptoms persisted for one week despite antimicrobials given. After discussion with the patient, he was started on highly active anti-retroviral therapy (HAART), and his symptoms abated two days after the initiation of treatment. He was later treated for latent syphilis as the rapid plasmin regain (RPR) test came back positive at a titre of 1:8.

CASE 2

A gentleman in his sixties was admitted for one week with a history of fever and suspected drug rash. He was seen for high fever and sore throat, diagnosed with URTI and prescribed oral Augmentin (amoxicillin and clavulanic acid) and symptomatic medications. He had taken three doses of Augmentin, with worsening skin rash after each dose. Skin redness, mainly involving the trunk and face, would develop around 2 - 3 hours after medication intake. The skin rash was not itchy or painful. He reported using Augmentin in the past without any allergic reaction. He had a history of hyperthyroidism in remission and was not taking any long-term medication.

He was admitted for further workup. Swinging fever persisted and he reported passing loose stools. On physical examination, he had a temperature of 39 °C. Blood pressure was 107/61 mmHg and heart rate was 67 per min. Neurological examination, cardiac and respiratory examination were unremarkable. There were 4 - 5 patches of scabs over the abdominal wall, which the patient reported had persisted for years. There was also a new faint maculopapular rash over the lower abdominal wall and upper chest and a 1 x 1 cm erythematous nodule over the abdominal wall (see Fig. 1).

The chest radiograph was clear. Cultures of blood, sputum, and urine were negative. The stool viral PCR panel was negative. Complete blood counts, including white cell differential count, were within normal limits. Eosinophil count was not elevated. Peripheral blood smear was unremarkable. Lactate dehydrogenase (LDH) was not elevated. Liver function panel, urea and electrolytes were all within normal limits. Procalcitonin level was minimally raised at 0.09 ng/mL. Nasopharyngeal swab for the respiratory virus panel was negative. Monospot test was negative. Anti-Streptolysin O titre (ASOT) was not elevated. *Treponema pallidum* antibodies were negative. Dengue and Rickettsia serology were negative. Abdominal wound swab culture was unrevealing, and molecular testing for herpes simplex 1 and 2 and Varicella zoster PCR were negative. Antibiotics were changed first to levofloxacin and then to meropenem in view of the persistent fever. The fever, URTI symptoms and skin rash gradually subsided over one week.

The patient gave a further history of sexual contact with multiple partners including commercial sex workers. He had visited a social hygiene clinic with HIV and STI screening six months prior and was told the results were negative. With the patient's consent, HIV testing was performed - HIV antigen was positive and antibody negative, indicative of acute HIV infection. Counselling was given to the patient. The CD4 count at diagnosis was 1,023 cells/uL. HIV viral load was 1.32 x 10^6 copies/mL. He was started on HAART and has remained well. He was scheduled to have penicillin skin testing for a suspected antibiotics allergy.

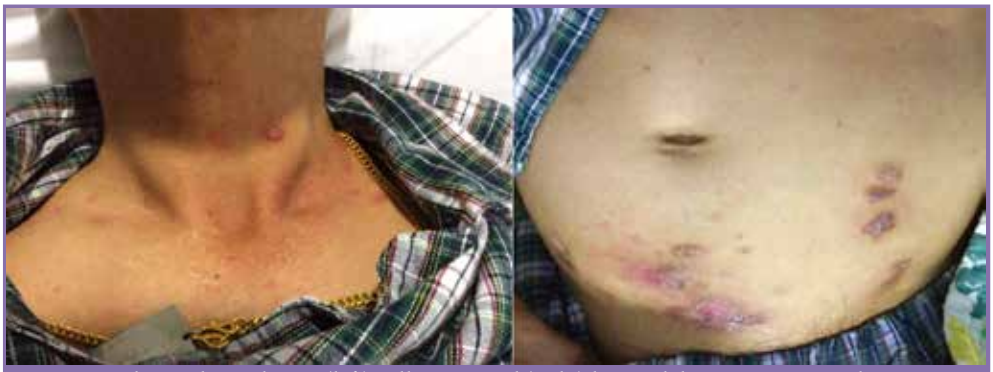

Fig. 1: Maculopapular rash over (left) collar area and (right) lower abdomen. He reported new maculopapular rash, on top on pre-existing scabbed lesions over lower abdomen. (Personal Collection)

PRIMARY HIV INFECTION

Up until the second quarter of 2023, there was a cumulative total of 11,830 HIV cases reported in Hong Kong[1]. The reported HIV incidence peaked in 2015 - 2016 and since then there has been a decreasing trend. In 2022, there were 409 new HIV cases reported, of which 62 were AIDS cases. Transmission was mainly through homosexual and bisexual transmission affecting males, particularly impacting the MSM population.

Primary HIV infection refers to the acute stage of HIV infection, when the virus multiplies rapidly and disseminates throughout the body, establishing the viral reservoir and seroconversion occurs. Anti-retroviral treatment prevents progression to AIDS and other complications. It represents the period where early intervention can limit the damage and preserve immune function.

As the viral load is very high during the acute stage, the infectivity is also high, and this represents an important source of HIV transmission. Models in different geographical locations estimate that the acute stage accounts for 38 - 50% of all cases of HIV transmission, and is 10 - 26 times more infectious than chronic HIV infection[2-4].

Clinical Presentation

The incubation period after HIV exposure is around 2 to 4 weeks. In 65 - 95 % of cases patients present with a flu-like syndrome, known as acute retroviral syndrome (ARS) – with fever, sore throat, lymphadenopathy, headache, muscle pain and skin rash (Table 1)[2, 5-7]. Symptoms with the strongest association with ARS are fever and skin rash[8]. Leukopenia, thrombocytopenia, and elevated liver enzymes are common. Aseptic meningitis, encephalitis, and facial nerve paresis have also been reported[7]. Symptoms usually resolve spontaneously after 4 to 6 weeks. As this is an early phase of HIV viral infection, opportunistic infection rarely occurs, though Candida stomatitis and esophagitis, CMV disease (viremia, hepatitis and colitis), multi-dermatomal herpes zoster and peripheral polyneuritis have been reported[6]. In general, symptoms and signs are non-specific. The majority of patients with HIV-1 infection could not recall an illness suggestive of ARS and did not pursue medical care[9].

Differential diagnoses include other viral illnesses, infectious mononucleosis, influenza, COVID-19, viral hepatitis, Streptococcal infection, syphilis, and drug rash.

Table 1. Common symptoms of Acute Retroviral Syndrome[8].

Symptoms	Frequency
Fever	80 %
Tiredness or fatigue	78 %
Arthralgias	54 %
Headache	54 %
Loss of appetite	54 %
Rash	51 %
Night sweats	51 %
Myalgia	49 %
Nausea	49 %
Diarrhoea	46 %
Sore throat	44 %
Oral ulcers	37 %
Weight loss	32 %

Diagnosis

Primary HIV infection can be further classified into acute infection - the period up to 30 days post infection, before HIV serology becomes positive; and recent infection - up to 6 months after HIV acquisition[10]. Fiebig stages refers to the different stages of primary HIV infection - its evolving viral dynamics and serological response (Fig. 2).

The fourth generation HIV test, also known as the antigen/antibody assay is a combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV p24 antigens. It is the recommended screening test for HIV infection (Fig. 3). Specimens with positive antigens but negative antibodies should be tested for HIV RNA. If HIV RNA can be detected, acute HIV infection is very likely. HIV infection should be confirmed with repeated quantitative testing and antibody testing to document seroconversion. A negative antibody and negative HIV RNA testing is suggestive of a false positive antigen assay. Regardless, in patients with a high probability of infection, interval HIV testing should be considered.

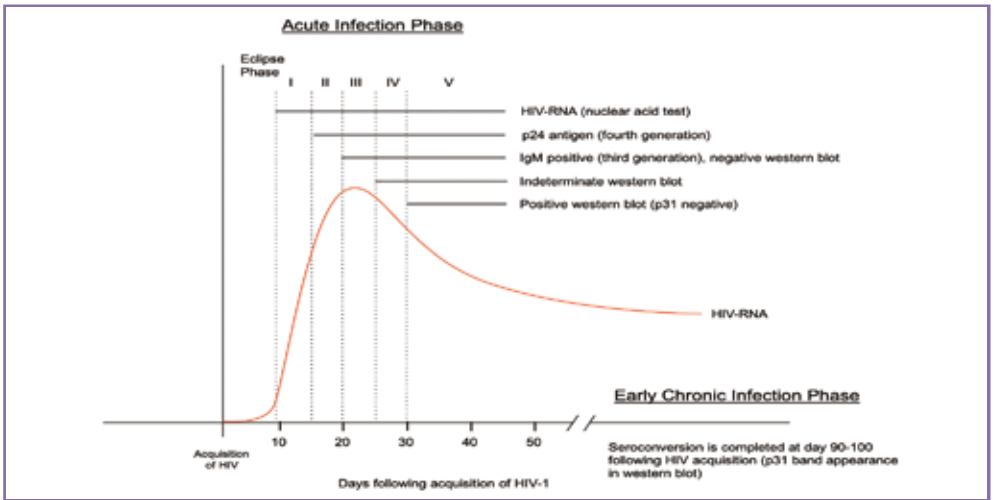

Fig. 2: Stages of primary HIV-1 Infection in non-pre-exposure prophylaxis users. The different stages are described by Fiebig in 2003 and referred as Fiebig stages. Eclipse phase refers to the period in which no diagnostic test can detect HIV. Viral load can peak at several millions copies per mL in the acute phase[11,12].

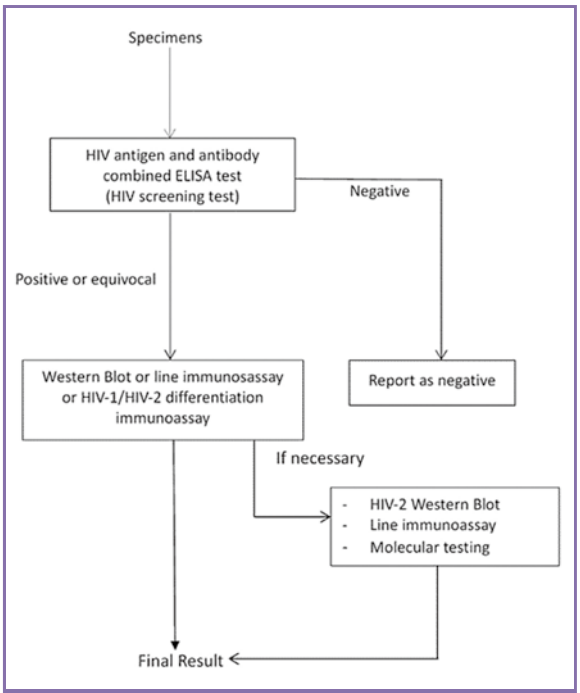

Fig. 3: General protocol for laboratory diagnosis of HIV infection. Ref: Algorithm 3, Diagnosis, classification and staging of HIV Disease, HIV Manual fourth edition Hong Kong[13].

Managing Acute HIV Infection

The health care provider has three roles with respect to acute HIV infection: detection and diagnosis; secondary prevention, which in some cases should include partner notification (and possibly postexposure prophylaxis with anti-retroviral therapy); and initiation of anti-retroviral therapy[11].

HIV treatment guidelines now recommend highly active anti-retroviral therapy (HAART) for all persons with a diagnosis of HIV, including primary HIV infection[14, 15]. Early initiation of anti-retroviral therapy has been shown to reduce the viral reservoir, preserve immune function and shorten the duration of infectivity[16 - 19]. This is also in line with treatment as a prevention strategy: 'undetectable is untransmissible' (U = U). This phrase was endorsed by the WHO. In 2023 the WHO stated that the risk of sexual transmission was almost zero from cases of HIV in whom the viral loads were less than 1,000 copies per mL[20, 21]. The main goals of HIV treatment are to maintain virologic suppression and to prevent transmission. Patients should continue anti-retroviral therapy for life. The long term benefits include not only the restoration of CD4 counts, thus reducing AIDS related events, but also reducing chronic inflammation thereby reducing morbidity and mortality from non-AIDS related events[22].

The initial treatment of HIV is to use HAART with a high resistance barrier, such as an integrase inhibitor (bictegravir or dolutegravir) or protease inhibitor (boosted darunavir). Nucleoside reverse transcriptase inhibitors should be used as the backbone. Treatment should not be delayed while waiting for drug resistance (genotype) testing results. Every effort should be made to continue to follow-up with the patient even if they are not yet ready to start treatment.

Screening for other sexually transmitted infections, like syphilis, gonorrhoea, chlamydia, and hepatitis B and C should be performed. Counseling should be provided for the patient, on the natural history and prognosis of HIV, preventive measures, and the importance of notifying partner(s). The social history and any history of recreational drug use should be sought. Pregnancy tests should be performed in all cases of childbearing age.

Use of PrEP and Primary HIV Infection

Preexposure prophylaxis (PrEP) has been shown to be highly efficacious in HIV prevention and has been

adopted by many developed countries. Current licensed PrEP by the FDA in the USA includes oral Tenofovir (TDF or TAF) with emtricitabine combination pills, and long acting cabotegravir injectable. Transmission of HIV in PrEP users is very uncommon. It can occur in 3 scenarios: (1) when PrEP was initiated when the patient was already infected but undiagnosed, (2) poor compliance to PrEP, and (3) or rarely, it is related to breakthrough infections from resistant strains.

It has been observed that the presentation of primary HIV infection is modified in PrEP users[12, 23, 24]. Patients usually have fewer symptoms or may be asymptomatic. The initial viremia is blunted. HIV RNA can be suppressed by the continued use of PrEP during the seroconversion period. The seroconversion time can be delayed (80 days with PrEP versus 49 days with placebo). Reassuringly, the delay in diagnosis has not been associated with an increased risk of resistance emerging. Resistant mutations can develop in patients with good drug compliance to PrEP after they have been infected.

This highlights the importance of adequate HIV screening before initiating PrEP. Physicians must be aware of the potential pitfalls in diagnostic tests and their non-specific presentation. The importance of regular screening, monitoring and follow up for all at-risk patients should be stressed.

In general, the management of primary HIV infection in PrEP users should be the same as for non-PrEP users. PrEP should be stopped and switched to a full HAART regimen. In patients prescribed long acting injectable cabotegravir for their PrEP, the further use of integrase inhibitors is cautioned against until INSTI resistance has been ruled out[15, 23].

SUMMARY

The above cases illustrate that primary HIV infection can present with non-specific symptoms. A careful history and a high index of suspicion may suggest the diagnosis and the need for HIV testing. Primary HIV infection represents the golden period in which early HAART use can preserve immune function, reduce the HIV reservoir, and reduce HIV transmission. All cases should be started on anti-retroviral therapy. The doctor should enquire about whether the patient has taken HIV preexposure prophylaxis (PrEP), as this can affect the choice of anti-retroviral therapy.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Two Cases of Acute Retroviral Syndrome" by Dr Thomas CHIK and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 January 2024. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/Fl., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

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

1. Non-nucleoside reverse transcriptase inhibitors (NNRTI) based ART, such as rilpivirine, is recommended as initial therapy for primary HIV infection.
2. HIV Infectious risk is high in primary infection.
3. Anti-retroviral therapy can reduce infectivity in primary HIV infection and provide public health benefits.
4. Primary HIV infection ranges from asymptomatic to fever, upper respiratory tract and viral syndrome.
5. If the patient is not symptomatic after diagnosis of primary HIV infection, one can delay starting anti-retroviral therapy as it is a drug burden.
6. Symptoms of acute HIV and HIV seroconversion can be attenuated in preexposure prophylaxis users.
7. Positive antigen and negative antibody result in HIV antigen/antibody combo test usually represents false positive test - the client should be advised to repeat the test 6 months later.
8. Pneumocystis pneumonia infection is a common infection in cases with primary HIV infection.
9. One should wait for the result of HIV drug resistant testing before starting on anti-retroviral therapy.
10. HIV antigen and RNA can be detected before antibody seroconversion in primary HIV infection.

ANSWER SHEET FOR JANUARY 2024

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2024 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Two Cases of Acute Retroviral Syndrome

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Specialist in Infectious Disease

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Answers to December 2023 Issue

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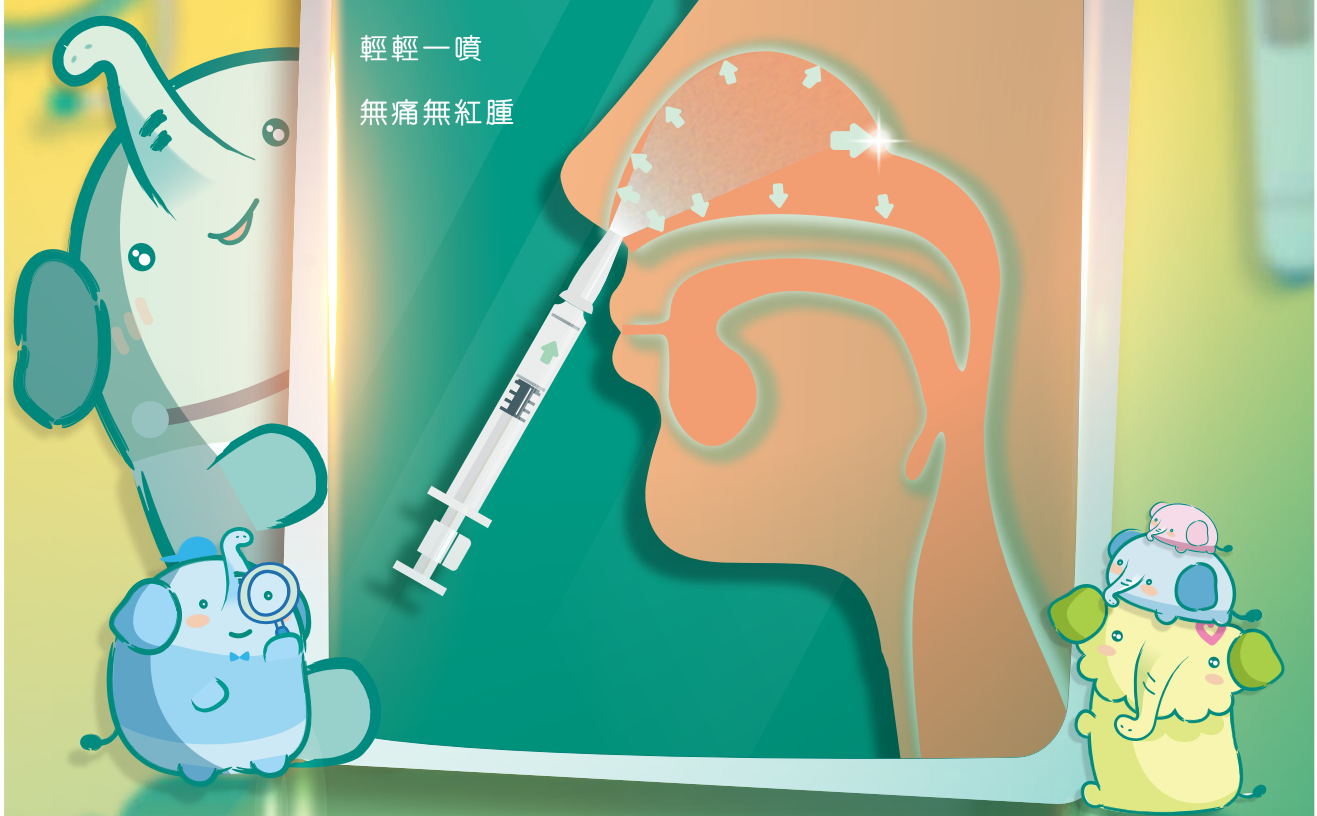

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Are We Ready for Pathogen X?

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Professor, University of Manitoba, Canada
Founding Director, International Diagnostic Centre Network

Prof Rosanna W PEELING

INTRODUCTION

Outbreaks of infectious diseases have been occurring more frequently and with greater severity in recent decades[1]. Transmission has been accelerated with the ease of global travel and fuelled by climate change, which has enabled disease vectors, such as mosquitos, to expand into areas with susceptible populations. For most countries, epidemic preparedness, in terms of public health infrastructure and healthcare systems responsiveness, has been developed traditionally for influenza outbreaks and is woefully inadequate to cope with novel pathogens, especially viral pathogens such as SARS-CoV-2, the cause of the COVID-19 pandemic. Are we ready for the next infectious disease emergency caused by an unknown Pathogen X?

While the COVID-19 pandemic was a time of global devastation, with more than 6.9 million lives lost, it was also a time of tremendous technological innovation. Vaccines and therapeutics were developed, evaluated, and made available for use within a year from the start of the pandemic - an amazing innovation superseding processes that normally take years to accomplish. But in that first year of the pandemic before drugs and vaccines were available, it was innovation in diagnostics that allowed countries to control the pandemic by rapidly identifying COVID-19 cases and implementing public health measures, such as quarantine or self-isolation, to interrupt the chain of transmission in communities. The focus of this article is to review the technological innovation in diagnostics during the pandemic and propose how these tools can best be used in future infectious disease emergencies.

DIAGNOSTIC NEEDS AND INNOVATION DURING THE COVID-19 PANDEMIC

At the start of the COVID-19 pandemic, Tedros Adhanom Ghebreyesus, Director-General of WHO, urged countries to 'test, test, test'[2]. He said testing, isolation, and contact tracing should be the backbone of the global pandemic response. Industry responded with more than a thousand brands of diagnostic tests for the COVID-19 pandemic. Three types of diagnostic tests are relevant to patient management and pandemic control: molecular or nucleic acid amplification tests, such as PCR tests that detect viral RNA; antigen tests that detect viral proteins, such as the nucleocapsid or spike proteins; and serology tests that detect host antibodies in response to infection, or vaccination, or both. Molecular and antigen tests can be used to diagnose acute infection when viral shedding is at its peak. Antibodies produced in response to infection provide indirect evidence of infection 1 - 2 weeks after exposure, regardless of whether the individual has symptoms or not. Antibody tests are therefore useful tools for measuring the true extent of an outbreak and are useful for surveillance. For patient management, antibody tests can be useful as a marker of exposure, i.e. determining whether a person has been infected or not. In the early days of the COVID-19 pandemic, there was some optimism that individuals with a positive antibody test result could be given an 'Immunity Passport' to show that they have protective immunity against the virus and no longer posed a public health threat to others. However, the Immunity Passport idea was abandoned in the end due to the lack of international consensus on correlates of protection against re-infection by SAR-CoV-2, the causative agent of the COVID-19 pandemic. Post vaccination, antibody testing can be useful to determine if an individual has achieved an adequate response. Antibody testing to monitor adequate vaccine response is especially important for immunocompromised individuals.

At the start of the pandemic, testing of symptomatic patients was crucial to refine the clinical case definition as SARS-CoV-2 was a novel pathogen. Diagnostic tests were needed to confirm clinical diagnosis for patient management, initiation of contact tracing and research to elucidate the mode of transmission to inform public health control strategies[3]. As molecular tests are highly sensitive and specific, they were used as the gold standard for the diagnosis of active SARS-CoV-2 infection. Several months into the pandemic when studies showed that more than 20 % of virus transmission could be attributed to individuals who were asymptomatic or pre-symptomatic, it was no longer sufficient to test symptomatic individuals alone. Mass testing was necessary for case detection in communities for effective disease control[4, 5, 6, 7]. However, scaling up molecular testing proved difficult because of a shortage of trained staff, global competition for reagents, and high costs. The increased demand for molecular testing led to long delays in receiving test results. An innovation that addressed this problem was the development of molecular tests which could yield faster results, i.e. 5 - 45 minutes instead of 2 hours or more[8]. Many point-of-care (POC) molecular technology platforms have been developed for the detection of tuberculosis and HIV viral load to increase testing capacity in settings with no laboratory access. There was hope that companies with these POC technology

platforms could add a SARS-CoV-2 detection test to their test menu to solve the problem of scaling up testing in communities. However, even after a number of these POC molecular tests were rapidly developed and validated for SARS-CoV-2, the availability of these tests was limited by the considerable time it took to manufacture both instruments and test cartridges.

RAPID ANTIGEN TESTS AS BOTH A DIAGNOSTIC AND A PUBLIC HEALTH TOOL

The solution to scaling up testing came with the availability of rapid antigen tests in single-use lateral-flow strip test formats that did not require any equipment and could be manufactured in the millions per month, making it easier for companies to meet global demand. These tests were easy to perform in a few steps, less expensive than molecular tests, and results were available in 15 - 20 minutes, making them the ideal test for mass testing[3, 9, 10]. The disadvantage is that rapid antigen tests are less sensitive than molecular tests. Most of the rapid antigen tests have a lower detection limit of 10^5 - 10^6 genome copies per mL compared with 10^2 - 10^3 copies per mL for molecular tests. Despite this limitation, rapid antigen tests were useful for rapidly triaging patients with high viral loads to reduce waiting time in crowded emergency departments and clinics. Hence, WHO recommended the use of rapid antigen tests for patients presenting with COVID-19-like symptoms in settings in which molecular testing was unavailable, or results were delayed by more than 48 - 72 hours due to the high volume of testing[11]. Having access to antigen tests as a rapid case detection tool enabled many countries to reduce the backlog of demand for molecular testing and enabled the implementation of public health measures without delay to slow the spread of COVID-19. The guidelines further recommended that symptomatic patients tested negative by the antigen test should have another specimen sent for molecular testing.

The most impactful innovation in the first year of the pandemic was using the rapid antigen test as a public health tool for community-based screening. Important studies conducted in Hong Kong and elsewhere on the temporal profiles of viral load during the course of infection and temporal dynamics of viral shedding and transmission provided key insights into how these rapid tests could become the most powerful tools for disease control before therapeutics and vaccines became available[12, 13, 14]. Studies showed that individuals with a viral load of less than 106 genome copies per mL were unlikely to transmit the virus, making rapid antigen tests a useful tool not only to identify asymptomatic or pre-symptomatic individuals most likely to transmit infection but also as a public health tool to ensure a safe environment for reopening of schools, businesses, and workplaces, and for the resumption of religious gatherings and social, cultural, and sports events[15, 16]. Rapid antigen tests were also useful for protecting the vulnerable if those working in or visiting long term care homes were regularly screened[17]. Many countries had imposed lockdowns to slow SARS-CoV-2 transmission, but lockdowns could only be time limited as they led to social and economic hardships. The low cost and ease of use allow for frequent testing, which could not be done with molecular testing[14]. Moreover, molecular testing with its high sensitivity, could not be used for these purposes as patients who were positive by molecular testing could remain positive for months, long after they were no longer infectious. When rapid antigen tests became available as self-tests, over 100 countries developed policies for their use, empowering the public to participate in the public health response to end the pandemic. WHO issued guidance on assuring the quality of the tests and testing[18].

The early introduction of rapid antigen tests for community-based and self-testing generated a lot of controversy as there was a misunderstanding that those tested with rapid antigen tests were given an inferior diagnostic tool. The development and use of a rapid test that can serve as both a diagnostic and public health tool to save lives and livelihoods is an important innovation that may spare communities from imposing lockdowns while improving the control of infectious disease emergencies. Multiplex rapid antigen tests that detect flu, RSV and COVID using a single nasal swab are now commercially available for healthcare provider testing or self-testing.

LOOKING TO THE FUTURE

Many countries are rebuilding their healthcare system after the pandemic with more diagnostic and surveillance capacity. Building a connected diagnostic system as the backbone of the healthcare system allows testing data to be turned into intelligence in real-time to provide early alerts of potential outbreaks and inform disease control strategies[3, 19]. The healthcare system should have appropriate diagnostic technologies at each level, starting with using multiplex molecular testing to test specimens from sentinel surveillance sites at reference laboratories to the use of rapid antigen testing in communities at lower levels of the health system and self-testing at home. Data connectivity ensures real time reporting for timely outbreak alerts and assessment of effectiveness of control strategies or interventions[20]. Data display on dashboards is also an important feature for transparency, which can engender public trust and dispel misinformation and myths.

Respiratory infections are the most common reason why people seek care. As many potential bacterial, viral or fungal causes exist, a definitive diagnosis has traditionally been difficult. Technological innovation developed during the pandemic can now be used to improve the accuracy of differential diagnosis and enable more rational use of antimicrobial medicines[18, 19]. Multiplex molecular tests used on sentinel surveillance samples allow public health authorities to provide accurate data on the prevalence of major bacterial and viral causative pathogens and their trends over time. The availability of local epidemiologic data on disease prevalence and trends to clinicians would allow them to make more informed differential diagnoses and, if needed, use POC molecular or antigen tests to rule in or rule out certain infections for their patients. Clinicians need to be familiar with the different types of tests, their performance, how they should be used and what the result means for guiding patient management.

Clinicians may also be approached by patients who have done self-testing and need help interpreting test results.

CONCLUSION

Widespread testing to detect COVID-19 cases followed by appropriate public health measures are critical components of pandemic control, especially in the first year of the pandemic before therapeutics and vaccines were available. Diagnostic innovation during the COVID-19 pandemic has led to the availability of faster molecular tests and rapid antigen tests that served as both rapid diagnostic and public health tools to identify those who were infected and at risk of transmission in order to provide a safe environment for the reopening of schools, workplace and resumption of public gatherings. Self-testing with rapid antigen tests has empowered the public to play their part in the public health response during the COVID-19 pandemic. Looking to the future, strengthening the healthcare system with more diagnostic capacity through the use of these tests will enable more timely alerts of potential outbreaks and the resilience to scale up an appropriate response. The availability of surveillance data on the prevalence and trends of infectious diseases of epidemic potential to clinicians will enable them to make more informed differential diagnoses with options of using POC molecular or rapid antigen tests to improve clinical decision making.

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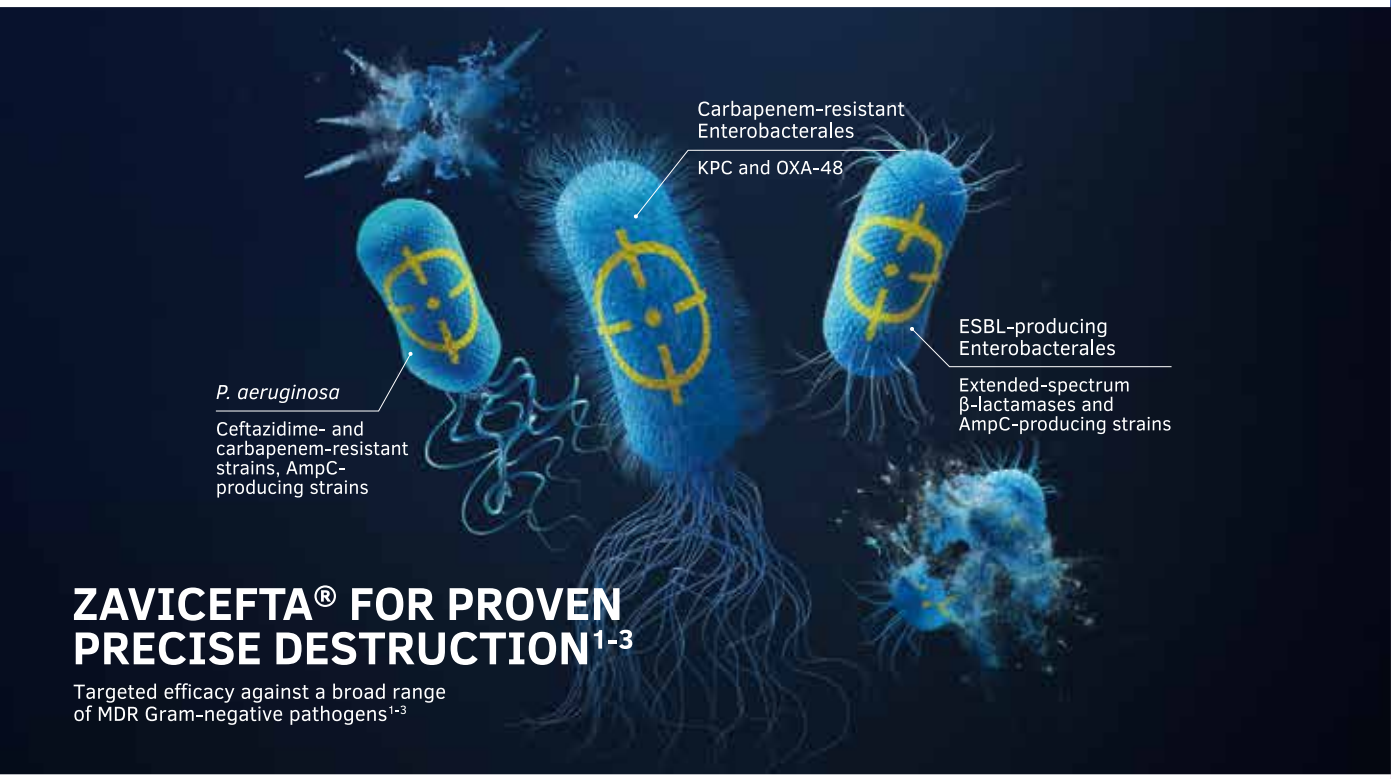
ZAVICEFTA™
ceftazidime and avibactam



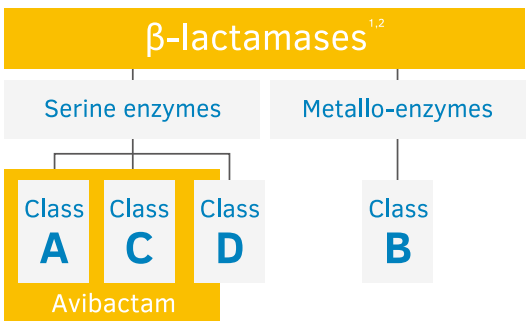
ZAVICEFTA® FOR PROVEN PRECISE DESTRUCTION[1-3]

Targeted efficacy against a broad range of MDR Gram-negative pathogens[1-3]

Indicated for[1]

- 3 months and older
  - *Complicated intra-abdominal infection (cIAI)*
  - *Complicated urinary tract infection, including pyelonephritis (cUTI)*
  - *Hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)*
- Adults
  - *ZAVICEFTA® is also indicated for the treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, cUTI, cIAI or HAP/VAP*

Novel β-Lactamases Inhibitor with Breakthrough Inhibition[1,2]



Avibactam inhibits both Ambler class A and class C β-lactamases and some class D enzymes, including :[1]*

- ESBLs
- KPCs
- OXA-48 carbapenemases
- AmpC enzymes

* Avibactam does not inhibit class B enzymes (metallo-β-lactamases) and is not able to inhibit many class D enzymes.[1] ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniae carbapenemase.

ZAVICEFTA ABBREVIATED PACKAGE INSERT

1. GENERIC NAME: ceftazidime pentahydrate/avibactam sodium **2. PRESENTATION:** Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam. The medicinal product is supplied in packs of 10 vials. **3. INDICATIONS:** Zavicefta is indicated in adults and paediatric patients aged 3 months and older for the treatment of the following infections: (a) complicated intra-abdominal infection (cIAI); (b) complicated urinary tract infection (cUTI), including pyelonephritis; (c) hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP); treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Consideration should be given to official guidance on the appropriate use of antibacterial agents. **4. DOSAGE AND ADMINISTRATION: Adults:** 2.5g administered by intravenous infusion Q8H over 2 hours. The recommended treatment duration for cIAI is 5-14 days, for cUTI including pyelonephritis is 5-10 days, for HAP/CAP is 7-14 days, and for bacteremia associated with, or suspected to be associated with any of the above infections, the duration of treatment should be in accordance with the site of infection. **Age 6 months to <18 years:** 62.5mg/kg to a maximum of 2.5g administered by intravenous infusion Q8H over 2 hours. **Age 3 months to <6 months:** 50mg/kg administered by intravenous infusion Q8H over 2 hours. In paediatric patients aged 3 months to <18 years, the recommended treatment duration for cIAI is 5-14 days, for cUTI including pyelonephritis is 5-14 days, and for HAP/CAP is 7-14 days. No dosage adjustment is required in elderly patients and in hepatic impairment. The safety and efficacy of Zavicefta in paediatric patients <3 months old have not been established. Please refer to prescribing information for dosage adjustments in patients with renal impairment. **Pregnancy and Lactation:** Zavicefta should only be used during pregnancy only if the potential benefit outweighs the possible risk. Ceftazidime is excreted in human milk in small quantities and a decision must be made whether to discontinue breast feeding or to discontinue/abstain from ceftazidime/avibactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **5. CONTRAINDICATIONS:** Hypersensitivity to active substances, to any of the excipients or to any cephalosporin antibacterial agent. Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of β-lactam antibacterial agent (e.g., penicillins, monobactams or carbapenems). **6. WARNINGS & PRECAUTIONS:** Hypersensitivity reactions and caution should be used if given to patients with a history of nßon-severe hypersensitivity to penicillins, monobactams or carbapenems; *Clostridioides difficile*-associated diarrhea; in patients with renal impairment; nephrotoxicity where concurrent treatment with high doses of cephalosporins an nephrotoxic medicinal products such as aminoglycosides or potent diuretics may adversely affect renal function; direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia; in patients with controlled sodium diet; in paediatric patients aged from 3 to less than 12 months of age where care should be taken when calculating the volume of administration of the dose; little or no activity against the majority of Gram-positive organisms and anaerobes. Ceftazidime may interfere with copper reduction methods (Benedict's, Fehling's, Clinitest) for detection of glycosuria leading to false-positive results. Ceftazidime does not interfere with enzyme-based tests for glycosuria. **7. DRUG INTERACTIONS:** Probenecid and chloramphenicol. Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g., furosemide) may adversely affect renal function. **8. OVERDOSE:** Overdose with ceftazidime/avibactam can lead to neurological sequelae including encephalopathy, convulsions, and coma, due to the ceftazidime component. Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis. **9. ADVERSE REACTION: Very Common:** Coombs direct test positive. **Common:** Candidiasis (including vulvovaginal candidiasis and oral candidiasis), eosinophilia, thrombocytosis, thrombocytopenia, headache, dizziness, diarrhea, abdominal pain, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, rash maculopapular, urticaria, pruritus, infusion site thrombosis, infusion site phlebitis, pyrexia. **10. PHARMACEUTICAL PRECAUTIONS:** Each vial is for single use only. The powder must be reconstituted with 10 mL of sterile water for injections and the resulting concentrate must then be immediately diluted prior to use. The reconstituted solution is a pale yellow solution and is free of particles. Please refer to the full prescribing information for the appropriate ceftazidime dose, volume of reconstituted solution, and volume of diluent. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

Reference: ZAVICEFTA HK PI (version: February 2021) **Date of preparation:** Jan 2022 **Identifier number:** ZAVI0122
FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

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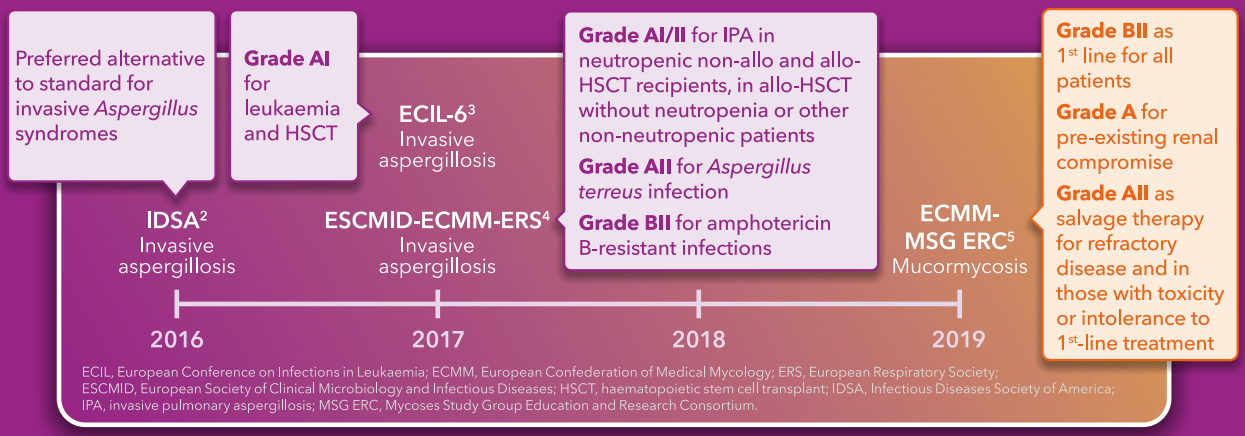
PP-ZVA-HKG-0062 03/2022

CRESEMBA® (ISAVUCONAZOLE)

A BEACON OF HOPE for difficult-to-treat invasive fungal infections[1]

Have greater confidence in treating invasive aspergillosis and mucormycosis with **CRESEMBA®**

- Indicated for the treatment of invasive aspergillosis, and mucormycosis in patients for whom amphotericin B is inappropriate[1]
- Designed for more than just survival*; recommended by the latest international guidelines[2-5]



ECIL, European Conference on Infections in Leukaemia; ECMM, European Confederation of Medical Mycology; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HSCT, haematopoietic stem cell transplant; IDSA, Infectious Diseases Society of America; IPA, invasive pulmonary aspergillosis; MSG ERC, Mycoses Study Group Education and Research Consortium.

*CRESEMBA (isavuconazole) combines standard-of-care efficacy against invasive aspergillosis and mucormycosis with improved tolerability, fewer drug-drug interactions, a simple dosing regimen and predictable pharmacokinetics.[1-11]

CRESEMBA® provides[1,6-11]:

- **CONFIDENCE** with non-inferior efficacy
- **REASSURANCE** with favourable safety profile
- **SIMPLICITY** through fewer drug–drug interactions than other azoles
- **RELIABILITY** through predictable pharmacokinetics

CRESEMBA® ABBREVIATED PACKAGE INSERT
1. TRADE NAME: CRESEMBA® **2. PRESENTATION:** Each vial contains 200mg isavuconazole powder for concentrate for solution for infusion (as 372.6 mg isavuconazonium sulfate); Each capsule contains 100mg isavuconazole (as 186.3 mg isavuconazonium sulfate) **3. INDICATIONS:** In adults for the treatment of invasive aspergillosis and mucormycosis in patients for whom amphotericin B is inappropriate **4. DOSAGE & ADMINISTRATION:** Loading dose: 200mg of isavuconazole every 8 hours for the first 48 hours. Maintenance dose: 200mg of isavuconazole once daily, starting 12 to 24 hours after the last loading dose. **For infusions:** To be reconstituted and then further diluted to a concentration corresponding to approximately 0.8mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour. Must only be given as an intravenous infusion. **For capsules:** Can be taken with or without food and should be swallowed whole. Do not chew, crush, dissolve or open the capsules. **Switching between oral and intravenous isavuconazole:** On the basis of high oral bioavailability (98%), switching between intravenous and oral administration is appropriate when clinically indicated. **Renal/hepatic impairment:** No dose adjustment is needed. **Pediatric:** Safety and efficacy of Cresemba in children aged below 18 has not been established. **Elderly:** No dose adjustment needed. **5. CONTRAINDICATIONS:** Hypersensitivity to isavuconazole or its excipients. Co-administration with ketoconazole. Co-administration with high-dose ritonavir (>200 mg every 12 hours). Co-administration with strong or moderate CYP3A4/5 inducers. Patients with familial short QT syndrome. **6. WARNINGS & PRECAUTIONS:** Hypersensitivity to azoles; Infusion-related reactions (IV only); Severe cutaneous adverse reactions. Contraindicated in patients with familial short QT syndrome and caution in patients taking other medicinal products known to decrease the QT interval. Monitoring of hepatic enzymes or in patients with severe hepatic impairment. Caution in patients having co-administration with strong CYP3A4/5 inhibitors, or CYP2B6 substrates. Avoid co-administration with mild CYP3A4/5 inducers. Appropriate therapeutic drug monitoring and dose adjustment may be necessary in patients with concomitant use of P-gp substrates or CYP3A4/5 substrates including immunosuppressants. **7. INTERACTIONS:** CYP450 isoenzymes (CYP3A4/5 inhibitors or inducers, CYP2B6 substrates); P-glycoprotein substrates; BCRP substrates; Organic cation transporter 2 substrates; UGT substrates **(IMPORTANT: Please refer to detailed information on Interactions with other Medicinal Products) 8. PREGNANCY AND LACTATION:** Cresemba must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections. Breastfeeding should be discontinued during treatment with Cresemba. **9. SIDE EFFECTS:** Common treatment-related adverse reactions include elevated liver chemistry tests, nausea, vomiting, dyspnea, abdominal pain, diarrhea, injection site reaction, headache, hypokalemia and rash.
Reference: HK PI (Version Date Dec 2018) Date of preparation: Nov 2019 Identifier number: CRES1119 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

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Melioidosis -An Emerging Masquerader under Climate Change

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INTRODUCTION

Melioidosis is a disease of humans and animals resulting from infection with the aerobic Gram-negative bacillus *Burkholderia pseudomallei*, formerly known as *Pseudomonas pseudomallei*, and is ubiquitous throughout the subtropics and tropics, particularly in Southeast Asia and northern Australia[1]. *B. pseudomallei* is a resilient environmental saprophyte and is widely distributed in soil and fresh surface water in endemic regions. Although its optimal temperature of survival ranges between 24 and 32 °C[2], it can resist temperature extremes, and acidic and alkaline conditions, and is able to persist in distilled water for 16 years[3]. Percutaneous inoculation, ingestion, and inhalation of contaminated soil or water are well recognised modes of transmission of melioidosis[4]. One in 4,600 seroconversion-associated exposures results in clinical disease, and 4 % of exposures result in latent infection[5]. The incubation period varies from 1 to 21 days (average nine days)[6] with the majority (85 %) of patients having acute presentation[6]. Melioidosis was first reported in Myanmar in 1911[7]. Hong Kong is considered an endemic area given the environmental suitability for *B. pseudomallei*, and the earliest report of human melioidosis could be dated back to 1984[8]. The seropositive rate among patients in a chest hospital was reported to be 14 % in a study performed in 1987[9], and the majority of seropositive subjects had no travel history to endemic areas. An increasing trend of a total of 61 cases was identified in the last two decades[10]. Hong Kong has seen a mysterious spate of melioidosis cases since August 2022, with a cluster emerging in the Sham Shui Po (SSP) district. Melioidosis has been included as a statutory notifiable infectious disease in Hong Kong (under Cap. 599) since 11th November 2022. At the time of writing, a total of 51 cases of melioidosis have been diagnosed since 2015 in Kowloon West Region. In this article, we will share our experiences in the clinical features, epidemiology, laboratory diagnosis and clinical management of melioidosis[11].

CLINICAL FEATURES

Among the 51 patients who had their first episode of culture-proven melioidosis diagnosed from January 2015 to May 2023, the median age of the patients was 71 years (range, 42 - 94 years), and 39 (76.5 %) of them were male. Worldwide, the median age of affected patients is 50, with a male predominance, ranging from 58.5 % to 84 %[12]. Possible explanations include an increased exposure to contaminated soil or water through high-risk occupations, such as agricultural or construction activities, or there is a higher prevalence of risk factors such as smoking or alcohol excess among the male patients. Diabetes mellitus is the most common comorbidity among our patients, contributing 56.9 % of cases. This risk factor is also in concordance with other case series[12]. Diabetes mellitus impairs immune function by decreasing chemotaxis, phagocytosis, cytokine response, and bacterial killing by polymorphonuclear leukocytes[13, 14]. Specifically, the release of the neutrophil signalling chemokine IL-8 from lung epithelial cells is delayed, and diabetics are therefore at greater risk of infection by inhalation[15].

Thirty-seven patients (73 %) had chest infections, of which 27 (73 %) patients presented with multi-lobar pneumonia, 23 (62 %) had concomitant bacteremia and 14 (38 %) had mediastinal involvement. The overall case fatality rate was 27.5 %. In our case cohort, there was a higher percentage of a chest infection but a comparable mortality rate when compared with the cases previously reported in Hong Kong (42.6 % pneumonia and 31 % mortality[10]). Less than 22 % of patients had an exposure history (6 patients worked near construction sites; 2 patients had travel history to Thailand; 2 had a history of farming; and 1 was a sewage worker). Six patients were in their nineties at the time of diagnosis,and two were nursing home residents. In fact, the residential address of 43 patients (84.3 %) was in the SSP district within an estimated area of 2.5 km^2.

Given the clinical presentation and epidemiological information, inhalation of aerosols containing a higher bacterial load during typhoons and rainstorms was therefore suspected to cause the sudden upsurge of cases in the SSP district. Higher lethality and shorter incubation period of aerosol inhalation of *B. pseudomallei* were demonstrated by animal models[16, 17], and rainfall two weeks before the presentation was an independent risk factor for pneumonia, septic shock and death[18]. Increased transport of the organism in eroded topsoil via the rise in the water table during heavy rainfall[19] and severe weather events and wind are associated with the dispersal of bacteria contaminated aerosol[20]. *Lau SK et al.*[21] demonstrated the presence of *B. pseudomallei* DNA in 6.8 % of soil samples collected in the oceanarium, and it was significantly correlated with ambient temperature and relative humidity. Additionally, Chen et al.[22] successfully detected *B. pseudomallei* DNA in 80 to 100 % of air samples with a significant correlation with the rainfall and the presence of typhoons. Furthermore, *Currie et al.*[23] cultured *B. pseudomallei* from air samples taken outside

the residence of a patient with mediastinal melioidosis, and whole genome sequencing confirmed the linkage between the isolates in the air sample and the patient sample. From 9th to 12th August 2022, there were four cultured proven Melioidosis cases (three *B. pseudomallei* isolates were recovered from blood culture while one was isolated from a sputum sample), and all patients resided in the SSP district. Preceding the presentation of the cases, the Amber Rain warning and the typhoon signal-3 (Wulan) were hoisted for three days and two days, respectively[24]. On 15th August 2022, 1 out of 8 air samples (1,000 L each) taken at a podium near a construction site in SSP recovered viable *B. pseudomallei* (Fig. 1), which was phylogenetically clustered with 27 patient isolates with less than 0.07 % core genome difference[11]. It belonged to a new multi-locus sequence type (MLST) ST-1996 and was identified as early as in a patient sample collected in 2016, suggesting that *B. pseudomallei* may have persisted in the nearby environment, of which its dispersal has been aggregated by reduction in vegetation in the area and extreme weather events due to climate change. Furthermore, the admission dates of cases were strongly associated with the rainfall and the hoisting of tropical cyclone warning signals[11].

The genitourinary system was the second most commonly (17.6 %) involved (5 patients had prostatic abscess; 4 patients had urinary tract infection). Melioidosis patients also presented a wide clinical spectrum: peritonsillar abscess, skin and soft tissue infection, bone and joint infection, continuous ambulatory peritoneal dialysis (CAPD) peritonitis, organ abscess (renal, liver and spleen), pericarditis, mycotic aneurysm and meningitis. Eleven patients (21.6 %) had multiple sites of infection, and four patients (7.8 %) had relapse of infection, with a range of 5 months to 3 years. Among the relapse cases, one had defaulted to oral eradication therapy, while two had doxycycline as the oral eradication drug due to intolerance to trimethoprim-sulfamethoxazole. In an Australian study, the recurrence rate was reported at 5.7 % with a median time to relapse of 9.4 months[25]. Relapse is commonly associated with poor compliance to antimicrobial treatment or eradication regimens containing either doxycycline or amoxicillin-clavulanate[26].

LABORATORY DIAGNOSIS

Culture

The culture of *B. pseudomallei* from blood, respiratory secretions, urine, cerebrospinal fluid, pus, and wound swabs remains the diagnostic gold standard. *B. pseudomallei* grows well on most routine laboratory media, such as blood, chocolate and MacConkey agars, revealing smooth, creamy colonies with a metallic sheen on blood agar. They are small Gram-negative bacilli with bipolar staining, giving them a safety pin appearance. The bipolar staining is due to the central accumulation of polyhydroxybutyrate granules, which do not retain the staining reagents[27]. As a consequence of prior antimicrobial treatment of the patients and the presence of normal flora in non-sterile specimens, the overall sensitivity of culture has been reported as only 60.2 %.[28] In our cohort, thirty-two patients (62.7 %) had bacteremia, which has been found in 38 to 73 % of melioidosis cases in other series[12]. In another study using the BacT/alert automated blood culture system (bioMérieux, Marcy ÍEtoile, France), 93 % of isolates could be detected within 48 hours of incubation, with a mean time of 23.9 hours to signal positive[29]. Among the nine patients having the genitourinary infection, however, only three of them had positive urine culture while additional four patients had pyuria. Urine samples are normally inoculated into cystein-lactose-electrolyte-deficient (CLED) agar for 24 hours' incubation per our laboratory protocol and this may account for the low rate of isolation of *B. pseudomallei*. For patients with suspected genitourinary tract infection and sterile pyuria, a request should be made to the laboratory for urine culture using nutrient agar for prolonged incubation. Notably, *B. pseudomallei* isolation in urine is consistent with renal parenchymal infection and not passive filtration into the urine[30].

Ashdown's medium, which contains Trypticase soy agar with 4 % glycerol, 4 mg/L gentamicin, 0.1 % crystal violet and 1 % neutral red, is the most widely used selective medium for improved isolation of *B. pseudomallei*[31]. Pinpoint, flat, dry, and wrinkled purple colonies are characteristic. It is able to grow at 42 °C and is positive for oxidase activity and motility. However, gentamicin may have inhibitory effects on the growth of *B. pseudomallei*, and incubation should be prolonged for at least 96 hours. Of note, rare gentamicin-susceptible strains from Sarawak, Malaysia, have been described[32]. Subsequently, a modified Ashdown's agar including norfloxacin, ampicillin, and polymyxin B (NAP-A) was evaluated to have improved selectivity but equal recovery of *B. pseudomallei*[33]. The use of an enrichment broth with Ashdown's medium and colistin (500,000 U/L) for incubation at 37 °C for 48 hours followed by inoculating into Ashdown's medium may further increase the yield, though with a compromise of increasing the time to identification[34]. In response to the surge of melioidosis cases, of which the diagnosis of four patients was delayed in the second hospital admission 3 to 6 weeks later, Ashdown's agar has been routinely added for the plating of respiratory specimens from the Caritas Medical Centre, whose catchment is in the SSP district. An additional six undiagnosed patients were identified through the surveillance culture by Ashdown's agar (0.25 % of specimens, unpublished data). Due to the non-specific clinical presentation of melioidosis, clinicians should request specific *B. pseudomallei* cultures for patients who present with severe community-acquired pneumonia or for those with risk factors such as diabetes mellitus or exposure history. Furthermore, during heavy rainfall or typhoon season, the routine addition of a selective medium to enhance the isolation of *B. pseudomallei* in respiratory specimens should also be considered.

Direct Molecular Detection

Given the non-specific clinical presentation and the high mortality of melioidosis, and the relatively poor yield of culture, a sensitive and specific PCR test that can detect *B. pseudomallei* directly from clinical specimens is imperative to aid early directed therapy. Meumann EM et al. reported the overall sensitivity and specificity of the T3SS-1 real-time PCR assay on urine, sputum, wound swabs, and drained pus to be 73.2 % and 89.2 %[35],

respectively. Sputum, in particular, represents a better sample than blood for PCR detection, due to the higher bacterial load[36]. A study on spiked blood demonstrated a 95 % probability of detection of *B. pseudomallei* at a concentration of 8.4 x 10^3 CFU/ml[37]. T3SS-1 real-time PCR test[37] was performed on culture positive samples in our laboratory (5 sputum and 1 blood culture); all were positive with cycle threshold (Ct) values ranging from 31.8 to 39.1 (unpublished data).

Serology

The serodiagnosis of melioidosis is difficult, due to a lack of commercial assays and high background seropositivity rates in endemic regions. In addition, serological tests generally have lower sensitivity than culture as 19 - 26 % of culture-confirmed melioidosis cases never seroconverted[38, 39]. Nevertheless, it can be a useful adjunct to the diagnosis of chronic melioidosis and neuro-melioidosis, when the negative predictive value of culture is low. The serum indirect hemagglutination assay (IHA), using poorly defined antigens from strains of *B. pseudomallei* adsorbed to sheep red blood cells, has been routinely performed in endemic areas and its cutoff values suggestive of infection are based on background seropositivity in the population. (e.g. a cutoff titre of ≥ 1:80 in Thailand[40] and ≥ 1:40 in Australia[41]) Alternatively, IgM and IgG enzyme-linked immunosorbent assay (ELISA) using inactivated cell suspension, recombinant hemolysin-coregulated protein (HcP) type VI secretion system or recombinant GroEL protein have been described with sensitivities ranging from 90 - 93.7 % and specificities ranging from 88.3 - 100 %[12]. The serum of 18 patients was sent to Queen Mary Hospital for a melioidosis antibody test (in-house ELISA antibody test using whole cell antigens, personal communication). Nine patients were both IgM and IgG positive (9 days to 10 weeks after onset) and one patient demonstrated seroconversion 17 days after onset of symptoms. Three patients with onset less than 14 days were IgM positive but IgG negative; on the contrary, one patient was only IgG positive five weeks after presentation. Possibly due to early presentation for less than seven days, two patients were both IgM and IgG negative. Further studies on the performance characteristics of serological tests, the time frame of the melioidosis antibody response and the relative importance of IgM and IgG detection are warranted.

MAMAGEMENT

Antimicrobial Susceptibility Testing

Currently, the Clinical and Laboratory Standards Institute (CLSI) only has interpretative breakpoints of imipenem (IMI), ceftazidime (CAZ), trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline (DOX), and amoxicillin-clavulanic acid (AMC) for a broth dilution method[42], while the European Committee on Antimicrobial Susceptibility Testing (EUCAST) also provides breakpoints for interpretation of zone diameters of the commonly used antimicrobials, including meropenem (MEM)[43]. In general, our isolates were susceptible to the most used antimicrobials [MIC_{90}: MEM, 2 ug/ml; IMI 2 ug/ml; CAZ 4 ug/ml; TMP-SMX 2 ug/ml; DOX 1 ug/ml; AMC 4 ug/ml; Etest (Liofilchem ®, Italy)], except three isolates being non-susceptible to TMP-SMX (MIC 4 ug/ml) and two isolates non-susceptible to MEM (MIC 4 ug/ml). The uncommon resistance to first-line antimicrobial therapy is consistent with overseas data[12].

Intensive Therapy

Meropenem or ceftazidime is the first-line antimicrobial for the intensive phase of treatment. The duration should last a minimum of 10 to 14 days, with longer intensive therapy for those with persistent septic shock, extensive pulmonary disease, organ abscesses, osteomyelitis, septic arthritis or neurological melioidosis (Table 1). Carbapenems, including meropenem and imipenem, have the greatest in vitro activity against *B. pseudomallei*[44] and provide post-antibiotic effect that may last up to 3.66 h[45]. Therefore, meropenem is recommended for severely infected patients who are under intensive care[46]. Adjunct therapy can potentially counteract the functional neutrophil defects that are crucial in the pathogenesis of severe melioidosis. The use of granulocyte colony-stimulating factor (G-CSF) was demonstrated in a randomised control trial to prolong survival when measured in hours, but there was no overall mortality benefit[47]. The Australian guideline recommends 300 μg of intravenous G-CSF daily for patients with septic shock for either ten days or the duration of intensive care unit stay[46]. Apart from medical treatment, surgical drainage is crucial in the treatment success of melioidosis, including single, large abscesses in the liver and muscles, prostatic abscesses greater than 1 cm, septic arthritis and mycotic aneyrysms[48]. The median time to resolution of fever, however, can be slow (up to 9 days)[49], and this may not stand as an indication for surgical intervention. For neurological melioidosis, osteomyelitis and septic arthritis, skin and soft tissue infections and genitourinary infection including prostatic abscesses, addition of TMP-SMX can be considered, given its excellent tissue penetration. Nevertheless, there is currently no evidence to support the routine combination of ceftazidime and TMP-SMX, as no survival benefit was conferred[50, 51].

Eradication Therapy

TMP-SMX is the preferred antimicrobial for eradication therapy to prevent recrudescence or relapse (Table 1). A time-kill study demonstrated that TMP-SMX could achieve bactericidal in vivo drug concentrations[52]. The dosing recommendations for TMP-SMX in melioidosis are higher than the standard doses and the duration of oral eradication therapy is 12 to 24 weeks. One open-label randomised trial revealed that a shorter therapy duration of less than 12 weeks would incur a 5.7-fold-increased risk of relapse[53]. Consequently, adverse effects, such as gastrointestinal symptoms, hyperkalaemia and rising levels of serum creatinine are reported in up to 40 % of patients[54]. If patients are intolerant to TMP-SMX despite dose modification or where TMP-SMX may be contraindicated due to pregnancy or young age, doxycycline and amoxicillin-clavulanic acid (AMC) are second line options. Of note, clavulanic acid is integral in the efficacy and

an oral dosage of AMC 20/5 mg/kg thrice per day is recommended. For example, the oral dosage for a 50 kg adult with normal renal function is 500 mg amoxicillin and 750 mg AMC thrice daily. Caution is required due to an increased risk of relapse and potential decreased efficacy for the second line options.

Table 1: Adapted from the work of Gassiep I, Armstrong M and Norton R12.

Phase	Drugs	Dosage for adults (40 - 60kg) with normal renal function	Infective source	Duration (weeks)
Intensive	Ceftazidime	2 g intravenous, every 6 hours	Pneumonia	2 - 4
			Primary bacteremia	2
	Meropenem	1 g intravenous, every 8 hours 2 g intravenous, every 8 hours for CNS infection	Skin and soft tissue	
	Consider adding Trimethoprim-sulfamethoxazole 240/1,200 mg every 12 hours in cases of neurological melioidosis, osteomyelitis and septic arthritis, skin and soft tissue infections and genitourinary infection including prostatic abscesses		Deep abscess	4
			Septic arthritis	
			Osteomyelitis	6
			Neurological	
			Mycotic aneurysm	
Eradication	Trimethoprim-sulfamethoxazole 240/1,200 mg orally, every 12 hours and folic acid 5 mg orally, daily		Pneumonia	12
			Primary bacteremia	
			Skin and soft tissue	
	Doxycycline 100mg orally, every 12 hours		Deep abscess	
			Septic arthritis	
	Amoxicillin-clavulanate 1000/250mg orally, every 8 hours		Osteomyelitis	24
			Neurological	
			Mycotic aneurysm	

Prophylaxis

TMP-SMX postexposure prophylaxis (PEP) achieved the best survival in a mouse modelcompared with AMC and doxycycline[55]. A 21-day course of TMP-SMX, or doxycycline or AMC as alternatives, at the same oral dosages as eradication therapy, is recommended for high-risk exposure to *B. pseudomallei*, such as percutaneous and mucosal exposure, and aerosol exposure outside a biosafety cabinet[56]. For specific at-risk populations, the potential benefit of PEP must be weighed against the severe adverse effects of TMP-SMX. One study reported that TMP-SMX PEP at an oral dose of 160/800 mg daily up to 26 weeks among haemodialysis patients might reduce the incidence of melioidosis during the wet season in a region of endemicity and appeared well tolerated[57].

CONCLUSION

With climate change, more adverse weather events such as heavy rainfall or typhoon cyclones are anticipated. Clinicians should be alert to the diagnosis of melioidosis in its various clinical presentations. For patients with risk factors such as diabetes mellitus, or pneumonia with multi-lobar or mediastinal involvement, specific *B. pseudomallei* sputum culture should be requested. A negative culture does not exclude the possibility of melioidosis, especially in patients partially treated with AMC. Serology thus serves as an adjunct to diagnosis. Directed intravenous intensive phase followed by a lengthy eradication course presents challenges in ensuring adherence, monitoring and management of adverse reactions.

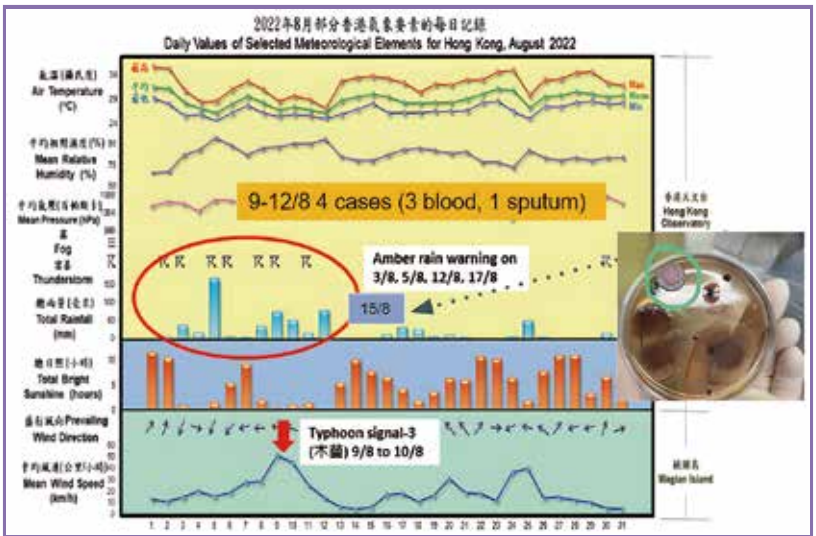

Fig. 1: Positive air sampling of B. pseudomallei after adverse weather events (Adapted from Hong Kong Observatory Monthly Weather Summary https://www.hko.gov.hk/en/wxinfo/pastwx/mws2022/mws202208.htm)

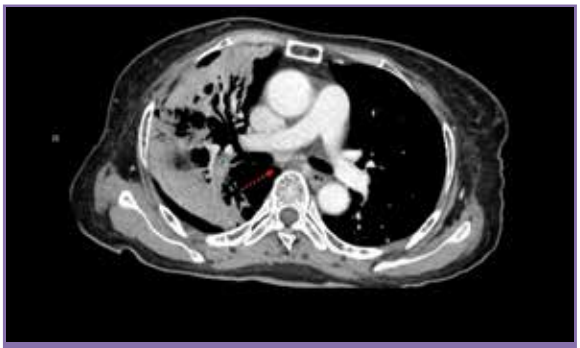

Fig. 2: Necrotizing pneumonia; mediastinal lymph nodes with necrotic centres (Personal Collection)

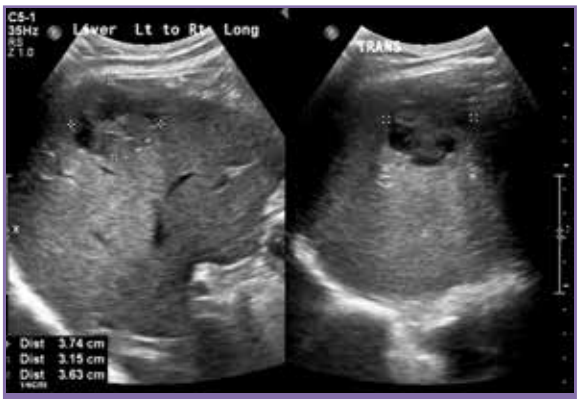

Fig. 3: Liver abscess (Personal Collection)

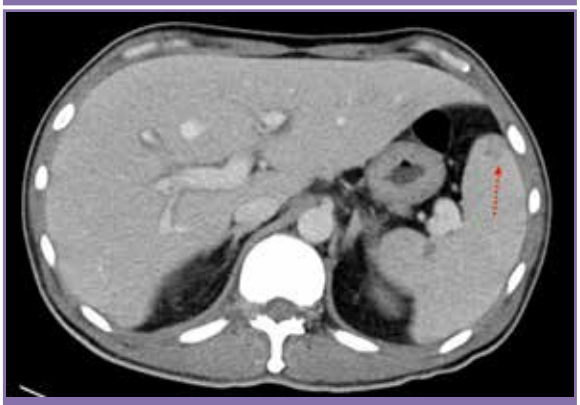

Fig. 4: Splenic micro abscesses (Personal Collection)

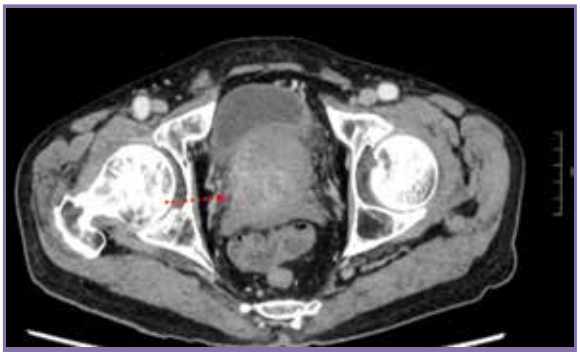

Fig. 5: Prostatic abscess (Personal Collection)

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Dermatology Quiz

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Specialist in Dermatology and Venereology

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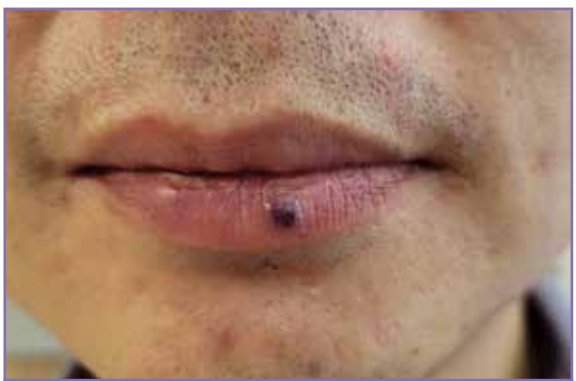

Fig. 1: Pigmented papule on the lower lip

A 45-year-old man complained of a solitary pigmented papule on his lower lip. He did not recall the duration of onset clearly. It seemed to start several years ago. Physical examination revealed a solitary, dark, purplish dome-shaped papule on the lower lip. There was no ulcer nor erosion; otherwise, it was asymptomatic (Fig. 1).

Questions

1. What is the diagnosis of the skin lesion?
2. What is the underlying pathology?
3. How do you manage this gentleman?

(See P. 40 for answers)

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* In clinical trials in treatment-naïve participants, efficacy at Week 48 (primary endpoint) was 91% for BIKTARVY® (pooled [n=634]), efficacy at Week 144 was 82%.[2,3] In the optional 96 week open-label extension phase, high rates of virologic suppression were achieved and maintained.[4] In clinical trials in virologically suppressed participants, efficacy at Week 48 (primary endpoint) was 94% in Study 1844 (n=282) and 92% in Study 1878 (n=290).[4,7] Efficacy defined as viral load <50 copies/mL.[2,3]

† In clinical studies of treatment-naïve participants receiving BIKTARVY®, the most frequently reported adverse reactions were headache, diarrhoea and nausea.[1] At Week 240, <1% (n=5/634) of participants initially randomised to BIKTARVY® discontinued treatment due to TRAEs.[4] In clinical studies in virologically suppressed participants, ≤1% of participants discontinued treatment with BIKTARVY® due to adverse events through the open-label extension phase of either study.[4,5]

‡ In pivotal Phase 3 trials, there was 0 treatment-emergent resistance in the final resistance analysis populations.[2,3]

TRAEs=treatment-related adverse events.

References: 1. BIKTARVY® Hong Kong prescribing information (HK-AUG21-EU-MAY21). **2.** Gallant J, *et al.* Lancet. 2017;390(10107):2063-2072. **3.** Sax PE, *et al.* Lancet. 2017;390(10107):2073-2082. **4.** Orkin C, *et al.* Lancet HIV. 2020;7(6):e389-e400. **5.** Wohl DA, *et al.* CROI 2022; 12-16 February 2022, virtual. Poster 494. **6.** Molina JM, *et al.* Lancet HIV. 2018;5(7):e357-e365. **7.** Daar ES, *et al.* Lancet HIV. 2018;5(7):e347-e356. **8.** Sax P, *et al.* International AIDS Conference 2022, 29 July–2 August; Montreal, Canada. Poster EPB150. **9.** Brar I, *et al.* Infectious Diseases (ID) Week 2020, 21–25 October. Poster 1028. **10.** Rockstroh JK, *et al.* HIV Glasgow 2020, 5–8 October; Glasgow, UK. Poster 036.

Pill not shown at actual size.

BIKTARVY® Abbreviated Prescribing Information
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Presentation: Each film-coated tablet contains bictegravir sodium equivalent to 50 mg of bictegravir, 200 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide. Purplish-brown, capsule-shaped, film-coated tablet debossed with "GSI" on one side and "9883" on the other side of the tablet. Each tablet is approximately 15 mm x 8 mm. **Indications:** Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir. **Dosage:** Adults: One tablet to be taken once daily with or without food. Elderly: No dose adjustment is required. Renal impairment: No dose adjustment for patients with estimated creatinine clearance (CrCl) ≥ 30 mL/min. No dose adjustment is required in adult patients with end stage renal disease (estimated CrCl < 15 mL/minute) who are receiving chronic haemodialysis. Not recommended in patients in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min, or < 15 mL/min who are not receiving chronic haemodialysis. Hepatic impairment: No dose adjustment for patients with mild or moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class A or B). Not recommended in patients with severe hepatic impairment (CPT Class C). Paediatric population: The safety and efficacy in children and adolescents aged less than 18 years not yet been established **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Co-administration with rifampicin and St John's Wort (*Hypericum perforatum*). **Warnings and Precautions:** Patients co-infected with HIV and hepatitis B or C virus: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Discontinuation of Biktarvy therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Biktarvy should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment. Liver disease: Patients with pre existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Lipid disorders should be managed as clinically appropriate. 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Sepsis, Septic Shock from Emergency Room to Intensive Care Unit

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Sepsis is a potentially life threatening clinical condition as a result of dysregulated host response to infection. Paoli CJ et al.[1] reported hospital mortality for severe sepsis and septic shock as 14.9 % and 34.2 % in 2018. There were over 250,000 deaths annually in the USA. It is the single most expensive condition treated in the hospital, corresponding to about 13 % of hospital expenses. Early identification and appropriate, timely measures in the initial hours improve outcomes. In the Prince Book III, 1498, Niccolo Machiavelli quoted, 'Hectic fever at its inception is difficult to recognise but easy to treat, left untended it becomes easy to recognise but difficult to treat.'

International experts in sepsis published the first Surviving Sepsis Campaign (SSC) guideline in 2004[2]. The latest revision was published in 2021[3]. It is hoped that through education and system improvement, medical professionals involved in handling patients with sepsis can help improve the outcomes.

DEFINITIONS

Infection is a clinical phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by these organisms.

Systemic inflammatory response syndrome (SIRS) is defined as an exaggerated defence response of the body to a noxious stressor to localise and eliminate the endogenous or exogenous source of the insult. It is characterised by at least 2 of the following;

1) Temperature > 38 or < 36 degree Celsius
2) Tachycardia (heart rate > 90 / min)
3) Tachypnoea (respiratory rate > 20 / min or PaCO2 < 32 mmHg)
4) White cell count > 12,000 /mm^3 or < 4,000 / mm^3 or > 10 % immature (band) forms

Sepsis is defined as SIRS in response to infection.

Severe sepsis is defined as sepsis with sepsis-induced organ dysfunction or tissue hypo-perfusion.

Septic shock is severe sepsis with persistent low blood pressure, despite adequate fluid resuscitation.

In 2016, a new consensus of using quick Sequential Organ Failure Score (qSOFA) to replace SIRS in identifying sepsis. The component of qSOFA includes the following:

1) Respiratory rate equal to or faster than 22 / min
2) SBP of 100 mmHg or less
3) Altered mental state

Sepsis is suspected when 2 of the above criteria are met. qSOFA was found to be a predictor of poor outcomes in patients with known or suspected infection; however, there was no analysis to support its use as a screening tool per se at that time. qSOFA is intended to be used outside the ICU setting; it is simple and quick, and does not require laboratory investigations. Numerous studies have investigated the potential use of qSOFA as a screening tool for sepsis, and there have shown that qSOFA is more specific but less sensitive than having two of four SIRS criteria for early identification of infection induced organ failure[4-6]. SSC 2021 guidelines recommend against the use of qSOFA as a single screening tool for sepsis or septic shock.

There is a wide variation in diagnostic accuracy of sepsis screening tools like systemic inflammatory response syndrome (SIRS), quick Sequential Organ Failure Score (qSOFA), Sequential Organ Failure Assessment (SOFA), National Early Warning Score (NEWS) or Modified Early Warning Score (MEWS). These screenings may have different target patients in various locations, but they also have different sensitivity and specificity; however, they are important to alert clinicians for timely intervention for potential septic patients.

WHAT SHOULD WE DO IN THE INITIAL STAGE?

Sepsis resuscitation involves a collection of targets orientated interventions. The famous Early Goal Directed Therapy introduced by RIVERS et al. in 2001[7] and subsequent studies, PROCESS[8], ARISE[9] and PROMISE[10] provided a good backbone and roadmap for us to manage these critically ill patients in a systematic manner. Different hospitals and units may have their standard operating protocols, early identification, lactate measurement, source identification, source control, fluids, early antibiotics, vasopressor and inotrope were the cornerstones for these.

Here, I summarise the latest key recommendations from the Surviving Sepsis Campaign 2021;

1) For adults suspected of having sepsis, lactate should be measured. Lactate should be used as a guide for resuscitation as well.
2) Patients requiring ICU admission should be admitted to ICU within the first 6 hours.
3) For adults with possible septic shock or a high likelihood of sepsis, empirical IV antimicrobials to cover all likely pathogens should be given immediately, ideally within 1 hour of recognition.
4) Rapid identification of a specific anatomical source of infection and implementation of source control intervention should be arranged as soon as medically and logistically practical.
5) For sepsis induced hypo-perfusion, at least 30 ml/kg of IV crystalloids, preferably a balanced solution, should be given within the first 3 hours. Using dynamic measures like a response to a passive leg raising or a fluid bolus, using stroke volume, stroke volume variation, pulse pressure variation or echocardiography to guide fluid resuscitation is recommended.
6) For patients requiring vasopressors, mean arterial pressure (MAP) of 65 mmHg should be targeted, preferably titrated with Noradrenaline, then vasopressin and Adrenaline, delay should be avoided for waiting central venous access to be secured.
7) For patients with cardiac dysfunction with persistent hypo-perfusion despite adequate volume status and MAP, either adding dobutamine to Noradrenaline or using Adrenaline should be tried.
8) For patients with septic shock and an ongoing requirements of vasopressor, IV corticosteroids should be used.
9) For adults with sepsis-induced hypoxaemia, high flow nasal oxygen should be tried.
10) For adults with sepsis-induced ARDS, protective ventilatory strategies with low tidal volume (6 ml/kg), plateau pressure of less than 30 cm H_2O, high PEEP, and traditional recruitment manoeuvres with sustained continuous positive airway pressure should be implemented.
11) Prone ventilation for more than 12 hours daily and VV-ECMO, when conventional mechanical ventilation fails in experienced centres should be the rescue measure for ventilatory support.
12) Stress ulcer prophylaxis, glucose control, nutrition support and pharmacological venous thromboembolism prophylaxis, preferably low molecular weight heparin, should be implemented unless there is a contraindication to such therapy being identified.
13) For patients without shock, rapid assessment should be carried out, including history taking, clinical examination, tests for both infectious and non-infectious cause(s) of acute illness, and immediate treatment of acute conditions that may mimic sepsis. Whenever possible, it should be completed within 3 hours of presentation and a decision should be made as to the likelihood of an infectious cause of the patient's presentation; timely antimicrobial therapy should be initiated if the likelihood of infection is believed to be high.

TIMELY INFECTIOUS DISEASE SPECIALIST CONSULTATION

Earlier involvement with infectious disease expertise in the management of these critically ill patients improves their outcomes[11, 12, 13, 14, 15]. Infectious disease expertise provides valuable advice in various aspects of the care journey;

1) Identification of the potential source(s) of sepsis
2) Empirical choice and dose of the antimicrobials
3) Advice on newly emergent infectious diseases, latest management guidelines and potential treatment options
4) Early and appropriate de-escalation of antimicrobials
5) Suggestion regarding the appropriateness of adjunctive measures. Although SSC does not recommend the routine use of IVIG, IVIG has been proven to be useful in certain infections like invasive Group A Streptococcal infection or multisystem inflammatory syndrome in children with COVID-19 infection.

THE HOUR-1 BUNDLE

SSC introduced the Hour-1 bundle for the initial resuscitation for patients being recognised to have sepsis or septic shock as below;

1) Sepsis, septic shock is a medical emergency.
2) The bundle should be initiated once sepsis or septic shock is recognised.
3) Measure lactate level and remeasure lactate if initial lactate is more than 2 mmol/L
4) Obtain blood cultures
5) Administer broad-spectrum antibiotics
6) Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate more than 4 mmol/ L
7) Start vasopressors if hypotensive during or after fluid resuscitation to maintain MAP more than 65 mmHg

The most important message that SCC emphasises is the timely recognition of sepsis and septic shock and its implementation of timely appropriate measures. Every hour delay in antibiotics[16] and other key steps translates to higher potentially preventable mortality.

ICU WITHOUT WALL

With the current busy ICU situation, timely ICU admission may not be feasible. Emergency physicians and sometimes colleagues working in a general ward, physicians, surgeons, orthopaedics surgeons, urologists, gynaecologists, neurosurgeons, and everybody managing these patients should have a high index of suspicion, timely implementation of the hour-1 bundle while waiting for ICU admission. Sepsis is a medical emergency; resuscitation should be started right from the time that sepsis or septic shock is being recognised. Therefore, resuscitation should begin even though the patient stays in the emergency room or general ward.

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12 FAQs on Klebsiella Pneumoniae Primary Liver Abscess (KLA)

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INTRODUCTION

Klebsiella pneumoniae, presenting as a monomicrobial pyogenic liver abscess, emerged in the 1980's. It was a community acquired syndrome often occurring in diabetics or healthy patients without biliary disorder. It subsequently became widespread in parts of Asia. It is now a major cause of pyogenic liver abscesses in Taiwan, Korea, Hong Kong and Singapore. A distinctive feature of this infection is a propensity to metastasise to distant sites, most commonly the eye, lung and central nervous system[1-3].

1. WHERE IS IT COMMONLY FOUND?

Primary (cryptogenic) liver abscess caused by a hypervirulent strain of *Klebsiella pneumoniae* has been reported mainly in Asian countries. Two case series in the USA showed that half the patients were of Asian ethnicity[4]. The infection is now reported worldwide[5,6]. A strong association was found between gastro-intestinal colonisation and the occurrence of liver abscesses. High rates of healthy carriage (up to 75 %) were found in Asia, and around one quarter of the typable strains in Taiwan were of hypervirulent strain K1 or K2[7]. Evidence suggests that gut scolonisation by the organism directly precedes infection in the same individual. It is still unclear whether the emergence of a hypervirulent strain of *Klebsiella pneumoniae* in Asia is due to genetic susceptibility or environmental or unknown factors.

2. WHAT ARE THE RISK FACTORS FOR ACQUISITION? CAN IMMUNOCOMPETENT HOSTS GET IT?

Diabetes mellitus (DM) is found to be one of the major observed risk factors for primary *Klebsiella pneumoniae* liver abscess and the development of metastatic infection. Fatty liver disease is also associated with KLA, whereas liver abscess due to other bacteria is not associated with fatty liver disease. KLA can also affect persons without any previous medical conditions.

3. WHAT CONTRIBUTES TO THE VIRULENCE OF THE BACTERIA?

There are four major classes of *Klebsiella pneumoniae* virulence factors. These consist of capsules, including the production of hypercapsules in hypervirulent strains; lipopolysaccharide, siderophores and pili. 'Classical' *Klebsiella pneumoniae* commonly causes healthcare-associated pneumonia, urinary tract infections, or bacteraemia in immunocompromised hosts. On the other hand, hypervirulent strains are mostly community acquired. The most well known serotypes, K1 or K2, are hypercapsular and have a greater expression of siderophores, giving them a higher resistance to phagocytosis and intracellular killing by neutrophils. Table 1 shows the differences between classical and hypervirulent strains.

Table 1. Comparison of classical and hypervirulent strains of Klebsiella pneumoniae (adapted and modified from references 8, 9)

Parameter	Classical strain	Hypervirulent strain
Common types of infection	Pneumonia, UTI, Bacteraemia	Primary liver abscess, bacteraemia, pneumonia, necrotising fasciitis, myositis, meningitis, endophthalmitis
Susceptible hosts	Immunosuppressed (e.g. diabetes mellitus, malignancy)	Diabetes mellitus, fatty liver, healthy people
Capsule type	Capsule serotype K1-K78	Hypercapsular serotype K1 (93 %) or K2
Primary infection type	Healthcare associated	Community associated
Geographical concentration	Global	Primarily Asia
Frequency of reports of antibiotic resistance	Frequent (ESBL and carbapenemase producing)	Infrequent but emerging in parts of Asia
Metastatic infection	2 % or less	12 % or more

4. HOW DO THE BACTERIA GET INTO THE LIVER?

There are four main routes by which bacteria can invade the liver: (1) biliary tree, (2) portal vein, (3) hepatic artery, and (4) direct extension from neighbouring focus of infection. A pyogenic liver abscess may result if the initial immune response fails to contain the bacteria. Biliary infections are associated mostly with strictures

due to gallstone disease or malignancy. The portal venous route may be due to bacteraemia or to intra-abdominal infection, such as, appendicitis, diverticulitis or colorectal cancer. The hepatic arterial route is usually caused by bacteraemia, especially those caused by *Staphylococcus aureus*. KLA is believed to result from disruption of the intestinal barrier by bacteria to disseminate to other organs.

5. CAN A PATIENT PRESENT WITH NO LOCALISING SIGNS OR SYMPTOMS?

The most common symptom is fever (93 % in one series)[10]. Right upper quadrant pain or tenderness was absent in 30 % of cases[10]. Other symptoms include chills, nausea and vomiting. In a series of over 800 patients with KLA from different countries, 12 % of patients had evidence of metastatic disease on presentation[4]. The most common metastatic sites include the eye, lung and central nervous system. Other metastatic sites include severe necrotising skin and soft tissue infection, bone infection, and seeding to the prostate, kidneys and spleen. In a Taiwanese study of 83 patients with bacteraemia, 23 % had no detectable focus of infection[11]. A pyogenic liver abscess often presents with features pointing neither to an abscess nor to the liver, thus posing a difficult diagnostic problem. Sometimes, the appearance of signs or symptoms of metastatic infection can be the first presentation of underlying invasive disease. Leucocytosis, thrombocytopenia, increased C-reactive protein, and abnormal liver function tests are common.

6. WHAT DIAGNOSITIC TOOLS ARE PREFERRED?

Ultrasound or computer tomography are the imaging modalities of choice. CT scan is more sensitive than ultrasound (100 % vs 85.8 %) and hence is recommended for diagnosis[12]. Typical contrast CT findings of KLA include single, unilobar, thin walled, multiseptated, solid mass with necrotic centres.

A search for an underlying occult liver abscess should be made in all patients, especially among diabetic Asians, presenting with *Klebsiella pneumoniae* bacteraemia, endophthalmitis, meningitis or other extrahepatic infections.

Microbiological diagnosis is made by sending an aspirate from an image-guided aspiration for Gram stain, aerobic and anaerobic cultures and multiplex PCR (if available). Blood cultures should be obtained from all patients with confirmed or suspected KLA. A special microbiological feature of hypervirulent strains is their hypermucoid appearance on agar plates. A positive 'string test' for hypermucoviscosity was shown by stretching a colony by at least 5mm with an inoculation loop (Fig. 1)[13]. Molecular diagnosis of a hypervirulent strain is made by detecting at least three or moreirulence genes: *iucA*, *iroB*, *peg-344*, *rmpA*, and *rmpA2*[14]. Such testing is not routinely available except in a research setting.

Fig. 1: Demonstration of a positive string test[13]

7. WHAT ARE THE BEST EMPIRICAL ANTIMICROBIAL(S) FOR TREATMENT?

Intravenous antibiotic therapy is needed. Empirical therapy should cover Streptococci, enteric gram-negative bacilli, and anaerobes associated with pyogenic liver abscess. Preferred regimens include beta-lactam/beta-lactamase inhibitors (e.g. pipercillin-tazobactam), or third generation cephalosporin (e.g. ceftriaxone), plus metronidazole. Alternative regimens include fluoroquinolone (e.g. levofloxacin or ciprofloxacin) plus metronidazole or carbapenem alone (e.g. meropenem or ertapenem). Carbapenems should be reserved for cases in which extended-spectrum-beta-lactamase is strongly suspected. There have been no trials comparing which antibiotics are best for treating KLA. Empirical therapy should take into account the possible differential diagnoses. It is important to cover a potential amoebic liver abscess (ALA) with metronidazole until it has been excluded. Thus KLA should be treated with beta-lactam/beta-lactamase inhibitors (e.g. pipercillin-tazobactam) or with a carbapenem alone (e.g. meropenem or ertapenem). Metronidazole should be added until amoebic liver abscess (ALA) has been excluded. A third-generation cephalosporin or carbapenem (when ESBL is suspected/confirmed) is preferred for central nervous system involvement due to better penetration into the cerebrospinal fluid.

8. WHAT IS THE BEST TARGETED ANTIMICROBIAL(S) FOR TREATMENT?

Targeted antibiotic therapy should be tailored to the results of antibiotic susceptibility testing. Once the susceptibility result is available, the antibiotic regime should be de-escalated from broad spectrum to targeted. A third-generation cephalosporin is preferred if the isolate proves to be sensitive. Historically, antimicrobial resistance was uncommon. However, resistant strains, including ESBLs and carbapenem resistance, are emerging creating a new challenge in combating this already difficult to treat infection.

In addition to systemic antibiotics, patients with metastatic infection will need specific local therapy. For example, intravitreal antibiotics and vitrectomy are indicated in patients with Klebsiella endophthalmitis. Automatic ophthalmic consultation should be considered in all cases of KLA in order to give early and appropriate therapy.

9. HOW LONG DOES THE PATIENT NEED TO BE TREATED?

For most cases, a 4 - 6 week course of antibiotics is adequate. Intravenous antibiotic(s) may be administered for the first two to three weeks until the patient has clinically improved and drainage is completed. The remaining course can be completed by switching to an appropriate oral antibiotic. Occasionally, longer courses of antibiotic therapy may be needed, for example, for patients with persistent radiographic features of an abscess or patients requiring subsequent drainage. Treatment should be continued until complete or near complete resolution of the abscess cavity, as seen on a CT scan. Sometimes, a CT abnormality may persist after the infection has been cured. Serial monitoring of inflammatory markers, for example, C-reactive protein and ESR, is useful to distinguish persistent or cured infections from still active infections.

10. WHAT IS THE ROLE OF DRAINAGE?

Management of KLA requires both adequate source control and adequate antibiotic therapy. For source control, percutaneous drainage is preferred over surgical drainage and is useful for both diagnosis and treatment. Drainage for treatment is recommended even in patients whose blood culture is positive, as drainage is associated with a decreased risk of metastasis and mortality. For pyogenic liver abscesses > 5 cm in diameter, percutaneous catheter drainage reduces the time to recovery and shortens the hospital stay compared to percutaneous aspiration alone[15]. Drainage of KLA during the initial stage is often difficult due to the solid appearance and multilocular characteristics of the abscess. In such cases, drainage can be postponed until the abscess is mature. Alternatively, one may insert and retain the drain and wait for the liquefication of the abscess. For severe disease, one study showed that aggressive hepatic resection resulted in a better outcome than percutaneous drainage[16].

11. WHAT ARE THE POSSIBLE COMPLICATIONS AND ASSOCIATED MORBIDITIES AND MORTALITY?

Patients with an invasive syndrome have a mortality ranging from 3 to 31 %. Patients with bacteraemia have a mortality of 35 % or higher. Antimicrobial resistance, septic shock, acute respiratory failure, and metastatic infection were all associated with higher mortality. Patients with metastatic endophthalmitis may be left with visual impairment or blindness. Patients with metastatic CNS infection may have persistent neurological deficits.

12. DOES THE PATIENT NEED A COLONOSCOPY FOR SUBSEQUENT WORKUP?

Case series and anecdotal reports revealed a strong association between pyogenic liver abscess and colorectal carcinoma[17]. There have been cases of recurrent *K. pneumoniae* pyogenic liver abscess due to unrecognised colorectal carcinoma as the underlying source of infection[18]. It is believed that a compromised mucosal barrier may facilitate the invasion of the portal circulatory system by bacteria via a hematogenous route. Apart from colorectal cancer, villous adenomas can also cause mucosal disruption similar to colon cancer[19] Therefore, colonoscopy should be considered in patients with liver abscesses.

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Hong Kong Medical & Healthcare Sector Beijing Visit (19 - 22 July 2023)

Dr Alson CHAN

Hon. Secretary, The Federation of Medical Societies of Hong Kong

It is my honour to represent FMSHK to join this rewarding visit organised by National Health Commission (NHC), led by Dr Ko,Wing-man and Dr Hon. David Lam, together with over 20 representatives from medical, dental, nursing and Chinese Medicine sectors. We were interviewed by Cao Xuetao (NHC vice-minister) and his team. Cao listened to our report on the current challenges in healthcare settings of Hong Kong, introduced the key tasks of NHC, and encouraged healthcare professionals in Hong Kong to uphold our unique role as an international knowledge hub to facilitate cutting edge healthcare research and specialist service provision. NHC will continue to fully support the integration of Hong Kong into the strategic plan of national healthcare development, and look forward to more collaborations between mainland and Hong Kong healthcare professionals. Besides, we also visited the office of Chinese Medical Association in Beijing, Peking University Health Science Centre, their research centres and affiliated hospitals.

Fig. 1: Representative from Hong Kong Medical & Healthcare Sector interviewed by NHC vice-minister Cao Xuetao (Ref: http://www.nhc.gov.cn/gjhzs/s3582/202307/e904ad42505b45a99e8bca140b018a7e.shtml)

Fig. 2: Meeting in progress with NHC vice-minister and his team (Personal collection)

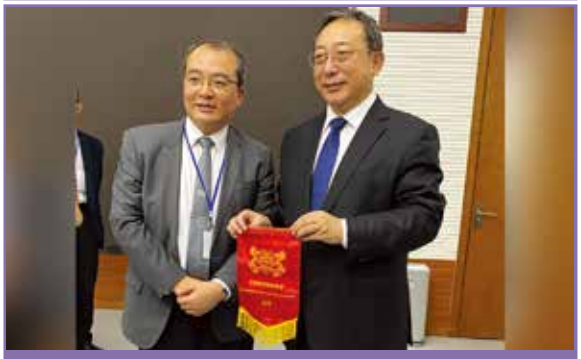

Fig. 3: FMSHK souvenir flag presentation after the meeting (Personal collection)

Fig. 4: Meeting in Peking Union Medical College Hospital (Personal collection)

Fig. 5: Visiting Head Office of Chinese Medical Association in Beijing (Personal collection)

Be A Rock Star

Dr Thomas HF TSANG
MBBS, FHKCCM

Dr Thomas HF TSANG

Fig. 1: Mineral photo (Personal Collection)

I like to tell friends that I have diamonds, rubies, sapphires and emeralds in my home. Wait, I don't own a jewellery shop or a bragging wife. I just happen to collect minerals.

How did I develop this obscure, trifling hobby? I am not exactly sure. Well, probably because of their fascinating shapes, mesmerising colours and indescribable aesthetic beauty. Like the human body, minerals are wonderful creations of Nature. Every time I hold a rock in my hand I feel a part of Earth's history. Minerals are also linked to lots of interesting history and stories. For example, ancient Romans believed that a drinking cup made of amethyst (a purple variety of quartz) would prevent one from getting drunk.

There are more than 5,000 different kinds of minerals, and like people, each mineral has a distinct personality. Minerals come in all shapes and sizes, colours, textures, weights and hardnesses. Most of them may be kept in the open for viewing pleasure, but a few are damaged by sunlight and need to be stored in the dark. Some must be kept moist, while others break down on contact with moisture. Like our patients, one must know the minerals well to avoid harming them.

I collect minerals just for the fun of it. I am not a professional who carries a bag of tools to dig out hidden treasures from caves and caverns. I just do a few clicks at home and order them via Taobao (best price), eBay (wide selection) and some other sites. There is also a Mineralogy Society in Hong Kong where members can exchange their collections. Of the commoner minerals, my favourites are fluorite, pyrite, celestite, azurite, crocoite, vanadinite, etc. They make superb household decorations thanks to their many vivid colours and enticing shapes and forms.

Wherever I travel, I try to look for mineral/geology museums not far away from where I stay. For instance, one can spend a whole day at the National History Museum in London or the Smithsonian collection at the National Museum of Natural History in Washington DC, USA. There, seeing a rare mineral is like seeing a rare clinical case. Guessing its identity is a bit like crunching out an unusual differential diagnosis. The joy of guessing correctly is huge. If you ever dream of an unorthodox travel experience, mining towns, where locals often turn old mines into tourists' adventures, might just be right for you. I visited a couple of them these years, for example, at Broken Hill / Australia, Freiberg / Germany, and Cornwall / UK. The mining landscapes range from barren to historic to absolutely scenic. Of course, don't forget Silver Mine Bay in our backyard, or the splendid mineral museums at our local universities.

Unexpectedly, my little hobby brings a few other good things. I like to "window shop" at jewellery shops not because I want to buy anything (I can't afford it), but because I like to guess how much those sparkling gems are worth based on what I learned from my hobby. I won't say I am good at estimating prices, but most of the time, I am not far off the mark. And finally, let me confess that the diamonds, rubies and sapphires that I own are not worthy at all. They are minerals, not gems. You can easily fetch a decent ruby rock on eBay for HK$100 - 200 a piece. But the fact is, the cost of buying minerals online has gone up quite markedly over the past 10 - 15 years, beating inflation by a mile. So, eventually, my little collection could turn out to be a nice little investment in my retirement.

Fig. 2: Aquamarine (Personal Collection)

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	* In-person / Zoom HKMA-HKSH CME Programme 2023-2024 Topic: Novel Diagnostics & Therapeutics in Allergy Practice 2	3	4	5	6
7	8	9	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed 10	* Zoom The HKMA CME Live Lecture Topic: Patient Counselling on Women's Health Disease: The Use of Hormonal Treatment 11	12	13
14	15	* In-person / Zoom HKMA-GHK CME Programme 2024 Topic: To-be-confirmed 16	17	* Zoom The HKMA CME Live Lecture Topic: Integrity and Professional Ethics for Doctors 18	* HKFMS Foundation Meeting * FMSHK Executive Committee Meeting 19	20
21	* Zoom The HKMA CME Live Lecture Topic: Respiratory Syncytial Virus (RSV) Infection: Disease Overview, Burden and Update on Management 22	23	* Zoom The HKMA CME Live Lecture Topic: The Modern Era Precision Medicine on Lung and Breast Cancer Treatment 24	* In-person / Zoom HKMA-HKSTP CME Programme 2023 (Lecture in Physical Attendance Mode + Online) Topic: To-be-confirmed 25	26	27
28	29	30	31			

Date / Time	Function	Enquiry / Remarks
2 TUE 2:00 PM	**In-person / Zoom** **HKMA-HKSH CME Programme 2023-2024** **Topic: Novel Diagnostics & Therapeutics in Allergy Practice** Organiser: The Hong Kong Medical Association and the Hong Kong Sanatorium & Hospital Speaker: Dr Marco Hok-kung HO Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
10 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker(s): Dr HO Yan-wa Chairman: Dr Kevin King-fai CHENG Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	CME Accreditation: 1.5 points College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
11 THU 2:00 PM	**Zoom** **The HKMA CME Live Lecture** **Topic: Patient Counselling on Women's Health Disease: The Use of Hormonal Treatment** Organiser: The Hong Kong Medical Association Speaker: Dr Linna LIAUW	HKMA CME Dept. Tel: 2527 8452 1 CME Point
16 TUE 2:00 PM	**In-person / Zoom** **HKMA-GHK CME Programme 2024** **Topic: To-be-confirmed** Organiser: The Hong Kong Medical Association and the Gleneagles Hong Kong Hospital Speaker: To-be-confirmed Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
18 THU 2:00 PM	**Zoom** **The HKMA CME Live Lecture** **Topic: Integrity and Professional Ethics for Doctors** Organiser: The Hong Kong Medical Association and the Hong Kong Business Ethics Development Centre of ICAC Speaker: To-be-confirmed	HKMA CME Dept. Tel: 2527 8452 1 CME Point
19 FRI 7:00 PM	**HKFMS Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
22 MON 2:00 PM	**Zoom** **The HKMA CME Live Lecture** **Topic: Respiratory Syncytial Virus (RSV) Infection: Disease Overview, Burden and Update on Management** Organiser: The Hong Kong Medical Association and the Centre for Health Education and Health Promotion, The Chinese University of Hong Kong Speaker: Prof Ivan Fan-ngai HUNG	HKMA CME Dept. Tel: 2527 8452 1 CME Point
24 WED 2:00 PM	**Zoom** **The HKMA CME Live Lecture** **Topic: The Modern Era Precision Medicine on Lung and Breast Cancer Treatment** Organiser: The Hong Kong Medical Association Speaker: To-be-confirmed	HKMA CME Dept. Tel: 2527 8452 1 CME Point
25 THU 2:00 PM	**In-person / Zoom** **HKMA-HKSTP CME Programme 2023 (Lecture in Physical Attendance Mode + Online)** **Topic: To-be-confirmed** Organiser: The Hong Kong Medical Association and the Hong Kong Science and Technology Park Speaker: To-be-confirmed Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point

Answers to Dermatology Quiz

Answers:

1. The diagnosis is a venous lake of the lip. It is a common bluish soft papule and is often diagnosed in middle-age or older people of any race. Although it may happen anywhere, it is often found on the lower lip. It can also happen on the face, ear, neck and upper trunk. The possible differential diagnoses are blue naevus, Kaposi's sarcoma, pyogenic granuloma, angiokeratoma, melanocytic naevus, pigmented basal cell carcinoma and even melanoma.

2. Venous lake is a benign cutaneous vascular dilatation. It is proposed that its development is due to long term solar damage to the vascular adventitia and the dermal elastic tissue that causes the dilatation of superficial venous structures. It also explains why it is often found in sun exposure areas like the lip, ear, and head & neck regions.

3. Venous lake is a benign cutaneous lesion;no treatment is generally required. Reassurance to the patient is very important. Cryotherapy, electrocautery, sclerotherapy, and vascular laser can be considered for the removing venous lake if there is a cosmetic concern. However, surgical excision and histopathological examination are indicated if malignancy is suspected.

Dr KWAN Chi-keung
MBBS(HK), MRCP(UK), FRCP(Lond, Glasg, Edin), Dip Derm(Glasg), PDipID(HK), FHKCP, FHKAM(Medicine)
Specialist in Dermatology and Venereology

MSD

TAKE ON THE CHALLENGES OF COVID-19[1]

TEST. TREAT. TAKE CHARGE. molnupiravir

Reference: 1. molnupiravir US EUA Product Insert.

MOLNUPIRAVIR Selected Safety Information

Authorized Use

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

Limitations of Authorized Use

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

Contraindications

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

Warnings and Precautions

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

Adverse Reactions

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

Drug Interactions

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

Breastfeeding

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

Males of Reproductive Potential

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

Before prescribing, please consult the full prescribing information.

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